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Conversion of *N,N'*-bis(*tert*-butoxycarbonyl)Guanidines to *N*-(*N'*-*tert*-butoxycarbonylamidino)Ureas

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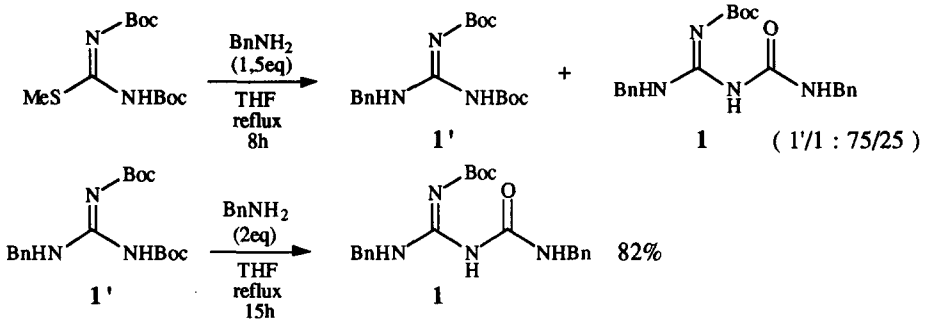
Abstract : Surprising aminolysis of bis-Boc-protected guanidines in refluxing THF leads to the corresponding monoBoc substituted amidinoureas.

These last few years, several methods of converting amines into guanidines *via* a bis-carbamate intermediate[1] have emerged. One of the major interest of this indirect procedure is that some of the newly developed guanylating reagents allow the synthesis of protected guanidines from poorly nucleophilic amines under mild conditions, when used in combination with a heavy metal salt[2] or with Mukaiyama's reagent.[3] In addition to the facile deprotection[4] of carbamate substituted guanidines, alkylation of these compounds has also been successfully investigated[5], offering an original route to internal guanidines.

During a program aimed at developing new ligands for the I receptors, we wanted to prepare the simple *N,N'*-bis-(*tert*-butoxycarbonyl)-*N''*-benzylguanidine **1'**. We have found that under certain conditions -i.e. prolonged heating and use of an excess of benzylamine - the desired product **1'** is formed together with a by-product. This latter compound has been isolated and identified as the amidinourea **1**. Furthermore, we have shown that formation of **1** results from the reaction of a second molecule of benzylamine with **1'**, as we have observed when treating isolated bis-Boc-protected guanidine **1'** with an excess of benzylamine (Scheme 1).

Scheme 1



A survey of the litterature reveals that except a recent report describing the preparation of monoalkyl substituted amidinourea from amines[6], the only existing methods of formation of dialkyl substituted amidinoureas, by treatment of guanidines with isocyanates[7] or hydrogenation of 3,5-diamino-1,2,4-oxadiazoles,[8] are either inefficient or require numerous steps. Thus, we have taken advantage of our unexpected result for studying its generalization to various examples (Scheme 2).[9] Results are summarized in Table 1.

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Scheme 2

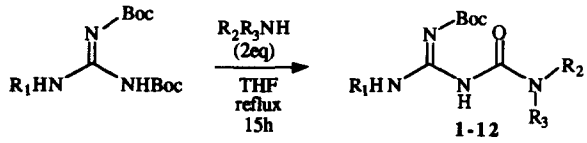


Table 1

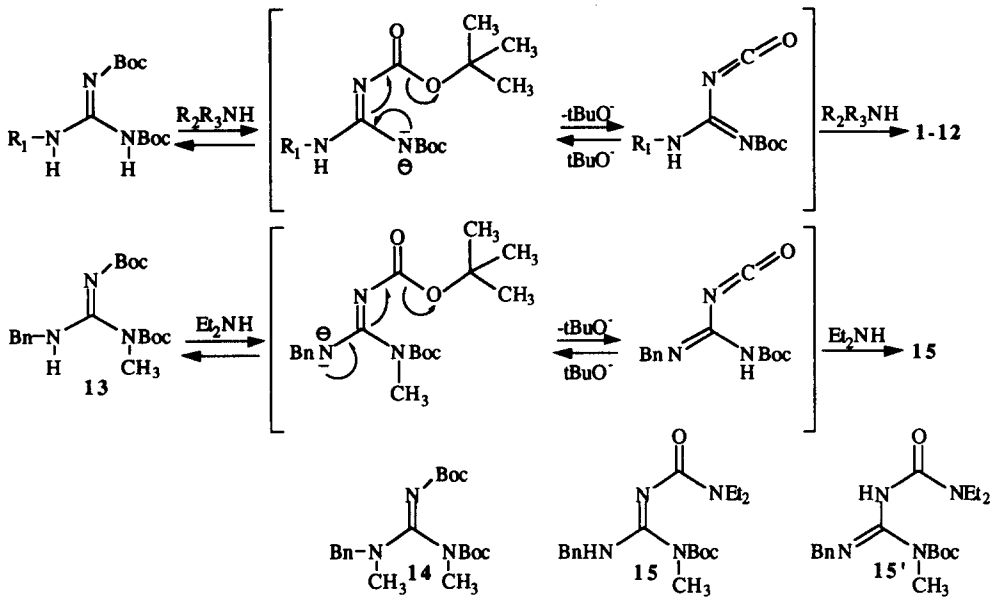
Entry/ product	R^1	R^2	R^3	Yield[a](%)
1	Bn	Bn	H	82
2	Bn	iPr	H	79
3	Bn	cyclohexyl	H	78
4	Bn	C_6H_5	H	65[b]
5	Bn	Et	Et	85
6	Bn	iPr	iPr	73
7	Bn	$PhCH_2CH(CO_2CH_2Ph)$	H	74
8	cyclohexyl	Et	Et	82
9	cyclohexyl	Bn	H	77
10	C_6H_5	Et	Et	81
11	$(CH_3)_2CHCH_2CH(CO_2CH_2Ph)$	$PhCH_2CH(CO_2CH_2Ph)$	H	72
12	$BocNH\text{-}(CH_2)_2CH_2$	Bn	H	75

[a] Isolated yield after chromatography [b] 24h were necessary to complete the reaction

Formation of Boc-substituted amidinoureas proceeds well with good yields even with poorly nucleophilic amines such as aniline (entry 4) and the bulky diisopropylamine[10] (entry 6). As can be expected, no significant changes on reactivity is observed when varying the starting guanidine. Interesting non-peptidic coupling between phenylalanine benzyl ester and the bis-Boc guanidino leucine benzylester has also been achieved (entry 11).

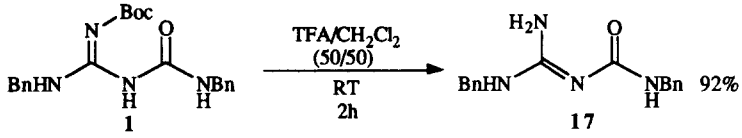
While aminolysis of various carbamates[11] (such as phenyl ones) is well documented, Boc protecting group is known to be strongly resistant toward many nucleophilic reagents.[12] However, Lamothe recently reported[13] on the conversion of Boc-protected amines into ureas via a probable isocyanate intermediate. Nevertheless, use of a strong base (BuLi or NaH) was essential to achieve the conversion. In its absence, no reaction took place.This has been confirmed with the selective aminolysis of a bis-Boc guanidino group (entry 12). If we consider that a similar mechanism as the one described by Lamothe takes place, this would mean that in our case, amines act both as bases to promote the formation of an isocyanate and as nucleophiles toward this latter intermediate. Indeed, the N-H protons of a bis-Boc-protected guanidine are expected to be much more acidic than the Boc amino ones, due to the possibility of delocalizing[5] the resulting negative charge through the guanidine and carbonyl functional groups. This would also explain the longer reaction time needed with less basic amines such as aniline (entry 4). We have then synthesized the *N*-alkylated bis-Boc benzylguanidine **13**. We have observed, although requiring one week of heating, the total aminolysis of a Boc group with diethylamine (product obtained as **15** instead of the tautomer **15'**). The intermediate isocyanate should in this case derive from the deprotonation of the less acidic N"H proton followed by the expulsion of a $tBuO^-$ group from the N' Boc group. Requirement of an NH proton for the reaction to occur has been confirmed by studying the chemical behaviour of the bis-methylated bis-Boc benzylguanidine **14** toward diethylamine. After 24 h of heating, TLC did not indicate any formation of aminolysis product. The two supposed mechanisms of aminolysis are figured on Scheme 3.

Scheme 3



Finally, one example of deprotection of Boc-substituted amidinoureas has been performed using a solution of trifluoroacetic acid in dichloromethane (Scheme 4).

Scheme 4



In conclusion, we have developed a simple and original method to prepare Boc-substituted amidinoureas from *N,N'*-bis-Boc-*N''*-alkylguanidines. Further work on the aminolysis of some other bis-Boc amidine derivatives[10b] and regioisomeric *N,N'*-bis-Boc-*N*-alkylguanidines[15] is in progress.

Typical experimental procedure: A solution of *N,N'*-bis(*tert*-butoxycarbonyl)-*N''*-benzylguanidine (1 g, 2.8 mmol) and benzylamine (600 mg, 5.6 mmol) in refluxing THF (10 ml) was stirred until TLC (petroleum ether/ethyl acetate 80/20) indicated the consumption of the starting guanidine. The solution was concentrated in vacuo. The residue was purified by flash chromatography column on SiO_2 eluting with petroleum ether/ethyl acetate (90/10) to afford **1** as a white solid, 890 mg (81%), mp 96°C. ^1H NMR (400MHz, $CDCl_3$ vs TMS) δ 1.45 (s, 9H), 4.37 (d, J= 5.8Hz, 2H), 4.50 (d, J=5.3Hz, 2H), 5.64 (s, 1H), 7.2-7.3 (m, 10H), 8.38 (brs, 1H), 12.14 (brs, 1H); ^{13}C NMR (100MHz, $CDCl_3$ vs TMS) 27.9, 44, 44.3, 82.4, 127, 127.3, 127.5, 128.4, 128.5, 137.9, 153.2, 154.3, 164.5; MS (EI) m/e 382 ($M^{+\cdot}$) 308, 282 [(MH-Boc)$^{+\cdot}$]

A solution of **1** (400 mg, 1.04 mmol) in TFA/CH_2Cl_2 (50/50, 10 ml) was stirred at room temperature for 2h. The solution was then concentrated in vacuo. The residue was dissolved in ethyl acetate. The resulting solution was washed with sat. $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated to give 271 mg (92%) of **17** as a white solid, mp 112°C. ^1H NMR (400MHz, $CDCl_3$ vs TMS) δ 4.28 (s, 4H), 6.53 (brs, 1H), 7.1–7.3 (m,10H), 8.59 (brs, 3H) ^{13}C NMR (100MHz, $CDCl_3$ vs TMS) 43.5, 45.0, 127.0, 127.1, 127.4, 128.5, 128.6, 129.2, 134.2, 137.7, 155.6, 156.4; MS (EI) m/e 284 ($M^{+\cdot}$+2), 283 ($M^{+\cdot}$+1), 282 ($M^{+\cdot}$)

References and notes

1.(a) Lammin, S.G.; Pedgrift, B.L. and Ratcliffe, A.J. *Tetrahedron Lett.* **1996**, *37*, 6815-6818 (b) Lal B. and Gangopadkyay, A.K. *Tetrahedron Lett.* **1996**, *37*, 2483-2486 (c) Bernatowicz, M.S.; Wu, Y. and Matsueda, G.R. *Tetrahedron Lett.* **1993**, *37*, 2483-86 (d) Drake, B.; Patel, M. and Lebl, M. *Synthesis* **1994**, 579-582 (e) Iwanowicz, E.J.; Poss, M.A. and Lin J. *Synth.Commun.* **1993**, *23*, 1443-1445 (f) Poss, M.A.; Iwanowicz, E.J.; Reid, J.A.; Lin, J. and Gu, Z. *Tetrahedron Lett.* **1992**, *33*, 5933-5936 (g) Bergeron, J. and Mc Manis, J.S. *J.Org.Chem.* **1987**, *52*, 1700-1703.

2.(a) Su, W. *Synth.Commun.* **1996**, *26* (2), 407-413 (b) Chandrakumar, N.S. *Synth.Commun.* **1996**, *26* (14), 2613-2616 (c) Kim, K.S. and Qian, L. *Tetrahedron Lett.* **1993**, *34*, 7677-7680.

3.Yaw, F.W.; Kowalski, J.A.; Lipton, M.A. *J. Org. Chem.* **1997**, *62*, 1540-1542.

4.For deprotection of bis-Cbz substituted guanidines, see ref. 2a and 2b. For deprotection of bis-Boc substituted guanidines, see Miel, H. and Rault, S. *Tetrahedron Lett.* **1997**, *38*, 7865-7866.

5.Ko, S.Y.; Lerpiniere, J. and Christophi, M.A. *Synlett* **1995**, 815-816.

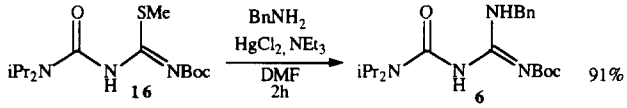
6.Chenguang, Y. and Williams, R.M. *Tetrahedron Lett.* **1996**, *37*, 1945-1948.

7.Tilley, J.W. and Blount, J.F. *Helv. Chem. Acta* **1980**, *63*, 841-859.

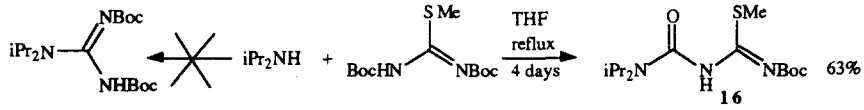
8.Tilley, J.W. and Blount, J.F. *Helv. Chem. Acta* **1980**, *63*, 832-840.

9.The starting bis-Boc substituted guanidines are prepared from the corresponding amines according to reported procedures (see ref. 2a and 2b) by replacing bis-Cbz isothiourea with bis-Boc isothiourea.

10.(a) The resulting product has also been synthesized by treatment of *N*-(*N''*,*N''*-diisopropylcarbamoyl)-*N'*-(*tert*-butoxycarbonyl)-S-methylisothiourea **16** with benzylamine in presence of mercuric chloride (for a recent report on the formation of guanidine derivatives promoted by $HgCl_2$, see ref.14).



(b) Unexpected formation of **16** was realized by reacting diisopropylamine with *N*,*N'*-bis-Boc isothiourea. Despite the presence of the electrophilic central amidino carbon of isothiourea, no expected formation of bis-Boc isopropylguanidine was observed.



Drake and coll. (see ref.1d) had also noted that reaction of diisopropylamine with another bis-Boc guanylating reagent (1-*H*-pyrazole-1-[*N*,*N'*-bis(*tert*-butoxycarbonyl)]carboxamidine) did not lead to the bis-Boc isopropylguanidine. The product they obtained was however not a pyrazole-Boc-carbamoyl carboxamidine resulting from the aminolysis of one Boc group but a diisopropylaminooxadiazinone.

11.Bounkham, T. *Synthesis* **1997**, 1189-1194 and references therein.

12.(a) Kocienski, P.J. *Protecting Groups*; Thieme, New York **1994**, 192-195 (b) Myers, A.G.; Yoon,T. *Tetrahedron Lett.* **1995**, *36*, 9429-9432.

13.Lamothe, M.; Perez, M.; Colovray-Gotteland,V. and Halazy, S. *Synlett* **1996**, 507-508.

14.Levallet, C.; Lerpiniere, J. and Soo, Y.K. *Tetrahedron* **1997**, *53*, 5291-5304.

15.Vaidyanathan, G. and Zalutsky, M.R. *J. Org. Chem.* **1997**, *62*, 4867-4869 see also Dharmpal, S.D. and Kozikowski, P.A. *Tetrahedron Lett.* **1994**, *35*, 977-980.