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A facile one-pot cyanation of primary and secondary alcohols. Application of some new Mitsunobu reagents

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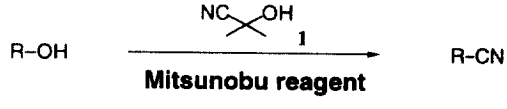
Abstract

Some new Mitsunobu reagents, especially *N,N,N′,N′*-tetramethylazodicarboxamide (TMAD)–tributylphosphine (TBP) and cyanomethylenetrimethylphosphorane (CMMP), mediated the direct transformation of primary and secondary alcohols into the corresponding nitriles in the presence of acetone cyanohydrin. This type of cyanation process can convert 3β-cholestanol to 3α-cyanocholestane in high yield with complete Walden inversion. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: Mitsunobu reactions; azo compounds; phosphorane; nitriles.

The conversion of an alcohol into the corresponding nitrile is a fundamental synthetic process for carbon chain elongation. Thus, in addition to the classical multistep processes, several interesting one-pot methodologies are found in the literature.[1–5] However, they all suffer from low yields when applied to secondary alcohols. The elegant Wilk's process which utilizes acetone cyanohydrin (**1**) under Mitsunobu conditions[6–8] (Scheme 1) also suffers from low yields in the case of secondary alcohols.



Scheme 1.

We have recently developed two types of new Mitsunobu mediators, the combination of azodicarboxamides (e.g. TMAD†[9]) and tributylphosphine (TBP), and cyanomethylenetrialkyl phosphoranes (CMBP†[10] and CMMP†[11]), and demonstrated that they are more versatile than the traditional combination of diethyl azodicarboxylate (DEAD)–triphenylphosphine (TPP) for *N*-, *O*-, and *C*-alkylation of various acids.[9–15] Now we have carried out a detailed comparative study and found that our reagents are

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† New Mitsunobu reagents: TMAD and CMBP are commercially available from Tokyo Chemical Industry Co., Ltd. (http://www.tokyokasei.co.jp). CMMP is prepared by the procedure described in a previous paper.[11]

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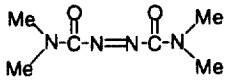
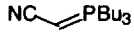
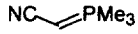
in general more efficient than DEAD–TPP in the direct cyanation by acetone cyanohydrin (**1**) of alcohols, in particular, secondary alcohols. The present paper describes these results.



TMAD



CMBP



CMMP

The reactions mediated by DEAD–TPP were carried out as described,[6] while those with both new azo and phosphorane reagents used our standard conditions.[‡] The results are summarized in Table 1.

As is shown in Table 1, the reactions mediated by our amide reagent TMAD–TBP are comparable with or better than those with DEAD–TPP (entry 1 versus entry 2, and entry 3 versus entry 4, respectively), and the yields are excellent (entries 2, 4 and 5) for the cyanation of primary alcohols. We did not examine the reactions of primary alcohols with the phosphorane reagents, since TMAD–TBP was quite satisfactory and the phosphorane reagents would have the obvious disadvantage of reacting with the acetone liberated from the cyanohydrin as the cyanation proceeds and an additional molar equivalent would be required for the completion of the desired cyanation.

For the reactions of secondary alcohols, however, the results with TMAD–TBP varied; it mediates the reaction of 2-undecanol more efficiently than DEAD–TPP but the yield is not satisfactory, and 3 molar equivalents are required to obtain a satisfactory yield (entries 6 and 7 versus 8). The phosphorane reagents are not outstanding in the reaction of this alcohol (entries 9 and 10), though CMMP is better than CMBP. Considering the disadvantage mentioned above with phosphoranes in this type of reaction, they are not the mediators of choice. The results are different in the reaction of 3β-cholestanol; TMAD–TBP gave a miserable yield in this case, even compared with DEAD–TPP,[6] but CMMP in DME mediated the reaction in three times the yield with complete Walden inversion.

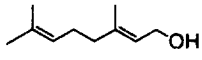
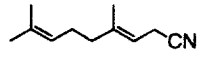
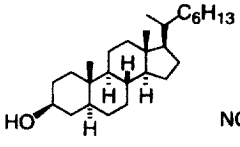
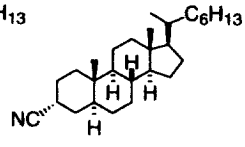
The difference in reactivity between prim. and sec. hydroxyl groups can be applied to the regioselective cyanation of diols. For example, 1,6-decanediol (**2**) was allowed to react with **1** (1.5 mol equiv.) in the presence of TMAD–TBP (1.5 mol equiv.) to give monocyanide **3** in 84% with only a trace of dicyanide **4** (Scheme 2). Furthermore, sensitivity to the steric situation around the carbinyl carbon was also observed in the reaction of a prim. diol. Thus, 2-methyl-1,8-octanediol (**5**)[§] gave 8-hydroxy-7-methyloctylcyanide (**6**), the product obtained by reaction at the less hindered 8-hydroxy group, in 75% yield, along with 1% of the regioisomer **7** and 24% of dicyanide **8**.

Thus, the present paper demonstrates that acetone cyanohydrin (**1**) can be used satisfactorily as a source of hydrogen cyanide in the presence of new Mitsunobu reagents, and the reaction should now be a standard synthetic procedure for the transformation of alcohols into the corresponding nitriles. The recommended practise is to try the TMAD–TBP mediator first, and, if it fails, then try CMBP or CMMP.

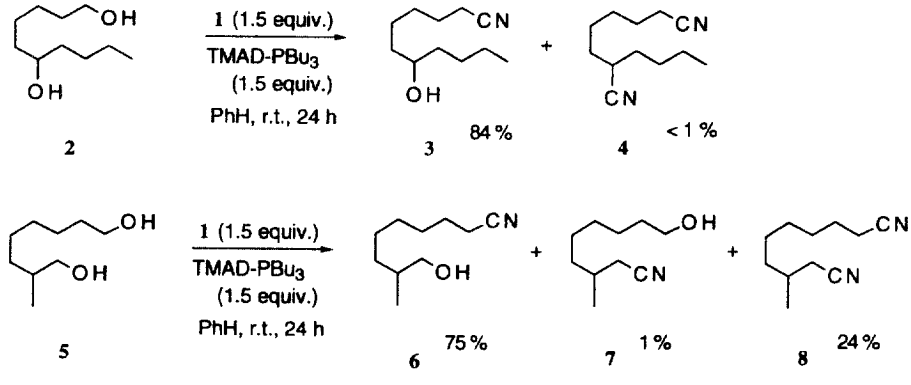
[‡] Experimental conditions: In a typical experiment with TMAD, TBP (1.5 mmol) and TMAD (1.5 mmol) were added consecutively to a dry benzene solution of an alcohol (1 mmol) and acetone cyanohydrin (1.5 mmol) with stirring at rt under argon atmosphere. Stirring was continued for 24 h. For the reactions with CMBP or CMMP at a higher temperature, the mixture of the reactants was heated in an Ace pressure tube (Ace Glass Inc. max. 200 psi), after careful manipulation under argon atmosphere. In all cases, the product was purified by silica gel column chromatography after the aqueous treatment of the reaction mixture, followed by extraction with an organic solvent and evaporation of the solvent in vacuo. All new compounds were characterized by IR, ^{1}H NMR, MS, analysis or High-MS. The ratios of regioisomers (**3** versus **4** and **6** versus **7**) in the products from diols **2** and **5** were determined by capillary GLC.

[§] Preparation of 2-methyl-1,8-octanediol (**5**): The DIBAL reduction of ε-caprolactone followed by Wittig reaction with (carbethoxyethylidene)triphenylphosphorane afforded ethyl 8-hydroxy-2-methyl-2-octenate in 91% yield (2 steps). The ester was hydrogenated (Pd–C) and reduced by $LiAlH_4$ to give **5** in 76% yield (2 steps).

Table 1
Conversion of alcohols to nitriles

Entry No.	Alcohol	Nitrile	conditions: equiv. of 1	reagent (equiv.)	solv.	temp. (period, h)	% yield
1	n-$C_{16}H_{33}OH$	n-$C_{16}H_{33}CN$	1.5	DEAD-TPP (1.5)	ether	r.t. (24)	67[a]
2			1.5	TMAD-TBP (1.5)	PhH	r.t. (24)	96
3	Ph-OH	Ph-CN	1.5	DEAD-TPP (1.5)	ether	r.t. (24)	89[b]
4			1.5	TMAD-TBP (1.5)	PhH	r.t (24)	91
5			1.5	TMAD-TBP (1.5)	PhH	r.t (24)	83
6	$^nC_9H_{19}$-OH	$^nC_9H_{19}$-CN	1.5	DEAD-TPP (1.5)	ether	r.t. (24)	42[a]
7			1.5	TMAD-TBP (1.5)	PhH	r.t (24)	60
8			3.0	TMAD-TBP (3.0)	PhH	r.t (24)	87
9			1.5	CMBP (3.0)	PhH	100°C (24)	63
10			1.5	CMMP (3.0)	PhH	100°C[c] (24)	71
11			1.5	DEAD (1.5)	ether	r.t. (24)	23[b]
12			1.5	TMAD-TBP (1.5)	PhH	r.t (24)	6
13			1.5	CMMP (3.0)	DME	100°C (48)	73

a: Using Wilk's procedure [6]. b: Reported yield by Wilk [6]. c: The yield was unchanged at 120 °C.



Scheme 2.

Acknowledgements

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