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1,1'-(Azodicarbonyl)dipiperidine-Tributylphosphine, A New Reagent System for Mitsunobu Reaction

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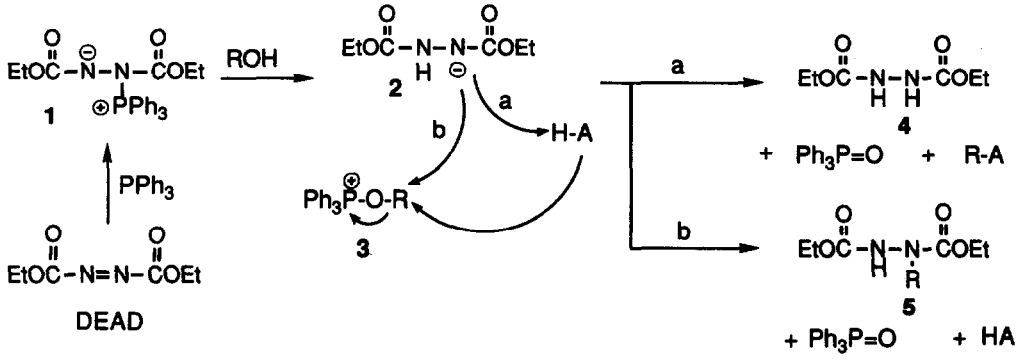
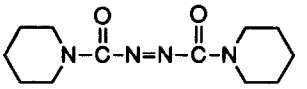
Abstract: *The1,1'-(azodicarbonyl)dipiperidine (ADDP)-tributylphosphine (TBP) system was developed as a new substitute of the Mitsunobu reagent. The new system activates nitrogen or carbon nucleophiles, known to be innert or poorly reactive with the Mitsunobu reagent, to react with alcohols satisfactorily forming C-N or C-C bonds. The inversion of stereogenic carbinyl carbons was confirmed in the acylaltion reaction of two* sec*-alcohols.*

The Mitsunobu reaction,[1] utilizing diethyl azodicarboxylate (DEAD)-triphenylphosphine (TPP) system and proceeding probably through the generally accepted path a shown in Scheme,[2] is a very versatile method for the condensation of alcohols (ROH) and various nucleophiles (or acids, HA) to give the products (RA), and widely used in organic synthesis. However, the reaction has a serious limitation; the acidic hydrogen in HA has to have pK_a smaller than 11 for the reaction to proceed satisfactorily. If HA has a pK_a larger than 11, the yield of RA lowers considerably, and with HA having larger pK_a than 13, the desired reaction does not occur.[3] Major byproduct in these cases is alkylated hydrazine derivative **5** formed through path b in the Scheme. Herein we introduce a new redox system, 1,1'-(azodicarbonyl)dipiperidine (ADDP) - tributylphosphine (TBP), which can satisfactorily be applied to the reaction of HA of pK_a larger than 11.



Scheme. Proposed Mechanism of Mitsunobu Reaction.

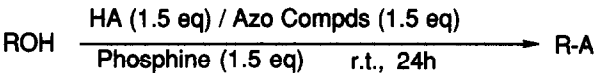
Consideration given to develop the improved redox system was 1) to increase nucleophilicity of phosphine in the formation of the intermediate **1**, 2) to localize the positive charge on P in **1** and **3** in order to facilitate the nucleophilic attack of $RO^{\ominus}$ or $A^{\ominus}$, respectively, and 3) to localize the negative charge at the azo-nitrogen in order to increase its basicity in the intermediate **2**. The first two considerations arrived at TBP, while the 3rd culminated in ADDP.

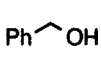
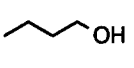
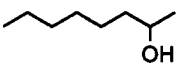
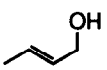
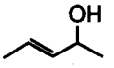
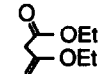
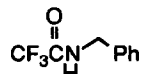


ADDP

Typical experimental procedure is as follows. Under argon atmosphere, alcohol (1 mmol), TBP (1.5 mmol) and, HA (1.5 mmol) were successively dissolved in dry benzene (3 ml) with stirring at 0°C, and solid ADDP[4](1.5 mmol) was added to the solution. After 10 min, the reaction mixture was brought to room temperature and the stirring was continued for 24h. Hexane was added to the reaction mixture and dihydro-ADDP separated out was filtered off. The product (RA) was purified by SiO_2 column chromatography after evaporation of the solvent *in vacuo*.[5]

Table. Mitsunobu Reaction of Some Alcohols and Acids (% Yield of RA).



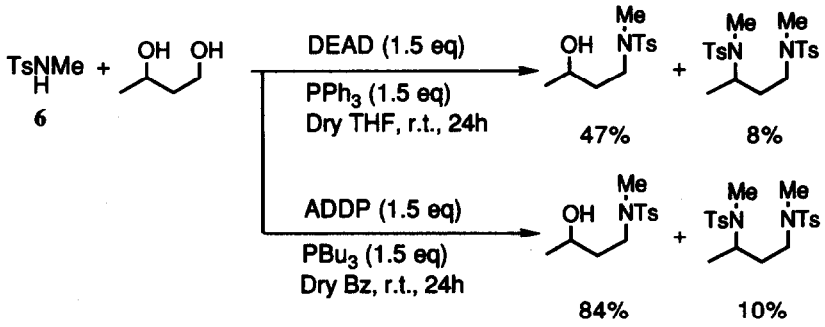
HA	ROH				
					
	D / A [1]	D / A	D / A	D / A	D / A
 (pK_a 11.7)	66[2] / 86	—[3] / 90	53 / 34	— / 99	— / 41
 (pK_a 13.3)	2 / 56	0[4] / 21	— / 3	— /40	— / 25
 (pK_a 13)[5]	3 / 53	— / 48	— / 3	— / 56	— / 11

1) D: DEAD-TPP in THF. A: ADDP-TBP in Bz. 2) see ref. 6. 3) — denotes no experimental result. 4) Yield with propanol (Ref. 3). 5) Estimated.

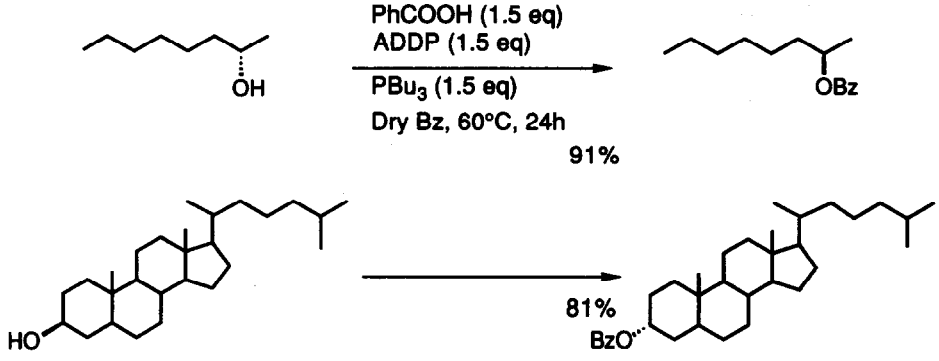
The efficiency of the ADDP-TBP system was compared with DEAD-TPP in THF for the reactions of *N*-methyltosylamide (**6**) (pK_a 11.7),[6] *N*-benzyltrifluoroacetamide and diethyl malonate (pK_a 13.3) with alcohols of different structure type. The results are shown in Table.

Table clearly shows that the ADDP-TBP system exhibits enhanced reactivity than DEAD-TPP for the reaction of HA of pK_a up to ~13 with primary alcohols.[8] However, *sec*-alcohols are much less reactive.

This difference in reactivity can be utilized for regioselective reactions of diols. For example, butane-1,3-diol and **6** react with ADDP-TBP system to give monotosylamide in 84% and ditosylamide in 10% yield, compared to 47% and 8%, respectively, with DEAD-TPP.



As expected, the reaction of *sec*-alcohols proceeds with complete Walden inversion with the present redox system as in the Mitsunobu reaction. Two examples, 2-octanol[9] and cholestanol,[10] are given below along with the reaction conditions.



Thus, the new redox system, ADDP-TBP, was shown to expand the versatility of the Mitsunobu reaction so that it can be used for synthesis of *sec*-amines.[11]

REFERENCES AND NOTES

1. For a review, see: Mitsunobu, O. *Synthesis* **1981**, 1-28.
2. a) Hughes, D. L.; Reamer, R. A.; Bergan, J. J.; Grabowoski, J. J. *J. Am. Chem. Soc.* **1988**, *110*, 6487-6491. b) Varasi, M.; Walker, K. A. M.; Maddox, M. L. *J. Org. Chem.* **1987**, *52*, 4235-4238. c) Crich, D.; Dyker, H.; Harris, R. J. *J. Org. Chem.* **1989**, *54*, 257-259. d) Pautard-Cooper, A.; Evans, S. A. Jr. *J. Org. Chem.* **1989**, *54*, 2485-2488.
3. For example, the yield of the products in the reactions with propanol is as follows: Ethyl acetoacetate (pK_a 10.7) 42% (a mixture of C- and O-alkylated products);[1] malononitrile (pK_a 11.2) 51% (Wada, M.; Mitsunobu, O. *Tetrahedron lett.* **1972**, 1279-1282); diethyl malonate (pK_a 13.3) 0% (*Idem, ibid.*).
4. Commercially available ADDP (Aldrich, Inc. or Tokyo Chemical Industry Co., Ltd.) was recrystallized from benzene-hexane.
5. In many cases, addition of hexane and filtration are not necessary as dihydro-ADDP is easily separated by SiO_2 column chromatography.
6. The Mitsunobu reaction of **6** was reported for the synthesis of *sec*-amines. However the yield was moderate; 50%[7a] and 33%[7b] with benzyl alcohol, and 58% with phenethyl alcohol.[7a]
7. a) Henry, J. R.; Marcin, L. R.; McIntosh, M. C.; Scola, P. M.; Harris, G. D. Jr.; Weinreb, S. M. *Tetrahedron Lett.* **1989**, *30*, 5709-5712. b) Edwards, M.L.; Stemerick, D. M.; McCarthy, J. R., *Tetrahedron Lett.* **1990**, *31*, 3417-3420.
8. Under the standard Mitsunobu conditions (ROH: HA: azo compd: phosphine=1:1:1:1), **6** and benzyl alcohol afforded *N*-benzyl-*N*-methyltosylamide in 45~49% with ADDP-TPP in THF or benzene, and in 60% with ADDP-TBP in THF.
9. Optical purity was determined by HPLC using CHIRALCEL OB-H--OB combination column. Cf. Mitsunobu, O.; Eguchi, M. *Bull. Chem. Soc. Jap.* **1971**, *44*, 3427-3430.
10. Bose, A. K.; Lal, B.; Hoffman III, W. A.; Manhas, M. S. *Tetrahedron Lett.* **1973**, 1619-1622.
11. Search for more versatile reagents is in progress in our laboratory as well as the practical synthesis of *sec*-amines.

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