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Total Deprotection of *N,N'*-bis(*tert*-butoxycarbonyl)Guanidines Using $SnCl_4$

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Abstract : The total deprotection of *N,N'*-bis-Boc guanidines using $SnCl_4$ proceeds smoothly in ethyl acetate at room temperature and leads to the easily isolable corresponding guanidinium chlorides.

New methods of introducing the guanidine moiety into organic molecules continue to emerge[1] due to its occurence in natural products, drug compounds and peptides. Two different pathways can be used for the conversion of the amino group into the guanidino group : the direct formation of the guanidinium salts **2** or the synthesis of a bis-urethane protected intermediate **1**. The latter method -which has extensively been studied these last five years[2]- gives much better yields particularly with poorly nucleophilic amines ; moreover, the ease of handling of bis-protected guanidines **1** allows the introduction of the guanidine group at any stage of a synthesis, contrarily to the former method. In addition, a recent paper has shown that intermediate **1** can also be synthesized from the corresponding alcohol *via* a Mitsunobu reaction.[3]

Scheme 1

The total deprotection of bis-Boc substituted guanidines has not yet been specifically studied. However, it has already been realized by different authors[2] using a solution of trifluoroacetic acid in dichloromethane. Nevertheless, from a pharmacological point of view, application of this procedure is often not acceptable since it leads to trifluoacetate salts. As displacement of these guanidinium salts is generally quite tedious to perform and lowers the yields of the desired product, we have looked for a better and straightforward deprotecting method.

The use of a solution of gaseous hydrochloric acid in acetic acid was not satisfactory since it lead to oily residues of guanidinium salts never free from acetic acid. Replacement of acetic acid by ether or ethyl acetate allowed us to isolate a mixture of partially and totally deprotected guanidines (**Scheme 2**). The relative insolubility of intermediates **3** accounts for the more difficult removing of the second Boc group. To improve its solubility, polarity of the medium was increased by addition of acetone. In every case, the reaction was not completed after 15h of stirring, leaving a small amount (5-10%) of monodeprotected adduct **3** ; in addition, crystallization of **2** was difficult to achieve. The use of hydrochloric acid being not satisfactory, we have studied the Boc deprotection with stannic chloride, a reagent which has recently been used in the mild deprotection of Boc protected aminoacids.[4] We have found that under neutral conditions and using 4 equivalents of $SnCl_4$, removal of

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the two Boc groups was quickly and simultaneously achieved[5] at room temperature with good to excellent yields and without isolation of any monoBoc guanidine intermediate. This method seems general and we report herein 11 examples (see **table 1**).[6]

Scheme 2

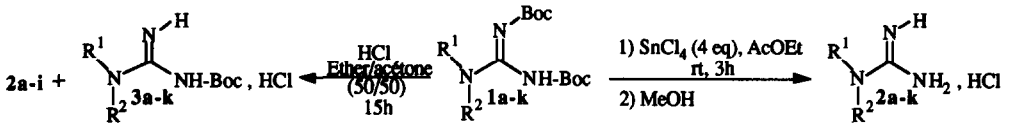

Table 1

2	R^1	R^2	Yield (%)
a	Bu	H	89
b	cyclohexyl	H	95
c	Bn	H	93
d	Ph	H	100
e	4-(OMe)C_6H_4-	H	91
f	-$(CH_2)_5$-		93
g	$PhCH_2CH(CO_2CH_2Ph)$-	H	85
h	CF_3CONH-$(CH_2)_2$-CH_2-	H	88
i	2-oxocyclopenta[*b*]thiophen-4-yl	H	91
j	BocNH-$(CH_2)_2$-CH_2-	H	88[a,b]
k	BocNH-CH(COOH)-$(CH_2)_2$-CH_2-	H	81[a,b]

a 6 equivalents of $SnCl_4$ were used

b no selectivity was observed when only one equivalent of $SnCl_4$ was used

In summary, stannic chloride is a good alternative to trifluoacetic acid for the deprotection of bis-Boc substituted guanidines, giving under mild and neutral conditions good yields of the corresponding solid guanidinium chlorides (trifluoroacetic salts are often liquids difficult to crystallize).

References and notes

1. Greenhill, J.L. ; Lue, P. *Amidines and Guanidines in Medicinal Chemistry* in "Progress in Medicinal Chemistry" Vol.**30**, Chapt.5, Ellis, G.P. ; Luscombe, D.K. eds. Elsevier Science, **1993**
2. Yong, Y.F. ; Kowalski, J.A. ; Lipton M.A. *J. Org. Chem.*, **1997**, *62*, 1540-1542 (and references therein)
3. Dodd, D.S. ; Kosikowski, A.P. *Tetrahedron Lett.*, **1994**, *35*, 977-980
4. Franck, R. ; Schutkowski, M. *J. Chem. Soc., Chem. Comm.*, **1996**, 2509-2510
   For a list of reagent used to cleave the Boc group, see : Greene, T.W. ; Wuts, P.G.M. *Protective Groups in Organic Synthesis*, 2nd Ed. ; John Wiley & Sons, New York, **1991** See also Evans, E.F. ; Lewis, N.J. ; Kapfer, I. ; Macdonald, G. and Taylor, R.J.K. *Synth. Commun.*, **1997**, *27*, 1819-1825 ; Stafford, J.A., Brackeen, M.F. ; Karanewski, D.S., Valvano, N.L. *Tetrahedron Lett.*, **1993**, *34*, 7873-7876
5. A typical experiment is as follows : to a stirred solution of *N,N'*- bis(*tert*-butoxycarbonyl)benzylguanidine (1g, 28mmol) in ethyl acetate is added stannic chloride (3g, 4eq). After 3h of stirring at room temperature, t.l.c. (ethyl acetate/petroleum ether : 70/30) indicates the complete consumption of the starting material. The solvent and the excess of $SnCl_4$ are evaporated *in vacuo*. The remaining solid is dissolved in methanol. Ether is then added until the formation of a white precipitate of benzylguanidine hydrochloride.

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