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An efficient method for the synthesis of disubstituted thioureas via the reaction of *N*,*N*′-di-Boc-substituted thiourea with alkyl and aryl amines under mild conditions

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Abstract

An efficient method for the synthesis of disubstituted thioureas via the reaction of *N*,*N*′-di-Boc-substituted thiourea **5** with alkyl and aryl amines under mild conditions has been developed. In the presence of NaH as a base, trifluoroacetic anhydride (TFAA) reacted with **5** providing intermediate **6**, which then reacted with amines giving thioureas **7** in excellent yields. This reaction conditions tolerated other functional groups such as amide, ester, enol ether and hydroxyl groups.

Thioureas have attracted much attention due to their bioactivities as pharmaceutics and pesticides. A variety of thiourea derivatives and their metal complexes exhibit analgesic,[1] anti-inflammatory,[2] antimicrobial,[3] anticancer[4] and antifungal activities.[5] Moreover, thioureas are important building blocks in the synthesis of heterocycles. For example, 2-amino-1,3-thiazoles can be readily prepared through the condensation of thioureas with α-halocarbonyl compounds.[6] Likewise, arylthioureas can be transformed into benzothiazoles upon treatment with bromine.[7] Other examples include the synthesis of iminothiazolines,[8] thiohydantoins,[9] 1,3,5-triazine[10] and 2-amino-oxazo-lidines.[11] Therefore, the synthesis of novel thioureas and the development of new methods for their preparation are of great importance in searching bioactive molecules as well as in synthetic chemistry.

To date, a variety of methods for the preparations of thioureas have been documented, including the reaction of alkali metal thiocyanates with amines in the presence of a strong acid,[12] aryl isothiocyanates with amines followed by basic hydrolysis,[13] isothiocyanates with ammonia or amines,[14] primary amines with carbon disulfide in the presence of mercury acetate and aqueous ammonia[15] and unsubstituted thioureas with primary alkyl amines at high temperature.[16] Recently, several other new methods for the preparation of substituted thioureas have also been reported.[17] However, many reported methods suffer from drawbacks and limitations related to harsh reaction conditions such as high reaction temperature, long reaction time, the use of a strong acid or base and noxious reagents such as hydrogen sulfide and carbon disulfide. Therefore, the development of a mild, efficient and environmentally benign method is highly desirable. Herein, we report a novel, mild and efficient method for the preparation of disubstituted thioureas via the reaction of *N*,*N*′-di-Boc-substituted thiourea with alkyl and aryl amines.

Recently, Charette and others reported the generation of imino **3** and iminium **4** triflates via the reaction of amide with triflic anhydride in the presence of a base. Those triflates can further react with a series of nucleophiles, such as alcohols, amines, aminothiols, H_2S and $H_2{}^{18}O$ to give the corresponding esters, amidines, thiazolines, thioamides and ^{18}O-labelled amides (Scheme 1).[18] Although this kind

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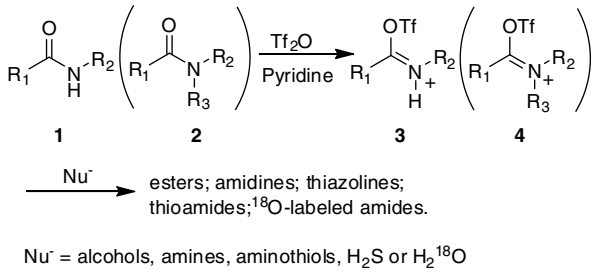
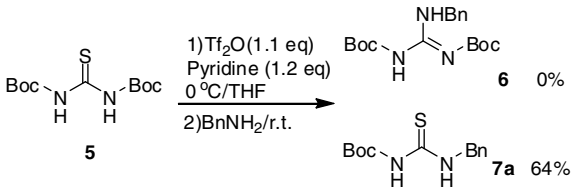


Scheme 1. Generation of imino **3** and iminium **4** triflates and their further transformations.

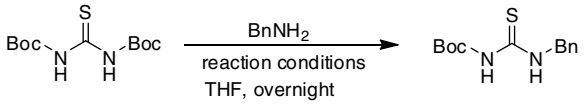
of reaction with an amide has been extensively used in organic synthesis, to the best of our knowledge, little exploration has been conducted with thiocarbonyl compunds. In view of the fact that the properties of triflates and thiotriflates are quite different, we envisioned that some new information could be obtained when the substrate is a thiocarbonyl compound. Initially, *N*,*N*′-di-Boc-substituted thiourea, prepared from thioureas according to a literature method,[19] was chosen as the substrate, and benzylamine as the nucleophile. After treatment of **5** with Tf_2O (1.1 equiv) and pyridine (1.2 equiv) at 0 °C for 1 h, followed by the addition of benzylamine (1.1 equiv), no expected guanidine derivative **6** was produced; instead, thiourea **7a** was formed in moderate yield (64%).[20] This unexpected but useful result nonetheless provides a novel method for the preparation of disubstituted thioureas under mild conditions (Scheme 2). Further efforts were made to adjust the reaction variants such as activator, base, reaction temperature and the amount of amine to optimize the conditions. The results are summarized in Table 1.

It was found that if $BnNH_2$ was used alone, the reaction did not produce thiourea **7a** at room temperature overnight, but guanidine **6** was formed in 75% yield (entry 1). When other activators such as Ac_2O, MsCl and TsCl are used, the yields were lower (entries 2–4) and TFAA (trifluoroacetic anhydride) as an activator gave rise to a little higher yield (entry 5). Meanwhile, other organic bases such as DIEA (*N*,*N*-diisopropylethylamine) or NMM (*N*-methylmorpholine) were used, **7a** was formed in lower yields along with many other unidentified by-products. To our delight, when NaH was used as a base to deprotonate and TFFA as an activator, the reaction yield was increased to 91% (entry 8). Surprisingly, increasing the amount of $BnNH_2$ (2.2 equiv, entry 9) led to a lower yield (73%) along with some deprotected by-product of **7a** (11%), possibly



Scheme 2. Reaction of **5** with benzyl amine using Tf_2O as an activator.

Table 1
Optimization of the reaction conditions



Entry	Reaction conditions	Yield [a] (%)
1	$BnNH_2$ (1.1 equiv)/rt	0[b]
2	Ac_2O (1.1 equiv)/pyridin (1.2 equiv)e/0 °C then $BnNH_2$/rt	58
3	MsC (1.1 equiv)/pyridine (1.2 equiv)/0 °C then $BnNH_2$ (1.1 equiv)/rt	60
4	TsCl (1.1 equiv)/pyridine (1.2 equiv)/0 °C then $BnNH_2$ (1.1 equiv)/rt	50
5	TFAA (1.1 eq)/pyridine (1.2 equiv)/0 °C then $BnNH_2$ (1.1 equiv)/rt	78
6	Tf_2O (1.1 equiv)/DIEA (1.2 equiv)/0 °C then $BnNH_2$ (1.1 equiv)/rt	25
7	Tf_2O (1.1 equiv)/NMM (1.2 equiv)/0 °C then $BnNH_2$ (1.1 equiv)/rt	32
8	TFAA (1.1 equiv)/NaH (1.2 equiv)/0 °C then $BnNH_2$ (1.1 equiv)/rt	91
9	TFAA (1.1 equiv)/NaH (1.2 equiv)/0 °C then $BnNH_2$ (2.2 equiv)/rt	73

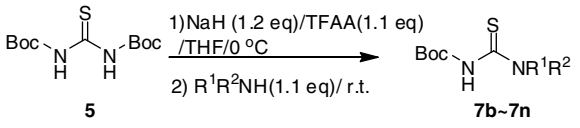
[a] Isolated yield.
[b] Guanidine was the only product isolated.

due to the deprotection of the Boc group in the presence of excessive $BnNH_2$.

Based on the results, we concluded that TFAA (1.1 equiv)/NaH (1.2 equiv)/0 °C then $BnNH_2$ (1.1 equiv)/rt in THF solvent are suitable conditions for this conversion. The scope of the reaction was then examined with different amines, and the results are summarized in Table 2. As can be seen, all primary amines worked well with **5** affording the desired compounds **7b**–**7f** in excellent yields (entries 1–4). It is also worth noting that under these reaction conditions, functional groups such as amide, ester, enol ether and hydroxyl are tolerated. Cyclic five or six-membered ring amines also afford the desired thioureas in good yields (entries 5–8). Importantly, under this condition, no epimerization of compound **7i** was observed based on ^1H NMR. In contrast, more hindered acyclic secondary amines did not lead to the desired products under these conditions (entry 9). Less nucleophilic primary arylamines also afford the desired products in excellent yields (entries 10 and 11). With aminophenol, only the thiourea product was isolated and no thiocarbamate was observed (entry 11). Similar to the acyclic secondary alkyl amines, acyclic secondary arylamines did not afford the desired product (entry 12). The reaction of **5** with phenyl hydrazine afforded exclusively the thiohydrozone product **7n** (entry 13).

In summary, an efficient method for the synthesis of mono- and N,N-disubstituted thioureas has been developed. This method involves the reaction of *N*,*N*′-di-Boc-substituted thiourea with amines in the presence of NaH and TFAA. This method can proceed under mild condi-

Table 2
Synthesis of thioureas via the reaction of **5** with amines[21]



5 **7b~7n**

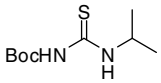
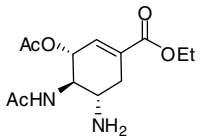
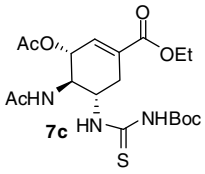
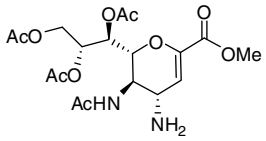
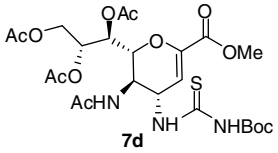
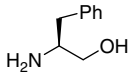
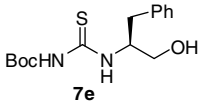
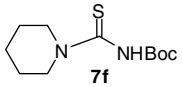
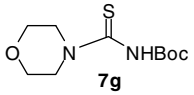
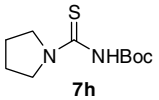
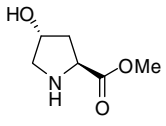
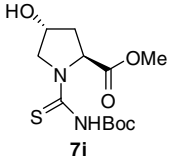
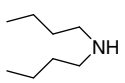
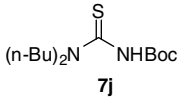
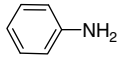
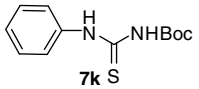
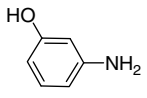
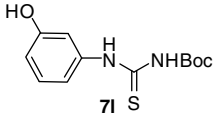
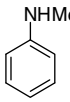
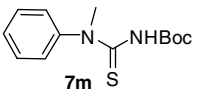
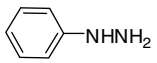
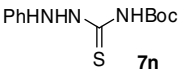
Entry	R_1R_2NH	Product	Yield (%)
1		 **7b**	94
2		 **7c**	78
3		 **7d**	88
4		 **7e**	82
5		 **7f**	84
6		 **7g**	90
7		 **7h**	82
8		 **7i**	89
9		 **7j**	0
10		 **7k**	91
11		 **7l**	81

Table 2 (*continued*)

Entry	R_1R_2NH	Product	Yield (%)
12		 **7m**	0
13		 **7n**	85

tions, and fuctionalized thioureas can be readily prepared. Not only primary alkyl amine but also secondary alkyl amine and primary arylamine substituted thioureas can be obtained in high yield. Importantly, no symmetric disubstituted thioureas formation was observed under the reaction conditions. Further studies including the detailed mechanism and the reaction of *N*,*N*′-di-Boc-substituted thiourea with other nucleophiles such as alcohols, stable carbanions to synthesize diverse thiocarbamates and thioamide derivatives are under way and will be reported in due course.

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20. *Spectral data for compound* **7a**: Solid, mp 147–148 °C. IR (KBr): ν_{max}: 3446, 3172, 2971, 1668, 1534, 1250, 1206, 1150, 964, 918, 750 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 9.97 (s, 1H), 7.94 (s, 1H), 7.38–7.29 (m, 5H), 4.86 (d, 2H, $J = 5.6$ Hz), 1.47 (s, 9H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 179.8, 151.8, 136.5, 128.8, 128.0, 127.9, 83.8, 49.5, 28.1. ESI-MS *m/z* (265, M^+-H). Anal. Calcd for $C_{13}H_{18}N_2O_2S$: C, 58.62; H, 6.81; N, 10.52; S, 12.04. Found: C, 58.44; H, 6.86; N, 10.64; S, 12.33.
21. *Typical procedure for thioureas formation (***7c***)*: To a mixture of *N*,*N*′-di-Boc-substituted thiourea (552 mg, 2 mmol) and THF (20 mL) was added 60% NaH (95 mg, 2.4 mmol) at 0 °C. The reaction mixture was stirred at the same temperature for 1 h, then TFAA (370 μL, 2.2 mmol) was added and the stirring continued for additional 1 h. Then amine (2.2 mmol) was added and the resulting reaction mixture was stirred at room temperature overnight. Ten millilitre of H_2O was added to quench the reaction and the mixture was extracted with EtOAc (15 mL × 3). The combined organic layers were dried over $MgSO_4$, and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography to afford compound **7c**. Solid, mp 104–105 °C. IR (KBr): ν_{max}: 3485, 2931, 1725, 1719, 1633, 1557, 1433, 1297, 1031, 774, 659 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 9.89 (d, $J = 6.4$ Hz, 1H), 7.94 (s, 1H), 6.67 (s, 1H), 6.32 (d, $J = 8.4$ Hz, 1H), 5.60 (d, $J = 8.8$ Hz, 1H), 4.87–4.84 (m, 1H), 4.41–4.36 (m, 1H), 4.24–4.18 (m, 2H), 3.00 (dd, $J = 6.0$ Hz, $J = 18.0$ Hz), 2.49–2.42 (m, 1H), 2.09 (s, 3H), 1.93 (s, 3H), 1.48 (s, 9H), 1.29 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 181.1, 170.9, 165.2, 151.3, 135.3, 130.7, 84.4, 71.9, 61.3, 53.9, 53.0, 30.4, 28.0, 23.3, 21.0, 20.9, 14.2; ESI-MS *m/z* (444, M^++H). Anal. Calcd for $C_{19}H_{29}N_3O_7S$: C, 51.45; H, 6.59; N, 9.47; S, 7.23. Found: C, 51.67; H, 6.33; N,9.50; S, 7.10.