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DIALKYL ACYLPHOSPHONATES: A NEW ACYLATING AGENT OF ALCOHOLS[1]

Mitsuo SEKINE, Akiko KUME, and Tsujiaki HATA*
Department of Life Chemistry, Tokyo Institute of Technology,
Nagatsuta, Midoriku, Yokohama 227, Japan

Summary: Diethyl benzoylphosphonate (1) underwent facile benzoylation of alcohols in the presence of DBU. Reactions of diols containing primary and secondary hydroxyl groups with 1 gave predominantly monobenzoates in which primary hydroxyl groups were highly selectively benzoylated. Related acylations were also described.

For various transformations of organic compounds, acylation of their functional groups is important as one of fundamental tools in organic synthesis. In the previous paper,[1] we have reported the benzoylation of various amines by means of dialkyl benzoylphosphonates. The facile nucleophilic cleavage of P-C bond is a characteristic feature of acylphosphonates, indicating their potential usefulness as acylating agents.[2] The reactions of acylphosphonates with alcohols have been reported independently in three papers up to date. Kadachnik[3] described that dimethyl benzoylphosphonate formed crystalline 1:1 addition products with simple aliphatic alcohols when they were mixted at room temperature. The adducts were converted in the presence of dry hydrogen chloride gas to carboxylic esters and dimethyl phosphonate in moderate yields (~78%). Sakurai[4] reported that acylphosphonates underwent slow acylation with a large excess amount of alcohols to give esters. Pudovic[5] reported the base-catalyzed acylation of alcohols with acylphosphonates in the presence of triethylamine.

In this paper, we wish to report a practical and useful method for acylation of alcohols by use of dialkyl acylphosphonates.

First, the benzoylation of phenethyl alcohol (2) by means of diethyl benzoylphosphonate (1) was examined. The reaction of 2 with one equiv. of 1 in ether or dioxane in the presence of p-TsOH·H_2O (cat.) under reflux for 4 h gave only a trace amount of phenethyl benzoate (3). Increasing the quantities of p-TsOH·H_2O did not affect the acylation. Next, the benzoylation of 2 with 1 was examined under basic conditions. We reported previously[1] that the acylation of 1 with amines was always accompanied with a byproduct of diethyl α-[(diethoxyphosphinyl)oxy]benzylphosphonate (4) which was formed by the successive reaction of 1 with diethyl phosphonate simultaneously formed. Therefore, two equiv. of 1 was used in the benzoylation of 2 in order to complete the reaction, whereupon

one equiv. of 1 served as a scavenger of diethyl phosphonate. When pyridine was employed as both the solvent and the base, no reaction took place at room temperature. However, after the mixture was refluxed for 2 h, the ester 3 was obtained in a poor yield of 23%. On the contrary, triethylamine was an effective base as reported by Pudovic.[5] When the reaction was prolonged in CH_2Cl_2 for 5 h, in the presence of the base, 3 was obtained in 91% yield. In this case, an equimolar amount of 4 was formed. In the above reaction, 4-(dimethylamino)pyridine (DMAP), known as a useful catalyst for acylations,[6] was ineffective. However, it was found that the use of 1,5-diazabicyclo[5,4,0]undec-5-ene (DBU) increased the rate of the acylation dramatically. When one equiv. of DBU was used in CH_2Cl_2, the acylation was completed within 10 min and 3 was obtained in 99% yield. Under these conditions, the formation of 4 was suppressed remarkably and only a trace of 4 was formed. Furthermore, the use of 0.1 equiv. of DBU gave 3 also in a high yield of 95%. It is noteworthy that this reaction proceeds effectively and stoichiometrically without the side reaction giving 4. These findings led us to examine the

$$R\overset{O}{\overset{\|}{C}}\text{-}P(OEt)_2 + R'OH \xrightarrow[CH_2Cl_2,\ r.t.]{DBU} R\overset{O}{\overset{\|}{C}}OR' + HP(OEt)_2$$

stoichiometric reaction of 1 with several kinds of alcohols. Consequently, primary alcohols gave the corresponding benzoates in high yields as shown in Table 2. The acylating ability of 1 decreased definitly in the order of primary > secondary ≫ tertiary. When 2-propanol was allowed to react with 1 in the presence of 0.1 equiv. of DBU, isopropyl benzoate was obtained in 52% yield. For the acylation of such a secondary alcohol, the use of two equiv. of 1 and one equiv. of DBU gave the benzoate in a better yield. In the case of t-butylalcohol no reaction took place at room temperature for 2 h. However, by addition of DMAP as a catalyst to the mixture, t-butyl benzoate was obtained in 57% yield after 48 h. The distinguished difference in reactivity of 1 between primary and secondary alcohols led us to study the selective benzoylation of diols having both primary and secondary hydroxyl groups.[7] These results are summarized in Table 3. In these reactions, 1.05 equiv. of 1 was employed. Table 3 implies that monobenzoylation proceeded predominantly over dibenzoylation and highly selectively at the primary hydroxyl group. The ratio of the primary ester to the secondary one was determined by 100 MHz NMR. Table 3 suggests that the formation of the dibenzoylated products might be mainly due to the slightly excess use of 1 since the yields of the dibenzoates were less than 8%. In order to improve the selectivity of acylation toward the primary and secondary hydroxyl groups, the substituent effect of alkyl ester residues of dialkyl benzoylphosphonates were examined. These results are summarized in Table 4. As a consequence, the selectivity could be enhanced by using diisopropyl benzoylphosphonate

Table 1. Benzoylation of 2 by use of 1[a)]

base (equiv.)	DMAP equiv.	solvent	temp.	time(h)	yield of 3 (%)
pyridine		pyridine	r.t.	16	no reaction
pyridine		pyridine	reflux	2	23
Et_3N 1.0		ether	reflux	3	55
Et_3N 1.0		CH_2Cl_2	r.t.	1	63
Et_3N 1.0	0.05	CH_2Cl_2	r.t.	1	61
Et_3N 1.0		CH_2Cl_2	r.t.	5	91
Et_3N 2.0	0.05	CH_2Cl_2	r.t.	5	98
DBU 1.0		CH_2Cl_2	r.t.	10 min	99
DBU 0.1		CH_2Cl_2	r.t.	30 min	95

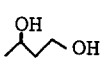
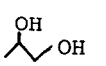
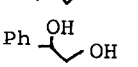
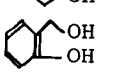
a) In these reactions, 1.6 mmol of 2 was allowed to react with 3.2 mmol of 1 in a solvent (10 ml).

Table 2. Benzoylation of alcohols by means of 1[a)]

alcohol	1 equiv.	DBU equiv.	DMAP equiv.	time(h)	yield of benzoate (%)
Ph~OH	1.0	0.1		0.5	93
~OH	1.0	0.1		0.5	85
>—OH	1.0	0.1		0.5	52
>—OH	2.0	1.0		0.5	80
—+—OH	2.0	1.0		2	0
—+—OH	3.0	1.0	0.05	48	57

a) In these reactions, 1.6 mmol of an alcohol was used.

Table 3. Selective benzoylation of diols by means of 1[a)]

diol	time(min)	yield(%) monobenzoate(prim./sec.)	yield(%) dibenzoate
	20	94 (88/12)	5
	20	86 (83/17)	8
	20	91 (82/18)	7
	20	96 (86/14)	0

a) In these reactions, 1.6 mmol of a diol was allowed to react with 1.68 mmol of (1.05 equiv.) of 1 in CH_2Cl_2 (10 ml).

to a ratio of 92:8. The use of more hindered dialkyl esters of benzoylphosphonates gave similar results. Finally, we studied the acylation of 2 by means of aliphatic dialkyl acylphosphonates. In these reactions, 1.0 equiv. of DBU was required. These results are summarized in Table 5.

In conclusion, the present reaction provides a new synthetic tool for acylation of hydroxyl groups which is applicable to the synthesis of complex molecules.

Table 4. Substituent effects of dialkyl benzoylphophonates in the benzoylation of 1,3-butanediol[a)]

PhC(O)P(O)(OR)$_2$ R	steric factor[8)]	time	yield (%) monobenzoate (prim./sec.)	yield (%) dibenzoate
Me	0.00	20 min	93 (88/12)	4
Et	-0.07	20 min	94 (88/12)	5
i-Pr	-0.47	16 h	95 (92/8)	5
i-Bu	-0.93	4 h	95 (92/8)	4
s-Bu	-1.13	4 d	76 (92/8)	1
Et_2CH	-1.98	4 d	67 (90/10)	2

a) In these reactions, 1.6 mmol of 1,3-butanediol was allowed to react with 1.68 mmol of a benzoylphosphonate in CH_2Cl_2 (10 ml) at room temperature.

Table 5. Acylation of 2 with aliphatic diethyl acylphosphonates[a)]

RC(O)P(O)(OEt)$_2$ R	DBU (equiv.)	time (h)	yield of ester (%)
Me	0.1	0.5	43
Et	0.1	0.5	16
i-Pr	0.1	24	13
Me	1.0	1.5	70
Et	1.0	10 min	70
i-Pr	1.0	10 min	81

a) In these reactions, 1.6 mmol of 2 was allowed to react with 1.68 mmol of an acylphosphonate in CH_2Cl_2 (10 ml) at room temperature.

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