A New Method for Silylation of Hydroxylic Compounds: Reaction of Phenols and Alcohols with Silanols Mediated by Diethyl Azodicarboxylate and Triphenylphosphine

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Summary: Phenols and alcohols react with silanols under Mitsunobu conditions to give the corresponding silyl ethers.

Protection of hydroxyl groups by silvlation is often used in synthetic work and a number of procedures are available.¹ Usually, the phenol or alcohol is treated with a silvl chloride in the presence of a base, and sometimes a catalyst, such as DMAP² or imidazole,³ is also employed.

During the course of synthetic studies related to the antitumor antibiotic, Fredericamycin A⁴ we wanted to convert phenol 1^5 into the corresponding silyl ethers 2 and 3. When we tried some of the standard techniques⁶ we were unable to obtain the desired silyl ethers. However, we have found that if the phenol is treated with *t*-butyldimethylsilanol⁷ under conditions of the classical Mitsunobu reaction⁸ then the silyl ether 2 is formed in high yield.

Although many examples of the Mitsunobu process have been reported,⁸ the method has not been applied before to silanols. We have used the procedure with a number of phenols and alcohols, as shown in Table 1, and find that the silyl ethers are generally formed in good yield. The conditions are very mild and they differ substantially from those normally employed for silylation.

Table 1



(a) See ref. 9 for preparation of the phenol. (b) From cholesterol. (c) From 5α -cholestanol.

In a typical experiment, diethyl azodicarboxylate (2.9 mmol) was added dropwise to a stirred and cooled (-78°C) solution of triphenylphosphine (3.0 mmol) in THF (20 mL). After 30 min (stirring) the silanol (*ca.* 10 mmol) was added rapidly by syringe and, when all the solids had dissolved (*ca.* 10 min) a solution of the phenol or alcohol (1 mmol) in THF (10 mL) was added at a fast dropwise rate, also from a syringe. Stirring was continued overnight, the cold bath being allowed to warm to room temperature. Evaporation of the solvent and flash chromatography of the residue over silica gel (or Florisil in the case of 3, 5, 6, 8, and 9) gave the pure (TLC, ¹H NMR) product.

The silanols needed for this method are easy to $prepare^{7,10}$ and we assume that they are converted into the phosphonium species 10 (possibly via the phosphorane 11) in accord with the standard mechanism for the Mitsunobu reaction.¹¹

$$Ph_3P^+-OSiR_3$$
 10 Ph_3P^+ 11 $OSiR_3$ 10 $OSiR_3$

Our experience with compound 1 shows that the present method, which is operationally simple, can be a useful alternative to the traditional conditions when these prove unsuitable.

All new compounds were characterized by spectroscopic methods, including accurate mass measurement. We thank the Natural Sciences and Engineering Research Council of Canada and the University of Alberta for financial support.

References and Footnotes

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