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Facile Preparation of Pyrimidinediones and Thioacrylamides by Reductive Functionalization of Amides

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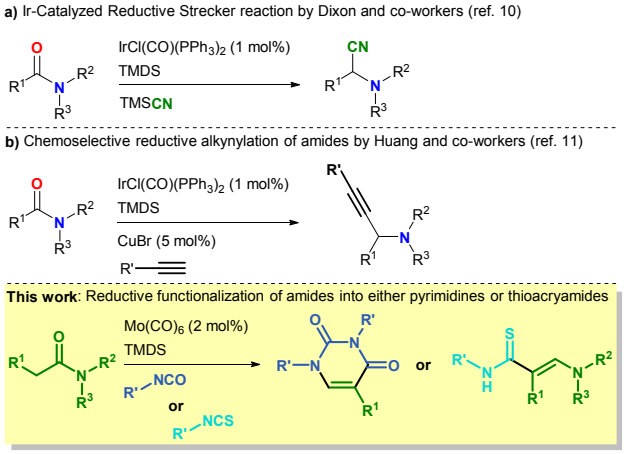
The development of an efficient protocol for the reductive functionalization of amides into pyrimidinediones and amino-substituted thioacrylamides is presented. Enamines are generated in a highly chemoselective amide hydrosilylation reaction catalyzed by molybdenum hexacarbonyl in combination with 1,1,3,3-tetramethyldisiloxane. The direct addition of either isocyanate or isothiocyanate generates the corresponding pyrimidinediones and 3-aminothioacrylamides in high yields.

The chemical stability of amides stems from the resonance over the C-N and C-O bonds and this functional group is considered as the least reactive among the carboxylic acid derivatives.[1] While these features makes the carboxamide an attractive functionality which is included in a wide variety of different compounds, the use of amides as synthetic intermediates is less widespread.[2] The concept of activation and functionalization of amides has been known for over a century;[2a,3] however, recent research based on triflic anhydride has made a substantial breakthrough in terms of selectivity and mildness in the transformation of amides, with notable contributions from Charette,[4] Maulide[5] and Huang.[6] Activation of amides can also be performed employing mild reduction protocols and functionalization can proceed through trapping of either the electrophilic species (iminium ion) or the nucleophilic species (enamine) being formed. The group of Chida has for instance reported on several protocols for the reductive functionalization of amides based on the Schwartz reagent.[7] Nagashima and co-workers have demonstrated a powerful Ir-catalyzed protocol for the chemoselective reduction of amides into amines or enamines,[8] this system have also been exploited in total synthesis and for the activation-functionalization of amides.[9] The groups of Dixon and Huang recently illustrated the prodigious potential of reductive functionalization of amides with their reported protocols for cyanation[10] and alkynylation (Scheme 1a-b).[11]



Scheme 1. Ir-catalayzed reductive functionalization of amides by the group of a) D. J. Dixon and b) P.-Q. Huang. This work, Mo-catalyzed reductive functionalization of amides into pyrimidinediones and thioacrylamides.

We have developed a highly chemoselective protocol for the reduction of amides into amines, aldehydes or enamines based on catalytic amounts of $Mo(CO)_6$ in combination with TMDS (1,1,3,3-tetramethyldisiloxane) as the reductant.[12] This catalytic system was recently applied in the reductive functionalization of amides into 4,5-dihydrotriazoles[13] and 4,5-dihydroisoxazoles.[14] Herein, we report on an efficient and high yielding methodology for the reductive functionalization of amides into pyrimidinediones and amino-substituted thioacrylamides. The pyrimidine functionality is of great biological significance and is found in nucleic acids and in vitamins. This substrate class has also been demonstrated to possess antineoplastic, antibacterial and antiviral properties.[15] 3-Aminothioacrylamides are well known as versatile synthons

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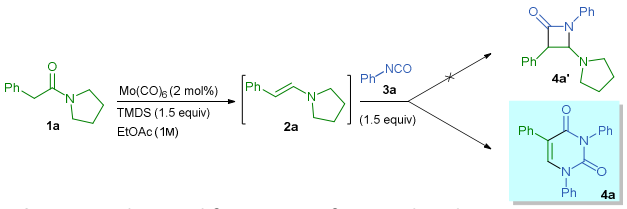
in organic chemistry.[16] The reductive functionalization protocol presented herein is based on a mild hydrosilylation of amides into the corresponding enamines. The enamine reaction towards isocyanate and isothiocyanate for the preparation of these compounds is known, albeit there is a lack in terms of versatility and the scopes of the available protocols are limited.[17]

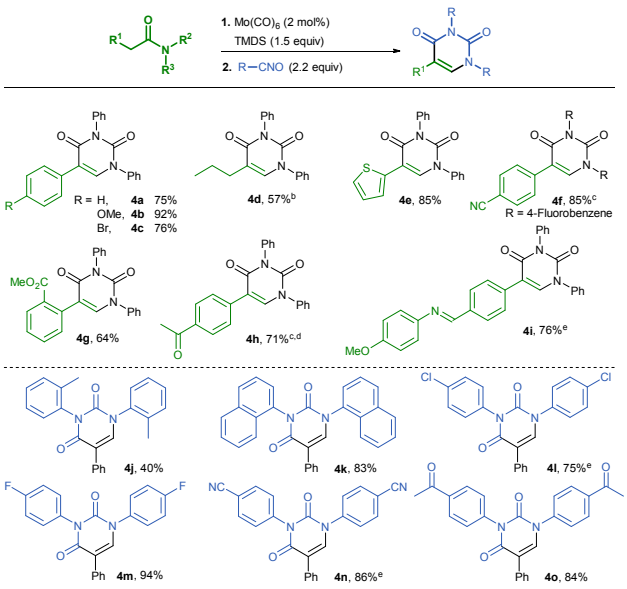
The initial screening for the $Mo(CO)_6$-catalyzed reductive functionalization of amides was aimed towards the formation of β-amino-β-lactams, since phenylisocyanate is known to react with enamines to form these products (Scheme 2, **4a'**).[18] The transformation would require one equivalent of the isocyanate reagent; however, β-amino-β-lactam **4a'** could not be observed and only pyrimidinedione **4a** was formed (Scheme 2). Two equivalents of the isocyanate are needed in the transformation of amide via enamine to pyrimidinedione and an optimization of the conditions for the preparation of **4a** was performed.



Scheme 2. Observed formation of pyrimidinedione **4a**.

The chemoselective reduction of the amides into enamines is performed using 2 mol% of $Mo(CO)_6$ in combination with 1.5 equivalents of TMDS. The reactions are carried out in the environmentally friendly solvent ethyl acetate at 65 °C, and the addition of 2.2 equivalents of phenylisocyanate to compound **2a** afforded pyrimidine **4a** in 75% isolated yield. The solubility of the pyrimidinedione products enables a facile purification process and they could be collected from the crude reaction media after precipitation with pentane. With the optimized conditions at hand we performed a substrate evaluation with initial focus on variation of the amides. Methoxy- and bromo-substituted amide gave pyrimidine **4b** and **4c** in 92% and 76% yields, respectively. The reduction of aliphatic amide substrates is not as selective towards enamine formation and some amount of amine is always observed, thus only a 57% yield of compound **4d** could be obtained. Heteroaromatic substituted amides are well tolerated and pyrimidine **4e** was isolated in 85% yield. We then evaluated amides substituted with other reducible functional groups. The highly chemoselective $Mo(CO)_6$-catalyzed reduction of amides ultimately gives access to pyrimidines functionalized with cyano, ester, ketone and even an imine group (**4f**-**4i**) in high yields. Notably, some of these enamines would be difficult to prepare *in situ* from the corresponding aldehydes.

Next, a selection of isocyanates was evaluated and halogen, cyano and keto-substituted substrates were all well tolerated (**4l**-**4o**). The diminished yield of pyrimidine **4j** is attributed to sterical hindrance imposed by the methyl groups in ortho position and for this compound we also observed rotamers in the NMR spectroscopic analysis. Benzyl and aliphatic isocyanates were also screened; however, unfortunately no pyrimidinediones were formed.

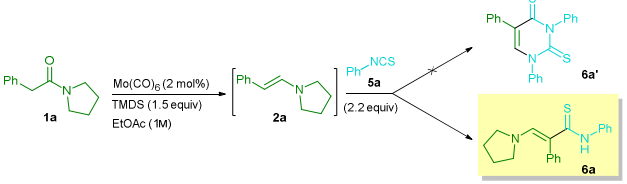


[a] **1.** The reduction using $Mo(CO)_6$ and TMDS (1.5 equiv) in EtOAc (1M) was performed at 65 °C for 0.5-5 h. **2.** Isocyanate (2.2 equiv), 65 °C, 4 h. [b] **1.** performed at 80 °C. [c] Isocyanate (3.5 equiv), 72 h. [d] **1.** performed at 40 °C. [e] **2.** 16 h.

Table 1 Substrate evaluation in the reductive functionalization of amides into pyrimidinediones.

We then decided to employ isothiocyanates to investigate if these substrates would lead to thioacrylamides as previously reported.[19] The drawback of these protocols is that the enamines had to be prepared and isolated before use, which can be problematic. Moreover, there is a two-step protocol available for thioacrylamide synthesis based on activation and functionalization of amides.[20] In this case a selection of tertiary acetamides was treated with $POCl_3$ and DMF to generate the corresponding chloro-substituted iminium perchlorates that were isolated. The desired thioacrylamides were subsequently afforded by subjecting these compounds to an aqueous solution of sodium sulfide (Na_2S).

The evaluation isothiocyanate **5a** (2.2 equiv) showed that no pyrimidinedithione (**6a'**) was formed and that only the corresponding amino-substituted thioacrylamide (**6a**) was generated (Scheme 4).



Scheme 3. Evaluation of isothiocyanates in the transformation of amides into amino-substituted thioacrylamides.

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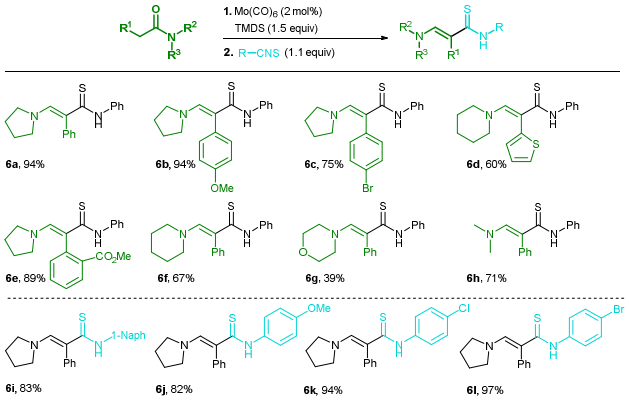
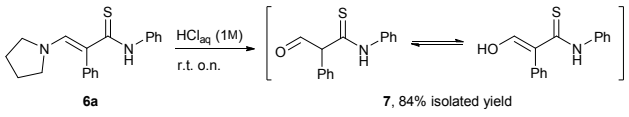
Thus, the reductive transformation of amides into thioacrylamides could be performed using 1.1 equivalents of isothiocyanate reagent and the scope can be found in Table 2. The screening of different amides showed that functional groups such as methoxy, bromo, thiophene and esters were tolerated (**6b**-**6e**). A decreasing trend in yield can be seen throughout amides derived from pyrrolidine (**6a**), *N*,*N*-dimethyl (**6h**), piperidine (**6f**) and morpholine (**6g**), which could be explained by the reactivity of the corresponding enamines where pyrrolidine enamine has the highest reactivity and morpholine based enamine is least reactive.[21] We also performed a small evaluation of different isothiocyanates such as 1-isothiocyanatonaphthalene (**6i**) and *p*-Meo (**6j**), *p*-Cl (**6k**) and *p*-Br-substituted (**6l**) isothiocyanatobenzenes in which all of the desired amino-substituted thioacrylamides were obtained in high yields (82%-97%).



[a] **1.** The reduction using $Mo(CO)_6$ and TMDS (1.5 equiv) in EtOAc (1M) was performed at 65 °C for 0.5-5 h. **2.** Isothiocyanate (1.1 equiv), 65 °C, 16 h.

Table 2. Substrate evaluation in the reductive functionalization of amides into 3-aminothioacrylamides.

The final thioacrylamide products viewed in Table 2 contains the same enamine moiety employed in the reaction; however, these do not react further in the presence of isothiocyanate in excess. Most likely due to the resonance stability of the system.[22] Nevertheless, it was possible to hydrolyze the thioamide-substituted enamine to afford the corresponding aldehyde (**7a**) in good yield by treating compound **6a** with HCl_{aq} (1M) (Scheme 4).



Scheme 4. Hydrolysis of enamine **6a** into the corresponding aldehyde.

A similar type of compound (3-oxo-*N*,3-diphenylpropanethioamide) was prepared by Pace *et al*. in their protocol for the synthesis of secondary thioamides by addition of organolithium reagents to isocyanates.[23] Their ^1H NMR analysis of this compound using $CDCl_3$ displayed a 1:1.2 ratio between the keto:enol form. In case of aldehyde-substituted thioamide **7**, the ^1H NMR spectra in $CDCl_3$ showed that this compound is completely shifted towards the enol form.

In conclusion, reductive functionalization of amides is an emerging area of research and recent developments have shown that amides can be transformed under mild conditions to a variety of different compounds. Herein, we have demonstrated that amides can be employed for a facile transformation into either pyrimidinediones or 3-aminothioacrylamides. All of the presented products are novel and have not previously been reported and the majority of the compounds were obtained in high yields. This protocol exhibits high chemoselectivity and functional group tolerance encompassing nitrile, ester, ketone and even aldimine functionalities, which clearly demonstrates the value of the concept of mild reductive functionalization of amides.

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