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An isocyanide based multi-component reaction under catalyst- and solvent-free conditions for the synthesis of unsymmetrical thioureas

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Abstract: A new and efficient method for the synthesis of thiourea derivatives by a sequential one-pot, three-component reaction between aromatic isocyanides, amines, and 1,2-di-*tert*-butyldisulfane (DTBS) was developed and **27** different examples were synthesized in good to excellent yields. DTBS was identified as an effective sulfur surrogate without the use of both catalysts and solvents. This protocol does not employ any transition metal catalyst or special experimental setup.

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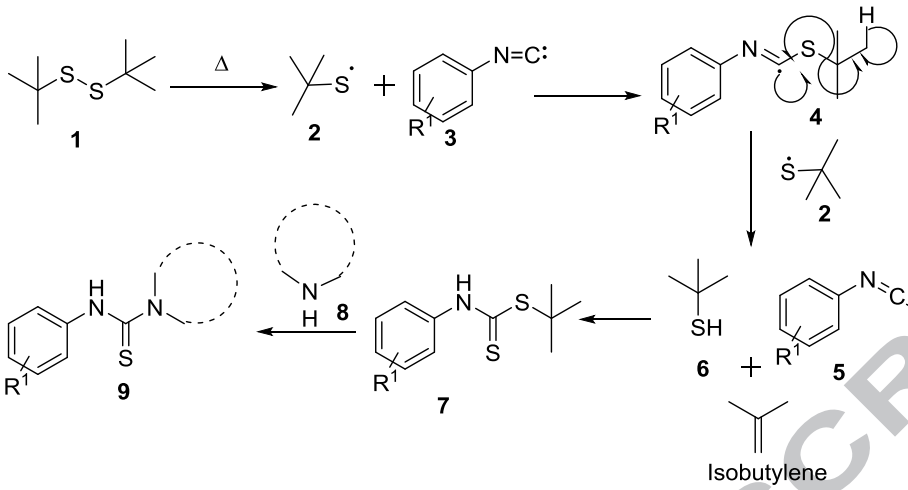
Catalyst- and solvent-free approaches towards organic synthesis have attracted an immense interest from the organic chemistry community over recent decades.[1-2] The avoidance of catalysts and solvents in well established chemical processes, or the replacement of toxic solvents with more environmentally-benign solvents, has become a major focus in the pharmaceutical industry. Also, multicomponent reactions (MCRs) have become an effective approach for rapid assembly of complex molecules from simple precursors in a one-pot procedure *via* the formation of carbon-carbon and carbon-heteroatom bonds.[3] These domino-type reactions involve multiple intermediate reactions where the product of the first is the starting substrate for the subsequent and can also incorporate "green chemistry" values such as atom economy, time, and labour economies.

Thiourea containing molecules have been reported to possess a plethora of biological properties such as anti-bacterial, anti-fungal, anti-inflammatory and anti-cancer.[4] In addition, they are used as supramolecular assemblies, and anion sensing.[5] On the other hand, the area of organocatalysts has been dominated by the cinchona-thiourea based catalysts for variety of organocatalytic transformations.[6] These intrinsic qualities of thioureas, in combination with

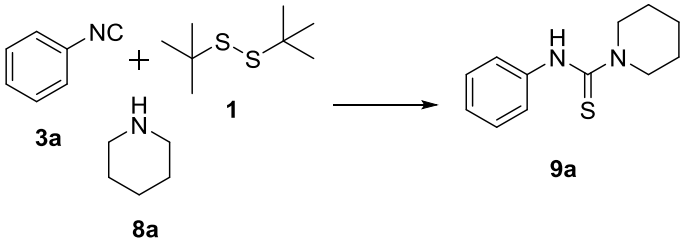
the avalanche of research on their use in the synthesis of various heterocyclic scaffolds, make them privileged building blocks for synthetic chemists.[7] Consequently, a great deal of effort have been focused on the development of newer synthetic strategies for this important building block. Until now, one of the most common methods for the synthesis of thiourea has been the reaction of primary or secondary amines with isothiocyanates.[8] Recently, Kaupp and co-workers developed a solvent-free thiourea synthesis involving gas phase reaction of amines and isothiocyanates, and subsequently, Li and Wang used microwave irradiation for the synthesis of thiourea using similar synthetic substrates.[9] Similarly, Liu et al. developed microwave assisted one-pot synthesis of symmetrical diaryl-substituted thioureas from arylamines and carbondisulphide.[10] Mane et al. developed unsymmetrical N,N′-diphenyl urea in aqueous medium under base and catalyst free condition from corresponding substituted isocyanate and amines.[11] Other methods, include the reaction of primary amines or secondary amines with thiophosgene, dithiocarbamates, unsubstituted thiourea.[12] These reported methods have their own disadvantages including the use of toxic reagents (thiophosgene & hydrogen sulphide), harsh reaction conditions, and/or are limited to the synthesis of symmetrical thiourea derivatives. Undoubtedly, taking into account the atom and step economy, the development of a catalyst- and solvent-free MCR would be highly desirable, as a part of our interest towards the development of newer isocyanide-based organic synthesis,[13] herein, we report a straightforward protocol to access thiourea derivatives from the multicomponent reaction of aryl isocyanide, amine, and DTBS. DTBS has been used as sulfur surrogate for transferring sulfur to isocyanide, which is otherwise reported to be very sluggish with elemental sulphur.[14]

Isocyanides **3** (Scheme 1) are privileged divalent carbon nucleophiles for the wide range of multi-component reactions. Whereas DTBS (**1)** is known to decompose readily at high temperature into the corresponding radical **2**.[15] We envisioned that the radical **2** might be attacked by isocyanide **3**[16] to generate an intermediate radical **4** which should undergo de-*tert*-butylation, followed by the reaction of intermediate 2-methylpropane-2-thiol **6** and isothiocyanate **5** to generate substituted *tert*-butyl phenylcarbamodithioate **7**. Reaction of intermediate **7** with amine **8** resulted in thiourea **9** (Scheme 1). In this one-pot assembly, two independent reactions should occur sequentially: reaction of isocyanide **3** with DTBS **1** to produce **7**, and a substitution reaction of **7** with amines **8** to generate thiourea derivatives through a cascade process.



Scheme 1. Proposed synthesis of thiourea **9** through a coupling of DTBS **1**, isocyanide **3** with amines **8**.

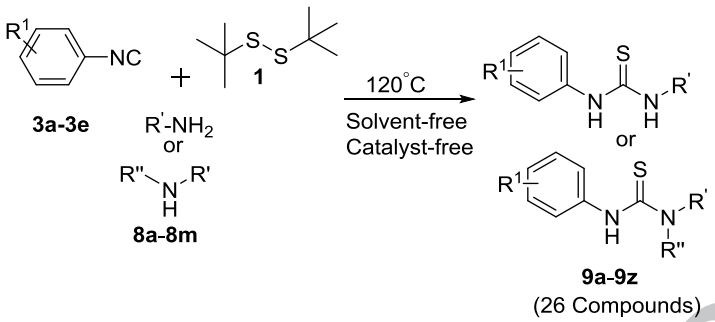
Table 1. Optimization of reaction condition for the synthesis of **9a**.[a]

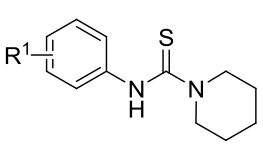


Entry	Temperature (°C)	Solvent	Time (h)	Yield (%)[b]
1	25	None	24	0
2	80	None	24	trace
3	100	None	12	46
4	120	None	6	87
5	120	None	1	23[c]
6	140	None	6	83
7	80	MeOH	24	0
8	110	Toluene	24	31

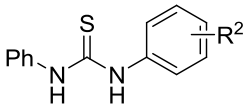
[a]Reaction condition: **1** (5 mmol), **3a** (1 mmol), **8a** (1.2 mmol). [b]Isolated Yield. [c]Microwave heating at 120 °C for 1 h using 300 W power.

Figure 1. Formation of thiourea derivatives (**9**) from DTBS (**1**), isocyanides (**3**), and amines (**8**).[a]

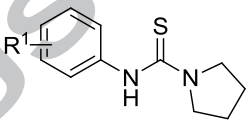




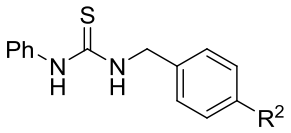
9a, R^1 = H, 87%
9b, R^1 = 4-OCH_3, 79%
9c, R^1 = 4-CH_3, 81%
9d, R^1 = 3-Cl, 90%



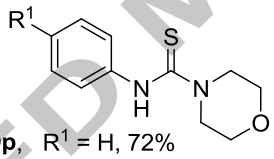
9e, R^2 = 4-OCH_3, 86%
9f, R^2 = 4-CH_3, 77%
9g, R^2 = 4-Cl, 69%
9h, R^2 = 3-Cl, 66%
9i, R^2 = 2-CH_3, 74%



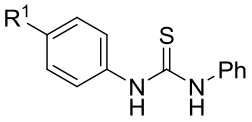
9j, R^1 = H, 84%
9k, R^1 = 4-CH_3, 80%
9l, R^1 = 4-OCH_3, 81%
9m, R^1 = 3-Cl, 98%



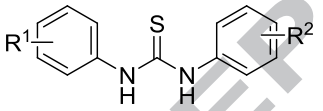
9n, R^2 = H, 85%
9o, R^2 = CH_3, 87%



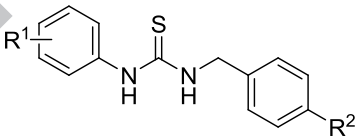
9p, R^1 = H, 72%
9q, R^1 = OCH_3, 56%
9r, R^1 = CH_3, 76%



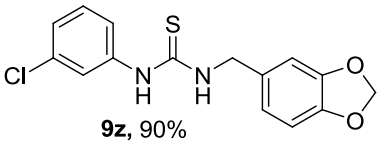
9s, R^1 = H, 73%
9t, R^1 = F, 94%



9u, R^1 = 4-F, R^2 = 4-Cl, 91%
9v, R^1 = 4-F, R^2 = 4-CH_3, 99%
9w,R^1 = 4-OCH_3, R^2 = 4-Cl, 78%



9x, R^1 = 4-OCH_3, R^2 = 4-Me, 84%
9y, R^1 = 3-Cl, R^2 = 4-OMe, 93%



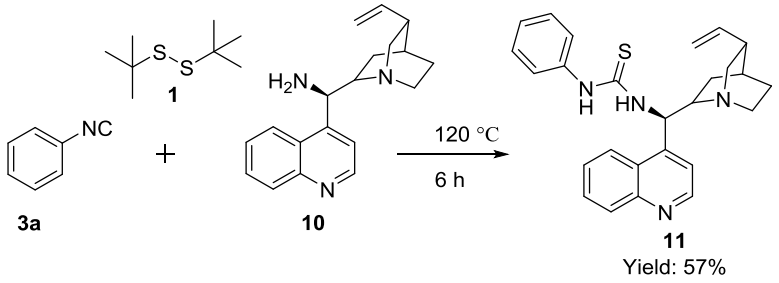
9z, 90%

[a]The reactions were carried out at 120°C using **1** (5 mmol), **3** (1 mmol), **8** (1.2 mmol). Yields refer to the isolated yields. All the reactions were heated for 5 h for 120 °C and 1 h at 60 °C after the addition of amines.

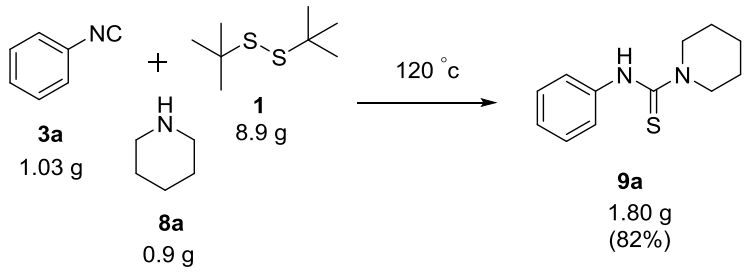
In order to check the feasibility of the concept, the reaction of phenyl isocyanide **3a** with piperidine **8a** and DTBS **1** under catalyst- and solvent-free conditions at various temperatures was first investigated (Table 1). When the reaction was performed at 25°C, no desired product was formed (entry 1). On the other hand, at 80°C for 24 h, product **9a** was obtained in trace (Table 1, entry 2). The desired product was obtained in increased yield with reduced reaction time at 120°C for 6 h in 87% isolated yield (Table 1, entry 4). The reaction under microwave irradiation lowered the yield to only 23% (Table 1, entry 5). Increasing the

reaction temperature to 140 °C for 6 h failed to improve the reaction yield (Table 1, entry 6). No reaction product was obtained in such as MeOH, though toluene as the reaction solvent afforded product in 31% (Table 1, entry 8). Thus the conditions shown for the entry-4 in Table 1, gave the best yield and were selected for further syntheses of different derivatives. The structure of **9a** was consistent with its spectroscopic data. Since the reaction is selective, the product formed exclusively and no column purification is required and the pure thiourea derivatives were isolated by simple filtration.

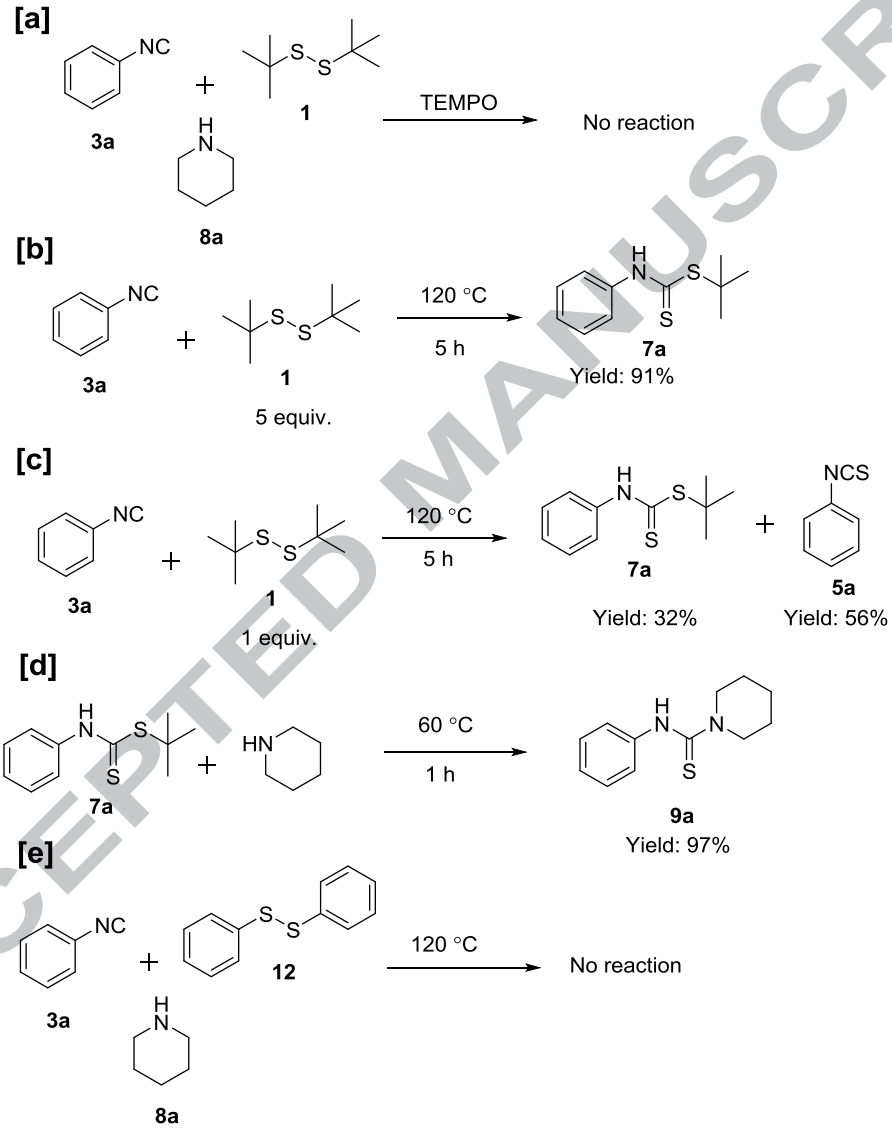
The results of a study into the scope and limitations of the methodology with a variety of different isocyanides **3** and amines **8** are shown in Figure 1. Aromatic isocyanides **3a**-**3e** were obtained by formylation of aromatic amines followed by dehydration using $POCl_3$.[17] A number of aromatic isocyanides derived from aromatic amines bearing electron withdrawing functional group gave very high yields (90−99%) of desired thiourea derivatives (Figure 1, **9d**, **9m**, **9t**, **9u**, **9v**, **9y**, **9z**,).[18] Aromatic isocyanides derived from electron rich aromatic amines, gave relatively lower yields (56−81%) of the thiourea derivatives (Figure 1, **9b**, **9c**, **9k**, **9l**, **9q**, **9r**, **9w**, **9x**). Having explored the scope of aromatic isocyanides for novel multi-component reaction, we attempted to explore the scope of structurally diverse amines including aliphatic, benzylic and aromatic amines, to afford the corresponding unsymmetrical thiourea. Gratifyingly the conditions optimized for various aromatic isocyanides and secondary aliphatic amine, provided equally significant isolated yields for aromatic amines without any further optimization (Figure 1, **9e-9i**, **9s-9w**). No obvious electronic effects of the aromatic amines were observed, and the products were obtained in good to excellent yields. To further illustrate the versatility of the developed protocol, the optically active thiourea based organocatalyst (**11**) was also synthesized (Scheme 2) by the reaction of **1**, **3a** and cinchonamine (**10**). Related cinchona-thiourea derivatives are known to be well suited for various organocatalytic enantioselective transformations. In order to expand the synthetic scope of our strategy, a gram-scale synthesis of **9a** (82%) was performed under the standard conditions (Scheme 3).



Scheme 2. Synthesis of organocatalyst under catalyst- and solvent-free condition.



Scheme 3. Gram scale synthesis of **9a**.



Scheme 4. Mechanistic investigations for thiourea synthesis.

With the scope of the process established, a series of experiments (Scheme 4) were conducted, with the aim of understanding the mechanism. Isocyanide **3a** was treated with DTBS **1** and piperidine **8a** in the presence of radical scavenger TEMPO under the standard condition. No reaction was observed due to radical quenching experiment, thus indicating the involvement of possible radical intermediates (Scheme 4a).

Subsequently, *tert*-butyl phenylcarbamodithioate **7a** (intermediate) was observed as sole product from the reaction of **3a** and 5 equiv. of **1**, (Scheme 4b), whereas use of 1 equiv. of DTBS (**1**) gave mixture of phenylisothiocyanate (**5a**) and *tert*-butyl phenylcarbamodithioate (**7a**) as depicted in Scheme 4c. Formation of compounds **5a** and **7a** can be explained by a plausible mechanism depicted in scheme **1**. On the other hand, the expected product was isolated in quantitative yield (Scheme 4d) for the reaction of *tert*-butyl phenylcarbamodithioate (**7a**) and piperidine (**8a**). This finding implied that **7a** and phenylisothiocyanate (**5a**) are probably key intermediates during the thiourea synthesis. Product **9a** could not be obtained from for the reaction of isocyanide (**3a**), amine (**8a**) and 1,2-diphenyldisulfane (**12**) indicating the importance of *tert*-butyl group in the sufur insertion for the synthesis of thiourea (Scheme 4e).

In summary, we have developed an efficient procedure for the synthesis of unsymmetrical thiourea under catalyst- and solvent-free condition. This one-pot, three-component reaction between aromatic isocyanide, amines and DTBS afforded the products in high yields.

Acknowledgements

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18. **General procedure for thiourea synthesis (Figure 1)**. To a 10 mL round bottom flask were added isocyanide **3a** (103 mg, 1.0 equiv.) and DTBS (5 mmol, 890 mg). Round bottomed flask was filled with N_2. The above reaction mixture was allowed to stir at 120 °C for 5 h and monitored by TLC. After complete consumption of isocyanide **3a**, the reaction mixture was cooled down to 60 °C and piperidine **8a** (100 mg, 1.2 equiv.) was added and further stir for 1 h, the reaction mixture was precipitated. The resulting precipitate was filtered and washed with cold ether to obtain pure product **9a**. *N-Phenylpiperidine-1-carbothioamide* (**9a**). White solid (191 mg, 87% yield); R_f = 0.52 (ethyl acetate/hexanes = 35:65); melting point: 96 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.66 (s, 6H), 3.76-3.78 (m, 4H), 7.09 (t, *J* = 8 Hz, 2H),7.13 (d, *J* = 7.5 Hz, 1H), 7.17 (s, 1H), 7.30 (t, *J* = 7.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.2, 25.6, 50.1, 122.7, 124.9, 129.2, 140.5, 183.0.

- We have developed a straightforward method to access unsymmetrical thioureas.
- Total 27 compounds were synthesized using multicomponent reaction.
- DTBS was identified as sulfur surrogate for transferring sulfur to isocyanide.
- Optically active thiourea based organocatalyst was also synthesized.
- A series of experiments were conducted with the aim of understand the mechanism.

Graphical Abstract

An isocyanide based multi-component reaction under catalyst- and solvent-free conditions for the synthesis of unsymmetrical thioureas

Karandeep Singh, Siddharth Sharma*

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