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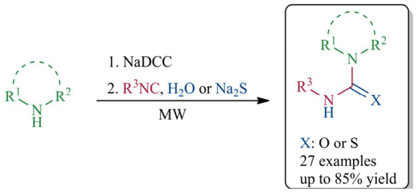

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A green, isocyanide-based three-component reaction approach for the synthesis of multisubstituted ureas and thioureas

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ABSTRACT

A one-pot, isocyanide based multicomponent protocol was presented starting from secondary amines towards (thio)urea derivatives and utilized for the construction of a diverse 27-membered chemical library. Following a green compatible microwave assisted condition, the formed *N,N'*-multisubstituted (thio)ureas were obtained in up to 85% yield.

1. Introduction

The formation of (un)symmetrical *N,N'*-multisubstituted (thio)ureas is well-known in the synthetic toolbar. They can be prepared easily from the corresponding amines upon treatment with iso(thio)cyanates or (thio)phosgene.[1-3] These conventional transformations proceed well but they are associated with high toxicity of the reagents. Therefore, recent efforts have focused on development of less toxic and more elegant routes involving catalysis and/or replacement of (thio)phosgene.

For novel urea synthetic approaches, most methods use transition metal catalyzed direct oxidative carbonylation of an amine with carbon dioxide or carbon monoxide[4], *in situ* formation of isocyanate[5a,b], transformations of carbamoyl azides, and carbamates as well as imidazole carbonylation of amines towards the corresponding carbamides[6a-g]. On the other hand, current synthetic strategies for the preparation of *N,N'*-substituted thioureas are based on classic methods such as application of thiophosgene[7], isothiocyanates[8] and carbon disulfide.[9] Hence, reactions of carbon disulfide as reactant with amines can afford a wide range of symmetrical and unsymmetrical thioureas in reasonable yields via a simple condensation in aqueous medium.[10]

A less explored synthetic strategy involves isocyanide-based redox reactions towards carbodiimides or carbamates as urea precursors (Figure 1). The oxidative treatment of isocyanides with bromine affords isocyanide dibromide, which can easily be converted into carbamate intermediates for the addition of primary alcohols.[11] Concerning the formation of carbodiimide and carbodiimidium salts, the simplest methods relied either on the assembly of isocyanides or

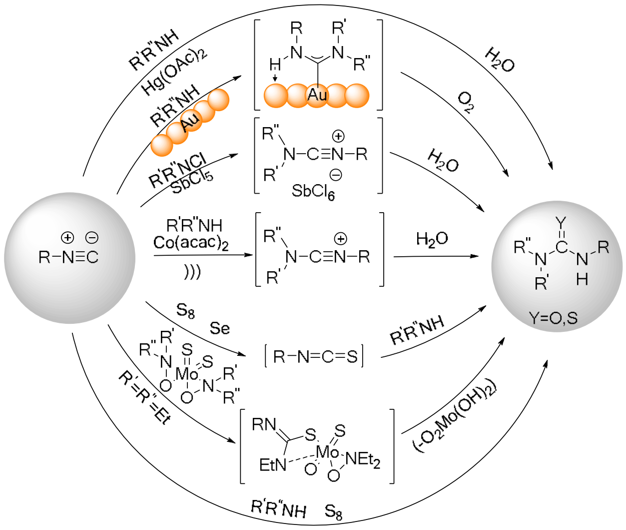

Figure 1. Isocyanide-based synthetic strategies towards (thio)ureas.

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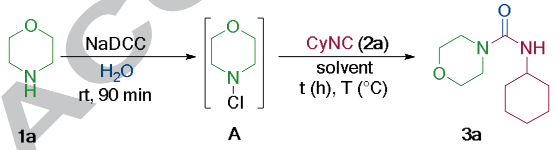
on isocyanide insertion into primary or secondary amines under oxidative conditions.[12-14] Of these, the work of Katriczky *et al.* should be mentioned as the first application of benzotriazole-1-carboximidoyl chlorides as *N*-chlorinated reactants with isocyanides. In this method, these compounds were exploited as precursors of stable synthetic equivalent intermediates for isocyanide dichloride towards the synthesis of *N,N'*-di- and –tri-substituted ureas. However, the applicability of this procedure is limited: the success of the final amination step depends strongly on the nucleophilicity of the amines.[13] The second exclusive example has disclosed isocyanide insertion into primary or secondary amines under oxidative conditions. The use of *tert*-butyl hydroperoxide (TBHP) and the presence of cobalt(II) acetylacetonate with additional ultrasonication afforded substituted ureas and thioureas. This method proceeded well with primary amines, but it was less effective for the treatment of secondary amines. Only two carbamides were represented in yields of 51 and 96% and only a single one from thiourea species with 21% yield. Other attempts led to traces of the products or no conversion.[14] Nevertheless, isocyanide-based transformations have a larger share in thiourea syntheses in comparison with the preparation of urea derivatives. Among others, a molybdenum-complex as sulfur and amine transfer reagent for isocyanide transformation towards thiourea and a selenium-induced isocyanide-to-isocyanate oxidation method were presented.[15-19] Furthermore, a three-component reaction (3CR) was also demonstrated by reacting isocyanides, aliphatic primary and secondary amines and sulfur as oxidant.[20]

Our aim was to develop a one-pot, facile and green 3CR method to synthesize highly diverse *N,N'*-multisubstituted carbamides and thiocarbamides from isocyanides and *in situ* formed *N*-chlorinated secondary amines in the presence of water or sodium sulfide as the third reactant.

2. Results and discussion

In a preliminary study, *N*-chloromorpholine **A** and cyclohexyl isocyanide **2a** were reacted. The required chlorination was accomplished *in situ* in water by treating morpholine **1a** with sodium dichloroisocyanurate (NaDCC).[21] After chlorination, subsequent addition of the isocyanide furnished desired compound **3a** isolated in a yield of 41%. Since unreacted NaDCC did not affect the formation and isolation of the target compound, the one-pot approach was applied for the further attempts and experiments.

First, our efforts focused on finding both a suitable water/solvent mixture and the optimal reaction temperature (Scheme 1 and Table 1).



Scheme 1. Model reaction.

For optimization, water-alcohol, water-dipolar aprotic media and biphasic systems (water with EtOAc, DCM and toluene) were tested at ambient (entries 2–10) and elevated temperatures (entries 11–15). In biphasic solvent mixtures (entries 2–4) no conversion (toluene) or poor yields were obtained (17% in DCM and 34% in EtOAc). Reactions carried out in dipolar-aprotic solvents such as DMF, MeCN, 1,4-dioxane and THF, provided moderate to good yields (50–67%, entries 5–8). Gratifyingly, the use of MeOH and 2-propanol (IPA) greatly increased the isolated yields (75% and 83%, Entries 9 and 10).

The application of the alcohol-water solvent mixtures at a temperature of 60 °C allowed shorter reactions. The yield in methanol was similar to that found at room temperature (72%, entry 11). The best isolated yield was accomplished in IPA (87%, entry 12). Further attempts were also made in IPA at higher temperatures to achieve improvements. Whereas a reaction at 80 °C (oil bath) proved to be less effective (73%, entry 13), application of microwave irradiation provided optimal conditions. Albeit, both 60 °C and 100 °C microwave temperatures afforded similar yields (83 and 85%, entries 14 and 15), dramatic decreases in reaction times are a great advantage. In accordance, further transformations were performed under highly-efficient microwave-assisted conditions (100 °C, 10 minutes, 250 W max. power).

Table 1. Solvent and temperature scope (optimization)[a]

Entry	Solvent	Temp. (°C)	Time (h)[b]	Isolated yield[c] (%)
1	H_2O	rt	24	41
2	toluene	rt	24	–
3	DCM	rt	24	17
4	EtOAc	rt	24	34
5	DMF	rt	24	50
6	MeCN	rt	24	65
7	1,4-dioxane	rt	24	66
8	THF	rt	24	67
9	MeOH	rt	24	75
10	IPA	rt	24	83
11	MeOH	60	2	72
12	IPA	60	2	87
13	IPA	80	1.5	73
14	IPA	60[d]	0.5	83
15	**IPA**	**100[d]**	**0.17**	**85**

[a] Reaction conditions: morpholine (0.5 mmol), NaDCC (0.55 mmol), water (0.5 mL), 90 min, rt, then solvent (1 ml), CyNC (0.5 mmol).

[b] Worked up when intermediate consumed.

[c] After recryst.

[d] μW: 100 °C, 10 min, 250 W.

With the optimal conditions in our hands, the transformation of several secondary amines (**1a-i**) such as heterocyclic (**1a-f**), aliphatic (**1g**) and benzylic derivatives (**1h** and **1i**) was conducted by cyclohexyl- (**2a**) *t*-butyl- (**2b**) 1,1,3,3-tetramethylbutyl (**2c**), 1-pentyl (**2d**), benzyl (**2e**) and phenylethyl (**2f**) isocyanides, affording the desired **3a-s** ureas with up to 85% yields (Figure 2). The applicability was limited for aliphatic isocyanides since aromatic isocyanides gave only trace amounts of the corresponding carbamides.[22] The best isolated yield was found in the reaction of *N*-chloromorpholine with cyclohexyl isocyanide (**3a**, 85%), whereas *N*-Boc-piperazine (**1c**) and decahydroquinoline (**1e**) as well as Walborsky's isocyanide **2c** gave the lowest yields. Hence, no significant correlation could be established regarding the amine type and reactivity.

Afterwards, our purpose was to exploit this optimal microwave-assisted protocol for the synthesis of thiourea derivatives with the use of sodium sulfide (Na_2S) as the nucleophilic partner. Unfortunately, the presence of water prohibited the formation of thiourea and preferred the urea synthesis. Thus, we slightly modified the reaction conditions and the one-pot, two-step protocol has been carried out in dry 2-propanol under argon atmosphere. Other efforts such as utilizing *in situ* generated H_2S from Na_2S in combination with acids (KH_2PO_4, sulfuric acid or acetic acid) or other sulfur-based reactants like sodium thiosulfate ($Na_2S_2O_3$) did not afford the desired final product.

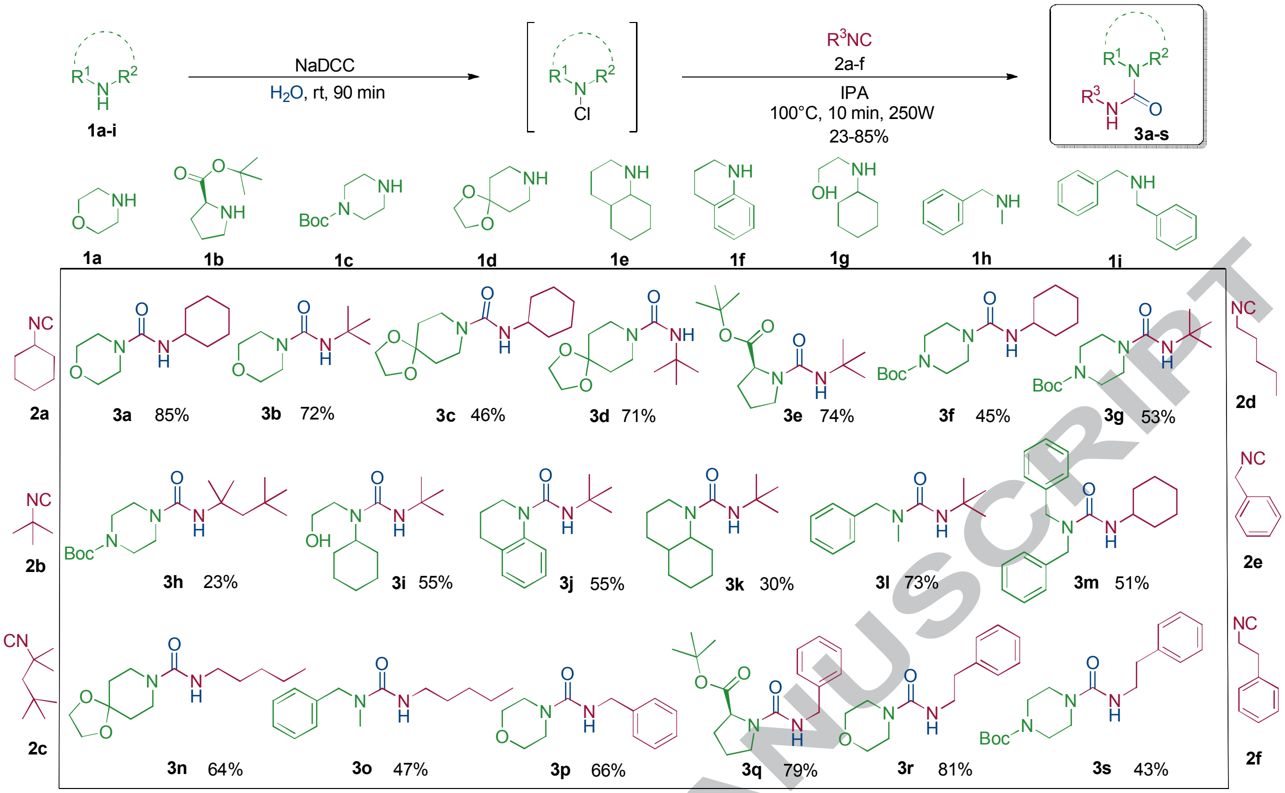
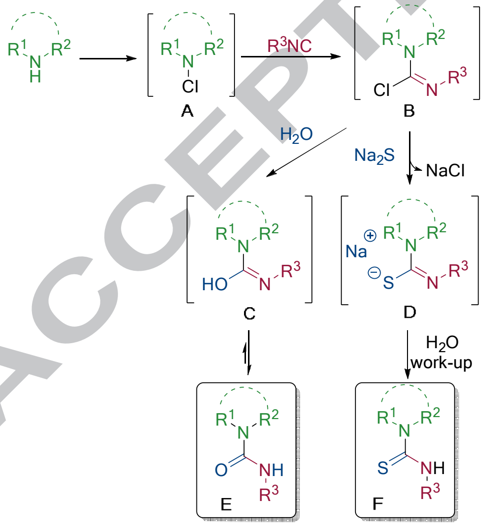


Figure 2. The prepared **3a-s** urea derivatives.

The absence of water is a requirement for the successful thiourea transformation as depicted in the proposed reaction mechanism (Scheme 2). Treatment of **A** with isocyanides generates intermediate **B**, which forms easily the corresponding isourea **C** in the presence of water stabilized towards the final product **E**. Since the formation of **C** is strongly preferred, the successful sulfur coupling and access to intermediate **D** require dry conditions and inert atmosphere.



Scheme 2. Proposed reaction mechanism.

The chlorination of the selected amines **1a,b,c,d,h** and **1i** underwent successfully in dry 2-propanol then the subsequent addition of isocyanide and Na_2S afforded the corresponding **4a-h** thiourea derivatives in acceptable yields of 27–68% (Figure 3). The best yields have been achieved with morpholine (**1a**) (52, 62 and 68%). Surprisingly, the thiocarbamide synthesis proceeded well with aromatic isocyanide **2g** and furnished product **4b** in a yield of 52%. In turn, *t*-butyl isocyanide **2b** proved to be a less effective isocyanide component under these conditions.

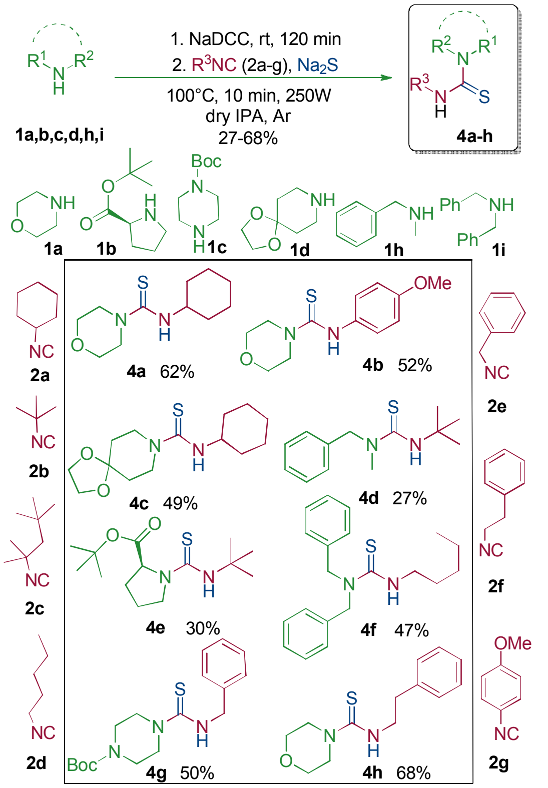


Figure 3. The synthesized **4a-h** thiourea derivatives.

3. Conclusion

In conclusion, we have developed a facile and green one-pot three-component reaction for the synthesis of a 27-membered *N,N'*-multisubstituted urea and thiourea library, based on the reaction of *in situ* generated secondary *N*-chloro amines, isocyanides and water or Na_2S under dry conditions.

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22. 4-fluoro- and 4-methoxyphenyl isocyanides were treated by N-chloro morpholine as amine component. According to quantitative ^{1}H-NMR analysis of the crude reaction mixtures, the 4-fluorophenyl and 4-methoxyphenyl isocyanides yielded ureas in 1% and 2% yields, respectively (see Supporting Information).

Supplementary data

Supplementary data (list of compounds along with their yield and copies of ^{1}H NMR and ^{13}C NMR spectra are included) associated with this article can be found, in the online version, at

Highlights

A green, isocyanide based multicomponent reaction was developed.

Unstable N-chlorinated amines, isonitriles and