

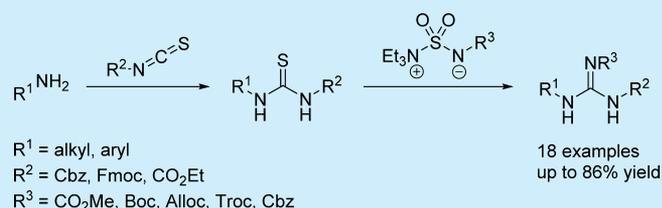
A Mild Method for the Synthesis of Carbamate-Protected Guanidines Using the Burgess Reagent

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S 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 guanylation 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-carboxamide (**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 reagent⁷ (**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 sulfi-

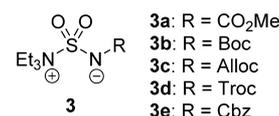
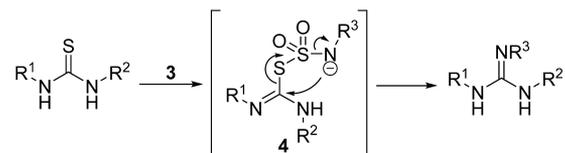


Figure 2. Burgess reagent **3a** and related compounds **3b–3e**.

mines.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).

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



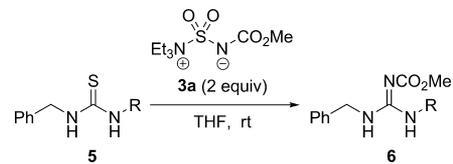
Herein, we describe a method for the synthesis of differentially *N,N'*-diprotected guanidines by desulfurative condensation of carbamoyl thiourea with **3** under mild reaction conditions. In this reaction, the Burgess reagent plays dual roles as a carbamate source and a desulfurizing agent. To the 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

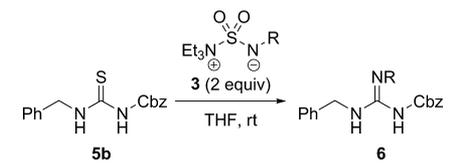


entry	5 (R)	time (h)	6	yield (%)
1	5a (Ph)	4	6aa	0
2	5b (Cbz)	2	6ab	73
3	5c (Ts)	3	6ac	63
4	5d (Bz)	1	6ad	29

dibenzylthiourea 5a did not give the desired product. Carbamoyl thiourea 5b prepared from benzylamine and Cbz-isothiocyanate 7¹³ 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

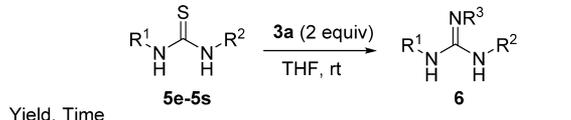
^a2.5 equiv of 3c were used. ^b3.0 equiv of 3e were used.

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 9–12 in high yields.

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



Yield, Time	5e-5s	6
62%, 8 h	6ae	6af
70%, 9 h	6af	6ag
61%, 2 h	6ag	6ch ^a
68%, 1 h	6ch ^a	6ai
59%, 1 h	6ai	6aj
77%, 3 h	6aj	6ak
66%, 7 h	6ak	6al
75%, 2 h	6al	6am
67%, 2 h	6am	6an
61%, 2 h	6an	6ao
64%, 9 h	6ao	6bp ^b
76%, 1 h	6bp ^b	6aq
72%, 2 h	6aq	6ar
25%, 3 h	6ar	6as ^{c, d}
0%, 5 h	6as ^{c, d}	8

^a2.5 equiv of 3c were used. ^b2.5 equiv of 3b were used. ^c4.0 equiv of 3a were used. ^d8 (Figure 3) was isolated in 61% yield.

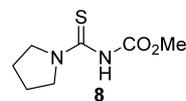
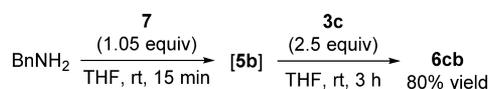


Figure 3.

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



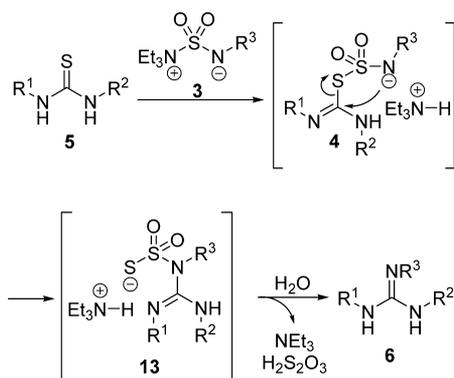
Based on literature precedents,^{7–12} we propose the following reaction mechanism (Scheme 3). The reaction of thiourea 5 with the Burgess reagent 3 affords intermediate 4. This postulated intermediate 4 rearranges to 13, which is hydrolyzed

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

entry	6 (R ¹ ,R ²)	conditions	product (R ³)	yield (%)
1	6ab (CO ₂ Me, Cbz)	H ₂ , Pd/C (5 mol %) MeOH/THF, rt, 1 h	9 (CO ₂ Me)	95
2	6bb (Boc, Cbz)	TFA/CH ₂ Cl ₂ = 1/1, rt, 1 h	10 (Cbz)	92
3	6bo (Boc, Fmoc)	TFA/CH ₂ Cl 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.