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# *N,N'*-Bis(benzyloxycarbonyl)acetamidine, a Versatile Reagent for the Conversion of Amines and Alcohols to Acetamidines.

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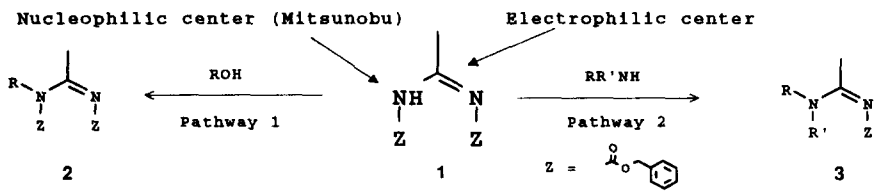
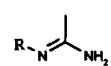
***Abstract:*** N,N'-*Bis(benzyloxycarbonyl)acetamidine is the prototype of a new class of versatile reagents for the conversion of amines and alcohols to substituted amidines. The preparation of* **1** *and its potential uses are described.*

In the course of research aimed at identifying new inhibitors of nitric oxide synthases, we required a versatile method to prepare *N*-substituted acetamidines. The recently reported extension of the Mitsunobu reaction between imides and alcohols[1] to *N,N'*-bis(alkoxycarbonyl)guanidines[2] prompted us to examine the use of substituted amidines (exemplified by compound **1**) as nucleophiles in Mitsunobu reactions. In addition to the potential synthesis of amidines from alcohols (pathway 1), the expected strongly electrophilic nature of the central carbon atom in **1** also led us to investigate the preparation of amidines from **1** and amines (pathway 2).




The crystalline and stable reagent **1** was easily synthesized by treatment of *N*-(benzyloxycarbonyl)acetamidine[3] with benzyl chloroformate.[4] As shown in table 1, the Mitsunobu reaction of compound **1** worked well with primary, secondary and benzylic alcohols producing the corresponding *N,N'*-bis(benzyloxycarbonyl)amidine **2** in good to excellent yield (table 1).[5] Removal of the protecting groups by catalytic hydrogenation using standard conditions afforded the corresponding free amidines **3**. These results demonstrate the usefulness of the method for the synthesis of substituted amidines from alcohols.

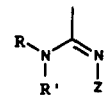
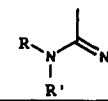
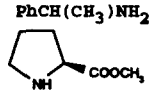
*Table 1: Conversion of alcohols to amidines using the Mitsunobu reaction*

| ROH |  (yield) |  (yield) |
|---|---|---|
| $PhCH_2OH$ | 2a (86 %)[a] | 4a (86 %)[b] |
| $PhCH_2CH_2OH$ | 2b (83 %)[a] | - |
| $PhCH(CH_3)OH$ | 2c[a] | 4c (54 %)[b,c] |

*(a) THF, $PPh_3$, DEAD, 0°C→20°C, 16h; (b) Pd 10%/C, rt; (c) Overall yield from alcohol.*

We next studied the reaction of **1** with representative amines including primary, secondary (deactivated), benzylic and aromatic ones (pathway 2). The results are listed in table 2: all amines studied could be converted in high yields to protected and/or free amidines.[5] Even the poorly nucleophilic aniline afforded good yields of *N*-phenyl-acetamidine. The reaction can be carried out in a variety of solvents (benzene, dichloromethane, ethanol). Ethanol is recommended for direct one pot, 2-step conversion of amines into free amidines without isolation of intermediates.

*Table 2: Conversion of amines to amidines*

| RR'NH |  (yield) |  (yield) |
|---|---|---|
| $PhCH_2CH_2NH_2$ | **3a** (92 %)[a] | **5a** (94 %)[b] |
| $PhCH(CH_3)NH_2$ | **3b** (88 %)[a] | - |
|  | **3c** (91 %)[c] | - |
| $PhNH_2$ | - | **5d** (64 %)[b] |

*(a) Benzene, rt, 10 min (**3a**) or 30 min (**3b**); (b) 1: EtOH, rt, 20 min [for N-(2-phenylethyl)-acetamidine] or reflux, 4 h, (for N-phenylacetamidine), 2: Pd 10%/C, rt, 2 h; (c) $CH_2Cl_2$, rt, 12 h.*

We have thus developed a powerful and versatile reagent allowing the smooth conversion of both alcohols and amines to the corresponding bis- or mono(benzyloxycarbonyl)- protected or free acetamidines. Particularly noteworthy are the very mild reaction conditions compatible with the use of labile precursors. Amidine derivatives such as **2** and **3** are now readily accessible using one of the two methods described in this paper. They are anticipated to be valuable reactive intermediates with useful synthetic applications.

## References and notes


1. Mitsunobu, O. *Synthesis*, **1981**, 1.
2. Dodd, D.S.; Kozikowski, A.P. *Tetrahedron Lett.* **1994**, *35*, 977.
3. Tamura, M.; Yamada, K.; Yabaneta, T.; Waseda, T. Jpn. Kokai Tokkyo Koho JP 61,137,852, **1986**.
4. *Preparation of* **1**: 6.6 g (38.7 mmol) of benzyl chloroformate were added to 14.9 g, (77.5 mmol) of *N*-(benzyloxycarbonyl) acetamidine dissolved in cold (0°C) $CH_2Cl_2$ (100 ml). The reaction mixture was stirred under Ar at 0°C for 1h then allowed to reach room temperature overnight. The precipitate was filtered off and the filtrate concentrated under reduced pressure. The crystalline residue was recrystallized from ether/hexane to afford pure **1** (4.59 g, 36%): mp 96-97°C.
5. Satisfactory analytical data ($^1$H NMR, mass spectroscopy and combustion analysis) have been obtained for all isolated new compounds (**1, 2a, 2b, 3a, 3b, 3c, 4c**).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