Organic LETTERS

Letter

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A Mild Method for the Synthesis of Carbamate-Protected Guanidines Using the Burgess Reagent

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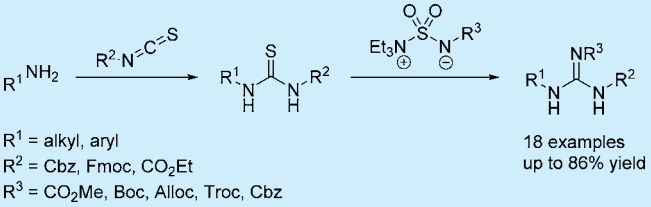
Supporting Information

ABSTRACT: A simple method for the synthesis of carbamate-protected guanidines from primary amines is described. A variety of thioureas derived from primary amines and isothiocyanates react with the Burgess reagent to give the corresponding guanidines via either a stepwise or one-pot procedure. By tuning the carbamoyl units of isothiocyanates and the Burgess reagent, differentially *N,N′*-diprotected guanidines can be obtained. Selective deprotection of the products affords *N*-monoprotected guanidines.



The guanidine moiety is found in a number of biologically active compounds.[1] Guanidines are also employed as base catalysts, chiral auxiliaries, and ligands in organic synthesis.[2] Consequently, a large number of synthetic methods have been developed to install the guanidine unit.[3]

While there are many methods for the synthesis of *N,N′*-diprotected guanidines,[4] only a few have been reported for the preparation of differentially *N,N′*-diprotected guanidines, which are valuable intermediates for the construction of more complex derivatives.[5,6] One example involves the reaction of amines with Boc, Cbz-protected methylisothiourea (**1**, Figure 1).[5] This method is mild and works well for a variety of amines

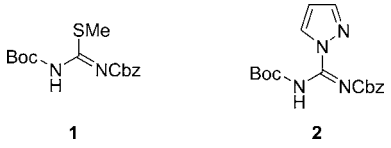


Figure 1. Examples of guanylating reagents.

but requires stoichiometric amounts of highly toxic $HgCl_2$ and generates insoluble mercuric sulfide, which often complicates the purification procedure. Another example involves the reaction of amines with Boc, Cbz-protected 1*H*-pyrazole-1-carboxamidine (**2**, Figure 1).[6] Although this reaction proceeds cleanly, preparation of **2** requires multistep synthesis[6b] and **2** is unstable and difficult to handle.[6a] Thus, there is a need for more convenient methods to produce such guanidines.

On the other hand, the Burgess reagent[7] (**3**, Figure 2) has been used as a powerful dehydrating agent in chemical synthesis for decades. It has also been employed as a convenient source of nitrogen in synthetically useful transformations such as the conversion of alcohols into carbamate derivatives,[7,8] 1,2-diols or epoxides into sulfamidates,[9,10] aminoalcohols into sulfamides,[9] and sulfoxides into sulfilimines.[11] On the basis of these findings, we hypothesized that it would be possible to prepare carbamate-protected guanidines through rearrangement of intermediate **4**, which can be generated *in situ* from thiourea and **3** (Scheme 1).

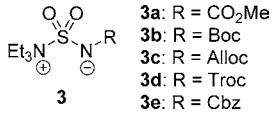
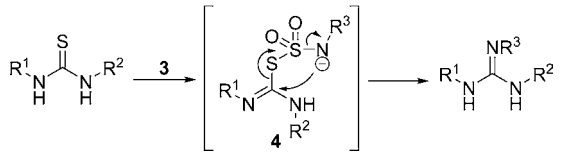


Figure 2. Burgess reagent **3a** and related compounds **3b**−**3e**.

Scheme 1. Strategy to Guanidines from Thioureas Using the Burgess Reagent 3



Herein, we describe a method for the synthesis of differentially *N,N′*-diprotected guanidines by desulfurative condensation of carbamoyl thiourea with **3** under mild reaction conditions. In this reaction, the Burgess reagent plays dual roles as a carbamate source and a desulflurizing agent. To the best of our knowledge, this is the first application of the Burgess reagent as a desulfurizing agent.[12]

We first investigated the desulfurative condensation of *N*-benzylthiourea derivatives **5a**−**5d** with **3a** (2 equiv) in THF at ambient temperature (Table 1). As expected, thioureas **5b**−**5d** with electron-withdrawing protecting groups, such as Cbz, Ts, and Bz, gave the desired guanidines **6ab**−**6ad**, while *N,N′*-

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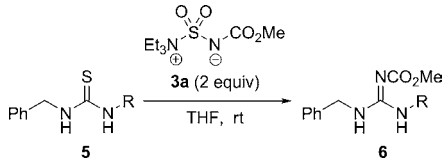
Table 1. Reactivity of 3a toward Diverse Thioureas 5a–5d

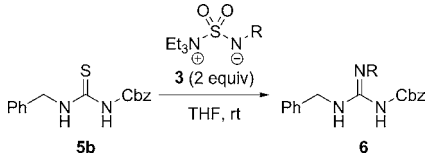


entry	5 (R)	time (h)	6	yield (%)
1	**5a** (Ph)	4	**6aa**	0
2	**5b** (Cbz)	2	**6ab**	73
3	**5c** (Ts)	3	**6ac**	63
4	**5d** (Bz)	1	**6ad**	29

dibenzylthiourea **5a** did not give the desired product. Carbamoyl thiourea **5b** prepared from benzylamine and Cbz-isothiocyanate **7**[13] gave the best results. The Cbz group was also found to be a superior protecting group compared to the Ts or Bz group.

Encouraged by these results, we next examined the reaction of **5b** with the Burgess-type reagents **3b–3e**[9,11] to incorporate more easily removable protecting groups, such as Boc, Alloc, Troc, and Cbz (Table 2). In all cases, the desired guanidines **6bb–6eb** were obtained in good yields similar to the case of **3a**.

Table 2. Reactivity of the Burgess-Type Reagents 3b–3e toward 5b



entry	3 (R)	time (h)	6	yield (%)
1	**3b** (Boc)	1	**6bb**	80
2[a]	**3c** (Alloc)	2	**6cb**	86
3	**3d** (Troc)	5	**6db**	63
4[b]	**3e** (Cbz)	3	**6eb**	79

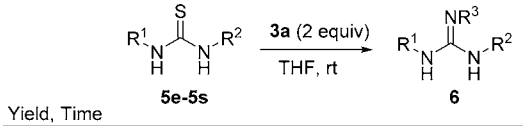
[a]2.5 equiv of **3c** were used. [b]3.0 equiv of **3e** were used.

To explore the generality and scope of this reaction, various substrates (**5e–5s**) were examined (Table 3). Thioureas derived from aliphatic and aromatic amines reacted with **3** to give the desired guanidines in good yields (**6ae**, **6af**, **6ag**, **6ch**, **6ai**). Functional groups such as ketone, ester, vinyl, alkynyl, nitrile, and silyl groups were also tolerated (**6aj**, **6ak**, **6al**, **6am**, **6an**, **6ao**). Fmoc or ethyl carbamate protected thiourea also gave the product in 76% and 72% yields, respectively (**6bp**, **6aq**). However, sterically demanding thiourea resulted in a low yield (**6ar**), and secondary amine derived thiourea gave none of the desired guanidines **6as**, but did yield the methyl carbamate protected thiourea **8**.

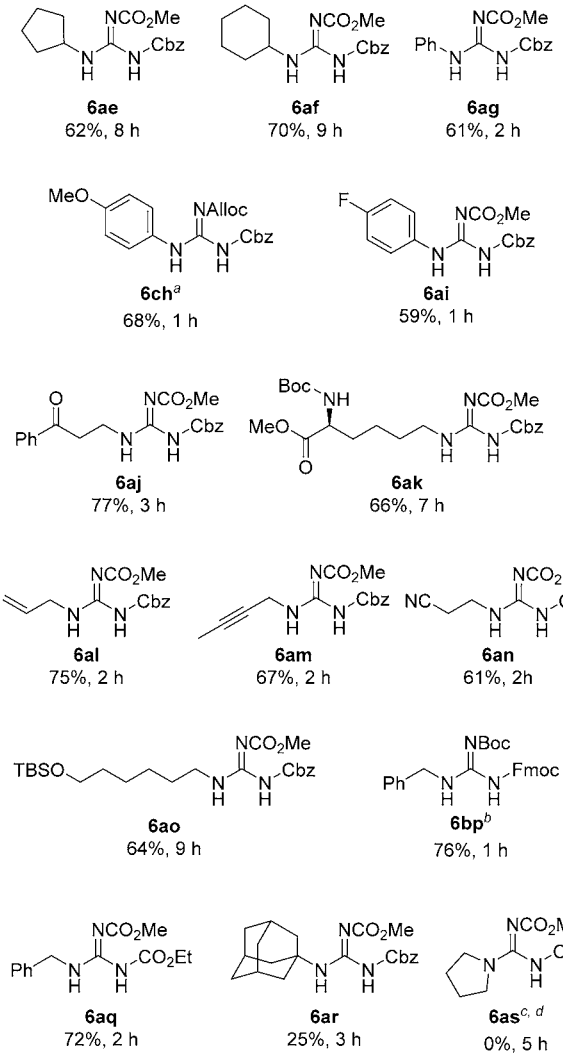
Next, we tried a one-pot synthesis of guanidine from the corresponding amine, isothiocyanate, and **3** (Scheme 2). Carbamoyl thiourea **5b**, which was prepared from benzylamine and **7** *in situ*, was directly treated with **3c** to give the desired guanidine **6cb** in 80% yield.

Finally, we demonstrated the selective deprotection of differentially *N,N′*-diprotected guanidines (Table 4). Cbz, Boc, and Fmoc protecting groups of guanidines **6ab**, **6bb**, and **6bo** were cleaved selectively under standard conditions (hydrogenolysis, acidic, and basic conditions) to afford the desired *N*-monoprotected guanidines[14] **9–12** in high yields.

Table 3. Desulfurative Condensation of Various Carbamoyl Thioureas 5 with the Burgess Reagent 3



Yield, Time



[a]2.5 equiv of **3c** were used. [b]2.5 equiv of **3b** were used. [c]4.0 equiv of **3a** were used. [d]**8** (Figure 3) was isolated in 61% yield.

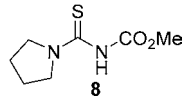
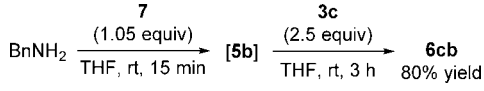


Figure 3.

Scheme 2. One-Pot Synthesis of 6cb from Benzylamine, 7, and 3c



Based on literature precedents,[7–12] we propose the following reaction mechanism (Scheme 3). The reaction of thiourea **5** with the Burgess reagent **3** affords intermediate **4**. This postulated intermediate **4** rearranges to **13**, which is hydrolyzed

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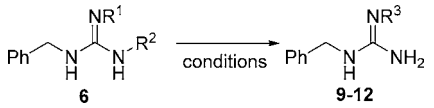
Table 4. Selective Deprotection of Differentially *N,N′*-Diprotected Guanidines

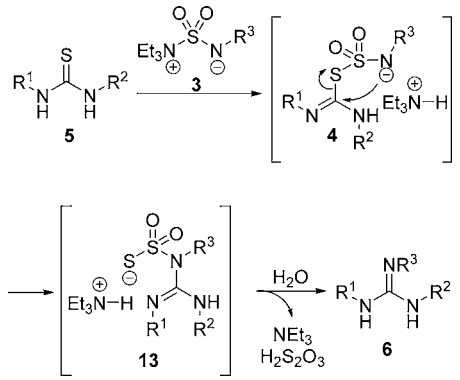


6 9-12

entry	**6** (R^1,R^2)	conditions	product (R^3)	yield (%)
1	**6ab** (CO_2Me, Cbz)	H_2, Pd/C (5 mol %) MeOH/THF, rt, 1 h	**9** (CO_2Me)	95
2	**6bb** (Boc, Cbz)	TFA/CH_2CI_2 = 1/1, rt, 1 h	**10** (Cbz)	92
3	**6bo** (Boc, Fmoc)	TFA/CH_2Cl_2 = 1/1, rt, 1 h	**11** (Fmoc)	99
4	**6bo** (Boc, Fmoc)	piperidine/DMF = 1/10, rt, 5 min	**12** (Boc)	91

to give guanidine **6** with the release of thiosulfuric acid under the workup conditions.

Scheme 3. Proposed Mechanism for the Synthesis of Guanidines from Thioureas Using the Burgess Reagent



In summary, we have developed a simple method for the synthesis of differentially *N,N′*-diprotected guanidines from carbamoyl thioureas by using the Burgess reagent. Further studies of the mechanistic aspects and the application of this approach to other types of desulfurative condensation are now underway.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, full characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ NOTE ADDED AFTER ASAP PUBLICATION

The header graphics in Tables 1 and 2 contained errors in the version published ASAP March 14, 2014; the correct version reposted March 18, 2014.

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