BENZOTHIAZOLE FUNCATIONALIZED PIPERIDINES VIA ACYL CYANIDE TRAPPING AND CYCLIZATION - A ONE POT SYNTHESIS

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[3,3]	[3,3]-sigmatropic rearrangement
[O]	oxidation
Ac	acetone
Boc	tert-butyloxycarbonyl
DBU	1,8-Diazabicyclo(5.4.0)undec-7-ene
DCM	dichloromethane
DMF	*N,N*-dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethyl Sulfoxide
EtOAc	ethyl Acetate
Hex	hexanes
HOAc	acetic acid
HPLC	high pressure liquid chromatography
MMPP	magnesium monoperoxyphthalate
NMR	nuclear magnetic resonance
Nu	nucleophile
PdL	palladium Ligand
Pg	protection group
reduct.	Reduction
R_f	retention factor
SET	single electron transfer
THF	tetrahydrofuran
Ts	tosyl group

Abstract

The construction of benzothiazole containing moieties is of interest to generate compounds with pharmaceutically interesting properties. Current methods to generate benzothiazoles rely on metal catalysis, iodine containing compounds or require additional redox steps to achieve the desired heterocycle.

Within is described a new approach to construct benzothiazole substituted heterocycles via oxidative amidation, using molecular oxygen and cesium carbonate, of *para*-malononitrile substituted piperidine and 2-aminothiophenol. The protocol follows a mild synthesis without temperatures exceeding 40 °C to achieve a structural moiety which is in focus for bioactivity studies and lays in interest for pharmaceutical applications.

1. Introduction

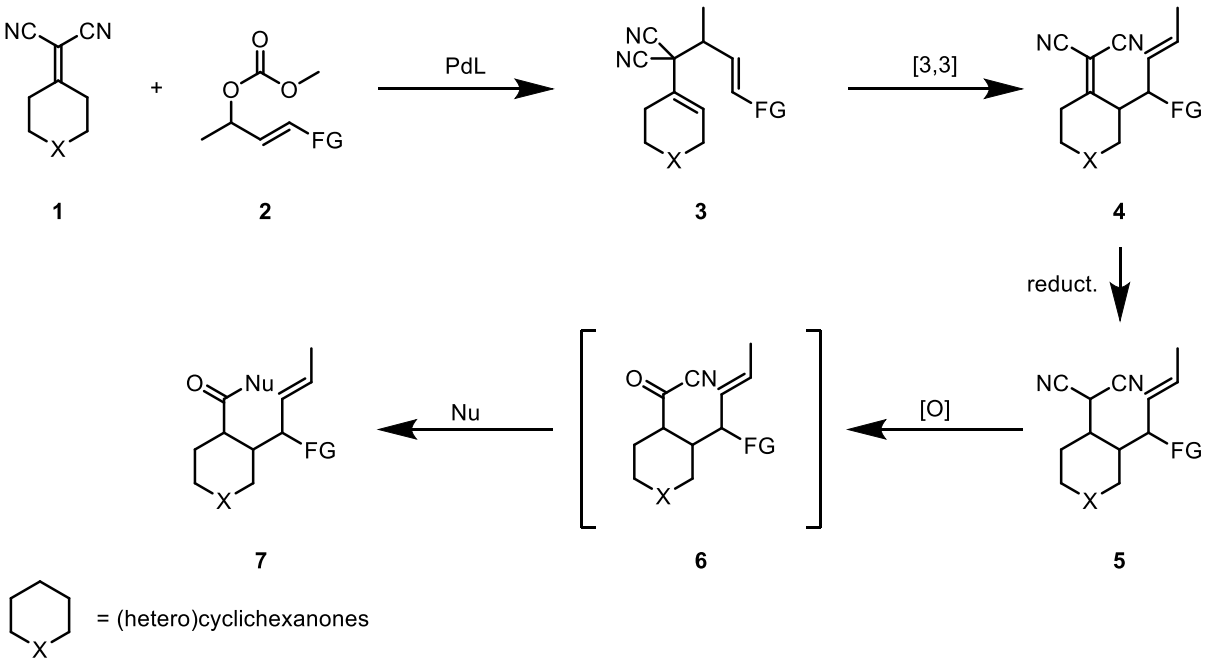
A rather novel approach in small molecule synthesis is by using carbon-based building blocks, comparable to tools in programming, to access known compounds or more complex structures of interest easily. In industries these kinds of substances are one of the key roles in the production of colorants, lotions, flavorings and perfumes. They also play a substantial role in drug production, whereby it is common practice to couple multiple small molecule fragments together to create a therapeutically relevant structure. These structural motifs are appealing as they can show among other things anti-cancer properties, anti-inflammatory properties, diabetes treatment, upregulation and downregulation of functionalities in the body, pain relief capabilities and may be included in medical imaging. The pharmaceutical industry continues to explore and innovate the current state of the art by fine tuning compounds using small molecule building blocks. The flexibility coming alongside those ideas and statements increases the interest in this field of chemistry.[1,2]

One example of the previously mentioned moieties which are appealing for medical treatment are benzothiazoles. Small molecules including this functional group show qualities interesting for pharmaceutical applications. There already exists medication which active ingredient includes benzothiazoles with different effects on the human body from reducing inflammation to diabetes treatment. The wider and more detailed span of possible applications for benzothiazoles is found later in this document.[3]

Other broadly used drug motifs are heterocyclic compounds, like piperidines. Those continue to garner interest for small molecule synthesis as there are several examples of medically relevant targets including polyfunctionalized heterocycles. Synthesis of these targets may include extreme conditions such as extreme heat or high energy consumption. Previously mentioned circumstances can lead to decomposition of wanted functionalities and therefore investigating a more mild, functional group tolerant way of synthesis is of great interest.[4]

Nature is excellent at creating amide bonds and this widely abundant functional group is found in focus for usage in a number of industries. Polypeptides, drugs, pesticides and polymers are examples of their utility. Nature forms amide bonds differently compared to research or manufacturing. The most common amide bond formation is achieved by forming an activated carboxylate from a carboxylic acid or using a catalytic pathway for direct amidation. Harsh conditions and increased reaction times are necessary using these methods, due to the lower reactivity of carboxylic acid, to achieve the desired amide. The wide occurrence of amide bonds in therapeutic and functionally useful compounds house led researchers to develop a wide variety of methods to access this valuable functional group. One example is the direct oxidative amidation of other functional groups containing an oxygen-carbon bond namely alcohols, esters, ketones, aldehydes or alkynes. Even if a broad range of amide bond formation is present today, a more efficient way of synthesizing this target is desired in the pharmaceutical industry as well as in organic chemistry.[5]

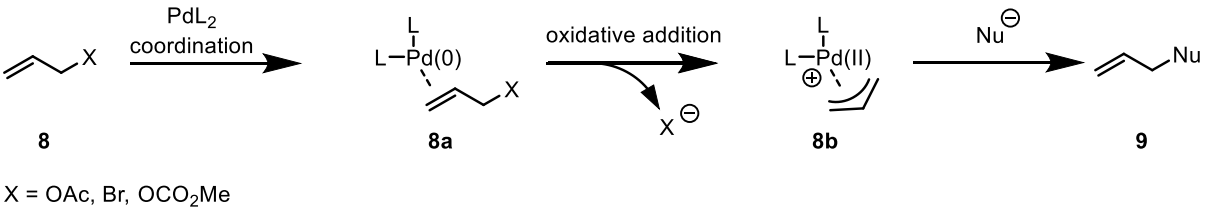
Two of the research topics Dr. Alexander Grenning and his group are focusing on is the polyfunctionalization of heterocycles and amide bond formation. As mentioned previously a moderate way of synthesis to access those molecules lays in interest as they show promise for use in pharmaceutically active molecules. The idea is to access these kinds of compounds via an alkylation using the Tsuji-Trost reaction, thereby inducing a contra-thermal Cope rearrangement via heating, followed by a reduction of the alkylidene malononitrile yielding in compounds such as **5** and finally generating polyfunctionalized heterocyclic substances similar to **7** by an oxidative amidation. A general outline of the ides is shown in Scheme 1.[6,7]



Scheme 1: General idea of addition of functional groups on (hetero)cyclic compounds through allylic alkylation, [3,3]-sigmatropic Cope rearrangement, followed by reduction, oxidation and nucleophilic addition

Tsuji-Trost allylic alkylation

The Tsuji-Trost reaction is widely known and consists of a palladium catalyzed allylic alkylation. The mechanism is strongly dependent on the nature of the used nucleophile. Here a general differentiation can be made between hard nucleophiles, which add through the metal center, and soft nucleophiles, which directly attack the allyl moiety. Although this distinction between nucleophiles is observed, the binding of the palladium zero complex happens in both cases the same way. First, the alkene (**8**) coordinates to Pd(0) forming an $\eta^2\pi$-allyl complex (**8a**), leading to an oxidative addition which expels the leaving group, here depicted as X, to afford intermediate **8b**. The positive charge is now distributed alongside the carbon chain, allowing a nucleophilic addition. A nucleophilic attack on the π-allyl complex then affords then product **9**, as shown in Scheme 2.[8]

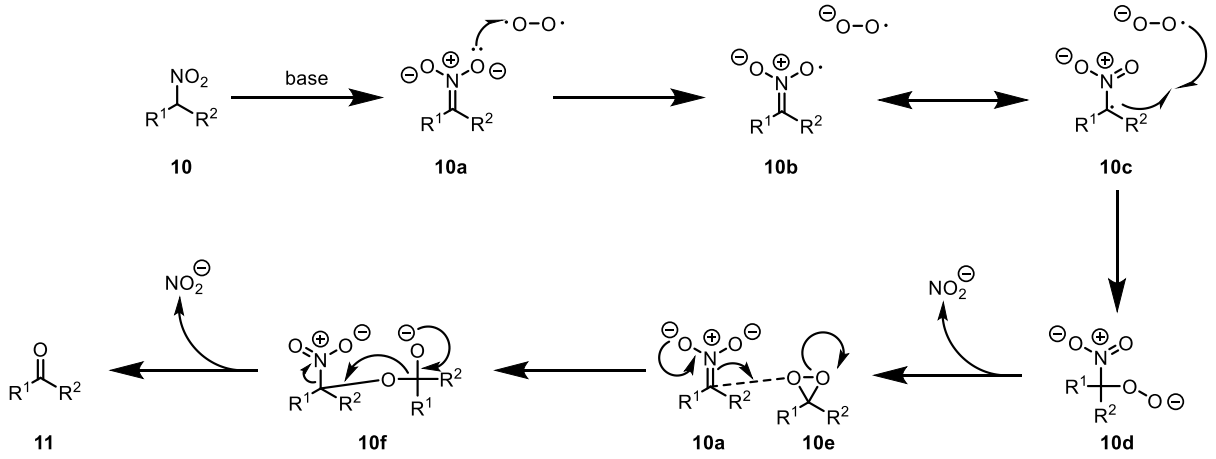


Scheme 2: General outline of addition of a nucleophile to a palladium π-allyl complex

The choice of the Palladium complex can lead to a racemic mixture, by using achiral ligands, or enantioenriched products, via the application of chiral ligands.[7,8]

Hayashi amidation

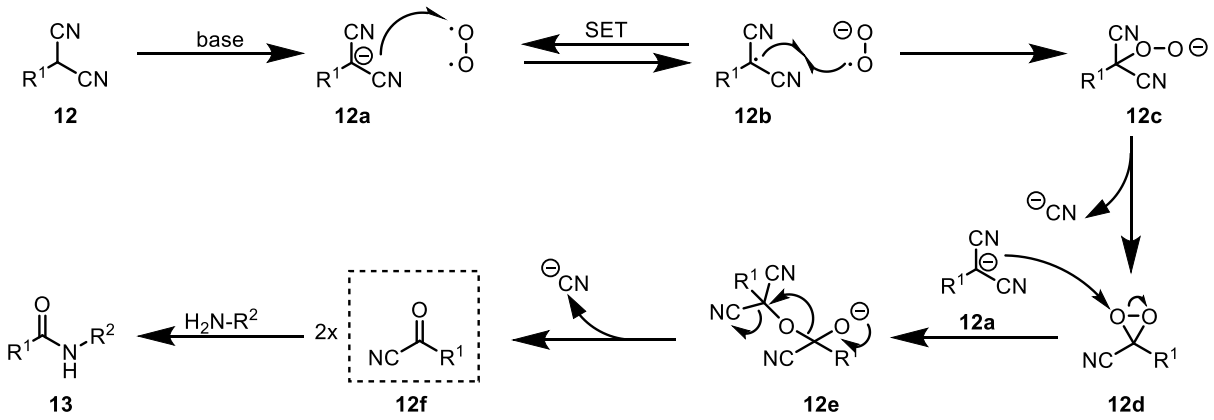
To overcome the challenging topic of amide bond formation in organic chemistry, Hayshi and his group started by developing a one pot Nef oxidation reaction in 2014. It was discovered that by treating nitroalkene or nitroalkane (**10**) with a base and molecular oxygen an aliquot ketone (**11**) is obtained. The general reaction mechanism is outlined in Scheme 3.[6]



Scheme 3: Proposed mechanism for one pot Nef reaction according to Hayashi[6]

Afterwards, the Hayashi group discovered that the radical and anionic intermediates **10e** and **10f** can be stabilized by exchanging the nitro group and one of the substituents on the starting material (**10**) with two electron stabilizing groups. For R^1 or R^2 NO_2, CN, SO_2R and $PO(OR)_2$ were chosen as suitable candidates. Lastly, he clamied that after the formation of the carbonyl **11** an oxidative amidation will occur if the newly added group acts as leaving group.[9]

Following mainly the same mechanistic pathway as depicted in Scheme 3, the addition of the amine at the end of the sequence differentiates both procedures yielding in amides (**13**). An example is the exchange of the nitro group to an α-substituted malononitrile (**12**) as outlined in Scheme 4. By sparging with gaseous oxygen and treating with cesium carbonate as base under anhydrous conditions, good to high yield was obtained with a variety of primary and secondary amines.[9]

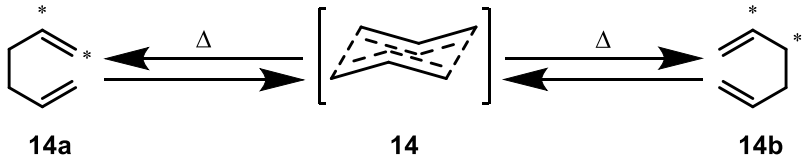


Scheme 4: Oxidative amidation of α-substituted Malononitriles with amines mechanism proposed by Hayashi[9]

By deprotonation of **12** a single electron transfer (SET) is enabled between **12a** and molecular oxygen. The yielded anionic peroxide (**12c**) can cyclize to form a dioxirane intermediate **12d**. The oxygen of the three membered ring in **12d** can then be attacked by the deprotonated form of the starting material (**12a**). The newly formed bond opens the ring generating a carboxy anion. Establishing an oxygen carbon double bond forces the cyanide ion to leave and two acyl cyanides (**12f**) can be obtained. Through a nucleophilic addition of an amine a variety of amides can be synthesized.[9]

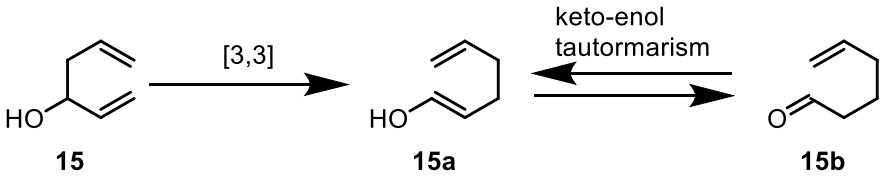
Cope rearrangement

Arthur C. Cope and Elisabeth Hardy discovered that 1,5-dienes under thermal conditions will undergo a [3,3]-sigmatropic rearrangement as shown in Scheme 5. This finding, known as the Cope rearrangement, is nowadays one of the most well known and widely used pericyclic reaction in organic chemistry. Over time, numerous modifications were established, and still new approaches are being developed to find new ways to achieve complex structures.[10]



Scheme 5: Traditional thermal Cope rearrangement with carbon labelled molecules

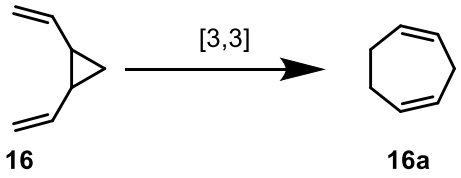
Differentiation of molecule **14a** and **14b** is not possible without any kind of marking, one easy and widely used way is radioactive labelling of carbon atoms. In Scheme 5 asterisks indicate labelled atoms. Taking this in mind it is observable that starting material **14a** and **14b** are not identical. Undergoing a chair confirmation transition state (**14**) is very much common for such rearrangements, especially in the case of carbon chains without any substituents.[10]



Scheme 6: Reaction scheme for Oxy-Cope rearrangement

Sigmatropic rearrangements are completely reversible and therefore the total energy of the starting materials and products have to be put into consideration.[10] An example for this is including heteroatoms as seen in

Scheme 6: Reaction scheme for Oxy-Cope rearrangement. The reaction is shifted to **15b** as the carbon-oxygen double bond shows higher stability compared to the carbon-carbon bond. After the [3,3]-sigmatropic rearrangement **15a** converts through keto-enol tautomerism to **15b**.[11]



Scheme 7: Cope rearrangement with strain release

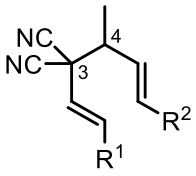
Former mentioned modifications of the Cope rearrangement are popular to overcome the necessary activation Energy. One driving force used to do so is strain release as shown in Scheme 7. The transformation of 1,2-diethenylcyclopropane (**16**) into cyclohepta-1,4-diene (**16a**) takes place under slightly elevated temperatures. Due to the lower energy state of **16a** compared to **16** the reverse reaction is less likely to happen.[10] Overall, sigmatropic rearrangemts are powerful tools for the stereoselective elaboration of important scaffolds for biologically interesting compounds and other materials of importance.[4]

Research in the Grenning lab

The research group of Prof. Alexander Grenning combined the information mentioned above and generated, as depicted in Scheme 1, a procedure which enables to achieve desired small molecules as **7**.[7]

To substitute the 3 position on the heterocyclic alkylidene malononitrile scaffolds (**1**) we first perform a palladium catalyzed allylic alkylation to form product **2**.[12] The position of the leaving group on **2** was chosen so that the addition via Tsuji-Trost mechanism

leaves a methyl group on the position 4 carbon on the 1-5-hexadiene scaffold of the molecule **3** (comparable to compound **15** in the simplified depiction Figure 1). The attachment enables the molecule to perform a [3,3]-sigmatropic Cope rearrangement under mild conditions according to previous studies of the Grenning group. It is believed that the primary driving forces are the Thorpe-Ingold effect, a weakened C3-C4 bond due to the steric strain on the vicinal quaternary/tertiary centers (C3 and C4) and the electron withdrawing effect resulting from the substituents on C3. This is illustrated in Figure 1.[13]



17

R^1 = alkyl substituents
R^2 = (hetero)benzyls and aliphatics

Figure 1: Illustration of the various driving forces that facilitate Cope rearrangement

Originally obtained from *gem*-dimethyl groups on an open carbon chain, Thorpe and Ingold published a paper in 1915 explaining the change of the bond angles on the disubstituted position. They proposed that the repulsion of the methyl groups cause an angle increase and therefore a contraction on the opposite angle.[14] We hypothesize that the explanation is suitable to describe the forces working on *gem*-dinitrile instead of *gem*-dimethyl as in molecule **17** on position 3. The decreased angle forces carbon 1 and 6 to come closer to each other which enhances the chances of cyclization of scaffolds similar to molecule **17**. In the case of a 1,5-hexadiene a [3,3]-sigmatropic rearrangement is preferred.[13,14]

Upon rearrangement, alkylidene malononitrile **4** must be reduced via sodium borohydride to obtain compound **5**. The nucleophilic addition on the α-carbon of the malononitrile was then achieved by following the Hayashi protocol to afford product **7**. Previous efforts in the Grenning group have shown a scope via this reaction outline proved possible nucleophiles like primary amines, secondary amines, methoxy methylamine and methanol.[7]

Benzothiazoles synthesis

The synthesis of benzothiazoles is of great interest due to its pharmaceutical value as a drug scaffold, due to the numerous applications which were observed of related compounds with anti-inflammatory, anti-cancer, antiallergic and pain-relieving

properties to name a few. A mild synthesis would be of interest to avoid possibilities of degradation or high energy consumption.[3,15]

Bandyopadhyay and colleagues published in 2011 an article in which was discovered that substituted benzothiazoles need in average half of the time to eliminate a scope of common bacteria compared to the widely known ciprofloxacin, which needs 48h. They tested their compounds against Gram-negative bacteria, *Vibrio cholerae* MTCC 3904, *Escherichia coli* MTCC 1610 and *Shigella dysenteriae* NICED, and Gram-positive bacteria, *Bacillus cereus* MTCC 430 and *Staphylococcus aureus* MTCC 3160. It is believed to enhance the chances to combat multi resistant bacteria, due to the minimalized exposure of the active compound in the drug to the dangerous microbe. Following it is proposed that the organism has limited time to adjust even if widely used and therefore has difficulties developing resistance to the treatment. The shortened duration of medication is additionally lowering the exposure of stress through the treatment in the human body. All together it ends in a computational relationship between benzothiazoles and structurally similar purines in anti-bacterial behavior as proposed by the authors.[16]

A study of benzothiazole series by D'Angelo et al. showed an *in vivo* inhibiting effect on the cell growth of multiple cancer types. By inhibiting a certain lipid kinase, which regulates the cell growth, survival and cell translation. It is believed that this plays a major role in cancer cell growth.[17] Additionally an *in vitro* study was performed to examine the anti-cancer properties of benzothiazole-2-thiols. Among the tested range of cancer cell lines good activity against breast cancer, lung cancer, colon cancer and pancreatic cancer were obtained. By introducing heterocycles to a benzothiazole moiety it was observed that these compounds show promising anti-cancer properties as well. It was planned to generate small molecules with even higher inhibiting effect on the cancer cell growth and benzothiazole substituted heterocycles were chosen to be the most promising. It is stated that the developed compound exceeded the expectation of inhibiting effect on eleven tested human cancer cells.[18]

A promising anti-inflammatory compound was discovered in 2012 containing benzothiazoles. Whereby its reactivity was compared to the widely known and used Ibuprofen. It showed better efficacy and showed no gastric ulceration in tested animal stomach tissue. Even though the compound showed high potency for pharmaceutical application, further studies would be necessary.[19] An additional promising non-

steroidal benzothiazole derivative was discovered by Gilani and his group showing anti-inflammatory effects. It inhibits the production of prostaglandins which are lipids with a hormone like functionality. The human body releases them during stress in form of a wound and they activate the feeling of pain and elevate the body temperature.[20,21]

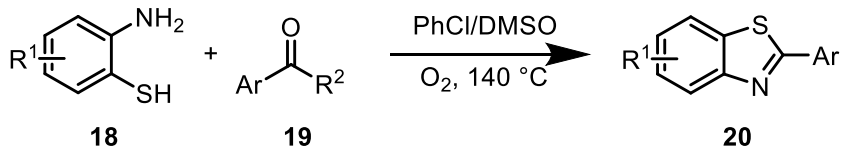
Benzothiazole substituted heterocycles were studied as potential key component in the treatment of diabetes, a disease that afflicts millions of people in the United States and its treatment costs over billions of dollars yearly. It is known that the elevated glucose level in the blood damages the nerves in the body. Known complications which affect people with diabetes mellitus are blindness, limb amputation and stroke. Those were certainly outcomes from the repeated exposure to higher blood sugar levels. Alongside the elevated presence of glucose, the cells fall into a state which is known as oxidative stress, which is mainly introduced through the aldose reductase and lead to cell and tissue damage. The main trade of the benzothiazole derivative is to inhibit the mentioned pathway and therefore lowers the possibility of oxidative stress. Welcomed side-effects of this kind of molecule is the normalization of nerve sugars and lower occurrence of diabetic cataracts.[3,22]

Nowadays there are three common ways of synthesizing benzothiazoles as further explained below: Condensation reaction of 2-aminothio, Reactions of *ortho-halogenated* anilines and Intramolecular cyclization.[23]

I. Condensation reaction of 2-aminothiophenol

A commonly used method for the preparation of benzothiazoles is condensation using 2-aminothiophenol. Possible reaction partners are aldehydes, ketones, carboxylic acids and acyl chlorides.[23]

Deng and his research group outlined a synthesis using ketones and molecular oxygen as oxidant, whereby they underline the importance of an equivalent amount of DMSO in chlorobenzene as solvent to achieve moderate yield of desired product.[24]



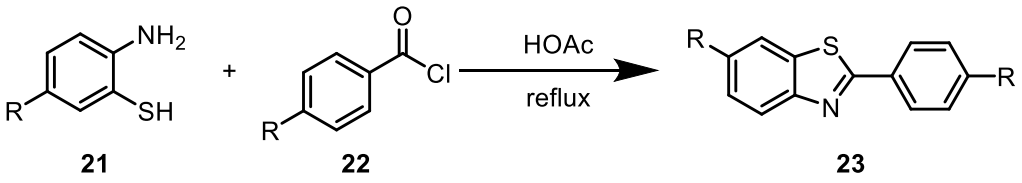
18 **19** **20**

R^1 = Me, OMe, Cl, Br
R^2 = H, Me, Et, CH_2CO_2Et, CHO
Ar = aryls

Scheme 8: Condensation and oxidation of 2-aminothiophenols and ketones[24]

Even though this method showed significantly less yield at lower temperatures, it does not need any metallic catalyst or I_2 and shows a broad range of possible reactants as depicted in Scheme 8.[24]

A very simple and straight forward synthesis was discovered by Racané et al. in 2010. Using compound **23** as starting material to produce more complex bioactive molecules, they obtained good yield by refluxing **21** with *para*-substituted benzoylchloride (**22**). As depicted in Scheme 9 the scope was limited to cyano and nitro substituents.[15]



21 **22** **23**

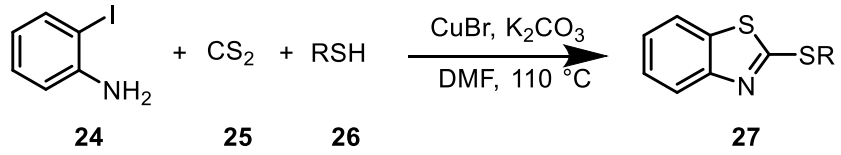
R = CN, NO_2

Scheme 9: Condensation of a 5-cyano/nitro substituted 2-aminothiophenol[15]

The scope of this study is testing its outcome as an antitumor compound and its acute toxicity. The outcome shows an inhibitory effect on the cell growth of human tumor cells as well as an acceptable toxicity against living cells, which proposed the interest of further *in vivo* studies.[15]

II. Reactions of *ortho*-halogenated anilines

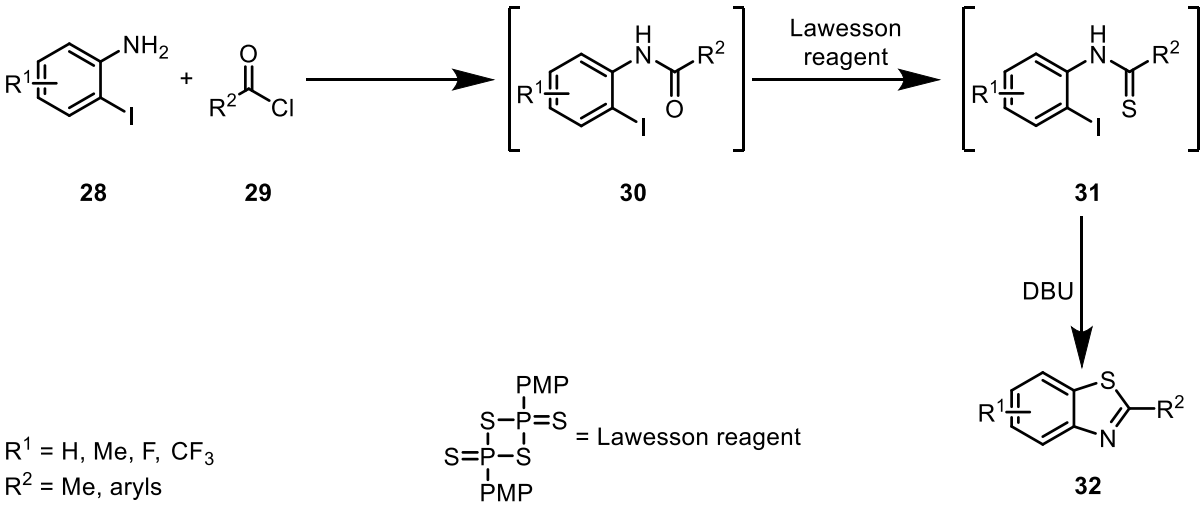
A method which is not dependent on 2-aminothiophenols uses *ortho*-halogenated anilines and a sulfur source. One example yields 2-thio-substituted benzothiazoles (**27**), which gather interest especially in anti-cancer treatment as they display desired biological activities in chemotherapy. Additionally, some showed potency in defeating tuberculosis. Starting with 2-iodoanilines (**24**) the additional reagents are carbon disulfide (**25**) and aliphatic or aromatic thiols (**26**), which are treated with potassium carbonate and copper bromide in DMF and heated to 110 °C as shown in Scheme 10.[25]



Scheme 10: Synthesis outline to produce 2-thio-substituded benzothiazoles[25]

The authors believe that the reaction goes through a condensation of carbon disulfide (**25**) and thiol (**26**), followed by a *S*-arylation of the 2-iodoaniline (**24**) and an intramolecular cyclization. Although this reaction is not dependent on 2-aminothiophenol it requires high temperatures and uses a transition metal and as stated previously the solvent DMF. It was reported that changing the solvent resulted in significantly lower yields.[25]

Another example is a metal free one pot three step synthesis using the Lawesson reagent as sulfur source. Starting again with *ortho*-halogenated anilines (**28**) and acyl chloride (**29**) it is believed that it will form amide **30** in situ, which will convert to the according thioamide **30** under the presence of the Lawesson's reagent after heating to 100 °C. The final cyclization happens after introducing DBU to obtain product **32** as shown in Scheme 11.[26]

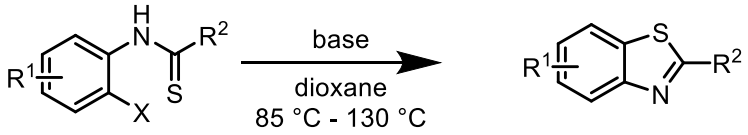


Scheme 11: Synthesis of benzothiazole using Lawesson's reagent and DBU[26]

Ding and his team provided this cascade one pot reaction in 2009 using two different solvents. While **28** and **29** is added in DCM, the Lawesson reagent is dissolved in toluene and added without former concentration of the reaction mixture.[26]

III. Intramolecular cyclization

Intramolecular cyclization starts with *ortho*-halogenated thioformanalides, similar as the intermediates **31** shown in Scheme 11. Feng and colleagues developed a base promoted reaction which yields 2-substituded benzothiazoles as outlined in Scheme 12. The method showed wide application and a diverse scope was recorded.[27]



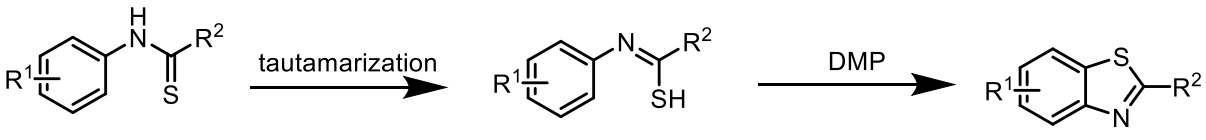
33 **34**

R^1 = F, Cl, CF_3, OMe
R^2 = *N'*, *O'* or *C'*-substituents
X = I, Br

Scheme 12: Metal free, base promoted intramolecular cyclization method to synthesize 2-substituted benzothiazols[27]

This reaction is metal free and only needs 2h for completion. Additionally, a change in the solvent did not affect the yield significantly. It was noted that the main influence on the change in temperature was dependent on the R^2 substituent. *O*'-substituted reagents need 80 °C while *N*'-substituted ones needed elevation of temperature up to 130 °C.[27]

A second metal free method (Scheme 13) using cyclization of thioformanalides at room temperature showing various applicable derivatives with DCM as solvent was discovered by Bose and his team in 2006. They envisaged that the oxidant DMP gains an electron from the tautomer **36** and causes a radical cyclization to yield in **37**.[28]



35 **36** **37**

R^1 = OMe, *t*-Bu, naphthalene
R^2 = substituted phenols

Scheme 13: Benzothiazole synthesis via cyclization of various thioformanalides in a one pot reaction[28]

The scope showed good yield at room temperature for a variety of phenolic derivatives as R^2, especially when the phenol is functionalized with a nitro group which was beforehand challenging due to decomposition of the starting material. They even

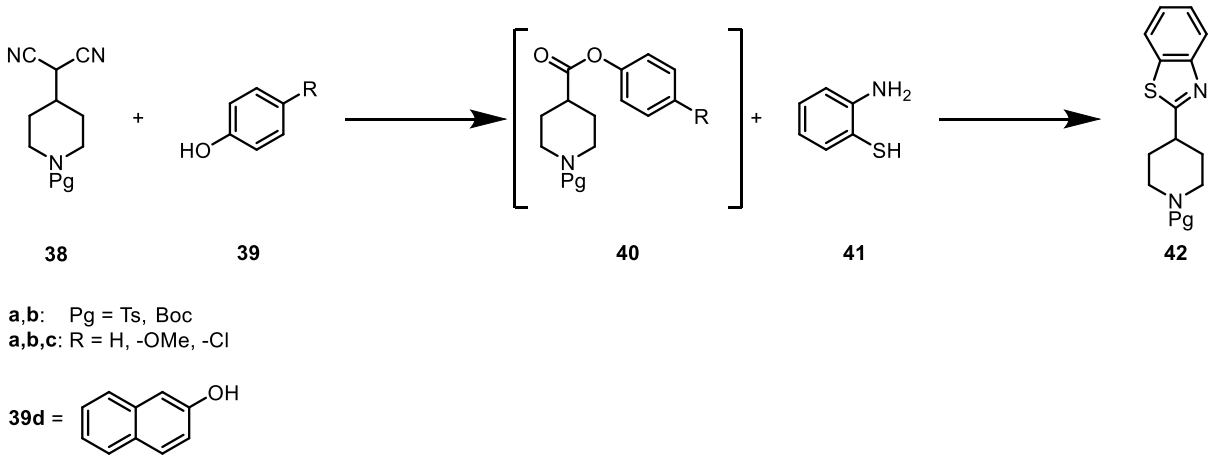
accomplished to connect two benzothiazoles via an oxygen bridge, whereby the substituent R^2 was chosen to be toluene.[28]

Reviewing above mentioned methods to obtain this moiety, it is noticeable that either high temperatures, metal catalysts or iodine containing reactants are needed. Knowing the importance of benzothiazole scaffolds in the pharmaceutical field, the Grenning lab envisages the development of a mild synthesis to access these molecules.

2. Objectives

The importance of heterocycles and benzothiazoles was laid out in detail beforehand. Consequently, the Grenning lab was interested in using 2-aminothiophenol (**41**) as nucleophile in the oxidative amidation of malononitrile. While investigating this substrate it was discovered that an oxidative amidation is not possible following the Hayashi protocol.

Creating a reaction which enables an attachment of **41** on a heterocycle and further cyclization to benzothiazole like molecule **42** as shown in Scheme 14 is the desired outcome of this research project. Without deviating from the Hayashi protocol too much, the fundamental thought is to form an ester intermediate (**40**) which then can be attacked by the nucleophilic 2-aminothiophenol (**41**), followed by a cyclization. To accomplish this synthesis, **38** will be subjected to Hayashi conditions in the presence of phenol to generate a reactive ester intermediate *in situ*. Molecular oxygen will then be removed from the reaction by sparging the flask with nitrogen and **41** will then be added to the solution.



Scheme 14: General outline of proposed synthesis to obtain benzothiazoles

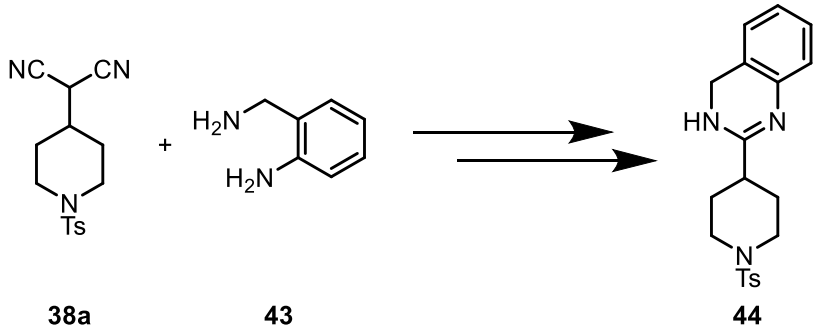
The heterocyclic scaffold for establishing this reaction was chosen to be piperidine, whereby the nitrogen should be protected by either a Tosyl group or a tert-Butyloxycarbonyl group. We plan on investigating nucleophilic alcohols to form the ester intermediate **40** to be phenol (**39a**), *para*-methoxyphenol (**39b**), *para*-chlorophenol (**39c**) and 2-naphthol (**39d**).

When this protocol is established, we further aim to try those conditions on higher substituted piperidines. This goal suggests that it is best if the newly discovered method be applicable for the procedure outlined in Scheme 1. This means previously mentioned allylic alkylation and alkylidene malononitrile reduction procedures will be used followed by developed methods to synthesize benzothiazoles.

Following the outline mentioned above, an easy and cheap one pot reaction will be developed to convert malononitriles into benzothiazoles. This synthesis also has the potential to solve any stability issues that may arise when using more challenging compounds unstable to the presence of oxygen, possibly increasing the scope of nucleophiles compatible with this reaction.

3. Results and Discussion

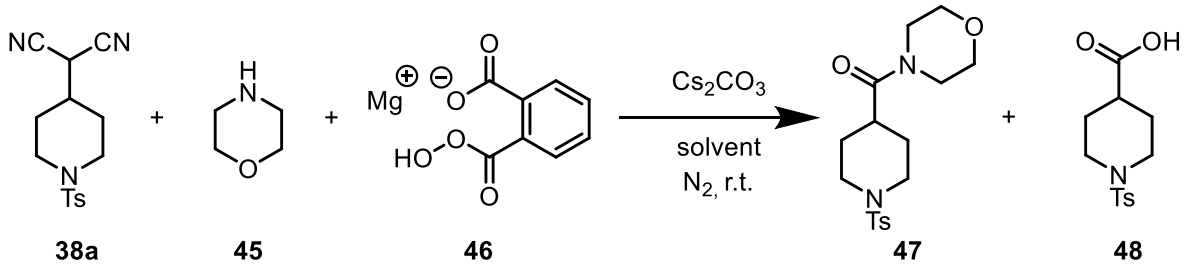
Starting with 2-(aminomethyl)aniline (**43**) as nucleophile and performing an oxidative amidation via Hayashi protocol, it was possible to further cyclize it to yield in **44** by refluxing it in $POCl_3$ a commonly used Lewis acid. We believe that the Lewis acid binds to the oxygen of the carbonyl (**54**, Scheme 19) and makes the carbon on that position more electrophilic, which facilitates cyclization. This showed that a second nucleophilic attack on the carboxy group is possible, if a second substituent on the aniline scaffold is present which can perform such reaction. The used procedure is explained further in the Experimental section.



38a **43** **44**

Scheme 15: Successful oxidative amidation of 2-(aminomethyl)aniline on piperidine scaffold followed by cyclization

Using more challenging substrates, such as 2-aminothiophenol, the first step of the synthesis was not yielding in desired product, as stated beforehand. By hypothesizing that the oxidation with O_2 would degrade **41**, which is knowingly unstable under air atmosphere, we tried to exchange molecular oxygen for magnesium monoperoxyphthalate (**46**). To establish a well functioning procedure we exchanged the target reactant **41** to morpholine (**45**) and used nitrogen atmosphere as depicted in Scheme 16. A detailed description of performed reactions is found in the following Experimental section.



Scheme 16: Exchange of molecular oxygen to stochiometric oxidant MMPP

We further found out through solvent screening (Table 1) that the reaction is very dependent on the factors of cesium carbonate as base and MMPP as oxidant is used. We hypothesize that the solubility of MMPP in more polar solvents aids in the conversion of malononitrile to the acyl cyanide intermediate (**14f**). Another very essential factor is the order of addition of the different substrates. Nearly complete conversion into **47** with nearly no conversion into the according carboxylic acid (**48**) was obtained through adding **38a**, morpholine (**45**), DMF and cesium carbonate to the flask and letting it stir for 10 minutes before adding MMPP (**46**).

Table 1: conversion of 2-(1-tosylpiperidin-4-yl)malononitrile into 1-tosylpiperidine-4-carboxylic acid and desired amidation product morpholino(1-tosylpiperisin-4-yl)methanone in percent

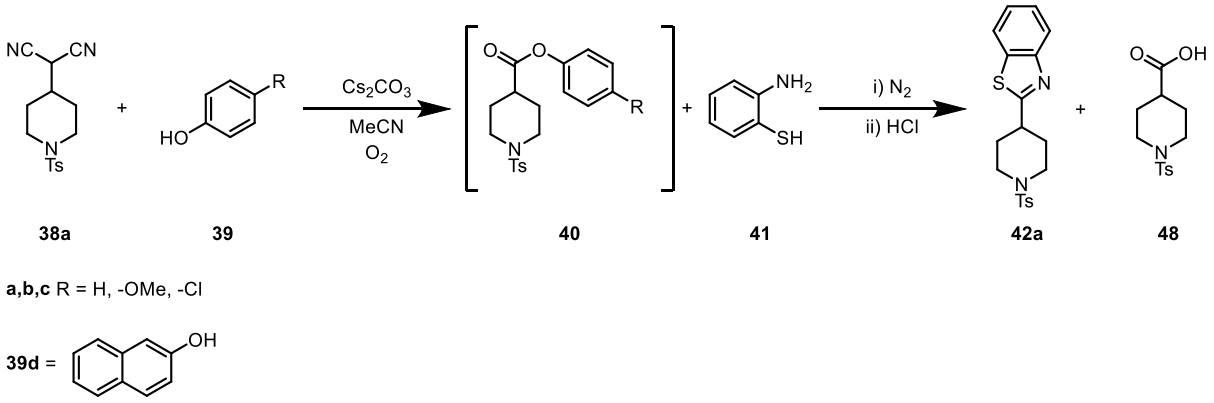
Solvents	Conversion of compound 36a into compound 45 and compound 46 [%]
MeCN	09%
THF	18%
DMSO	22%
CH2Cl2	38%
DMF	95%

By using drying agent like molecular sieves to dehydrate the solution and therefore diminish the possibility of generating **48,** no difference in conversion was observed. Counterintuitive to the expected outcome, nearly no yield was recorded using additional drying agents following the established procedure. Firstly, we added the activated drying agent together with the starting materials, but almost no conversion could be obtained. Afterwards we tried to pre-dry the mixture by adding the drying agent into two solutions. One contains the drying agent together with compound **38a** as solution 2 and later on add solution 1 which consists of morpholine (**45**), MMPP (**46**) and cesium carbonate, as well as extra drying agent. Even after altering the addition of substrates the highest recorded observation was still only a 17% purified yield of the carboxylic acid **48** compared to previous efforts.

After obtaining these results we changed morpholine to 2-aminothiophenol and discovered that even by changing the oxidant the amidation will not proceed. We next hypothesized that by exchanging the oxygen atmosphere to nitrogen it should be a stable environment for **41** to react with the intermediate **14g**. It was found that the acyl cyanide is not stable enough to hold through a change of atmosphere on its own.

Driven by the idea that an amide bond is more stable than an ester bond, we tried to synthesize esters via the Hayashi protocol and by further introducing a nitrogen containing nucleophile to yield the desired amide bond formation. We chose to test a variety of phenol derivatives which will act as good leaving groups to enhance the probability of the nucleophilic attack to form the amide bond later on. The formation of esters using phenol, *para*-chlorophenol, *para*-nitrophenol and *para*-cyanophenol and starting material **38a** was proven via crude 1HNMR analysis. Unfortunately, we could not continue investigating this pathway due to the fact that the esters synthesized were not stable under purification via silica gel column. We assume that the good leaving group ability of the previously mentioned phenolic derivatives leads to hydrolyzation on the slightly acidic silica yielding in the according carboxylic acid **48**.

Following this discovery, we wanted to attempt to trap the acyl cyanide. The trapping agent should function as a nucleophile via the Hayashi condensation and after adding 2-aminothiophenol as leaving group. This concludes that the newly formed bond between **38a** and the trapping substance has to be weaker than an amide bond. We found phenol (**39a**) and phenolic derivatives (**39b, c, d**) most suitable for this idea.



Scheme 17: More detailed description of target reaction

Following the Hayashi protocol we were able to treat the starting malononitrile substituted piperidine (**38a**) with phenol, change the oxygen atmosphere to a nitrogen atmosphere by sparging with gaseous N_2, then add **41** to obtain the desired benzothiazole. In the beginning we were not able to confirm the formation of **42a**, but after quenching the reaction with 0.5 M HCl to see the conversion to the according carboxylic acid (**48**) the benzothiazole product occurred. Even if the exact reasoning of the acid is not declared, we assume that the more stable amide bond is formed after addition of **41** and the attack of the nucleophilic thiol towards the carboxy group takes place followed by condensation and loss of water to obtain **42a**.

Table 2: Ratio of conversion from starting material to target molecule and according carboxylic acid by changing the solvent

solvent	Ratio of conversion of 40a to 46 [40a : 46]
MeCN	1 : 0.20
DMSO	0 : 1
DMF	0 : 1

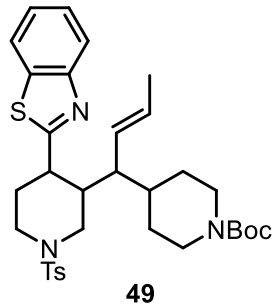
After investigating needed time to yield in the best conversion to desired product in acetonitrile, a solvent screening was performed (Table 2) and showed that acetonitrile is the most suitable one. Contrary to previous solvent studies (Table 1) DMF and DMSO performed worse compared to MeCN.

Once an appropriate solvent was obtained, different phenol derivatives were tested as shown in Table 3. The ratio was determined via 1HNMR in $CDCl_3$ of the crude material between two distinguished peaks for each entry.

Table 3: Ratio of conversion from starting material to target molecule and according carboxylic acid by changing the trapping nucleophile

nucleophile	Ratio of conversion of 40a to 46 [40a : 46]
37a	1 : 0.20
37b	1 : 0
37c	1 : 0.52
37d	1 : 0.46

A possible explanation for this outcome could be the nucleophilicity of the phenols and stability of the ester formed in situ. The electron donating effect of the ether substituent of *para*-methoxyphenol into the conjugated π-system makes through resonance and the inductive effect the *para*-methoxyphenol more nucleophilic, which helps the attack from the phenolic derivative **39b** to generate intermediate **40b**. Because the phenol anion shows more stable resonance structure and is therefore a better leaving group it could be that this leads to the formation of carboxylic acid **48**. The building of **48** is probably due to the effect of water in the reaction mixture. Even if dry solvents were used and the glassware was dried it could not be guaranteed that no water was in the system. It is plausible that the mechanism follows the same outline as in Scheme 4 but instead of an amide H_2O, or more probably the deprotonated form hydroxide as we generate a basic environment, acts as a nucleophile. We assume that this is the main source of the generation of carboxylic acid. In contrast, the resulting ester may be more stable to hydrolysis as para-methoxyphenol is a less stable leaving group and therefore slower to form the undesired carboxylic acid (**48**). After purification a small amount of left over ester was found, which lead to the belief that the amidation step after adding 2-aminothiophenol was not gone to completion. Longer reaction time did not yield in full conversion of **40b**. Therefore, elevated temperature was tested and 40 °C were found to be enough to let the amidation run to completion.



49

Figure 2: di-substituted piperidine scaffold

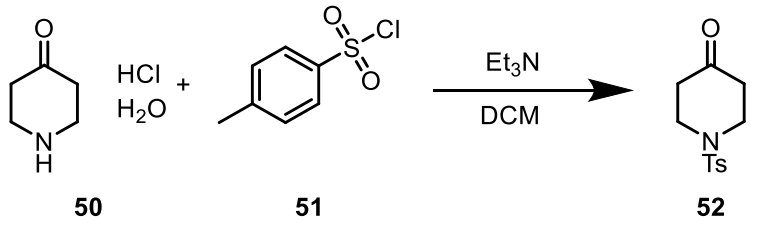
Lastly, it was possible by following the same procedure to synthesize **49** in 47% yield. This shows that the established protocol is feasible for Scheme 1 and therefore former work of the Grenning research group. The Grenning group looks forward to trying Boc protected piperidines (**38b**) in the near future. Nonetheless the synthesis of 49 provides a precedent for the possibility of this reaction to create polyfunctionalized compounds. Further research regarding this topic could yield in *tri*-substituted piperidines. Another application of this procedure could focus on asymmetry. As mentioned in the Tsuji-Trost allylic alkylation part of this work by using chiral ligands in the palladium catalyzed reaction enantioenriched starting materials could be generated and if the oxidative amidation afterwards will be followed by cyclization to yield benzothiazoles.

4. Experimental

If not otherwise specified heating if given was achieved on stir-heat plates using aluminum heating blocks (Pie-Blocks, ChemGlass Life Science). Glassware was flamed dried or in the oven at 38 °C for at least 24 h. Dry toluene, THF and DCM were achieved by running them through an activated alumina column under argon done by a commercial solvent purification system. Commercially available substances were not further purified. Air and moister sensitive allylic alkylation were performed under nitrogen flow and nitrogen atmosphere in dried glassware.

Reaction progress was monitored by thin-layer chromatography (TLC) and visualized by UV irradiation and KMnO4 stain. 1H NMR spectra were obtained at 298 K in $CDCl_3$, DMSO-d_6 or CD_3CN on 400 MHz or 500 MHz spectrometer from Bruker and referenced to residual solvent peaks. The chemical shifts (δ) are reported in parts per million (ppm). Coupling constants (*J*) are reported in Hz. The following notation is used: br – broad signal, s – singlet, d – doublet, t – triplet, q – quartet, p – pentet, m – multiplet, dd –doublet of doublets, dt – doublet of triplets, dq – doublet of quartet, dp – doublet of pentet, and ddd – doublet of doublet of doublets.[7]

Tosylation of 4-piperidone



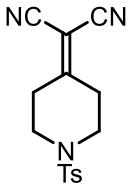
50 **51** **52**

Scheme 18: Preperation of 1-tosylpiperidin-4-one

To obtain 1-tosylpiperidin-4-one (**52**) a mixture of 4-piperidone monohydrate hydrochloride (**50**) (1.00 equiv., 3.07 g, 20.00 mmol) and triethylamine (Et_3N) (2.10 equiv., 5.30 mL, 42.00 mmol) in DCM (40 mL, 0.5 M) was stirred at room temperature for 5 minutes before adding slowly 4-toluenesulfonyl chloride (**51**) (1.01 equiv., 3.85 g, 20.20 mmol) and continuing stirring for an additional hour. Reaction completion was monitored via TLC in 25% EtOAc in Hex. The mixture was transferred with an aliquot of 10 mL DCM into a 250 mL separatory funnel and partitioned with 40 mL of deionized water and brine. The aqueous layer was extracted twice with 40 mL DCM and the combined organic layers were washed with 120 mL saturated ammonium chloride solution to remove triethylamine and twice with brine. Then the solution was dried over Na_2SO_4 and concentrated via rotary evaporator. A crude yield of 80% (4.04 g) was recorded.

R_f = 0.21 in 25% EtOAc in Hex

Synthesis of alkylidenemalononitrile



53

Figure 3: alkylidenemalononitrile

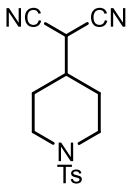
To synthesize 2-(1-tosylpiperidin-4-ylidene)malononitrile (**53**) into a solution of crude 1-tosylpiperidin-4-one (**42**) (1.20 equiv., 6.02 g, 20.00 mmol) in toluene (17.00 mL, 1 M) malononitrile (1.00 equiv., 1.10 g, 16.66 mmol), ammonium acetate (0.5 equiv., 0.64 g, 10 mmol), and glacial acetic acid (0.10 equiv., 0.10 mL, 2.00 mmol) were added. The reaction vessel was equipped with a Dean-Stark apparatus and heated at reflux overnight. Joints were greased with commercially available lubricant. The

reaction mixture was then concentrated under vacuum and 38 °C. Crude material was dissolved in 50 mL DCM, transferred into a 500 mL separatory funnel and washed with 50 mL $NaHCO_3$ (sat. aq.) to quench any remaining acetic acid. The aqueous layer was extracted twice with 50 mL DCM. The combined organics were washed with 50 mL deionized water and two times with 50 mL brine, dried over anhydrous Na_2SO_4, and concentrated by rotary evaporation. The crude material was then columned on silica gel with 25% EtOAc and Hex as an eluent and showed 24% yield. 1H NMR spectra in $CDCl_3$ showed full conversion of starting material and purity of 95% or greater.

R_f = 0.45 in 25% EtOAc in Hex

1H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, *J* = 8.2 Hz, 2H), 7.35 (d, *J* = 8.0 Hz, 2H), 3.27 (t, *J* = 5.8 Hz, 4H), 2.85 (t, *J* = 5.8 Hz, 4H), 2.45 (s, 3H)

Synthesis of 2-(1-tosylpiperidin-4-yl)malononitrile



38a

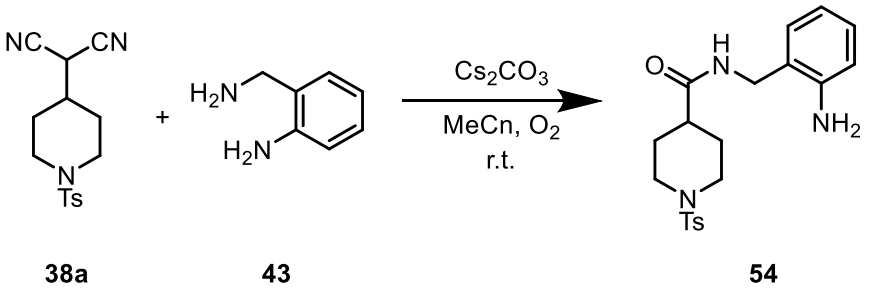
Figure 4: 2-(1-tosylpiperidin-4-yl)malononitrile

2-(1-tosylpiperidin-4-yl)malononitrile (**38a**) was achieved by a reductive Knoevenagel reaction. To a solution of crude 1-tosylpiperidin-4-one (**52**) (1.00 equiv., 2.04 g, 8.04 mmol) in DMSO (32.10 mL, 0.25 M) malononitrile (1.20 equiv., 0.64 g, 9.64 mmol), diethyl 2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (1.20 equiv., 2.44 g, 9.64 mmol) commonly known as Hantzsch ester and piperidine (0.20 eqiv., 0.16 mL, 1.61 mmol) were added. The solution was heated to 60 °C and stirred overnight. Reaction completion was monitored via TLC in 30% Ac in Hex. After completion the reaction was cooled down in an ice bath and slowly quenched with 20 mL of 0.5 M HCl solution, cooled in an ice bath, and 20 mL deionized water. Crashed out yellowish white precipitation was filtered off via vacuum filtration and washed with cold EtOH. 1H NMR spectra in $CDCl_3$ showed full conversion of starting material and purity of 95% or greater and no further purification was needed. Reported yield was 57%.

R_f = 0.57 in 30% Ac in Hex

1H NMR (400 MHz, $CDCl_3$) δ 7.69 – 7.62 (m, 1H), 7.35 (d, *J* = 8.1 Hz, 1H), 3.97 (s, 1H), 3.58 (s, 0H), 2.45 (s, 1H), 2.39 – 2.27 (m, 1H), 2.06 – 1.88 (m, 2H), 1.71 – 1.57 (m, 1H)

Synthesis of 2-(1-tosylpiperidin-4-yl)-3,4-dihydroquinazoline



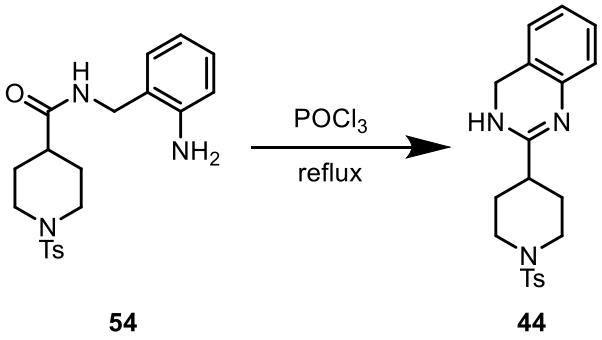
38a **43** **54**

Scheme 19: Synthesis of N-(2-aminobenzyl)-1-tosylpiperidine-4-carboxamide

For the synthesis of 2-(1-tosylpiperidin-4-yl)-3,4-dihydroquinazoline a cyclization was performed of N-(2-aminobenzyl)-1-tosylpiperidine-4-carboxamide. A solution of **38a** (1.00 equiv., 0.30 g, 1.00 mmol), 2-(aminomethyl)aniline (**43**) (2.00 equiv., 0.24 g, 2.00 mmol) and cesium carbonate (2.00 equiv., 0.65 g, 2.00 mmol) in MeCN (10.00 mL, 0.10 M) at room temperature was sparged with O_2 for at least 20 minutes and stirred for 5 h under O_2 atmosphere. The complete conversion of **38a** was observed via TLC in 30% EtOAc + Hex. After reaction completion the mixture was then concentrated. The crude material was then purified via column chromatography on silica gel using 3% MeOH in DCM as an eluent and a yield of 58% was recorded. 1H NMR spectra in $CDCl_3$ showed full conversion of starting material and purity of 95% or greater.

R_f = 0.21 in 3% MeOH in DCM

1H NMR (400 MHz, $CDCl_3$) δ 7.30 (t, *J* = 6.0 Hz, 1H), 6.79 (d, *J* = 8.0 Hz, 2H), 6.61 (d, *J* = 7.9 Hz, 2H), 6.14 – 6.04 (m, 2H), 5.75 (dd, *J* = 7.9, 1.2 Hz, 1H), 5.64 (td, *J* = 7.3, 1.2 Hz, 1H), 4.15 (s, 2H), 2.75 (dt, *J* = 11.5, 3.7 Hz, 2H), 1.67 (p, *J* = 1.8 Hz, 4H), 1.58 (s, 3H), 1.42 (td, *J* = 11.7, 2.7 Hz, 2H), 1.35 – 1.24 (m, 1H), 0.97 – 0.88 (m, 2H), 0.75 (qd, *J* = 11.5, 4.1 Hz, 2H)



54 **44**

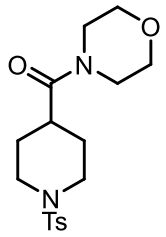
Scheme 20: Preperation of 2-(1-tosylpiperidin-4-yl)-3,4-dihydroquinazoline

To obtain the final product 2-(1-tosylpiperidin-4-yl)-3,4-dihydroquinazoline (**44**) N-(2-aminobenzyl)-1-tosylpiperidine-4-carboxamide (**54**) (1.00 equiv., 0.04 g, 0.10 mmol) was stirred in $POCl_3$ (0.50 mL, 0.20 M) and heated to 105 °C and refluxed in a pressure vial for 90 minutes. The reaction completion was observed via TLC in 5% MeOH in DCM. After full conversion the reaction mixture was allowed to reach room temperature, followed by an ice bath to reach 0 °C and then slowly 2.00 M NaOH was added until a pH of 7 was observed, which was about 20 mL over a duration of half an hour. For pH measurement pH test paper rolls (Fisherbrand) were used, ranging from 1 to 12. The reaction mixture was then three times extracted with 20 mL DCM and the combined organic layers washed twice with 60 mL brine and dried over Na_2SO_4. The solution was then filtered and concentrated via rotary evaporation. The crude product was then dissolved under heating in $CHCl_3$ and after cooling the precipitate was filtered off. Due to solubility a 1H NMR was performed in $DMSOd_6$ and showed purity of 95% or higher. A yield of 32% was obtained.

R_f = 0.11 in 5% MeOH in DCM

1H NMR (400 MHz, DMSO) δ 7.64 (d, *J* = 8.1 Hz, 2H), 7.46 (d, *J* = 7.9 Hz, 2H), 7.19 – 7.09 (m, 1H), 7.06 – 6.96 (m, 2H), 6.91 (d, *J* = 7.9 Hz, 1H), 4.55 (s, 2H), 3.72 (dt, *J* = 12.2, 3.5 Hz, 2H), 2.42 (s, 3H), 2.35 – 2.25 (m, 1H), 2.20 (td, *J* = 12.0, 2.6 Hz, 2H), 1.94 – 1.86 (m, 2H), 1.77 (qd, *J* = 12.3, 3.9 Hz, 2H)

oxidative amidation using MMPP



47

Figure 5: Morpholino(1-tosylpiperidin-4-yl)methanone

A reaction outline is shown in Scheme 16. The solvent screening (Table 1) was done under the same conditions throughout. The starting material **38a** (1.00 equiv., 0.06 g, 0.20 mmol), the base cesium carbonate (3.00 equiv.,0.20 g, 0.60 mmol), morpholine (**45**) (5.00 equiv., 0.10 mL, 1.00 mmol) were stirred under N_2 atmosphere for 10 minutes in the solvent (4.00 mL, 0.05 M). MMPP (**46**) (1.20 equiv., 0.15 g, 0.24 mmol) was added and stirred for an additional 3 hours. The reaction was quenched with 4 mL of deionized water. The mixture was extracted twice with 4 mL DCM, the combined organic layers were washed with 15 mL deionized water and brine, dried over Na_2SO_4 and concentrated via rotary evaporation. The conversion of **36a** was recorded via 1H NMR 400 MHz spectra in $CDCl_3$ and TLC in 15% Ac in Hex. Aside from the amidation product morpholino(1-tosylpiperisin-4-yl)methanone (**47**) we obtained 1-tosylpiperidine-4-carboxylic acid as side-product (**48**). The best outcome was observed using DMF as solvent and recorded a yield of 50% after purification of the crude material via silica gel column with 30% Ac in Hex as an eluent.

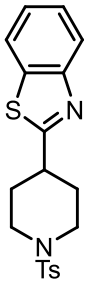
R_f = 0.19 in 30% Ac in Hex

1H NMR (400 MHz, $CDCl_3$) δ 7.68 – 7.62 (m, 2H), 7.32 (d, *J* = 7.8 Hz, 2H), 3.80 – 3.73 (m, 2H), 3.63 (s, 5H), 3.58 (s, 2H), 3.40 (s, 2H), 2.43 (s, 3H), 2.48 – 2.33 (m, 3H), 1.98 – 1.83 (m, 2H), 1.75 (dd, *J* = 13.9, 3.7 Hz, 2H), 1.25 (s, 3H), 0.86 (s, 1H)

The altered reaction using 3 Å molecular sieves proceeded as following. The drying agent was activated by continuous stirring under high vacuum and heated in an oil bath to 210 °C overnight and afterwards was stored in an oven. Two solution were prepared under N_2 atmosphere. Solution one containing cesium carbonate (3 equiv., 0.20 g, 0.60 mmol), MMPP (1.20 euiv., 0.15 g, 0.24 mmol) and 0.10 g of molecular sieves in 2 mL of DMF and stirred at room temperature for 10 minutes. Solution two contained **38a** (1.00 equiv., 0.06 g, 0.20 mmol) and 0.10 g of molecular sieves in 2 mL

DMF and stirred for 10 minutes at room temperature. Afterwards solution one was transferred in solution two via syringe and stirred for additional 10 minutes. Afterwards morpholine (5.00 equiv., 0.10 mL, 1.00 mmol) was added and stirred overnight. The completion of the reaction was monitored via TLC in 30% Ac in Hex. The mixture was then quenched with 2 mL 0.5M HCl and extracted twice with 5 mL DCM. The combined organic layers were washed with 15 mL deionized water and brine. The crude material was purified via column chromatography over silica gel using 15% Ac in Hex as an eluent. A pure yield of 17% was recorded.7

Synthesis of benzothiazole



42a

Figure 6: 2-(1-tosylpiperidin-4-yl)benzo[d]thiazole

An outline of the reaction to synthesize **42a** is shown previously in Scheme 17. For Table 2 and Table 3 the same procedure was used. **38a** (1.00 equiv., 0.06 g, 0.20 mmol), *para*-methoxyphenol (**39b**) (2.00 equiv., 0.05 g, 0.40 mmol) and cesium carbonate (2.00 equiv., 0.13 g, 0.40 mmol) in MeCN (2.00 mL, 0.10 M) were sparged with O_2 and stirred under O_2 atmosphere for 2h at room temperature. Afterwards the reaction mixture was sparged with N_2 under continuous stirring and N_2 atmosphere was established before adding 2-aminothiophenol (2.00 equiv., 0.04 mL, 0.40 mmol). The reaction was stirred under N_2 atmosphere overnight. Then the reaction was quenched with 6 mL 0.5 M HCl and stirred for an additional 2h. Reaction completion was monitored via TLC in 25% EtOAc in Hex. After completion the mixture was three times extracted with 2 mL DCM. The combined organic layers were washed with 10 mL deionized water and following with 10 mL brine and dried over Na_2SO_4, then filtered and concentrated via rotary evaporization. The crude material was then purified via column chromatography on silica gel with 10% EtOAc in Hex as an eluent. Via 1HNMR in $CDCl_3$ the product was observed with an impurity of 7% of **40b**.

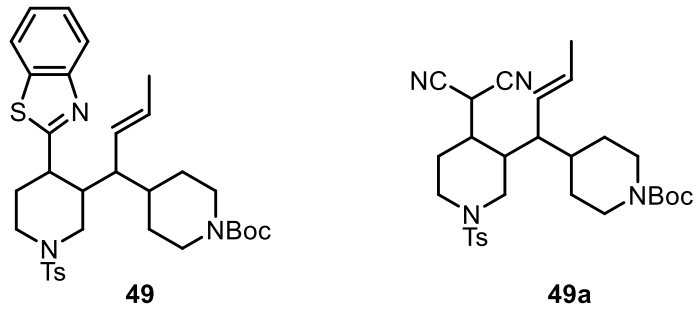
The yield of **42a** was recorded with 54% using phenol (**49a**) with a purity of 95% or higher according to 1HNMR in $CDCl_3$.

Heating the reaction mixture after adding 2-aminothiophenol to 40°C and continuing the procedure as explained above a yield of 61% was recorded with a purity of 95% or higher according to 1HNMR in $CDCl_3$ using *para*-methoxyphenol (**39b**).

R_f = 0.31 in 25% EtOAc + Hex

1H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.3 Hz, 1H), 7.85 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.71 – 7.64 (m, 2H), 7.50 – 7.41 (m, 1H), 7.36 (t, *J* = 8.3 Hz, 3H), 3.88 (dd, *J* = 12.1, 3.7 Hz, 2H), 3.05 (tt, *J* = 11.4, 3.8 Hz, 1H), 2.51 (td, *J* = 11.8, 2.7 Hz, 2H), 2.45 (s, 3H), 2.24 (dd, *J* = 13.6, 3.6 Hz, 2H), 2.12 – 1.98 (m, 2H), 1.25 (s, 1H)

Synthesis of *di*-substituted piperidine



49 **49a**

Figure 7: di-substituded piperidine and according starting material

The starting material **49a** was synthesized following the protocol of former work of the Grenning research group, found in the supplementary information of "*Vicinal Stereocenters via Asymmetric Allylic Alkylation and Cope Rearrangement: A Straightforward Route to Functionally and Stereochemically Rich Heterocycles*" by Nilova et al. 2023.[7] Afterwards the procedure was carried out as in the Synthesis of benzothiazole as described before. Reaction completion was monitored via TLC in 30% EtOAc in Hex. After completion the mixture was three times extracted with 2 mL DCM. The combined organic layers were washed with 10 mL deionized water and following with 10 mL brine and dried over Na_2SO_4, then filtered and concentrated via rotary evaporization. The crude material was purified via column chromatography with 25% EtOAc in Hex as eluent. Via 1HNMR in $CDCl_3$ a purity of 95% or higher was observed in a yield of 47%.

R_f = 0.44 in 30% EtOAc in Hex

1H NMR (400 MHz, $CDCl_3$) δ 7.67 – 7.60 (m, 2H), 7.35 – 7.24 (m, 2H), 6.91 – 6.81 (m, 4H), 5.51 – 5.37 (m, 1H), 5.27 – 5.16 (m, 1H), 4.12 (qd, *J* = 7.2, 1.4 Hz, 1H), 3.80 – 3.75 (m, 3H), 3.10 (s, 1H), 3.04 (s, 2H), 2.42 (d, *J* = 10.1 Hz, 3H), 2.31 – 2.23 (m, 1H), 2.17 (s, 1H), 2.17 (s, 3H), 2.11 – 1.96 (m, 3H), 1.72 – 1.58 (m, 3H), 1.57 (d, *J* = 13.0 Hz, 1H), 1.45 (d, *J* = 1.4 Hz, 9H), 1.31 – 1.21 (m, 3H)

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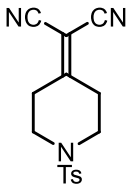
6. Appendix



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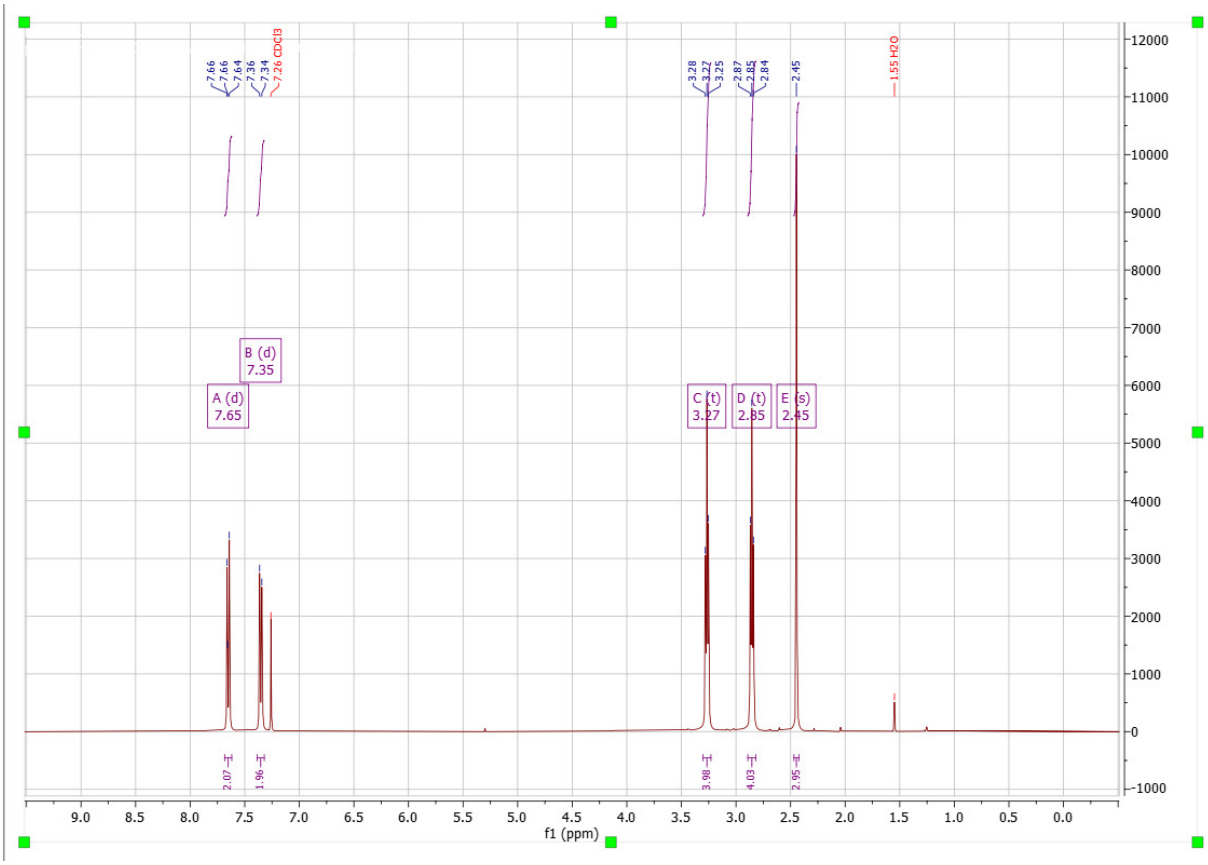

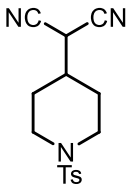
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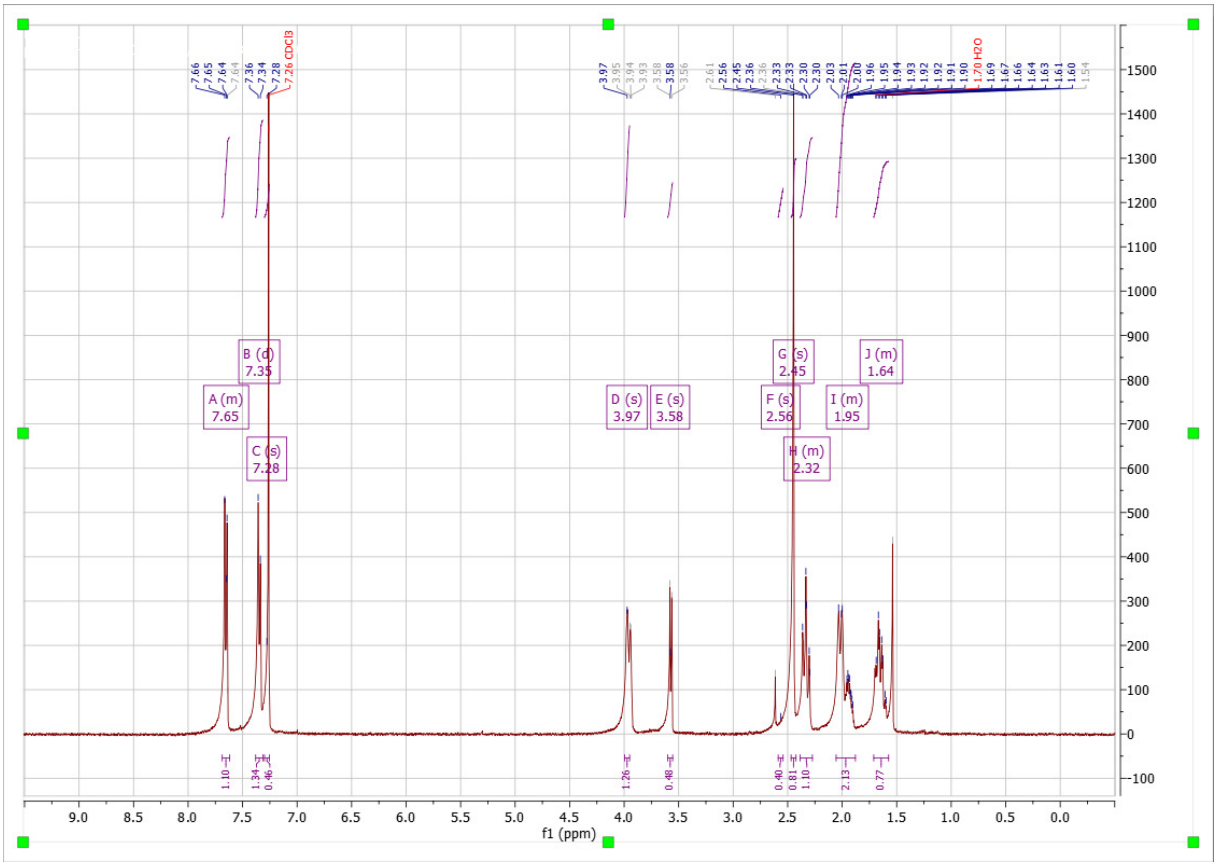
Ts

38a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I (m)
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J (m)
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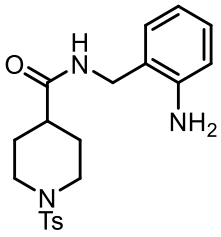
f1 (ppm)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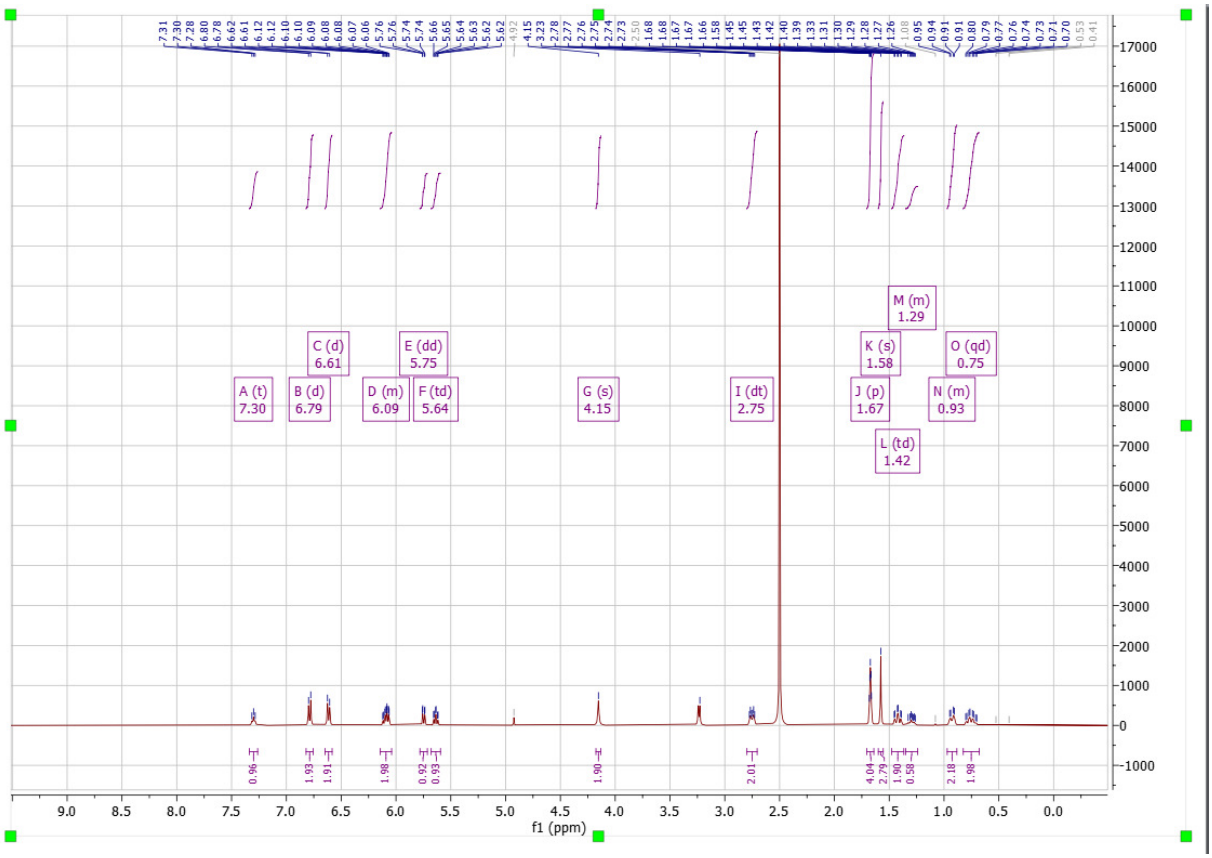
H
N
NH2
N
Ts

54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I (dt) 2.75
J (p) 1.67
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L (td) 1.42
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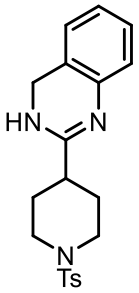
N (m) 0.93
O (qd) 0.75
f1 (ppm)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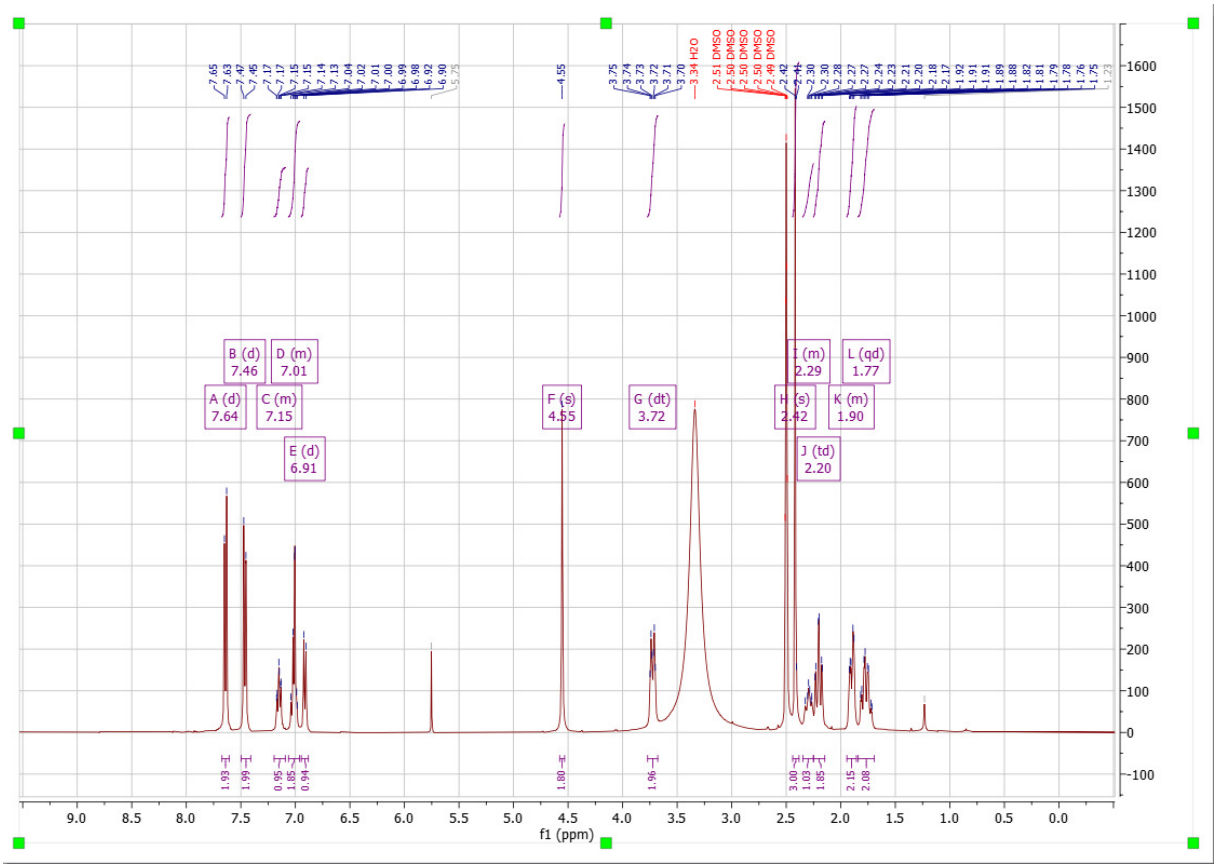
N
N
Ts

44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K (m) 1.90
J (td) 2.20
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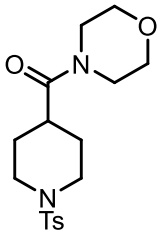
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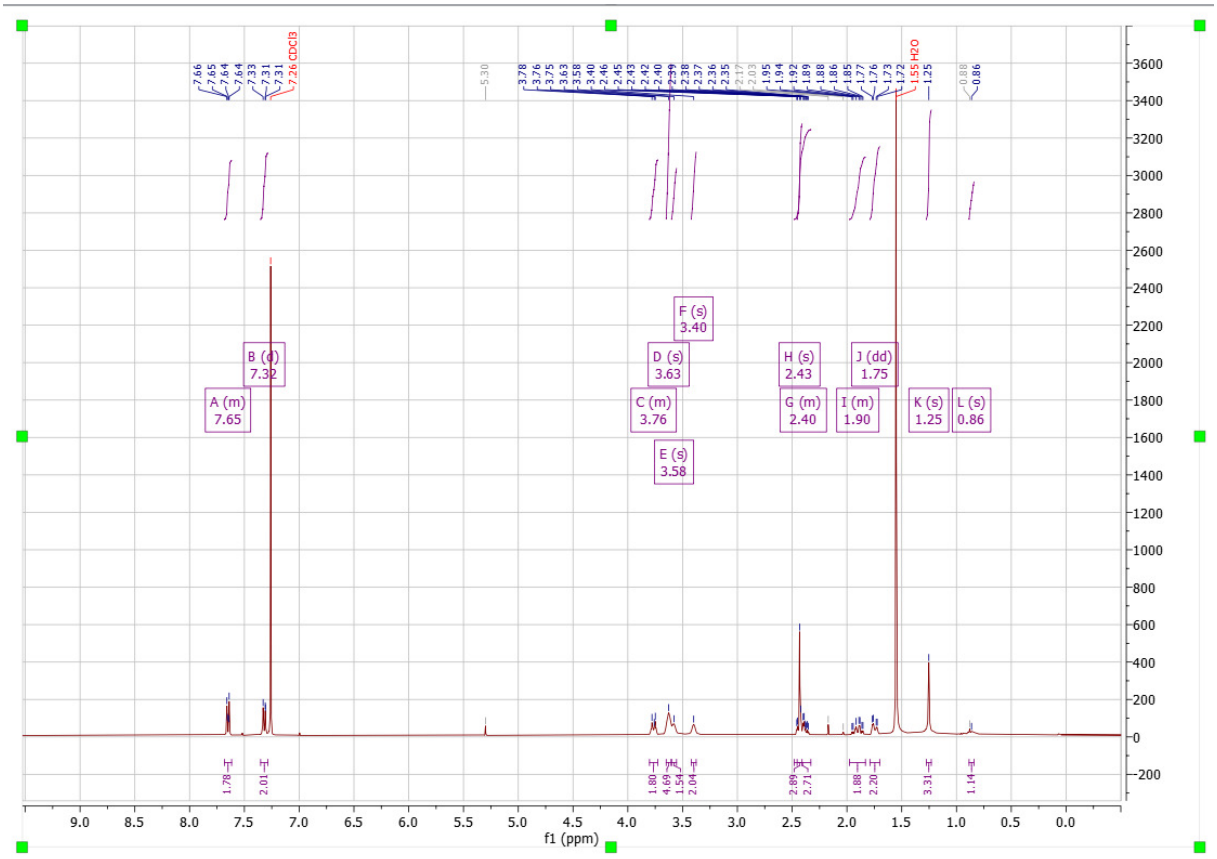
N
O
N
Ts

47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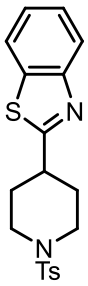
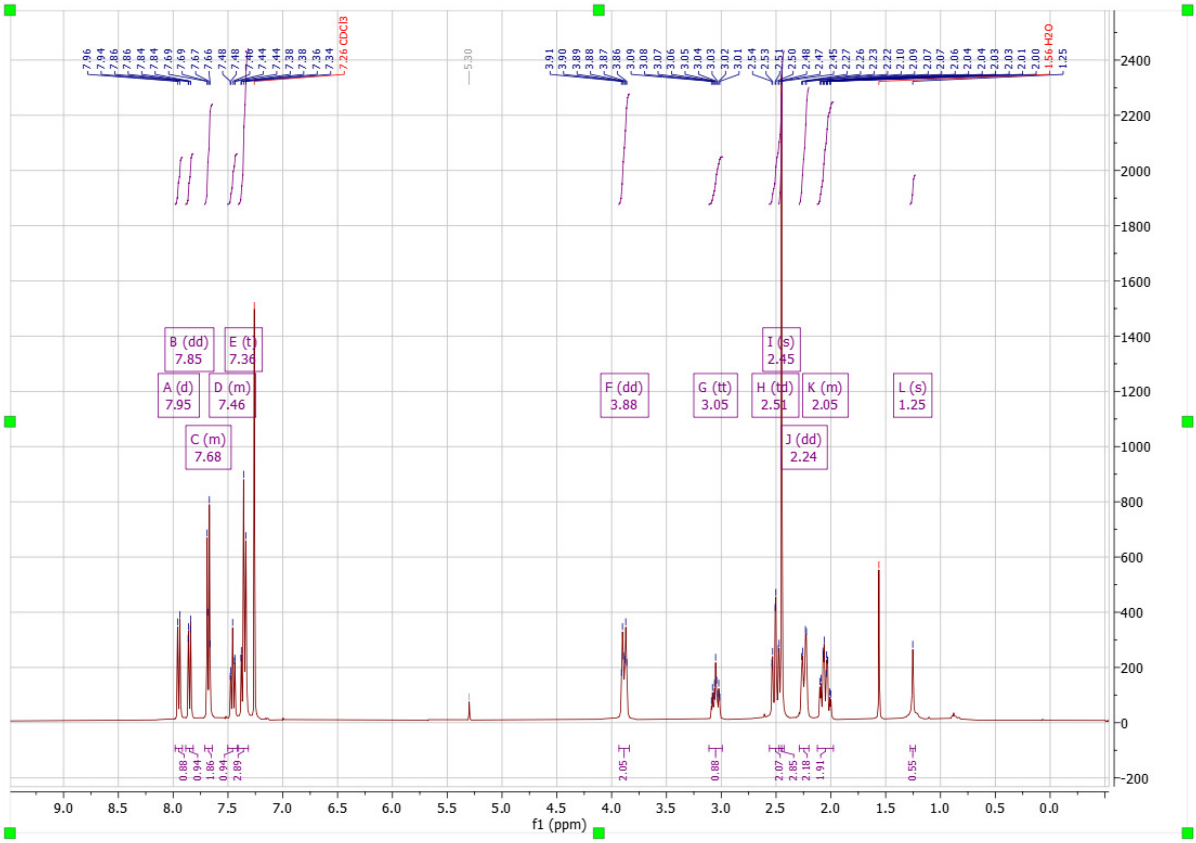

S
N
N
Ts

42a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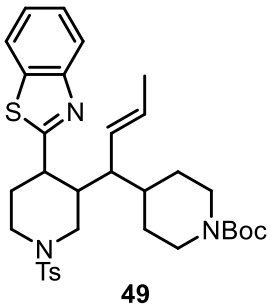
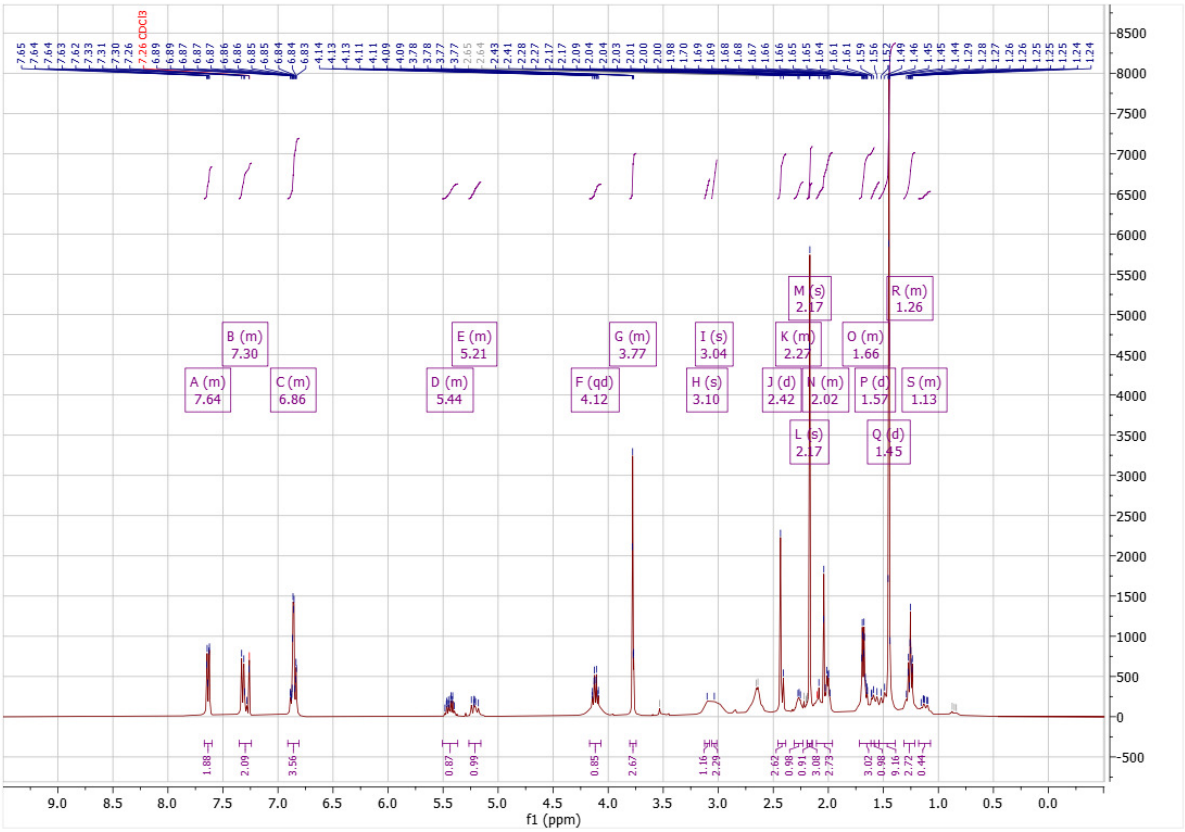
f1 (ppm)


S
N
N
Ts
NBoc

49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H (s) 3.10
I (s) 3.04
J (d) 2.42
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L (s) 2.17
M (s) 2.17
N (m) 2.02
O (m) 1.66
P (d) 1.57
Q (d) 1.45
R (m) 1.26
S (m) 1.13
f1 (ppm)