A Convenient Synthesis of Disubstituted Guanidines via the Mitsunobu Protocol

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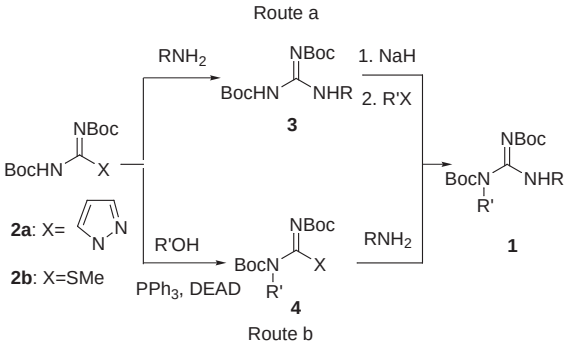
Received 8 December 1998

Abstract: An efficient synthetic method for the preparation of disubstituted guanidines is described. Primary and secondary alcohols were treated with guanylating agents under Mitsunobu conditions and their subsequent reactions with amines provided disubstituted guanidines.

Key words: disubstituted guanidines; Mitsunobu reaction; mono-alkylated guanylating agents

During the course of our investigation in the area of anti-coagulation,[1] we required a facile synthetic method for the preparation of N,N'-unsymmetrical disubstituted guanidines **1** (Scheme), which is applicable to solid phase synthesis.[2]



Scheme 1

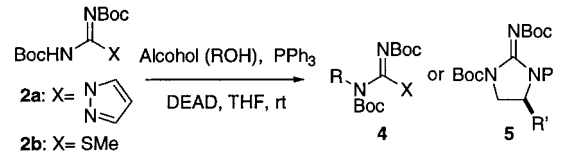
Although there are a variety of synthetic methods available to prepare monosubstituted guanidines,[3,4] few methods have been developed for the synthesis of disubstituted guanidines.[5,6] One general approach toward this type of compound involves the alkylation of the monoalkylated guanidine **3** which, in turn, is prepared from the reaction of amines with the guanylating agents **2a** and **2b** (Route **a** of Scheme).[5] The known procedure appears unattractive to apply to solid phase synthesis due to the harsh reaction conditions. We envisioned that alcohols (R'OH) could be used as the alkylating source to prepare the guanylating agent **4** by use of the Mitsunobu conditions[3] and subsequent reaction with amines under mild conditions to afford the disubstituted guanidines **1** (Route **b** in Scheme).

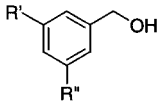
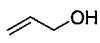
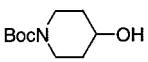
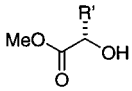
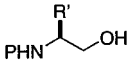
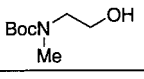
In order to test this approach, commercially available bis-Boc-thiopseudourea **2b** was treated with benzyl alcohol in the presence of PPh_3 and DEAD (Table).[7] The desired alkylated thiopseudourea **4a** was isolated in 87 % yield within a few hours (Entry 1). Based upon this encouraging result, we prepared thiopseudoureas **4b**, **4c**, and **4d** (Entry 2, 3 and 4) by using thiourea, **2b**, or pyrazole derivative **4e** (Entry 5) by using **2a**[4] from several different alcohols *i.e.* *m*-nitrobenzyl, *m,m'*-dinitrobenzyl, and allyl alcohol in good to excellent yields.

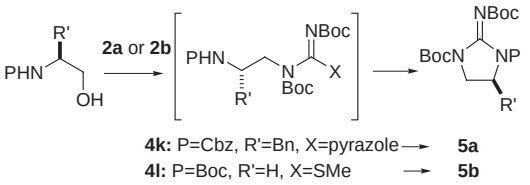
Additionally, we investigated secondary alcohols. Several secondary alcohols including (S)-methyllactate were used for this purpose. The expected thioureas **4f** (Entry 6), **4i** (Entry 9) and pyrazole derivatives **4g** (Entry 7), **4j** (Entry 10) were obtained in moderate yields, presumably due to steric interaction.

β-Amino alcohols were reacted with **2a** or **2b** under the same reaction conditions to provide cyclic guanidine derivatives **5a** (Entry 11) and **5b** (Entry 12) presumably via the mono-alkylated **4k** and **4l** (Eq. 1). However, when N-Boc-N-methyl aminoethanol was treated with **2b** under the same reaction conditions, the desired **4m** was obtained in 92% yield (Entry 13 and Eq. 2).

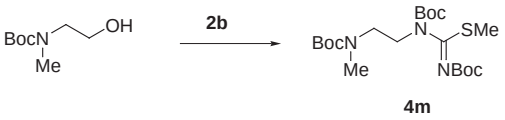
Table: Preparation of Monosubstituted Guanylating Reagent



Entry	Alcohol	Reagent	Product	Yield(%)
1.		**2b**	**4a**: R', R"=H	87
2.		**2b**	**4b**: R'=H, R"=NO_2	100
3.		**2b**	**4c**: R',R"=NO_2	70
4.		**2b**	**4d**	100
5.		**2a**	**4e**	86
6.		**2b**	**4f**	51
7.		**2a**	**4g**	39
8.		**2b**	**4h**: R'=H	35
9.		**2b**	**4i**: R'=Me	32
10.		**2a**	**4j**: R'=Me	54
11.		**2a**	**5a (4k)**: P=Cbz, R'=Bn	81
12.		**2b**	**5b (4l)**: P=Boc, R'=H	90
13.		**2b**	**4m**	92

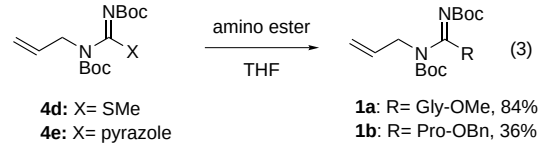


Equation 1

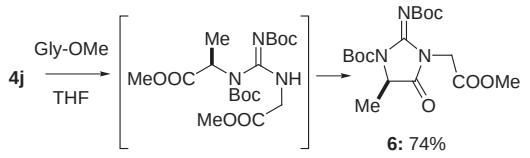


Equation 2

From the monosubstituted guanylating agents **4d** and **4e**, we synthesized disubstituted guanidine **1a** and **1b** by reaction with glycine or proline esters in 84% and 36% yields respectively (Eq. 3). Again, the moderate yield of **1b** is likely due to the steric encumbrance of the secondary amino group of the proline. When **4j** was treated with Gly-OMe, only cyclic guanidine **6** was isolated in 74% yield presumably via the disubstituted guanidine (Eq. 4).

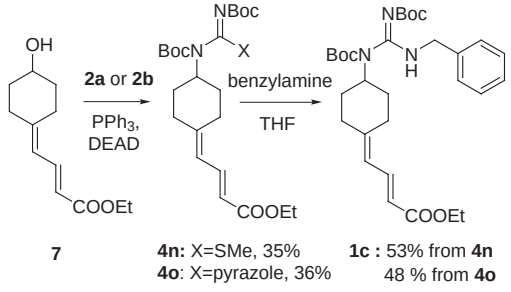


Equation 3



Equation 4

Finally, we applied this synthetic method to the preparation of disubstituted guanidine **1c**[8] under the same reaction conditions from the cyclohexanol derivative **7** (Eq. 5).



Equation 5

In summary, we have developed an efficient and mild synthetic method for the preparation of disubstituted guanidines **1** by the reaction of N-substituted pyrazole carboxamidine or N-substituted pseudothiourea with amines. The N-substituted guanylating reagents were synthesized by the treatment of primary or secondary alcohols with bis-Boc pyrazole carboxoamidine **2a** or bis-Boc pseudothiourea **2b** under Mitsunobu conditions in moderate to excellent chemical yields. Further synthetic application of this method to the solid phase synthesis will be reported in due course.

Acknowledgement

The authors are grateful to Professor Michael Kahn and Dr. Mark Blaskovich for the helpful discussion. We thank Dr. Thomas Vaisar and Tom Little for obtaining the mass spectra and preparation of **2a**.

References and Notes

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(7) Typical Reaction for the Preparation of **4**. To a stirred solution of benzyl alcohol (10 μL, 0.1 mmol) with 1,3-bis-Boc-2-methyl-2-thiopseudourea (**2b**) (30 mg, 0.1 mmol), triphenylphosphine (40 mg, 0.15 mmol) in THF (1 mL) was added diethylazodicarboxylate (25 μL, 0.15 mmol) at rt. After completion of reaction by TLC, the solution was concentrated to purify by preparative TLC (hexane:EtOAc =95:5) to provide **4a** as an oil (33 mg, 87%). NMR (500 MHz, $CDCl_3$) δ 1.39 and 1.55 (two s, 18H), 2.28 (s, 3H), 4.78 (s, 2H), 7.35 (m, 5H): MS AP^+ m/z 181.0 (100), 225.0 (25), 281.0 (5), 381(2, $M+H^+$).

(8) Typical Reaction for the Preparation of **1**. The mixture of **4n** (50 mg, 0.10 mmol) with benzylamine (34μL, 0.3 mmol) in THF (1 mL) was heated at 60 °C for 2h. The solution was concentrated and purified by flash chromatography (hexane:EtOAc = 95:5 to 80:20) to provide **1c** as an oil (30 mg, 53%). NMR (500 MHz, $CDCl_3$) δ 1.30 (t, *J*=7.5Hz , 3H), 1.49 and 1.56 (two s, 18H), 1.55 - 2.1 (set of m, 5H), 2.25 (m, 1H), , 2.36 (d, *J*=15Hz, 1H), 3.00 (d, *J*=13Hz, 1H), 4.02 (m, 1H), 4.20 (q, *J*=7.5Hz, 2H), 4.46 (s, 2H), 5.81 (d, *J*=15Hz, 1H), 5.95 (d, *J*=12Hz, 1H), 7.2 - 7.4 (set of m, 5H), 7.55 (dd, *J*=12, 15Hz, 1H): MS ES^+ m/z 542.4 (100, $M+H^+$).