

SYNLETT Spotlight 65

This feature focuses on a reagent chosen by a postgraduate, highlighting the uses and preparation of the reagent in current research

Mitsunobu Reagent [Triphenylphosphine (TPP) and Diethyl Azodicarboxylate (DEAD)/Diisopropyl azodicarboxylate (DIAD)]

Compiled by Satish Kumar Nune

Satish Kumar Nune was born in Bodhan, India in 1977 and received his BSc degree (1997) from Osmania University, India. He completed his MSc degree (1999) in Chemistry at the University of Hyderabad, India. He is currently working towards his PhD with Prof. K. C. Kumara Swamy at the University of Hyderabad in the area of 'Synthetic Organophosphorus Chemistry'. His research interests include the use of phosphorus-based catalysts in Organic Synthesis and the application of cycloaddition reactions in the synthesis of novel phosphorus based heterocycles. He thanks Prof. K. C. Kumara Swamy for valuable suggestions.

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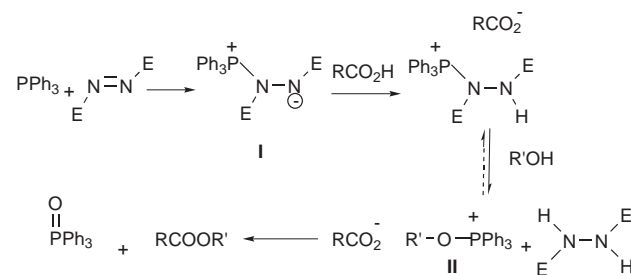
Dedicated to Professor Mitsunobu who died on the 4th April 2003.



Introduction

The Mitsunobu reaction is perhaps the most favored method for the inversion of chiral secondary alcohols.¹ It involves the reaction of an acid component (RCO₂H) with a mixture of triphenylphosphine (TPP), diethyl azodicarboxylate (DEAD)/diisopropyl azodicarboxylate (DIAD), and an alcohol (Scheme 1).¹ It is supposed that the initial nucleophilic addition of TPP to DEAD/DIAD affords the betaine **I**;^{2,3} attack of an acid followed by an alcohol on **I** leads to the formation of a highly reactive alkoxyphosphonium intermediate **II** which undergoes nucleophilic displacement with virtually complete inversion of configuration at the electrophilic center under mild and nearly neutral conditions. The traditionally used acidic

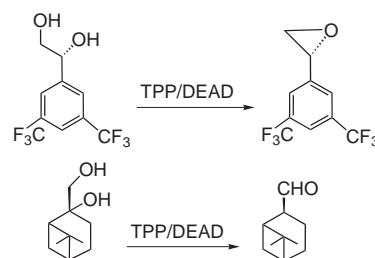
component can be replaced by metal halides (LiBr),^{4a} silanols,^{4b} amides/ imides,^{4c} nitronates,^{4d} fluorinated alcohols^{4e} and compounds possessing an active methylene group,^{4f} thus rendering the reaction widely applicable in organic synthesis.



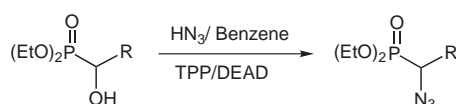
Scheme 1

Abstracts

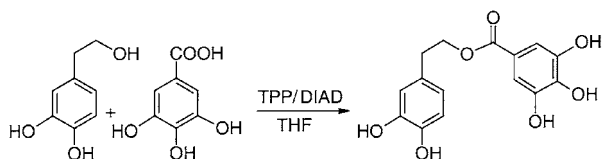
(A) Epoxides are obtained from acyclic 1,2-diols^{5a,b} and cyclic *trans*-1,2-diols^{5c} under the Mitsunobu conditions. 1,1-Disubstituted-1,2-diols lead to the formation of aldehydes or ketones.^{5d}



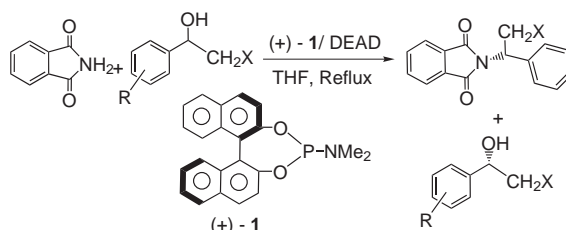
(B) Azidation of alcohols^{6a} and α -hydroxy(alkyl)phosphonates^{6b} can also be achieved under Mitsunobu conditions.



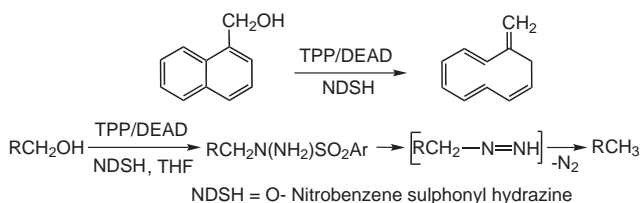
(C) The Mitsunobu reaction can be used to distinguish between alcohol and phenol hydroxyls in esterification reactions.⁷



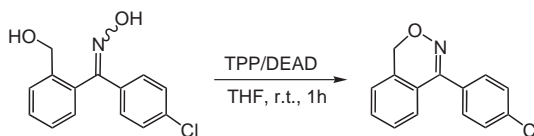
(D) Kinetic resolution of the racemic secondary alcohols^{8a} can be effected by using the enantioselective Mitsunobu reaction of these alcohols with phthalimide in the presence of a chiral tri-coordinate phosphoramidite.^{8b}



(E) Single-step reductive deoxygenation of unhindered alcohols takes place under Mitsunobu conditions.⁹



(F) Intramolecular Mitsunobu reaction of 2-(hydroxyl iminomethyl) benzyl alcohols or 1,2-aminoalcohols gives benzoxazines^{10a} or aziridines^{10b} respectively.



References

- (1) (a) Mitsunobu, O.; Yamada, M. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 2380. (b) Mitsunobu, O.; Eguchi, M. *Bull. Chem. Soc. Jpn.* **1971**, *41*, 3427. (c) Mitsunobu, O.; Wada, M.; Sano, T. *J. Am. Chem. Soc.* **1972**, *94*, 679. (d) Mitsunobu, O. *Synthesis* **1981**, 1.
- (2) (a) Camp, D.; Hanson, G. R.; Jenkins, I. D. *J. Org. Chem.* **1995**, *60*, 2977. (b) Hughes, D. L. *Org. React.* **1992**, *42*, 335.
- (3) For exceptions see: (a) Satish Kumar, N.; Kommana, P.; Vittal, J. J.; Kumara Swamy, K. C. *J. Org. Chem.* **2002**, *67*, 6653. (a) Hulst, R.; van Basten, A.; Fitzpatrick, K.; Kellogg, R. M. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2961.
- (4) (a) Manna, S.; Falck, J. R.; Mioskowski, C. *Synth. Commun.* **1985**, *15*, 663. (b) Clive, D. L. J.; Kellner, D. *Tetrahedron Lett.* **1991**, *32*, 7159. (c) Hughes, D. L. *Org. Prep. Proced. Int.* **1996**, *28*, 127. (d) Falck, J. R.; Yu, J. *Tetrahedron Lett.* **1992**, *33*, 6723. (e) Falck, J. R.; Yu, J. C. h. o. H. S. *Tetrahedron Lett.* **1994**, *35*, 5997. (f) Takacs, J. M.; Xu, Z.; Jiang, X.-T.; Leonov, A. P.; Theriot, G. C. *Org. Lett.* **2002**, *4*, 3843.
- (5) (a) Mitsunobu, O.; Keido, T.; Nishida, M. *Chem. Lett.* **1980**, 1613. (b) Weissman, S. A.; Rossen, K.; Reider, P. J. *Org. Lett.* **2001**, *3*, 2513. (c) Guthrie, R. D.; Jenkins, I. D.; Yamasaki, R. *J. Chem. Soc., Chem. Commun.* **1980**, 784. (d) Barrero, A. F.; Alvarez-Manzaneda, E. J.; Chahboun, R. *Tetrahedron Lett.* **2000**, *41*, 1959.
- (6) (a) Viaud, M. C.; Rollin, P. *Synthesis* **1990**, 130. (b) Gajda, T.; Matusaik, M. *Synthesis* **1992**, 367.
- (7) Appendino, G.; Minassi, A.; Daddario, N.; Bianchi, F.; Tron, G. C. *Org. Lett.* **2002**, *4*, 3839.
- (8) (a) Chandrasekhar, S.; Kulkarni, G. *Tetrahedron: Asymmetry* **2002**, *13*, 615. (b) Li, Z.; Zhou, Z.; Wang, L.; Zhou, Q.; Tang, C. *Tetrahedron: Asymmetry* **2002**, *13*, 145.
- (9) Myers, A. G.; Movassaghi, M.; Zheng, B. *J. Am. Chem. Soc.* **1997**, *119*, 8572.
- (10) (a) Kai, H.; Nakai, T. *Tetrahedron Lett.* **2001**, *42*, 6895. (b) Xu, J. *Tetrahedron: Asymmetry* **2002**, *13*, 1129.