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N,*N*′,*N*″-Tri-Boc-guanidine (TBG): a common starting material for both *N*-alkyl guanidines and amidinoureas

Panchami Prabhakaran and Gangadhar J. Sanjayan*

Division of Organic Synthesis, National Chemical Laboratory, Dr. Homi Bhabha Road, Pune 411 008, India

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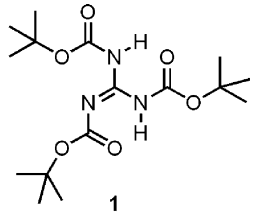
Abstract—In this Letter, we describe the unexpected reaction pattern of *N*,*N*′*N*″-tri-Boc-guanidine (TBG) with amines at room temperature and under reflux conditions affording N-substituted guanidines and amidinoureas, potentially important compounds with extensive applications in medicinal chemistry. This investigation shows that TBG is an excellent, readily available common starting material for the synthesis of various *N*-alkyl guanidines as well as *N*-alkyl-N′-substituted amidinoureas by simply manipulating the reaction conditions.

Towards the end of his illustrious career,[1] Murray Goodman, a pioneer peptide chemist,[2] first introduced tri-Boc-guanidine (TBG) **1**, as a versatile guanidinylating reagent for the synthesis of N-substituted guanidines **3a** by its reaction with alcohols under Mitsunobu conditions.[3]



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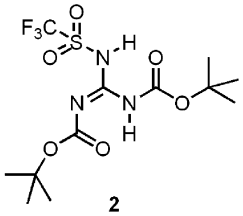

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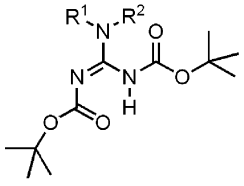
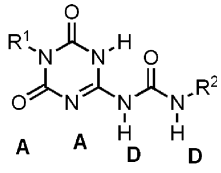


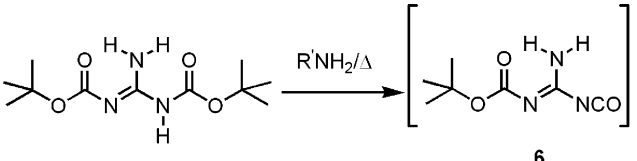
3a R^1 = ^{t}BuOCO; R^2 = Alkyl
b R^1 = H; R^2 = Alkyl / Aryl



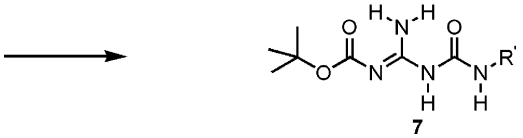
4 R^1= R^2 = Alkyl

A related trifluoro sulfonyl analog **2**, which is found to be one of the most powerful guanidinylating reagents so far, was also introduced by Goodman for the efficient synthesis of substituted guanidines, under extremely mild conditions by its reaction with amines.[4] The reaction proceeds with attack of amines at the amidine carbon eliminating the trifluoro sulfonamide and cleanly furnishing the protected guanidines **3b**. In one of our recent programmes directed towards the synthesis of highly stable quadruply hydrogen-bonding systems with degenerate prototropy,[5] we required an efficient procedure for the construction of **4**, a self-assembling system adorned with AADD-type quadruple hydrogen-bonding arrays.

Di-Boc guanidine[4] **5** has been shown to react with amines under an elevated temperature to afford amidinoureas **7**.[6]



5 **6**



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Keywords: *N*,*N*′,*N*″-Tri-Boc-guanidine; *N*-Alkyl guanidines; Amidinourea.
* Corresponding author. Tel.: +91 20 25902982; fax: +91 20 25893153; e-mail: gj.sanjayan@ncl.res.in

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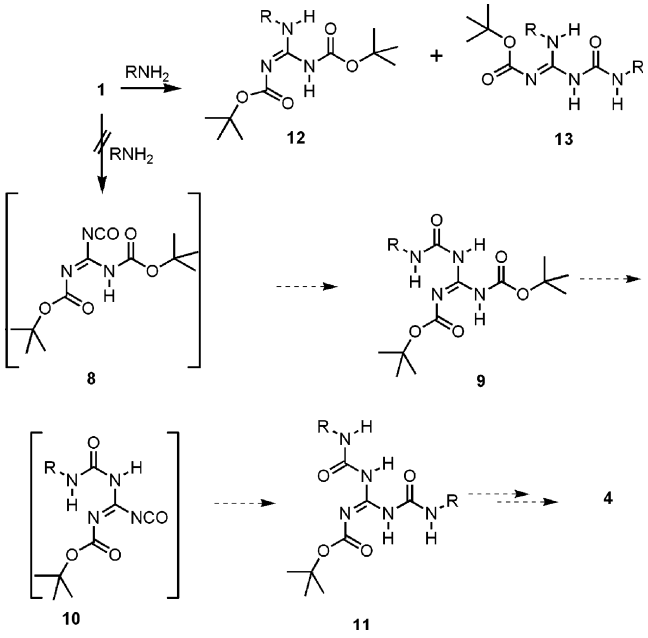
In this reaction, the intermediacy of isocyanate **6**, generated in situ by the elimination of *t*-butanol, has been advocated, which reacts with the amines to form amidinoureas **7**.[7]

In this context we anticipated that TBG **1** would also react with amines in a similar way, to eventually afford **11**, through intermediates **8** and **10**, which in turn could be subjected to cyclization to form the quadruple H-bonded self-complimentary AADD-type self-assembling system **4** (Scheme 1). As reported in the case of di-Boc guanidine **5**, we envisaged that the reaction of **1** with amines would involve the intermediacy of an isocyanate.[7]

Unexpectedly, TBG reacted with primary amines at room temperature in an entirely different fashion affording N-substituted, *N*′,*N*″-di-Boc guanidine **12**, which led us to explore further the reaction chemistry of TBG with various amines under different conditions. A summary of the reactions performed under different conditions with the isolated yields is given in Table 1, which suggests that the reaction of **1** with amines can be manipulated to afford either N-substituted guanidines **12** or *N*-alkyl amidinoureas **13** under relatively mild reaction conditions.



Scheme 1. Reaction of TBG **1** with amines.

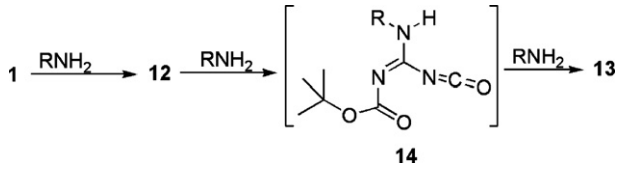
It is noteworthy that amidinoureas are of considerable interest in medicinal chemistry;[8a–c] for instance in treating irritable bowel syndrome, gastrointestinal, spasmolytic and cardiovascular disorders and parasitic infestations. Furthermore, amidinourea has also been shown to be the essential structural feature for the potent antibacterial activity of TAN-1057A-D,[9] a naturally occurring potent antibiotic dipeptide-amidinourea isolated from the bacteria *Flexibacter* sp. PK-74 and PK-176. Moreover, it has been noted that long chain N-substituted amidinoureas find industrial application as non-toxic and non-polluting stabilizers and dispersants (multifunctional) for middle distillate fuels.[10] The methods so far known in the literature for the preparation of amidinoureas include, the reaction of guanidines with isocyanates,[11] the hydrogenation of 5-amino-3-amino-l,2,4-oxadiazoles,[12] the reaction of carbamic esters with guanidine,[13] the hydrolysis of cyanoguanidines under strongly acidic conditions[14] and the reaction of acyl-*S* methylisothiourea with amines.[15]

The reactions of TBG **1** with amines under different conditions were investigated in order to understand the reaction pattern. Unlike the reaction of di-Boc guanidine **5** with an amine[6] to afford substituted amidinoureas **7** through the isocyanate mechanism, TBG reacted with primary amines at room temperature resulting in the formation of the corresponding N-alkylated di-Boc guanidines, **12** (entries 1, 5, 10, 12 and 14, Table 1) in good yields. Enhancement in the rate of the reaction as well as the yield was examined by carrying out the

Table 1. Reaction of TBG **1** with amines under different conditions

Entry	Amine	TBG/amine (equiv)	Base/LA	Solvent, temp	**12** (%)	**13** (%)
1	Benzyl amine	1:1	—	THF, rt	98	—
2	Benzyl amine	1:1	—	THF, reflux	38	30
3	Benzyl amine	1:4	—	THF, reflux	—	90
4	Benzyl amine	1:3	TMA	Toluene, reflux	20	30
5	Isobutyl amine	1:1	—	THF, rt	60	—
6	Isobutyl amine	1:1	—	THF, reflux	50	22
7	Isobutyl amine	1:3	—	THF, reflux	—	86
8	Isobutyl amine	1:1	DBU	THF, rt	61	—
9	Isobutyl amine	1:1	DBU	DMSO, 50 °C	40	40
10	Dodecyl amine	1:1	—	THF, rt	97	—
11	Dodecyl amine	1:3	—	THF, reflux	—	91
12	Cyclohexyl amine	1:1	—	THF, rt	52	—
13	Cyclohexyl amine	1:3	—	THF, reflux	—	60
14	Isopropyl amine	1:1	—	THF, rt	40	—
15	Isopropyl amine	1:4	—	THF, reflux	—	52
16	Aniline	1:1	—	THF, rt	—[a]	—[a]
17	Diethyl amine	1:1	—	THF, rt	—[a]	—[a]

LA: Lewis acid, TMA: trimethyl aluminium.
[a] An intractable mixture of products was obtained.



Scheme 2. Proposed mechanism of reaction of TBG **1** with amines.

reaction at elevated temperature and also by the addition of an external base (DBU). When primary amines were reacted with TBG **1** under reflux in a 1:1 ratio, both N-substituted guanidines **12** and amidinoureas **13** were obtained (entries 2 and 6, Table 1). It is noteworthy that the use of excess amine under reflux dramatically increased the yield of **13** and amidinoureas were the only products isolated under these conditions (entries 3, 7, 11, 13 and 15, Table 1). These observations suggest that N-substituted guanidines **12** are formed first by nucleophilic attack of the amines at the highly electrophilic quaternary carbon of TBG flanked by the three carbamate groups. Further reaction of **12**, presumably proceeding through the isocyanate intermediate **14**, affords N-substituted amidinoureas **13** (Scheme 2).

In the presence of the strong base DBU, the reaction of TBG with isobutylamine in an equimolar ratio under ambient conditions proceeded with no significant difference in the yield of substituted guanidine **12** (compare entries 5 and 8, Table 1). However, raising the reaction temperature had a minor effect on the product distribution (compare entries 6 and 9, Table 1). These results also suggest that the formation of **12** *precedes* **13** and that even strong bases like DBU fail to promote TBG to form isocyanate intermediate **8**, which would have led to the formation of **9** (Scheme 1). The difference in the reaction when compared with di-Boc guanidine may be due to the increased electrophilicity at the quaternary carbon of the guanidine moiety due to the additional Boc group. In order to understand the reaction pattern of aromatic amines, TBG was reacted with aniline (entry 16, Table 1). However, this reaction led to the formation of an intractable mixture of products. A similar outcome also occurred using a secondary amine (entry 17, Table 1). Finally, in an effort to react TBG with amines to afford **11**, which could have been cyclocondensed to furnish the self-assembling system **4**, TBG was reacted with excess benzylamine in the presence of trimethyl aluminium (TMA). However, this reaction led to the formation of a mixture N-substituted guanidine and amidinourea (entry 4, Table 1).

In conclusion, this work demonstrates that TBG reacts in an unusual manner with amines under various conditions, in stark contrast to the manner by which di-Boc guanidine **5** reacts. Our finding suggest that TBG can act as an excellent, readily available starting material for the selective synthesis of both *N*-alkyl guanidines and amidinoureas in good yields by reaction with primary aliphatic amines under various reaction conditions. Further work is in progress to evaluate the synthetic potential of TBG.

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Supplementary data

General experimental procedures, ^{1}H, ^{13}C, DEPT-135 NMR spectra and ESI mass spectra of **12a–e** and **13a–e** can be found, in the online version, at doi:10.1016/j.tetlet.2007.01.055.

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