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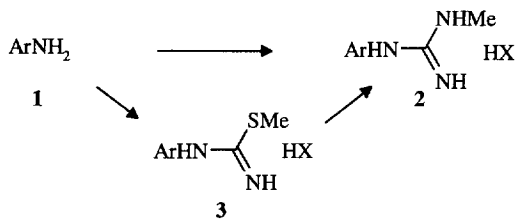
Conversion of Anilines to Bis-Boc Protected N-Methylguanidines

Simon G. Lammin, Brian L. Pedgrift and Andrew J. Ratcliffe*

Department of Chemistry, Rhône-Poulenc Rorer Central Research,
Dagenham Research Centre, Rainham Road South,
Dagenham, Essex, RM10 7XS, U.K.

Abstract: The reaction of a variety of anilines with a new N-methylguanylating agent **5** to produce bis-Boc protected N-methylguanidines is reported. Copyright © 1996 Elsevier Science Ltd

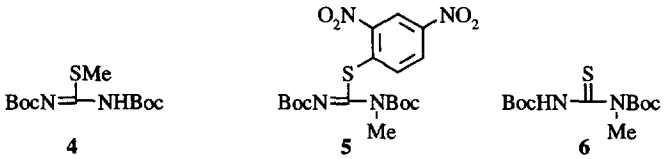
The guanidine moiety is an important feature in many biologically active compounds[1]. During a recent programme directed toward antagonists of the C-5a complement system[2], a method was required to effect conversion of a series of anilines **1** to their corresponding N-methylguanidines **2** (Scheme 1).



Scheme 1

Whilst the above transformation could be accomplished via reaction of the appropriate S-methylisothiouronium salt[3] **3** (X=I) with methylamine (Scheme 1), the necessity for a three step synthesis of **3** from **1**[4], coupled with the release of the noxious gas methyl mercaptan, prompted search for a N-methylguanylating agent capable of undergoing a direct reaction with anilines. A survey of the literature revealed only a limited number of routes into N,N'-disubstituted guanidines. Poss and coworkers[5] described a method for the synthesis of dialkyl substituted guanidines through the reaction of acyl thioureas with aliphatic amines. Unfortunately further work[6] suggested the reaction was limited to reactive amines and would be ineffective in the case of anilines. N-Alkylaminoiminomethanesulphonic acids have been reported to react with a variety of anilines[7]. However, in our hands treatment of the N-methyl analogue[8] with 4-methoxyaniline, as a test bed reaction, failed to deliver the corresponding N-methylguanidine under a variety of conditions. Of other possible N-methylguanylating agents known, those derived from the pyrazole-1-carboxamidine system[9] would be predicted to possess insufficient reactivity[10] for any practical or generalised use with anilines.

Given the lack of a suitable method the possibility of adapting one of the numerous procedures known for the synthesis of monosubstituted guanidines was explored. In this respect Bergeron and McManis[11] reported reaction of a primary amine with guanylating agent **4**. Based on **4**, but addressing the environmental issue, as well as incorporating a far more activated sulphur leaving group for displacement with anilines, this letter reports on the design of a new N-methylguanylating agent in the form of **5**.

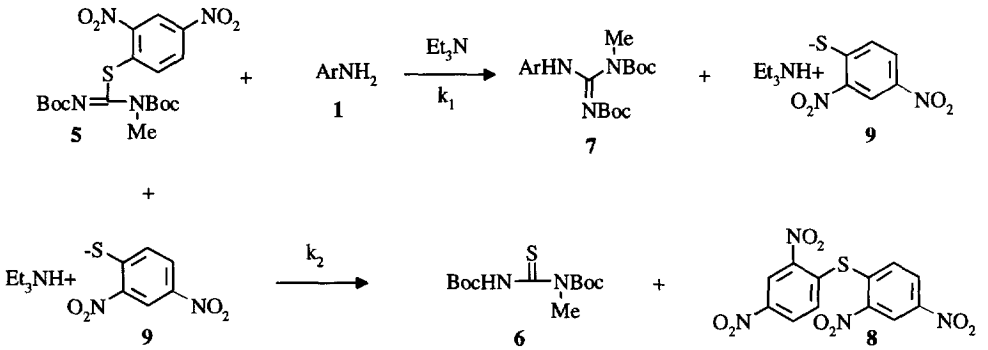


Formation of **5** entailed reaction of commercially available N-methylthiourea with Boc_2O (NaH, THF)[5,12] to provide **6**[13] (mp 92-93°C) in 68% yield. Treatment of **6** with 2,4-dinitrofluorobenzene (Sanger's reagent) (K_2CO_3, MeCN) then furnished **5**[13] (mp 143-144°C) as a stable pale yellow solid[14] in 86% yield after extractive workup and trituration.

The results of the combination of **5** with a variety of anilines in the presence of one equivalent of Et_3N in THF at room temperature are shown in Table 1[13].

Reaction of 4-methoxyaniline (entry 1) and 4-aminophenol (entry 2) with one equivalent of **5** proceeded quickly and cleanly to afford high yields of the bis-Boc N-methylguanidines **7a** and **7b** respectively. However, in comparison slower rates of reaction were observed with aniline (entry 3) and 2-methoxyaniline (entry 4). A further noticeable difference was the product profile of each, which consisted not only of the corresponding bis-Boc N-methylguanidines **7c** and **7d**, albeit in moderate yields, but also significant quantities of **6** and bis(2,4-dinitrophenyl)sulphide **8**[15].

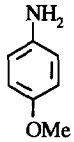
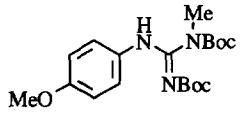
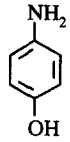
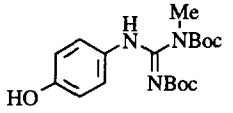
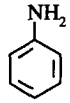
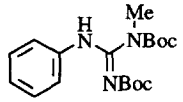
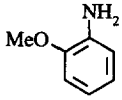
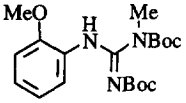
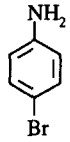
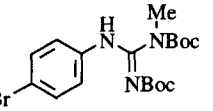
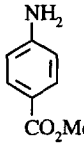
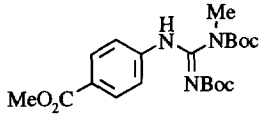
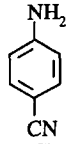
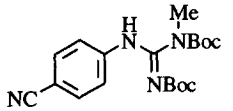
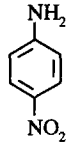
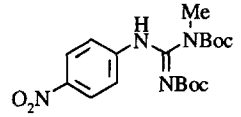
In order to rationalise the above results a general reaction cycle is suggested as shown in Scheme 2, in which the ratio of the reaction rates, k_1/k_2, dictates the product profile. For relatively highly nucleophilic anilines, as in entries 1 and 2, $k_1 >> k_2$ and bis-Boc N-methylguanidine **7** formation predominates. However, for anilines of reduced nucleophilicity, as in entries 3 and 4, the latter through a steric effect, the ratio k_1/k_2 is substantially reduced, such that consumption of **5** by **9** leads to detectable formation of **6** and **8**. Nucleophilic aromatic substitution by thiophenoxide **9** on **5** is a likely mechanism for the formation of **6** and **8**[17].



Scheme 2

In support for such a reaction cycle use of two equivalents of **5** with both aniline (entry 3) and 2-methoxyaniline (entry 4) led not only to shorter reaction times but increases in the yields of isolated bis-Boc N-methylguanidines **7c** and **7d** respectively. Given the above reactivity profile two equivalents of **5** was subsequently used for the remaining 4-substituted anilines (entries 5-8). Although 4-bromoaniline (entry 5) gave a high yield of the bis-Boc N-methylguanidine **7e**, methyl-4-aminobenzoate (entry 6) gave only a moderate yield of the bis-Boc-N-methylguanidine **7f** after a 48 h time period, having failed to completely react with **5**. The latter scenario became an even more prominent feature with the much weaker nucleophilic 4-cyanoaniline (entry 7) and 4-nitroaniline (entry 8), where only poor yields of the corresponding bis-Boc N-methylguanidines **7g** and **7h** were isolated.

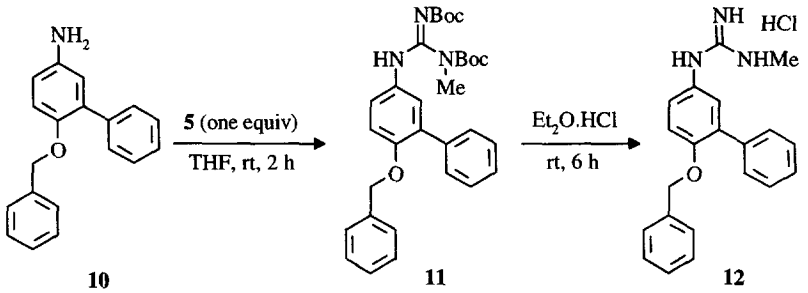
Table 1

Entry	Aniline	5 (equiv)	t (h)	Bis-Boc N-Methylguanidine	% Yield[a]	mp (°C)
1		1	0.5	**7a** 	92	110-111
2		1	0.75	**7b** 	88	Foam
3		1 2	8 3	**7c** 	66 86	112-113
4		1 2	8 4.5	**7d** 	53 79	Oil
5		2	13.5	**7e** 	83	145-147
6		2	48	**7f** 	59 (81)[b]	117-118
7		2	48	**7g** 	21 (55)[b]	119-120
8		2	48	**7h** 	10 (39)[b]	76-79

[a] These are isolated yields after column chromatography [b] % Yield based on recovered starting aniline.

As an example of the use of **5** within the context of our programme, reaction with **10** gave the bis-Boc N-methylguanidine **11**[13] as a foam in 86% yield. Removal of both Boc groups occurred smoothly on treatment of **11** with $Et_2O.HCl$, the resulting N-methylguanidine **12**[13,18] precipitating from solution in 59% yield as the hydrochloride salt, mp 210-211°C (Scheme 3).

In summary a new environmentally friendly N-methylguanylating agent has been developed and its reactivity with a series of anilines profiled. Although limitations noted for highly deactivated anilines the current methodology should find general applications for the synthesis of N,N'-disubstituted guanidines, and complements the recent disclosure on the use of bis-urethane protected derivatives of 1H-pyrazole-1-carboxamidine for the efficient production of monosubstituted guanidines from relatively unreactive amines, including anilines[19].



10 11 12

Scheme 3

General procedure for bis-Boc-N-methylguanidines: To the aniline (1 mmol) in dry THF (4 ml) was added a solution of Et_3N (1 mmol) and **5** (1 or 2 mmol) in dry THF (2 ml). The resulting solution was stirred at room temperature for 0.5 to 48 h. The THF was then removed under reduced pressure and the residue partitioned between water (25 ml), brine (25 ml) and EtOAc (50 ml). The layers were thoroughly stirred, separated and the aqueous phase further extracted with EtOAc (2 x 25 ml). The combined organic extracts were treated with activated charcoal, dried over $MgSO_4$ and solvent removed under reduced pressure. The crude mixture was chromatographed on silica gel eluting initially with CH_2Cl_2 and then CH_2Cl_2/EtOAc mixtures to give the product bis-Boc N-methylguanidine **7**.

Acknowledgements: We thank Drs. T. N. Majid and D. J. Daley for helpful discussions.

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13. All new compounds demonstrated satisfactory ^1H nmr and C, H, N analysis or mass spectra.
14. No change in mp, tlc or ^1H nmr spectrum was evident with **5** over a 6 month period.
15. The structure of **8** was confirmed with comparison to known physical and spectroscopic data from the literature. Mp 194-196°C (Lit.[16] mp 193°C). Anal. Calc. for $C_{12}H_6N_4O_8S$: C, 39.35; H, 1.65; N, 15.30; S, 8.76. Found: C, 39.48; H, 1.58; N, 15.25; S, 8.53.
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