Preparation of Various Carboxylic Acid Esters from Bulky Alcohols and Carboxylic Acids by a New Type Oxidation-reduction Condensation Using 2,6-Dimethyl-1,4-benzoquinone

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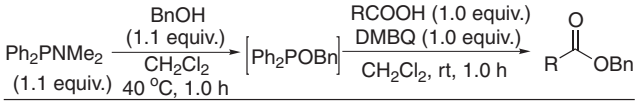
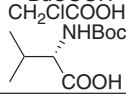
A new-type oxidation-reduction condensation by using 2,6-dimethyl-1,4-benzoquinone (DMBQ), carboxylic acids and in situ formed alkoxydiphenylphosphines (**1**) including the bulky alkoxy group-substituted ones proceeded smoothly to afford the corresponding carboxylic acid esters in good to high yields. Alkoxydiphenylphosphines were formed in situ by treating either *N*,*N*-dimethylaminodiphenylphosphine (Ph_2PNMe_2) with primary or secondary alcohols or chlorodiphenylphosphine with the lithium salts of primary, secondary and tertiary alcohols.

Preparation of carboxylic acid esters is one of the most fundamental and important reactions which is well-established and widely used in synthetic organic chemistry.[1] Of these esterifications, preparation of bulky secondary or tertiary alkyl esters is known to be more difficult compared with that of primary alkyl esters. Of a number of methods reported for the synthesis of bulky alkyl esters,[2] preparation of such hindered esters in high yields under mild conditions is a still difficult problem because the reaction generally needed long reaction time using large excess amount of either carboxylic acids or alcohols. In our previous communications, preparations of various carboxylic benzyl esters[3] and alkyl phenyl ethers[4] in high yields were shown as new types of oxidation-reduction condensation which used alkoxydiphenylphosphine having a primary, secondary or tertiary alkoxy group, oxidizing agent such as DMBQ, and carboxylic acids or phenols. The important point of this new condensation is that the reaction is carried out under mild and neutral conditions without any acids or bases assistance. Here, we would like to describe the condensation of various primary, bulky seconddary or tertiary alcohols with carboxylic acids to form the corresponding carboxylic esters; that is, the reaction of 1, formed in situ from the lithium salts of alcohols and Ph_2PCl, with carboxylic acids and DMBQ by oxidation-reduction condensation.

It was known that the phosphorus-nitrogen bond of *N*,*N*-disubstituted diarylphosphine was thermo-stable, therefore, tautomeric transformations of trivalent phosphine compounds to the corresponding pentavalent phosphine compounds did not occur.[5] More importantly, the above aminophosphines are easily converted to the alkoxy ones by replacement of the amino group with the alkoxy group of alcohols.[6] Then, it was considered that the alkoxydiphenylphosphine should be formed by alcoholysis of the corresponding aminophosphine with alcohols. In the first place, benzylation of various carboxylic acids with benzyloxydiphenylphosphine, in situ formed from Ph_2PNMe_2[7] and benzyl alcohol, was tried (Table 1). Benzylation of benzoic acids having electron-donating or electron-withdrawing groups, and saturated or unsaturated aliphatic carboxylic acids proceeded smoothly to afford the corresponding carboxylic acid benzyl esters in high yields under mild conditions. Similarly, the reactions of *N*-*tert*-butoxycarbonyl-L-valine and chloroacetic acid were performed.

Table 1. Benzylation of various carboxilic acids using Ph_2PNMe_2 and benzyl alcohol

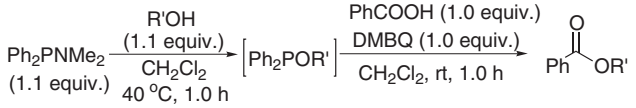


Entry	RCOOH	Yield /%	Entry	RCOOH	Yield /%
1	PhCOOH	96	5	PhCH=CHCOOH	92
2	*p*-MeO-PhCOOH	96	6	^{n}BuCOOH	93
3	*p*-NO_2-PhCOOH	90	7	$CH_2ClCOOH$	91
4	$Ph(CH_2)_2COOH$	90	8		89[a]

[a]No epimerization was observed by HPLC using Daicel CHIRALPAK AF.[3]

Condensation of benzoic acid and several alkoxydiphenylphosphines generated from primary alcohols and Ph_2PNMe_2 was tried under the above conditions (Table 2). When benzyl alcohols having electron-donating or electron-withdrawing groups, and saturated or unsaturated aliphatic alcohols were used, the corresponding esters were obtained in excellent yields. Also, the desired ester was obtained in 86% yield when 2-pyridine-

Table 2. Esterification of benzoic acid using Ph_2PNMe_2 and various primary alcohols



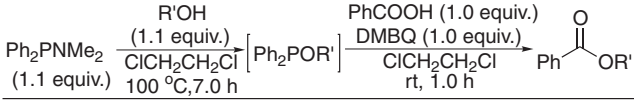
Entry	R′OH	Yield /%	Entry	R′OH	Yield /%
1	$PhCH_2OH$	96	4	$Ph(CH_2)_2OH$	94
2	*p*-MeO-$PhCH_2OH$	91	5	^{n}BuOH	96
3	*p*-NO2-$PhCH_2OH$	95	6	2-pyridyl-CH_2OH	86
7	$(CH_3)_2C{=}CH(CH_2)_2C(CH_3){=}CH(CH_2)_2OH$				96

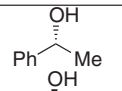
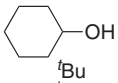
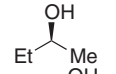
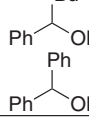
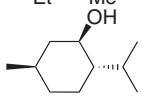
methanol having heterocyclic moiety was used (Entry 6).

Next, in order to extend the scope of present reaction, condensation of benzoic acid and several bulky secondary alcohols was tried after forming an intermediate Ph_2POR' in situ (Table 3). Alkylation of benzoic acid smoothly proceeded to afford the corresponding alkyl esters in high to excellent yields in 1,2-dichloroethane under the conditions shown in Table 4. In addition, it was observed that the corresponding benzoic acid alkyl esters were obtained in excellent yields with perfect inversion of stereochemistry when chiral secondary alcohols were used by S_N2 replacement.

Further, condensation of benzoic acid and tertiary alcohols by using Ph_2PNMe_2 was tried. However, in case of tertiary alcohols, replacement of *N*,*N*-dimethylaminodiphenylphosphine by alco-

Table 3. Esterification of benzoic acid using Ph_2PNMe_2 and various secondary alcohols



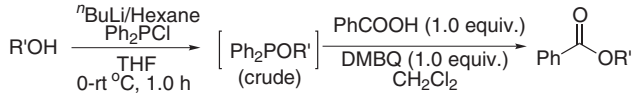
Entry	R'OH	Yield /%	Entry	R'OH	Yield /%	$[\alpha]_D$
1	^{i}PrOH	94[d]	5[a]		94	$[\alpha]_D^{24}$ = +26.6 (*c*3.08, EtOH)
2		95				
3		96	6[b]		88	$[\alpha]_D^{21}$ = -35.3 (*c*1.10, $CHCl_3$)
4		94	7[c]		88[e]	$[\alpha]_D^{23}$ = +92.0 (*c*1.16, C_6H_6)

[a] $[\alpha]_D^{25} = -28.7$ (*c*1.02, EtOH) (preparation from PhCOCl, Et_3N, alcohol).[8] In addition, Daicel Chiralcel OD column was used for chiral HPLC analysis.
[b] $[\alpha]_D^{22} = +34.6$ (*c*1.16, $CHCl_3$) (preparation from PhCOCl, Et_3N, alcohol).[9]
[c] $[\alpha]_D^{24} = -93.5$ (*c*1.23, C_6H_6) (preparation from PhCOCl, Et_3N, alcohol). Diastereoselectivities determined by ^{1}H NMR spectroscopy.[10] Also, intermediate L-menthoxydiphenylphosphine was prepared by mixture of L-menthol with Ph_2PNMe_2 stirred for 10 h at 100 °C.
[d] 90% Yield by Mitsunobu reaction.[11] [e] 27% Yield by Mitsunobu reaction.[11]

hols to form alkoxydiphenylphosphine did not take place at all. Then, preparation of the phosphine from Ph_2PCl and alcohols using ^{n}BuLi was tried according to Evans's procedure.[12] The esterification of various in situ formed tertiary and secondary alkoxy diphenylphosphines having sterically hindered bulky groups with benzoic acid was examined under the above conditions (Table 4). When tertiary alcohols were used, the desired esters were obtained in good yields under the conditions shown in Table 4 (Entries 1–7). Whereas the corresponding esters were afforded in high yields with perfect inversion of stereochemistry with secondary alcohols by S_N2 replacement (Entries 8–9). According to this procedure, primary alcohol gave the corresponding alkoxydiphenylphosphine smoothly, therefore, the desired ester was afforded in high yield by one-pot procedure by treating with benzoic acid (Entry 11).

Typical experimental procedure is as follows: to a solution of alcohol (5.0 mmol) in THF (18 mL) was dropped a solution of 1.56 M ^{n}BuLi /Hexane (5.0 mmol) at 0 °C under argon atmosphere. After the solution was stired at room temperature for 1.0 h, Ph_2PCl (5.0 mmol) was added at 0 °C. The reaction mixture was stirred for 1.0 h at room temperature and was concentrated in vacuo. After the residue was diluted with the mixed solution of hexane (8 mL) and ethyl acetate (1 mL), lithium chloride etc. were removed by filtration through celite (3.0 g) after passing through alumina (basic) (Wako pure chemical industries, LTD) (20 g). The diluted solution was concentrated in vacuo, and crude but virtually pure alkoxydiphenylphosphines were obtained. To a mixture of carboxylic acid (0.60 mmol) and DMBQ (0.60 mmol) under argon atmosphere was added a solution of the above crude alkoxydiphenylphosphine in dichloromethane (0.50 mL) under the conditions shown in Table 4. After completion of the reaction (detected by TLC), it was quenched with water and the mixture was extracted with dichloromethane. The organic layers were dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by preparative TLC to afford the corresponding carboxylic esters.

Table 4. Esterification of benzoic acid using ^{n}BuLi and various bulky secondary and tertiary alcohols



Entry	R′OH	Ph_2POR' /equiv.	Condition	Yield /%
1	^{t}BuOH	1.2	reflux, 6.0 h	79
2	Et_3COH	1.2	reflux, 6.0 h	72
3	$PhC(CH_3)_2OH$	1.2	rt, 15 h	81
4	$PhCH_2C(CH_3)_2OH$	1.2	rt, 6.0 h	81
5	1-Adamantanol	1.2	reflux, 15 h	83
6	1-Methylcyclopentanol	1.2	rt, 15 h	82
7	1-Methylcyclohexanol	1.5	reflux, 3.0 h	78
8[a]	L-(−)-Menthol	1.1	rt, 3.0 h	86
9[b]	*R*-(+)-Phenylethanol	1.1	rt, 1.0 h	93
10[c]	trans-2-Phenyl-1-cyclohexanol	1.1	rt, 3.0 h	85
(11	BnOH	1.1	rt, 1.0 h	98)

[a] $[\alpha]_D^{14} = +92.4$ (*c*1.22, C_6H_6). The corresponding ester was obtained with perfect inversion of stereochemistry by of S_N2 replacement. [b] $[\alpha]_D^{23} = +27.3$ (*c*1.22, EtOH). [c] 58% Yield Mitsunobu reaction.[11]

Thus, a new and efficient method for the preparation of carboxylic esters from various primary, bulky secondary and tertiary alcohols and carboxylic acids was established and the corresponding carboxylic acid esters were afforded in good to high yields by way of a new-type oxidation-reduction condensation using in situ formed alkoxydiphenylphosphines, DMBQ, and carboxylic acids. Alkoxyphosphines were prepared in situ from Ph_2PNMe_2 and primary or secondary alcohols, and primary, secondary or tertiary alkoxydiphenylphosphines were formed alternatively in situ by initially treating alcohols with ^{n}BuLi and then to add Ph_2PCl. In addition, the corresponding carboxylic acid alkyl esters were obtained with perfect inversion of stereochemistry by S_N2 replacement in the cases of using chiral secondary alcohols. Further study on this type of condensation reaction is now in progress.

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