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Base-mediated three-component system for the synthesis of *S*-substituted *N*-acyl ureas

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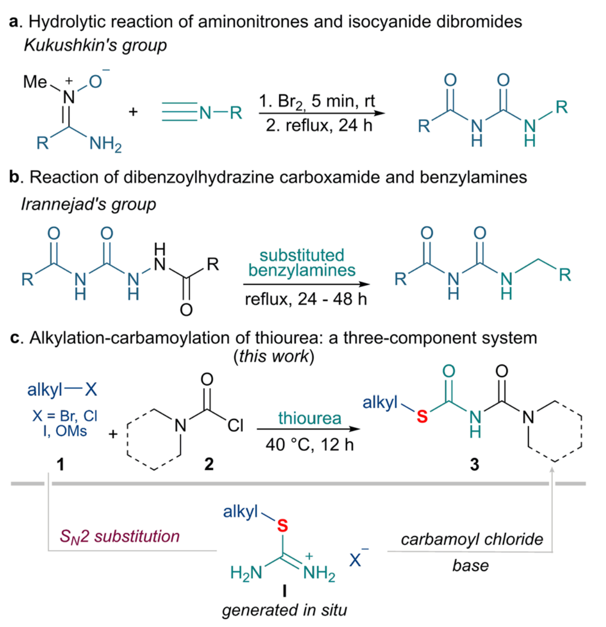
N-Acyl ureas are crucial intermediates in the synthesis of biologically active molecules, and their preparation traditionally relies on multi-step synthesis under reflux conditions. Here, we report a three-component system that combines widespread alkyl halides, thiourea and carbamoyl chlorides. Crucial to this strategy is the synthesis of specific *S*-substituted *N*-acyl ureas *via* the formation of the isothiouronium salt intermediates. This developed three-component system affords scalable and functional group-tolerant reactivity, furnishing the desired products in good to excellent yields under mild conditions.

Introduction

N-Acyl ureas are important intermediates in a wide range of biologically active molecules.[1–5] For example, the *N*-acyl urea motif is incorporated in molecules active as anti-cancer,[6–8] anti-inflammatory,[9,10] anti-convulsant[11] and anti-diabetic[12,13] agents. Therefore, the advancement of efficient synthetic methods for their preparation is of considerable interest. Over the years, a cascade of strategies for synthesising these motifs has been reported.[14–23] Traditional synthetic methods typically involve the acylation of amides and ureas,[14–17] nucleophilic substitution of acyl carbamates,[18] coupling of carboxylic acids with cyanamides and carbodiimides,[19,20] and the addition of amines to acyl isocyanates.[21,22] However, these approaches require transition-metal catalysts as well as multi-step synthesis.

To overcome these limitations, a few alternative methods have been developed.[24–28] Notably, Kukushkin's group developed a transition metal-free, one-pot stepwise *N*-acyl urea synthesis using a reactive aminonitrone-isocyanide system. However, substrate scope was limited and reflux conditions were required (Scheme 1a).[29] Recently, Irannejad's group reported the use of dibenzoylhydrazine carboxamide and benzylamines under reflux conditions, although this protocol is limited to five *N*-benzyl-*N*-acyl ureas (Scheme 1b).[30] Clearly, the establishment of more protocols that would provide unique and efficient access to different classes of *N*-acyl ureas under mild conditions would be highly advantageous.

Here, we present a one-pot three-component system for the alkylation and carbamoylation of thiourea for the synthesis of *S*-substituted *N*-acyl ureas (Scheme 1c). This study draws inspiration from the well-documented S_N2 interaction of alkyl halides and thiourea to generate isothiouronium salts **I**.[31–36] We posited that a nucleophilic attack of the salt **I** on the carbamoyl chloride would furnish the desired product under mild reaction conditions (40 °C) (Scheme 1c). The reports that demonstrated the acylation of ureas using acyl halides further supported the feasibility of our plan.[2,37]



Scheme 1 (a) Two-step hydrolytic synthesis of *N*-acyl ureas.[29] (b) Reaction of dibenzoylhydrazine carboxamide and benzylamines.[30] (c) One-step, three-component strategy for the preparation of *S*-substituted *N*-acyl ureas.

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Results and discussion

We began our investigations with benzyl bromide **1a**, *N*,*N*-dimethyl carbamoyl chloride **2a**, thiourea (**A**) and sodium carbonate (Na_2CO_3) as a base in tetrahydrofuran (THF) solvent at 40 °C for 12 h (Table 1). The reaction proceeded almost quantitatively, furnishing the desired *S*-substituted *N*-acyl urea product **3a** in 92% yield (entry 1). Attempts to use other solvents such as acetonitrile (MeCN) and ethanol (EtOH) (entries 2 and 3) as well as H_2O and diethyl ether (Et_2O) (entries 4 and 5) resulted in either diminished **3a** yields (69–71%) or no product formation, respectively. Moreover, testing other bases resulted in comparable yields but lower efficiencies (entries 6–9, 81–89%). Further optimisation revealed that reactions conducted for 6 hours (entry 10, 77%) and lowering the temperature to 25 °C (entry 11, 75%) result in good yields, although still in lower efficiencies. Notably, no product was formed in the absence of thiourea and the base (entries 12 and 13). Given the lower effectiveness of greener solvents (entries 3 and 4), THF was selected due to its optimal reactivity.

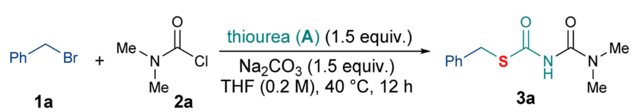
With the crystal structure of the desired product **3a** obtained from single-crystal X-ray analysis and optimised reaction conditions described in entry 1 of Table 1, we then explored the reaction scope for the *S*-substituted *N*-acyl urea synthesis using a diverse range of alkyl halides **1** with *N*,*N* dimethylcarbamoyl chloride **2a** (Fig. 1). The benzyl halides with different substituents on the phenyl ring; 4-nitro **1b**, 2-bromo **1c**, and 2,4,6-trimethyl **1d** moieties, reacted efficiently to form the corresponding **3b**–**3d** products with good to excellent yields (74–84%). The protocol also exhibited excellent tolerance towards cinnamyl bromide **1e** and valuable alkyl halides bearing a 5-membered heterocyclic isoxazole ring **1f**–**1g**,[38] furnishing the corresponding products **3e** (83%), **3f** (88%) and **3g** (86%) in excellent yields. Furthermore, straight-chain alkyl halides such as iodomethane **1h**, 1-bromobutane **1i**, 1-bromopentane **1j** and 1-iodohexane **1k** efficiently reacted to give the corresponding products **3h**–**3k** in excellent yields (81–91%). However, longer chains such as 1-bromodecane, 1-bromoundecane and 1-bromohexadecane, as well as secondary alkyl halides, failed to produce the corresponding products **3**. This is presumably due to the inability of these long-chain and secondary alkyl halides to form the isothiouronium salt **I** under the identified reaction conditions (Table 1, entry 1). A complete list of failed substrates is reported in Fig. S1 of the SI. Additionally, straight-chain alkyl halides with reactive functional groups, including terminal alkenes **1l**–**1m**, alkyne **1n**, and cyano **1o** moieties, were suitable substrates, furnishing products **3l**–**3o** in good to excellent yields (77–93%), thus demonstrating the versatility of the developed protocol. Furthermore, the alkoxy group (**1p**) did not hinder the reaction (**3p**, 80%).

We next explored various carbamoyl chlorides **2** with benzyl bromide **1a** and thiourea (**A**), demonstrating the effectiveness of the developed reaction protocol (Fig. 1). For example, increasing the steric bulk around the carbamoyl *N*-centre did not impede the reaction, as demonstrated by the nearly quantitative product yields obtained in the coupling of carbamoyl chlorides containing *N*,*N*-diethyl **2q** and *N*,*N*-isopropyl **2r** moieties to produce products **3q** (85%) and **3r** (91%). Similarly, unsymmetrical carbamoyl chlorides **2s** and **2t** furnished products **3s** and **3t** in good to excellent yields (75–87%). Furthermore, with the abundance of *N*-cyclic motifs in biologically active molecules,[39] carbamoyl chlorides **2u**–**2w** with cyclic moieties were also well-tolerated, furnishing products **3u**–**3w** in excellent yields (82–89%). Finally, it was envisioned that this reaction protocol could be particularly suitable for gram-scale synthesis. Gratifyingly, a yield of 89% of product **3a** for a 20 mmol scale was obtained (Fig. 1). This yield is comparable to that observed for small-scale synthesis (1 mmol scale). Additionally, 2D NMR experiments, such as HMBC and HSQC, were conducted on product **3j**, and no structural rearrangements of the product were observed (see SI).

The effectiveness of this method was also demonstrated by developing a one-pot two-step telescoped procedure where benzyl bromide **1a** could be converted to product **3a** (93%). This telescoped procedure did not require any solvent evaporation but sequential addition of reagents (Fig. 2a). Furthermore, given the easy preparation and isolation of stable, odourless isothiouronium salts **I**,[31] product **3a** was obtained in excellent yield (85%) (see Section 4.5 of the SI). We then envisaged that the same isothiouronium salt **I** technique could provide reactivity to previously unreactive alkyl halides. Gratifyingly, the long straight-chained alkyl halides furnished the desired products in excellent yields (**3x**, 91% and **3y**, 93%) (Fig. 2b), demonstrating the easy access of the desired *S*-substituted *N*-acyl ureas **3x** and **3y** *via* isothiouronium salt **I** utility.

Finally, as a feature of our reaction design, it was anticipated that halides might be substituted by a different leaving group suitable for S_N2 reactivity. In particular, alcohols **4** – abundant

Table 1 Optimisation and control experiments[a]



Entry	Variations	Yield[b] (%)
1	None	92
2	MeCN	71
3	EtOH	69
4	H_2O	0
5	Et_2O	0
6	Et_3N	81
7	DIPEA	84
8	DBU	86
9	K_3PO_4	89
10	6 h	77
11	25 °C	75
12	No thiourea	0
13	No base	0

[a] Optimisation and control experiments. Reactions performed on the scale: **1a** (1.5 mmol) and **2a** (1 mmol). [b] Reported yields are isolated yields. DIPEA: *N*,*N*-diisopropylethylamine; DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene.

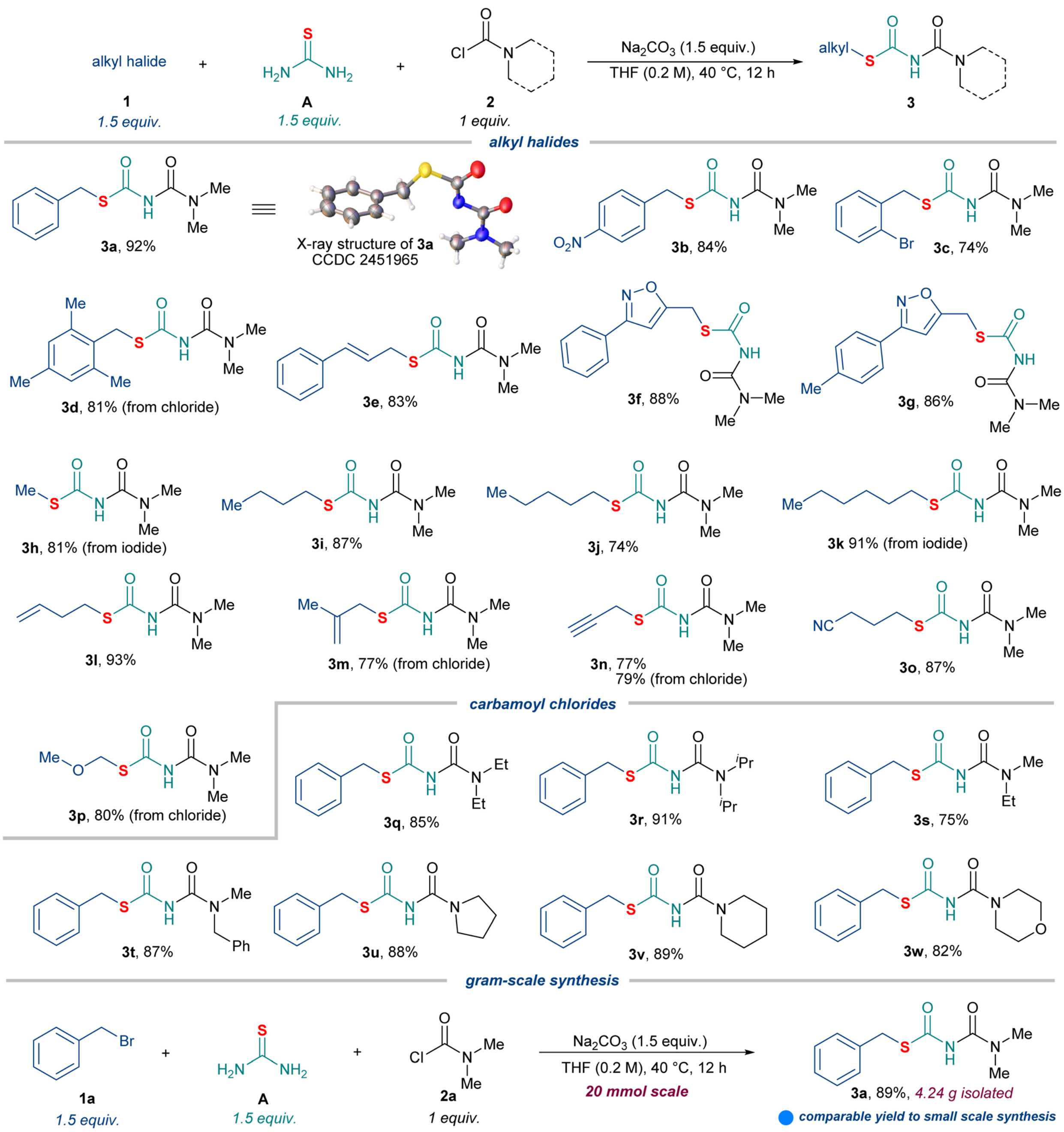


Fig. 1 *S*-Substituted *N*-acyl ureas synthesis substrate scope and gram-scale synthesis. Reactions performed on a 1 mmol scale. Alkyl bromides were used, unless otherwise stated. Reported yields are isolated yields.

feedstock with wide commercial availability – could serve as attractive precursors, a substitute for alkyl halides **1**.[40] To this end, we investigated alkyl mesylates **5** reactivity generated from one-step sulfonation of commercially available benzyl alcohol **4a**, 4-methoxybenzyl alcohol **4b**, and methanol **4c** (Fig. 2c). The reaction of benzyl mesylate **5a** with various carbamoyl chlorides furnished the desired products **3a** (74%), **3q** (79%), **3u** (65%), and **3w** (62%) in good to excellent yields. Lastly, 4-methoxybenzyl mesylate **5b** and methyl mesylate **5c** were also suitable electrophiles as demonstrated by the reaction with *N*,*N*-dimethylcarbamoyl chloride **2a**, furnishing products **3h** (60%) and **3z** (70%), respectively, in good yields.

From the onset, it was envisioned that, mechanistically, the isothiouronium salt formation *via* S_N2 reactivity of the alkyl halides **1** and thiourea (**A**) would be critical for this reaction (Fig. 2d).[34,41] We propose that the nucleophilic attack of the *in situ* generated isothiouronium salt **I** on the carbamoyl chloride **2** would follow.[42] The resulting iminium intermediate **II**, which, upon hydrolysis, would furnish the desired product **3**.

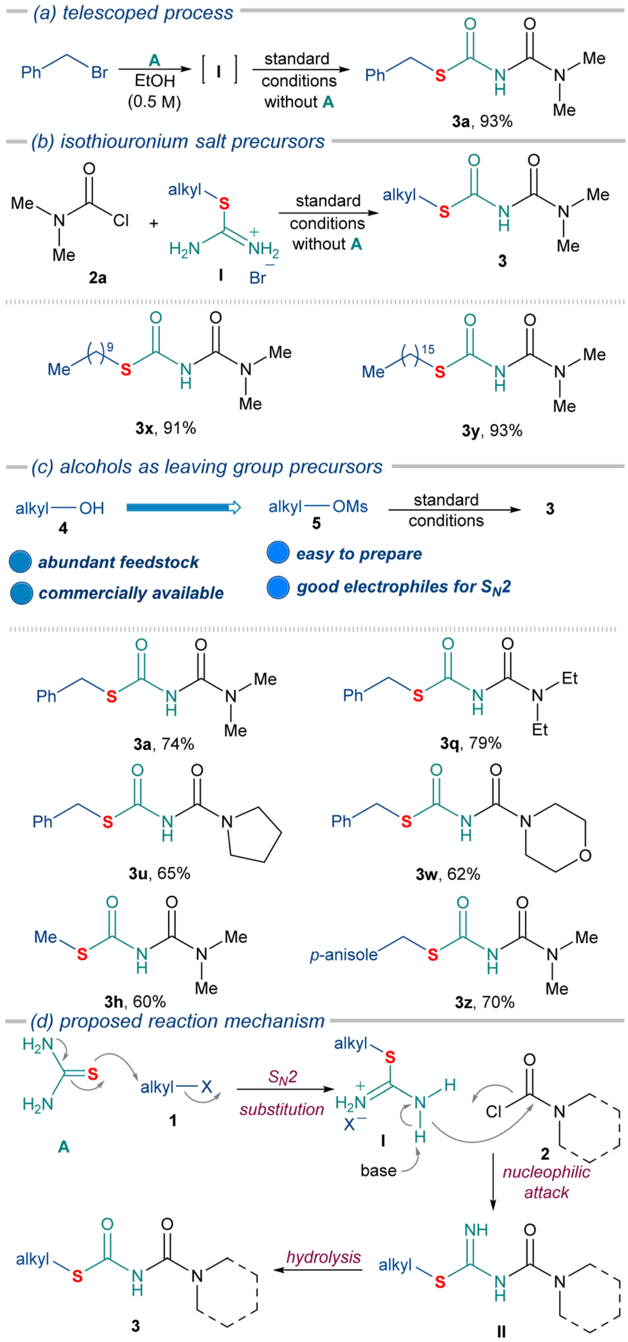


Fig. 2 (a) One-pot, two-step telescoped synthesis. (b) *S*-Alkyl isothiouronium salt utility. (c) Alkyl alcohols utility as leaving group precursors. (d) Proposed reaction mechanism. Reactions were performed on a 1 mmol scale. Reported yields are isolated yields.

Conclusion

In summary, we report the one-pot, three-component synthesis of *S*-substituted *N*-acyl ureas using a combination of alkylation and carbamoylation of the thiourea approach. Isolated product yields of up to 93% were obtained despite the electronic, steric, and structural variations of the alkyl halides and carbamoyl chloride substrates. Furthermore, we disclose the practicality of this protocol by demonstrating the underutilised mesylates as precursors for the *in situ* formation of the isothiouronium salt **I**, delivering the desired *N*-acyl urea products in good to excellent yields. Given the importance of *N*-acyl ureas in bioactive structures, we anticipate that this protocol will find broad use in the synthetic community.

Author contributions

Conceptualisation, M. P. S., J. L. L., and P. T. M.; methodology, M. P. S., and A. R. N. All authors have read and agreed to this version of the manuscript.

Conflicts of interest

There are no conflicts to declare.

Data availability

CCDC 2451965 (**3a**) contains the supplementary crystallographic data for this paper.[43]

The data supporting this article have been included in the supplementary information (SI). Supplementary information is available. See DOI: **https://doi.org/10.1039/d5ra05563f**.

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