Reactivity of Halodiazoacetates and Halodiazoamides

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Master Thesis

Organic Chemistry

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Lastly, I want to thank my girlfriend, Marianne, for supporting me throughout the ups and downs, and always being there. I am also grateful for the help you gave me obtaining half-life data clicking the measure bottom on the computer every tenth minute when I was occupied with other tasks.

Oslo, May 2022

Jørgen Marcus

Abstract

The work in this thesis is divided into four parts:

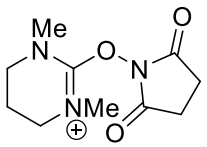
1. The study and development of a novel synthesis of 2,5-dioxopyrrolidin-1-yl 2-diazoacetate, a much desired building block (BB) for synthesis of diazo-esters and -amides. The existing literature procedure gave low yields. Hence, a new synthesis for making the BB was developed based on a coupling reaction of a carboxylic acid and *N*-hydroxysuccinimide (NHS). The reaction was optimized by investigating reaction conditions like solvent, base, concentrations, reaction temperature, reaction time and coupling reagents. The developed method gave better yield than the existing literature procedure. The scope and limitation of BB as a reagent for synthesizing diazo-amides and -esters was investigated by synthesizing a series of diazoamides and a diazoester.

2. Investigation of the thermal stability of a series of halo diazo-esters and -amides. Halo diazo-esters and amides have low thermal stability and their thermal decomposition rates have been investigated with a method based on IR spectroscopy. Significant differences in thermal stability of secondary and tertiary diazo-amides and -esters was uncovered.

3. A DFT-study of the singlet-triplet gap and the barriers towards release of N_2 (g) from the diazo compound to produce the corresponding carbenes. DFT calculations were carried out to compliment the experimental results. The height of the calculated transition barriers correlated with the measured half-lives. Differences in the triplet-singlet gap for diazo-esters and -amides were uncovered.

4. A brief exploration and investigation of a few selected test reactions. The reactivity of the halo diazo-amides and -esters were briefly studied in a few selected cyclopropanation and C-H insertion reactions under catalytic conditions. Among the test reactions was rhodium catalyzed cyclopropanation of styrene, uncovering differences in the diasteromeric ratio of the cyclopropane product of Br-2,2,2-trifluoroethyl 2-diazoacetate (TFEDA) and Br-2,2,2-trichloroethyl 2-diazoacetate (TCEFA) compared to Br-ethyl diazoacetate (EDA). In test reactions with halo diazoamides no cyclopropanation or C-H insertion products were found. The products that were found in all the test reactions had gone through the same type of reaction.

Graphical Abstract



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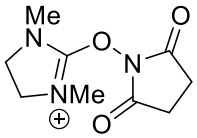

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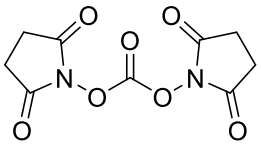

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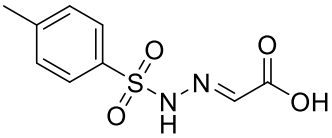

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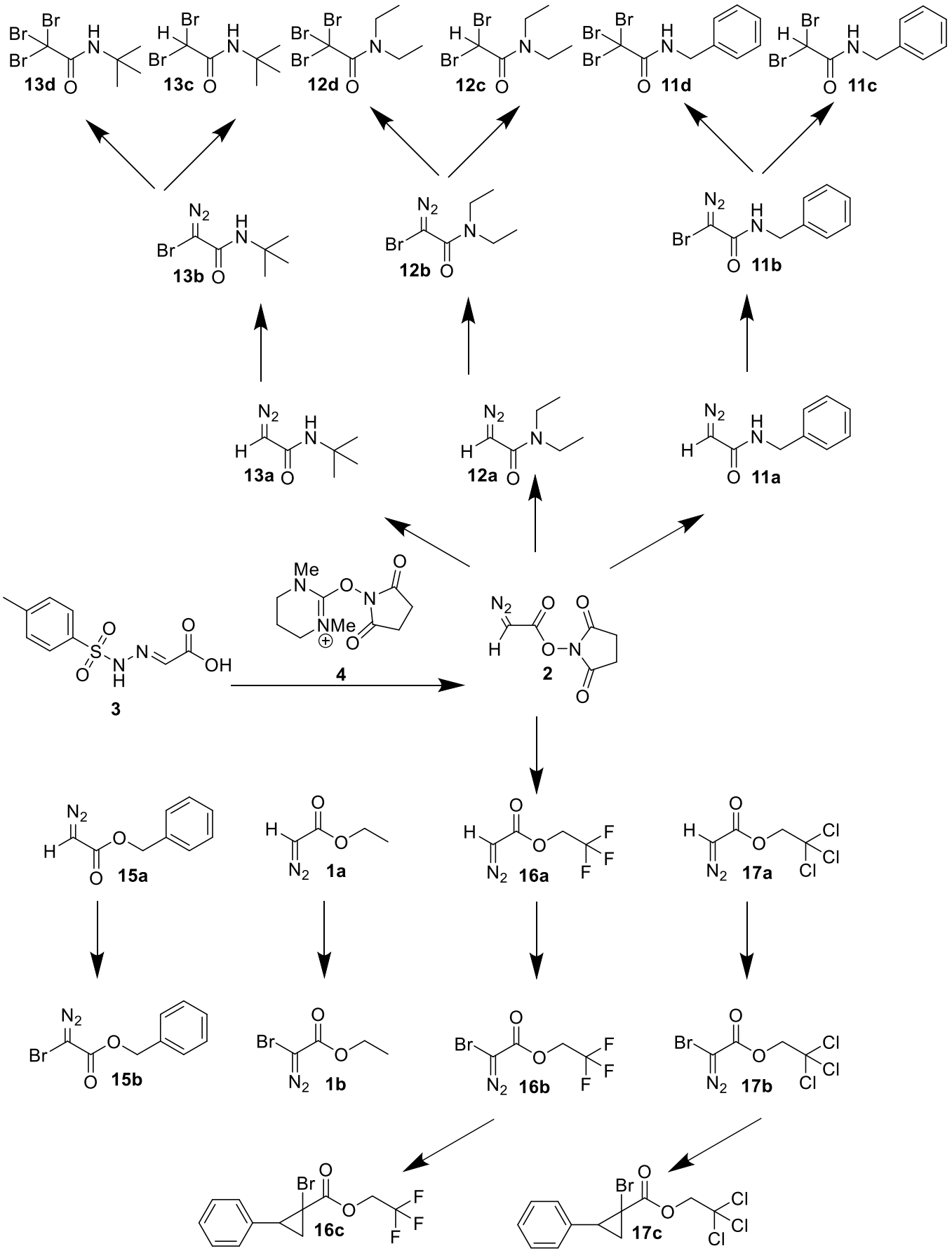
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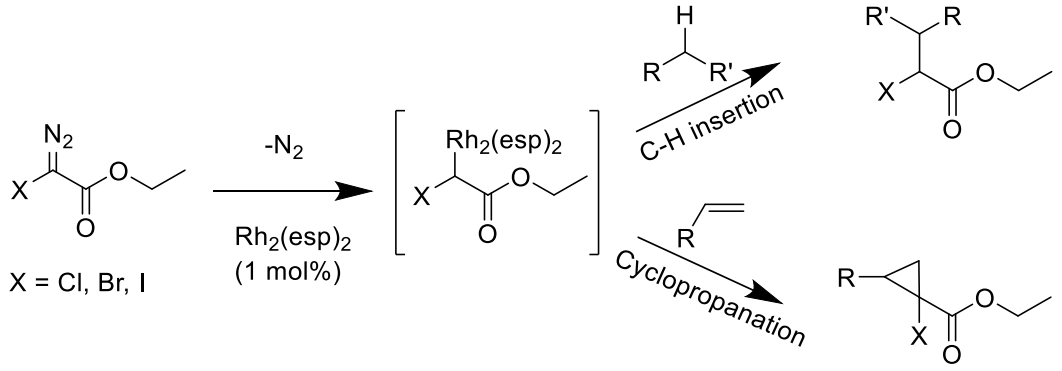
Abbreviations

a.u.	Atomic unit
AT	Ambient temperature
BB	2,5-dioxopyrrolidin-1-yl 2-diazoacetate
d	Doublet
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCM	Dichloromethane
dd	Double doublet
DFT	Density functional theory
DMF	Dimethylformamide
DMPU	1,3-Dimethyl-1,3-diazinan-2-one
DMSO	Dimethylsulfoxide
dq	Double quartet
dr	Diasteromeric ratio
-d_x	Deuterated form of solvent
EDA	Ethyl diazoacetate
eq.	Equivalent
EtOAc /AcOEt	Ethylacetate
g	Gas phase
h	Hours
HR-MS	High resolution mass spectroscopy
IR	Infrared
J	Coupling constant
m /min	Minutes
m/*z*	Mass-to-charge ratio
MeCN	Acetonitrile
MS	Mass spectroscopy
NBO	Natural bond orbital
NHS	*N*-Hydroxysuccinimide
NMR	Nuclear magnetic resonance
NXS	*N*-halosuccinimide
p	Pentet
ppm	Parts per million
q	Quartet
R_f	Retardation factor

s	Singlet
t	Triplet
*t*BuNH$_2$	Tertbutylamine
TCE	2,2,2-trichloroethyl
TCEDA	2,2,2-trichloroethyl 2-diazoacetate
TFE	2,2,2-trifluoroethyl
TFEDA	2,2,2-trifluoroethyl 2-diazoacetate
THF	Tetrahydrofuran
TS	Transition state
Ts	Toluenesulfonyl group
TXC	2,2,2-trihaloethyl
X	Halogen (F, Cl, Br)
δ	Chemical shift (NMR)

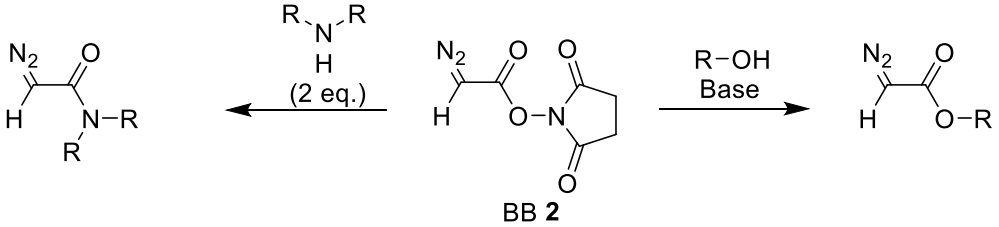
Description and aim of project

The investigation of diazocompounds and their corresponding carbenes has been a central part of the work in the Bonge-Hansen group for many years.[1-7] There has been a big focus on the reactivity of X-EDA and how the corresponding carbenes react.[1, 4, 5, 8-11] With one exception,[5, 8] all the studies including cyclopropanation- and C-H insertion reactions, have been done in the presence of catalyst.



Scheme 0.1: *C-H insertion- and cyclopropanation reactions of X-EDA in presence of rhodium catalyst.*[5, 11]

Earlier work in the research group has shown that X-EDA have shorter half-lives and decomposes at lower temperatures than EDA.[8] These properties opens up for the possibility of performing thermal, non catalyzed reactions like cyclopropanation and C-H insertion under very mild reaction conditions at room temperature. The thermal, non-catalyzed version of the cyclopropanation reaction displayed in **Scheme 0.1** has been briefly explored, but the yields were not synthetically useful. In order to increase the yield and broaden the scope of the thermal, uncatalyzed reactions, it is necessary to study the effect of different halogens, esters and amides against half-life and selected test reactions. In order to make a series of diazo-esters and -amides, it was desirable to do so through a one-step reaction using the diazoacetyl transfer reagent **2** as a general building block (**Scheme 0.2**).



Scheme 0.2: *Generic reaction between BB **2** and amines, and alcohols to give the corresponding esters and amides.*

The reported synthesis of BB from literature gave low yields and had to be improved.[12]

The goals for this master thesis can therefore be summarized as follows:

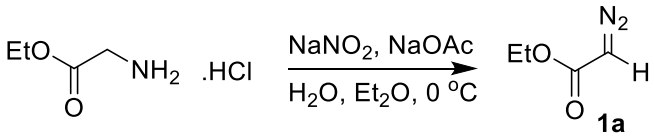
1) Improve the synthesis of BB.
2) Apply BB in the preparation of a series of diazo-esters and -amides.
3) Examine the thermal stability and reactivity of the corresponding halogenated diazo-esters and -amides.
4) Support the experimental observations with DFT calculations.

Table of content

1. Theory and Background

1.1. Introduction to diazo compounds

The first time a diazo compound was reported in literature was in 1858 by Peter Grieß.[13] He discovered and identified the first aromatic diazo compound. It was not before 25 years later the first aliphatic diazo compound was reported by Theodor Curtius in 1883.[14, 15] He synthesized ethyl diacoacetate **1a** by diazotization of glycine illustrated in **Scheme 1.1**.



Scheme 1.1: *Theodor Curtius synthesis of EDA **1a** from ethyl glycinate hydrochloride.*[14]

The conformation of the two *N*-atoms in the diazo group was for a long time a mystery. Whether the two *N*-atoms had an open, liner or a cyclic adjoining (**A Figure 1.1**) to the diazo carbon, was first established by Clusius and Lüthi in 1957. They confirmed that the diazo group was open, liner.[16, 17] The high nucleophilicity of the diazo carbon can be described from the two resonance forms **B** and **C** in **Figure 1.1**.

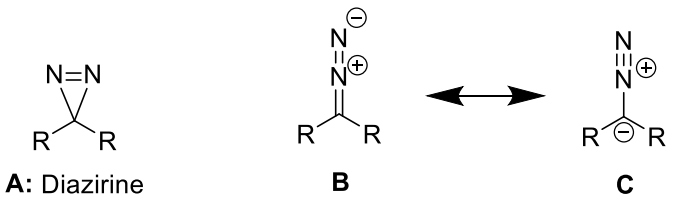
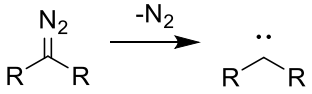


Figure 1.1: *3-membered ring geometry structure **A** (diazirine), compared to the resonance structures of a general diazo compound **B** and **C**.*[16] *R = alkyl, aryl.*

Today diazo compounds have a more significant role in organic chemistry and can undergo a variety of reactions. Some of these are in combination with transition metals, decomposing the diazo compound into the corresponding metal carbenoid. C-H insertion,[18] cyclopropanation[19] and

heteroatom-H insertion[20] are some examples of transformationes the generated metal carbenoid are involved in. These transformationes are frequently used in today's syntheses of natural products and medicinal chemistry, due to their ability to functionalize substrates with high chemo-, regio-, and stereoselectivity.[21, 22]

Diazo compounds have low thermal stability, high toxicity, explosiveness and carcinogenicity.[23] As a result, safety precautions are of great importance when working with diazo compounds. The diazo compound can easily release N_2 gas due to thermal or photolytic decomposition, and form the highly reactive carbene as shown in **Scheme 1.2**.[24]



Scheme 1.2: *Release of N_2 gas from a general diazo compound to form the corresponding carbene. R = alkyl, aryl.*

For a long time diazo compounds were looked upon as unpractical to use in syntheses due to the low thermal stability and hazards, which gave them limited synthetic value. Further studies has shown that the diazo group can be stabilized by having an electron withdrawing group at the carbon α to the diazo group, making them safe to utilize.[8, 23]

1.2. Thermal stability of diazo compounds

Aliphatic, none stabilized diazo compounds, such as diazometane, are thermally unstable. In room temperature, they easily decomposes within hours. They are also unstable in acid and the diazo group has a lot of nucleophilic character at the diazo carbon (see **Figure 1.1, C**).[17] By means of substituents on the diazo carbon the thermal stability can be altered. Electron withdrawing groups on the α carbon to the diazo will have a stabilizing effect due to resonance.

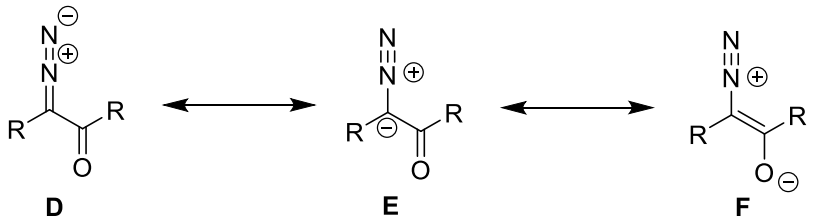


Figure 1.2: *Resonance structure of a general diazoketone compound.[25] R = alkyl, aryl.*

Resonance structure **E**, **Figure 1.2**, illustrates the diazo carbon basic and nucleophilic character, and are important for describing thermal release of N_2. Compared to structure **D**, the double bond character between the diazo carbon and the nitrogen is weakened in structure **E** and the diazo group is "activated" for N_2 release.[17] The stabilizing resonance effect of the ketone, structure **F**, can be explained by moving the electron pair at the diazo carbon in structure **E** to the more electronegative ketone oxygen.[25] Delocalizing the electron pair will lead to decrees of nucleophilicity and basicity at the diazo carbon.

If compering diazomethane with EDA based on thermal stability, EDA would have a stabilizing energy of about 4 Kcal/mol due to resonance effects.[25] This will have an enormous impact on how the chemicals should be handled. While diazomethane is a gas at room temperature, reported to spontaneously explode under distillation or in contact with uneven surfaces, the EDA is a yellow liquid at room temperature that can be stored undiluted at 0 °C for months without significant amount of decomposition.[5, 26]

1.2.1. General trends for thermal stability

As mentioned earlier, the thermal stability of diazo compounds vary according to the substituent α to the diazo carbon, but as Staudinger stated already in 1916, there are few general trends across substituent classes.[27] Later Regitz and Mass gathered thermal data available for a variety diazo compounds.[17] The comparison of thermal decomposing rates and half-life rates in solution was challenging due to a great diversity in conditions for decomposition and experimental methods used for the collection of data.[17] Although, some general trends of α substituents influence on thermal reactivity could be made.

The carbonyl group in α position in EDA will resonance stabilize EDA relative to diazomethane. The stabilizing effect of an electron withdrawing group in α position would vary as a function of the group's electronegativity. A carbonyl group that is less electron withdrawing, for example an ester, would stabilize the diazo better than the more electron withdrawing keton.[17]

Jugelt and coworkers tried to correlate diazo compounds basicity to thermal stability.[28] This was done by acid-catalyzed hydrolysis for a series of diazoester compounds and analogues diazo phosphonates.[28-31] The observations from these studies showed that the diazoester compounds was protonated 2-6 times slower than their phosphorus analogues. Which suggests that the ester delocalize the electron density at the diazo carbon more than the phosphorus analogues, and has more presence of resonance form **F** in **Figure 1.2**.[32, 33] Thermally the phosphorus analogues was shown to be more stable than the diazoesters, suggesting that phosphorus analogues have more presence of resonance form **D** in **Figure 1.2** than the diazoesters, since the stronger double bond character of the C=N bond adverse N_2 release.[29] The correlation between basicity and thermal stability are summarized in **Figure 1.3**.

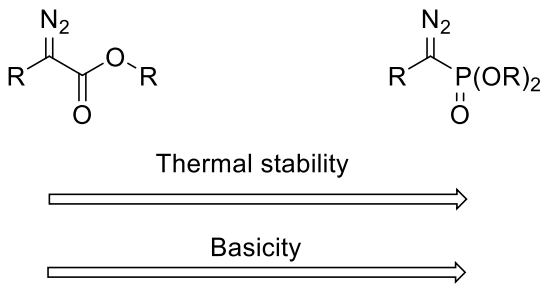


Figure 1.3: *The correlation between basicity and thermal stability.*[29, 32]

Even though this correlation between basicity and thermal stability is found for a series of diazo compounds, it is not always the case.[33]

If the diazo group is stabilized with more than one electron withdrawing group in α position, this may destabilize the diazo compounds thermally. Substitution of another electron withdrawing group in α positon of EDA decreases the thermal stability.[17] It was observed that ethyl nitro diazoacetate emits N_2 10^3 times faster than EDA.[34] Equivalent effect was observed for the α-cyano substituded diazo compounds.[35]

α-aryl substituents stabilize diazo compounds relative to diazomethane. This effect is explained by the possibility of the aryl substituent for π-conjugation with the diazocarbon.[17] α-Halogen substitution has a destabilizing effect on diazo compounds. It is reported that substitution of hydrogen in diazomethane with bromine or chlorine destabilize the diazo compound thermally.[36] A study of the effect of α-halogen substitution of EDA **1a** had the same conclusion.[1, 5, 8, 37] The larger increase of π-donation from the halogen caused the lower thermal stability. The thermal stability trends of the α-halo EDA are summarized in **Figure 1.4**.

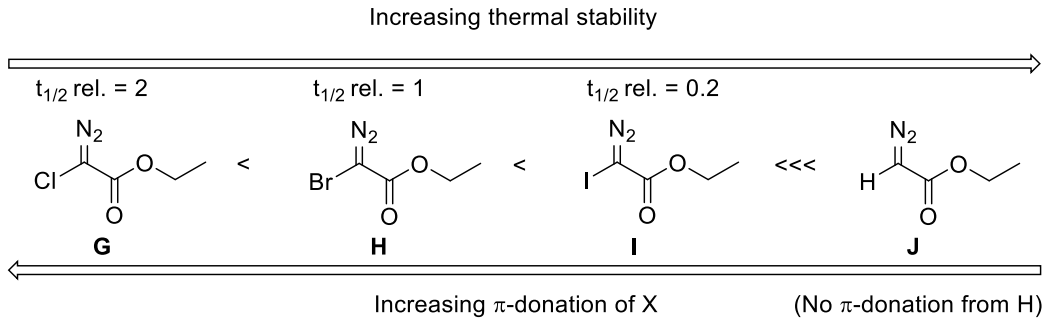


Figure 1.4: *Thermal stability of α-halo EDA and the α-substituents contribution to π-donation.*[5, 8]

1.3. Carbenes

Diazo compounds can decompose thermally or photochemically with release of N_2 (g) to form the corresponding carbene.[17] Carbenes have six valence electrons, where two are located in non-bonding orbitals. They are neutral and divalent. Carbenes can be divided into two major groups based on electron configuration. These groups are singlet carbenes and triplet carbenes, and are shown in **Figure 1.5**.

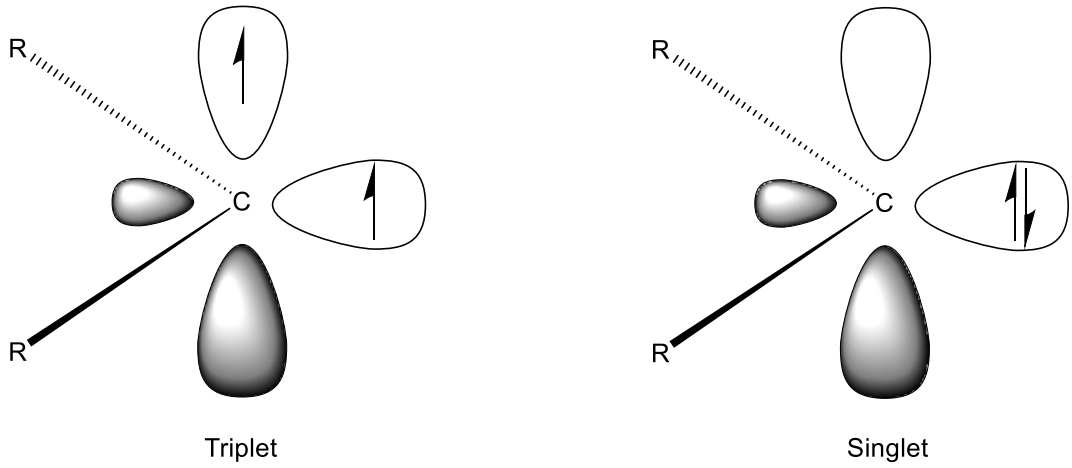


Figure 1.5: *Triplet carbene and singlet carbene.*

Triplet carbenes have one electron in each non-bonding orbitals. The electrons have parallel spins and triplet carbenes are regarded as diradicals.[38] Singlet carbenes has one empty *p*-orbital and two electrons in a non-bonding sp^2-orbital. This electron configuration give singlet carbenes both electrophilic and nucleophilic character.[39] The electron configuration of the carbene generated from X-EDA have singlet ground state configurations.[38, 40]

The lifetime of a carbene can vary a lot. Usually they are considered as reactive species with short lifetimes, but they can also be stable, isolatable molecules.[38] Carbenes can be stabilized by inductive electron withdrawing substituents through σ-bond at the carbene-carbon, or by π-donating substituents that donates electrons to the empty *p*-orbital of the carbene-carbon.[38] A combination of both stabilization effects are also possible. Steric substituents can contribute stabilizing the carbenes as well.[41] Examples of good π-donors are: nitrogen, phosphorus and oxygen substituents. Halogens are both π-donors by donation of a free electron pair and inductively σ electron withdrawing.

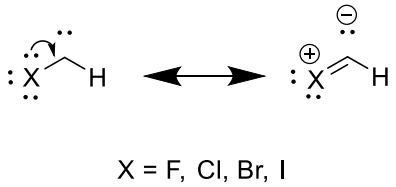


Figure 1.6: *Resonance structures of a halogen substituted carbene.*[42]

An important contribution to the stability of halo carbenes is the halogens ability for π-donation, as illustrated in **Figure 1.6**.[43, 44] Halo carbenes can form ylide structures through resonance where there is a formal positive charge at the halogen and a formal negative charge at the carbene carbon. The degree of stabilization from halogens are implied from several studies, and the order is F > Cl > Br > I, where F has the largest stabilizing effect.[44]

1.3.1. Carbenes reactivity and selectivity

Carbenes show a broad range of reactivity and stability. The carbene derived from diazomethane is the simplest carbene and gave a statistical product distribution for C-H insertion with 2,3-dimethylbutane for primary, secondary and tertiary C-H bonding products.[45] A low chemoselectivity also appeared in cyclopropanation, allylic C-H insertion and vinylic C-H insertion reactions.[46] The low chemoselectivity of :CH_2 can be modified by substituents.[47, 48] Compared to halo carbenes, :CCl_2 and :CBr_2, the chemoselectivity for cyclopropanation of hexene are better than for :CH_2.[47] The relationship between reactivity and selectivity among substituted carbenes have been actively studied and systematic trends for substituents effect of the reactivity are uncovered.[42, 49] A scale that ranks carbenes electronic properties from electrophile to nucleophile has been established by quantifying the reactivity of a series alkenes with diverse substituents in a cyclopropanation reaction.[50] Chemoselectivity of cyclopropanation of alkenes with carbenes generated from Br-EDA was better than for the more reactive carbene analog generated from EDA.[5, 8] This can be explained by halogens π-donation to the *p*-orbital of the carbene.[51] The carbenes are illustrated in **Figure 1.7**.

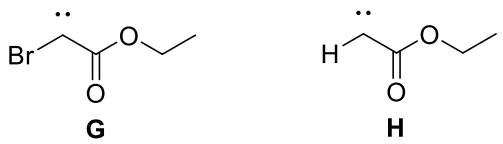
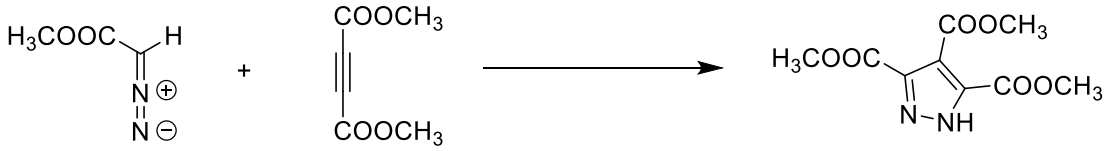


Figure 1.7: *Carbenes generated from Br-EDA (G) and EDA (H).*

1.4. Reactivity of diazo compounds

Diazo compounds has developed into an interesting group of compounds for the organic chemist. Diazo compounds can react in a variety of useful reactions from thermal or photochemical decomposed carbenes, with and without catalysis by transition metals as Lewis acid.[1, 52] They have even taken part in cycloaddition reactions without loss of N_2. The very first 1,3 cycloaddition reaction was done by Buchner in 1888.[53] Continuation of his work led to the discovery of the hitherto unknown compound pyrazole the year after. This was done in a reaction of methyl diazoacetate with dimethyl ethynedicarboxylate shown in **Scheme 1.3**.[54] Buchner's reaction was not classified as 1,3-dipolar cycloaddition until 1960 by Rolf Huisgen.[55]



Scheme 1.3: *The Buchner reaction of methyl diazoacetate with dimethyl ethynedicarboxylate, one of the first 1,3-dipolar cycloadditions.*[54]

1.4.1. Decomposition of diazo compounds with transition metals

Decomposition of diazo compounds with a transition metal forms the corresponding metal carbenoide. The first metal carbenoide, made by decomposition of a α-diazoketone in presence of copper, was proposed by Yates in 1952.[56] Generally, the metal carbenoides are less reactive than the free carbenes described in **Section 1.3**. Less reactive carbenoides opens the possibility for more selective reactions. There are several parameters influencing the reactivity of the carbenoides. Two of the parameters are the substituents α to the carbenoid-carbon and the metal ligands.[57, 58] On the basis of the changing properties of the carbenoids due to different substituents α to the carbenoid-carben, Davies classified the carbenoid intermediates into three major groups, as shown in **Figure 1.8**.[59]

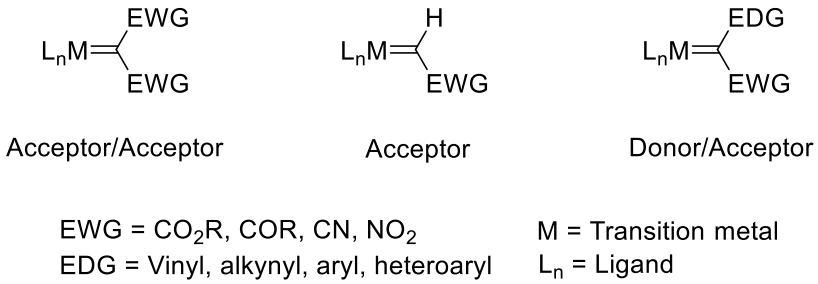
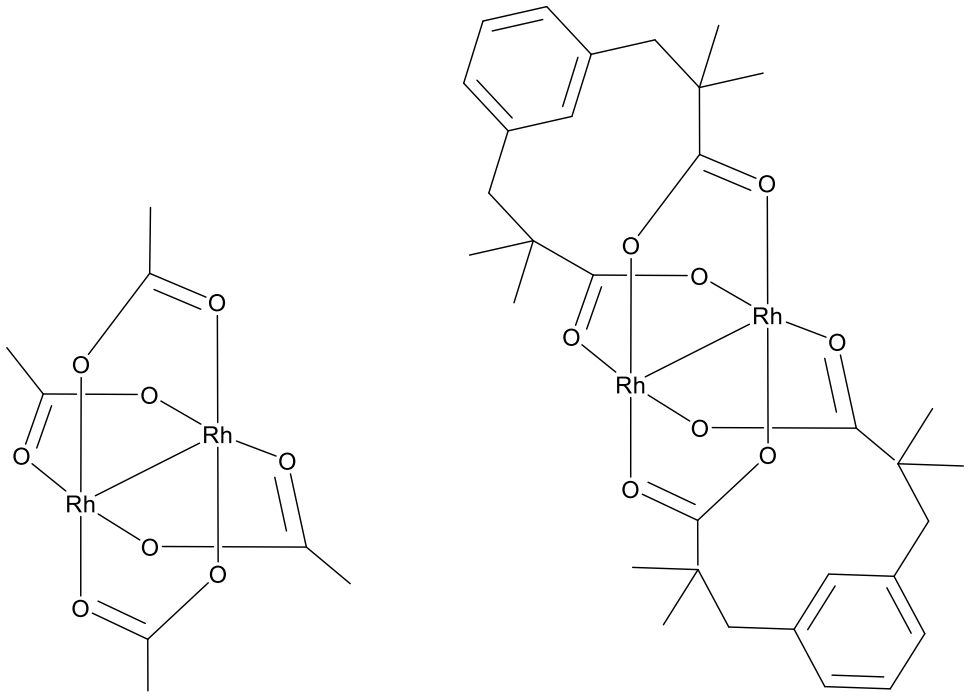


Figure 1.8: *Classification of carbenoid intermediates by Davies.*[59]

Electron donating groups (EDG) makes the metal carbenoid less electrophilic, reducing its reactivity and increasing its selectivity. Electron withdrawing groups (EWG) have the opposite effect. Metal carbenoides with both donor and acceptor characteristics were introduced by Davies. These carbenoids have turned out to be reactive and stabile enough for selective reactions.[59, 60]

The list of transition metal complexes used in reactions with diazo compounds to form carbenoids are long.[61-63] The search for regio-, diasterio-, and enantioselective reactions can be blamed for that. Copper, rhodium, rubidium, cobalt, nickel, yttrium, silver and gold complexes are all mentioned in litterature.[62, 63]

Rhodium is among the most used metals, and rhodium(II) complexes have been used in a variety of reactions with diazo decomposition. In **Figure 1.9**, two commonly-used rhodium(II) catalysts are illustrated.[64] For making the metal carbenoids these rhodium(II) catalysts have axial coordination seats available. Rhodium(II) catalysts are electrophilic and considered Lewis acids. Their activity towards decomposition of diazo compounds has a direct relation of the degree of electrophilicity.[64] With the usage of chiral ligands, rhodium(II) complexes can construct asymmetric reactions.[65, 66] In this research, the $Rh_2(esp)_2$ catalyst has been used for the catalytic reactions.



$Rh_2(OAc)_4$ $Rh_2(esp)_2$

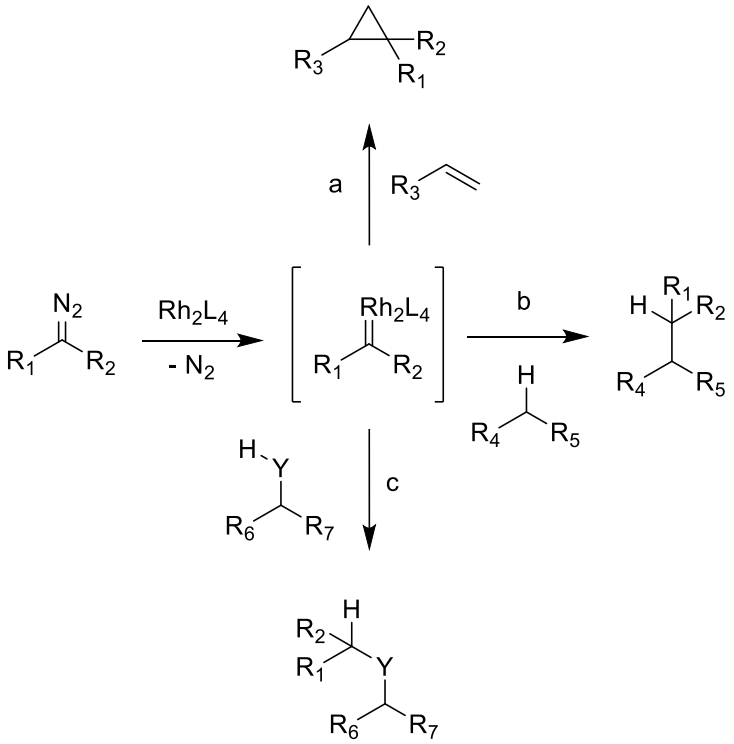
Figure 1.9: *Rhodium(II) catalysts used in decomposition of diazo compounds.*

1.4.2. Reactions with rhodium(II) carbenoids

In **Scheme 1.4**, a selection of reactions with rhodium(II) carbenoids derived from diazo compounds is shown.

Cyclopropanation of alkenes (route a, **Scheme 1,4**) is one of the most studied and used reactions with metal carbenoids. It is often used as a model reaction when trying out new catalysts and diazo compounds.[67] As of the name, the reaction gives cyclopropanes as products. Cyclopropane is a common structural subunit in organic chemistry and often occurs in natural products.[68-70] They often react further in ring opening and rearrangement reactions because of their ring strain.[68, 71] It is also possible to make the corresponding cyclopropane form an alkyne in a similar reaction.[72]

C-H insertion (route b, **Scheme 1,4**) is yet another abundant exploited reaction. This is because rhodium(II) carbenoids often can functionalize unactivated C-H bonds and create carbon-carbon bonds. The reaction can occur both intermolecularly[73] and intramolecularly,[74] and with good regio- and enantioselectivityt.[75] Related Si-H insertion with rhodium(II) carbenoids are also known reactions.[76]



Scheme 1.4: *Examples of reactions with rhodium(II) carbenoids derived from diazo compounds. Y = heteroatom; R_n = aryl, alkyl; L = ligand.*

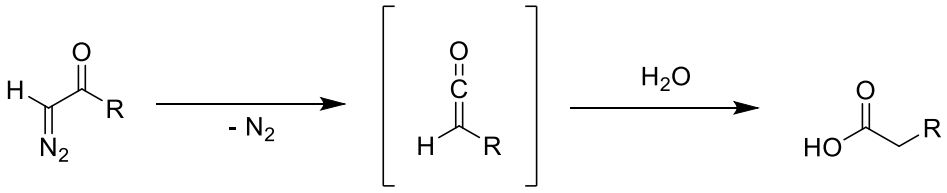
Insertion reactions with rhodium(II) carbenoids can not only be done with C-H and Si-H bonds. In addition it can be done to polar heteroatom-H bonds (route c, **Scheme 1,4**). Commonly the heteroatom in insertion reactions is nitrogen,[77] oxygen[78] or sulfur.[79] Halogens as heteroatom in insertion reactions are less familiar, but reported.[80] The heteroatom-H insertion reactions have had practical value in the pharmaceutical industry. One example is the antibiotic (+)-thienamycin that has been commercially produced by Merck with a metal catalyzed intermolecular N-H insertion reaction.[81] To perform asymmetric insertion reactions the catalyst needs to be chiral.[82, 83]

1.4.3. Thermal decomposition reactions of diazo compounds

Most decomposition reactions of diazo compounds are today performed with metal catalysts. Historically, the thermolysis of diazocarbonyl compounds have been carried out under reflux conditions.[84-86] There are few new reactions of thermal decomposition of diazo compounds with importance that gives better yields and selectivity than the analogue metal catalyzed reaction.[37, 87] Although, there are some examples of cyclopropanation with alkenes[88] and N-H insertion with

amines[89] by thermolysis of aryl diazoacetate in trifluorotoluene under reflux and intermolecular C-H insertion at ambient temperature (AT).[52] The Buchner ring expansion reaction from 1886 is an old example of a thermal reaction with good yields.[54, 90]

The most common thermolysis reaction of diazocarbonyl compounds is the Arndt-Eistert homologation of carboxylic acid derivatives via Wolff rearrangement illustrated in **Scheme 1.5**.[91]

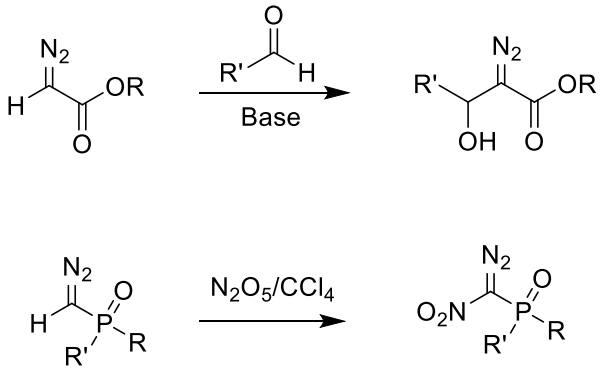


Scheme 1.5: *The Arndt-Eistert homologation of carboxylic acid derivatives via Wolff rearrangement.[91] R = alkyl, aryl.*

After loss of N_2 under thermolysis, and carbene formation, the Wolff rearrangement, a 1,2-rearengement to a ketene takes place. The carboxylic acid is given by Arndt-Eistert homologation, hydrolysis of the ketene.[92] Wolff rearrangement is also common after photolysis of diazocarbonyls.[93, 94] This reaction route has set out to be a profitable tool for amino acid and peptide modification regarding natural products and antibiotics.[95, 96]

1.5. Functionalization of diazo compounds

Diazo compounds has the ability to be functionalized by α-substitution on the diazo carbon without loss of N_2, and to generate complex diazo compounds from readily available starting materials. These α-substitution reactions on diazo alkanes are called "electrophilic diazo alkane substitutions" because diazo alkanes reacts as nuclophiles.[97, 98] Diazo alkyl compounds with proton-activating groups like carbonyl and phosphine oxide at the α carbon to the diazo have the ability to stabilize the generated anion, illustrated in **Scheme 1.6**, and are therefore common in α-substitution reactions.[99, 100]



Scheme 1.6: *Reactions with Diazo alkyl compounds having proton-activating groups.*[99, 100]

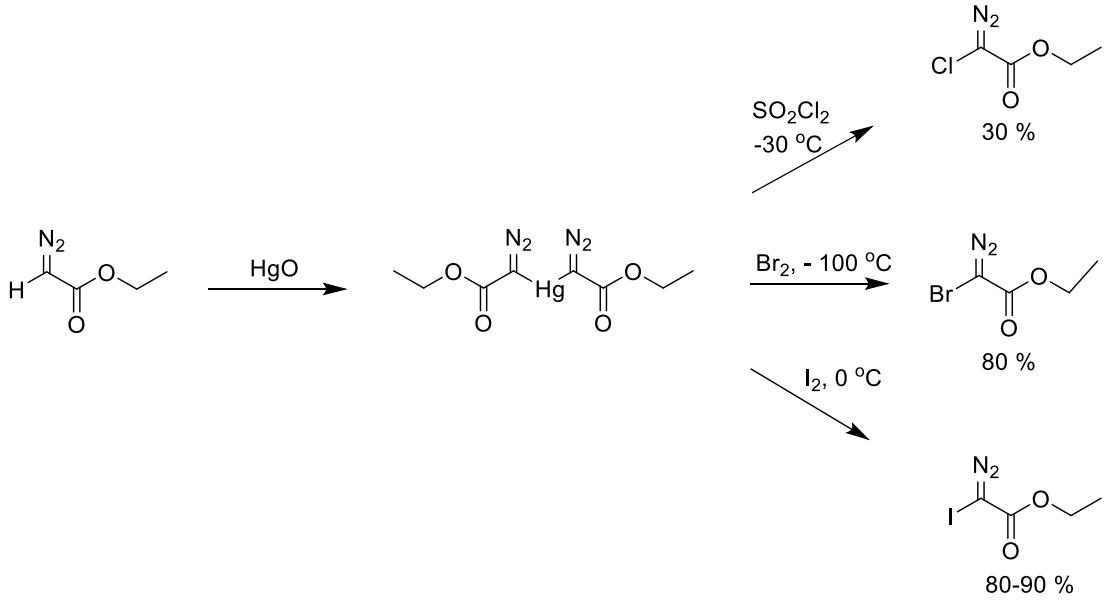
There are several available strategies for functionalizing diazo compounds. Electrophilic substitution,[101] nucleophilic substitution,[102] aldol reactions,[103] and palladium catalyzed coupling reactions are some of them.[104] One central reaction for this project is the α-halogenation reaction.

1.5.1. α-Halogenation of diazo-esters and -amides

α-Halogenation reactions of diazo-esters and -amides are an interesting type of functionalization reactions for multiple reasons. The interest for this group of diazo compounds has recently increased as a result of the development of a new and safer method for halogenation.[1, 8, 9, 11] α-Halo diazo-esters and -amides have the ability to introduce both a halogen function and carbonyl group in a molecule at the same time. Halogenated species and various ways of introducing halogens to complex molecules

are a central part of modern drug design.[9, 105] The thermal instability of α-halo diazo-esters and -amides in combination with the new halogenation procedure opens for thermolysis of diazo-esters and -amides at AT, but also in combination with rhodium catalysts.

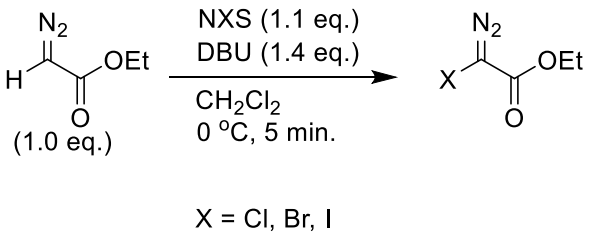
The first reported X-EDA was reported in 1968 by Scöllkopf *et al.*[37, 106] and is shown in **Scheme 1.7**.



Scheme 1.7: *The halogenation synthesis by Scöllkopf.*[37, 106]

The synthesis gives good yields of the brominated and iodinated analogs, but the use of mercury causes a problem related to toxicity. However, the slightly less toxic silver oxide was reported as an alternative to mercury oxide in the first step of the synthesis. Unfortunately, the α-silver diazo compound intermediate had some issues with explosivness.[37]

In 2008 our group developed a new and safe synthesis to halogenate diazo compounds, illustrated in **Scheme 1.8**.[1] The method gave near quantitative yields in five minutes and was done by using the halogenation agent *N*-halosuccinimide (NXS) in an electrophilic substitution reaction.[1] DBU was used as a base, increasing the nucleophilic character of the diazo carbon. The halo-diazoester and -diazoamide products decomposes thermally in AT.[1, 8] Therefore, the synthesis and purification was done under ice cold conditions. The purification was done by filtration of the reaction solution through a silica column with DCM as eluent, both precooled to -30 °C. The halo diazoesters are usually used the same day; however, Br-EDA can be stored in solution at -30 °C for days with minimal decomposition.[1, 9]



Scheme 1.8: *The new and safe halogenation synthesis of diazo compounds.*[1]

This new halogenation synthesis has made it easier for the organic scientists to investigate the properties of the halogenated diazo species, and this synthesis is a key step in the work that is going to be presented later in this thesis.

1.6. Making diazo-ester and -amide compounds

Since Theodor Curtius synthesized EDA for the first time in 1883, the development of new methods for making diazo-ester and -amide compounds has come a long way.[14] Today there are several routes and different methods for making diazo-esters and -amides, including (**A**) acylation of diazoalkanes, (**B**) diazo transfer reaction, (**C**) diazotization of primary amines, (**D**) dehydrogenation of hydrazones and tosylhydrazones, and (**E**) triazene fragmentation, illustrated in **Figure 1.10**.[15] In this section, the different ways to introduce the diazo function in the diazo-esters and -amides will be illuminated. For functionalization reactions of diazo-ester and -amide compounds already having the diazo- and carbonyl- function present, see **Section 1.5**.

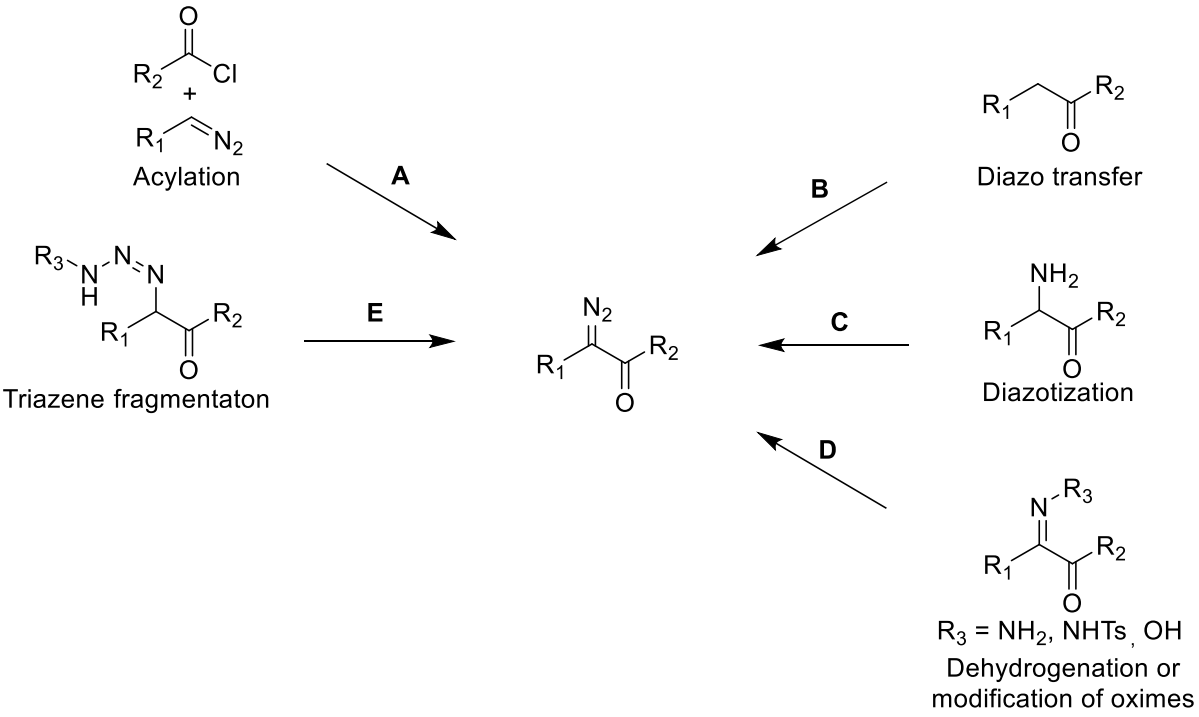
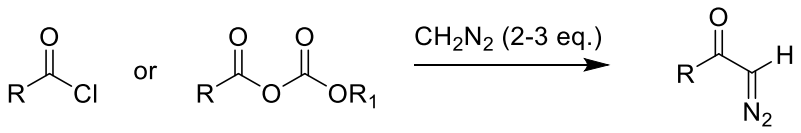


Figure 1.10: *Different methods for making diazo-esters and -amides.*[15]

1.6.1. (**A**) Acylation of diazoalkanes

In this method, an acyl chloride is added a solution of diazomethane. To prevent the formation of chloroketones the use of excess diazomethane is necessary. Another solution to avoid this side reaction is to use a base, for example trimethylamine. However, the usage of base can enolize the acyl chloride, leading to a competitive reaction route, and therefore works better with non-enolizable acyl chlorides.[91, 107, 108] The acyl chloride can be exchanged with anhydrides as acylation agents as shown in **Scheme 1.9**.[109]



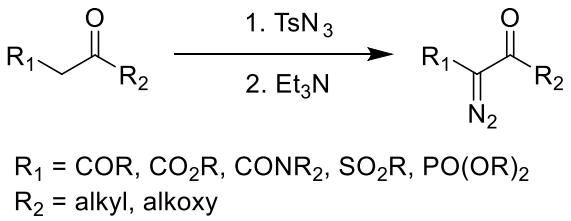
Scheme 1.9: *Synthesis of diazocarbonyl compounds by acylation.*[108, 109]

One of the main limitations of diazomethane acylation is that the reaction is not suitable for α,β-unsaturated substrates because dipolar cycloaddition often occurs between the conjugated double bond and the diazomethane.[110, 111]

Working with pure diazomethane is hazardous, because it is an exploding gas, extremely toxic and highly irritating.[23] Therefore, many necessary precautions must be made if this synthesis method should be used, making this approach for constructing diazo-esters and -amides unpleasant and desirable to avoid if possible.

1.6.2. (**B**) Diazo transfer reaction

Diazo transfer reactions are a method that simply transfer the diazo group from a donor, such as sulfonyl azide, to a carbonyl compound with relative acidity α to the carbonyl. If the α-carbonyl diazo methylene group is not already reactive towards diazo transfer reactions a base can be used to activate it futher.[112-114] A diazo transfer reaction is illustrated in **Scheme 1.10** using triethylamine as base.

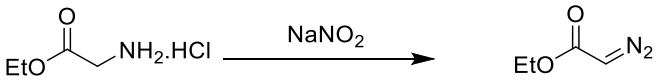


Scheme 1.10: *Synthesis with diazocarbonyl compounds in diazo transfer reactions.*[112]

Several diazoketones can be made with diazo transfer reactions, both cyclic and acyclic, as well as α,β-unsaturated substrates.[115-119] This method has some limitations regarding thermal stability of the diazo transfer reagents and difficulties removing the sulfonamide by-product.[120]

1.6.3. (**C**) Diazotization of primary amines

Diazotization of primary amines can be performed between a nitrosating agent, such as sodium nitrite, and a primary amine, in the presence of acidic aquatic solution shown in **Scheme 1.11**.[121]



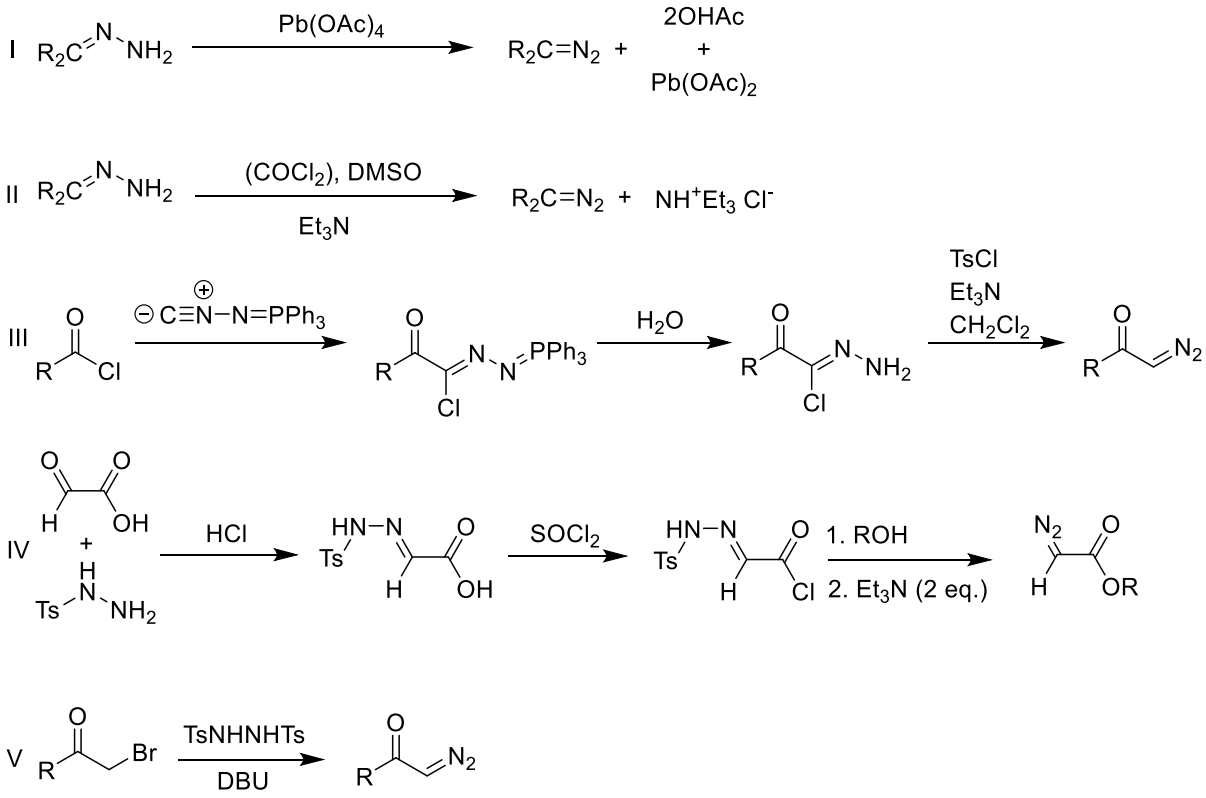
Scheme 1.11: *Amine diazotization to produce EDA **1a**.*[121]

There are examples of diazotization reactions making thermally unstable fluorinated diazoalkanes used in asymmetric synthesis of trifluoromethyl substituted cyclopropanes.[122]

1.6.4. (**D**) Dehydrogenation of hydrazones and tosylhydrazones

Dehydrogenation of hydrazones is an oxidation reaction of hydrazone. Earlier the oxidizing agent usually was a heavy metal like lead(IV), mercury oxide or silver oxide, among others.[123] To avoid the

use of metals, and reduce the difficulty of oxidation, the hydrazones were modified by substituents.[23, 124, 125] Today there are several metal free approaches for constructing diazo-esters and -amides, and a variety hydrazones being used as illustrated in **Scheme 1.12**.



Scheme 1.12: *Five different approaches for dehydrogenation of hydrazone constructing diazo-ester and -amide compounds.*[123-127]

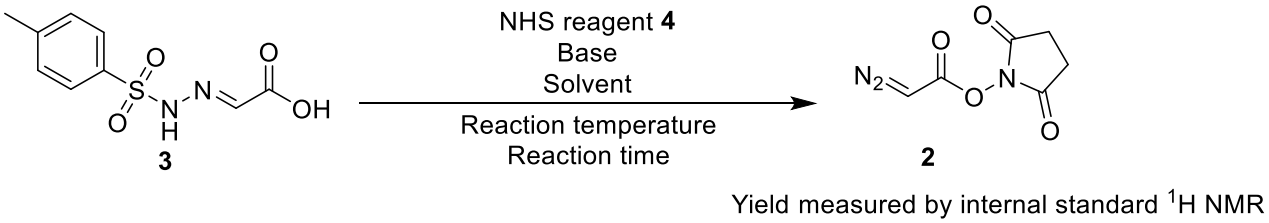
In reaction **I Scheme 1.12** a mercury complex is used as oxidation agent.[123] However, in reaction **II** a metal free approach is illustrated using chlorosulfodimethyl chloride as the oxidation agent made in situ from DMSO and oxalylchloride in the precense of triethylamine as base.[127] In reaction **III** the hydrazone is being modified, reacting with acyl chlorides. This method can make many of the same products as acylation with diazomethane, without the need for working with diazomethane.[124]

Reaction **IV** and **V** is probably the most important pathways of making diazo-esters and -amides concerning this thesis. The first step of reaction **IV** is used for making one of the starting materials, tosylhydrazono acetic acid **3**, used in the construction of BB.[125] One of the main goals for this thesis was to find a better way of making BB than the one from literature.[12] Reaction **V** can be done on a variety of bromoacetates and bromoamides treated with *N*,*N*'-ditosylhydrazine and DBU, and is a widely used synthetic route for making diazoacetamides.[52, 126]

2. Results and Discussion

2.1. New synthesis of BB

The synthesis of BB **2** derived by tosylhydrazono acetic acid **3** and NHS **7** with DCC as a coupling reagent, is known to give yields up to 65 %.[12] However, when trying to reproduce this synthesis the workup of the product was challenging, and the yield was usually about 20 % after necessary purifications. Therefore an alternative synthesis was developed.



Scheme 2.1: *General reaction procedure of BB.*

The ideas behind the new approach was based on a review article giving a summary of the syntheses of NHS-esters.[128] The methods presented take advantage of direct activation of the carbocyclic acid, usually with a base, and NHS-transfer reagents. Using these methods as starting points the reaction conditions were examined by varying solvent, concentrations, base, reactant equivalents, NHS-transfer reagent, reaction temperature and time. The reaction is illustrated in **Scheme 2.1** and the results are presented in **Table 2.1**. The rest of the reactions which present the different NHS-reagents and purification methods will be presented in **Section 2.1.7.** and **Section 2.1.8.**

Table 2.1: *Results from optimization of reaction conditions in the synthesis of BB **2**.*

Entry	Solvent	Tosylhydrazono acetic acid	NHS-Reagent 4	Base	Reaction Time	Reaction Temperature	Product (IS)
1	DMF (2.5 mL)	1 eq. (0.5 mmol)	1 eq.	1 eq. Triethylamine	1 h.	AT	N/A
2	CH_3CN (2.5 mL)	1 eq. (0.5 mmol)	1 eq.	1 eq. Triethylamine	1 h.	AT	49%
3	DMF (2.5 mL)	1 eq. (0.5 mmol)	1 eq.	1 eq. Triethylamine	1 h.	AT	3%
4	THF (2.5 mL)	1 eq. (0.5 mmol)	1 eq.	1 eq. Triethylamine	1 h.	AT	5%
5	DCM (2.5 mL)	1 eq. (0.5 mmol)	1 eq.	1 eq. Triethylamine	1 h.	AT	26%
6	CH_3CN (1 mL)	1 eq. (0.5 mmol)	1 eq.	1 eq. Triethylamine	1 h.	AT	36%
7	CH_3CN (2.5 mL)	1 eq. (0.5 mmol)	1 eq.	2.1 eq. Triethylamine	1 h.	AT	51%
8	CH_3CN (1 mL)	1 eq. (0.5 mmol)	1 eq.	2.1 eq. Triethylamine	1 h.	AT	45%
9	CH_3CN (2.5 mL)	1.2 eq. (0.6 mmol)	1 eq.	1 eq. Triethylamine	1 h.	AT	46%
10	CH_3CN (2.5 mL)	1 eq. (0.5 mmol)	1 eq.	2.1 eq. Triethylamine	17 h.	AT	41%
11	CH_3CN (2.5 mL)	1 eq. (0.5 mmol)	1 eq.	2.1 eq. Triethylamine	5 min.	AT	54%
12	CH_3CN (2.5 mL)	1 eq. (0.5 mmol)	1.5 eq.	2.1 eq. Triethylamine	1 h.	AT	66%
13	CH_3CN (2.5 mL)	1 eq. (0.5 mmol)	1 eq.	2.1 eq. Triethylamine	1 h.	0 ^{0}C	64%
14	CH_3CN (2.5 mL)	1 eq. (0.5 mmol)	1 eq.	2.1 eq. Cesium carbonate	1 h.	AT	N/A
15	DMF-*d*7 (0.6 mL)	1 eq. (0.5 mmol)	1 eq.	2.1 eq. Triethylamine	1 h.	AT	28%
16	CH_3CN (2.5 mL)	1 eq. (0.5 mmol)	1.5 eq.	2.1 eq. Triethylamine	1 h.	0 ^{0}C	90%
17	CH_3CN (2.5 mL)	1 eq. (0.5 mmol)	1.2 eq.	2.1 eq. Triethylamine	1 h.	0 ^{0}C	78%
18	CH_3CN (2.5 mL)	1 eq. (0.5 mmol)	1.5 eq.	2.1 eq. Triethylamine	0.5 h.	0 ^{0}C	86%

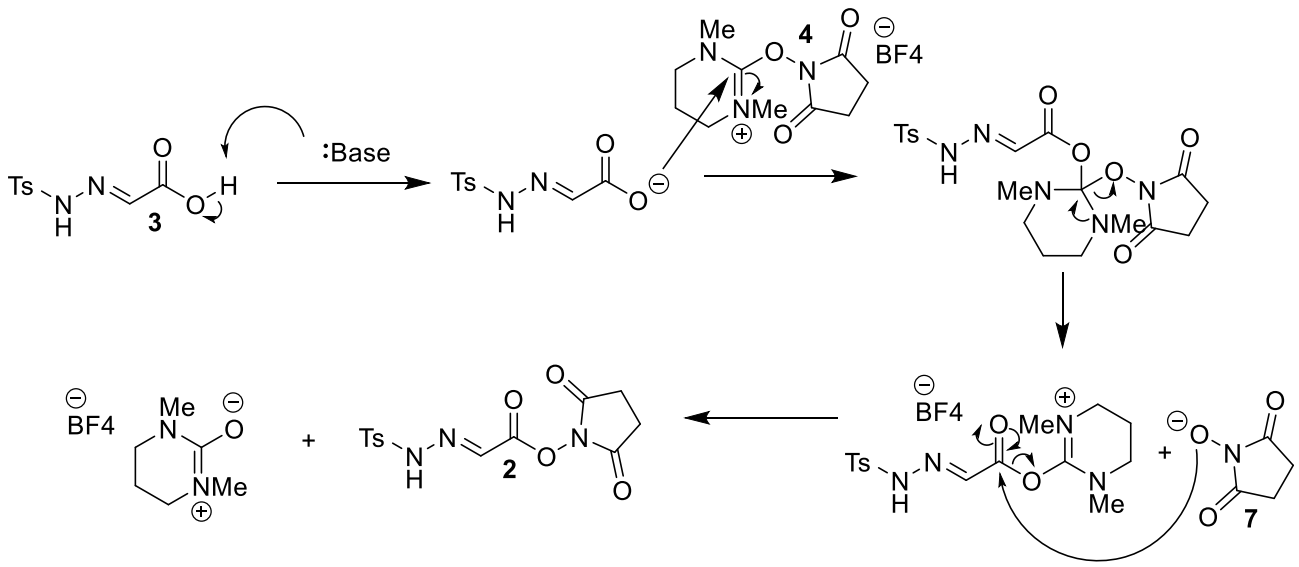
2.1.1. Method and product yield

To achieve direct comparable results, all steps in the implementation of the synthesis were done in the same order. Tosylhydrazono acetic acid **3** and NHS-reagent **4** was dissolved in the designated solvent. For reactions at 0 ^{0}C the solution was cooled in an ice bath for 10 minutes, before adding the base. The reaction time started when the base was added. After the given reaction time the solvent was removed under reduced pressure, internal standard was added, and the crude product was resolved in $CDCl_3$. The yield was measured by internal standard and integration in the ^{1}H NMR spectra and an example of the calculations is provided in the appendix. Under the study of the reaction condition, purification of the product was yet to be examined. Internal standard ^{1}H NMR-yield measurements allowed the yield to be determined without further purifications, which made the process of studying the reaction condition efficient and time-saving.

2.1.2. Solvents and reaction mechanism

Based on methods for NHS-esters from literature,[129] the choice of solvent was DMF with a concentration of 0.2 M and 1 equivalent of **3**. The equivalent ratio between the **3**, NHS-reagent **4** and triethylamine was 1:1:1, with a reaction time of 1 hour at AT. Using this experimental setup as a foundation for the optimization, the solvent was the first parameter to be investigated.

When choosing solvents there was some things to consider. The reaction mechanism is likely to go via several intermediates where charges are formed, see **Scheme 2.2**. Mechanisms involving charged species are usually favored using polar solvents. However, if the solvent are protic the solvent may interfere with the reaction resulting in unwanted by-products and reduced yields. Therefore, these polar, aprotic solvents were selected: DMF, THF, DCM and MeCN.



Scheme 2.2: *Anticipated reaction mechanism for the reaction of NHS-regent **4** with the carboxylic acid **3**.*[130, 131]

The yields obtained was respectably 3% for the reaction in DMF (Entry 3), 5% for the reaction in THF (Entry 4), 26% for the reaction in DCM (Entry 5) and 49% for the reaction in MeCN (Entry 2). Since MeCN gave best yield, it was used as the new solvent of choice for further optimization.

Since the reaction in DMF only gave a yield of 3% it was investigated whether the amended procedure may have caused the poor yield. The reaction mixture with DMF was diluted with water and extracted with EtOAc before evaporating the solvent under reduced pressure. To avoid the extraction step and directly measure the yield by NMR, the reaction was performed again in deuterated DMF giving a significant better yield of 28% (Entry 15). Although the yield was better in the deuterated solvent, it was still lower than for the reaction in MeCN. More benefits of using MeCN versus DMF were fewer and easier purification steps.

2.1.3. Base

The next reaction condition that was investigated was the base. In the standard reaction the amount of base used was 1 equivalent. However, when adding base it should also dehydrogenize the hydrazone in an oxidation reaction converting the hydrazone to a diazo group. Therefor the reaction was tried with 2.1 equivalents of base. In the literature procedure with DCC-coupling, the hydrazone decomposes spontaneous without the presence of base, which suggests that base is not always required

to cause the hydrazone to decompose.[12] The result was about the same for Entry 2 with 49 % yield with one equivalent and for Entry 7 with 51% yield with two equivalents.

The effect of swapping triethylamine as base with cesium carbonate was investigated (Entry 14) using the same method as for triethylamine. The first problem encountered was related to the solubility of cesium carbonate in $CDCl_3$ solvent. The precipitate of the base in the NMR tube made the peaks in the spectra broad and overlapping in the area used for calculating yield. Therefore, the cesium carbonate had to be filtered off before obtaining yield. Even after the filtration, the product peak could not be found in the ^1H NMR spectra. No more effort was made investigating the reaction with the use of cesium carbonate as base, or other bases, since triethylamine already gave good and promising yields.

After these investigations of the effect of base, 2.1 equivalents of triethylamine was used for furthers optimization.

2.1.4. Reaction concentrations

The effect of varying the concentration was briefly investigated. The concentration was increased from 0.2 M to 0.5 M and was done at 0.5 mmol scale. The concentration of reactants could affect the reaction rate, and the results in yields of increasing the concentration to 0.5 M was of 36 % (Entry 6) against 49 % (Entry 2) for 0.2 M. The same concentration experiments were performed with 2.1 equivalents of base and 0.5 M concentration giving a yield of 45% (Entry 8). The yields were higher at the lower concentration, therefore, the concentration was kept at 0.2 M for further optimization.

2.1.5. Reaction time and temperature

As a result of the poorer yields at higher concentrations, which usually increase the reaction rate, the effect of reaction time and the stability of the product under the given reaction condition were investigated. This was done by altering the reaction time and performing the reaction at 0 ^0C instead of AT.

The initial reaction was performed at AT with both 5 minutes and 17 hours reaction time giving a yield of 54 % (Entry 11) and 41 % (Entry 10). Compared to the yield of 1 hour reaction time of 51 %

(Entry 7), the yield of 5 minute reaction time was almost identical implying the ideal product reaction time to be somewhere in between since the product yield became lower over time. These results also suggests that the product may not be stable when kept under these conditions.

When the effect of the reaction temperature was studied, it gave a yield of 64 % at 0 ^{0}C (Entry 13), which is an increase in yield compared to the corresponding AT reaction (Entry 7). The higher yields might be caused by an increase of the stability of the product at 0 ^{0}C or a more selective reaction. Therefore, the reaction temperature was set to be 0 ^{0}C from here on. The reaction time was kept at one hour, despite the yield might peak somewhere in between 5 minutes and 1 hour.

2.1.6. Reactant equivalents and final adjustments

To begin with, the equivalent of tosylhydrazono acetic acid **3** was raised from 1.0 to 1.2 equivalents in a reaction at AT, resulting in a yield of 46 % (Entry 9). The yield was lower than for the corresponding reaction at 1.0 equivalent (Entry 7).

Then, the equivalent of NHS-reagent **4** was raised from 1.0 to 1.5 equivalents in a reaction at AT, resulting in a yield of 66% (Entry 12) which was an increase in yield compared to 51% (Entry 7). One reason for this might be water content in the NHS salt **4** that has to be corrected when weighting out the reagents. Another reason might be that the excess of the NHS-reagent **4** was of importance for the order in which the two reaction steps are triggered by the base. In order to achieve the product, the reaction step introducing the NHS group to the product **2**, was considered to take place before the hydration of the hydrazone group.

Since the excess of NHS-reagent **4** gave an improvement of the yield compared to the corresponding reaction with 1.0 equivalent done at AT, it was of interest to combine the 1.5 equivalents of **4** with a reaction temperature of 0 ^{0}C which also improved the yield of the reaction. When performing a reaction combining these reaction conditions the yield became 90 % (Entry 16). To optimize this reaction further, the excess of NHS-reagent **4** was lowered from 1.5 equivalents to 1.2 equivalents and reduction of the reaction time to 30 minutes.

The reaction time was set to be 30 minutes because the earlier results of reaction time suggesting an ideal reaction time of somewhere between 5 minutes and 1 hour. Although, these investigations was done at AT and the reaction time would probably be affected somewhat by the lowered reaction temperature at 0 ^{0}C. If the reaction time could be reduced by 30 minutes without adversely affecting

the yield, this will result in a less time consuming experimental procedure. Even though, a reaction with a reaction time of 1 hour is a relatively fast reaction anyway.

The yields of 1.2 equivalents excess of NHS-reagent **4** was respectably 78 % (Entry 17) and of the reduced reaction time of 30 minutes was 86 % (Entry 18), which was both lower than for Entry 16 which gave a yield of 90 %. Therefore, the reaction time was maintained at 1 hour with a NHS-reagent **4** excess of 1.5 equivalent (Entry 16) for further work.

2.1.7. Purification

In this section the purification of the BB **2** will be presented. The purification steps are shown in **Table 2.2**. The purification methods used were extraction, flash chromatography and recrystallization in that order.

Table 2.2: *Purification attempts of BB.*

Entry	Dilution/Extraction	Flash Chromatography	Recrystallization	Mass yield	Adequately clean
19	Solved sat. NaCl solution DCM 2x	Silica plug DCM/EtOAc 95:5	Chloroform/Heptane	164 %	No
20	Solved sat. NaCl solution EtOAc 2x	Silica plug Hexanes/EtOAc 1:1	Chloroform/Heptane	37%	Yes
21	Solved sat. NaCl solution EtOAc 3x	Silica plug DCM	Chloroform/Heptane	63%	No
22	Solved sat. NaCl solution DCM 3x	Silica column DCM	Chloroform/Heptane	20%	Yes

The crude reaction mixture was diluted with saturated NaCl-solution and then extracted with DCM or EtOAc both of which seemed to transfer the product to the organic phase. There was three spots at the TLC plate after the extraction, one at the bottom line, the product **2** in the middle and one slightly over the middle, see **Figure 2.1**.

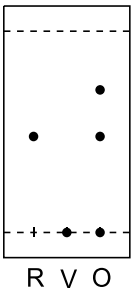
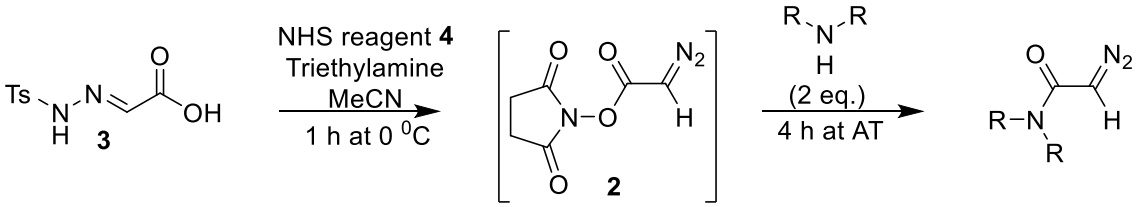


Figure 2.1: *TLC analysis in Hexanes/EtOAc 1:1 of the product after extraction. R = product reference, V = aqueous phase, O = organic phase*

The eluentsystems used in the flash chromatography were DCM/EtOAc 95:5, hexanes/EtOAc 1:1 and DCM. Since the product had yellow color it could be followed visually through the plug/column and collected in one fraction. However, some of the impurities both at the bottom line and at the top was to be found in the fraction after the plug/column, which resulted in a brown, slimy residue after evaporation.

To obtaining a pure product the brown residue was recrystallized by solvation in chloroform and then adding a layer of heptane carefully on top. The chloroform would than evaporate slowly, leaving the product as a yellow precipitate after 18 hours, resulting in yields between 20 % and 37 %. However if there was too much impurities in the brown residue the recrystallization would not work. When gathering the product in several smaller fractions, it turned out that the fractions containing the first impurity would not recrystallize. To solve this problem it was suggested to use a two eluent system during flash chromatographing. The first eluent system, being hexanes/DCM 1:1, had the task of eluting the first impurity without the product being eluted significantly. The second eluent system, DCM/EtOAc 95:5 or DCM should elute the product. However, this solution was not explored because other reactions in this thesis was prioritized.

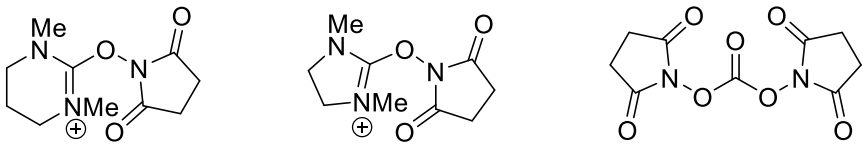


Scheme 2.2: *Synthesis of BB directly used in further reaction.*

As a result of the lack of good yields after purification, despite the good internal standard yields, a new approach skipping the purification step using the product immediately as reactant in further reactions

was investigated (**Scheme 2.2**). This was done by adding 2 equvivalents tertbutylamine to the reaction after 1 hour of reaction time for then to react for another 4 hours at AT. The yield of 26 % **13a** was obtained by internal standard ^{1}H NMR, which was a poor yield seen in context of the fact that the internal standard yield of BB was 90 % and the reaction with tertbutylamine usually gave good yields as will be illustrated in **Section 2.2**.

2.1.8. Use of different NHS-reagents



4 **5** **6**

Figure 2.2: *The three NHS-reagents used in further reaction optimization.*

The NHS-reagent **4**, **Figure 2.2**, was synthesized as described in **Section 3.1**. The procedure was straight forward giving expected yields of about 63 %. However, the major drawback using **4** as an NHS-reagent was the time consuming synthesis, requiring at least 3 days. In addition, the by-products from the reactions with **4** caused separation problems, giving **2** in low purified yields.

The five membered ring analogue **5** was synthetically available in only one step from commercial reagents and was made available by others in the group. In a synthesis using **5**, an internal standard yield of 80% was obtained (Entry 23). On the basis of the good yield it is plausible that this reagent can be used as an alternative reagent to **4**.

Due to the difficult purification when using NHS-reagent **4** and **5**, a third reagent **6** was introduced. Compound **6** was commercial available in large quantities at a low price, and the purification process was easier. With a new NHS-reagent the kinetics of the reaction was likely to change. Therefore a few further test reactions were performed.

Table 2.3: *Results from varying the NHS-reagent in the synthesis of BB.*

Entry	Solvent	Tosylhydrazono acetic acid. 3	NHS-Reagent	Base	Reaction Time	Reaction Temperature	Product (IS)
23	CH_3CN (2.5 mL)	1 eq. (0.5 mmol)	1.5 eq. **5**	2.1 eq. Triethylamine	1 h.	0 ^{0}C	80%
24	CH_3CN (2.5 mL)	1 eq. (0.5 mmol)	1.5 eq. **6**	2.1 eq. Triethylamine	1 h.	0 ^{0}C	49%
25	CH_3CN (2.5 mL)	1 eq. (0.5 mmol)	1.5 eq. **6**	2.1 eq. Triethylamine	10 min.	0 ^{0}C	61%

When performing the reaction with the optimized conditions, Entry 24, **Table 2.3**, the yield obtained by internal standard ^{1}H NMR was 49 %.

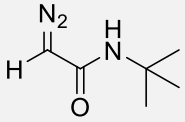
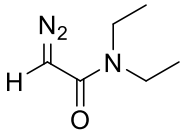
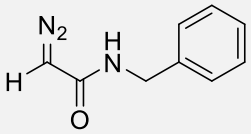
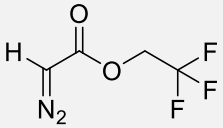
Further the reaction was performed (Entry 25) with 1 equivalent of NHS **7** in addition to all the usual reagents as a result of the purposed reaction mechanism in **Scheme 2.2** and the reaction time of 1 hour was reduced to 10 minutes. The reaction mixture was diluted with EtOAc and washed with saturated $NaHCO_3$ solution removing the excess base to prevent the product from decomposing. The internal standard yield after extraction was measured to be 61% and the isolated yield after flash chromatography was 47%.

To summarize the optimization process the reaction conditions that was found to give a good yield was 1.5 and 2.1 equivalents of NHS-reagent **6** and trietylamine with a stirring time of 5 minutes at 0 ^{0}C and with a concentration of 0.2 M. The product should be purified by diluting with EtOAc and washing with $NaHCO_3$ solution, flash chromatography and recrystallization if needed. These optimized reaction conditions gave a pure yield of 47 % that is an improvement to 20 % yield in the known reactions from literature.

2.2. 2,5-Dioxopyrrolidin-1-yl 2-diazoacetate as a useful reactant in the synthesis of diazo-amides and -esters

In this section the possibilities and limitations of BB as reagent to synthesize diazo-amides and -esters will be presented. The experimental procedure of diazoamides from BB are described in **Section 4.4.1.** and the experimental procedure of diazoesters are described in **Section 4.4.2.** From the results presented in **Table 2.4**, the range of this reaction is illustrated.

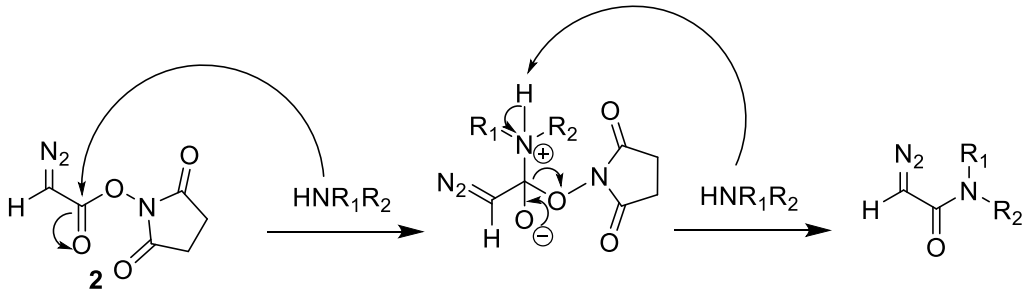
Table 2.4: *Products from synthesis with BB as reagent and respective yields.*

Product	Entry	Yield
	**1**	94%
	**2**	85 %
	**3**	70 %
	**4**	0 %
	**5**	60 %[a]

a*: Internal standard yield.*

The reaction of BB to diazo-amides and -esters occurred by nucleophilic acyl substitution at the carbonyl group where NHS is the leaving group illustrated in **Scheme 2.3**. Since the reaction is a nucleophilic acyl substitution reaction 2 equivalents of amine, one having the role as nucleophile and the other the role as base, is necessary for theoretically achieving 100 % yield. Alcohols does not have

the same basic and nucleophilic properties as amines and a base must be added in addition to the alcohol to promote the reaction.



Scheme 2.3: *General reaction mechanism of BB with amines.*

In the reactions with amines in entry **1**, **2** and **3** (**Table 2.4**) the reaction gave good to excellent yields of 70-94 % and illustrated that the reaction could be done with primary, secondary and benzylic amines.[132] However, in reaction with hexametyildisilazan (HMDS) (entry **4**), which is known to be a non-nuclephilic hindered Brønsted base,[133] no desired product could be found. For the reaction with trifluoroethanol (entry **5**) the obtained ^{1}H NMR internal standard yield was 60 %.

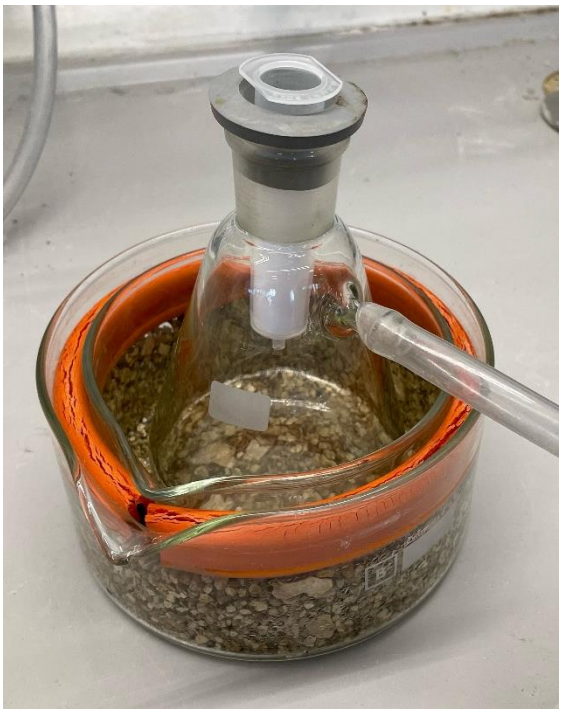
The reaction using BB as reactant for making diazo-amides and -esters has several advantages compared to the most used reactions **IV** and **V** from **Scheme 1.12**. Compared to reaction **IV** the reaction conditions are milder and the purification easier for the reaction with BB. The generated acid chloride in reaction **IV** requires completely dry and inert conditions, and reacts easily back to the carboxylic acid with trace amounts of water. The reported yields from reaction **IV** and with BB are about the same.[134]

Compared to reaction **V** the reaction conditions are milder and the purification easier for the reaction of BB. Reaction **V** is a two-step reaction, and the overall yields are usually better for the reaction with BB. The preferred method for making diazo-amides would therefore be the reaction with BB.

2.3. Synthesis of α-halo diazo-esters and -amides

As mentioned in the introduction, a new and safe method for halogenation of diazo-esters and -amides have recently been developed in our research group (**Scheme 1.8, Section 1.5.1**). This method was also used in this thesis to prepare a series of halo-diazoacetamides and halo-diazoacetates for studying the reactivity and half-life of the brominated diazo compounds presented in **Section 2.4.** and **2.5.**

While applying the method, some changes was made due to convenience. The scale of the bromination reactions was usually performed at less than 1 mmol, because that was the amount needed to perform the following test reactions and the short half-life measurements. The original silica gel plug purification used a slight overpressure of air and was effective but not convenient. Therefore, a short plug with suction was equipped as shown in **Picture 2.1**.



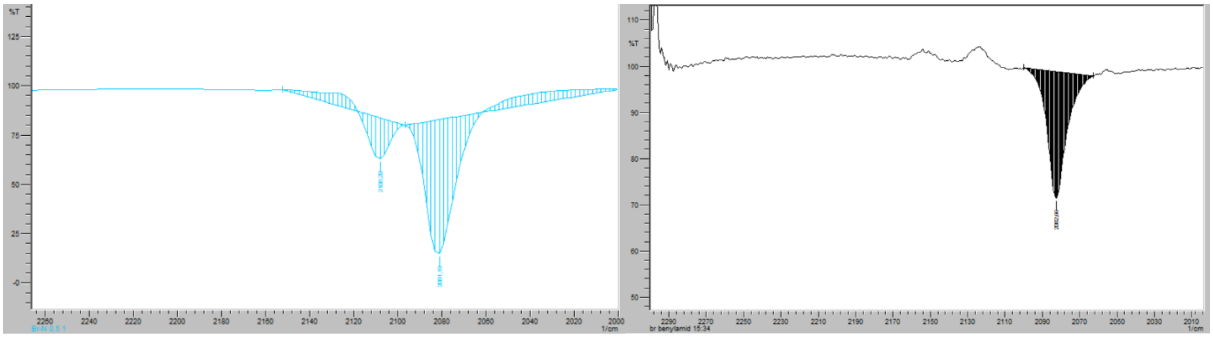
Picture 2.1: *Purification setup of a short plug with suction used for purification in brominaton reaction of diazo compounds.*

This modification of the procedure minimized the time the diazo compound needed through the silica plug and at the same time eliminated the need to use long glass columns.

In an attempt to completely remove the plug, extraction with 1 M sodium thiosulfate was tried. The result of this purification method was investigated by ^{1}H NMR. In the NMR spectra, there was a

singlet approximately where the succinimide signal was expected to be, which suggested that succinimide was still present and the method was rejected.

The only half-life measurements carried out by the group on a halo diazoamide prior to this work gave a short half-life in the order of 1-2 minutes.[2, 6, 52] Therefore, the bromination reaction of diazoamides was performed at -78 ^{0}C instead of 0 ^{0}C to prevent thermal decomposition. At 0 ^{0}C the diazo compounds were fully brominated within 5 minutes. However, at -78 ^{0}C the reaction was expected to take longer before fully conversion. The conversion was investigated with IR spectroscopy, since the diazo function gives a strong characteristic peak around 2100 cm^{-1} and the diazo compound and the analogue halo-diazo compound give a unique diazo peak which were well separated.[135, 136] The first experiments with diazoamides were performed with 10 minutes reaction time at -78 ^{0}C, double the time needed for full conversion at 0 ^{0}C. As shown in **Figure 2.3**, there were two IR peaks in the diazo frequency range, which means that fully conversion was not achieved.



Figur 2.3: *IR spectra of N-benzyl-2-bromo-2-diazoacetamide **11a** after 10 minutes (left) and 20 minutes (right) reaction time of the bromination reaction at -78 ^{0}C.*

The reaction time was increased to 20 minutes, resulting in only one IR peaks in the diazo frequency range, indicating full conversion of the diazo compound to the corresponding bromo diazo compound at -78 ^{0}C.

2.4. Reactions of bromo diazo-esters and -amides with rhodium catalyst

In this section, the reactivity of some selected bromo diazo-esters and -amides will be presented. As mentioned in **Section 1.4.2.** the carbenoides derived from diazo compounds are known to react in cyclopropanation- and C-H insertion reactions. The reactivity of halo diazoesters in cyclopropanation- and C-H insertion reactions have previously been studied only for X-EDA and are completely unknown for halo-diazoamides. It is therefore of interest to investigate the reactivity of halo diazo-esters and -amides in cyclopropanation- and C-H insertion reactions.

2.4.1. Reaction of brominated diazoacetates with rhodium catalyst

The diazoacetates that was selected for reactivity investigations in cyclopropanation- and C-H insertion reactions was 2,2,2-trichloroethyl 2-diazoacetate (TCEDA) **17a** and 2,2,2-trifluoroethyl 2-diazoacetate (TFEDA) **16a**. Commercially available EDA was the only diazoacetate previously worked on in the group and was chosen as a reference molecule for further work when the scope of diazo acetates was to be extended.

When the scope of halo-diazoacetates was to be extended the alcohol-group at the ester had to be changed. From literature the group at the ester should not be a longer alkane chain than ethyl due to problems with intramolecular side reactions with the generated carbenoide.[137, 138] TCEDA and TFEDA was natural choices due to Davies former work with rhodium catalyzed C-H insertion reactions with donor/acceptor carbenes derived from aryl diazo acetates. In the search of better enantioselective intermolecular C-H functionalization of methyl ethers and deactivated substrates, he discovered that by changing the methyl group (right compound, **Figure 2.4**) with the TCE group (left compound, **Figure 2.4**) this was achieved.[139, 140] Further he was able to selectively functionalize unactivated terminal secondary C-H bonds in the presence of electronically activated benzylic C-H bonds by using different TXE groups.[141] Through this work, Davis showed that TCE- and TFE-esters could influence the reactivity of the generated carbenoide in rhodium catalyzed reactions. These groups are therefore of interest in halo diazoesters as well.

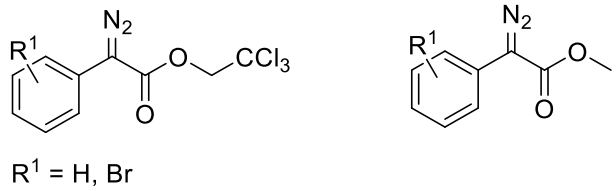
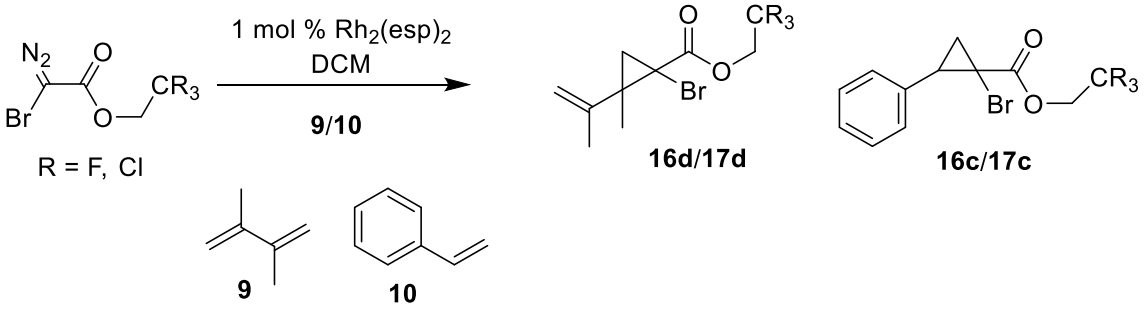


Figure 2.4: *Davies aryl diazoacetate compounds. Left = TCE aryl diazoacetate, Right = methyl aryl diazoacetate.*

The results of the halo diazoacetate compounds in selected test reactions are shown in **Table 2.5**.

Table 2.5 *Results of rhodium catalyzed reactions of brominated diazoacetamides with a series of substrates.*



R	Compound	Reactant	Product	dr
F	**16b**	**9**	**-**	**-**
F	**16b**	**10**	**16c**	**13:1**
Cl	**17b**	**9**	**-**	**-**
Cl	**17b**	**10**	**17c**	**11:1**

In the test reactions with **9** as reactant the obtained spectroscopic data from NMR and MS were complex, and the proposed cyclopropanation products could not be found. Neither could any other product with *m*/z-values in MS-analysis corresponding to the proposed cyclopropanation products.

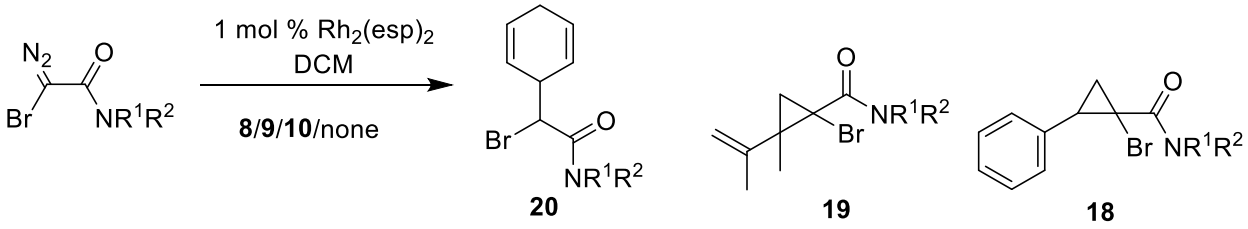
However, in the test reactions with **10** as reactant the proposed cyclopropanation product (**16c** and **17c**) could be found in the crude NMR spectra and with the correct molecular mass peak in the MS spectra. The product was not purified because there was hardly any time left for laboratory work at this stage. Hence, the diasteromeric ratios could be determined from ^{1}H NMR spectra due to analogy to previous work with Br-EDA. The diasteromeric ratio for the cyclopronation product derived from Br-EDA was 9:1 in this exact reaction from earlier work.[8] When comparing the diasteromeric ratio of

16c and **17c**, with that of the cyclopropanation product of **1b**, the ratio was slightly higher for **16c** and **17c**. The ratio was respectably 11:1 for **17c** and 13:1 for **16c.**

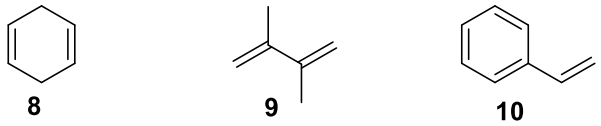
2.4.2. Reaction of brominated diazoacetamides with rhodium catalyst

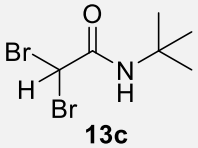
When investigating reactions of brominated diazoacetamides with a rhodium catalyst, a primary, secondary and benzylic diazo acetamide was chosen. Halo-diazoacetamides are a relatively new class of diazo compounds with unexplored reactivity. The reactivity of the selected diazoacetamides was investigated in test reactions with styrene **10**, 1,4-cyclohexene **8**, 2,3-dimethyl-1,3-diene **9** and by itself illustrated in **Tabel 2.6**.

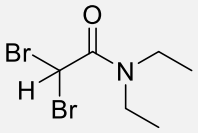
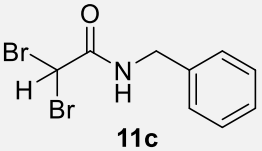
Table 2.6: *Results of rhodium catalyzed reactions of brominated diazoacetamides with a series of substrates.*



(R^1, R^2) = (t-butyl, H), (ethyl, ethyl), (benzyl, H)



(R^1, R^2)	Compound	Reactant	Anticipated Product	Main Product
(t-butyl, H)	**13b**	**8**	**20**	 **13c**
(t-butyl, H)	**13b**	**9**	**19**	**13c**
(t-butyl, H)	**13b**	**10**	**18**	**13c**
(t-butyl, H)	**13b**	None	Unknown	**13c**

(ethyl, ethyl)	**12b**	**8**	**20**	 **12c**
(ethyl, ethyl)	**12b**	**9**	**19**	**12c**
(ethyl, ethyl)	**12b**	**10**	**18**	**12c**
(ethyl, ethyl)	**12b**	None	Unknown	**12c**
(benzyl, H)	**11b**	**8**	**20**	 **11c**
(benzyl, H)	**11b**	**9**	**19**	**11c**
(benzyl, H)	**11b**	**10**	**18**	**11c**
(benzyl, H)	**11b**	None	Unknown	**11c**

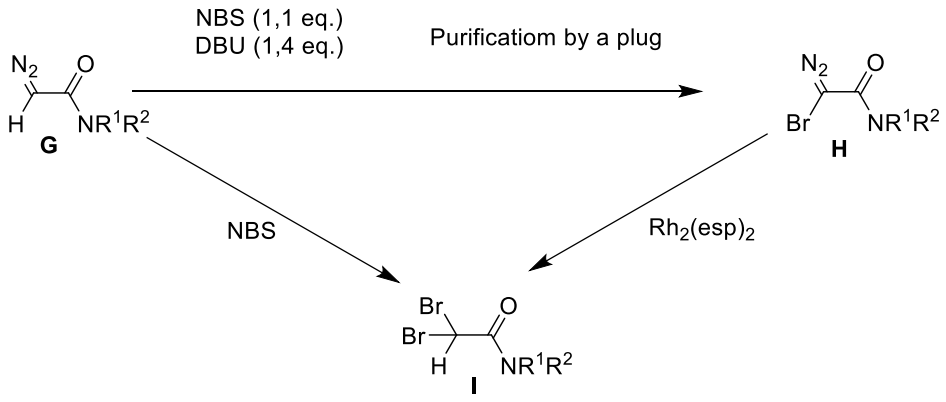
The investigation of the brominated diazo compounds were done by dividing the purified bromo-diazoacetamide-solution into 4 and adding it dropwise to each substrate or only to catalyst without substrate.

None of the bromo-diazoamides reacted the same way as the corresponding bromo-diazoacetates. The product that was found in all experiments was the corresponding di-brominated compounds **11c**, **12c** and **13c**, and in some of the reactions the tri-brominated analogs were found as well. Similar reactivity of the halo-diazoamides in reactions with $Rh_2(esp)_2$ as catalyst have been reported previously by the group.[7]

Product **11c**-**13c** and **11d-13d** are rather uncommon as they only appear in a few publications and patents. The compounds may still be of practical significance as they have been used to protect corn from herbicides.[142]

There are two probable methods for the formation of **I** shown in **Figure 2.5**. One of the methods is through the halogenation agent NBS (**G** to **I**) [143] and the other is halogen functionalization of bromo-diazoamides with loss of N_2 in the presence of $Rh_2(esp)_2$ (**H** to **I**). It is important to separate the methods by making sure that **H** is completely clean when the thermal decomposition of N_2 starts. When bromination of the halo-diazoacetamide with NBS as a possible synthetic route has been eliminated, the only source of Br is from the pure compound **H**. There must than have been a transfer of Br between two halo-diazo compounds and/or carbenoides or a mix of these. This will then be a

method for bromination that is explored to a minimum in literature and is therefore of interest to investigate further.



Figur 2.5: *Possible routes from starting material G to product I.*[1, 143]

Obtaining a ^{1}H NMR spectra of **H** (**Figure 2.5**) immediately after the plug would give information about the reaction and the experimental setup. In that way one can with greater certainty exclude the possibility of presence of excess NBS and I from after the plug effecting the reaction with $Rh_2(esp)_2$. Another possibility for gathering information about the reaction could be repeating the reaction with NBS as limited reactant. Obtaining ^{1}H NMR spectra of bromo-diazoacetamides **H** could be challenging since the solvent must be changed to a NMR solvent and the spectra has to be obtained. One solution might be using *N*-benzyl-2-bromo-2-diazoacetamide **9**, which will be presented in the next section, and turns out to have a significantly longer half-life than the other diazoacetamides.

2.5. Half-life measurements

The precursors to the α-halo diazo-amides and -esters are relatively stable and can be stored in a refrigerator for a long time without significant thermal decomposition. However, the α-halo diazo-amides and -esters are less stable than their precursors and typically have a thermal half-life of minutes or hours at AT.[2, 8]

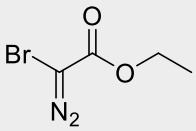
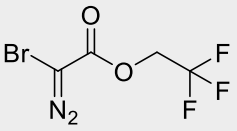
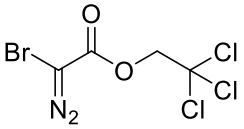
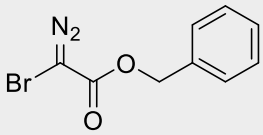
Former work in the group investigating the half-life of X-EDA has shown that temperature, solvent and choice of halogen have a significant effect on the half-life of X-EDA.[8] The former investigations also revealed that X-EDA had a significant shorter half-life in halogenated solvents. In this project the focus has mainly been on investigating the effect of varying the groups at the ester and amide, keeping the temperature, solvent and halogen constant. It has also been investigated whether the TFE and TCE groups at the ester can amplify the halogen effect of the diazo observed in the earlier study with halogenated solvents.

The half-life measurements were obtained using IR spectroscopy. As the diazo stretch gave a strong signal at approximately 2100 cm^{-1} and there was no overlapping signals at this wavelengths, IR spectroscopy could be used for quantitative analyses by using the relationship between transmittance and concentration from Beer-Lamberts law. The thermal decomposition reaction of diazo compounds, through the release of N_2 forming the carbene, was described as a first order reaction.[17] Therefore the natural logarithm of the concentration was plotted against time, which gave the rate constant as the negative slope of the linear regression curve. The half-life was than calculated by dividing the natural logarithm of 2 by the rate constant. An example of the calculations is provided in appendix together with the plots.

2.5.1. Half-life of bromo diazoacetates

The results of the half-life measurements of the bromodiazoacetates are displayed in **Table 2.7**. The half-life of Br-EDA was the only half-life of diazoacetates that had been previously measured by the group, but those measurements were obtained with a different method using ^{13}C NMR. Br-EDA was therefore included as a standard and reference. The half-life measured of Br-EDA in DCM was 2 hours at 30 ^0C, and 6 hours and 5 minutes in toluene at 30 ^0C, which had good fit with the previous measured half-lives at 25 ^0C and 35 ^0C done by ^{13}C NMR for both solvents.[8]

Table 2.7: *Half-lives of bromodiazoacetates.*

diazo compound	solvent	T (^{0}C)	$t_{1/2}$	$t_{1/2}$ rel.
	DCM	30-31	2:00 h:m[a]	1.0
	Toluene	29-30	6:05 h:m[a]	3.0
	DCM	30-31	3:18 h:m[a]	1.7
	DCM	28-29	4:37 h:m[a]	2.2
	DCM	29-30	1:57 h:m[a]	1.0

[a] one measurement.

The compounds with TXE groups at the ester had a small increase in stability in comparison to the Br-EDA. The increase in stability might come from inductive effects caused by the electron withdrawing halogens, making the oxygen in the ester pull stronger on the electrons at the diazo carbon, stabilizing the diazo group. Another explanation might be interactions between the halogen and the diazo group as shown in **Figure 2.6**.

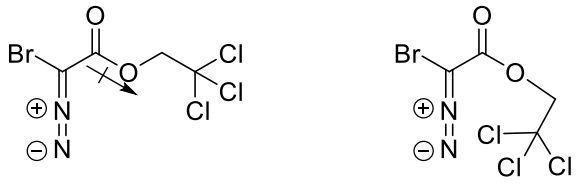


Figure 2.6: *Possible explanations for the increased stability relative to Br-EDA **1b**.*

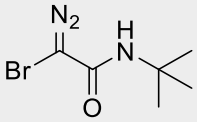
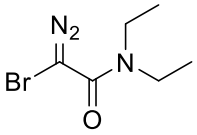
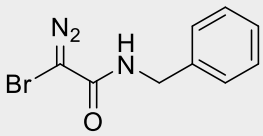
When comparing **16b** and **17b**, it was difficult to draw definite conclusions. The differences in measured half-lives were small with a difference of 1 hour and 19 minutes. There was also a temperature difference of 2-3 ^{0}C, where **17a** with the longest half-life was measured at the lowest temperature. In the study using ^{13}C NMR, the half-life of Br-EDA was halved in DCM going from 25 ^{0}C to 35 ^{0}C.[8] The IR spectroscopy method lacked accurate temperature control, and the temperature

could vary by a few degrees from day to day making it difficult to compare small differences in half-lives in the summer time when the temperature varied the most.

The half-life of bromo benzyl diazoacetate **15b** was the same as for Br-EDA at 2 hours and changing the ethyl group with a benzyl group had little effect on the half-life of bromo diazoacetates.

2.5.2. Half-life of bromo diazoacetamides

Table 2.8: *Half-lives of bromodiazoacetamides.*

diazo compound	solvent	T (^{0}C)	$t_{1/2}$	$t_{1/2}$ rel.
	DCM	30-31	11 m[a]	1.0
	DCM	30-31	2 (+/- 0.2) m[b]	0.2
	DCM	30-31	4:08 h:m[a]	22.5

[a] one measurement. [b] average of 3 measurements.

The half-life of a bromo diazoacetamide has only been obtained one time earlier by the group, measuring the half-life of a tertiary amide with the same IR spectroscopy method. The half-life of the tertiary amide **12b** (**Table 2.8**) was measured to be 2 (+/- 0.2) minutes and was in the same order of magnitude as the previously measured tertiary amide. The half-life of the secondary amide **13b** was 11 minutes, while the measured half-life of the benzyl amide **11b** was 4 hours and 8 minutes. The trend observed for the bromo diazoamides in **Table 2.8** was as following: secondary > tertiary, where the secondary amides had the longest half-lives.

The half-life measured for **11b** clearly stands out with a factor of 22.5 times the half-life of the other secondary amide **13b**. The great stabilization effect observed for the benzyl group for **11b** was only observed for the amides, and may be of interest to investigate further.

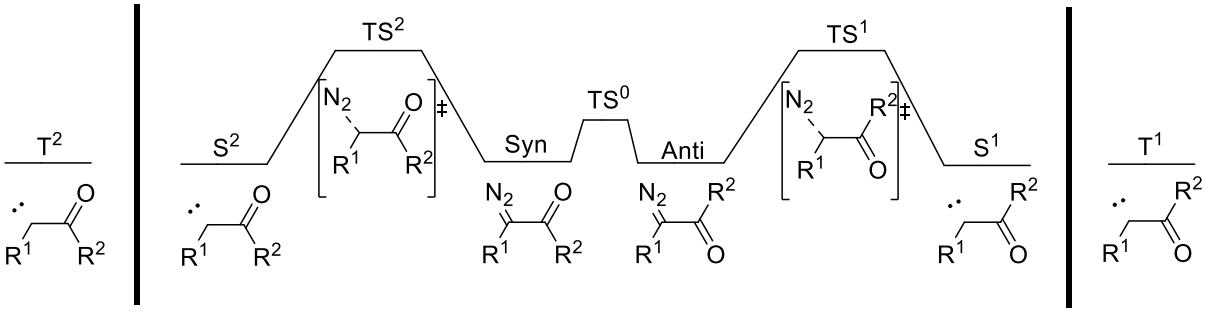
2.6. DFT Calculations

It has earlier been done a DFT calculation study on X-EDA which has investigated thermal decomposition by the release of N_2 to form the free radical.[8] When expanding the scope it was of interest to investigate whether the observed trends for X-EDA were transferable to other diazo-ester and amides. The compounds that was selected were the same diazo-esters and -amides that have been investigated experimentally. The work was done with b3lyp/def2tzvp scrf=(smd,solvent=dichloromethane) iop(3/124=40) as metode and basis sett in Gaussian 09W and an overview of the calculation results are presented in **Table 2.9**. The missing data in the dataset in **Table 2.9** for the diazoacetates is due to convergence difficulties and lack of time.

2.6.1. Transition barriers of diazoacetates and halo diazoacetates

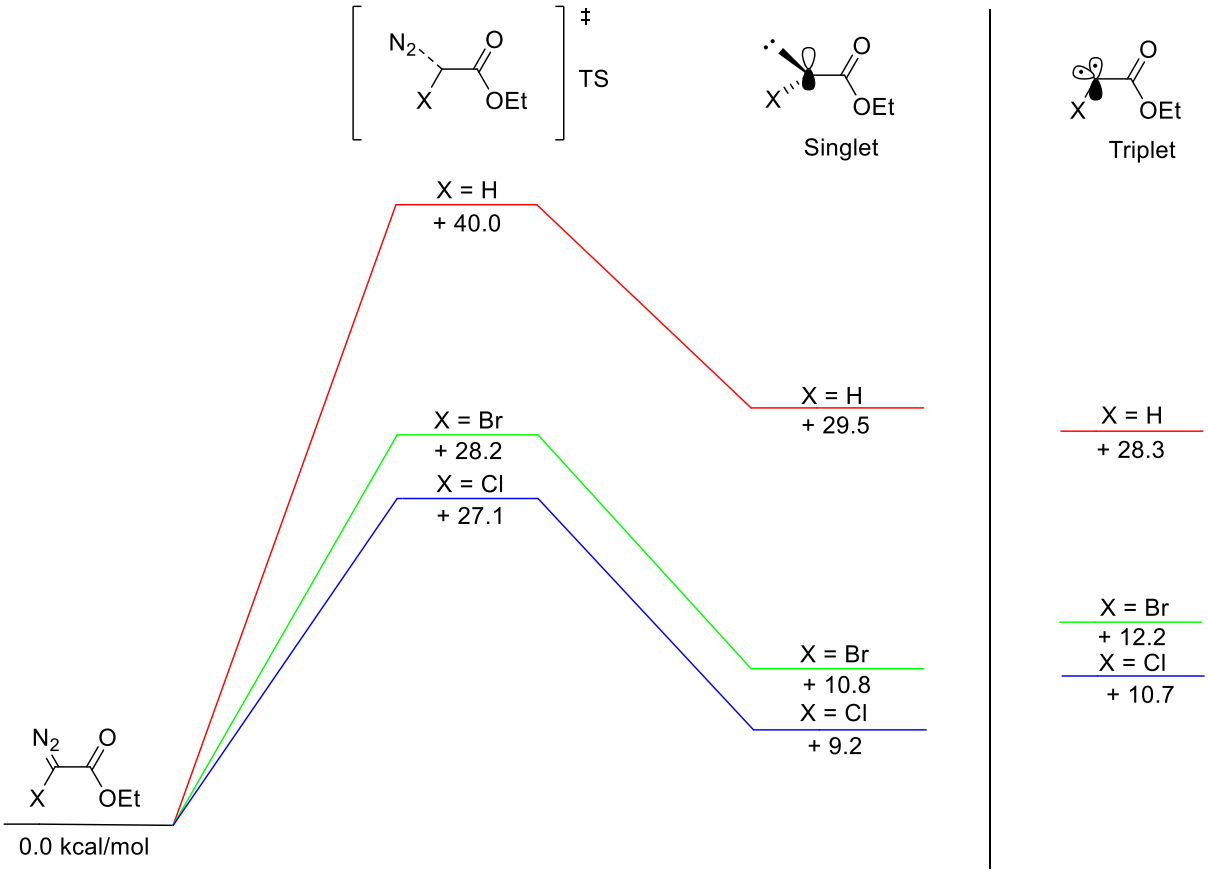
Even though the EDA series had been investigated earlier it was included in this work as well, because another basis set and solvent field was used for the calculations in this work. The transition barrier height of all the diazoacetates and halodiazoacetates calculated were consistent with the previous trend found for X-EDA (**Figure 2.7**). With diazoacetates having the highest barrier for loss of N_2. For the halo diazoacetates the trend was as following: Br > Cl. The loss of N_2 resulting in the free carbene was found to be endothermic for the diazoacetates and halodiazoacetates. According to the Hammond's postulate, the transition barrier of endothermic reactions should be closer in energy to the product than the reactant. The energy gap from the transition state to the carbenes were 10-12 kcal/mol for the diazoacetates and 26-29 kcal/mol for the halodiazoacetates. This stabilization effect of the resulting halocarbenes were described by the π-donation of an electron pair from the halogen to the empty p orbital of the carbene carbon, and was involved in lowering the transition state. All the trends for diazoacetates and halo-diazoacetates discussed so far converged with the former trends found, although there were some differences on the size of the numbers.

Table 2.9: *Relative free energy (kcal/mol) of reactant, carbene and transition state of thermal decomposition by the release of N_2 to form the free radical for a series diazo compounds.*



Nr.	R^1	R^2	T^2	S^2	TS^2	Syn	Anti	TS^1	S^1	T^1
13a	H	$NHC(CH_3)_3$	Wolff	Wolff	39.6	0	1.2	35.9	24.3 [a]	24.7
-	Cl	$NHC(CH_3)_3$	9.3	6.4 [a]	27.6	0	2.3	27.3	6.4 [a]	9.3
13b	Br	$NHC(CH_3)_3$	9.7	7.2 [a]	28.2	0	0.6	27.6	7.2 [a]	9.7
11b	Br	$NHCH_2Ar$	10.8	8.2 [a]	29.5	0	1.8	27.9	8.2 [a]	10.8
12b	Br	$N(CH_2CH_3)_2$	2.9	-0.9 [a]	24.2	0	-0.4	27.9	-0.9 [a]	2.9
1a	H	OCH_2CH_3	28.3	29.5 [b]	40.4	0	0.2	-	-	-
16a	H	OCH_2CF_3	28.8	31.1 [b]	41.4	0	4.0	-	-	-
17a	H	OCH_2CCl_3	28.8	31.5 [b]	40.8	0	10.7	-	-	-
21a	H	OCH_2CBr_3	-	31.1 [b]	40.5	0 [c]	47.4	-	-	-
-	Cl	OCH_2CH_3	-	-	-	0	-1.1	26.0	8.1 [b]	9.6
-	Cl	OCH_2CF_3	-	-	-	0	-1.2	25.9	8.5 [b]	9.5
-	Cl	OCH_2CCl_3	-	-	-	0	-0.5	-	-	-
-	Cl	OCH_2CBr_3	-	-	-	0	0.8	26.8	10.0 [b]	9.9
1b	Br	OCH_2CH_3	13.7	10.3 [b]	28.6	0	-0.5	27.8	10.3 [b]	11.7
16b	Br	OCH_2CF_3	-	-	-	0 [c]	-12.7	27.1	10.7 [b]	10.9
17b	Br	OCH_2CCl_3	-	-	-	0	0.1	28.5	11.9 [b]	12.6
21b	Br	OCH_2CBr_3	-	-	-	0	-0.2	-	-	-

[a] Connected with IRC. [b] Not connected with IRC. [c] Not Converged.



Figur 2.7: *Transition state energies (kcal/mol) for the release of N_2 and formation of the singlet carbene for* ***1a***, ***1b*** *and Cl-EDA. The corresponding triplet carbenes are displayed to the right.*

One of the trends found in the former half-life studies of X-EDA was that the half-life was shorter in halogenated solvents compared to non-halogenated solvents. Based on Hammond's postulate a hypothesis for the observed trend was made, explaining the shorter half-life in halogenated solvents with intermolecular interactions between the halogens in the solvent and the carbene, stabilizing the carbene and lowering the transition state barrier. To investigate whether the same effect could be found intramolecularly, calculations of the carbene derived from **17b** was performed from the conformation shown in **Figure 2.8**. The goal was to find a local minima where the chlorine halogens were in close proximity to the carbene. From the NBO analysis in the local minima, no donation of electrons from the halogens to the carbene carbon could be found. See appendix for calculation result numbers.

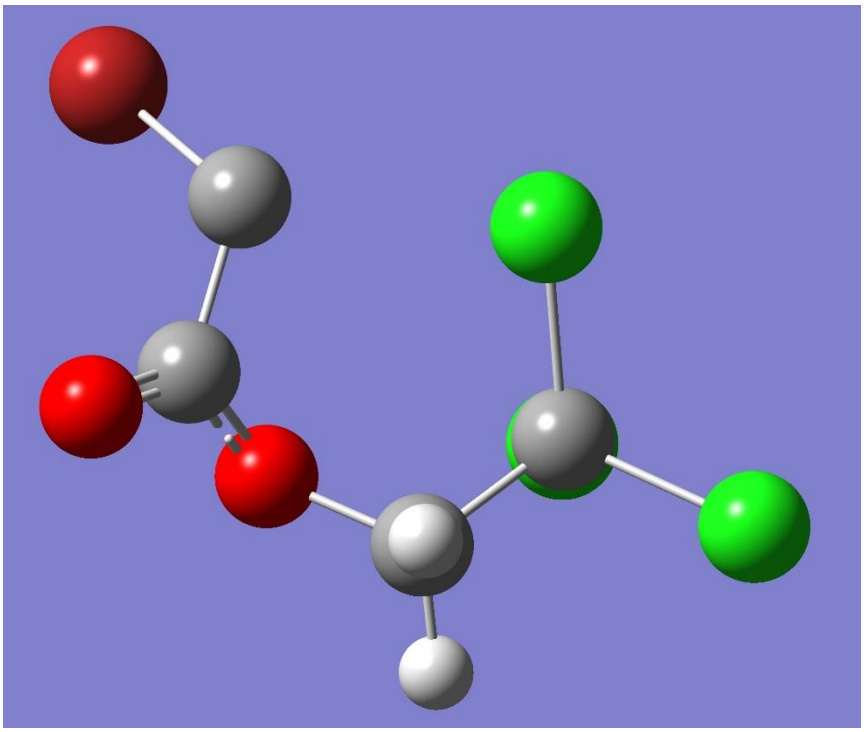
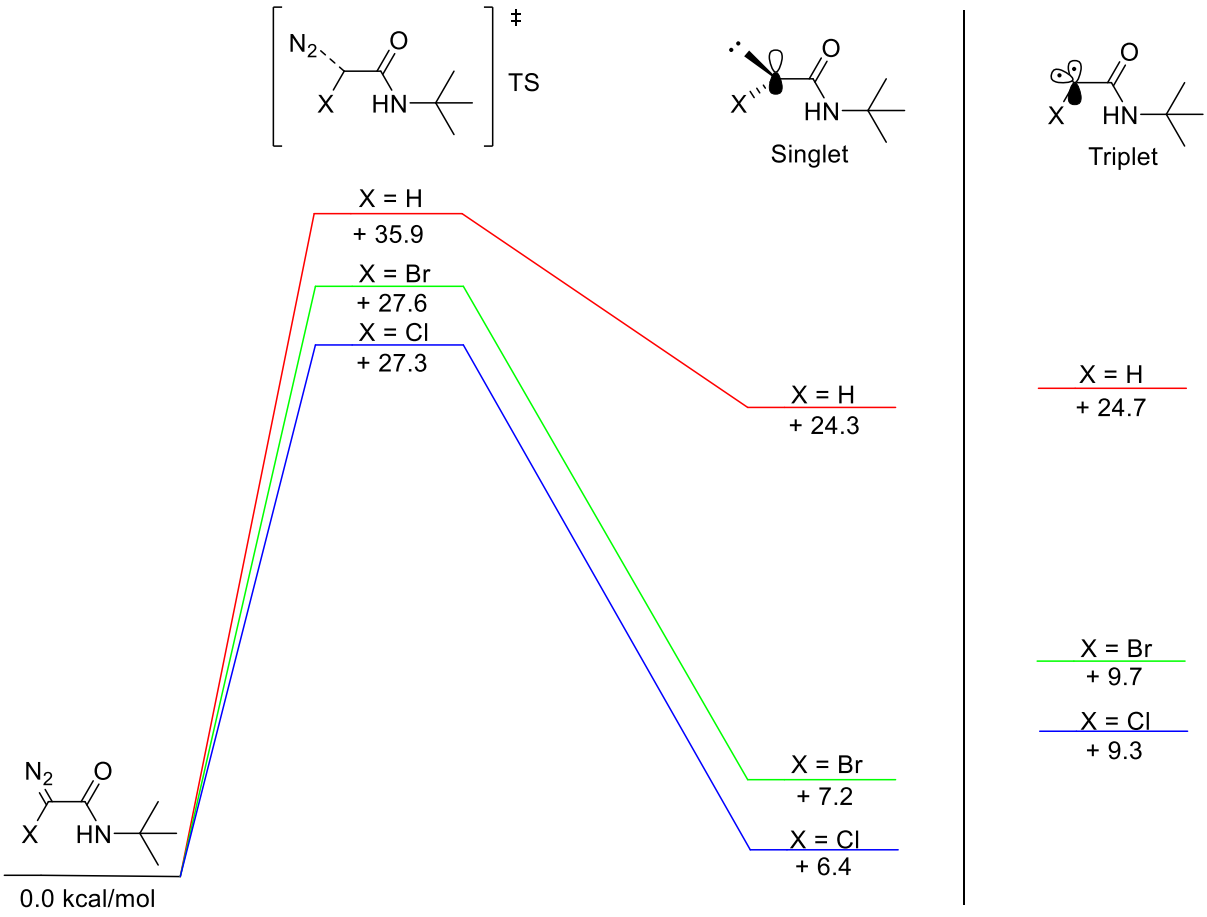


Figure 2.8: *Start conformation for DFT calculations searching for local minima with carbene derived from* ***17b****.*

2.6.2. Transition barriers of diazoamides and halo diazoamides

Halo-diazoamides are a relatively new class of diazo compounds and few experiments obtaining knowledge about this class of diazo compounds have been done. It was therefore initially interesting to investigate whether the same trends could be found for halo-diazoamides as for halo-diazoesters. The effect of halogenating diazoamides is displayed in **Figure 2.9**, and was: H >> Br > Cl. The energy gap from the transition state to the free carbene was 11.6 kcal/mol for **13a**, 19-21 kcal/mol for the secondary halo amides **13b** and **11b**, and 25.1 kcal/mol for the tertiary halo amide **12b**. The loss of N_2 resulting in the free carbene was found to be less endothermic for the halo-diazoamides, than for the halo-diazoacetates. The reaction of the only tertiary halo amide **12b** was slightly exothermic. Both the activation barrier and the free carbene was lower in energy for the halo-diazoamides compared to the halo-diazoacetates, which correspond with the in general lower half-life of halo-diazoamides.



Figur 2.9: *Transition state energies (kcal/mol) for the release of N_2 and formation of the singlet carbene for **13a**, **13b** and Cl-**13**. The corresponding triplet carbenes are displayed to the right.*

The energy barrier for the transition state of the three bromo-diazoamides was compared (**Figure 2.10**). The energy barrier for the transition state was found to be highest for the secondary amides and lower for the tertiary amide. Even though the activation barriers observed did not translate exactly into the $t_{1/2}$, they followed the same trend.

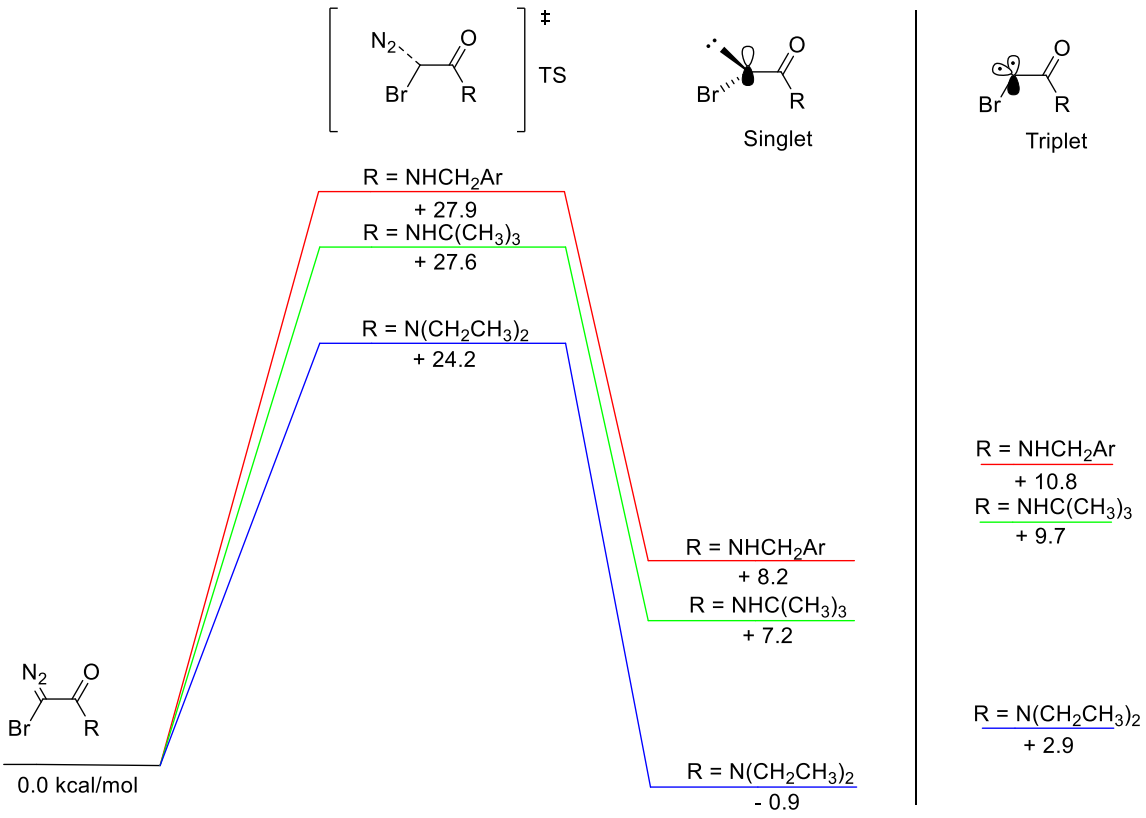


Figure 2.10: *Transition state energies (kcal/mol) for the release of N_2 and formation of the singlet carbene for **11b**, **12b** and **13b**. The corresponding triplet carbenes are displayed to the right.*

2.6.3. Singlet-Triplet energy gap for free carbene generated from α-halo-diazoamides and -diazoesters

From the earlier DFT study of the generated carbene of EDA and the halogenated analogs the singlet-triplet gap was in favor of triplet state for EDA and in favor of singlet state for the X-EDA species. The same trend could be found for the generated carbenes of the esters (**Figure 2.11**). However, for the generated carbenes of the amides all the halogenated and the non halogenated species were favoring singlet state. In all cases the trend was as following: Cl > Br > H, where Cl favored the singlet state the most. Another trend that could be observed was that the carbenes generated from amides were favoring the singlet state more than those of esters were. When comparing the effect of changing the ethyl group on the ester with TXE-groups the trend was: Cl > F > H, where Cl favored the singlet state the most.

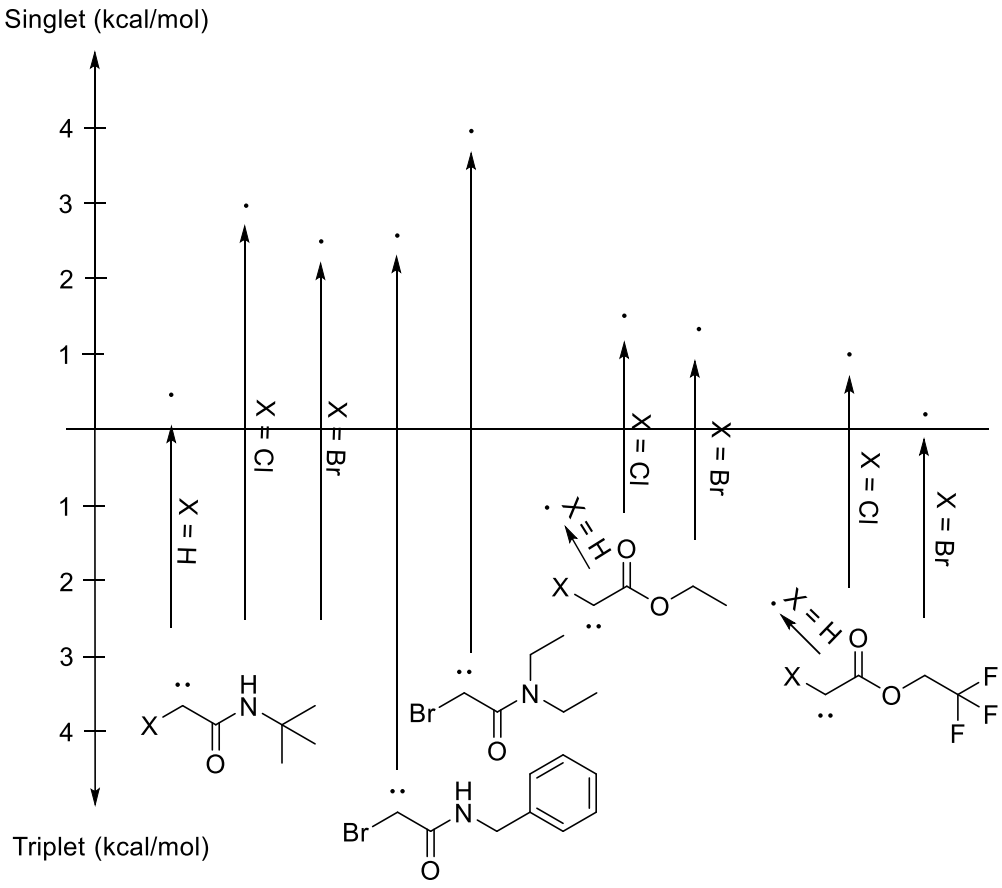
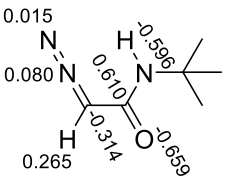


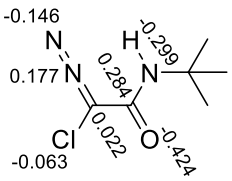
Figure 2.11: *Energy (kcal/mol) in favor of singlet state (up) and for triplet state (down).*

2.6.4. NBO calculations and IR frequencies

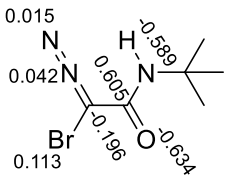
When comparing the IR frequencies of the halogenated and non halogenated diazo-esters and -amides (**Figure 2.12**) the non halogenated diazo-esters and -amides were found to have a higher diazo stretch frequency and a lower C=O stretch frequency. In general the diazo stretch frequency and C=O stretch frequency were slightly lower for Cl diazo-esters and -amides than for Br. From the NBO charges the nucleophilicity of the diazo carbon was H > Br > Cl, where H had the greatest nucleophilicity. The diazo carbon of X-diazoamides were found to be slightly less nucleophilic than the diazo carbon of the corresponding X-diazoesters.



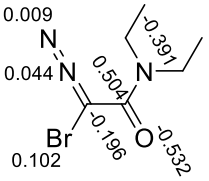
exp ν_{diazo} = 2104
calc ν_{diazo} = 2165
exp $\nu_{C=O}$ = 1629
calc $\nu_{C=O}$ = 1664



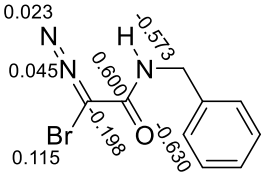
calc ν_{diazo} = 2137
calc $\nu_{C=O}$ = 1690



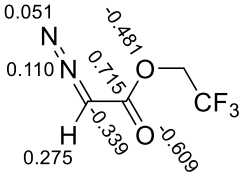
exp ν_{diazo} = 2079
calc ν_{diazo} = 2137
calc $\nu_{C=O}$ = 1692



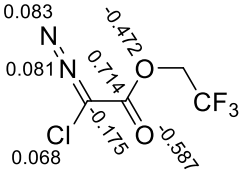
exp ν_{diazo} = 2076
calc ν_{diazo} = 2146
calc $\nu_{C=O}$ = 1662



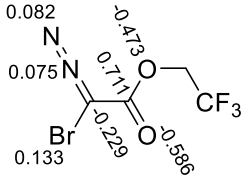
exp ν_{diazo} = 2110
calc ν_{diazo} = 2143
calc $\nu_{C=O}$ = 1690



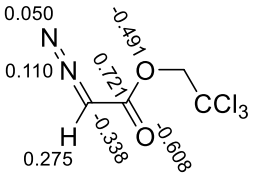
exp ν_{diazo} = 2125
calc ν_{diazo} = 2218
exp $\nu_{C=O}$ = 1712
calc $\nu_{C=O}$ = 1726



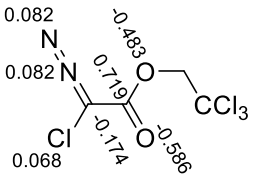
calc ν_{diazo} = 2189
calc $\nu_{C=O}$ = 1745



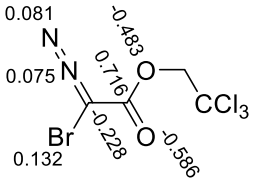
exp ν_{diazo} = 2093
calc ν_{diazo} = 2190
calc $\nu_{C=O}$ = 1746



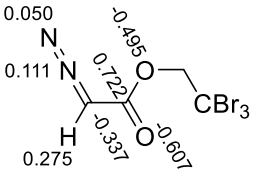
exp ν_{diazo} = 2119
calc ν_{diazo} = 2218
exp $\nu_{C=O}$ = 1707
calc $\nu_{C=O}$ = 1724



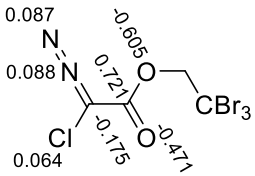
calc ν_{diazo} = 2189
calc $\nu_{C=O}$ = 1743



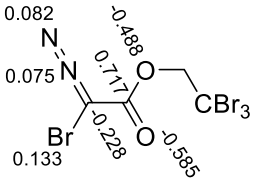
exp ν_{diazo} = 2092
calc ν_{diazo} = 2190
calc $\nu_{C=O}$ = 1744



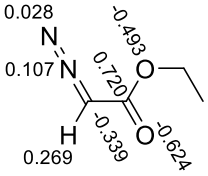
calc ν_{diazo} = 2219
calc $\nu_{C=O}$ = 1725



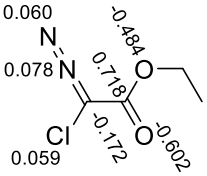
calc ν_{diazo} = 2197
calc $\nu_{C=O}$ = 1715



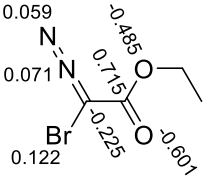
calc ν_{diazo} = 2191
calc $\nu_{C=O}$ = 1745



calc ν_{diazo} = 2206
calc $\nu_{C=O}$ = 1711



calc ν_{diazo} = 2178
calc $\nu_{C=O}$ = 1732



exp ν_{diazo} = 2085
calc ν_{diazo} = 2178
calc $\nu_{C=O}$ = 1733

Figure 2.12: *NBO atomic charges and IR stretching frequencies calculated[144] and experimentally recorded.*

3. Conclusion

The synthesis of BB has been considerably improved. With purified yields of 47 % it gives much higher yields than what was obtained from the existing literature procedure. The improved synthesis using NHS-reagent **6** was the procedure that gave the highest isolated yields, although it was NHS-reagent **4** that was found to give the highest internal standard yield. The reaction performs better at low temperatures and low concentrations with excess of NHS-reagent and base.

BB proved to be an excellent reagent for synthesis of diazoamides. Diazoesters can also be made, but only one example was made. The reaction conditions are mild and the diazo compounds can be easy purified. Giving yields from 60-94 % in reactions with an alcohol and a series of amines, this method for making diazo-amides and -esters are a good synthetic alternative. The limitations of the reaction was uncovered in a reaction with the bad nucleophile HMDS, giving no expected product.

In rhodium catalyzed test reactions with bromo diazo-amides, the product obtained in all test reactions was the di-brominated compounds **11c**-**13c**. None of the anticipated cyclopropanation or C-H insertion products were observed. With these observations a general trend for the reactivity of halo diazoamides catalyzed by $Rh_2(esp)_2$ is starting to take shape.

In rhodium catalyzed test reactions with bromo diazo-esters, the test reaction with **9** gave products with complex spectroscopic data and no peak with the mass of the anticipated cyclopropanation product could be observed in the crude MS-spectrum. However, in the test reactions with **10** the expected cyclopropanation product was observed and a diasteromeric ratio was measured. The diasteromeric ratio for **16c** and **17c** was higher than for the product of **15b** and it is therefore of interest to examine the non catalyzed version of the same reaction with **16c** and **17c**.

Half-life measurements and DFT-calculations of novel halo diazo-esters and -amides have expanded our knowledge and insights into this relatively new class of diazo compounds. From the half-life measurement of bromo diazo-esters and -amides, the half-lives of bromo diazo-esters were found to be longer than the half-lives of bromo diazoamides, with exception of **11b**. Inward among the bromo diazoesters the TXE-esters **16b** and **17b** were found to have slightly longer half-lives than Br-EDA and **15b**, which had about the same half-life. For the bromo diazoamides the secondary amides were found to have longer half-lives than tertiary amides. Compound **11b** stood out from the other amides in the studied series with a measured half-life that was 22.5 times longer than the other secondary amide **13b**. The measured half-lives had a good fit with previous measurements and the same trends were found both for the half-lives measurements and in the DFT calculations. Furthermore, there are of interest to investigate the substituent effect of halo diazo-esters and -amides in non halogenated solvents.

4. Experimental section

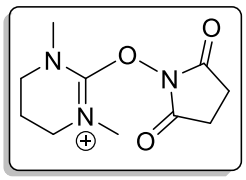
Chemicals and solvents was used as delivered from Sigma Aldrich, AK scientific and VWR International AS, unless stated otherwise. All DCM, MeCN, THF and DMF used in synthesis was dried using Günter. Deuterated solvents for NMR was used as provided form sigma Aldrich and Cambridge Isotope Laboratories. Hexane, DCM and EtOAc was distilled before use. EDA **1a** provided by Sigma Aldrich contained 12 wt.% DCM and was taken into account when used.

60 F_{254} silica coated alumina plates from Merck was used for thin layer chromatography (TLC) and silica gel from Merck (Silicagel 60, 40-0.60 µm, 460-520 m^2/g, pH 6.5-7.5) used for flash chromatography performed ether manually or with an Isco inc. CombiFlash Companion with PealTrack software (v.1.4.10).

The ^1H and ^{13}C NMR specters was obtain in $CDCl_3$, acetonitrile-*d3* or benzene-*d6* on a Bruker Avance AVIII400, AVneo400, AVI600 or AVII600 instrument. The residual peaks were used as references ($CDCl_3$ 7.26 ppm/77.16 ppm, DMSO-*d6* 2.50 ppm/39.53 ppm, acetonitrile-*d3* 1.94 ppm and benzene-*d6* 7.16 ppm). All internal standard spectra obtained with ^1H NMR had D1 = 30 seconds.

IR was measured on IRAffinity-instrument and proceed with IRsolution software.

4.1. Synthesis of 2-(((2, 5-dioxopyrrolidine-1-yl)oxy)methyl)-1, 3-dimethyl-3, 4, 5, 6-tetrahydropyrimidin-1-ium **4**



To a 100 ml round flask with DMPU (5.2403 g, 40.88 mmol), DMF (0.3 mL) and DCM (40 mL) was added dropwise oxalyl chloride (4.8 mL, 55.92 mmol). The solution was stirred for 1 h at AT and then refluxed for 24 h.

The solvent was evaporated under reduced pressure leaving a solid, which was stirred with portions of DCM (2 x 10 mL) and evaporated under reduced pressure between each treatment.

The solid was dissolved in MeCN (60 mL) and $NaBF_4$ (5.275 g, 48.04 mmol) were added. The mixture was stirred for 24 h at AT and to the resulting suspension was added NHS (5.1052 g, 44.36 mmol). Triethylamine (7 mL, 50.19 mmol) was added dropwise and the resulting suspension was stirred at AT for 5 h and then at 45 ^{0}C for 1 h.

The crude product was purified by filtration through a celite plug. The solvent was evaporated under reduced pressure and the product was obtained after decantation in 1:5 MeOH/isopropanol (20 mL) solution leaving the product as a white powder.

Yield: 63% (Calculations in the appendix)

^{1}H NMR (400 MHz, DMSO-d_6) δ 3.53 (t, J = 5.9 Hz, 4H), 3.15 (s, 6H), 2.82 (s, 4H), 1.99 (p, J = 5.9 Hz, 3H).

^{13}C NMR: (151 MHz, DMSO-d_6) δ 170.62, 156.48, 49.53, 38.71, 26.23, 20.52.

This compound is reported in literature.[129]

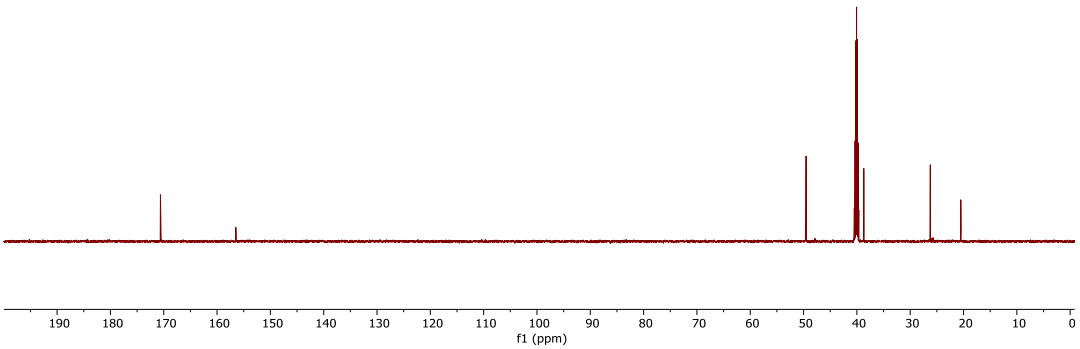


Figure 4.1: *^{13}C NMR spectra of **4** (151 MHz, DMSO-d_6).*

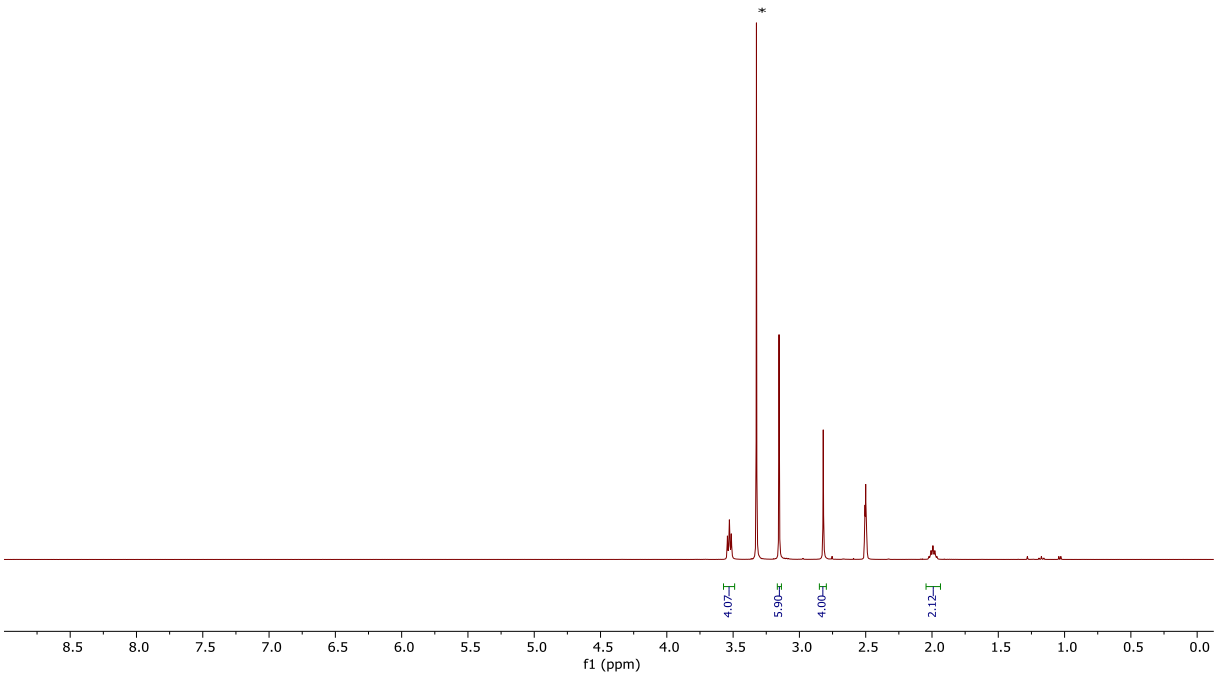
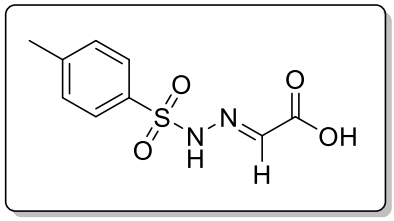


Figure 4.2: *^{1}H NMR spectra of **4** (400 MHz, DMSO-d_6). *Water*

4.2. Synthesis of (E)-2-(2-tosylhydrazineylidene) acetic acid **3**



To a solution of glyoxylic acid monohydrate (9.39 g, 102.01 mmol, 1 eq.) in type two water (110 mL) were added p-toluenesulfonyl hydrazide (19.52 g, 104.82 mmol, 1 eq.) in 2.5 M aquatic HCl solution (66 mL). The suspension was heated at 65 ^{0}C until everything was solved, and stirred for 15 minutes.

The reaction mixture was cooled at 0 ^{0}C to maximize the precipitation. The precipitation was filtered off and washed with ice cold type two water (10 mL), and dried under reduced pressure for 24h.

The crude product were recrystallized by adding portions EtOAc and heating it to 77 ^{0}C until everything were solved. Hexane was then added until the solution was cloudy. The solution was cooled at 0 ^{0}C to maximize the precipitation. The product was obtained after filtration and dried under reduced pressure for 24h.

Yield: 73%

TLC (reverse phase plates; eluent MeOH:H_2O 1:1): R_f = 0.73.

^{1}H NMR (400 MHz, Methanol-d_4): δ 7.80 (d, *J* = 8.4 Hz, 2H, H-7, H-12), 7.38 (d, *J* = 8.2 Hz, 2H, H-8, H-11), 7.17 (s, 1H, H-1), 2.40 (s, 3H, H-9).

^{13}C NMR (101 MHz, Methanol-d_4): δ 165.76, 145.95, 137.44, 136.88, 130.83, 128.68, 21.52.

MS (ESI, Methanol): m/z (relative intensity): 265 (M-1H+1Na, 17%), 287 (M-1H+2Na, 100%)

HR-MS (ESI, Methanol): 287.007 [M – H^+ + 2Na^+]: Calculated for $C_9H_9N_2Na_2O_4S$: 287.008 (Δ 0.1 ppm)

This compound is reported in literature.[125]

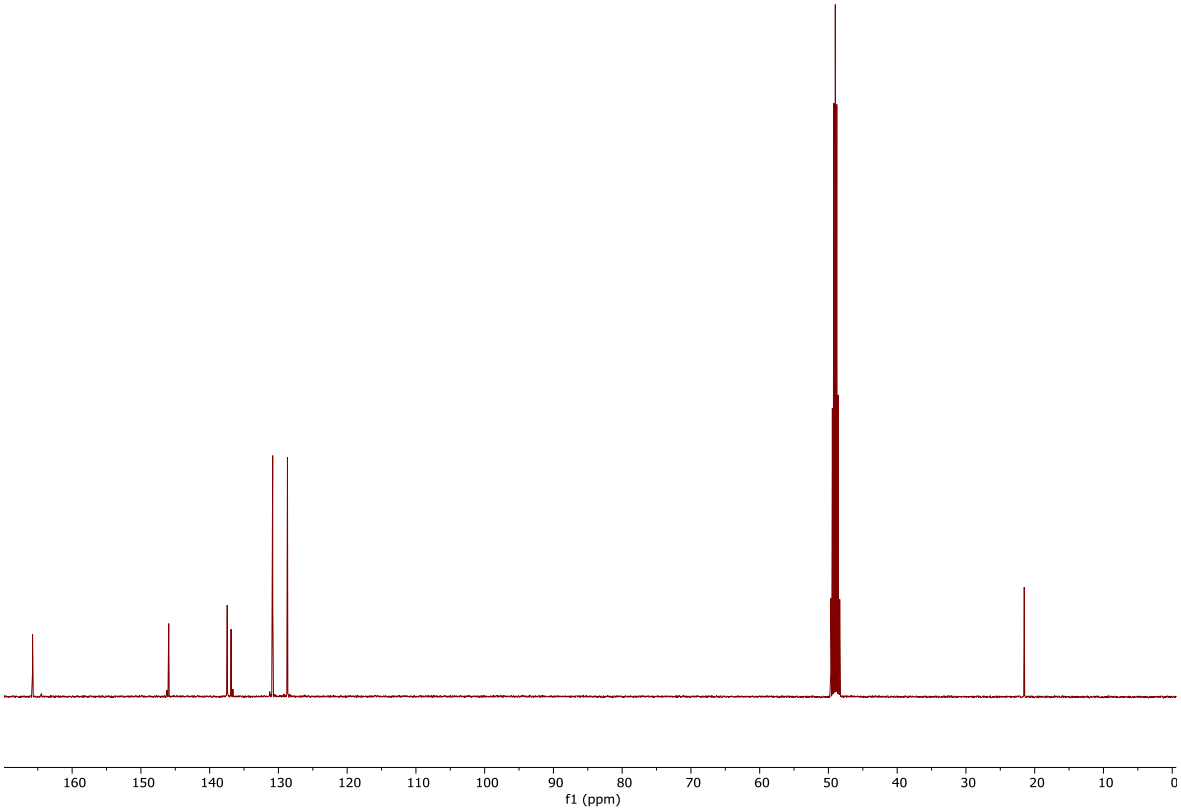


Figure 4.3: *^{13}C NMR spectra of **3** (101 MHz Methanol-d_4).*

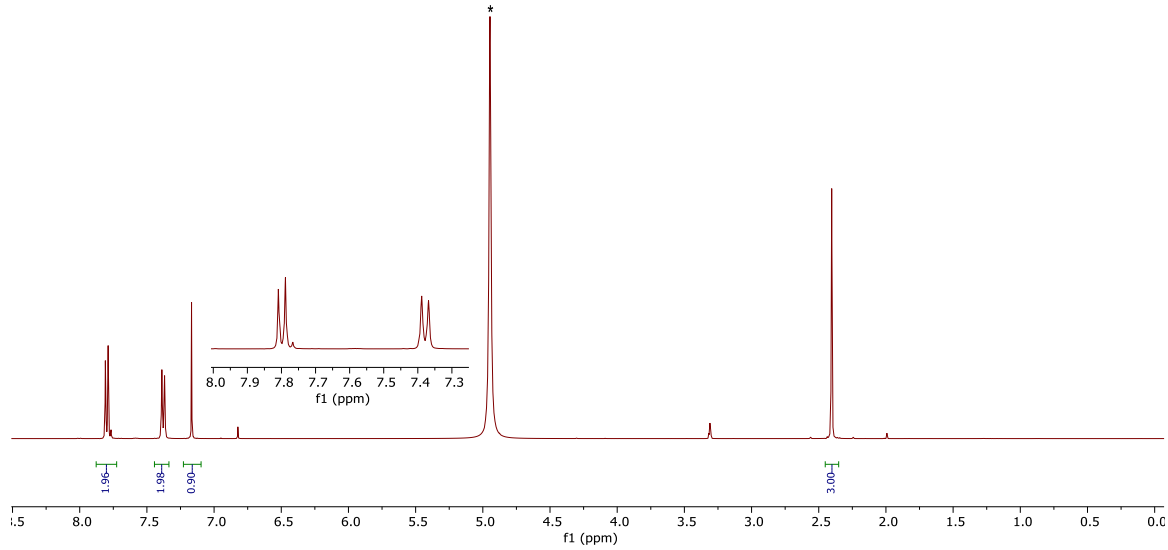
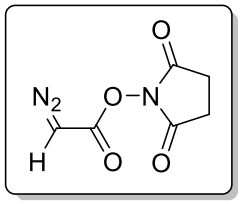


Figure 4.4: *^{1}H NMR spectra of **3** (400 MHz, Methanol-d_4). *Water*

4.3. Synthesis of BB **2**



(Entry 25, Table 2.3) Tosylhydrazono acetic acid **3** (0.242 g, 1 mmol, 1 eq.), NHS **7** and NHS-reagent **6** (0.384 g, 1.5 mmol, 1.5 eq) was solved in MeCN (5 mL) and cooled at 0 ^{0}C for 10 minutes. Triethlylamine (0.28 mL, 2 mmol, 2 eq.) was added and the reaction mixture was stirred for 10 minutes at 0 ^{0}C. The reaction mixture was diluted with EtOAc (20 mL) and extracted with saturated $NaHCO_3$ solution (3 x 15 mL). The organic phase was dried with $MgSO_4$, and purified with flash chromatography (silica colomn, eluent DCM). The yellow bond was gathered in fractions that was investigated by TLC. Fractions with product were combined in a round bottle and the solvent was removed under reduced pressure. The product was recrystallized by diluting the crude product in a minimum of DCM and coating the DCM with a thin layer hexanes. The DCM evaporated in AT overnight leaving the product as a white precipitate that was filtered of.

Yield: 60%

TLC (reverse phase plates; eluent MeOH:H_2O 1:1): R_f = 0.41.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.13 (s, 1H), 2.83 (s, 4H).

^{13}C NMR: (101 MHz, Chloroform-*d*) δ 169.49, 45.25, 25.61.

This compound is reported in literature.[12]

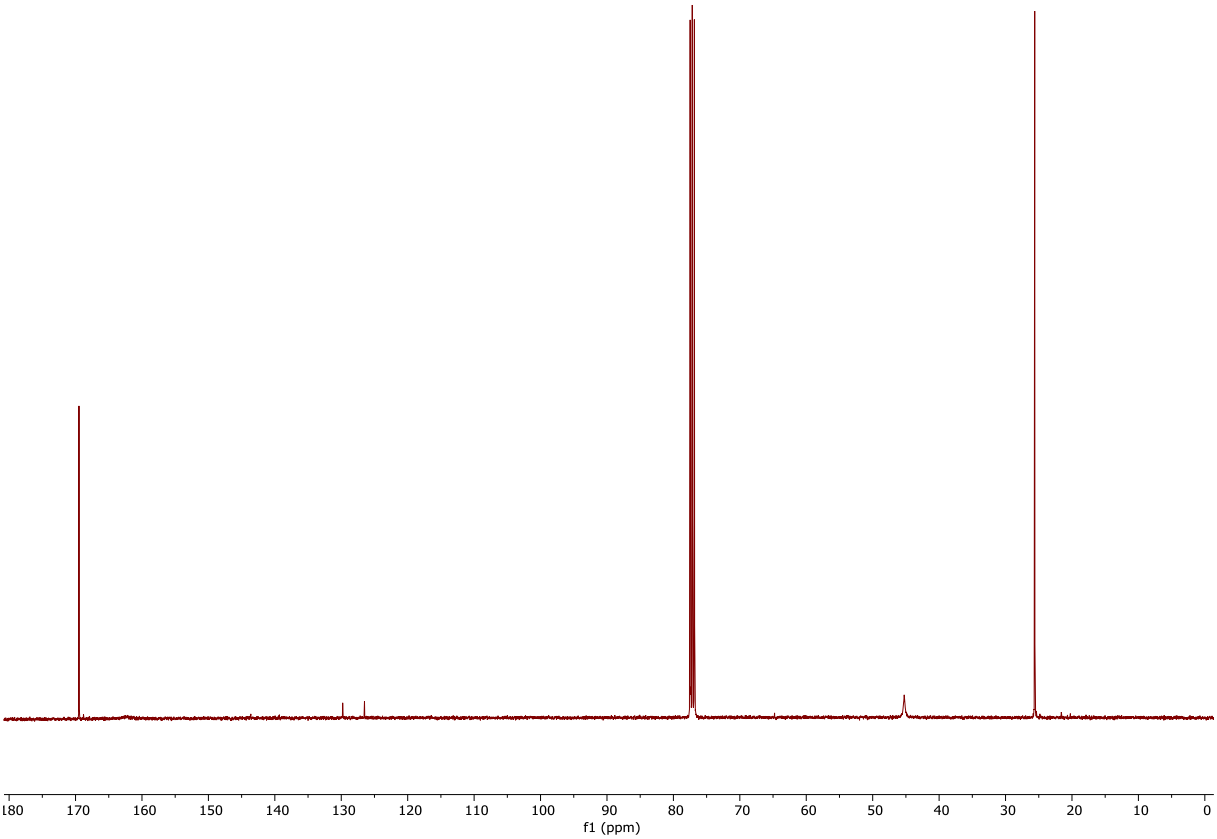


Figure 4.5: *^{13}C NMR spectra of **2** (101 MHz, Chloroform*-d*).*

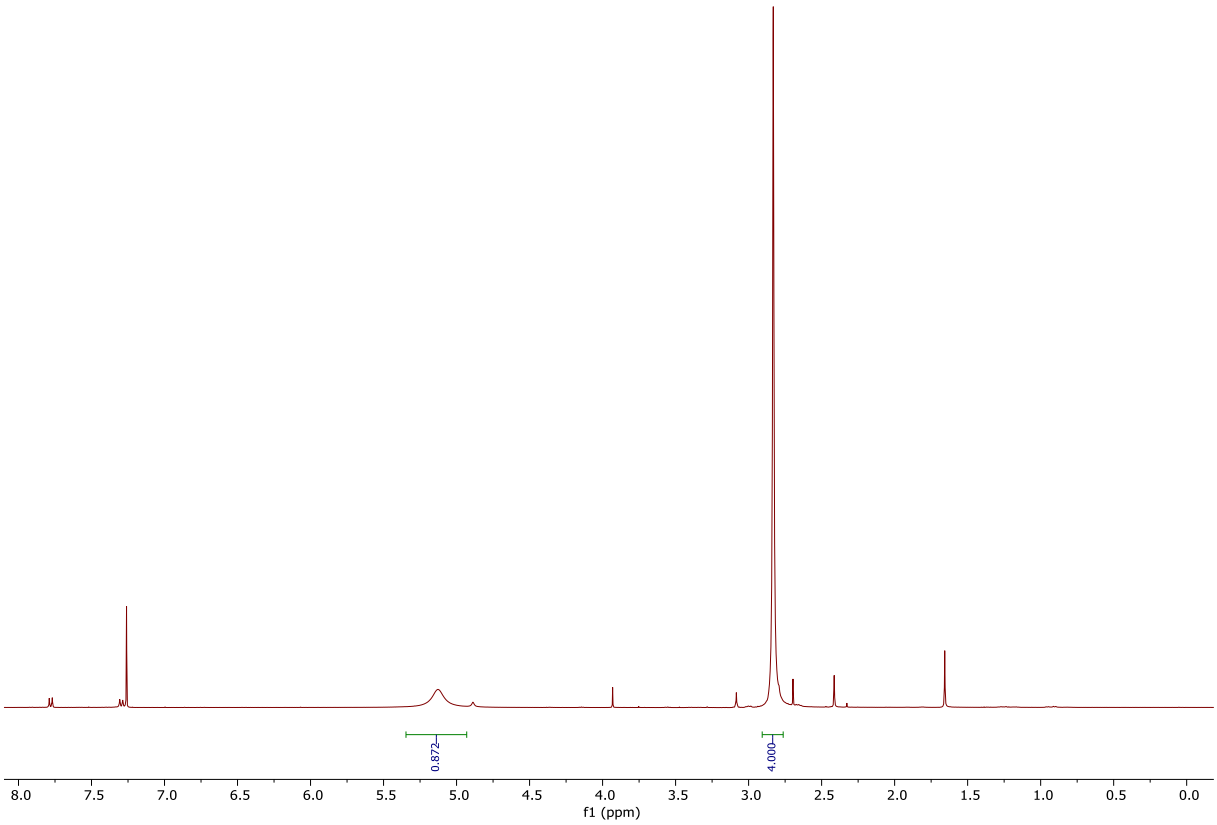


***Figure 4.6*: ^{1}H NMR spectra of *2* (400 MHz, Chloroform*-d*).**

4.3.1. Procedure for optimization of reaction conditions

Tosylhydrazono acetic acid **3** and NHS-reagent was solved in designated solvent. The base was added and the reaction was stirred for a given time at a given temperature. The reaction was monitored by reverse phase TLC with 1:1 MeOH/H_2O as eluent. After the given reaction time the solvent was removed under reduced pressure, internal standard (1,3,5-Trimethoxybenzene) was added, and the crude was resolved in $CDCl_3$. The yield was calculated from internal standard ^{1}H NMR. The amount of reagents, base and solvent can be found in **Table 2.1.** and **Table 2.3.**

For reactions at 0 ^{0}C the solution was cooled in an ice bath for 10 minutes, before addition of the base.

Due to high boiling point of DMF, it was added saturated NaCl-solution (10 mL) before extraction with EtOAc (3 x 10 mL) when used as solvent. The EtOAc solution was evaporated under reduced pressure.

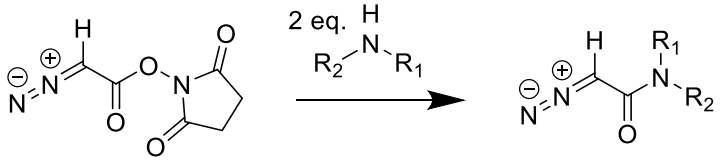
For the internal standard ^{1}H NMR 1,3,5-trimethoxybenzene was used as internal standard and D1 was set to 30 seconds to ensure complete relaxation between each pulse. The product peak in ^{1}H NMR was found by overlaying an earlier obtained spectra of the product in the same solvent.

The entries in **Table 2.2** was performed with the same procedure as described for Entry 16**, Table 2.1**. After the end of the reaction the solvent was removed under reduced pressure. The crude reaction mixture was dissolved in saturated NaCl-solution and extracted with EtOAc/DCM (2-3 times). The crude product was purified by flash chromatograph using a silica coluomn/plug with DCM/EtOAc 95:5, hexanes/EtOAc 1:1 or DCM as eluent and then recrystallized by solvation in chloroform and adding a thin layer of heptane carefully on top. The chloroform evaporated slowly at AT, leaving the product as a yellow precipitate after 18 hours.

The variables of the different entries are described in **Table 2.2**.

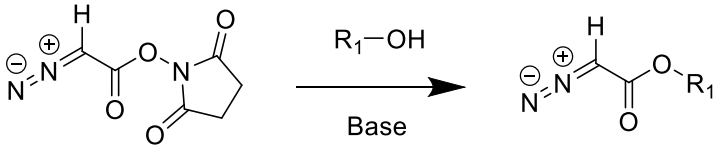
4.4. General procedures

4.4.1. Synthesis of diazo amides from BB



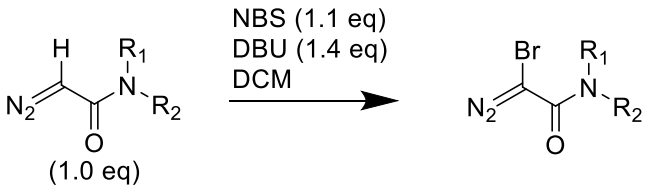
BB (2 mmol, 1 eq) was added THF (8 mL) and amine (4 mmol, 2 eq). The reaction was stirred at AT for 2-24h and the conversion of BB was monitored by TLC. The product was purified with a silica powder plug with 3:1 EtOAc/Hexanes as eluent.

4.4.2. Synthesis of diazo esters from BB



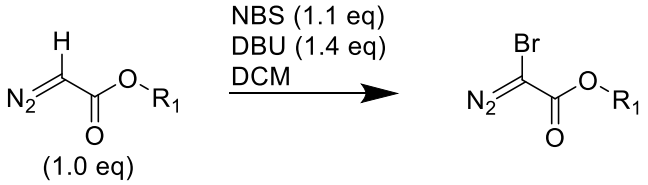
BB (0.1 mmol, 1 eq) was added THF (1 mL), triethylamine (0.11 mmol, 1.1 eq) and alcohol (0.11 mmol, 1.1 eq). The reaction was stirred at AT 24h+ and monitored by TLC.

4.4.3. Bromination procedure of diazo amides



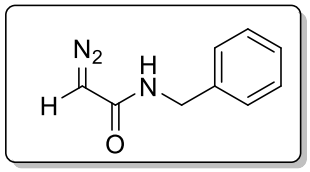
Diazoamide (0.5 mmol, 1 eq) was solved in DCM (5 mL) and DBU (0.5 mmol, 1.4 eq) was added while stirring at -78 ^{0}C. NBS (0.55 mmol, 1.1 eq) was added no earlier than 10 minutes after DBU and the stirring was continued for 15-20 minutes at -78 ^{0}C. During the stirring time the color of the solution changed from yellow to red. The product was purified with a silica plug precooled to -30 ^{0}C and DCM at -30 ^{0}C as eluent, using suction, gathering the yellow band. The product solution was stored at -78 ^{0}C for a few hours before being used in further reactions.

4.4.4. Bromination procedure of diazo esters



Diazoester (0.5 mmol, 1 eq) was solved in DCM (5 mL) and DBU (0.5 mmol, 1.4 eq) was added while stirring at -0 ^{0}C. NBS (0.55 mmol, 1.1 eq) was added no earlier than 10 minutes after DBU and the stirring was continued for 5-10 minutes at -0 ^{0}C. During the stirring time the color of the solution changed from yellow to red. The product was purified with a silica plug precooled to -30 ^{0}C and DCM at -30 ^{0}C as eluent, using suction, gathering the yellow band. The product solution was up concentrated under reduced pressure at 0 ^{0}C to about 10 mL and could be stored at -30 ^{0}C for a few hours or days before being used in further reactions.

4.5. Synthesis of *N*-benzyl-2-diazoacetamide **11a**



N-benzyl-2-diazoacetamide **11a** was synthesized by procedure 4.4.1. Benzylamine was used as amine.

Yield: 70%

TLC (silica plates; eluent EtOAc:Hexanes 1:3): R_f = 0.58.

^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.32 (m, 5H), 5.28 (s, 1H), 4.72 (s, 1H), 4.48 (d, *J* = 5.5 Hz, 2H).

^{13}C NMR (101 MHz, Chloroform-*d*): δ 165.88, 138.43, 128.66, 127.55, 127.45, 47.11, 43.85.

HR-MS (ESI, Acetonitrile): 198.0638 [M + Na^+]: Calculated for $C_9H_9N_3NaO$: 198.0638 (Δ 0.1 ppm).

IR (DCM): 2110 cm^{-1}

This compound is reported in literature.[145]

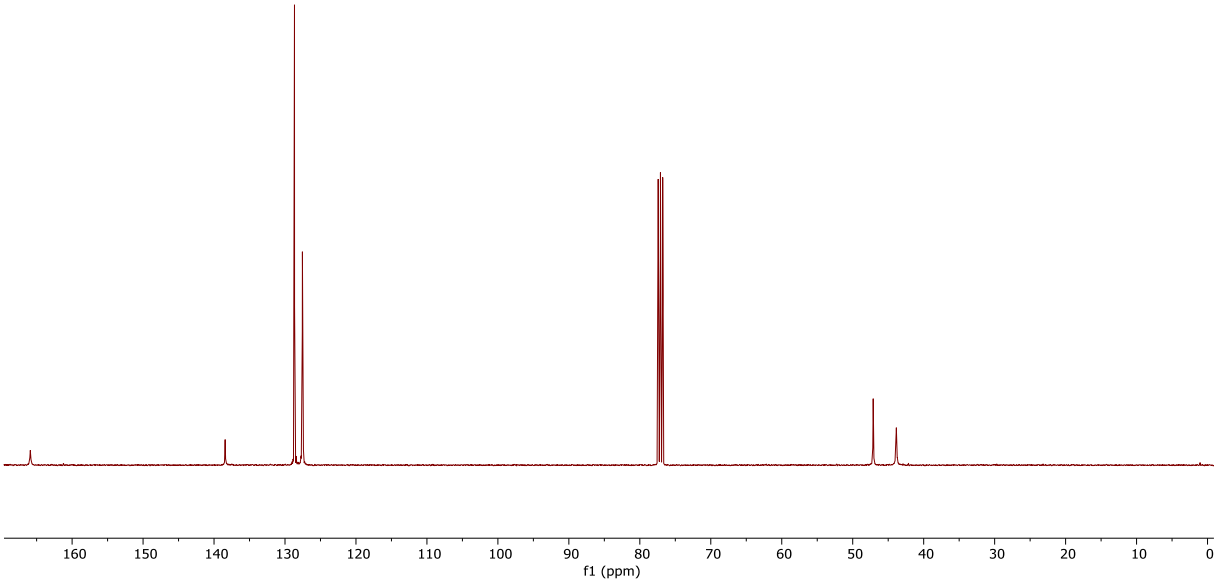


Figure 4.7: *^{13}C NMR spectra of **11a** (101 MHz, Chloroform-*d*).*

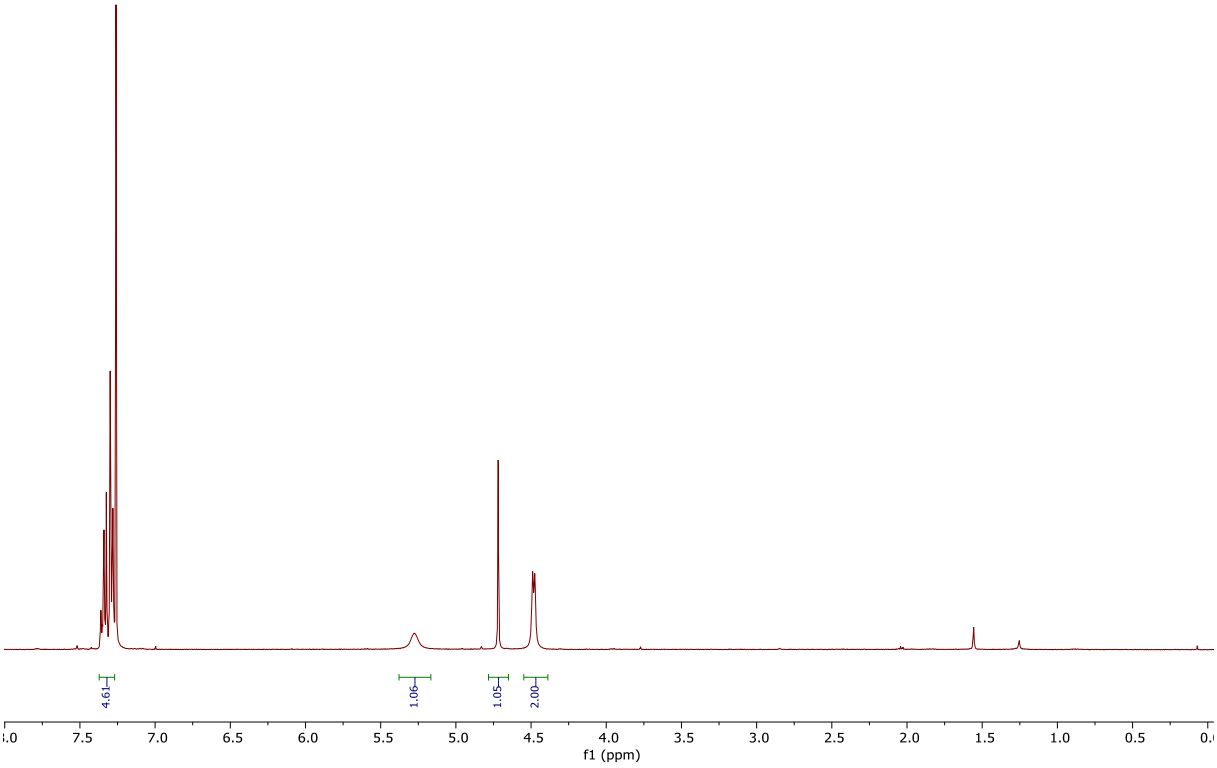
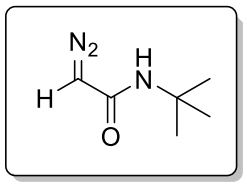


Figure 4.8: *^{1}H NMR spectra of **11a** (400 MHz, Chloroform-*d*).*

4.6. Synthesis of *N*-(tert-butyl)-2-diazoacetamide **13a**



N-(tert-butyl)-2-diazoacetamide **13a** was synthesized by procedure 4.4.1. Tertbutylamine was used as amine. BB was fully converted after 2 hours and 45 minutes. The product was purified either with a short silica plug or by extraction with saturated $NaHCO^3$ solution, both of which gave adequate purity. The yield was 98 % and 94 %.

Yield: 94%

TLC (silica plates; eluent EtOAc:Hexanes 1:1): R_f = 0.68.

^{1}H NMR (400 MHz, Chloroform-*d*): δ 4.91 (s, 1H), 4.62 (s, 1H), 1.37 (s, 9H).

^{13}C NMR (101 MHz, Chloroform-*d*): δ 164.71, 51.96, 29.22.

HR-MS (ESI, Acetonitrile): 164.0793 [M + Na^+]: Calculated for $C_6H_{11}N_3NaO$: 164.0794 (Δ 0.6 ppm).

IR (DCM): 2104 cm^{-1}, 1741 cm^{-1}, 1629 cm^{-1}

This compound is reported in literature.[146]

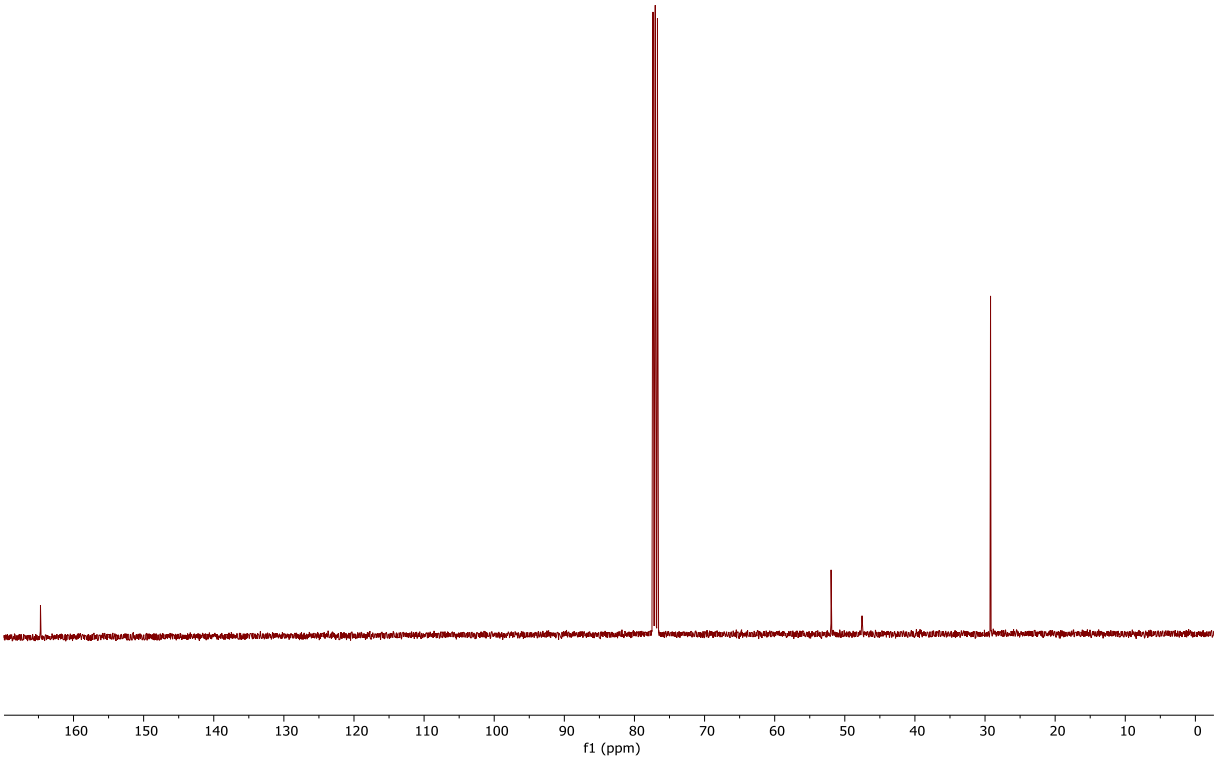


Figure 4.9: *^{13}C NMR spectra of **13a** (101 MHz, Chloroform-*d*).*

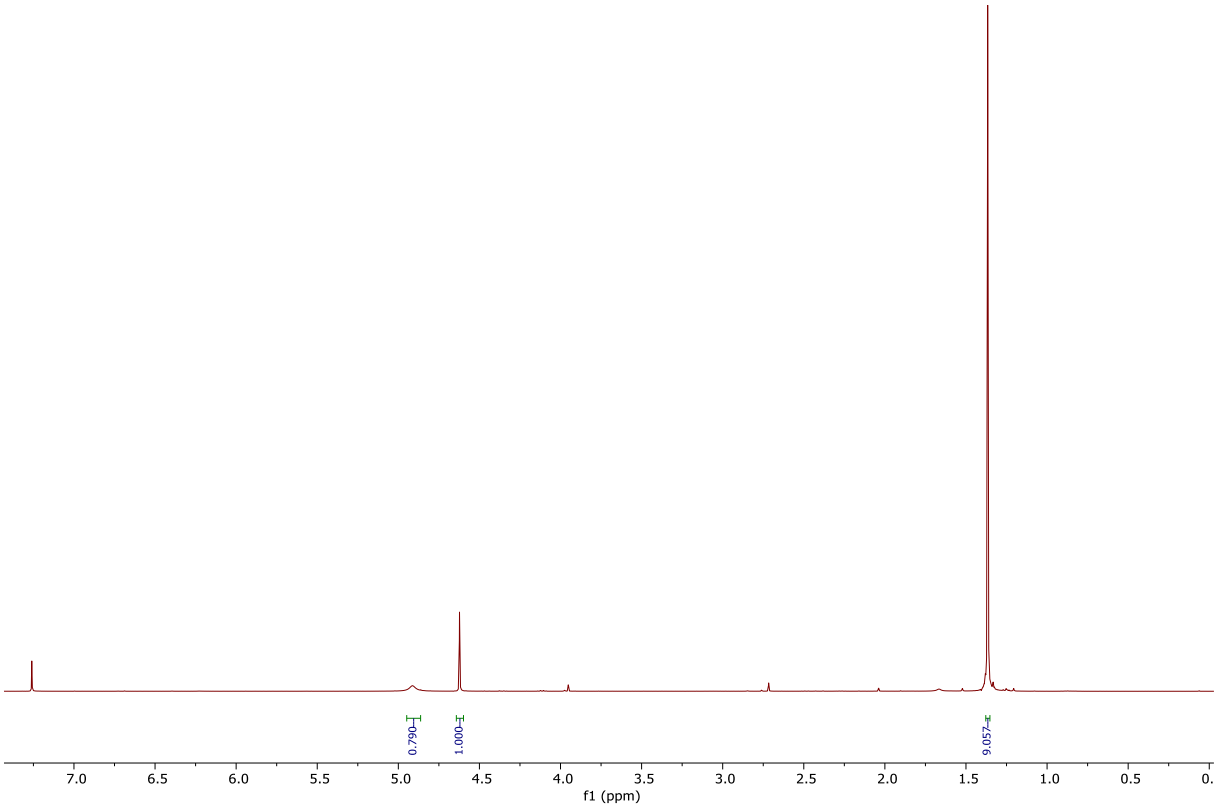
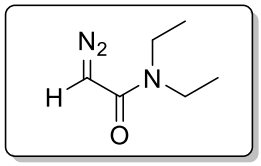


Figure 4.10: *^{1}H NMR spectra of **13a** (400 MHz, Chloroform-*d*).*

4.7. Synthesis of 2-diazo-*N*,*N*-diethylacetamide **12a**



2-Diazo-*N*,*N*-diethylacetamide **12a** was synthesized by procedure 4.4.1. Diethylamine was used as amine.

Yield: 85%

TLC: (silica plates; eluent EtOAc:Hexanes 1:1): R_f = 0.23.

^{1}H NMR (400 MHz, Chloroform-*d*): δ 4.93 (s, 1H), 3.22 (s, 4H), 1.10 (t, *J* = 7.2 Hz, 6H).

^{13}C NMR (101 MHz, CDCl3): δ 164.75, 46.29, 41.35, 13.83.

MS (ESI, Methanol): m/z (relative intensity):

HR-MS (ESI, Acetonitrile): 164.0795 [M + Na^+]: Calculated for $C_6H_{11}N_3NaO$: 164.0794 (Δ 0.4 ppm).

IR (DCM): 2110 cm^{-1}, 1600 cm^{-1}

This compound is reported in literature.[147]

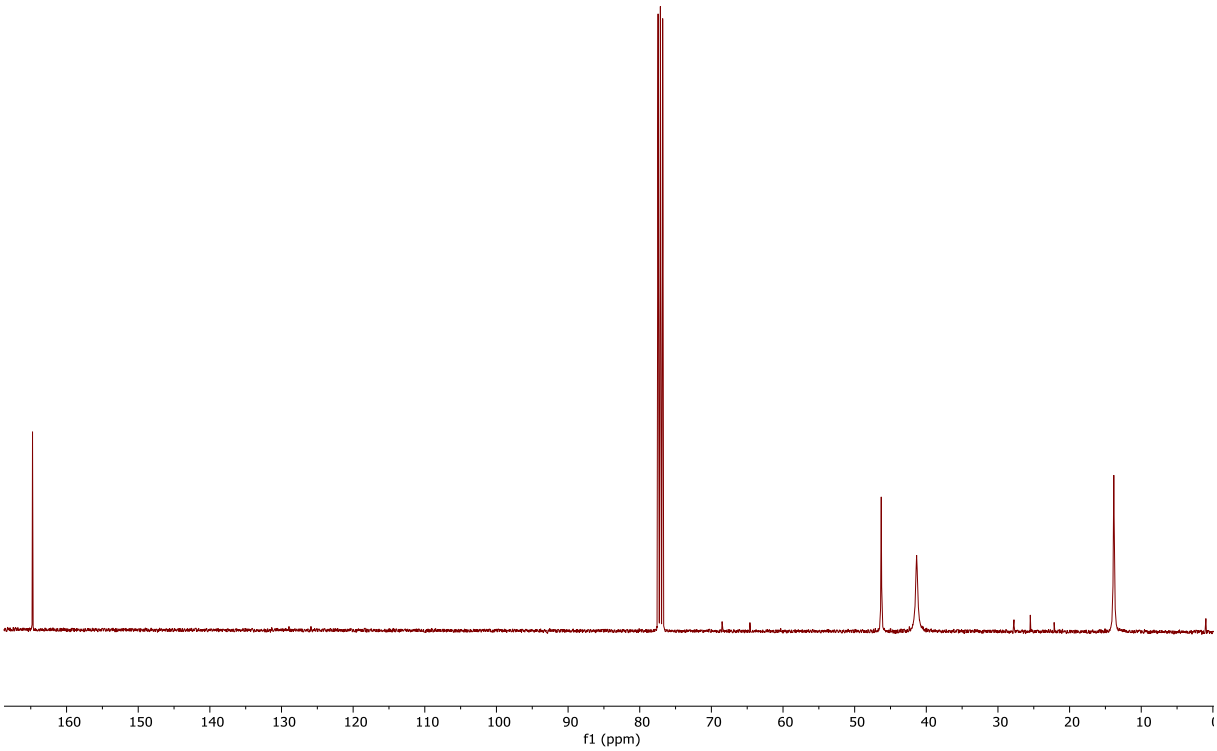


Figure 4.11: *^{13}C NMR spectra of **12a** (101 MHz, Chloroform-*d*).*

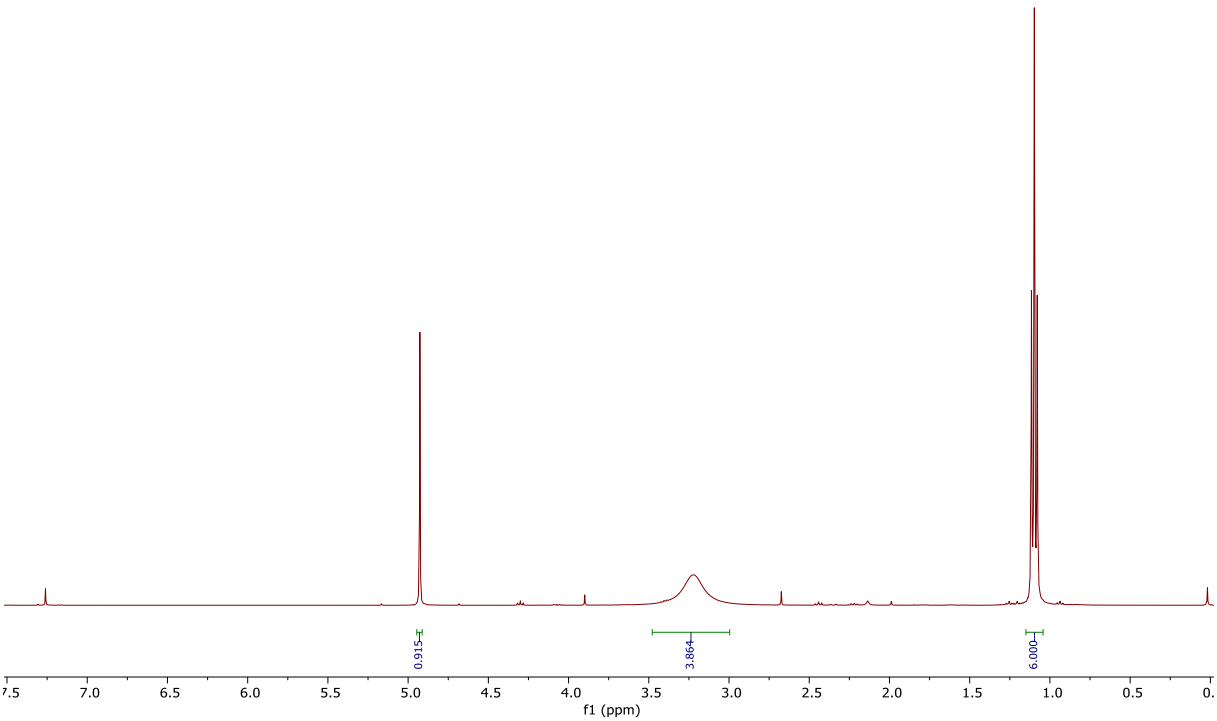
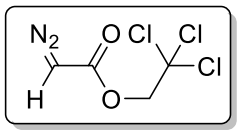


Figure 4.12: *^{1}H NMR spectra of **12a** (400 MHz, Chloroform-*d*).*

4.8. Synthesis of TCEDA **17a**



TCEDA **17a** was provided by others on the group.

TLC: (silica plates; eluent EtOAc:Hexanes 1:1): R_f = 0.86.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.87 (s, 1H), 4.72 (s, 2H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 165.04, 94.97, 73.52, 46.47.

MS (ESI, Methanol): m/z (relative intensity): No molecule peak observed

IR (DCM): 2119 cm^{-1}, 1707 cm^{-1}.

This compound is reported in literature.[148]

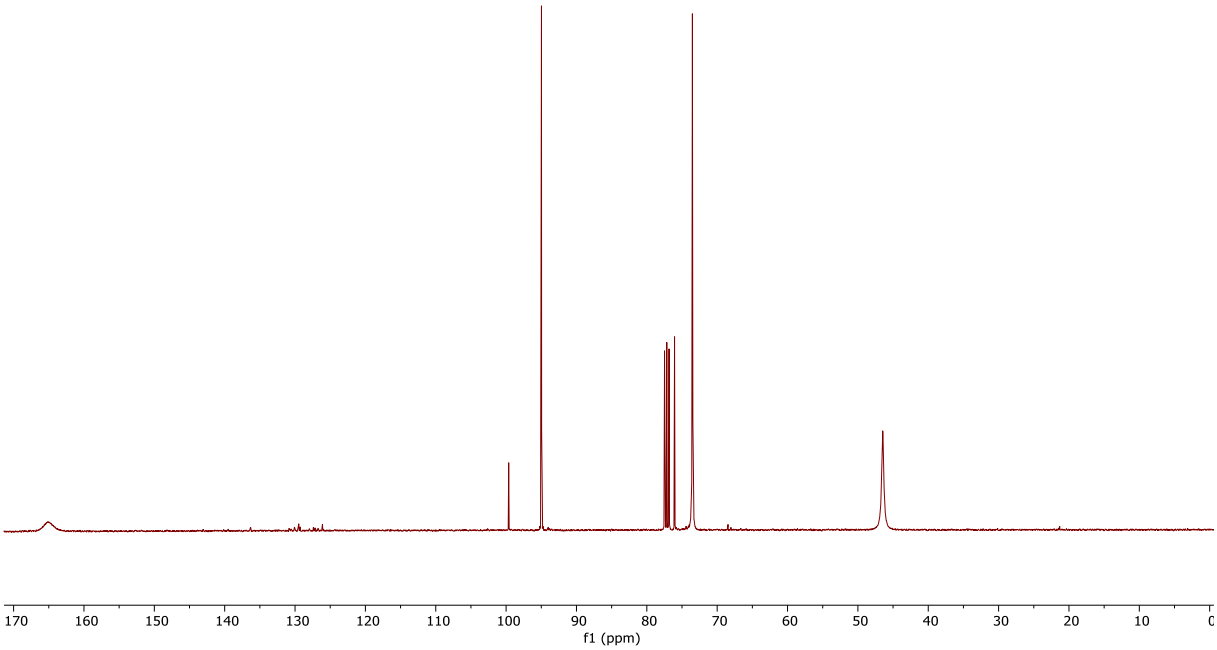


Figure 4.13: *^{13}C NMR spectra of **17a** (101 MHz, Chloroform-*d*).*

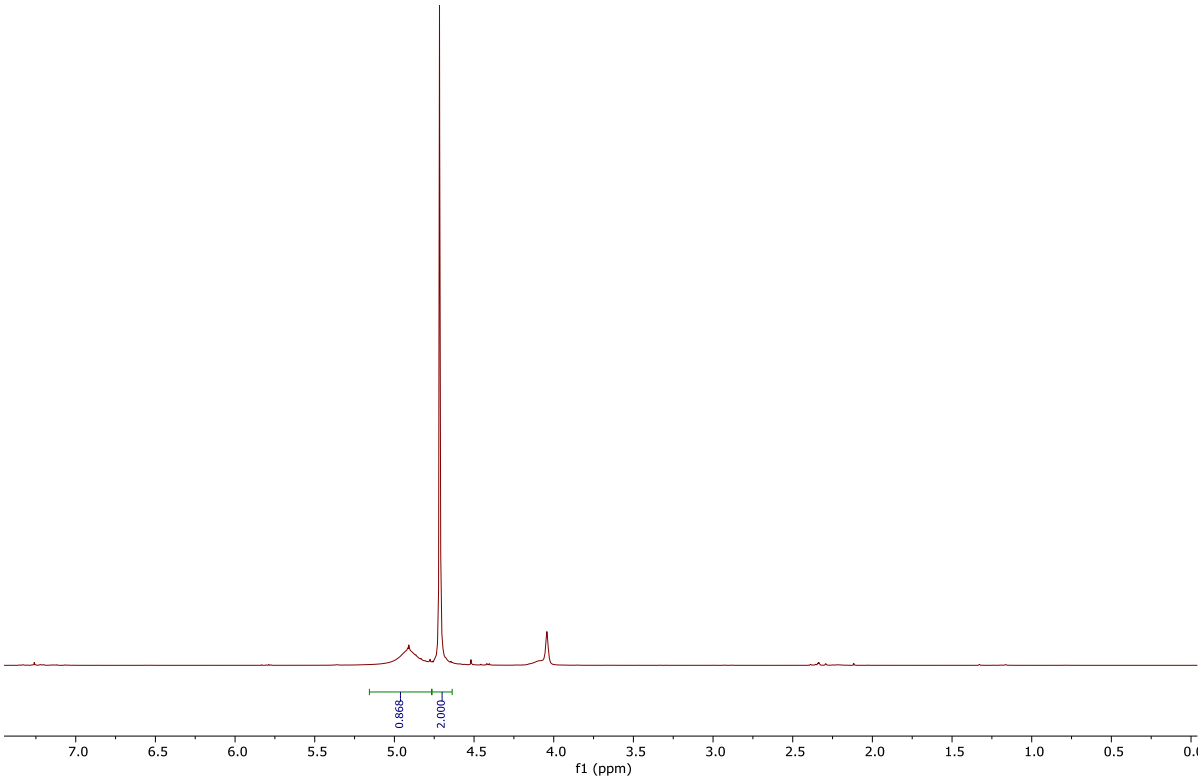
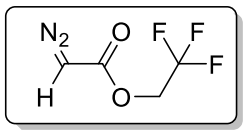


Figure 4.14: *^{1}H NMR spectra of **17a** (400 MHz, Chloroform-*d*).*

4.9. Synthesis of TFEDA **16a**



TFEDA **16a** was synthesized by procedure 4.4.2. 2,2,2-Trifluoroethanol was used as alcohol, triethylamine as base and acetonitrile-*d3* as solvent. Internal standard (1,3,5-Trimethoxybenzene) was added and the yield was calculated from internal standard ^{1}H NMR.

Yield (IS): 60%

TLC: (silica plates; eluent EtOAc:Hexanes 1:1): R_f = 0..

^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.89 (s, 1H), 4.54 (q, *J* = 8.4 Hz, 2H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 165.26, 122.88 (q, *J* = 277.4 Hz), 60.21 (q, *J* = 36.7 Hz), 46.43.

MS (ESI, Methanol): m/z (relative intensity): No molecule peak observed

IR (DCM): 2125 cm^{-1}, 1712 cm^{-1}.

This compound is reported in literature.[149]

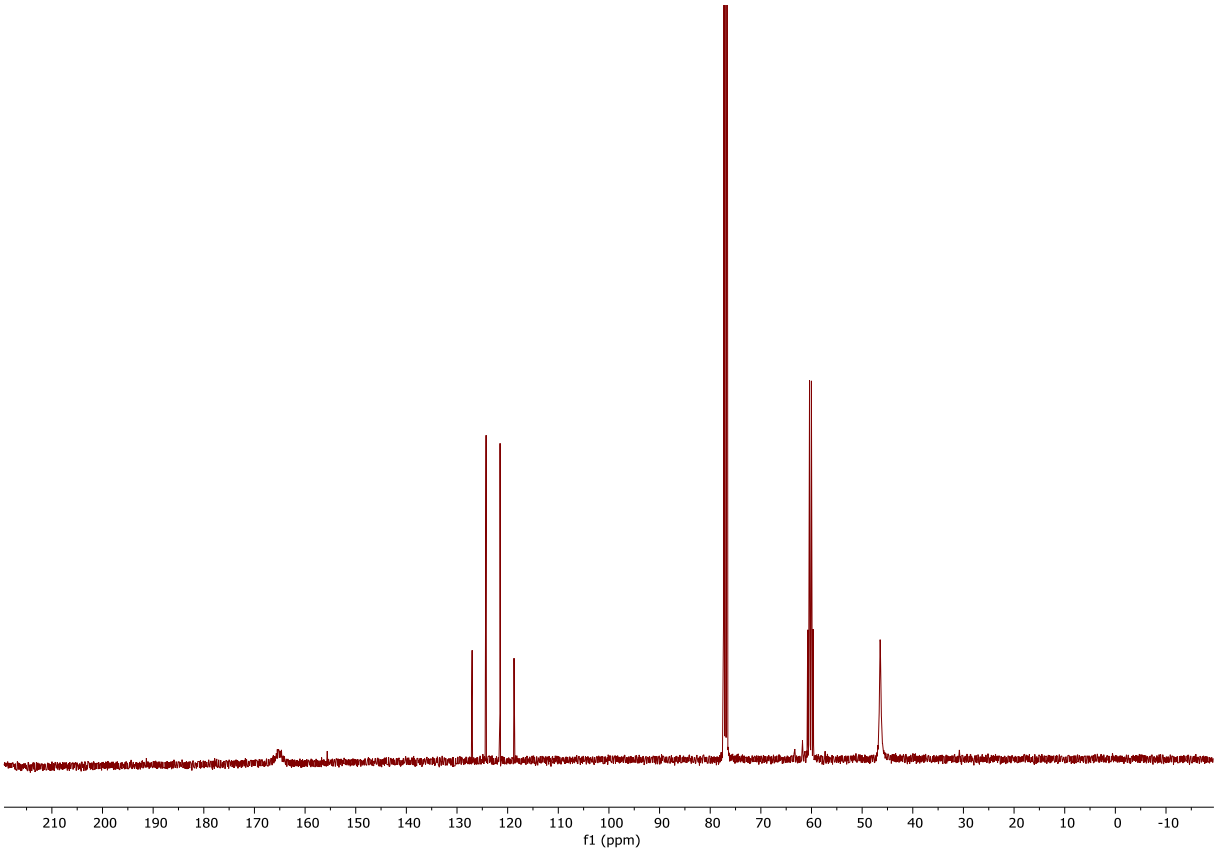


Figure 4.15: *^{13}C NMR spectra of **16a** (101 MHz, Chloroform-*d*).*

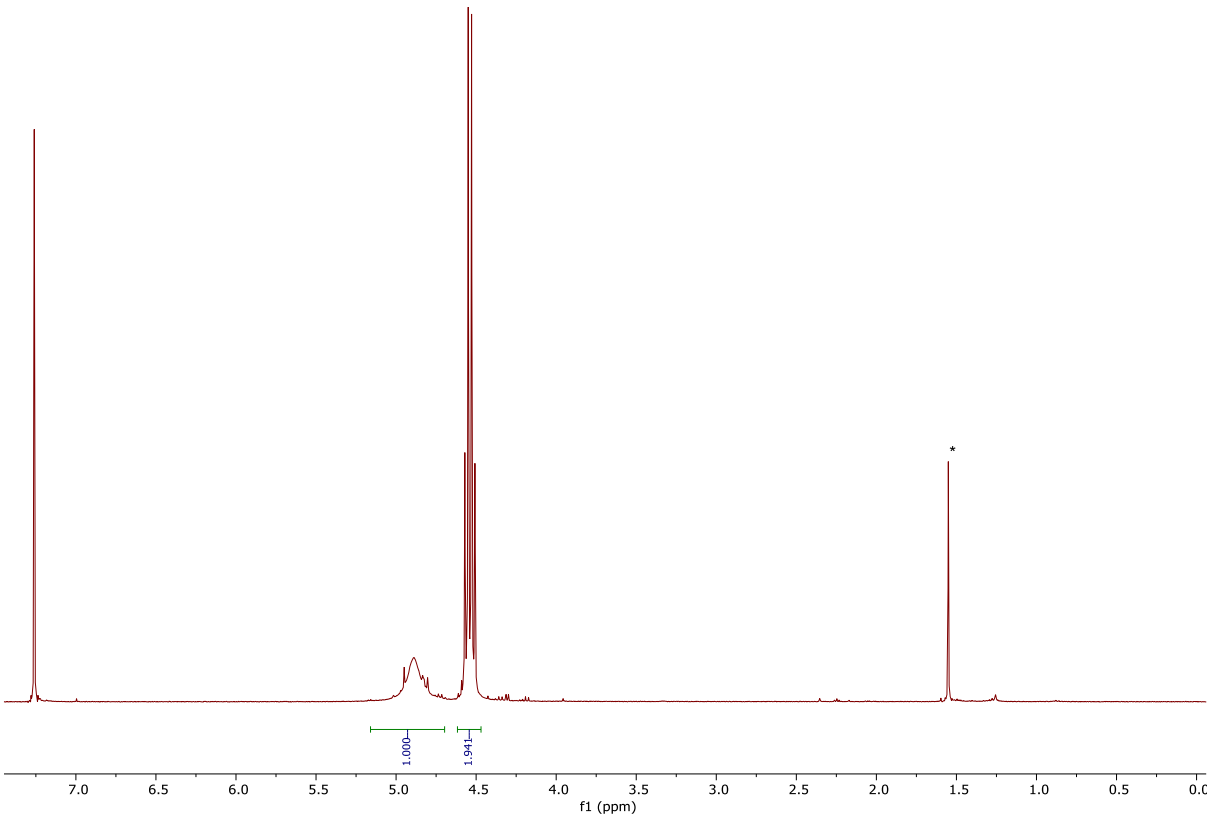
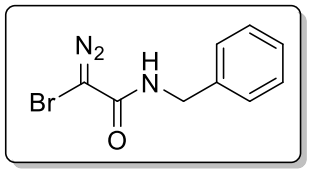


Figure 4.16: *^{1}H NMR spectra of **16a** (400 MHz, Chloroform-*d*). *Water*

4.10. Synthesis of *N*-benzyl-2-bromo-2-diazoacetamide **11b**



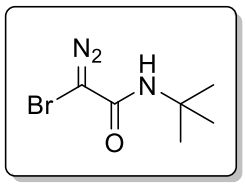
N-benzyl-2-bromo-2-diazoacetamide **11b** was synthesized by procedure 4.4.3. *N*-benzyl-2-diazoacetamide **11a** was used as diazoamide.

IR (DCM): 2083 cm^{-1}

$\mathbf{t_{1/2}}$ (IR, DCM, 30-31 ^{0}C): 4 hours, 8 minutes

This compound is not reported in literature.

4.11. Synthesis of 2-bromo-*N*-(tert-butyl)-2-diazoacetamide **13b**



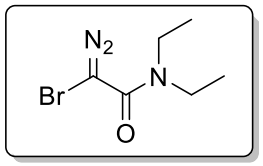
2-Bromo-*N*-(tert-butyl)-2-diazoacetamide **13b** was synthesized by procedure 4.4.3. *N*-(tert-butyl)-2-diazoacetamide **13a** was used as diazoamide.

IR (DCM): 2079 cm^{-1}

$t_{1/2}$ (IR, DCM, 30-31 ^{0}C): 11 minutes

This compound is not reported in literature.

4.12. Synthesis of 2-bromo-2-diazo-*N*,*N*-diethylacetamide **12b**



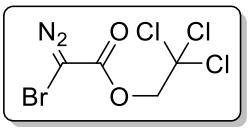
2-Bromo-2-diazo-*N*,*N*-diethylacetamide **12b** was synthesized by procedure 4.4.3. 2-Diazo-*N*,*N*-diethylacetamide **12a** was used as diazoamide.

IR (DCM): 2076 cm^{-1}

$\mathbf{t_{1/2}}$ (IR, DCM, 30-31 ^{0}C): 2.0 (SD = 0.2) minutes

This compound is not reported in literature.

4.13. Synthesis of Br-TCEDA **17b**



Br-TCEDA **17b** was synthesized by procedure 4.4.4. TCEDA **17a** was used as diazoester.

^{1}H NMR (400 MHz, Benzene-d_6) δ 4.52 (s, 2H).

IR (DCM): 2092 cm^{-1}

$t_{1/2}$ (IR, DCM, 28-29 ^{0}C): 4 hours, 39 minutes

This compound is not reported in literature.

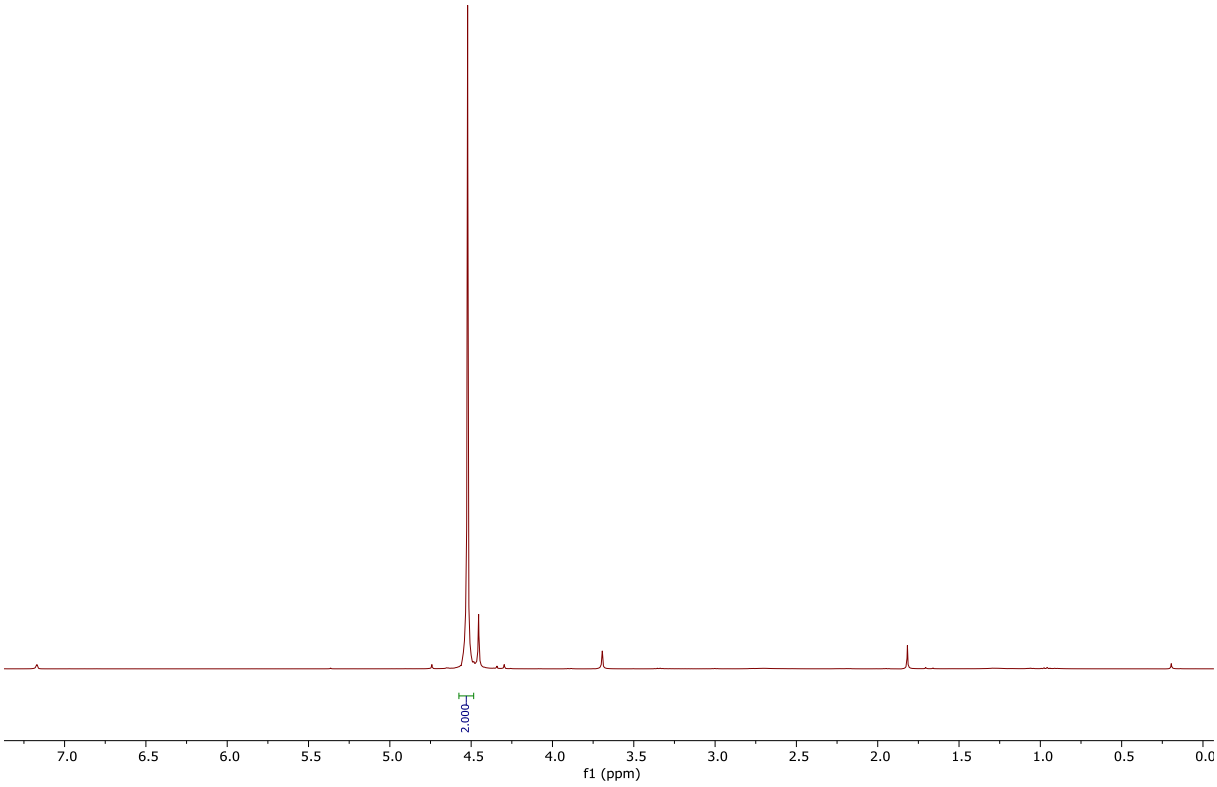
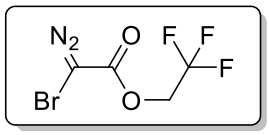


Figure 4.17: *^{1}H NMR spectra of **17b** (400 MHz, Benzene-*d_6*).*

4.14. Synthesis of Br-TFEDA **16b**



Br-TFEDA **16b** was synthesized by procedure 4.4.4. TFEDA **16a** was used as diazoester.

^{1}H NMR (400 MHz, Benzene-d_6) δ 4.44 (s, 2H).

IR (DCM): 2093 cm^{-1}

$t_{1/2}$ (IR, DCM, 30-31 ^{0}C): 3 hours, 34 minutes

This compound is not reported in literature.

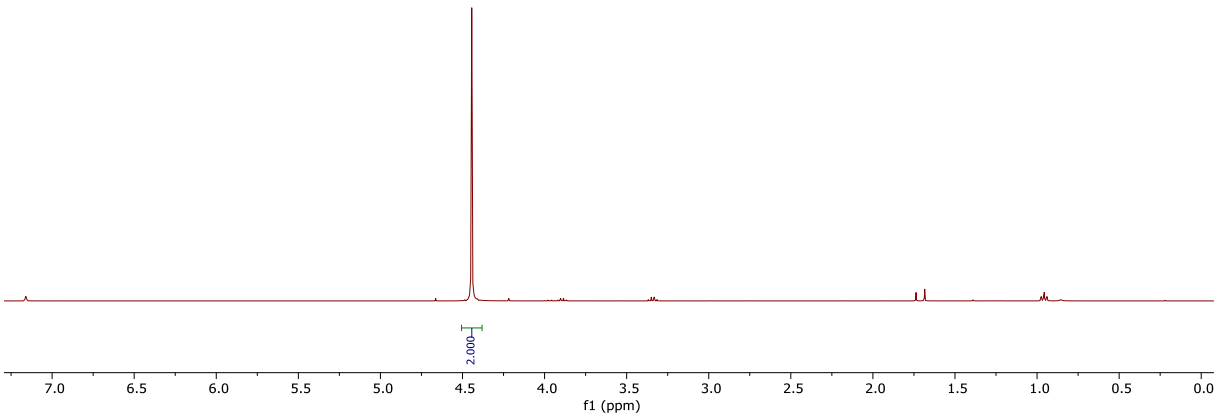
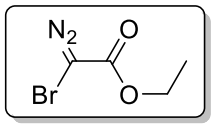


Figure 4.18: *^{1}H NMR spectra of **16b** (400 MHz, Benzene-*d_6*).*

4.15. Synthesis of Br-EDA **1b**



Br-EDA **1b** was synthesized by procedure 4.4.4. EDA was used as diazoester.

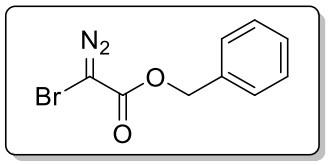
IR (DCM): 2085 cm^{-1}

IR (toluene): 2081 cm^{-1}

$\mathbf{t_{1/2}}$ (IR, DCM, 30-31 ^{0}C): 1 hour, 59 minutes

This compound is reported in literature.[102]

4.16. Synthesis of benzyl 2-bromo-2-diazoacetate **15b**



Benzyl 2-bromo-2-diazoacetate **15b** was synthesized by procedure 4.4.4. Benzyl 2-diazoacetate was used as diazoester and provided by others on the group.

IR (DCM): 2086 cm^{-1}

$\mathbf{t_{1/2}}$ (IR, DCM, 29-30 ^{0}C): 1 hour, 57 minutes

This compound is not reported in literature.

4.17. Reactivity of halo diazoesters in selected test reactions

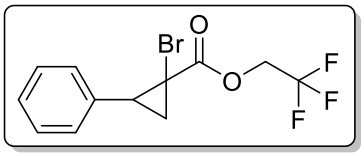
Diazoester (0.5 mmol, 2 eq) was brominated by procedure 4.4.4. The bromo diazoester solution was divided in 2 and added dropwise with an addition funnel at 0 ^{0}C over 1 hour to bottles with substrates. The first bottle contained $Rh_2(esp)_2$ (1 mol%) and styrene **10** (1.0 mmol, 2 eq) in DCM (3 mL), and the second contained $Rh_2(esp)_2$ (1 mol%) and 2,3-dimethyl-1,3-diene **9** (2.5 mmol, 5 eq) in DCM (3 mL). The reaction mixture was stirred for 2 hours at AT, excess reagents were removed under reduced pressure and the crude mixture was analyzed by TLC, MS and NMR.

The crude mixture in the bottle that contained styrene **10** (1.0 mmol, 2 eq) in DCM (3 mL), was purified by flash chromatograph with a silica gel column by the flash master. The eluent gradient started at EtOAc:hexanes 5:95 and ended at EtOAc:hexanes 100:0 after 45 minutes. The first detected compound that eluted was **16c-17c**. The products were not fully purified.

The entries are shown in **Table 2.5**.

Product **16c** and **17c** are not reported in literature.

4.17.1. Spectroscopic data of product **16c**



^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.45 – 7.18 (m, 5H), 4.58 (dq, *J* = 8.3, 3.4 Hz, 2H), 3.02 (dd, *J* = 10.2, 8.7 Hz, 1H), 2.30 (dd, *J* = 10.2, 6.3 Hz, 1H), 1.90 (dd, *J* = 8.7, 6.3 Hz, 1H).

HR-MS (ESI, Acetonitrile): 344.9707 [M + Na^+]: Calculated for $C_{12}H_{10}BrF_3NaO_2$: 344.9706 (Δ 0.4 ppm).

ds (^{1}H NMR): 13:1

TLC (silica plates; eluent EtOAc:Hexanes 1:3): R_f = 0.78.

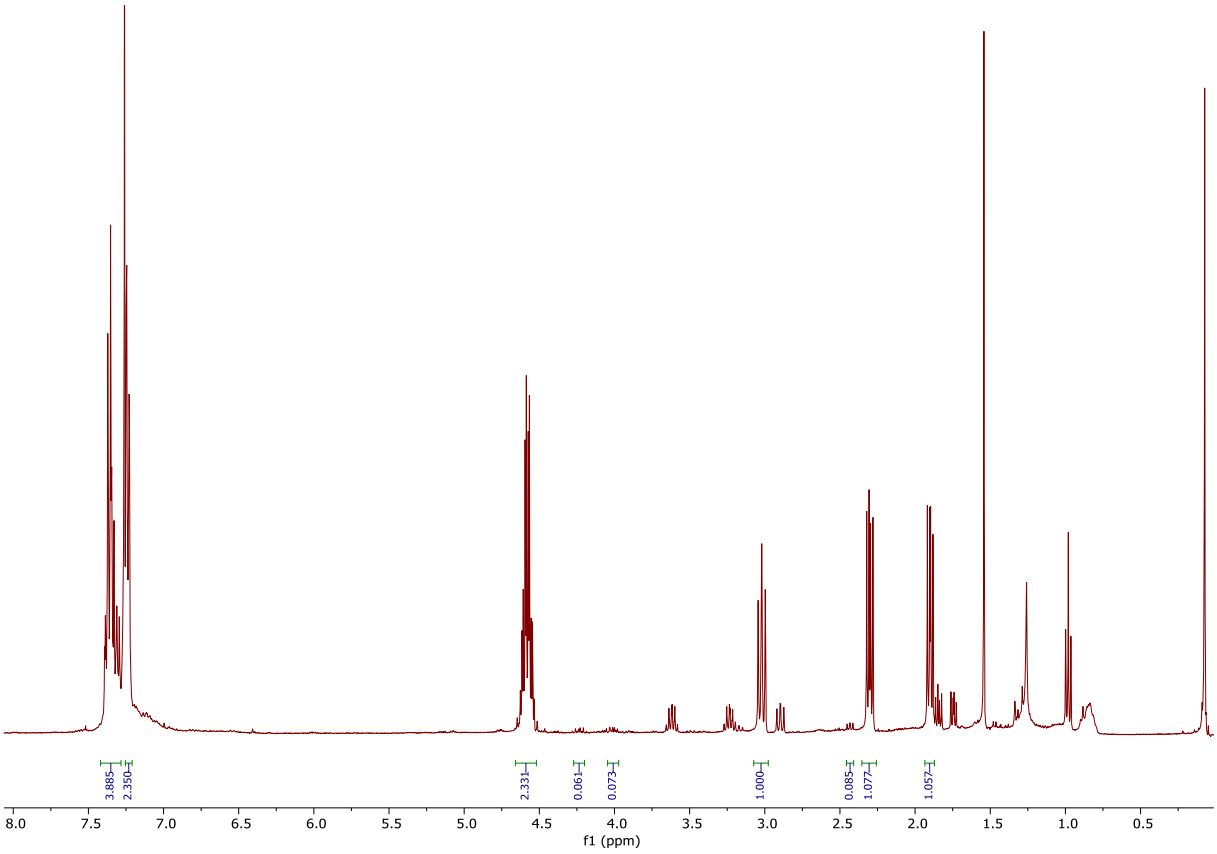
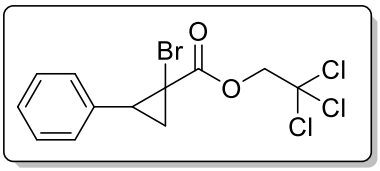


Figure 4.19: *^{1}H NMR spectra of **16c** (400 MHz, Chloroform-*d*).*

4.17.2. Spectroscopic data of product **17c**



^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.47 – 7.27 (m, 4H), 7.24 (s, 1H), 4.84 (q, *J* = 11.8 Hz, 2H), 3.10 (dd, *J* = 9.6, 9.2 Hz, 1H), 2.37 (dd, *J* = 10.2, 6.2 Hz, 1H), 1.92 (dd, *J* = 8.7, 6.2 Hz, 1H).

HR-MS (ESI, Acetonitrile): 392.8822 [M + Na^+]: Calculated for $C_{12}H_{10}BrCl_3NaO_2$: 392.8822 (Δ 0.1 ppm).

ds (^{1}H NMR): 11:1

TLC (silica plates; eluent EtOAc:Hexanes 1:4): R_f =0.59.

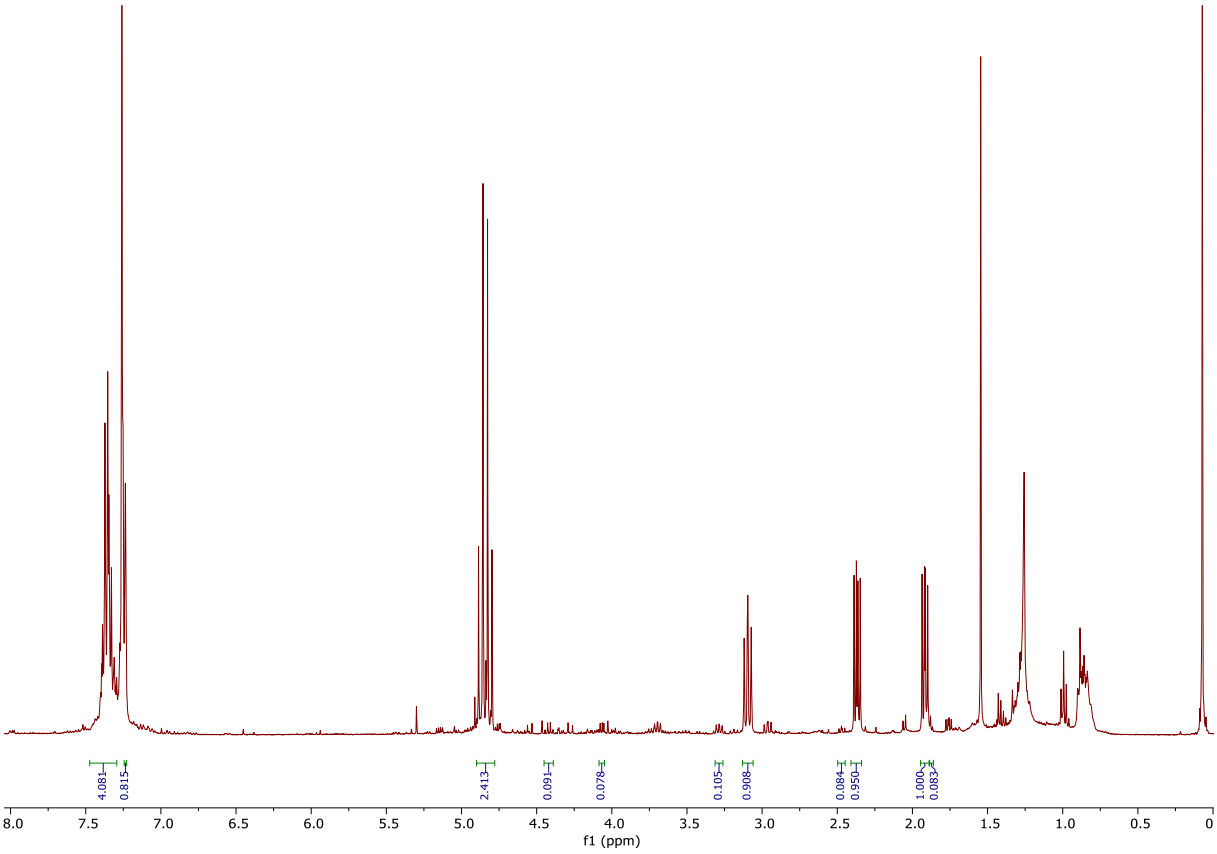


Figure 4.20: *^{1}H NMR spectra of **17c** (400 MHz, Chloroform-*d*).*

4.18. Reactivity of halo diazoamides in selected test reactions

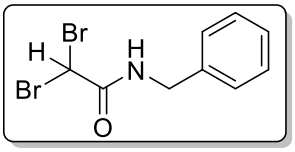
Diazoamide (0.5 mmol, 2 eq) was brominated by procedure 4.4.3. The bromo diazoamide solution was divided in 4 and added dropwise with an addition funnel at -78 ^{0}C over 15 minutes to bottles with substrates. The first bottle contained $Rh_2(esp)_2$ (1 mol%) and styrene **10** (1.0 mmol, 2 eq) in DCM (3 mL), and the second contained $Rh_2(esp)_2$ (1 mol%) and 2,3-dimethyl-1,3-diene **9** (2.5 mmol, 5 eq) in DCM (3 mL). The third bottle contained $Rh_2(esp)_2$ (1 mol%) and 1,4-cyclohexene **8** (1.0 mmol, 2 eq) in DCM (3 mL), and the forth contained $Rh_2(esp)_2$ (1 mol%) in DCM (3 mL). The reaction mixture was stirred for 2 hours at AT, excess reagents were removed under reduced pressure and the crude mixture was analyzed by TLC, MS and NMR.

The crude mixture in the bottle that only contained $Rh_2(esp)_2$ (1 mol%) in DCM (3 mL), was purified by flash chromatograph with a silica gel column by the flash master. The eluent gradient started at EtOAc:hexanes 5:95 and ended at EtOAc:hexanes 100:0 after 45 minutes. The first detected compound that eluted was **11d-13d** and the second compound was **11c-13d**. The products were not fully purified.

The entries are shown in **Table 2.6**.

The products **11c**,[150] **11d**,[151] **12c**,[152] **12d**,[153] **13c**[154] and **13d**[155] are reported in literature.

4.18.1. Spectroscopic data of **11c**



^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.41 – 7.27 (m, 5H), 6.77 (s, 1H), 5.86 (s, 1H), 4.52 (d, *J* = 5.9 Hz, 2H).

HR-MS (ESI, $CDCl_3$): [M + Na^+]: 327.8942 Calculated for $C_9H_9Br_2NNaO$: 327.8943 (Δ 0.3 ppm).

TLC (silica plates; eluent EtOAc:Hexanes 1:4): R_f = 30.

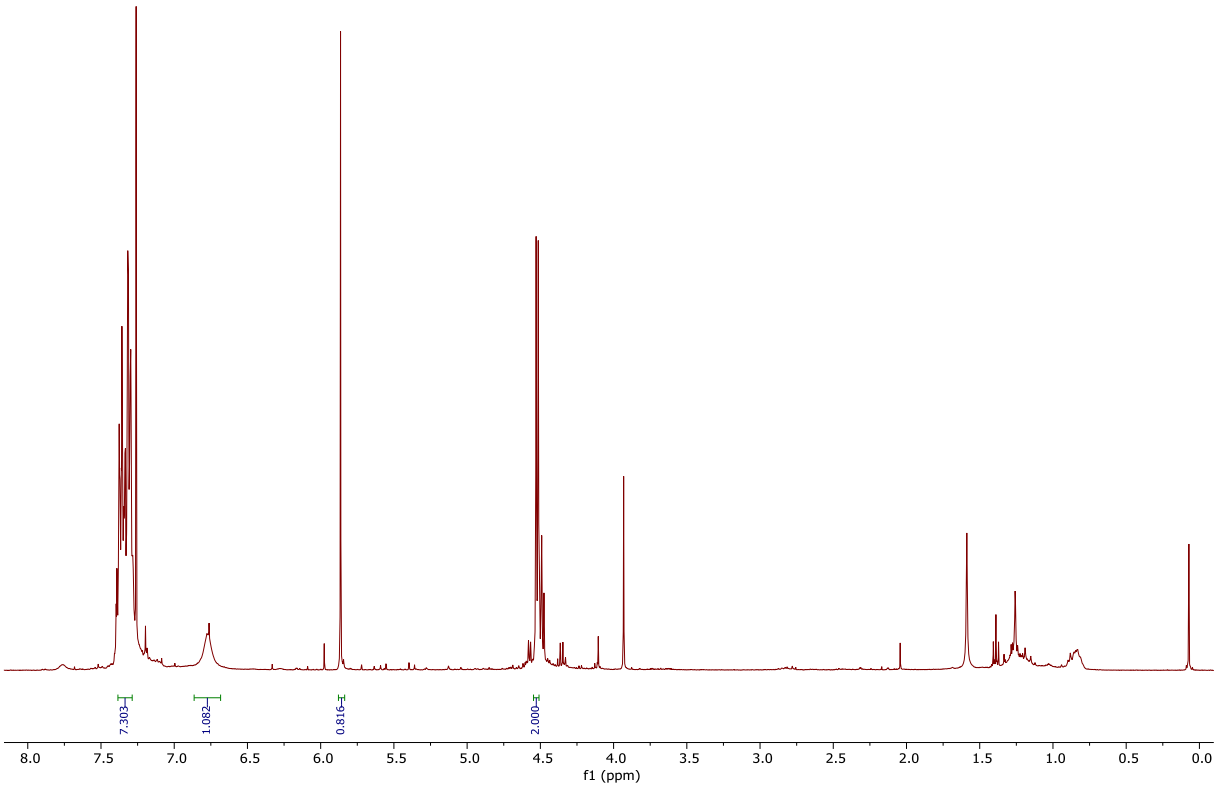
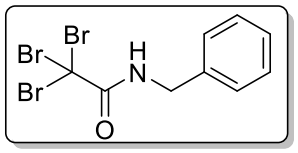


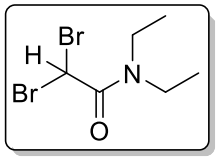
Figure 4.21: *^{1}H NMR spectra of **11c** (400 MHz, Chloroform-*d).

4.18.2. Spectroscopic data of **11d**



TLC (silica plates; eluent EtOAc:Hexanes 1:4): R_f = 44.

4.18.3. Spectroscopic data of **12c**



^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.16 (s, 1H), 3.45 (dq, *J* = 27.1, 7.2 Hz, 4H), 1.29 (t, *J* = 7.2 Hz, 3H), 1.16 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, CDCl3) δ 163.30, 43.23, 41.83, 35.43, 14.30, 12.36.

HR-MS (ESI, $CDCl_3$): [M + Na^+]: 293.9099 Calculated for $C_6H_{11}Br_2NNaO$: 293.9100 (Δ 0.2 ppm).

TLC (silica plates; eluent EtOAc:Hexanes 1:4): R_f = 45.

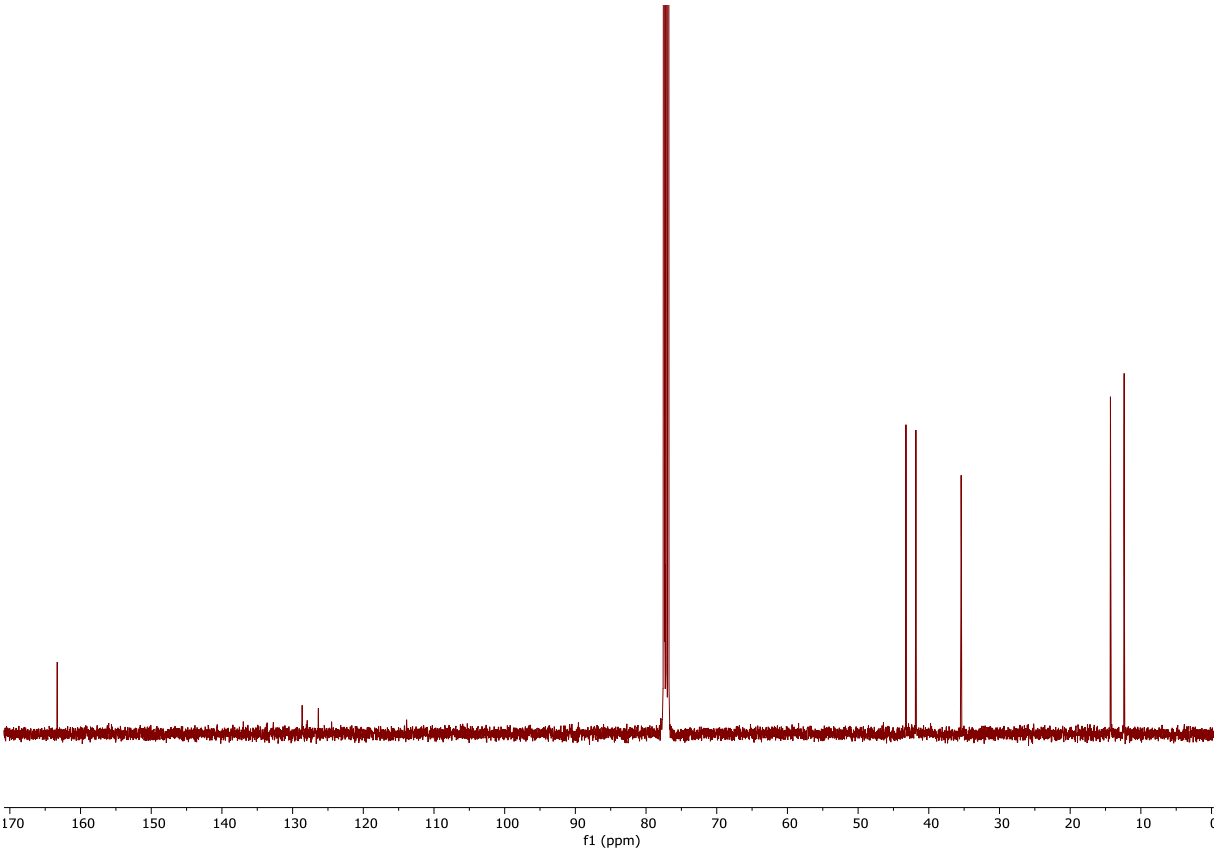


Figure 4.22: *^{13}C NMR spectra of **12c** (101 MHz, Chloroform-d).*

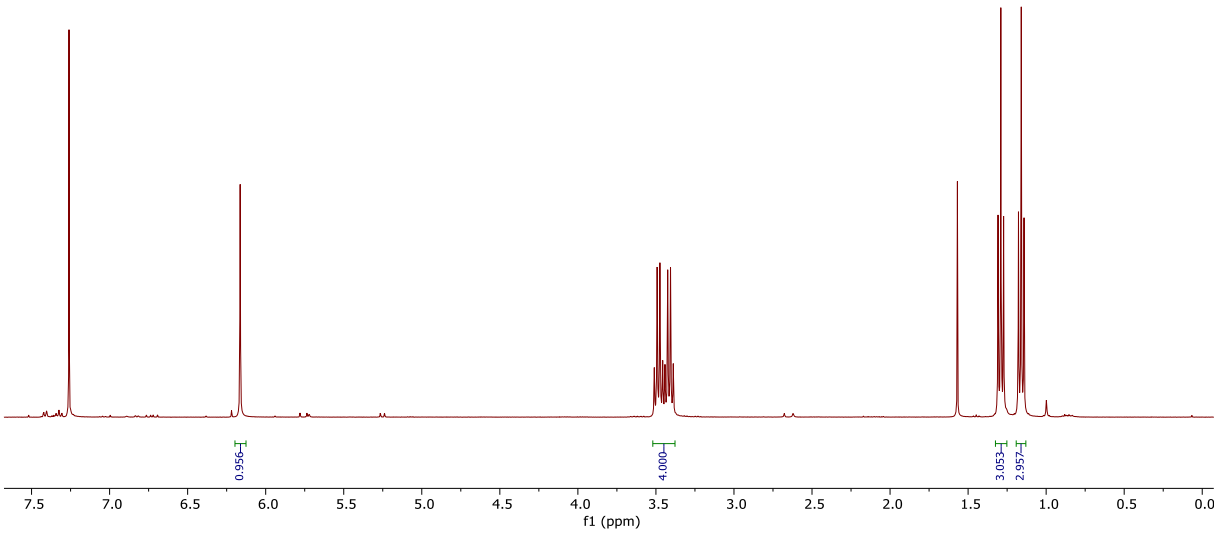
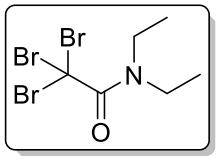


Figure 4.23: *^{1}H NMR spectra of **12c** (400 MHz, Chloroform-*d).

4.18.4. Spectroscopic data of **12d**



^{1}H NMR (400 MHz, Chloroform-*d*) δ 3.81 (s, 2H), 3.47 (s, 2H), 1.31 (s, 3H), 1.21 (s, 3H).

HR-MS (ESI, $CDCl_3$): 371.8203 [M + Na^+]: Calculated for $C_6H_{10}Br_3NNaO$: 371.8205 (Δ 0.4 ppm).

TLC (silica plates; eluent EtOAc:Hexanes 1:4): R_f = 66.

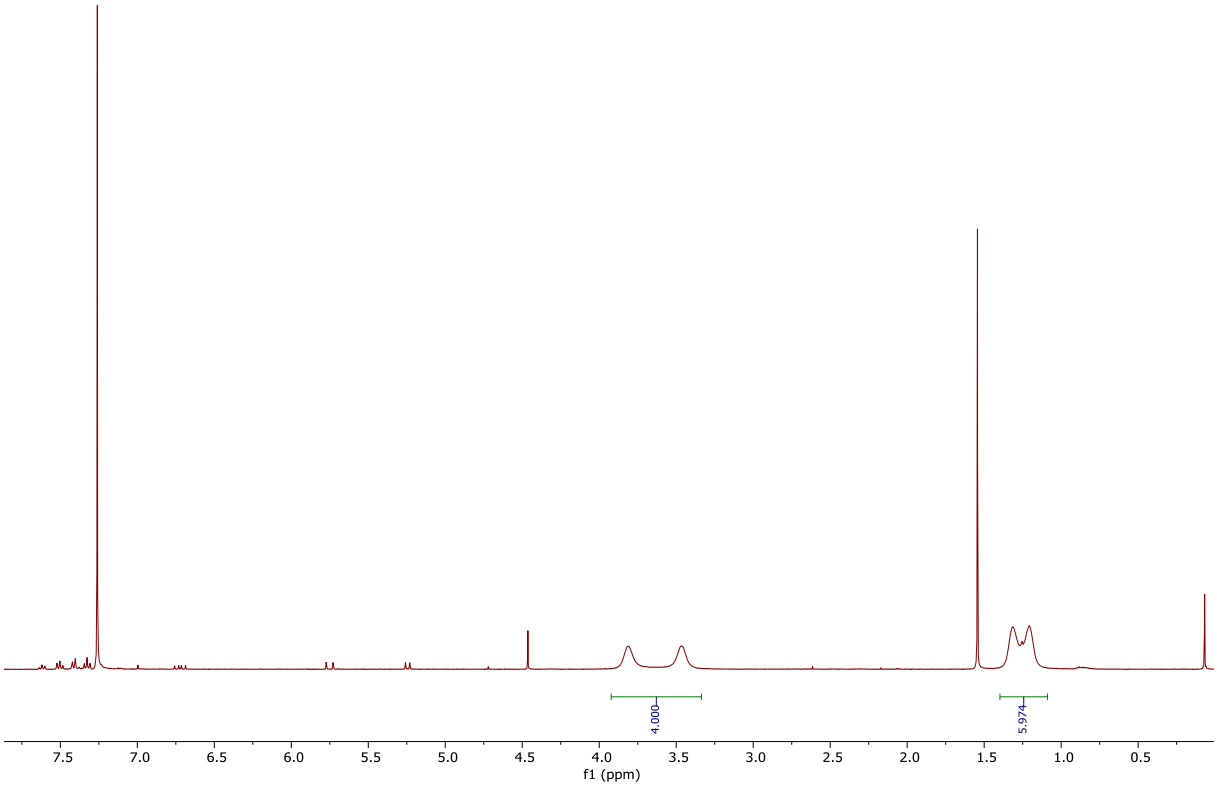
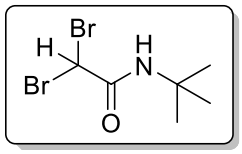


Figure 4.24: *^{1}H NMR spectra of **12d** (400 MHz, Chloroform-*d*).*

4.18.5. Spectroscopic data of **13c**



^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.24 (s, 1H), 5.70 (s, 1H), 1.40 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 163.55, 52.47, 37.92, 28.30.

HR-MS (ESI, $CDCl_3$): 293.9099 [M + Na^+]: Calculated for $C_6H_{11}Br_2NNaO$: 293.9100 (Δ 0.3 ppm).

TLC (silica plates; eluent EtOAc:Hexanes 1:3): R_f = 0.65.

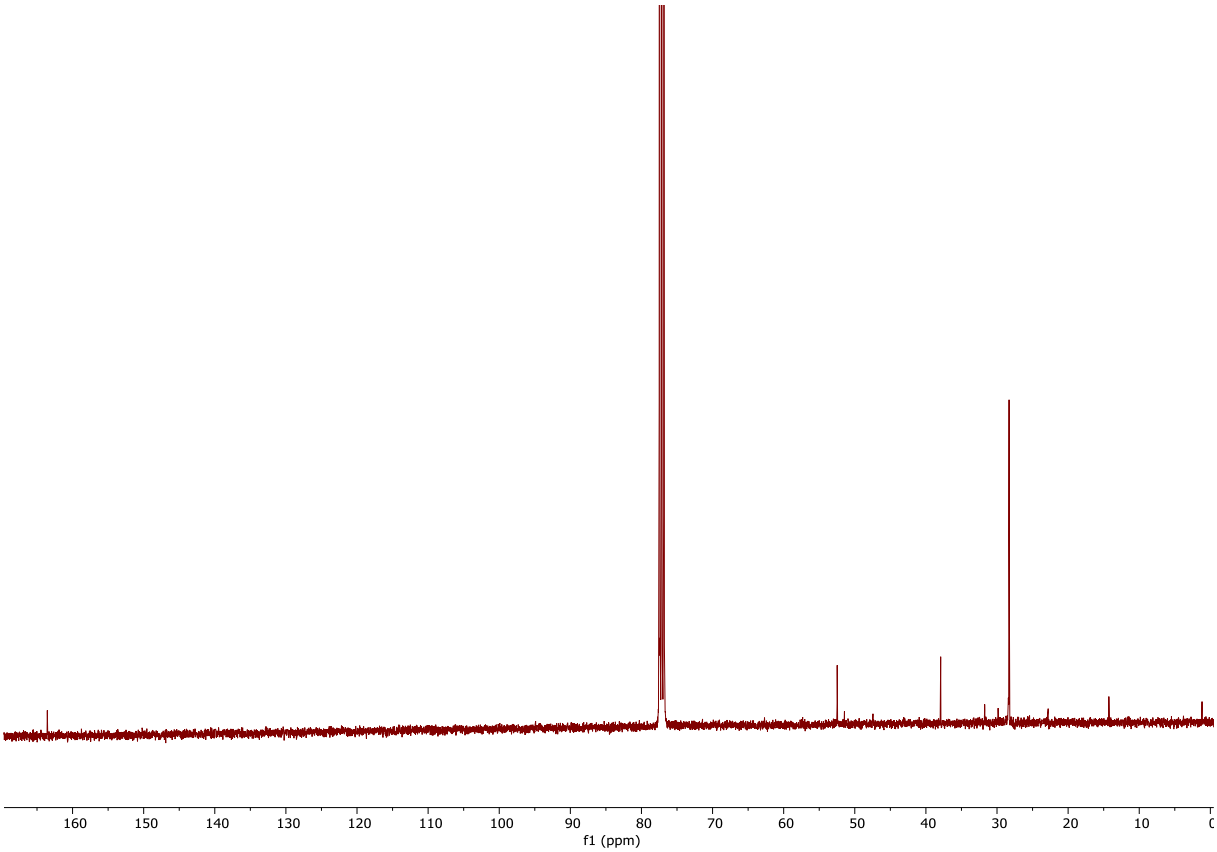


Figure 4.25: *^{13}C NMR spectra of **13c** (101 MHz, Chloroform-d).*

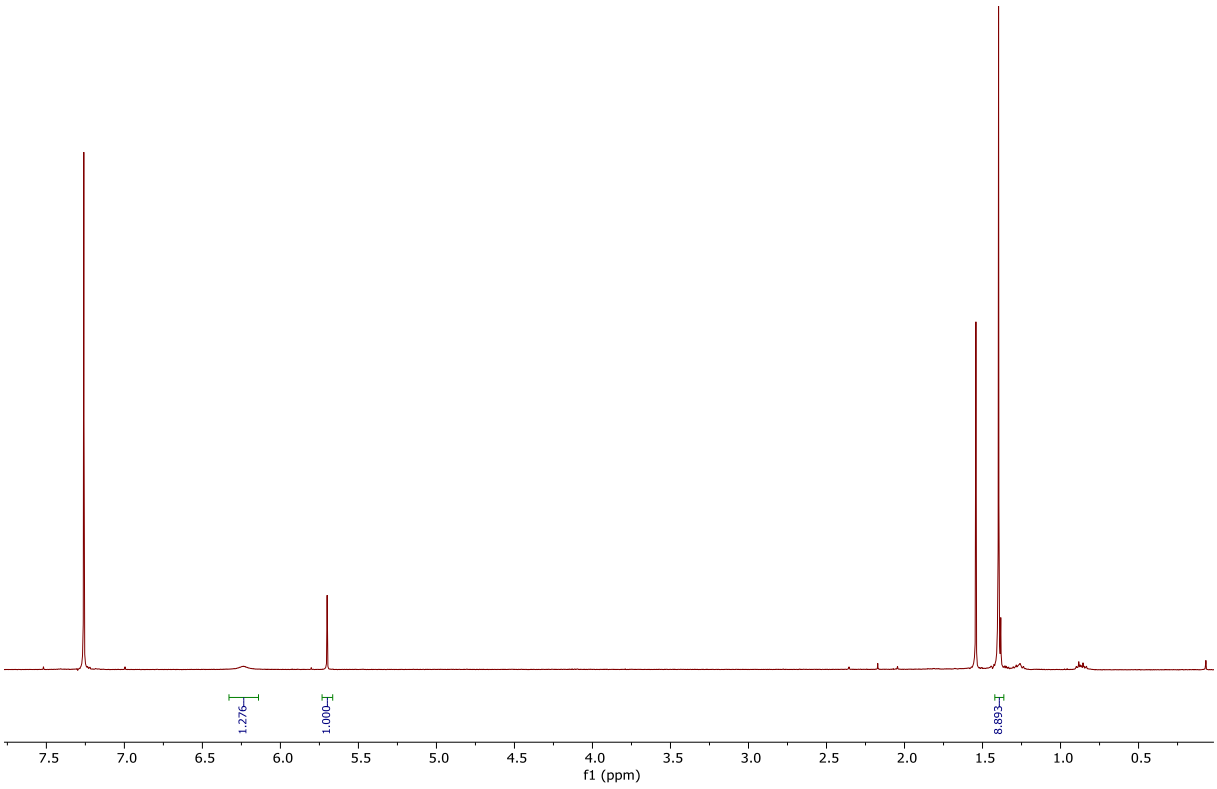


Figure 4.26: *^{1}H NMR spectra of **13c** (400 MHz, Chloroform-*d).

4.19. Half-life measurements of halo diazoesters

The diazoesters was brominated with procedure 4.4.4. and concentrated to about 0.0025 M under reduced pressure at 0 ^{0}C. The NaCl plated liquid IR-spectrocopy cell was filled with Br-diazoester solution. When using another solvent in the half-lives measurement than DCM, the designated solvent (toluene) was added under the concentration process.

The sample was placed in an IR-instrument which had already recorded a background spectra of the designated solvent (DCM or toluene). Spectra were recorded at frequent intervals, and the time between each spectra was noted. Each measurement point consisted of an average of 5 scans.

The transmittance of the diazo frequency from each spectra was noted. The change of the transmittance with time was used to calculate the relative change of concentration and plot a graph of the natural logarithm of the concentration vs time. From the linear regression curve of the graph, the rate constant k was found as the negative slope, and half-lives were calculated by the formula given in appendix.

The entries are found in **Table 2.7**.

4.20. Half-life measurements of halo diazoamides

The diazoamides was brominated with procedure 4.4.3. The NaCl plated liquid IR-spectroscopy cell was filled with Br-diazoamide solution.

The sample was placed in an IR-instrument which had already recorded a background spectra of the designated solvent (DCM). Spectra were recorded at frequent intervals, and the time between each spectra was noted. Each measurement point consisted of an average of 5 scans.

The transmittance of the diazo frequency from each spectra was noted. The change of the transmittance with time was used to calculate the relative change of concentration and plot a graph of the natural logarithm of the concentration vs time. From the linear regression curve of the graph, the rate constant k was found as the negative slope, and half-lives were calculated by the formula given in appendix.

The entries are found in **Table 2.8**.

4.21. DFT calculations

The program Gaussian 09W was used for the calculations and GaussView 6.0.16. was used for construction of molecules. The calculations were performed with b3lyp as method, def2tzvp as basis set, scrf=(smd,solvent=dichloromethane) as solvent and solvent model, and iop(3/124=40) as internal options.

5. Appendix

5.1. Calculations

5.1.1. Example of calculating yield: 2-(((2, 5-dioxopyrrolidine-1-yl)oxy)methyl)-1, 3-dimethyl-3, 4, 5, 6-tetrahydropyrimidin-1-ium **4**

Amount of starting material (DMPU) = 44.88 mmol

1 $mmol\ substrate \leftrightarrow 1\ mmol\ product$

Theoretical amount of product **3** = 44.88 mmol

Experimental amount of product **3** = $\frac{6.1979\ g}{0.240282\ \frac{g}{mmol}} = 25.8\ mmol$

Yield = $\frac{25.8\ mmol}{40.88\ mmol} \times 100\ \% = 63\ \%$

5.1.2. Example of calculating yield with internal standard: BB **2**

From ^{1}H NMR, the ratio between internal standard and product **2** was determined from the integrals for the 3 hydrogens in the aromatic area for the internal standard and the 4 hydrogens in the succinimide group in **2**.

Internal standard:	$3.000/_{3H} = 1.000$
Product **2**:	$6.731/_{4H} = 1.683$
Ratio internal standard : product	$1.000 : 1.683$
Amount of internal standard added:	$0.1469\ mmol$
Experimental amount of product **2**:	$0.1469\ mmol \times 1.683 = 0.247\ mmol$
Theoretical amount of product **2**:	$0.501\ mmol$
Yield:	$\frac{0.247\ mmol}{0.501\ mmol} \times 100\ \% = \underline{49\ \%}$

5.1.3. Example of calculating diasteromeric ratio: **16c**

From ^{1}H NMR, the ratio between cis and trans diastereomers was determined from the integrals of one cis hydrogen peak and the corresponding trans hydrogen peak.

One isomer:	$^{1.077}/_{1H} = 1.077$
Other isomer:	$^{0.085}/_{1H} = 0.085$
Ratio isomer : isomer	$1 : 13$

5.1.4. Relationship between transmittance and concentrations from Beer-Lamberts Law

$$A = \varepsilon l c$$

$$\frac{A_1}{\varepsilon l c_1} = \frac{A_2}{\varepsilon l c_2}$$

$$c_2 = \frac{A_2}{A_1} \times c_1$$

$$A = -\log(T)$$

$$c_2 = \frac{-\log(T_2)}{-\log(T_1)} \times c_1$$

A = absorbance, ε = molar absorptivity, l = optical path length in cm, c = concentration, T = trancmittance

5.1.5. Concentration of a first order reaction solved for half-life

Concentration of a first order reaction: $[c] = [c]_0 e^{-kt}$

$$ln[c] = ln[c]_0 - kt$$

Half of concentration at t_0: $[c] = \frac{[c]_0}{2}$

Solve with respect to time: $ln\frac{[c]_0}{2} = ln[c]_0 - kt$

$$ln[c]_0 - ln2 = ln[c]_0 - kt$$

$$t_{1/2} = \frac{ln2}{k}$$

[c] = current concentration, $[c]_0$ = concentration at t_0, e = Euler's number , k = rate constant, t = time

The rate constant k was determent from plot of the natural logarithm of the concentration versus time, where k = -slope of the linear regression curve.

5.2. Plots

5.2.1. *N*-benzyl-2-bromo-2-diazoacetamide **11b**

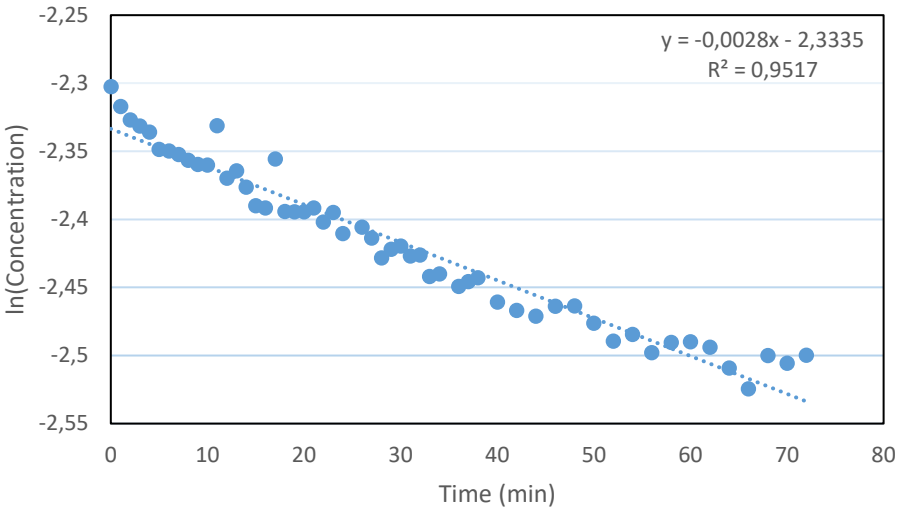


Figure 5.1: *Plot of the natural logarithm of concentration versus time of N-benzyl-2-bromo-2-diazoacetamide* ***11b****.*

5.2.2. 2-bromo-*N*-(tert-butyl)-2-diazoacetamide **13b**

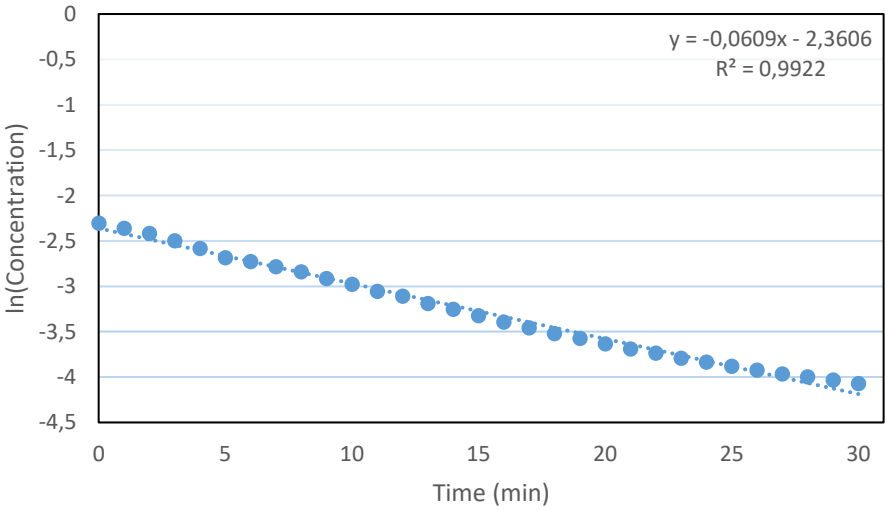


Figure 5.2: *Plot of the natural logarithm of concentration versus time of 2-bromo-N-(tert-butyl)-2-diazoacetamide* ***13b****.*

5.2.3. 2-bromo-2-diazo-*N*,*N*-diethylacetamide **12b**

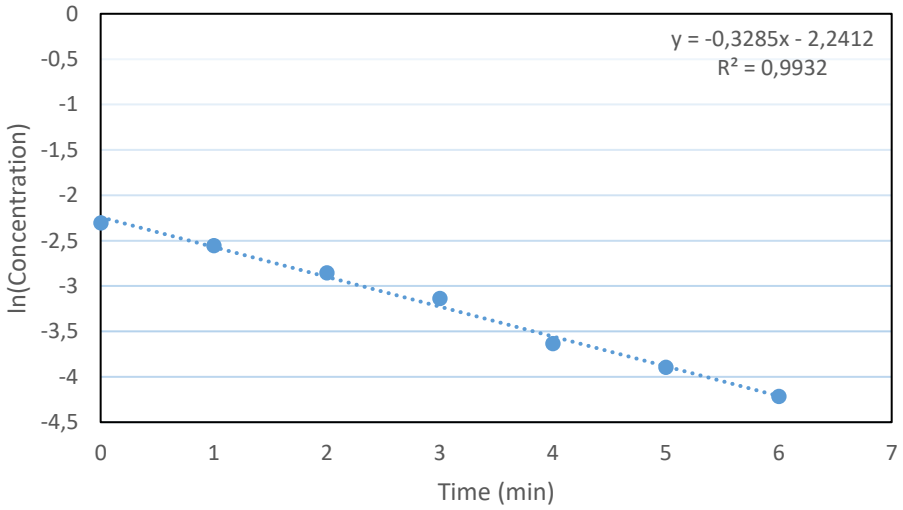


Figure 5.3: *Plot of the natural logarithm of concentration versus time of measurement 1 of 2-bromo-2-diazo-N,N-diethylacetamide* ***12b****.*

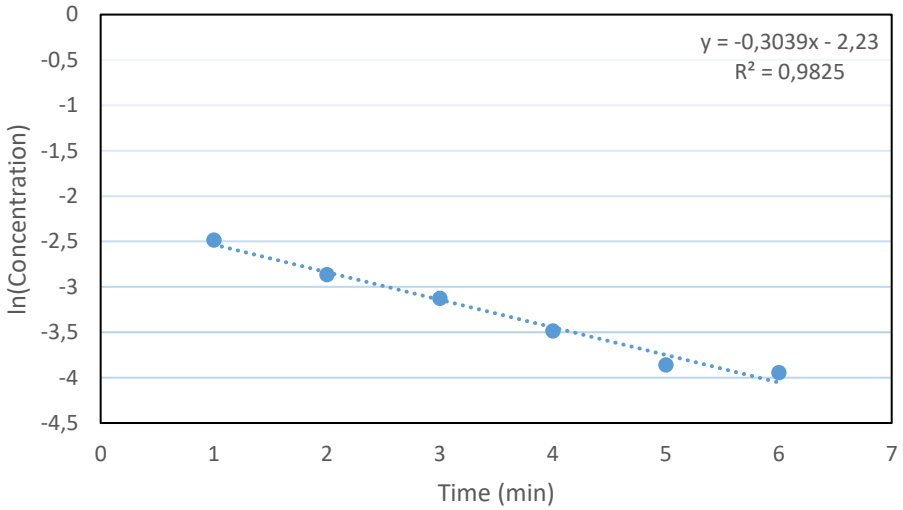


Figure 5.4: *Plot of the natural logarithm of concentration versus time of measurement 2 of 2-bromo-2-diazo-N,N-diethylacetamide* ***12b****.*

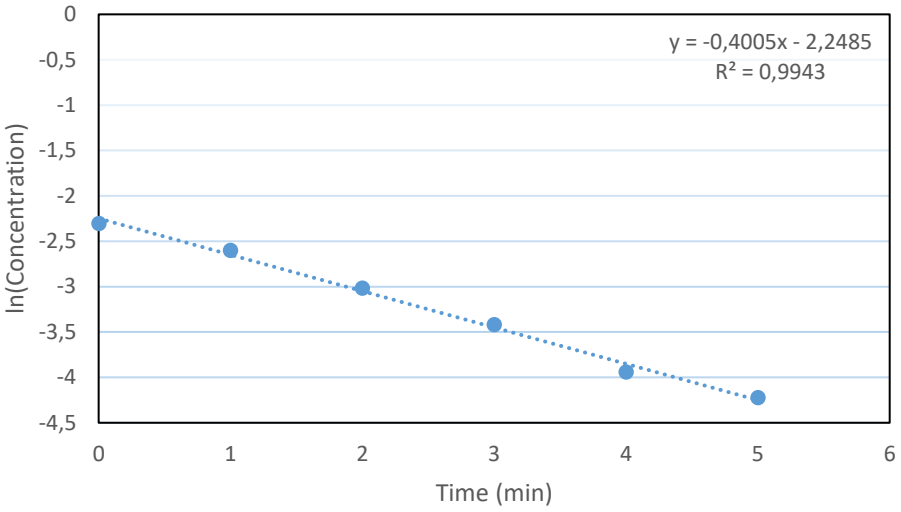


Figure 5.5: *Plot of the natural logarithm of concentration versus time of measurement 3 of 2-bromo-2-diazo-N,N-diethylacetamide* ***12b****.*

5.2.4. Br-TCEDA **17b**

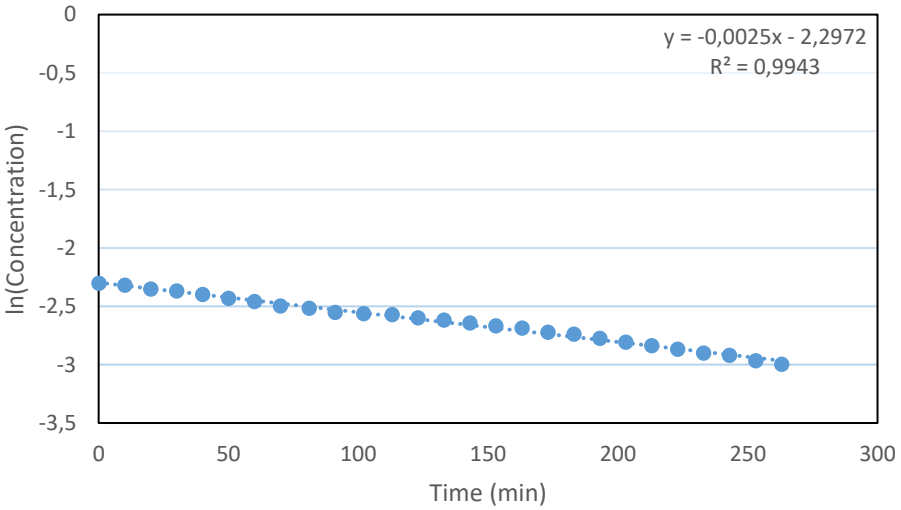


Figure 5.6: *Plot of the natural logarithm of concentration versus time of Br-TCEDA* ***17b****.*

5.2.5. Br-TFEDA **16b**

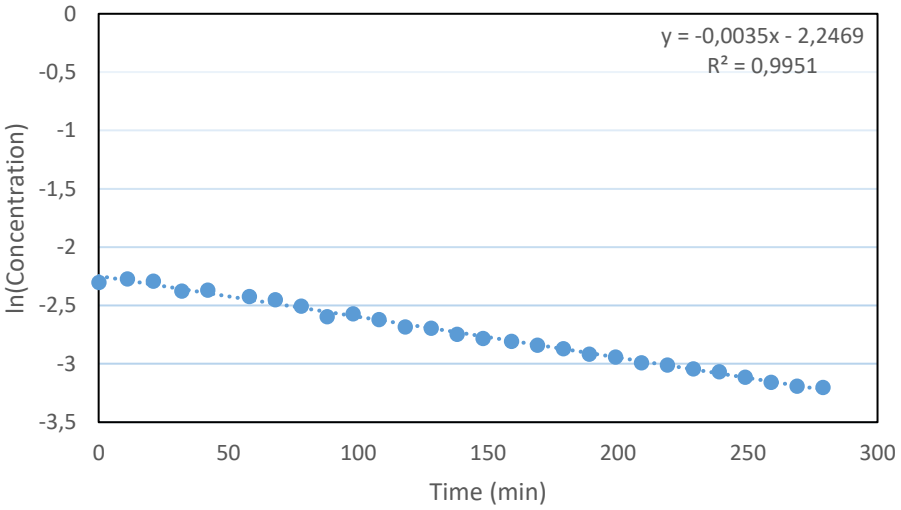


Figure 5.7: *Plot of the natural logarithm of concentration versus time of Br-TFEDA **16b**.*

5.2.6. EDA **1a**

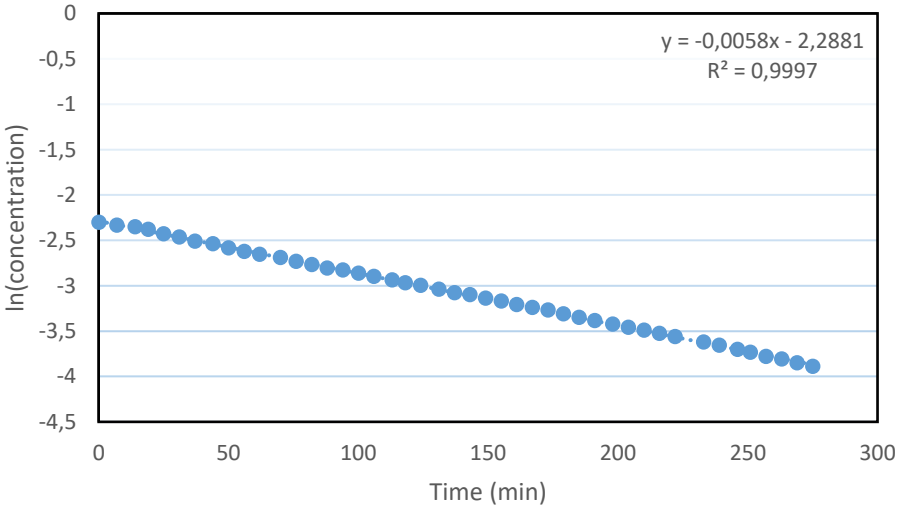


Figure 5.8: *Plot of the natural logarithm of concentration versus time of EDA **1a** in DCM.*

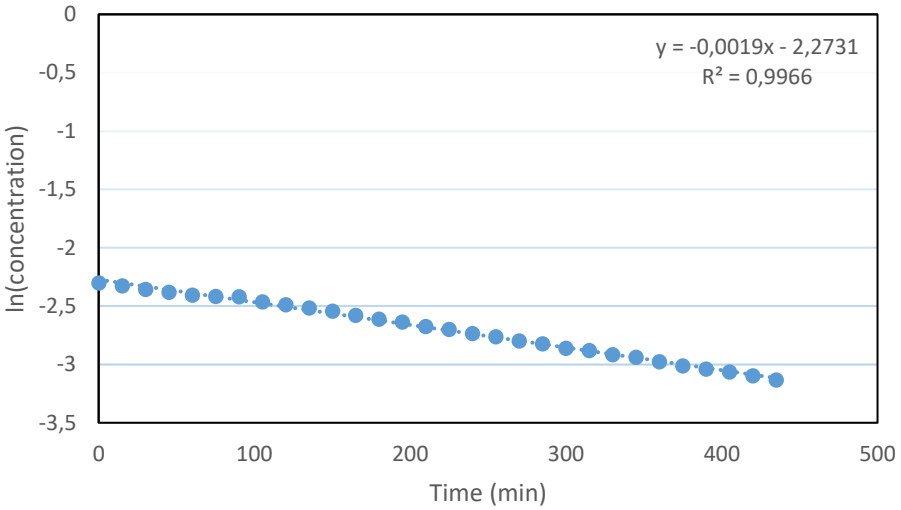


Figure 5.9: *Plot of the natural logarithm of concentration versus time of EDA **1a** in toluene.*

5.2.7. Benzyl 2-bromo-2-diazoacetate **15b**

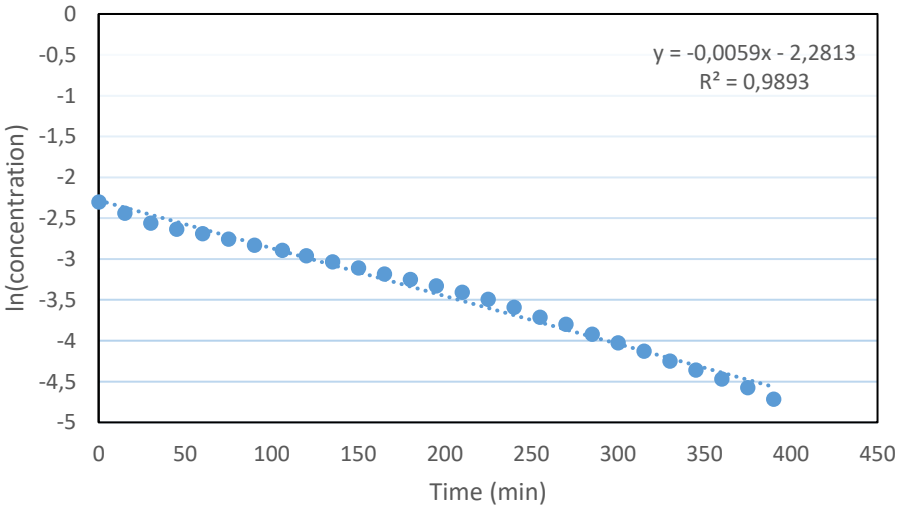


Figure 5.10: *Plot of the natural logarithm of concentration versus time of benyl 2-bromo-2-diazoacetate **15b**.*

5.3. Second order perturbation theory analysis of fock matrix in NBO basis

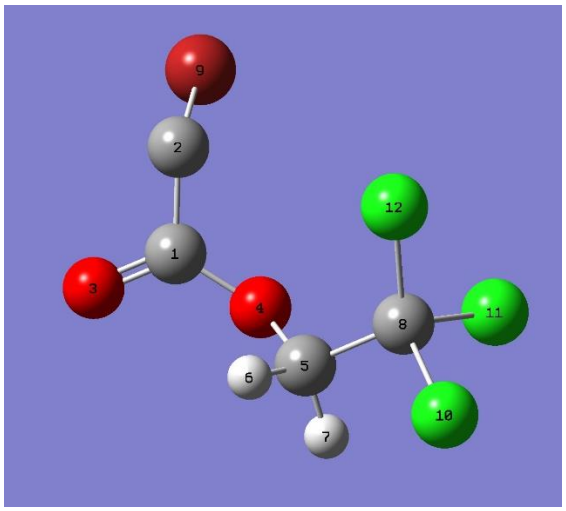


Figure 5.11: *Atom numbering for Table 5.1.*

Table 5.1: *Second order perturbation theory analysis of fock matrix in NBO basis of structure Figure 5.11.*

Threshold for printing: 0.50 kcal/mol

Donor NBO (i)	Acceptor NBO (j)	E(2) kcal/mol	E(j)-E(i) a.u.	F(i,j) a.u.
1. BD (1) C 1 - C 2	/ 66. RY*(2) C 1	1.21	2.05	0.047
1. BD (1) C 1 - C 2	/ 70. RY*(6) C 1	0.75	3.16	0.046
1. BD (1) C 1 - C 2	/ 91. RY*(1) C 2	1.89	1.29	0.046
1. BD (1) C 1 - C 2	/ 94. RY*(4) C 2	0.52	1.37	0.025
1. BD (1) C 1 - C 2	/ 95. RY*(5) C 2	0.65	1.73	0.031
1. BD (1) C 1 - C 2	/ 97. RY*(7) C 2	1.57	1.73	0.049
1. BD (1) C 1 - C 2	/106. RY*(16) C 2	2.19	3.61	0.083
1. BD (1) C 1 - C 2	/107. RY*(17) C 2	1.06	21.43	0.141
1. BD (1) C 1 - C 2	/112. RY*(22) C 2	1.48	3.69	0.069
1. BD (1) C 1 - C 2	/113. RY*(23) C 2	0.90	3.88	0.055
1. BD (1) C 1 - C 2	/115. RY*(25) C 2	0.76	3.65	0.049
1. BD (1) C 1 - C 2	/116. RY*(1) O 3	1.07	1.39	0.036
1. BD (1) C 1 - C 2	/142. RY*(1) O 4	1.56	1.37	0.043
1. BD (1) C 1 - C 2	/232. RY*(3)Br 9	1.54	1.35	0.043
1. BD (1) C 1 - C 2	/238. RY*(9)Br 9	0.61	1.46	0.028

1. BD (1) C 1 - C 2	/344. BD*(1) C 1 - C 2	4.57	1.02	0.063
1. BD (1) C 1 - C 2	/347. BD*(1) C 1 - O 4	1.02	0.90	0.028
1. BD (1) C 1 - C 2	/348. BD*(1) C 2 - O 3	177.87	1.02	0.387
1. BD (1) C 1 - C 2	/349. BD*(1) C 2 -Br 9	63.22	0.78	0.203
1. BD (1) C 1 - C 2	/351. BD*(1) O 4 - C 5	1.75	0.79	0.034
2. BD (1) C 1 - O 3	/ 65. RY*(1) C 1	1.38	2.25	0.050
2. BD (1) C 1 - O 3	/344. BD*(1) C 1 - C 2	0.53	1.54	0.026
2. BD (1) C 1 - O 3	/347. BD*(1) C 1 - O 4	1.22	1.42	0.038
2. BD (1) C 1 - O 3	/348. BD*(1) C 2 - O 3	0.70	1.55	0.031
2. BD (1) C 1 - O 3	/349. BD*(1) C 2 -Br 9	1.23	1.30	0.036
2. BD (1) C 1 - O 3	/351. BD*(1) O 4 - C 5	0.92	1.31	0.031
3. BD (2) C 1 - O 3	/346. BD*(2) C 1 - O 3	0.61	0.39	0.015
3. BD (2) C 1 - O 3	/350. BD*(2) C 2 -Br 9	2.78	0.51	0.033
3. BD (2) C 1 - O 3	/351. BD*(1) O 4 - C 5	1.47	0.62	0.027
4. BD (1) C 1 - O 4	/168. RY*(1) C 5	1.94	1.88	0.054
4. BD (1) C 1 - O 4	/348. BD*(1) C 2 - O 3	1.44	1.37	0.042
4. BD (1) C 1 - O 4	/354. BD*(1) C 5 - C 8	0.51	1.15	0.022
5. BD (1) C 2 - O 3	/ 66. RY*(2) C 1	1.84	1.74	0.053
5. BD (1) C 2 - O 3	/ 67. RY*(3) C 1	0.54	1.20	0.024
5. BD (1) C 2 - O 3	/ 68. RY*(4) C 1	1.53	2.89	0.062
5. BD (1) C 2 - O 3	/ 81. RY*(17) C 1	0.51	2.81	0.035
5. BD (1) C 2 - O 3	/ 94. RY*(4) C 2	0.53	1.06	0.022
5. BD (1) C 2 - O 3	/ 97. RY*(7) C 2	0.71	1.42	0.030
5. BD (1) C 2 - O 3	/106. RY*(16) C 2	0.74	3.30	0.046
5. BD (1) C 2 - O 3	/232. RY*(3)Br 9	0.57	1.04	0.023
5. BD (1) C 2 - O 3	/344. BD*(1) C 1 - C 2	21.83	0.71	0.115
5. BD (1) C 2 - O 3	/345. BD*(1) C 1 - O 3	3.11	0.83	0.047
5. BD (1) C 2 - O 3	/347. BD*(1) C 1 - O 4	42.11	0.59	0.143
5. BD (1) C 2 - O 3	/348. BD*(1) C 2 - O 3	22.37	0.71	0.115
5. BD (1) C 2 - O 3	/349. BD*(1) C 2 -Br 9	23.71	0.47	0.096
6. BD (1) C 2 -Br 9	/ 91. RY*(1) C 2	1.19	1.02	0.032
6. BD (1) C 2 -Br 9	/ 95. RY*(5) C 2	0.73	1.46	0.030
6. BD (1) C 2 -Br 9	/ 97. RY*(7) C 2	0.76	1.46	0.030
6. BD (1) C 2 -Br 9	/106. RY*(16) C 2	0.97	3.34	0.052
6. BD (1) C 2 -Br 9	/107. RY*(17) C 2	0.52	21.16	0.095
6. BD (1) C 2 -Br 9	/112. RY*(22) C 2	0.71	3.42	0.045
6. BD (1) C 2 -Br 9	/232. RY*(3)Br 9	0.86	1.08	0.028
6. BD (1) C 2 -Br 9	/344. BD*(1) C 1 - C 2	5.05	0.75	0.055

6. BD (1) C 2 -Br 9	/348. BD*(1) C 2 - O 3	48.48	0.76	0.178
6. BD (1) C 2 -Br 9	/349. BD*(1) C 2 -Br 9	22.20	0.51	0.095
7. BD (2) C 2 -Br 9	/ 67. RY*(3) C 1	1.79	1.59	0.048
7. BD (2) C 2 -Br 9	/ 91. RY*(1) C 2	0.79	1.36	0.030
7. BD (2) C 2 -Br 9	/346. BD*(2) C 1 - O 3	5.92	0.63	0.057
7. BD (2) C 2 -Br 9	/347. BD*(1) C 1 - O 4	0.73	0.97	0.024
7. BD (2) C 2 -Br 9	/348. BD*(1) C 2 - O 3	5.46	1.10	0.073
8. BD (1) O 4 - C 5	/ 67. RY*(3) C 1	1.01	1.76	0.038
8. BD (1) O 4 - C 5	/344. BD*(1) C 1 - C 2	0.84	1.26	0.029
8. BD (1) O 4 - C 5	/346. BD*(2) C 1 - O 3	2.99	0.80	0.046
8. BD (1) O 4 - C 5	/355. BD*(1) C 8 -Cl 10	1.51	0.88	0.033
9. BD (1) C 5 - H 6	/144. RY*(3) O 4	0.59	1.39	0.026
9. BD (1) C 5 - H 6	/206. RY*(3) C 8	0.81	1.25	0.029
9. BD (1) C 5 - H 6	/351. BD*(1) O 4 - C 5	1.27	0.74	0.028
9. BD (1) C 5 - H 6	/356. BD*(1) C 8 -Cl 11	4.84	0.59	0.049
10. BD (1) C 5 - H 7	/206. RY*(3) C 8	0.71	1.24	0.027
10. BD (1) C 5 - H 7	/347. BD*(1) C 1 - O 4	2.57	0.84	0.042
10. BD (1) C 5 - H 7	/357. BD*(1) C 8 -Cl 12	6.97	0.59	0.058
11. BD (1) C 5 - C 8	/261. RY*(2)Cl 10	0.55	1.46	0.025
11. BD (1) C 5 - C 8	/347. BD*(1) C 1 - O 4	0.64	1.00	0.023
12. BD (1) C 8 -Cl 10	/288. RY*(1)Cl 11	0.70	1.44	0.028
12. BD (1) C 8 -Cl 10	/316. RY*(1)Cl 12	0.74	1.45	0.029
12. BD (1) C 8 -Cl 10	/351. BD*(1) O 4 - C 5	3.29	0.91	0.049
12. BD (1) C 8 -Cl 10	/357. BD*(1) C 8 -Cl 12	0.51	0.76	0.018
13. BD (1) C 8 -Cl 11	/168. RY*(1) C 5	0.80	1.67	0.033
13. BD (1) C 8 -Cl 11	/317. RY*(2)Cl 12	0.62	1.47	0.027
13. BD (1) C 8 -Cl 11	/352. BD*(1) C 5 - H 6	1.84	1.05	0.039
13. BD (1) C 8 -Cl 11	/357. BD*(1) C 8 -Cl 12	0.57	0.77	0.019
14. BD (1) C 8 -Cl 12	/169. RY*(2) C 5	0.83	1.64	0.033
14. BD (1) C 8 -Cl 12	/260. RY*(1)Cl 10	0.61	1.43	0.027
14. BD (1) C 8 -Cl 12	/353. BD*(1) C 5 - H 7	1.27	1.06	0.033
14. BD (1) C 8 -Cl 12	/355. BD*(1) C 8 -Cl 10	0.54	0.77	0.019
14. BD (1) C 8 -Cl 12	/356. BD*(1) C 8 -Cl 11	0.60	0.77	0.020
15. CR (1) C 1	/ 91. RY*(1) C 2	0.96	10.92	0.092
15. CR (1) C 1	/ 94. RY*(4) C 2	0.80	11.00	0.084
15. CR (1) C 1	/119. RY*(4) O 3	0.80	11.48	0.086
15. CR (1) C 1	/347. BD*(1) C 1 - O 4	0.59	10.53	0.073
15. CR (1) C 1	/348. BD*(1) C 2 - O 3	3.26	10.65	0.178

15. CR (1) C 1	/349. BD*(1) C 2 -Br 9	0.73	10.40	0.080
15. CR (1) C 1	/351. BD*(1) O 4 - C 5	0.93	10.42	0.088
16. CR (1) C 2	/ 66. RY*(2) C 1	1.11	11.65	0.102
16. CR (1) C 2	/ 71. RY*(7) C 1	0.70	11.58	0.080
16. CR (1) C 2	/345. BD*(1) C 1 - O 3	0.65	10.74	0.075
16. CR (1) C 2	/347. BD*(1) C 1 - O 4	0.93	10.50	0.091
16. CR (1) C 2	/348. BD*(1) C 2 - O 3	4.30	10.62	0.204
17. CR (1) O 3	/ 65. RY*(1) C 1	6.79	19.99	0.330
17. CR (1) O 3	/347. BD*(1) C 1 - O 4	1.21	19.16	0.140
18. CR (1) O 4	/ 66. RY*(2) C 1	1.57	20.45	0.160
18. CR (1) O 4	/168. RY*(1) C 5	0.98	19.94	0.125
19. CR (1) C 5	/206. RY*(3) C 8	2.38	10.85	0.144
19. CR (1) C 5	/351. BD*(1) O 4 - C 5	2.49	10.35	0.144
20. CR (1) C 8	/171. RY*(4) C 5	0.62	11.30	0.075
20. CR (1) C 8	/354. BD*(1) C 5 - C 8	0.62	10.50	0.074
20. CR (1) C 8	/355. BD*(1) C 8 -Cl 10	0.64	10.32	0.074
20. CR (1) C 8	/356. BD*(1) C 8 -Cl 11	0.77	10.33	0.081
20. CR (1) C 8	/357. BD*(1) C 8 -Cl 12	0.84	10.33	0.085
23. CR (3)Br 9	/ 91. RY*(1) C 2	2.58	12.19	0.158
36. CR (2)Cl 10	/204. RY*(1) C 8	1.63	11.32	0.122
36. CR (2)Cl 10	/205. RY*(2) C 8	0.85	11.31	0.088
36. CR (2)Cl 10	/206. RY*(3) C 8	0.67	11.45	0.078
41. CR (2)Cl 11	/205. RY*(2) C 8	2.52	11.31	0.151
41. CR (2)Cl 11	/206. RY*(3) C 8	0.71	11.45	0.081
46. CR (2)Cl 12	/204. RY*(1) C 8	2.48	11.32	0.150
46. CR (2)Cl 12	/205. RY*(2) C 8	0.84	11.31	0.087
46. CR (2)Cl 12	/354. BD*(1) C 5 - C 8	0.61	10.96	0.074
50. LP (1) C 2	/ 66. RY*(2) C 1	0.87	1.86	0.037
50. LP (1) C 2	/230. RY*(1)Br 9	2.28	1.01	0.044
50. LP (1) C 2	/344. BD*(1) C 1 - C 2	0.79	0.82	0.023
50. LP (1) C 2	/345. BD*(1) C 1 - O 3	0.63	0.94	0.022
50. LP (1) C 2	/346. BD*(2) C 1 - O 3	12.67	0.36	0.063
50. LP (1) C 2	/347. BD*(1) C 1 - O 4	2.83	0.70	0.040
50. LP (1) C 2	/348. BD*(1) C 2 - O 3	8.11	0.83	0.076
50. LP (1) C 2	/349. BD*(1) C 2 -Br 9	1.38	0.58	0.026
51. LP (1) O 3	/ 65. RY*(1) C 1	17.57	1.91	0.164
51. LP (1) O 3	/344. BD*(1) C 1 - C 2	1.77	1.20	0.041
51. LP (1) O 3	/347. BD*(1) C 1 - O 4	3.60	1.08	0.057

51. LP (1) O 3	/348. BD*(1) C 2 - O 3	0.51	1.20	0.023
52. LP (1) O 4	/ 65. RY*(1) C 1	0.70	1.68	0.031
52. LP (1) O 4	/ 66. RY*(2) C 1	1.71	2.01	0.053
52. LP (1) O 4	/ 69. RY*(5) C 1	0.63	2.07	0.033
52. LP (1) O 4	/168. RY*(1) C 5	0.99	1.50	0.035
52. LP (1) O 4	/170. RY*(3) C 5	1.04	2.02	0.042
52. LP (1) O 4	/345. BD*(1) C 1 - O 3	4.75	1.09	0.065
52. LP (1) O 4	/346. BD*(2) C 1 - O 3	12.06	0.51	0.073
52. LP (1) O 4	/352. BD*(1) C 5 - H 6	2.81	0.88	0.045
52. LP (1) O 4	/354. BD*(1) C 5 - C 8	0.65	0.76	0.020
52. LP (1) O 4	/355. BD*(1) C 8 -Cl 10	0.53	0.59	0.016
53. LP (2) O 4	/ 70. RY*(6) C 1	0.54	2.97	0.037
53. LP (2) O 4	/172. RY*(5) C 5	0.54	1.66	0.028
53. LP (2) O 4	/344. BD*(1) C 1 - C 2	7.77	0.83	0.073
53. LP (2) O 4	/345. BD*(1) C 1 - O 3	7.04	0.95	0.075
53. LP (2) O 4	/346. BD*(2) C 1 - O 3	6.25	0.37	0.044
53. LP (2) O 4	/347. BD*(1) C 1 - O 4	0.51	0.71	0.017
53. LP (2) O 4	/349. BD*(1) C 2 -Br 9	0.53	0.59	0.016
53. LP (2) O 4	/353. BD*(1) C 5 - H 7	4.10	0.74	0.050
53. LP (2) O 4	/354. BD*(1) C 5 - C 8	6.53	0.62	0.057
54. LP (1)Br 9	/ 91. RY*(1) C 2	2.17	1.59	0.052
54. LP (1)Br 9	/ 92. RY*(2) C 2	0.51	1.66	0.026
55. LP (2)Br 9	/ 91. RY*(1) C 2	1.07	1.11	0.031
55. LP (2)Br 9	/344. BD*(1) C 1 - C 2	3.62	0.84	0.050
55. LP (2)Br 9	/346. BD*(2) C 1 - O 3	1.26	0.38	0.021
55. LP (2)Br 9	/348. BD*(1) C 2 - O 3	0.77	0.85	0.024
56. LP (1)Cl 10	/204. RY*(1) C 8	2.37	1.51	0.053
56. LP (1)Cl 10	/205. RY*(2) C 8	1.32	1.50	0.040
56. LP (1)Cl 10	/206. RY*(3) C 8	1.20	1.64	0.040
56. LP (1)Cl 10	/211. RY*(8) C 8	0.67	2.18	0.034
56. LP (1)Cl 10	/354. BD*(1) C 5 - C 8	0.92	1.15	0.030
56. LP (1)Cl 10	/356. BD*(1) C 8 -Cl 11	0.71	0.98	0.024
56. LP (1)Cl 10	/357. BD*(1) C 8 -Cl 12	0.66	0.98	0.023
57. LP (2)Cl 10	/204. RY*(1) C 8	0.74	0.92	0.023
57. LP (2)Cl 10	/205. RY*(2) C 8	0.74	0.90	0.023
57. LP (2)Cl 10	/351. BD*(1) O 4 - C 5	1.26	0.54	0.023
57. LP (2)Cl 10	/354. BD*(1) C 5 - C 8	2.25	0.56	0.032
57. LP (2)Cl 10	/357. BD*(1) C 8 -Cl 12	7.65	0.39	0.049

58. LP (3)Cl 10 /205. RY*(2) C 8 1.00 0.90 0.027
58. LP (3)Cl 10 /206. RY*(3) C 8 0.65 1.04 0.024
58. LP (3)Cl 10 /351. BD*(1) O 4 - C 5 0.95 0.54 0.020
58. LP (3)Cl 10 /354. BD*(1) C 5 - C 8 1.79 0.56 0.028
58. LP (3)Cl 10 /356. BD*(1) C 8 -Cl 11 8.50 0.39 0.052
59. LP (1)Cl 11 /205. RY*(2) C 8 3.72 1.49 0.066
59. LP (1)Cl 11 /206. RY*(3) C 8 1.25 1.63 0.040
59. LP (1)Cl 11 /208. RY*(5) C 8 1.06 1.88 0.040
59. LP (1)Cl 11 /209. RY*(6) C 8 0.94 2.15 0.040
59. LP (1)Cl 11 /354. BD*(1) C 5 - C 8 1.34 1.15 0.036
59. LP (1)Cl 11 /355. BD*(1) C 8 -Cl 10 0.74 0.97 0.024
59. LP (1)Cl 11 /357. BD*(1) C 8 -Cl 12 0.63 0.98 0.023
60. LP (2)Cl 11 /204. RY*(1) C 8 0.53 0.92 0.020
60. LP (2)Cl 11 /206. RY*(3) C 8 0.51 1.05 0.021
60. LP (2)Cl 11 /208. RY*(5) C 8 0.85 1.29 0.030
60. LP (2)Cl 11 /352. BD*(1) C 5 - H 6 0.72 0.67 0.020
60. LP (2)Cl 11 /354. BD*(1) C 5 - C 8 4.13 0.56 0.043
60. LP (2)Cl 11 /355. BD*(1) C 8 -Cl 10 0.53 0.39 0.013
60. LP (2)Cl 11 /357. BD*(1) C 8 -Cl 12 5.48 0.39 0.042
61. LP (3)Cl 11 /204. RY*(1) C 8 1.72 0.91 0.036
61. LP (3)Cl 11 /355. BD*(1) C 8 -Cl 10 8.67 0.38 0.052
61. LP (3)Cl 11 /357. BD*(1) C 8 -Cl 12 3.12 0.38 0.031
62. LP (1)Cl 12 /204. RY*(1) C 8 3.90 1.51 0.069
62. LP (1)Cl 12 /205. RY*(2) C 8 1.25 1.50 0.039
62. LP (1)Cl 12 /207. RY*(4) C 8 1.11 1.83 0.040
62. LP (1)Cl 12 /211. RY*(8) C 8 0.63 2.18 0.033
62. LP (1)Cl 12 /354. BD*(1) C 5 - C 8 1.94 1.15 0.043
62. LP (1)Cl 12 /355. BD*(1) C 8 -Cl 10 0.64 0.98 0.023
62. LP (1)Cl 12 /356. BD*(1) C 8 -Cl 11 0.64 0.98 0.023
63. LP (2)Cl 12 /205. RY*(2) C 8 1.06 0.90 0.028
63. LP (2)Cl 12 /207. RY*(4) C 8 0.61 1.24 0.025
63. LP (2)Cl 12 /354. BD*(1) C 5 - C 8 2.67 0.56 0.035
63. LP (2)Cl 12 /356. BD*(1) C 8 -Cl 11 8.72 0.39 0.052
64. LP (3)Cl 12 /205. RY*(2) C 8 0.73 0.90 0.023
64. LP (3)Cl 12 /354. BD*(1) C 5 - C 8 2.71 0.56 0.035
64. LP (3)Cl 12 /355. BD*(1) C 8 -Cl 10 8.73 0.38 0.052
346. BD*(2) C 1 - O 3 / 71. RY*(7) C 1 0.61 1.42 0.075
346. BD*(2) C 1 - O 3 /350. BD*(2) C 2 -Br 9 4.90 0.12 0.060

346. BD*(2) C 1 - O 3 /351. BD*(1) O 4 - C 5 1.96 0.23 0.050
347. BD*(1) C 1 - O 4 / 66. RY*(2) C 1 0.93 1.16 0.118
347. BD*(1) C 1 - O 4 / 67. RY*(3) C 1 0.78 0.62 0.079
347. BD*(1) C 1 - O 4 /344. BD*(1) C 1 - C 2 2.80 0.12 0.056
347. BD*(1) C 1 - O 4 /345. BD*(1) C 1 - O 3 0.52 0.24 0.036
347. BD*(1) C 1 - O 4 /348. BD*(1) C 2 - O 3 3.81 0.13 0.045
347. BD*(1) C 1 - O 4 /352. BD*(1) C 5 - H 6 5.44 0.02 0.037
347. BD*(1) C 1 - O 4 /353. BD*(1) C 5 - H 7 1.26 0.03 0.019
348. BD*(1) C 2 - O 3 / 65. RY*(1) C 1 1.65 0.71 0.083
348. BD*(1) C 2 - O 3 / 66. RY*(2) C 1 0.67 1.03 0.065
348. BD*(1) C 2 - O 3 / 67. RY*(3) C 1 0.60 0.49 0.043
348. BD*(1) C 2 - O 3 / 70. RY*(6) C 1 0.83 2.13 0.106
348. BD*(1) C 2 - O 3 / 91. RY*(1) C 2 14.18 0.27 0.153
348. BD*(1) C 2 - O 3 / 93. RY*(3) C 2 0.60 0.45 0.041
348. BD*(1) C 2 - O 3 / 94. RY*(4) C 2 0.69 0.35 0.039
348. BD*(1) C 2 - O 3 / 95. RY*(5) C 2 3.65 0.71 0.127
348. BD*(1) C 2 - O 3 / 97. RY*(7) C 2 5.01 0.71 0.150
348. BD*(1) C 2 - O 3 /106. RY*(16) C 2 3.11 2.59 0.225
348. BD*(1) C 2 - O 3 /107. RY*(17) C 2 1.19 20.40 0.391
348. BD*(1) C 2 - O 3 /111. RY*(21) C 2 0.56 2.53 0.095
348. BD*(1) C 2 - O 3 /112. RY*(22) C 2 2.15 2.67 0.190
348. BD*(1) C 2 - O 3 /113. RY*(23) C 2 1.39 2.86 0.159
348. BD*(1) C 2 - O 3 /115. RY*(25) C 2 1.27 2.62 0.145
348. BD*(1) C 2 - O 3 /117. RY*(2) O 3 0.96 0.44 0.051
348. BD*(1) C 2 - O 3 /230. RY*(1)Br 9 1.92 0.19 0.047
348. BD*(1) C 2 - O 3 /232. RY*(3)Br 9 6.76 0.32 0.118
348. BD*(1) C 2 - O 3 /233. RY*(4)Br 9 2.24 0.35 0.070
348. BD*(1) C 2 - O 3 /234. RY*(5)Br 9 1.02 0.42 0.052
348. BD*(1) C 2 - O 3 /238. RY*(9)Br 9 2.06 0.44 0.075
348. BD*(1) C 2 - O 3 /245. RY*(16)Br 9 0.62 0.84 0.057
348. BD*(1) C 2 - O 3 /345. BD*(1) C 1 - O 3 10.59 0.11 0.081

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