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Transformation of Amides into Highly Functionalized Triazolines

Tove Slagbrand,[a] Alexey Volkov,[a] Paz Trillo,[a] Fredrik Tinnis[a] and Hans Adolfsson*[a,b]*

a) Department of Organic Chemistry, Arrhenius Laboratory, Stockholm University, SE-106 91 Stockholm, Sweden.

b) Department of Chemistry, Umeå University, SE-901 87 Umeå, Sweden.

KEYWORDS: Triazolines • Amides • Enamines • Chemoselective Reduction • Azides

ABSTRACT: Triazoles and triazolines are important classes of heterocyclic compounds known to exhibit biological activity. Significant focus has been put into the development of synthetic approaches for the preparation of triazoles and they are today easily obtainable through a large variety of protocols. The number of synthetic procedures for the formation of triazolines on the other hand is limited and further research in this field is required. The protocol presented here gives access to a broad scope of 1,4,5-substituted-1,2,3-triazolines through a one-pot transformation of carboxamides. The two step procedure involves a $Mo(CO)_6$-catalyzed reduction of tertiary amides to afford the corresponding enamines, followed by *in situ* cycloaddition of organic azides to form triazolines. The amide reduction is chemoselective and allows for a wide variety of functional groups such as esters, ketones, aldehydes and imines to be tolerated. Furthermore, a modification of this one-pot procedure gives access to the

corresponding triazoles. The chemically stable amide functionality is demonstrated to be an efficient synthetic handle for the formation of highly substituted triazolines or triazoles.

INTRODUCTION:

Triazolines have been evaluated as potential anticonvulsant drugs are also important intermediates in organic synthesis.[1] Wolff and co-workers discovered that 1,2,3-triazolines could be prepared by a 1,3-dipolar addition reaction of olefins and azides in 1912.[2] Huisgen and L'abbé have demonstrated that the reactivity of the alkenes in this type of cycloaddition is significantly influenced by the electronic properties of the double bond and reactions with electron deficient alkenes required long reaction times, weeks or even months.[3] Weinreb and co-workers later reported that the rate of cycloaddition could be increased substantially by employing high pressure (12 kbar) and a selection of 1,4,4-trisubstituted triazolines were prepared.[4] Electron-rich olefins such as enamines are much more reactive and have been demonstrated to readily undergo a regiospecific 1,3-dipolar addition with azides to afford 1,2,3-triazolines under mild conditions (Figure 1a).[5] Nevertheless, in these cases the enamines were prepared and isolated prior to use which limited the overall yields and the scope of the target heterocycles. Only a few examples of *in situ* formation of enamines in azide cycloaddition reactions have been reported. Bianchetti *et al*. showed that enamines prepared from acetone and aliphatic amines reacted with aryl azides in a tandem reaction to yield triazoles but merely a few triazolines were isolated.[6] Stradi and Pocar later employed aldehydes or ketones in combination with primary or secondary amines to form enamines *in situ*.[7] A good number of triazolines were isolated in low to excellent yields in this case; however, only 4-nitrophenylazide was used as the azide component (Figure 1b). Amine-catalyzed formation of enamines has also been employed

in some cases for subsequent cycloaddition reactions.[8] The use of an azide in this type of reaction only gives the saturated triazoline as an intermediate yielding triazole as the final product after elimination of the amine catalyst (Figure 1c).[9] An alternative route for the formation of triazolines can be achieved through the cycloaddition reaction of diazo compounds with Schiff bases.[10]

Herein we demonstrate a mild and efficient one-pot transformation of stable amides that gives access to a wide scope of highly functionalized triazolines (Figure 1d). We also show that 1,2,3-triazoles, which normally are obtained by the Cu-catalyzed azide-alkyne cycloaddition reaction (the "click"-reaction),[11] can be generated using our protocol.

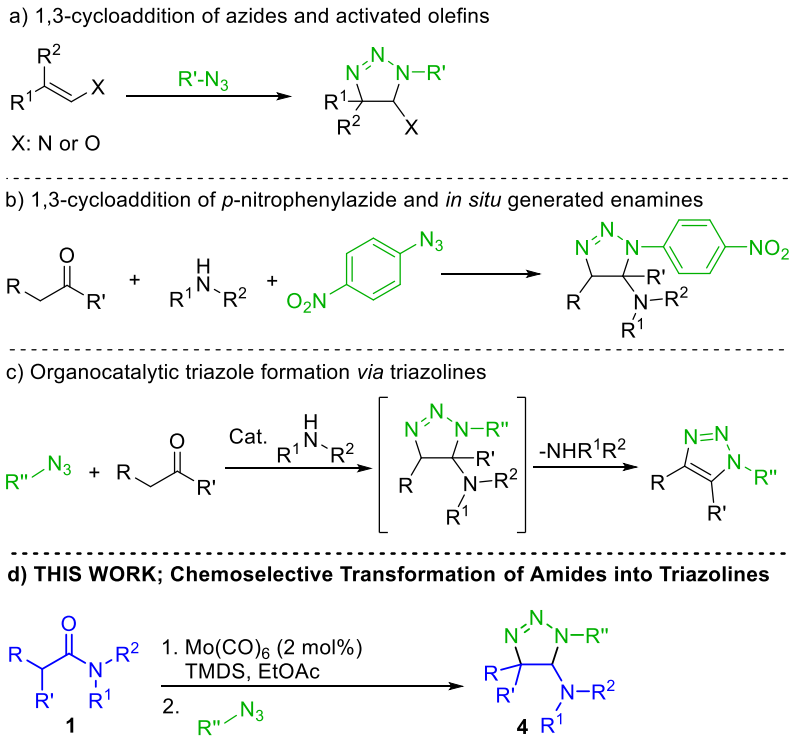


Figure 1. 1,3-dipolar cycloaddition of enamine and azide to yield triazolines or triazoles.

The developed protocol involves the reduction of amides to enamines using catalytic amounts of $Mo(CO)_6$ in combination with the inexpensive and stable silane 1,1,3,3-tetramethyldisiloxane (TMDS). An unprecedented chemoselectivity of this transformation is demonstrated and functional groups such as nitro, nitrile, ester, ketone, imine and aldehydes were tolerated. The target heterocyclic compounds were obtained via *in situ* cyclization reaction of enamines with a wide scope of aromatic and aliphatic azides.

RESULTS AND DISCUSSION:

We have recently reported on a mild and chemoselective protocol for the hydrosilylation of tertiary amides into either aldehydes or amines (Figure 2).[12] Enamine formation was observed when employing benzylic and aliphatic amides. Since only a limited amount of amide reduction protocols are known to afford enamines,[13] we initiated an optimization of the conditions for the $Mo(CO)_6$-catalyzed system to furnish these valuable compounds. Furthermore, we envisioned that a mild and chemoselective formation of enamines from highly stable carboxamides could be exploited in the synthesis of 1,2,3-triazolines, and that this approach would considerably broaden the scope and synthetic accessibility of these heterocycles.

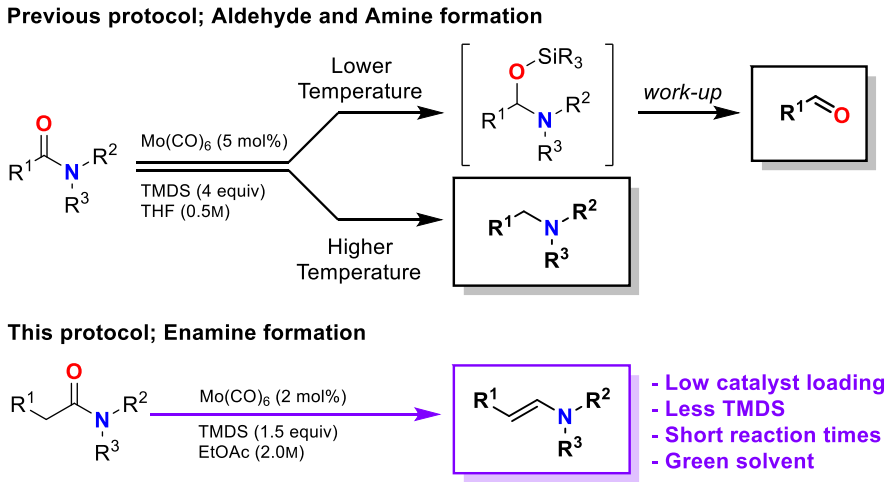
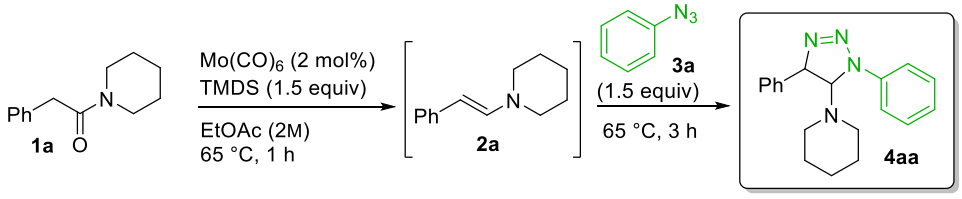


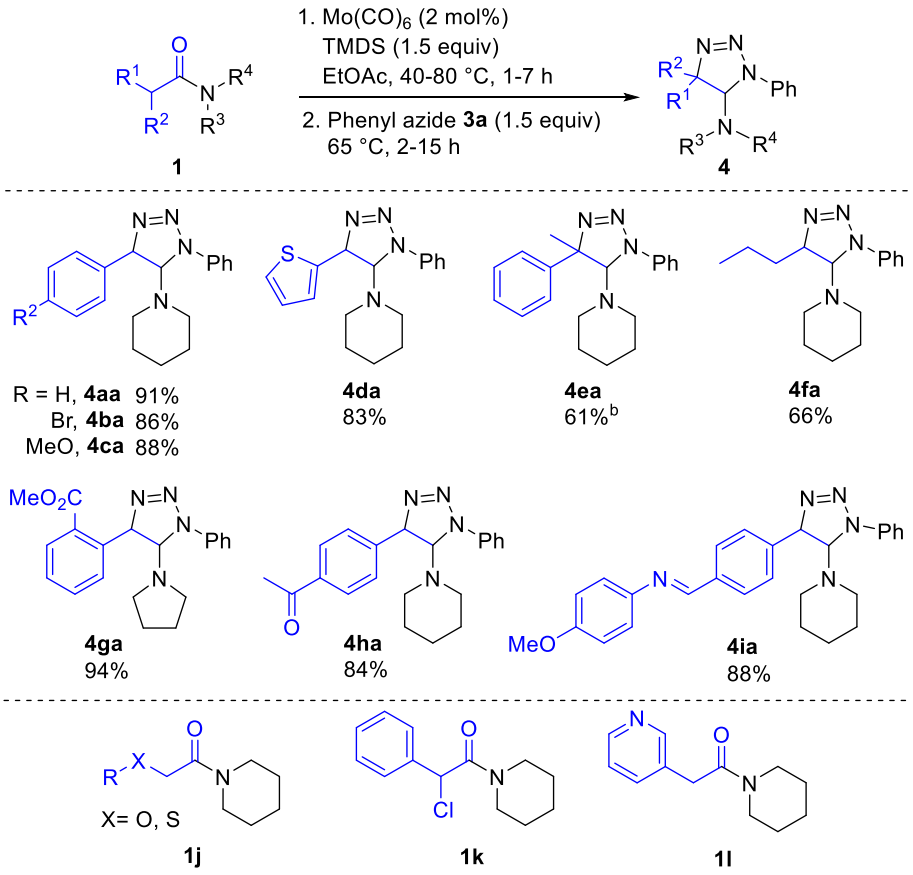
Figure 2. $Mo(CO)_6$-catalyzed chemoselective reduction of amides extended to include formation of enamines.

After thorough optimization of the conditions it was found that the catalytic loading of $Mo(CO)_6$ can be decreased to 2 mol% and the amount of TMDS to 1.5 equivalents allowing for high conversion of this type of amides to the corresponding enamines. Surprisingly, the screening of different solvents revealed that the reduction of the amides could be performed in ethyl acetate[14] (see Supporting Information), which further demonstrates the high chemoselectivity of the system. With the optimized conditions for the enamine formation in hand we decided to attempt the 1,3-dipolar addition reaction using phenyl azide **3a** (Scheme 1). The enamine reaction was completed in 1 hour and by the subsequent addition of 1.5 equivalents of **3a**, compound **4aa** could be isolated in 91% yield after 3 h reaction time. We then investigated if the transformation could be performed as a tandem process with all the components present from the start. It was observed that the reduction of the amide was retarded and progressed very slow; however, some amount of triazoline was detected in the crude ^{1}H NMR, suggesting that the catalyst is poisoned by the final product rather than the azide. The product inhibition of the catalyst was also demonstrated by employing 5 mol% of triazoline from the start in the reduction of amide, which resulted in a very low ^{1}H NMR yield of the enamine compared to the standard reaction (see Supporting Information).



Scheme 1. One-pot procedure for the formation of triazolines from amides.

Initially, a substrate evaluation investigating the reduction of different amides into enamines was performed. High ^{1}H NMR yields of the corresponding enamines derived from amides **1a**-**1d** were observed by employing catalytic amounts of $Mo(CO)_6$ and TMDS as the hydride source. The subsequent cycloaddition using phenylazide (**3a**) readily gave the triazolines **4aa-4da** in high isolated yields (Scheme 2). Munk and co-workers previously reported the cycloaddition between azides and enamines to be regiospecific and in the recent mechanistic study, the group of Houk found evidence for the reactions to be concerted.[5b,5c] The regiochemistry of the 1,4,5-substituted triazoline **4da** as shown in scheme 2 was confirmed by 1D NOE irradiation (see Supporting Information) which is in line with previous reports. An α-disubstituted amide (**1e)** was evaluated in the enamine formation reaction resulting in a mixture of *cis* and *trans* isomers. After the cycloaddition step the corresponding triazoline (**4ea**) was obtained as two diastereomers in a 2:1 ratio. The major diastereomer was separated and the relative stereochemistry was determined using ^{1}H NMR NOE experiment. By irradiating the signal of the CH_3-group an increase in intensity of the signal belonging to the adjacent proton was observed, indicating a cis relationship between these two groups. A few amide substrates were observed to be challenging to reduce and only small amounts of the corresponding enamines **2j**-**2l** were detected by ^{1}H NMR (Scheme 2). The enamine formation of purely aliphatic amides did not display a high selectivity and some amount of amine was detected by ^{1}H NMR spectroscopy. Thus, the propyl substituted triazoline **4fa** was obtained in a moderate yield of 66%. We were pleased to see that the high chemoselectivity of the amide reduction allowed for the presence of easily reducible functional groups such as esters, ketones and imines, ultimately accessing triazolines **4ga**, **4ha** and **4ia** in 94%, 84% and 88% yields, respectively.

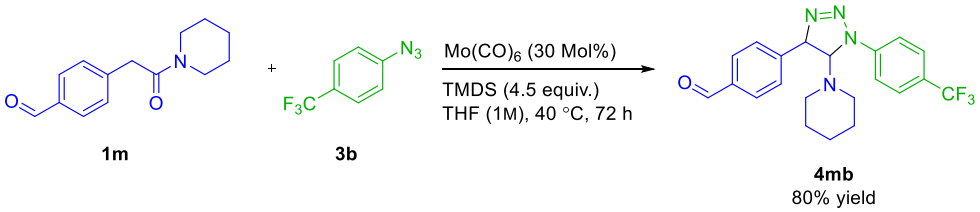


[a] Isolated yields. Step 1: $Mo(CO)_6$ (0.02 mmol), amide (1.0 mmol), dried ethyl acetate (0.5 mL, 2M), TMDS (1.5 equiv), 65 °C for 1 h. Step 2: azide (1.5 equiv), 65 °C for 2 h. For information about the conditions for each substrate see Supporting Information Tables S2-3. [b] Diastereomers were obtained in a 2:1 ratio in which the major compound was determined to have a cis relationship between the phenyl group and the piperidine moiety.

Scheme 2. Evaluation of tertiary amides in the chemoselective reduction and subsequent cycloaddition reaction with organic azides.[a]

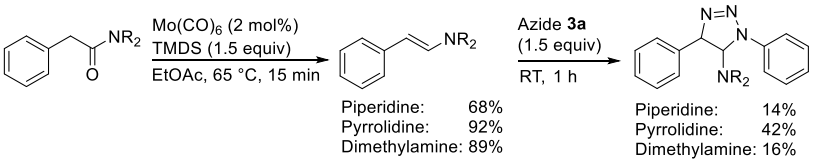
It was observed that aldehyde substituents on the amide were not affected by the reduction conditions but rather from the enamine being formed during the reaction. We hypothesized that the presence of an azide from the start would intercept the enamine and although the tandem

reaction was observed to be slow we adopted this strategy for the *p*-aldehyde substituted amide **1m** (scheme 3). To overcome the issue of catalyst poisoning by triazoline, the loading of $Mo(CO)_6$ had to be increased to 30 mol% and the reaction required 72 h to reach completion. Nevertheless, this demonstrates that the $Mo(CO)_6$-catalyzed reduction of amides to enamines can even tolerate aldehydes and triazoline **4mb** was isolated in 80% yield.



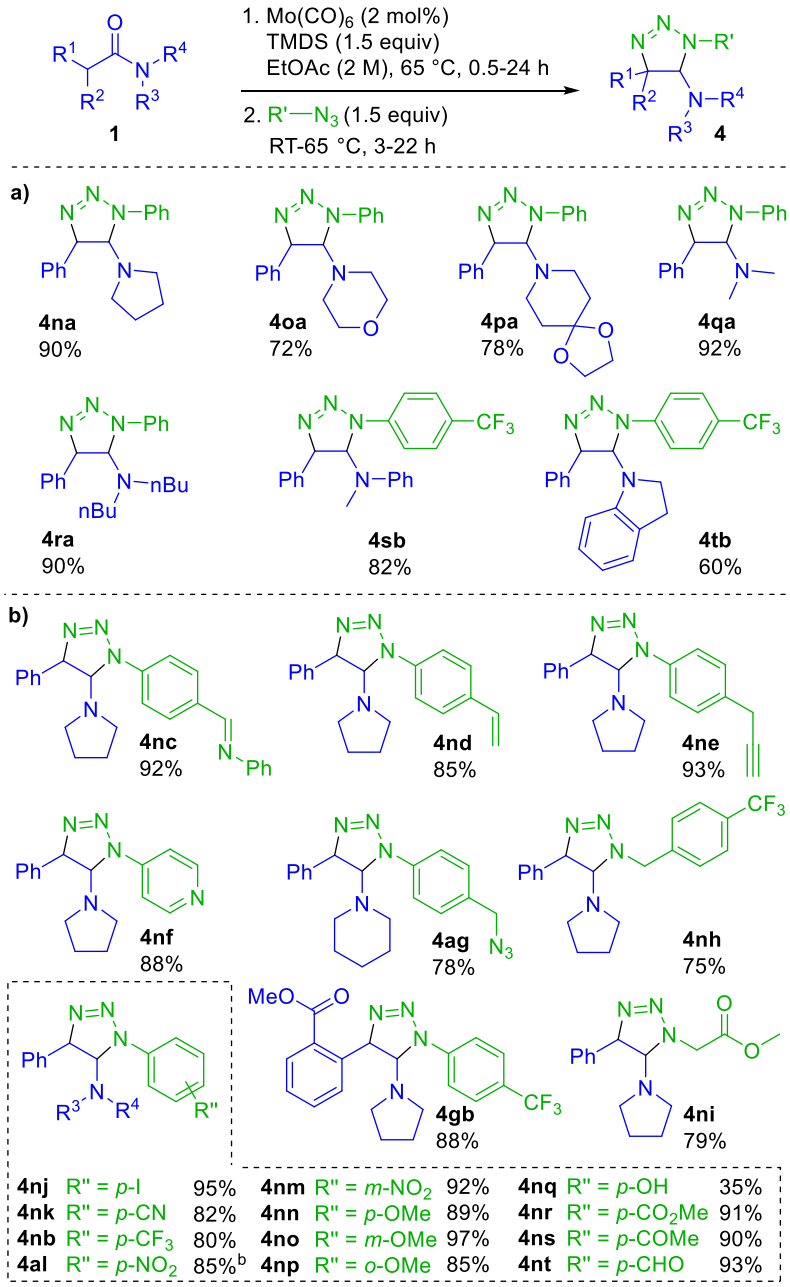
Scheme 3. Transformation of aldehyde containing amide in a tandem process.

We decided to evaluate how different amine parts affected the reactivity in the reduction step towards enamine and in the 1,3-cycloaddition reaction (Scheme 4). An aliquot of the $Mo(CO)_6$ – catalyzed reduction was taken and analyzed by ^{1}H NMR after 15 minutes reaction time. Amides derived from both pyrrolidine and dimethylamine showed high conversion into the corresponding enamines, while the piperidine amide reacted slower (Scheme 4). The pyrrolidine based enamine was proven to be most reactive in the cycloaddition reaction, which is in line with previous studies.[15] The dimethylamine and piperidine derived enamines were less reactive and only about 15% of the corresponding triazolines were observed after 1 h reaction time.



Scheme 4. Investigation on the reactivity of different amides in enamine and triazoline formation.

Amides derived from cyclic as well as non-cyclic amines were evaluated in the transformation and the corresponding triazolines were obtained in good to excellent yield (Scheme 5a). The *N*-methyl-*N*-phenyl amide **1s** proved to be more difficult to reduce and a mixture of enamine, amine and products of C-N bond cleavage were observed under the standard reaction conditions. The mechanism of $Mo(CO)_6$-catalyzed amide reduction was thoroughly investigated by Pannell and co-workers demonstrating the formation of silylhemiaminal as intermediate.[16] It was envisioned that the presence of a catalytic amount of base would promote the collapse of tetrahedral intermediate into enamine yielding a cleaner reaction. Gratifyingly, the addition of triethyl amine (10 mol%) to the reaction mixture resulted in the selective formation of the corresponding enamine (**2s**) in >95% ^{1}H NMR yield after 15 hours. The more reactive *p*-CF_3 phenyl azide (**3b**) was used in the subsequent cycloaddition reaction and the target triazoline **4sb** was obtained in 82% isolated yield. Primary and secondary amides were also evaluated in the $Mo(CO)_6$-catalyzed reduction; however, the corresponding enamines were not observed. Next, the azide scope of the 1,3-cycloaddition reaction was evaluated using pyrrolidine amide **1n** in most of the cases (Scheme 5b). The one-pot system showed to be compatible with a wide variety of azides substituted with functional groups such as aldimine (**4nc**), olefin (**4nd**), alkyne (**4ne**), iodo (**4nj**), cyano (**4nk**), nitro (**4al**), ester (**4nr**) and ketone (**4ns**). In the cyclization reaction with aldehyde substituted azide (**3t**) high isolated yield of the corresponding triazoline (**4nt**) could be obtained. This further demonstrates that an electron-poor azide reacts more readily with the enamine in comparison to the aldehyde. It was observed that benzyl azides reacted sluggish at 65 °C and employing the compound **3g** containing both aromatic and benzylic azides resulted in the selective formation of triazoline **4ag** in 78% yield with preservation of the benzylic azide.

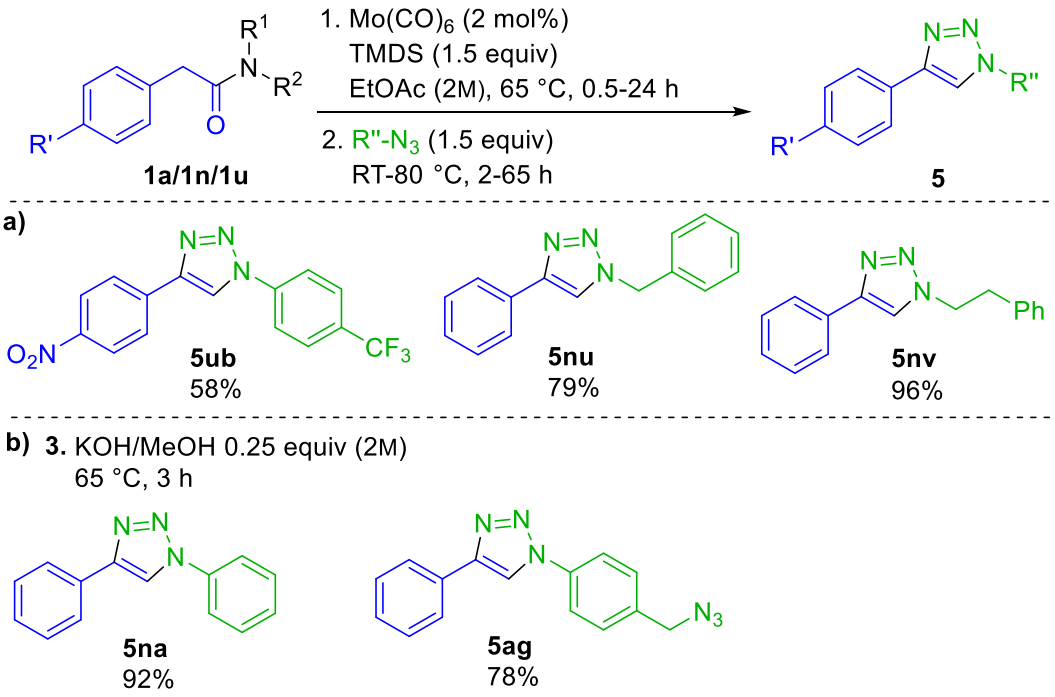


[a] Isolated yields. Step 1: $Mo(CO)_6$ (0.02 mmol), amide (1.0 mmol), dry ethyl acetate (0.5 mL, 2M), TMDS (1.5 equiv), 65 °C for 30 min. Step 2: azide (1.5 equiv) at 65 °C for 3 h. For information about conditions for each substrate see Supporting Information Table S2-3. [b]piperidine substituted triazoline.

Scheme 5. Scope evaluation of a) the amine part of the amide substrates and b) different organic azides.[a]

On the other hand the *p*-CF_3 substituted benzyl azide was demonstrated to be more reactive which enabled access to the benzylated triazoline **4nh** after a prolonged reaction time of 18 h. Heteroaryl azide and an aliphatic azide bearing electron-withdrawing groups could also be employed under mild reaction conditions and the corresponding triazolines **4nf** and **4ni** were obtained in 88% and 79% yield, respectively.

It was noticed that the cyclization reaction was highly influenced by electronic properties of the azides and whereas the electron-deficient substrates reacted readily, the electron-rich required longer reaction times and higher reaction temperatures. Xie *et al.* recently reported on 1,3-cycloadditions of enamines employing a variety of perfluorinated aryl azides.[15] The triazolines formed with these electron-deficient groups were unstable and rearranged spontaneously into the corresponding amidines. When we evaluated the combination of enamine and azide both bearing electron withdrawing substituents, the corresponding triazole was obtained instead. Thus, the unsaturated heterocyclic compound **5ub** was isolated in 58% yield under standard reaction conditions (Scheme 6). Furthermore, forcing unreactive benzyl and aliphatic azides to undergo cycloaddition at higher reaction temperatures (80 °C) enabled the access to the corresponding triazoles (**5nu**, **5nv**) in good to excellent yields in 24 h and 65 h, respectively. Triazolines are known to be thermally labile[4] and the elevated temperature required for these substrates most likely promoted the elimination of the amine to form triazole. Munk and co-workers showed that triazoles were obtainable from the corresponding triazolines by subjecting them to an excess of KOH/MeOH solution under reflux conditions.[5a] A minor screening of conditions was therefore performed in order to evaluate if triazoles could be accessed in a 3-step one-pot fashion.



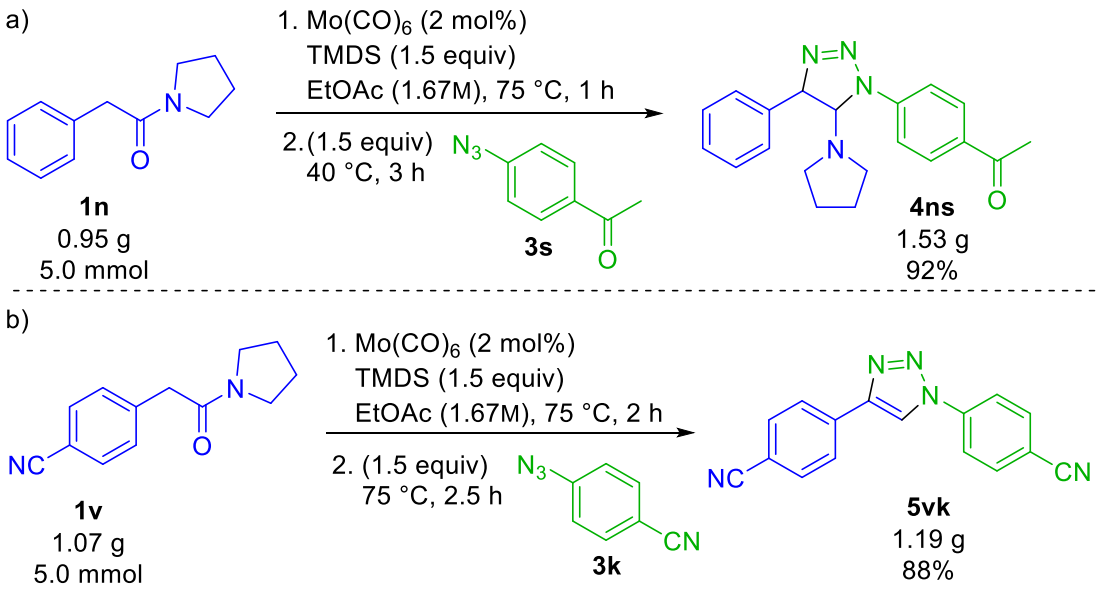
[a] Isolated yields. Step 1: $Mo(CO)_6$ (0.02 mmol), amide (1.0 mmol), dried ethyl acetate (0.5 mL, 2M), TMDS (1.5 equiv), 65 °C for 30 min. Step 2: azide (1.5 equiv) at 65 °C, 3 h. Information of conditions for each substrate see Supporting Information Table S4

Scheme 6. a) Direct transformation of amides into triazoles. b) 3 step / one-pot procedure for triazole formation.[a]

It was found that the addition of catalytic amounts of base, after the completed triazoline reaction, initiated the amine elimination and pure triazole products could be obtained. Triazoles **5na** and **5ag** were isolated in good to high yield using this one-pot methodology (Scheme 6b).

To demonstrate the versatility of the one-pot procedures for triazoline and triazole formation, we carried them out in preparative scale (Scheme 7). Although we never experienced any issues one should always be aware of the explosion risks associated with organic azides.[17] By performing the reaction on a 5 mmol scale in a two-necked round bottomed flask fitted with a condenser,

triazoline **4ns** could be obtained in a 92% yield (1.53 g) (Scheme 7a). Nitriles were well tolerated in the $Mo(CO)_6$-catalyzed amide reduction and the reaction of **1v** and *p*-cyano phenyl azide (**3k**) led directly to the formation of the corresponding unsaturated heterocycle and did not require the catalytic addition of base. Thus, triazole **5vk** was obtained in 88% yield after washing the crude reaction mixture with pentane (Scheme 7b).



Scheme 7. Large-scale transformation of amides into a) triazoline and b) triazole.

CONCLUSIONS:

To conclude, we have for the first time demonstrated a mild an efficient transformation of stable carboxamides into either triazolines or triazoles. The amides were reduced into enamines employing catalytic amounts of $Mo(CO)_6$ in combination with TMDS as the hydride source using EtOAc as solvent. The reduction is characterized by an unprecedented level of chemoselectivity and functional groups such as nitro, nitriles, esters, and imines were tolerated.

Moreover, using the developed reduction protocol it was possible to form enamines containing ketone and aldehyde functionalities which cannot be accessed through classical condensation reaction. The enamines were subjected to organic azides to undergo 1,3-cycloaddition reaction in a one-pot procedure to yield the corresponding triazolines. The preparation of these heterocyclic compounds from amides is a new concept that should be found useful and a broad scope of the triazolines was obtained using this methodology. Direct formation of triazoles was observed for certain substrates. Alternatively, triazoles were generated from the triazolines by the addition of a catalytic amount of base in a three-step one-pot procedure. The attractive properties of this system along with the scalability and low cost/high stability of TMDS should make this method applicable in both academic and industrial settings. Due to the mildness and high level of chemoselectivity it can easily be envisioned that amides could serve as stable protection groups, which can be transformed into triazolines or triazoles at the late stage of synthesis.

ASSOCIATED CONTENT

Supporting Information. This material is available free of charge via the Internet at http://pubs.acs.org.

The following files are available free of charge.

Experimental data and compound characterization (PDF)

AUTHOR INFORMATION

Corresponding Author

Hans Adolfsson* E-mail: hans.adolfsson@umu.se

Fredrik Tinnis* E-mail: fredrik.tinnis@su.se

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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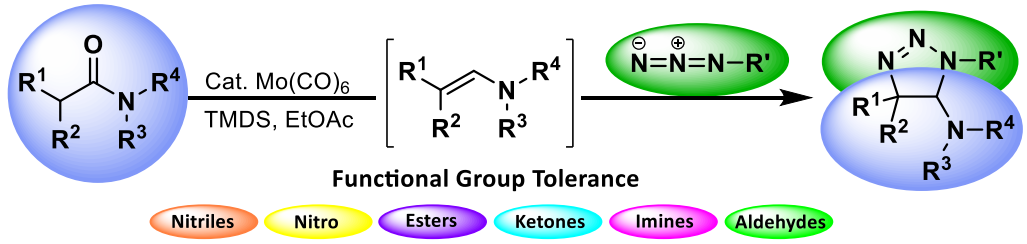
SYNOPSIS


Cat. Mo(CO)6
TMDS, EtOAc
Functional Group Tolerance
Nitriles
Nitro
Esters
Ketones
Imines
Aldehydes