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Mitsunobu-type Alkylation with Active Methine Compounds

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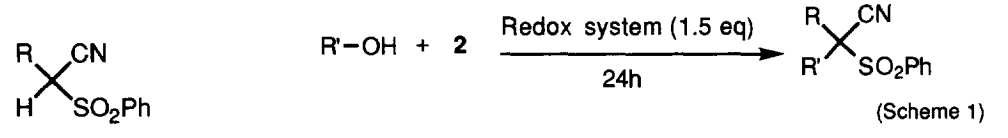
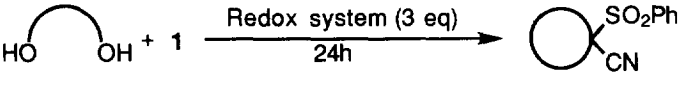
Abstract: Intermolecular reaction of two active methine compounds with primary or secondary alcohols in the presence of new Mitsunobu-type reagents afforded alkylation products in excellent (with primary alcohols) to fair yields (with secondary alcohol) except one case. It demonstrates that the new reagents, especially cyanomethylenetrimethylphosphorane, are excellent mediators for this type of alkylation. The double alkylation of an active methylene compound with diols under similar conditions gave cyclization products in good to excellent yields.

The traditional Mitsunobu reagent, diethyl azodicarboxylate (DEAD) - PPh_3, is known to be inefficient for C-C bond forming reaction except a few cases because of weak acidity ($pK_a > 9$) of the C-nucleophiles.[1,2] We have shown recently that the combination of 4,7-dimethyl-3,5,7-hexahydro-1,2,4,7-tetrazocin-3,8-dione (DHTD) and PBu_3,[3a] one of the new Mitsunobu reagent systems of azadicarboxamide type,[3] and cyanomethylenetributylphosphorane (CMBP), a phosphorane reagent,[4] mediated the coupling of phenylsulfonylacetonitrile (**1**) with alcohols of different structure types.[3a] Falck group reported also recently that the use of PMe_3 in place of PBu_3 with or without additional imidazole increased the reactivity of 1,1'-(azodicarbonyl)dipiperidine (ADDP)[3b] for the reaction of **1**.[5] Thus, Mitsunobu reaction is now a very attractive methodology for the C-C bond formation in organic synthesis. Though the reaction has been applied to some active methylene compounds, e.g. **1**, however, there seems no report on the reaction of methine compounds, e.g. **2**, except some intramolecular reactions.[2,5] Intrigued by the observation that DHTD or CMBP promoted double alkylation of **1**,[3a] we further investigated the alkylation of some active methine compounds. Herein we describe successful intermolecular reactions of two active methine compounds **2** (Scheme 1), and double alkylation of the active methylene **1** with some diols (Scheme 2), utilizing our reagents including cyanomethylenetrimethylphosphorane (CMMP),[6] a new phosphorane.



(Scheme 1)



(Scheme 2)

Previous investigations implied that, in both azodicarboxamide[3c] and phosphine[2,7] series, smaller the reagent size, the larger the reactivity of sterically hindered alcohols, such as secondary alcohols, and/or congested nucleophiles, such as **2**. Accordingly, we studied the efficiency of DHTD-PBu_3, CMBP and CMMP for the alkylation of 2-phenylsulfonylhexanenitrile (**2a**) and -3-methylnonanenitrile (**2b**) with primary and secondary alcohols, and double alkylation of **1** with diols.[8] The results are listed in Table 1 and 2.[9]

Table 1. Alkylation of active methine compounds **2a** and **2b**.[9]

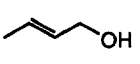
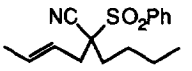
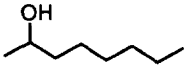
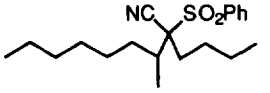
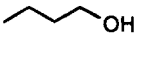
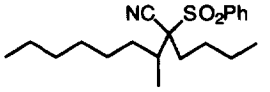
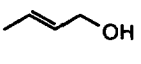
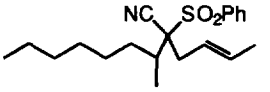
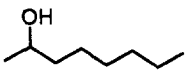
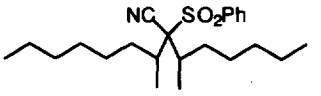
Entry	Nucleophile	Alcohol	Reagents (temp. (°C))	Product	% Yield
1	**2a**		DHTD-PBu_3 (r.t.) CMBP (120)		89 89
2	**2a**		DHTD-PBu_3 (r.t.) CMBP (120) CMMP (100)		45 53 74
3	**2b**		DHTD-PBu_3 (r.t.) CMBP (120)		80 82
4	**2b**		DHTD-PBu_3 (r.t.) CMBP (120)		93 90
5	**2b**		DHTD-PBu_3 (r.t.) CMBP (120) CMMP (120)		0 0 0

Table 1 clearly shows that **2a** and **2b** are capable of C-C bond formation with various alcohols affording alkylation product in fair to excellent yields expect one case (entry 5) when they are mediated with DHTD-PBu_3, CMBP or CMMP (entries 1~4). The DHTD-PBu_3 mediates the reaction at ambient temperature, while phosphorane reagents need higher temperatures.[4] It is also noted that 1) for the reactions of allylic alcohols (crotyl alcohol), the difference in sterically congestion at anionic centers between **2a** and **2b** and that in mediator used shows practically no effect on the efficiency of the alkylation (entries 1 and 4), 2) the reaction of primary alcohols (butanol) and **2b** is still synthetically acceptable though the yield lowers to some extent (entry 3). However, in the reactions of secondary alcohols (2-octanol), a large difference in the yield was observed between **2a** and **2b** (entries 2 and 5) and also between mediators (entry 2). Among the mediators, the phosphorane reagents, especially CMMP, are better than azadicarboxamide reagent, DHTD-TBP. The effect of steric congestion is smaller when more crowded **2b** is reacted with a primary alcohol (entry 3) compared to the reaction of the less crowded **2a** with a secondary alcohol, disclosing that the steric congestion in the alcohol used is more critical than that in the anionic center, and suggesting the importance in the

reaction consequence, bulkier alcohol first to be reacted with **1**, in practical syntheses.

The reaction was applied to the double alkylation of **1** leading to cyclic compounds (Scheme 2). Since this type of alkylation was already realized with DEAD-PPh_3 for the reaction of bis(phenylsulfonyl)methane[2] and with ADDP-PMe_3 for the reaction of **1**,[5] we concentrated our attention again to the new Mitsunobu reagents on the diols with a secondary hydroxyl group, as the situation in the 2nd step resembled that of the entry 2 in Table 1. The results are shown in Table 2.[9]

Table 2. Double alkylation of active methylene compound **1**.[9]

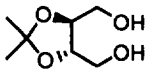
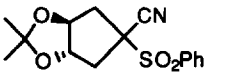
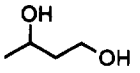
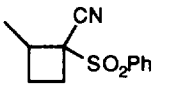
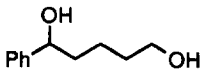
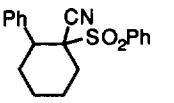
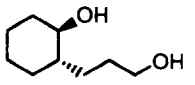
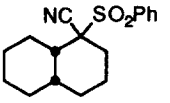
Entry	Alcohol	Reagents (temp. (°C))	Product	% Yield
1		DHTD-PBu_3 (r.t.) CMBP (120)		21 90
2		DHTD-PBu_3 (r.t.) CMBP (120)		50 99
3		DHTD-PBu_3 (r.t.) CMBP (120) CMMP (120)		63 66 74
4		DHTD-PBu_3 (r.t.) CMBP (120) CMMP (120)		22 62 73

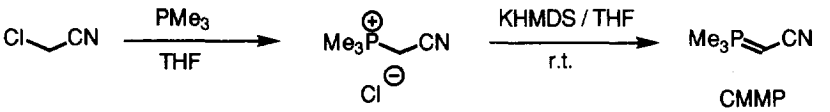
Table 2 disclosed that 1) the phosphorane reagents were generally better than DHTD-PBu_3, 2) CMMP was better than CMBP, 3) CMBP was as effective as the reported ADDP-PMe_3[5] for the primary diol (entry 1), 4) for the reactions of diols with a secondary hydroxyl group, the cyclobutane formation (1,3-butandiol) proceeded quite efficiently with CMBP (entry 2), but the cyclohexane formation went rather unsatisfactorily even with CMMP (entries 3 and 4). This may be due to the difference in steric congestion in the diol precursors and/or the entropy difference in the ring closure. 5) The stereochemistry of the reaction was complete inversion as was verified by the formation of the *cis*-decaline derivative from the *trans*-2-(3-hydroxypropyl)cyclohexanol (entry 4).

Since the desulfurization reactions of the sulfonamides have been established,[3a,5] the reactions presented herein would conform as an excellent novel methodology for the C-C bond formation applicable to various stages of organic syntheses.

REFERENCES AND NOTES

1. Reviews: Mitsunobu, O. *Synthesis* **1981**, 1-28. Hughes, D. L. The Mitsunobu Reaction, in *Organic Reactions*; Beak, P. *et al.* Eds; John Wiley & Sons, Inc.: New York, **1992**, Vol. 42, pp 335-656.

2. Falck *et al.* recently achieved the DEAD-PPh_3 or -PMe_3 mediated alkylation of bis(phenylsulfonyl)methane and its derivatives in good to excellent yields (Yu, J.; Cho, H.-S.; Falck, J. R. *J. Org. Chem.* **1993**, *58*, 5892-5894, Yu, J.; Cho, H.-S.; Falck, J. R. *Tetrahedron Lett.* **1995**, *36*, 8577-8580).
3. a. Tsunoda, T.; Nagaku, M.; Nagino, C.; Kawamura, Y.; Ozaki, F.; Hioki, H.; Itô, S. *Tetrahedron Lett.* **1995**, *36*, 2531-2534. b. Tsunoda, T.; Yamamiya, Y.; Itô, S. *Tetrahedron Lett.* **1993**, *34*, 1639-1642. c. Tsunoda, T.; Otsuka, J.; Yamamiya, Y.; Itô, S. *Chemistry Lett.* **1994**, 539-542.
4. Tsunoda, T.; Ozaki, F.; Itô, S. *Tetrahedron Lett.* **1994**, *35*, 5081-5082.
5. Lai, J-Y.; Yu, J.; Hawkins, R. D.; Falck, J. R. *Tetrahedron Lett.* **1995**, *36*, 5691-5694.
6. CMMP is a new compound and was prepared as follows. To chloroacetonitrile (15 mL, 0.24 mol) was added slowly a THF solution of trimethylphosphine (1.0 M, 196 mL, available from Aldrich Chem. Co.) over 1 h with stirring. The reaction temperature was maintained at ca 40°C by cooling (water) the exothermic reaction. The reaction mixture was stirred at room temperature for 2 days during which colorless solid was precipitated. The solid was purified by recrystallization (from 2-propanol) to give in quantitative yield cyanomethyltrimethylphosphonium chloride, colorless granules, m.p. 208-253°C (decomp.). ^{1}H-NMR: δ 1.01 (9H, d, J = 15.4), 3.08 (2H, 16.6). The phosphonium chloride (3.43 g, 22.6 mmol) in dry THF (110 mL) and potassium hexamethyldisilylamide in toluene (0.5 M, 40 mL) were mixed with stirring at 0°C under argon atmosphere. After stirring at room temperature for 4.5 h, KCl precipitated from the reaction mixture was removed by decantation. Supernatant solution was evaporated *in vacuo*. The residual solid was recrystallized from dry benzene (12 mL) to give cyanomethyltrimethylphosphorane, pale yellow fine granules, m.p. 57-62°C (94% yield). ^{1}H-NMR: δ 1.03 (1H, s), 1.64 (9H, d, J = 12.8). Very sensitive to air. All procedures for the preparation and purification of CMMP as well as its reactions should be carried out under strictly dry argon atmosphere.



7. We found that the combination of *N,N,N',N'*-tetramethylazodicarboxamide (TMAD)-PMe_3 is much more effective (89% yield) than TMAD-PBu_3 for the reaction of 2-octanol and *N*-methyl-*p*-tosylamide (40%).[3c]
8. The reactivity of other reagents, such as TMAD-PBu_3 and ADDP-PMe_3-imidazole (Falck's conditions),[5] was confirmed in the reaction of **2a** with 2-octanol to give the alkylation product in 0% and 54% yield, respectively. Compare the values with those in entry 2 in Table 1.
9. In a typical experiment, a phosphine (1.5 mmol) and an azo compound (1.5 mmol) were added successively to a dry benzene solution of an alcohol (1 mmol) and a sulfonyl compound (1.5 mmol) with stirring under argon atmosphere. In the reactions with CMBP or CMMP, the reagent (1.5 mmol) was added to the benzene solution with stirring under argon atmosphere. For the reactions of **1** with diols, 3 mmol of reagent was used. Stirring was continued at room temperature for 24 h. For the reactions at higher temperatures, the reaction mixture was heated under argon atmosphere in a sealed tube. The products were purified by silica-gel column chromatography after evaporation of the solvent *in vacuo*. All new compounds were characterized by elemental analyses or high resolution mass spectra, and IR, ^{1}H-NMR , and mass spectra.

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