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Acetylation and Formylation of Alcohols with Triphenylphosphine and Carbon Tetrabromide in Ethyl Acetate or Ethyl Formate

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Abstract: Alcohols were acetylated or formylated with triphenylphosphine and carbon tetrabromide in ethyl acetate or ethyl (or methyl) formate at room temperature. THP or TBDMS ether of primary alcohol got converted into formate or acetate under the experimental conditions employed in one pot operation.

During the multistep synthesis of natural products, the efficiency of the synthetic protocol employed often depends largely on protection and deprotection of the functional groups involved. To this end, protecting groups have been playing a crucial role during the synthesis of complex natural products.[1] Among the various protecting groups used for hydroxyl function, acetyl is the most common group in view of its easy introduction, stability to acidic reaction conditions and also ease in its removal by mild alkaline hydrolysis. Although there are several literature precedents for hydroxyl protection in general, procedures reported for selective acetylation of primary alcohols are limited because of its higher reactivity and lesser steric requirement of acetylating reagents.

Among the common methods used for acetylation, heating of an alcohol with aluminum oxide in ethyl acetate is reported to give primary acetate,[2] though a large quantity of aluminum oxide was required for the success of the reaction. Alternatively, heating with *N*-acetylimidazole in chloroform provides primary acetylsugar,[3] though acetylation of 5-hydroxynonanol under the said reaction condition was too sluggish. Transesterification mediated by enzyme,[4] or use of limited amount of acetic anhydride in pyridine at low temperature are some of the other procedures reported.[5] Among such methods, acetylation using a small excess of acetyl chloride in presence of bulky base such as 1,2,2,6,6-pentamethylpiperidine at low temperature provides an efficient method for the selective protection of primary alcohols.[6] Formyl group is also a useful protecting group[7] because selective deprotection is possible in presence of other groups like acetyl or benzoyl though its utility for the moment has been overlooked.

In connection with the synthesis of a natural product, we were required to protect selectively, primary hydroxyl group in a dihydroxyl compound.[8] In fulfillment of such need, we had previously reported the selective acetylation of primary alcoholic group with acetylimidazole[9] in a solid state reaction[10] during

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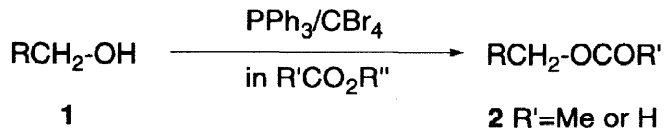
which, the primary alcohols and phenols were acetylated with fair selectivity. In continuation of our interest, we delineate herein an alternative simple and selective procedure for acetylation of primary alcohols using triphenylphosphine and carbon tetrabromide in ethyl acetate at room temperature (Scheme 1). This procedure is also applicable to formylation of alcohols using ethyl or methyl formate (*vide infra*).



Scheme 1

For optimizing the reaction conditions leading to selective acetylation, cetyl alcohol was used as the substrate and the results are listed in Table 1.

Table 1. Acetylation of cetyl alcohol with triphenylphosphine and carbon tetrabromide in ethyl acetate

Entry	Cetyl alcohol : PPh_3 : CBr_4 : AcOEt	Reaction condition	Cetyl acetate (%)	Cetyl bromide (%)
1	1 : 1.2 : 0 : 100	reflux, 4hr	0	0
2	1 : 0 : 1.2 : 100	reflux, 24hr	20	0
3	1 : 0.5[a] : 0.5 : 100	room temp., 10.5hr	51	0
4	1 : 1.7 : 1.7 : excess	room temp., 21hr	70	30
5	1 : 0.1 : 0.1 : 100	room temp., 29.5hr	93	0
6	1 : 1.2 : 1.2 : 100	reflux., 18.5hr	95	4
7	1 : 1.2 : 1.2 : 100	room temp., 19hr	96	0
8	1 : 0.5 : 0.5 : 100	room temp., 23hr	100	0
9	1 : 0.5 : 0.5 : 100[b]	room temp., 23hr	55	0
10	1 : —[c] : — : 100	room temp., 26.5hr	11	0
11	1 : —[d] : — : 100	room temp., 24hr	98	0

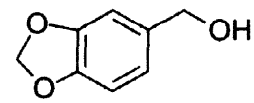
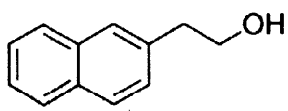
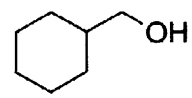
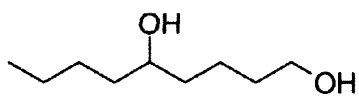
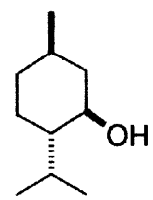
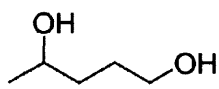
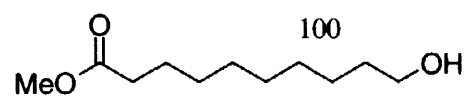
[a] CHI_3 was used. [b] Vinyl acetate was used; [c] A few drops of conc. HCl was used; [d] A few drops of hydrobromic acid was used.

As it is seen (entry 8), cetyl acetate was obtained in quantitative yield when reaction was carried out by using 0.5 equivalents of triphenylphosphine and carbon tetrabromide in ethyl acetate at room temperature for 23hr. A large scale acetylation (50 mmol) was also possible to give the acetate quantitatively. In the absence of carbon tetrabromide, cetyl alcohol was recovered back unchanged (entry 1). Without the addition of triphenylphosphine, cetyl acetate was obtained in 20% yield after refluxing for 24hr (entry 2). When the amount of triphenylphosphine and carbon tetrabromide were increased, substantial quantity of cetyl bromide[11] was obtained along with cetyl acetate (entry 4). With iodoform, cetyl acetate was produced in 51% yield (entry 3). Other polyhalogenated reagents such as carbon tetrachloride, bromoform, dibromomethane or 1,2-dibromoethane gave cetyl acetate only in 0~12% yield. When vinyl acetate was used instead of ethyl acetate, acetylation proceeded rather sluggishly to give the acetate in 55% yield along with 36% of recovered cetyl alcohol (entry 9).

In order to explore further, the synthetic utility of this procedure, some selected alcohols were acetylated under the optimized reaction condition (Table 1, entry 8), as shown in Table 2. As expected, the primary alcohols were acetylated preferentially as can be seen in entries 6 and 7. Conventional method of acetylation employing acetic anhydride in pyridine normally produces diacetate in case of such substrates thereby indicating no selectivity for acetylation between primary and secondary alcohols. Cyclohexanemethanol was consumed completely though yield was low due to volatile nature of the resulting acetate (entry 9). Yields of menthyl acetate and cholesteryl acetate were only 5 (entry 10) and 19% (entry 11) respectively, indicating the low reactivity of secondary alcoholic group towards acetylation. When ethyl pentanoate was used as a solvent, cetyl pentanoate was obtained in 53% yield along with 11% of cetyl bromide after refluxing the reaction mixture for 30.5hr. Methyl 10-acetoxydecanoate was obtained in 100% yield (entry 12).

Another characteristic feature of the present acetylation is the direct displacement of the tetrahydropyranyl (THP)[1,2] or *tert*-butyldimethylsilyl (TBDMS) protecting groups from the respective ethers by acetate group. For example, cetyl THP or TBDMS ether was transformed into cetyl acetate quantitatively in presence of 2 to 3 equiv. of H_2O in a one pot reaction (entries 2 and 3).

Table 2. Acetylation of some selected alcohols.

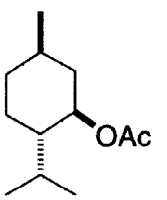
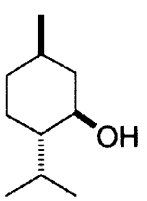
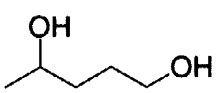
Entry	Starting Material	Yield of Acetate (%)	Entry	Starting Material	Yield of Acetate (%)
1	$CH_3(CH_2)_{15}$-OH	100[a]			
2		100[b]	8		33
3		96[c]			
4	$C_8H_{17}CH{=}CH(CH_2)_8$-OH	97			
5		89	9		29
6		82 (6)[d]	10		4.5
7		60 (16)[d,e]	11	Cholesterol	19
			12		100

[a] From cetyl alcohol; [b] From cetyl alcohol THP ether in the presence of 3 equiv. of H_2O; [c] From cetyl alcohol TBDMS ether in the presence of 3 equiv. of H_2O; [d] Amount of diacetate; [e] 0.2 equiv. of PPh_3/$CBr_4$was used.

Normally, when formate is used as a protecting group, it is deprotected into alcohol using $KHCO_3$ in aq. methanol, thereby enabling selective deprotection even in presence of other ester groups. In spite of having such selectivity while deprotection, protection of alcohol as formate is not well recognized and a suitable

procedure for formylation has not been thoroughly investigated. Under the circumstances, we found that the above mentioned method can be also applied to formylation using methyl or ethyl formate. Some of the representative results are listed in Table 3. Since ethyl or methyl formate is much more reactive, unlike selective acetylation, the selectivity in formylation between primary and secondary alcohol was lost as both the groups were formylated under the reaction condition (entries 7 and 11). Exchange of protecting groups were also observed from cetyl TBDMS ether and THP ether (entries 4 and 5). Moreover, acetyl group was replaced with formyl in presence of 3 equiv. of H_2O as can be seen in the case of cetyl acetate (entry 6) or menthyl acetate (entry 10) only at reflux temperature. The difference between methyl or ethyl formate is subtle under the reaction conditions employed. Phenol such as thymol was recovered unchanged.

Table 3. Formylation of some selected alcohols and their derivatives.

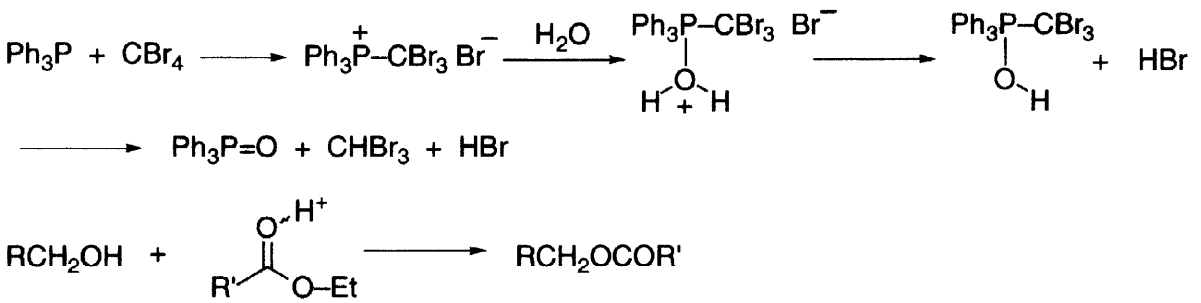
Entry	Starting Material	Yield of Formate[a] (%)	Entry	Starting Material	Yield of Formate[a] (%)
1	$CH_3(CH_2)_{15}$-OH	90 (10)[b]			
2		85 (15)[c]	10		73 (14)[c, e]
3		88 (8)[c, d]			
4	$CH_3(CH_2)_{15}$-OTBDMS	86 (13)[c]			
5	$CH_3(CH_2)_{15}$-OTHP	85 (11)[c]			
6	$CH_3(CH_2)_{15}$-OAc	83 (15)[c, e]			
7		76 (22)[b]	11	cholesterol	63 (36)[c]
8		70 (21)[c]			
9		68 (19)[c, f]	12		46[g] (32)[h]

[a]Yield in parentheses is amount of alcohol recovered; [b]HCO_2Me was used; [c]HCO_2Et was used; [d]0.5 equiv. of HBr was used; [e]in the presence of 3 equiv. of H_2O at reflux; [f]1 equiv. of PPh_3 and CBr_4 were used; [g]a mixture of primary and secondary mono-formate (3.1 : 1); [h]Amount of diformate.

As far as mechanism of the present acetylation reaction is concerned, it may be noted that along with the respective acetate, triphenylphosphine oxide and bromoform were isolated after the reaction. In an attempt to obtain more information about the mechanistic pathway, NMR spectra of a solution of cetyl alcohol, triphenylphosphine, carbon tetrabromide and ethyl acetate in the ratio of 1:1:1:20 using $CDCl_3$ as solvent was measured periodically over a period of 16hr. This exercise revealed the information that bromination of the substrate proceeds preferentially. This was supported by the fact that when a solution of cetyl alcohol, triphenylphosphine, carbon tetrabromide and ethyl acetate in the proportion of 1:1:1:20 was allowed to stand for 16 hr at room temperature, bromide was the sole product of the reaction and not the acetate. In this case, the higher concentration of the reagents/substrates drives the reaction towards bromination and not to acetylation. In case of menthyl acetate, the configuration of the acetate group remained unchanged, judging from the coupling constants of the proton on the carbon bearing acetoxy

group (δ 4.67, td, J =10.9 and 4.4 Hz). When molecular sieves (4 Å) were added to the reaction mixture, acetylation was completely suppressed resulting in the recovery of cetyl alcohol. It is interesting to note that no bromination occurred under such conditions. In the reaction using ethyl formate, formation of ethyl bromide was not observed by NMR monitoring of the reaction mixture. This result rules out the intervention of formyloxytriphenylphosphonium bromide as a reactive species which can be generated by the reaction of tribromomethyltriphenylphosphonium bromide and ethyl formate. At the time of completion of the reaction, the pH of the reaction mixture was acidic to litmus (pH 1~2). It was also observed that addition of 1 or 2 equiv. of H_2O accelerated the acetylation reaction. These results signals towards a transesterification mechanism catalyzed by protic acid as depicted in Scheme 2. Phosphonium bromide intermediate is hydrolyzed by H_2O to generate hydrogen bromide which catalyzes the ester exchange reaction. The triphenylphosphine oxide and bromoform produced during the course of the reaction do not play any role in the suggested transesterification mechanism. This hypothesis can be supported by the fact that when cetyl alcohol was stirred with equimolar quantities of bromoform and triphenylphosphine oxide in ethyl acetate, no cetyl acetate was obtained. However, addition of hydrobromic acid to the reaction mixture furnished cetyl acetate in comparable yield. Though, hydrobromic acid catalyzed acetylation of cetyl alcohol gave cetyl acetate in 98 % yield (Table 1, entry 11), acetylation 4-hydroxypentanol under the same condition produced 4-hydroxypentyl acetate in only 5 % yield. In order to realize selective acetylation as in the case of diol (Table 2, entry 7), the stoichiometry of PPh3/CBr4 is crucial in the present procedure.

Scheme 2



In summary, we have clearly demonstrated that primary alcohols were selectively acetylated in presence of 0.5 equiv. of triphenylphosphine and carbon tetrabromide in ethyl acetate at room temperature. It is known that acetylation of alcohols is usually carried out by using acetic anhydride in the presence of pyridine and a catalytic amount of dimethylaminopyridine. However, removal of excess of pyridine and acetic anhydride used in the reaction calls for a careful and tedious work-up procedure especially in case of volatile acetates. However, the present procedure developed by us, avoids these complications. The simplicity of the reaction procedure and the satisfactory selectivity exhibited during acetylation renders the present method more attractive during the synthesis of compounds with multi functional groups.[13]

Experimental

IR spectra were recorded on a Shimadzu FT/IR-4200 spectrophotometer. ^{1}H NMR spectra were obtained for solutions in deuteriochloroform with Varian Gemini 200H (200 MHz) instrument with tetramethylsilane as internal standard.

General experimental procedure for acetylation.
A solution of alcohol (1 mmol), triphenylphosphine (0.5 mmol) and carbon tetrabromide (0.5 mmol) in ethyl acetate (5 ml) was stirred at room temperature under nitrogen atmosphere and the reaction was monitored by TLC. Evaporation of ethyl acetate followed by flash column chromatography provided the acetate.

General experimental procedure for formylation.
A solution of alcohol (1 mmol), triphenylphosphine (0.5 mmol) and carbon tetrabromide (0.5 mmol) in ethyl or methyl formate (5 ml) was stirred at room temperature under nitrogen atmosphere and the reaction was monitored by TLC. Evaporation of the solvent followed by flash column chromatography provided the formate.

General experimental procedure for direct acetylation of cetyl alcohol tetrahydropyranyl or t-butyldimethylsilyl ether.
A solution of ether (0.5 mmol), triphenylphosphine (0.25 mmol), carbon tetrabromide (0.25 mmol) and H_2O (1.5 mmol) in ethyl acetate (5 ml) was stirred at room temperature under nitrogen atmosphere and the reaction was monitored by TLC. The resulting solution was dried over sodium sulfate and subsequent evaporation of the solvent followed by flash column chromatography provided the acetate.

Cetyl acetate.—Yield, 100%; ν_{max}/cm^{-1} (neat) 2932, 2855, 1744, 1468, 1366, 1238 and 1040; δ 0.88 (br t, 3H), 1.21–1.38 (br s, 26H), 1.61 (quint, 2H, *J* 6.7 Hz), 2.05 (s, 3H) and 4.05 (t, 2H, *J* 6.7 Hz).

Oleyl acetate.—Yield, 97%; ν_{max}/cm^{-1} (neat) 3005, 2920, 2855, 1744, 1240 and 1040; δ 0.87 (br t, 3H), 1.18–1.45 (br s, 24H), 1.62 (t, 2H, *J* 6.7 Hz), 2.01 (br t, 4H), 2.04 (s, 3H), 4.05 (t, 2H, *J* 6.7 Hz) and 5.35 (br t, 2H).

2-(2-Naphthyl)ethyl acetate.—Yield, 89%; ν_{max}/cm^{-1} (neat) 3048, 1738, 1237 and 1046; δ 2.04 (s, 3H), 3.41 (t, 2H, *J* 7.4 Hz), 4.41 (t, 2H, *J* 7.4 Hz) and 7.32–8.12 (m, 7H).

5-Hydroxynonyl acetate.—Yield, 82%; ν_{max}/cm^{-1} (neat) 3409, 2956, 1742, 1244 and 1046; δ 0.90 (br t, 3H), 1.20–1.70 (m, 13H), 2.05 (s, 3H), 3.60 (m, 1H) and 4.07 (t, 2H, *J* 6.5 Hz).

4-Hydroxypentyl acetate.—Yield, 60%; ν_{max}/cm^{-1} (neat) 3400, 2967, 1738, 1370, 1256 and 1040; δ 1.21 (d, 3H, *J* 6.2 Hz), 1.42–1.86 (m, 5H), 2.05 (s, 3H), 3.83 (qt, 1H, *J* 6.2, 6.2 Hz) and 4.09 (t, 2H, *J* 6.5 Hz).

Piperonyl acetate.—Yield, 33%; ν_{max}/cm^{-1} (neat) 1738, 1502, 1447, 1244 and 1040; δ 2.08 (s, 3H), 5.00 (s, 2H), 5.96 (s, 2H), 6.80 (s, 1H), 6.83 (d, 1H, *J* 6.1 Hz) and 6.84 (d, 1H, *J* 6.1 Hz).

Cyclohexylmethyl acetate.—Yield, 29%; ν_{max}/cm^{-1} (neat) 2928, 1746, 1451, 1364, 1244 and 1038; δ 0.85-1.80 (m, 11H), 2.06 (s, 3H) and 3.88 (d, 2H, *J* 6.4 Hz).

l-Menthyl acetate.—Yield, 4.5%; ν_{max}/cm^{-1} (CCl_4) 1734, 1456, 1370, 1246 and 1024; δ 0.76 (d, 3H, *J* 7.0 Hz), 0.896 (d, 3H, *J* 7.2 Hz), 0.900 (d, 3H, *J* 6.0 Hz), 0.95–1.74 (m, 8H), 1.85 (m, 1H), 2.03 (s, 3H) and 4.67 (ddd, 1H, *J* 10.9, 10.9, 4.4 Hz).

Methyl 10-acetoxydecanoate.— Yield, 100%; ν_{max}/cm^{-1} (neat) 2932, 1742, 1366, 1240 and 1038; δ 1.30 (br s, 10H), 1.50–1.70 (m, 4H), 2.05 (s, 3H), 2.31 (t, 2H, *J* 7.5 Hz), 3.67 (s, 3H) and 4.05 (t, 2H, *J* 6.7 Hz).

Cetyl formate.—Yield, 90%; ν_{max}/cm^{-1} (neat) 2932, 2860, 2744, 1734, 1472, 1382 and 1180; δ 0.88 (t, 3H, *J* 6.4 Hz), 1.21–1.38 (br s, 26H), 1.66 (m, 2H), 4.16 (td, 2H, *J* 6.7, 0.8 Hz) and 8.06 (s, 1H).

Cholesteryl formate.—Yield, 63%; ν_{max}/cm^{-1} ($CHCl_3$) 2934, 2870, 2735, 1721, 1682, 1468, 1381 and 1179; δ 0.68 (s, 3H), 0.86 (d, 6H, *J* 6.6 Hz), 0.92 (d, 3H, *J* 6.4 Hz), 1.03 (s, 3H), 0.95–2.05 (m, 26H), 2.36 (br d, 2H, *J* 7.8 Hz), 4.74 (m, 1H), 5.39 (br d, 1H, *J* 4.0 Hz) and 8.04 (s, 1H).

l-Menthyl formate.—Yield, 76%; ν_{max}/cm^{-1} (neat) 2936, 2876, 2732, 1734, 1460, 1392 and 1180; δ 0.77 (d, 3H, *J* 7.0 Hz), 0.90 (d, 3H, *J* 7.0 Hz), 0.92 (d, 3H, *J* 6.4 Hz), 0.94–1.77 (m, 7H), 1.90 (qqd, 1H, *J* 7.0, 7.0, 2.7 Hz), 2.02 (m, 1H), 4.81 (ddd, 1H, *J* 10.9, 10.9, 4.4 Hz) and 8.08 (s, 1H).

4-Hydroxypentyl formate.—Yield, 35%; ν_{max}/cm^{-1} (neat) 3412, 2936, 2744, 1734, 1470, 1380 and 1188; δ 1.22 (d, 3H, *J* 6.2 Hz), 1.46–1.92 (m, 4H), 2.23 (br s, 1H), 3.85 (qt, 1H, *J* 6.2, 6.2 Hz), 4.21 (td, 2H, *J* 6.3, 0.8 Hz) and 8.07 (s, 1H).

5-Hydroxy-2-pentyl formate.—Yield, 11%; ν_{max}/cm^{-1} (neat) 3428, 2948, 2880, 2752, 1728, 1456, 1384 and 1192; δ 1.29 (d, 3H, *J* 6.2 Hz), 1.53–1.89 (m, 5H), 3.67 (t, 2H, *J* 6.0 Hz), 5.08 (m, 1H) and 8.06 (s, 1H).

1,4-Pentanediol diformate.—Yield, 32%; ν_{max}/cm^{-1} (neat) 2944, 2744, 1730, 1468, 1386 and 1180; δ 1.29 (d, 3H, *J* 6.0 Hz), 1.53–1.86 (m, 4H), 4.19 (t, 2H, *J* 5.8 Hz), 5.08 (qt, 1H, *J* 6.0, 6.0 Hz) and 8.06 (br s, 2H).

References

1 Greene, T. W.; Wuts, P. G. M., in *Protective Groups in Organic Synthesis*, John Wiley & Sons, Inc., New York, **1991**.

2 Posner, G. H.; Oda, M. *Tetrahedron Lett.*, **1981**, 22, 5003; Posner, G. H.; Okada, S. S.; Baliak, K. A.; Miura, K.; Rose, R. K. *Synthesis*, **1981**, 789; Rana, S. S.; Barlow, J. J.; Matta, K. L.*Tetrahedron Lett.*, **1981**, *22*, 5007.

3 Staab, H. A. *Angew. Chem. Int. Ed. Engl.*, **1962**, *1*, 351; Lemieux, R. U.; Driguez, H. *J. Amer. Chem. Soc.*, **1975**, *97*, 4063-4068; Vernon, J.; Roseman, S.; Lee, Y. C. *Carbohydr. Res.* **1980**, *82*, 59.

4 Bashir, N. B.; Phythian, S. J.; Reason, A. J.; Roberts, S. M. *J. Chem. Soc., Perkin Trans. 1*, **1995**, 2203.
5 Stork, G.; Takahashi, T.; Kawamoto, I.; Suzuki, T. *J. Amer. Chem. Soc.*, **1978**, *100*, 8272.
6 Ishihara, K.; Kurihara, H.; Yamamoto, H. *J. Org. Chem.*, **1993**, *58*, 3791.
7 Reber, F.; Lardon, A.; Reichstein, T.; *Helv. Chim. Acta*, **1954**, *37*, 45; Zemlicka, J.; Beranek, J.; Smrt, J. *Collect. Czech. Chem. Commun.*, **1962**, *27*, 2784.
8 Hagiwara, H. ; Kon-no, M.; Nakano, T.; Uda, H. *J. Chem. Soc., Perkin Trans. 1*, **1995**, 777; *idem., ibid.*, **1994**, 2417.
9 Hagiwara, H.; Morohashi, K.; Suzuki, T.; Ando, M.; Yamamoto, I.; Kato, M. *Synth. Commun.* in press.
10 Hagiwara, H.; Ohtsubo, S.; Kato, M. *Tetrahedron*, **1997**, *53*, 2415.
11 Calzada, J. G.; Hooz, J. *Org. Synth.*, **1988**, *Coll. Vol. 6*, 634.
12 Jacobson, M; Redfern, R. E.; Jones, W. A.; Aldridge, M. H. *Science* **1970**, *170*, 542.
13 Vedejs, E.; Bennett, N. S.; Conn, L. M.; Diver, S. T.; Gringras, M.; Lin, S.; Oliver, P. A.; Peterson, M. J. *J. Org. Chem.*, **1993**, *58*, 7286; Vedejs, E.; Daugulis, O. *ibid.*, **1996**, *61*, 5702; Ishihara, K.; Kubota, M; Kurihara, H.; Yamamoto, H., *J. Amer. Chem. Soc.*, **1995**, *117*, 4413; Ishihara, K.; Kubota, M.; Kurihara, H.; Yamamoto, H. *J. Org. Chem.*, **1996**, *61*, 4560; Barrett, A. G. M.; Braddock, D. C. *J. Chem. Soc., Chem. Commun.*, **1997**, 351; Tashiro, D.; Kawasaki, Y.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.*, **1997**, *62*, 8141.