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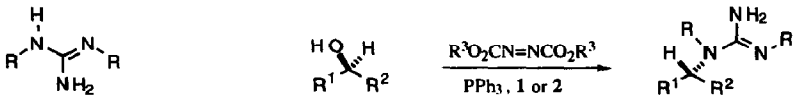
Conversion of Alcohols to Protected Guanidines Using the Mitsunobu Protocol

Dharmpal S. Dodd and Alan P. Kozikowski*
Neurochemistry Research, Mayo Foundation for Medical Education and Research,
4500 San Pablo Road, Jacksonville, FL 32224, U.S.A.

Abstract: An efficient method for the direct conversion of alcohols to guanidines is presented. A variety of alcohols react with 1 and 2 under Mitsunobu conditions to give the corresponding guanidines in high yield.

The guanidine moiety is an important feature in many biologically active compounds.[1] While there are several methods and reagents for the preparation of guanidines,[2] almost all of the current procedures involve the conversion of an amine to a guanidine. The most commonly used reagents include *S*-alkylisothiouronium salts[3] and *N*-nitro-[4] or *N,N'*-bis(alkoxycarbonyl) protected *S*-alkylisothiourea derivatives,[5] *O*-methylisouronium sulfate,[6] 3,5-dimethylpyrazole-1-carboxamidine nitrate,[4] 1*H*-pyrazole-1-carboxamidine hydrochloride,[2b] and amino(imino)methanesulfonic acid.[7] Although most of these reagents give reasonable yields, their utility is limited by the availability of the starting amines. We wish now to report an alternative procedure that is efficient, mild, and does not require amines as starting materials for the preparation of protected guanidines.

Scheme 1



1: R = Boc
2: R = Cbz

3

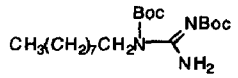
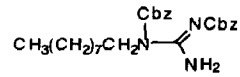
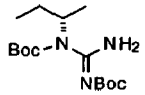
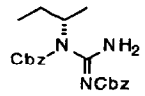
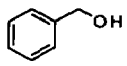
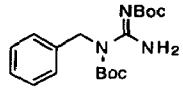
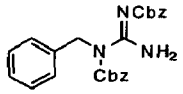
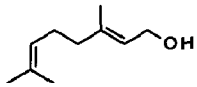
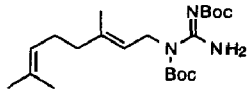
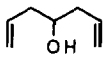
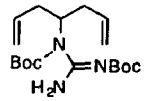
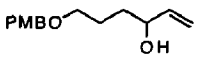
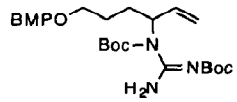
4

Our methodology utilizes *N,N'*-bis(*tert*-butyloxycarbonyl)guanidine (**1**)[8] and *N,N'*-bis(benzyloxycarbonyl)guanidine (**2**)[8] as the nucleophiles in the Mitsunobu protocol[9] to generate substituted guanidines starting from alcohols . This reaction is extremely facile and gives guanidines in very high yield (Scheme 1).

The reaction is general for most primary and secondary alcohols including benzylic and allylic alcohols. Typically, for one molar equivalent of the alcohol, 1.5-2.0 equivalents of **1** or **2** and 1.5 equivalents of the azodicarboxylate-PPh_3 complex are sufficient to convert all of the alcohol to product. Although the reaction proceeds equally well in both toluene and THF with **1**, reagent **2** is insoluble in

toluene, and therefore THF is the solvent of choice. The reaction is complete within 4-5 hours. Typical yields are listed in Table 1.[10,11]

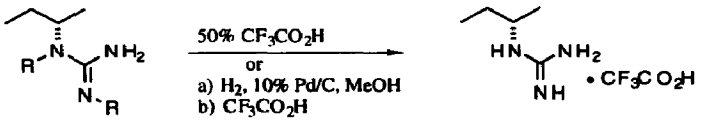
Table 1. Yields for the reaction of **1** and **2** with alcohols.

Entry	Alcohol[a]		Reagent	Product		Yield (%)[b]
1	$CH_3(CH_2)_7CH_2OH$	(3a)	1		(4a)	>95
2	(3a)		2		(4b)	>95
3		(3b)[c]	1		(4c)	>95
4	(3b)		2		(4d)	>95
5		(3c)	1		(4e)	>95
6	(3c)		2		(4f)	>95
7		(3d)	1		(4g)	93
8		(3e)	1		(4h)	64
9		(3f)[d]	1		(4i)	91

[a]Unless specifically stated, alcohols were purified either by distillation or by chromatography on silica gel before use. [b]Reported yields are for purified compounds. [c]Purchased from Aldrich and used without further purification. [d]PMB = *p*-methoxybenzyl

To establish that the substitution reaction proceeds with inversion of configuration for aliphatic alcohols, guanidines **4c** and **4d** were prepared by the reaction of (*R*)-2-butanol (**3b**) with **1** and **2**, respectively. The Boc groups of **4c** were removed by treatment with 50% trifluoroacetic acid in CH_2Cl_2 for 1 h to give guanidinium trifluoroacetate **7**, $[\alpha]_D^{22}$ + 19.1° (*c* = 0.34, MeOH). Alternatively, hydrogenation of **4d** using 10% Pd on charcoal as the catalyst at atmospheric pressure for 20 h followed by treatment with trifluoroacetic acid (Scheme 2) also gave **7**, $[\alpha]_D^{22}$ + 19.2° (*c* = 0.33, MeOH).

Scheme 2

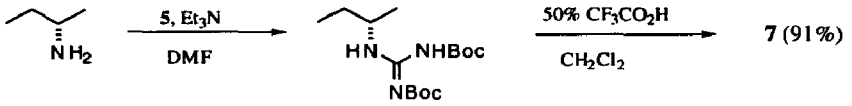


4c: R = Boc
4d: R = Cbz

7 (88-92%)

An authentic sample of **7** was then prepared using existing methods. Commercially available (*S*)-2-butylamine (**8**) was allowed to react with *N,N'*-bis(*tert*-butyloxycarbonyl)-*S*-methylisothiourea (**5**)[8,5b] in the presence of triethylamine to give **9** (Scheme 3). Compound **9** was then treated with 50% TFA in CH_2Cl_2 to give an authentic sample of **7** possessing *S* stereochemistry, $[\alpha]_D^{22}$ + 19.4° (*c* = 0.33, MeOH). These results unambiguously show that the reaction of **1** and **2** with **3b** proceeds with inversion of configuration at the hydroxyl center.

Scheme 3



8

9 (87%)

In summary, an efficient route to the preparation of guanidines starting from alcohols has been developed. This alternative approach gives guanidines in very high yields and avoids the requirement of amine starting materials as in classical methods of guanidine synthesis.

Acknowledgement: We are indebted to the Mayo Foundation for support of this research.

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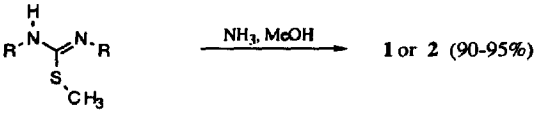
(8) **1** and **2** are easily prepared as crystalline solids by the treatment of *N,N'*-bis(*tert*-butyloxycarbonyl)-*S*-methylisothiourea[5b] (**5**) and *N,N'*-bis(benzyloxycarbonyl)-*S*-methylisothiourea[5a] (**6**), respectively, with methanolic ammonia. **1** displays a mp of 144 °C, and **2** has a mp of 151 °C. It is imperative that **5** be absolutely pure before it is reacted with NH_3. An impurity, presumed to be $BocNH_2$ derived from Boc_2O contaminant, which may be present from the preparation of **5**[5b] interferes in the Mitsunobu reaction. If the impurity is present, it can be removed by two recrystallizations from ethyl acetate-hexanes.



5: R = Boc
6: R = Cbz

(9) (a) Mitsunobu, O.; Yamada, M.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 935; (b) Mitsunobu, O.; Eguchi, M. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 3427; for recent reviews on C-N bond forming reactions using the Mitsunobu protocol, see (c) Hughs, D. L. *Org. React.* **1992**, *42*, 335; (d) Castro, B. R. *Org. React.* **1983**, *29*, 1; (e) Mitsunobu, O. *Synthesis* **1981**, 1.

(10) Typical procedure: To a solution of **1** (259 mg, 1.0 mmol) and PPh_3 (200 mg, 0.75 mmol) in dry toluene (5 mL) under argon was added *via* syringe **3b** (0.046 mL, 0.5 mmol). The mixture was cooled to 0 °C, and diisopropyl azodicarboxylate (0.150 mL, 0.75 mmol) was added dropwise over 15 min. The reaction was stirred at rt for 5 h. Five drops of water were added, and the solvent was evaporated *in vacuo*. The crude mixture was chromatographed on silica gel using 10% ethyl acetate in hexanes to give **4c** (151 mg, 96%): mp 66 °C; IR (film) 3381, 2976, 1709, 1610, 1504, 1273, and 1251 cm^{-1}; ^1H and ^{13}C NMR spectra display signals for major/minor tautomers. Chemical shifts are given only the for major tautomer: ^1H NMR ($CDCl_3$) δ 9.33 (br s, 2H), 5.22 (m, 1H), 1.80 (m, 1H), 1.60 (m, 1H), 1.52 (s, $C(CH_3)_3$), 1.48 (s, $C(CH_3)_3$), 1.30 (d, 3H, J = 7.0 Hz), 0.83 (t, 3H, J = 7.0 Hz). ^{13}C NMR ($CDCl_3$) δ 164.1, 161.8, 155.6, 83.6, 78.7, 52.3, 28.4, 27.8, 19.1, 11.2. Anal. Calcd. for $C_{15}H_{29}N_3O_4$: C, 57.10; H, 9.27; N, 13.33. Found: C, 57.14; H, 9.09; N, 13.27.

(11) All new compounds were fully characterized using ^1H and ^{13}C NMR spectroscopy, IR, HRMS, and/or combustion analysis.

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