CHEMISTRY LETTERS, pp. 539-542, 1994.

N, N, N', N'-Tetramethylazodicarboxamide (TMAD), A New Versatile Reagent for Mitsunobu Reaction. Its Application to Synthesis of Secondary Amines

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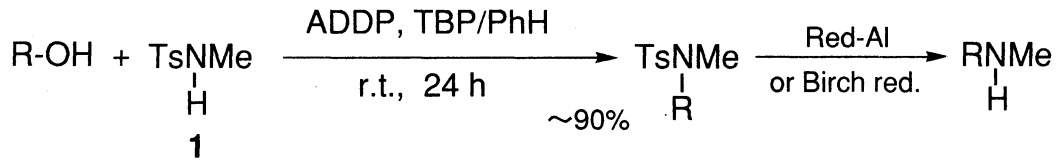
N, N, N', N'-Tetramethylazodicarboxamide, TMAD, was found to be more versatile in the Mitsunobu reaction than traditional diethyl azodicarboxylate or recently developed 1,1'-(azodicarbonyl)dipiperidine, when used in combination with tributylphosphine in benzene. The usefulness of the reagent was demonstrated by the highly efficient two-step synthesis of benzylcrotylamine from *N*-benzyltrifluoroacetamide.

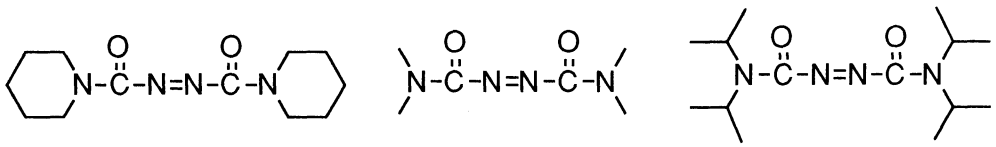
Recently, we introduced 1,1'-(azodicarbonyl)dipiperidine-tributylphosphine (ADDP-TBP)[1] as a new reagent system for the Mitsunobu alkylation reaction[2] applicable to the acid HA (nucleophile) of higher pK_a where traditional diethyl azodicarboxylate-triphenylphosphine (DEAD-TPP) is not satisfactory. For an example, *N*-methyltosylamide (**1**, pK_a = 11.7[3]) was successfully alkylated with primary alcohols using the new system. Thus, the synthesis of dialkylamines through this route became feasible when combined with the known reduction procedure of the S-N bond.[4,5]



The Mitsunobu reaction is particularly valuable in principle for the synthesis of allylic secondary amines, because it is devoid of various undesired reactions encountered by the other methods which require the activation of allylic alcohols to halides or tosylates.[6] However, the reduction conditions mentioned above are sometimes too drastic, causing epimerization at the allylic and/or benzylic chiral centers. In order to avoid such complications, more versatile Mitsunobu reagents were needed. We investigated the reactions of *N*-benzyltrifluoroacetamide (**2**, pK_a =13.6[7]) using two more azodicarboxamides, *N, N, N', N'*-tetramethyl- and -tetraisopropylazodicarboxamides, abbreviated as TMAD and TIPA, respectively. Both of them were found to be as effective as ADDP, all three in turn were much better than traditional DEAD. TMAD showed the best results for all cases examined. The results are presented herein in some detail.

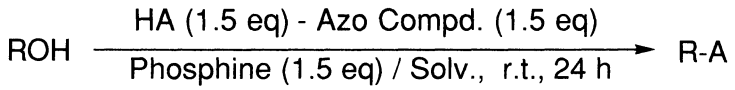
Both TMAD and TIPA can easily be prepared from diphenyl hydrazo-1,2-dicarboxylate (**5**),[8,9] while the former is a known compound. These reagents were evaluated under the standard conditions described previously,[1] that is, under argon atmosphere, a solid azo compound (1.5 mmol) was added all at once with

stirring at 0 °C to a benzene (3 mL) solution of an alcohol (1 mmol), TBP (1.5 mmol) and HA (1.5 mmol). After 10 min, the reaction mixture was brought to room temperature and stirred for 24 h, during which colorless solid (the corresponding hydrazo compound) precipitated out normally. The product was purified by silica gel column chromatography after filtration of the solid and evaporation of the solvent. Effectiveness of TMAD and TIPA was compared with that of DEAD and ADDP for the reaction of **1** and **2** with alcohols of four different structure types. The results are summarized in the Table 1.



ADDP **TMAD** **TIPA**

Table 1. Mitsunobu Alkylation with Some Azo Compounds (% Yield of RA)



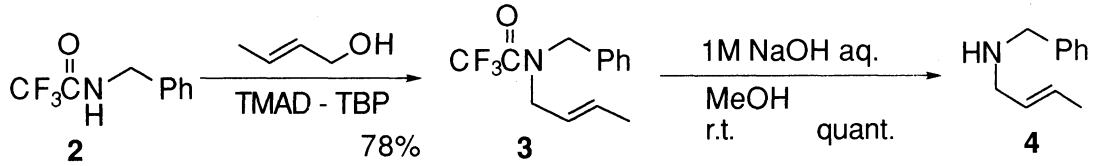
ROH	HA							
	TsNMe H **1** (pK_a 11.7)				CF_3CNCH_2Ph H **2** (pK_a13.6)[a]			
	D	TI	A	TM[b]	D	TI	A	TM
Ph⌒OH	66	98	86	99	3	77	53	86
⌒OH	65	70	90	100	–[c]	30	48	83
OH	53	6	34	40	–	*[d]	3	11
⌒OH	51	100	99	96	–	70	56	78

a) Estimated value. See Ref. 7. b) D: DEAD-TPP in THF, TI: TIPA-TBP in PhH, A: ADDP-TBP in PhH, TM: TMAD-TBP in PhH. c) – no experimental result. d) * very low yield of the desired product.

The Table 1 clearly discloses the following facts for the reactions of primary alcohols. a) All azodicarboxamides (amide reagents) activate the reactions of both amides (HA) more efficiently than traditional DEAD. b) Effectiveness of the amide reagents is not significantly different for the reaction of **1** (pK_a = 11.7). c) However, difference in yield is quite significant for the reaction of **2** of a larger pK_a. d) TMAD having the smallest alkyl groups on the amide nitrogens gives the best overall results, enabling the HA of $pK_a \simeq 13.5$ be alkylated in satisfactory yields. e) The reactions of crotyl alcohol also follow the general trend. For the

reaction of secondary alcohols, however, f) none of the reagents examined was satisfactory for the reactions of 2-octanol with either **1** or **2**.[10]

The efficient alkylation with TMAD of trifluoroacetamide **2** provides an excellent new method for the synthesis of secondary amines, especially allylic amines, since the hydrolysis of trifluoroacetamides generally proceeds nicely under mild conditions.[11] In fact, the *N*-(2*E*)-crotylacylamide **3** obtained by the reaction of **2** was hydrolyzed quantitatively at room temperature with a weak alkali to give pure benzyl-(2*E*)-crotylamine (**4**).



Thus, the TMAD-TBP reagent developed here was shown to expand the versatility of the Mitsunobu reaction and provide an excellent entry to the synthesis of allyl amines, and also of secondary amines in general.

References

1) T. Tsunoda, Y. Yamamiya, and S. Itô, *Tetrahedron Lett.*, **34**, 1639 (1993).

2) For a review, see: O. Mitsunobu, *Synthesis*, **1981**, 1.

3) G. Dauphin and A. Kergomard, *Bull. Soc. Chim. Fr.*, **1961**, 486.

4) M. L. Edwards, D. M. Stemerick, and J. R. McCarthy, *Tetrahedron Lett.*, **31**, 3417 (1990); J. R. Henry, L. R. Marcin, M. C. McIntosh, P. M. Scola, G. D. Harris, Jr., and S. M. Weinreb, *ibid.*, **30**, 5709 (1989).

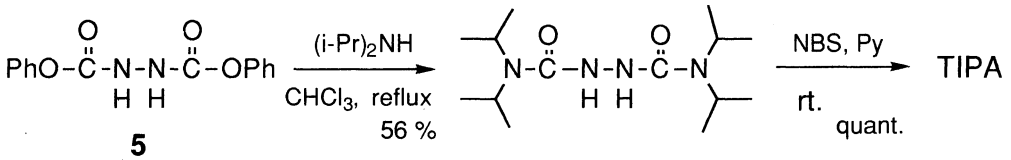
5) Further example is shown in the following paper by T. Tsunoda, S. Tatsuki, K. Kataoka, and S. Itô.

6) For instance, (*E*)-crotyl chloride prepared from pure (*E*)-crotyl alcohol is only 85% pure and (*E*)-crotyl tosylate is difficult to handle. See M. J. Kurth and O. H. W. Decker, *J. Org. Chem.*, **50**, 5769 (1985).

7) The pK_a value was estimated using the following data: pK_a = 15.1 for acetamide (F. G.Bordwell and D. Algrim, *J. Org. Chem.*, **41**, 2507 (1976)). pK_a = 10.36 for trifluoroacetamide (T. V. Kashik, G. V. Rassolova, S. M. Ponomareva, E. N. Medvedeva, T. I. Yushmanova, and V. A. Lopyrev, *Izv. Akad. Nauk SSSR, Ser. Khim.*, **1982**, 2230). pK_a = 18.3 for *N*-methylacetamide (M. Gosselet, S. Sibille, and J. Perichon, *Bull. Soc. Chim. Fr.*, **1975**, 249).

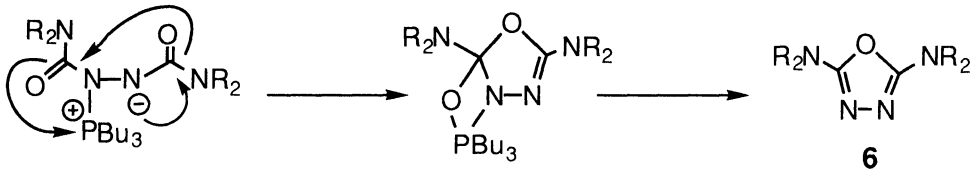
8) E. E. Smissman and A. Makriyannis, *J. Org. Chem.*, **38**, 1652 (1973). R. J. Crawford and R. Raap, *ibid.*, **28**, 2419 (1963). R. M. Fantazier and J. E. Herweh, *J. Org. Chem.*, **38**, 2560 (1973). TMAD is commercially available from Aldrich Inc. It is easily prepared from diphenyl hydrazo-1,2-dicarboxylate (**5**) by consecutive treatment with excess dimethylamine (dil. MeOH, reflux, 94% yield) followed by bromine oxidation (1 equiv. in pyridine, rt, 84% yield). Also see Ref. 9.

9) TIPA can be prepared from **5** following the sequence shown below.



TIPA: orange plates (Hex-PhH), mp 147.5-148.5 °C; IR (KBr) 1694 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.20 (12 H, d, J = 6.6 Hz), 1.47 (12 H, d, J = 6.8 Hz), 3.76 (2 H, sep, J = 6.7 Hz), 3.93 (2 H, sep, J = 6.7 Hz); MS m/z 286 (M^++2), 128, 86, 43 (base). These carboxamides are very stable and easy to handle when compared with DEAD. They were recrystallized before use.

10) Most of the azo compound and TBP used was consumed even in cases where no desired product was obtained. In such cases, a large amount of the oxadiazole **6** was obtained probably through the pathway shown below.



6

6 (R = isopropyl): colorless granules (Hex), mp 101-102 °C; IR (KBr) 1651 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.27 (24 H, d, J = 6.8 Hz), 3.91 (4 H, septet, J = 6.8 Hz); MS m/z 268 (M^+, base).

11) J. E. Nordlander, D. B. Eatalane, T. H. Eberlein, L. V. Farkas, R. S. Howe, R. M. Stevens, and N. A. Tripoulas, *Tetrahedron Lett.*, **1978**, 4987.

(Received December 22, 1993)