The Regioselective *C*-Hydroxyalkylation of 1,3-Diphenyl-1,3-propanedione with Halo Alcohols, Involving Intramolecular Alcoholysis: the Synthesis of Oxoalkyl Esters†

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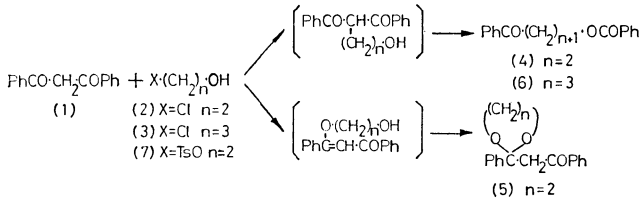
The reaction of 1,3-diphenyl-1,3-propanedione (**1**) with 2-chloroethanol (**2**) or 3-chloro-1-propanol (**3**) was performed in the presence of potassium carbonate and sodium iodide as an improved procedure for regioselective *C*-hydroxyalkylation, involving intramolecular alcoholysis; the effects of the solvents, the temperature, and the amounts of potassium carbonate and sodium iodide were also investigated. The reaction with **2** afforded 3-benzoylpropyl benzoate (**4**) (*ca.* 70% yield), together with 2-benzoylmethyl-2-phenyl-1,3-dioxolane (**5**) (*ca.* 15% yield). The reaction with **3**, on the other hand, gave 4-benzoylbutyl benzoate (92—94% yield); the corresponding 1,3-dioxane derivative was detected only in a trace. Moreover, the reaction of **1** with 2-hydroxyethyl tosylate was similarly performed, but the yields of both **4** and **5** were unexpectedly low.

The *C*-hydroxyalkylation of 1,3-dicarbonyl compounds was first demonstrated by the reaction of 2,4-pentanedionatosodium with ethylene oxide in ethanol at 0 °C; this gave 3-(2-hydroxyethyl)-2,4-pentanedione (20% yield).[1] On the other hand, the synthesis of methyl ketones has been accomplished by the *C*-alkylation of 2,4-pentanedione with benzyl halides in ethanol in the presence of potassium carbonate, involving simultaneous ethanolysis.[2] Based on these facts, a novel synthetic route to 4-oxoalkanols has been established ; *i.e.*, the reaction of 2,4-pentanedione with 1,2-epoxyoctane in the presence of potassium carbonate and sodium iodide in ethanol under reflux gave a 28% yield of 5-hydroxy-2-undecanone.[3] There have recently been reported the syntheses of some eleven-membered cyclic ketolactones by the *C*-alkylation of 2-substituted dimedones with 4-chloro-2-butenyl acetate in the presence of potassium *t*-butoxide and potassium iodide, followed by the hydrolysis of the esters and intramolecular alcoholysis.[4] On the other hand, we recently demonstrated that the sodium iodide-catalyzed reactions of ethylene carbonate with some active methylene compounds, which are assumed to proceed *via* 2-iodoethanol, afforded the corresponding 4-oxoalkyl esters as predominant products.[5] In view of the mechanism of these reactions, therefore, we set out to develop an improved procedure for a more-highly regioselective and effective *C*-hydroxyaltion of 1,3-dicarbonyl compounds involving intramolecular alcoholysis by the use of 1,3-diphenyl-1,3-propanedione (**1**) and 2-chloroethanol (**2**) or 3-chloro-1-propanol (**3**); we wish now to report our results.

Results and Discussion

Although ethanol has usually been used as a solvent in the alkylation of 1,3-dicarbonyl compounds, we examined a series of solvents for the reaction; a mixture of **1** (10 mmol), **2** (45 mmol), potassium carbonate (10 mmol), and sodium iodide (13 mmol) in a solvent



Scheme 1.

Table 1. Examination of solvent effect on the reaction of 1,3-diphenyl-1,3-propanedione (**1**) with 2-chloroethanol (**2**)[a]

Entry	Solvent	Temp (°C)	Yield of product		Recovery of
			4 (%)	**5** (%)	**1** (%)
1	Hexane	80—90	6	—	74
2	Benzene	75—85	trace	—	86
3	Chloroform	80—90	6	—	73
4	Diethyl ether	80—90	—	—	89
5	1,4-Dioxane	80—90	8	2	82
6	Ethyl acetate	85—95	41	trace	53
7	Acetonitrile	70—85	40	trace	44
8	1,2-Dimethoxyethane	85—95	59	trace	26
9	Acetone	80—90	50	trace	38
10	*N*,*N*-Dimethylformamide	80—90	39	7	44
11	Dimethyl sulfoxide	80—90	28	14	22
12	Hexamethylphosphoric triamide	80—90	29	47	20
13[b]	*ditto*	80—90	8	48	34

a) All the reactions were performed by the use of **1** (10 mmol), **2** (45 mmol), K_2CO_3 (10 mmol), and NaI (13 mmol) in a solvent (50 ml). b) This reaction was performed without NaI.

was stirred for 2 days in an autoclave under the conditions given in Table 1. As expected, the products obtained were the same as those formed in the reaction of ethylene carbonate;[5] we obtained small amounts of acetophenone and 2-chloroethyl benzoate in addi-

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tion to the main products of the corresponding 4-oxoalkyl ester and ethylene acetal derivative, namely, 3-benzoylpropyl benzoate (**4**) and 2-benzoylmethyl-2-phenyl-1,3-dioxolane (**5**). When hexane, benzene, chloroform, diethyl ether, and 1,4-dioxane were used, scarcely none of the benzoate, **4**, was obtained, and the starting material, **1**, was recovered in the yields shown in the table. In contrast with these, ethyl acetate, acetonitrile, 1,2-dimethoxyethane, and acetone were effective for the coupling reaction, giving **4** in 41, 40, 59, and 50% yields respectively, together with traces of **5**. On the increasing polarity of solvents in turn from *N,N*-dimethylformamide up to dimethyl sulfoxide and hexamethylphosphoric triamide, however, we obtained **4** (39, 28, and 29% yields respectively) and **5** (7, 14, and 47% yields respectively), in addition to the recoveries of **1** seen in the table. The last entry clearly demonstrated the importance of the addition of sodium iodide to the reaction system, resulting in the formation of **4** in only an 8% yield.

In order to check if an elevated temperature brings about any improvement in the reaction, we performed some of the reactions in acetone, 1,2-dimethoxyethane, acetonitrile, and ethyl acetate at 150 °C. However, no improved results were obtained, giving **4** (49, 28, 21, and 27% yields respectively) and **5** (trace, trace, 9% yield, and trace respectively)(see Table 2). Judging from the yield of **4** and the easy of handling the solvents, it was concluded that it is more advantageous to perform the reaction at around 90 °C in acetone.

Subsequently, the molar proportions of **2** and potassium carbonate in the reaction were examined; the conditions used and the results thus obtained are summarized in Table 3. The results led us to the conclusion that the reaction gives the desired compound, **4**, in 60—71% yields, provided the proportions of **2** and potassium carbonate were 3.75 : 1—1.5 : 1.

Table 2. The reaction of **1** with **2** in some solvents at an elevated temperature[a]

Entry	Solvent	Yield of product **4** (%)	Yield of product **5** (%)	Recovery of **1** (%)
1	Acetone	49	trace	41
2	1,2-Dimethoxyethane	28	trace	51
3	Acetonitrile	21	9	69
4	Ethyl acetate	27	trace	69

a) All the reactions were performed by the use of **1** (2 mmol), **2** (15 mmol), K_2CO_3 (2 mmol), and NaI (2.7 mmol) in a solvent (20 ml) in an autoclave at 150 °C for 1 day.

Table 3. Examination on effect of the amounts of **2** and K_2CO_3 in the reaction in acetone[a]

Entry	**2** (mmol)	K_2CO_3 (mmol)	Yield of product **4** (%)	Yield of product **5** (%)	Recovery of **1** (%)
1	75	2	—	—	99
2	15	2	18	6	74
3[b]	15	2	29	7	64
4	15	6	69	11	18
5	7.5	2	74	14	12
6	6	2	69	16	14
7	4.5	2	67	14	18
8	3	2	65	13	21
9	6	4	71	17	11
10	3	4	41	10	42
11[c]	6	4	33	3	55

a) All the reactions were performed by the use of **1** (2 mmol) and NaI (2.7 mmol) in acetone (20 ml) at 90 °C for 2 days. b) This reaction was performed for 6 days. c) This reaction was performed in ethyl acetate for the sake of comparison.

The utilization of an excess amount of **2** (75 mmol) in relation to potassium carbonate (2 mmol), however, gave no product at all. This may arise from the predominant reaction of **2** with potassium carbonate, by which the surface of potassium carbonate was covered with the resultant potassium chloride; this may make the potassium carbonate ineffective in the objective reaction. As may be seen from the third entry, the elongation of the reaction time was not fruitful; a 4 day-elongation improved the yield by only 11%. For reference, the reaction in ethyl acetate was checked by the use of 1.5 : 1 **2**–potassium carbonate as is shown in the last entry; this gave **4** (33% yield) in parallel with the results shown in Table 2.

Consequently, the reaction system for a highly regioselective *C*-hydroxyalkylation has been furhter investigated in terms of the reaction involving **3** in

Table 4. Reactions of 1,3-diphenyl-1,3-propanedione (**1**) and 3-chloro-1-propanol (**3**) in the presence of potassium carbonate and sodium iodide[a]

Entry	Solvent	**3** (mmol)	Temp (°C)	Period (day[b])	Yield of product **6** (%)	Yield of recovered **1** (%)
1	Acetone	2.3	reflux	2	59	40
2	Acetone	4.6	reflux	2	68	26
3	Acetone	12	reflux	2	71	19
4	Acetone	12	reflux	4	94	trace
5	Acetone	12	90	2	92	—
6	Acetone	12	150	15 h	79	20
7	1,2-Dimethoxyethane	12	reflux	2	80	—

a) All the reactions were performed by the use of **1** (2 mmol), K_2CO_3 (2 mmol), and NaI (2.7 mmol) in a solvent (20 ml). b) Unless otherwise noted.

Table 5. Reactions of 1,3-diphenyl-1,3-propanedione (**1**) with 2-hydroxyethyl tosylate (**7**) in the presence of potassium carbonate and sodium iodide in acetone[a)]

Entry	**7** (mmol)	K_2CO_3 (mmol)	Temp (°C)	Yield of product **4** (%)	Yield of product **5** (%)	Recovery of **1** (%)
1	2.1	4	reflux	10	3	71
2	4.2	4	reflux	21	4	63
3[b)]	2.1	4	reflux	2	20	65
4	2.1	4	90	41	6	41
5	4.2	4	90	35	11	42
6	2.1	8	90	14	5	68

a) All the reaction were performed by the use of **1** (2 mmol) and NaI (2.7 mmol) in acetone (20 ml) for 2 days. b) This reaction was performed without NaI.

place of **2** under the conditions summarized in Table 4. In this case, the reaction was almost regiospecifically induced on the methylene carbon of **1** to give a 92% yield of 4-benzoylbutyl benzoate (**6**) as is shown in the fifth entry. In addition, it should be noticed that this reaction could also be performed in acetone under reflux, giving **6** in a 94% yield together with a trace amount of a by-product which was barely confirmed as 2-benzoylmethyl-2-phenyl-1,3-dioxane by PMR spectroscopy. The sixth entry shows that an elevated temperature is also inadequate for this reaction. Moreover, the reaction in 1,2-dimethoxyethane (Entry 7) also gave **6** in an 80% yield. The mechanism of these reactions is conceivably similar to that proposed in the sodium iodide-catalyzed reaction of ethylene carbonate with **1**[5)] as follows: the chloro-substituent of **2** or **3** may first be replaced by the iodide ion to give the corresponding iodoalkanols, which are then subjected to the coupling reaction with **1** in the presence of potassium carbonate to give the corresponding intermediary 3,3- or 4,4-dibenzoyl-1-alkanol. Subsequently, the resulting dibenzoylalkanols may undergo intramolecular alcoholysis to give **4** or **6** as is depicted in Scheme 1.

Finally, we performed the reaction of 2-hydroxyethyl tosylate (**7**), in place of **2**, with **1** in order to compare it with the above reactions, since **7** seems to behave similarly to **2**, judging from the nucleofugacity of the tosyloxy function. The conditions and the results thus obtained are summarized in Table 5. We observed a similar trend in the yields of **4**, although they were inferior to those obtained in the reactions of **2** with **1**.

Experimental

The PMR spectra were recorded on a Varian T-60 instrument in deuteriochloroform with tetramethylsilane (TMS) as the internal standard. The IR spectra were recorded on a Hitachi 285 spectrophotometer. The column chromatographic separations were performed by the use of Wakogel C-300 (Wako Pure Chemicals, Japan), and TLC, by the use of Merck silica gel 60 F_{254} precoated plates (thickness, 0.25 mm); spots were detected with a UV lamp (S. L. Light, Tokyo Machinery Co., Ltd. 253.7 and 365 nm).

Materials. We purchased commercially 2-chloroethanol (**2**) and 3-chloro-1-propanol (**3**) (Aldrich Chemical Co., Inc.). 1,3-Diphenyl-1,3-propanedione (**1**) was prepared from 1,3-diphenyl-2-propene-1-one according to the method of Allen *et al.*;[6)] mp 77—78 °C (from MeOH) (lit,[6)] 77—78 °C). 2-Hydroxyethyl tosylate (**7**) was prepared according to the method of Rompuy *et al.*;[7)] the PMR spectrum of the product was identical with that of an authetic specimen.

*Examination of the Solvent Effect on the Reaction of **1** with **2**.* A mixture of **1** (2.24 g, 10 mmol), **2** (3 ml, 45 mmol), potassium carbonate (1.40 g, 10 mmol), and sodium iodide (2.0 g, 13 mmol) in a solvent (50 ml) was stirred in an autoclave at 90 °C for 2 days. The resulting mixture was evaporated *in vacuo*, and the residue was triturated with chloroform (50 ml). The supernatant was filtered and evaporated. When DMSO, DMF, or HMPT was used as the solvent, the resulting mixture was made weakly acidific by the use of 1 M (=1 mol dm^{-3}) hydrochloric acid and then extracted with chloroform (20 ml×3). The extracts were combined and evaporated, after drying over anhydrous magnesium sulfate. The syrups thus obtained were subjected to chromatographic separation on a column of silica gel by the use of 1 : 1 v/v benzene-cyclohexane to give 1,3-diphenyl-1,3-propanedione (**1**), 3-benzoylpropyl benzoate (**4**), and 2-benzoylmethyl-2-phenyl-1,3-dioxolane (**5**) in turn. The PMR spectra of these products were superimposable with those of the corresponding authentic specimen.[5)] The results thus obtained are summarized in Table 1.

The Reaction at 150 °C. The products were similarly chromatographed on a column of the silica gel after stirring a mixture of **1** (448 mg, 2 mmol), **2** (1 ml, 15 mmol), K_2CO_3 (280 mg, 2 mmol), and NaI (400 mg, 2.7 mmol) in a solvent at 150 °C for 1 day. The results thus obtained are summarized in Table 2.

*Examination of Appropriate Amounts of **2** and K_2CO_3 in the Reaction.* In acetone, a mixture of the agents as described above with various proportions of **2** and K_2CO_3 was treated in the same way as above; the results thus obtained are summarized in Table 3.

*The Reactions of **1** with **3** in the Presence of K_2CO_3 and NaI.* A mixture of **1** (448 mg, 2 mmol), **3** (2.3—12 mmol), K_2CO_3 (280 mg, 2 mmol), and NaI (400 mg, 2.7 mmol) in a solvent (20 ml) was stirred under reflux, at 90 °C or at 150 °C for 15 h, 2 days, or 4 days in an autoclave. The purification of the products thus obtained was performed in the same way as described above to give **1** and 4-benzoylbutyl benzoate (**6**); IR (NaCl): 1720, 1680, 1270, and 1110 cm^{-1}; PMR ($CDCl_3$-TMS) : δ1.7—2.1 (4H, m, C-CH_2CH_2-C), 3.03* (2H, PhCO-CH_2-), 4.36* (2H, O-CH_2-), and 7.2—8.2 (10 H, m, aromatic). The *J*-values with an asterisk could not be determined by the first-order analysis because of virtual coupling. Found: C, 76.48; H, 6.39%. Calcd for $C_{18}H_{18}O_3$: C, 76.57; H, 6.43%. The results thus obtained are summarized in Table 4.

*The Reaction of **1** with **7** in the Presence of K_2CO_3 and NaI.* A mixture of **1** (448 mg, 2 mmol), **7** (2.1 or 4.2 mmol), K_2CO_3 (4 or 8 mmol), and NaI (400 mg, 2.7 mmol) in acetone (20 ml) was treated under reflux or at 90 °C in an autoclave with stirring for 2 days; the solvent was then evaporated after the addition of some water to dissolve the insoluble crystals. The resulting aqueous residue was weakly acidified with 1 M hydrochloric acid, followed by extraction with chloroform (10 ml×3). After the organic layer had been dried over anhydrous sodium sulfate, the filtrate was evaporated; the residue was subjected to chromatographic separation on a column of silica gel. The results thus obtained are summarized in Table 5.

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