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Novel Reactivity of Stabilized Methylenetributylphosphorane: A New Mitsunobu Reagent

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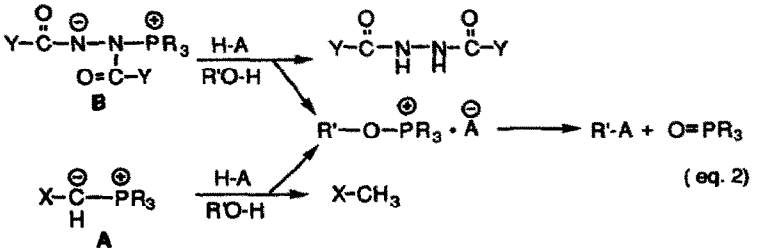
Abstract: Cyanomethylenetributylphosphorane was shown to mediate the direct condensation of alcohols with *O*- and *N*-nucleophiles. A *secondary* alcohol, 2-octanol, reacted satisfactorily with Walden inversion of its carbinyl carbon.

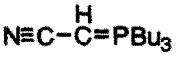
The Mitsunobu reaction is a very versatile method for the alkylation with alcohols of various nucleophiles (or acids, HA), utilizing the redox system of diethyl azodicarboxylate (DEAD)-triphenylphosphine (TPP) (eq. 1).[1] Without any prerequisite activation of the alcohols, it is a unique alkylation reaction and widely applied to various phases of organic synthesis.

$$\text{R-OH} + \text{HA} \xrightarrow[\text{PPh}_3]{\text{DEAD}} \text{R-A} \qquad \text{(eq. 1)}$$

Although one of the limitations of the reaction, i.e. its restricted applicability to the acids of smaller pK_a, is significantly reduced for those with *primary* alcohols by our recent finding of the combination of *N*, *N*, *N'*, *N'*-tetramethylazodicarboxamide (TMAD) and tributylphosphine (TBP),[2] there still remained a need for a versatile reagent or a combination of reagents which is applicable to the reactions of *secondary* alcohols with acids of larger pK_a. In our search for such reagents,[3] we recognized the similarity in the electronic structures between stable phosphorous ylides (**A**) and the zwitter ions (**B**) which are believed to be formed in the 1st step of the Mitsunobu reaction,[1] and envisaged a similarity in their behavior towards a mixture of an alcohol and an acid (eq.2); if X in **A** is a stabilizing electron-withdrawing group, such as an ethoxycarbonyl or a cyano group, the by-products would then be a phosphine oxide, and ethyl acetate or acetonitrile, greatly facilitating the product purification. Subsequently, cyanomethylenetributylphosphorane (CMBP)[4,5] was found to be very effective in the reactions of a *secondary* alcohol and the acids of pK_a up to 12. The results are described herein.



(eq. 2)



CMBP

In a typical experiment, an alcohol (1 mmol) and HA (1.5 mmol) were successively dissolved in dry benzene (5 mL) with stirring under an argon atmosphere, and CMBP (1.5 mmol) was added all at once, using a syringe. The reaction mixture was heated at 100°C for 24 h with stirring in a sealed tube. The product was purified by silica gel column chromatography after evaporation of the solvent *in vacuo*. The efficiency of CMBP was examined for the reactions of benzoic acid, *N*-methyltosylamide, and *N*-benzyltrifluoroacetamide with alcohols of 4 different structure types. The results are shown in the Table together with those of the DEAD and TMAD mediated reactions.

Table. *N*- and *O*-Alkylation with DEAD, TMAD and CMBP

H-A	PhCOOH (pK_a 4.2)				TsNHMe (pK_a 11.7)				$F_3CCONHCH_2Ph$ (pK_a 13.6)			
Reagent[a]	D	T	B		D	T	B		D	T	B	
R-OH Temp. (°C)	r.t.	60	r.t.	100	r.t.	r.t.	r.t.	100	r.t.	r.t.	r.t.	100
C_4H_9OH	85[b]	95	91	99	65	100	99	100	—[c]	83	80	75
$PhCH_2OH$	—[c]	100	73	100	66	99	81	100	3	86	77	68
$MeCH{=}CHCH_2OH$	85[b]	93	79	90	51	96	83	100	—	78	70	79
$C_6H_{13}CH(OH)CH_3$	20[b]	93	39	96	53	40	60	89	—	11	3	4

a. D: DEAD-TPP / THF, T: TMAD-TBP / PhH, B: CMBP / PhH. b. Reference 1a.
c. The reaction was not carried out.

The reactions proceed at room temperature with CMBP to give the desired alkylation products in most cases with higher yield than with DEAD but not as high as with TMAD. However, CMBP is stable at higher temperature and at 100°C it gives as good yields of the alkylation products as TMAD does. Furthermore the reaction with 2-octanol is noteworthy, because none of the other reagents developed so far[2] is satisfactory for the reactions of amides of pK_a = 12 with *secondary* alcohols, and CMBP is the first reagent to be applicable satisfactorily in such reactions. An exception is the reaction of *N*-benzyltrifluoroacetamide (pK_a = 13.6); the other product is that of *O*-alkylation, with most of the starting material being recovered.

The reaction of 2-octanol with benzoic acid or *N*-methyltosylamide proceeds with complete Walden inversion.[6]

Thus, we exploited the novel reactivity of CMBP to develop a versatile Mitsunobu type methodology which has significance in the alkylation with *secondary* alcohols.

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2. a. Tsunoda, T.; Otsuka, J.; Yamamiya, Y.; Itô, S. *Chem. Lett.* **1994**, 539-542. b. Itô, S.; Tsunoda, T. *Pure & Appl. Chem.* in press. Cf. Tsunoda, T.; Yamamiya, Y.; Itô, S. *Tetrahedron Lett.* **1993**, *34*, 1639-1642.
3. Azodicarboxyamides with smaller alkyl groups on nitrogens (e.g. TMAD) seemed to give better results than those with larger groups (e.g. tetraisopropyl compound).[2] However, nonsubstituted or *N, N'*-disubstituted azocarboxamides can not be used because of their poor solubility.
4. CMBP is a new compound and was prepared as follows. To a CH_3NO_2 (150 mL) solution of tributylphosphine (0.13 mol) was added chloroacetonitrile (0.13 mol) and the mixture was stirred for 21 h at r.t. The solvent was removed *in vacuo*, and the residual solid was recrystallized from AcOEt-$CHCl_3$ to give cyanomethyltributylphosphonium chloride, colorless needles, m.p. 98-100°C (75% yield). ^{1}H-NMR: δ 1.00 (9H, t, J = 7.1), 1.5-1.8 (12H, complex), 2.6-2.8 (6H, complex), 5.28 (2H, d, J = 15.9). The phosphonium chloride (25.5 mmol) in dry THF (100 mL) and butyllithium in hexane (1.5 M, 17 mL) was mixed with stirring at 0°C under argon atmosphere. After 1 h, the solvent mixture was evaporated at room temperature *in vacuo*. LiCl formed was filtered off from the dry hexane-benzene solution of the residue. The filtrate was evaporated and the residue was distilled (bulb to bulb) to give CMBP (91% yield), a pale yellow oil, b.p. 250-260°C / 0.4 mm Hg. ^{1}H-NMR: δ0.80 (1H, s), 0.96 (9H, t, J = 7.0), 1.4-1.8 (18H, complex). Sensitive to air and moisture. Should always be handled under dry argon atmosphere.
5. Nonstabilized phosphoranes, such as methylene- and phenylmethylenetriphenylphosphoranes, did not work at all. With ethoxycarbonyl- or cyanomethylenetriphenylphosphoranes, the stabilized phosphoranes, the reaction of benzyl alcohol and *N*-methyltosylamide was very slow at room temperature. When heated (PhH, 100°C, 48h), the yields of *N*-benzyl-*N*-methyltosylamide were 70% and 92%, respectively, compared with the 100% yield with CMBP (PhH, 100°C, 24h) (Table).
6. The configuration and optical purity of the products were confirmed by comparison of their liquidchromatogram on chiral column with those of authentic samples prepared from 2-(*S*)-octanol (98%e.e.) by Mitsunobu procedure.[1]

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