Pergamon

Tetrahedron Letters 40 (1999) 7795–7798

TETRAHEDRON
LETTERS

Mild Air-Oxidation of 1,3-Dicarbonyl Compounds with Cesium Salts: Novel α-Hydroxylation Accompanied by Partial Hydrolysis of Malonate Derivatives

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Received 30 April 1999; revised 16 August 1999; accepted 20 August 1999

Abstract: 1,3-Dicarbonyl compounds (**1**) were efficiently oxygenated at the α-position with cesium salts, such as CsF or Cs_2CO_3 (0.1 Meq) in DMF at room temperature. Reaction of malonate derivatives (**1a, b**) with excess amount (2 Meq) of Cs_2CO_3 gave α-hydroxylmonoester (**3**) formed by oxygenation and partial hydrolysis, which was decarboxylated to a lactic acid derivative (**5**). © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: carbonyl compounds; cesium and compounds; hydrolysis; oxidation

A number of methods for oxygenation of α-position to carbonyl are known.[1] The oxidizing reagents commonly used are heavy-metal salts [*e.g.*, $Pb(OAc)_4$, $Hg(OAc)_2$], molecular oxygen combined with strong bases (*e.g.*, *t*-BuOK, NaH), or other oxidants [*e.g.*, sulfonyloxaziridines, MoOPH, $PhI(OAc)_2$]. Several problems arise with use of these reagents, in that some of them are environmentally toxic or influence other labile functional groups in the molecule. Recently we reported some reactions with cesium fluoride (CsF) as a base, attributable to its strong ability to form hydrogen bonds.[2,3] In this paper, we report mild air-oxidation of 1,3-dicarbonyl compounds with cesium salts as easily handling and environmentally benign reagents.

Air-oxidation of diethyl 2-benzylmalonate (**1a**) with cesium salts (2 Meq.) was examined at room temperature.[4] The solvent used was *N,N*-dimethylformamide (DMF), and with other solvents ($CHCl_3$, toluene) the reaction did not proceed effectively. The major product of the reaction with CsF was expected to be a 2-hydroxy compound (**2a**) (Table 1, entry 1) identical to the reported compound.[5] However, the major product of the reaction with cesium carbonate (Cs_2CO_3) (Table 1, entry 2) was not **2a**, but an acidic compound. The ^{1}H-NMR spectrum indicated that the number of ethyl protons was reduced to half compared to **2a**. Further spectral data and elemental analysis suggested that this unexpected compound was an oxygenated and partially hydrolyzed ester (**3a**).[6] With other alkali bases, this air-oxidation did not proceed efficiently concurrent with the formation of a half-ester (**4**) (Table 1, entries 3-6). Additionally, the reaction of **1a** with Cs_2CO_3 in EtOH gave no oxidized products (**2a** or **3a**), only half-ester (**4**) exclusively.

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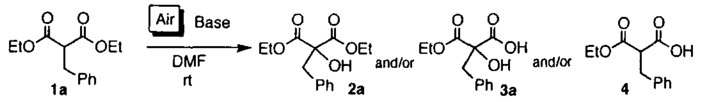
0040-4039/99/$ - see front matter
PII: S0040-4039(99)01618-4

Table 1. Air-Oxidation of Diethyl 2-Benzylmalonate (1a); Effect of Base



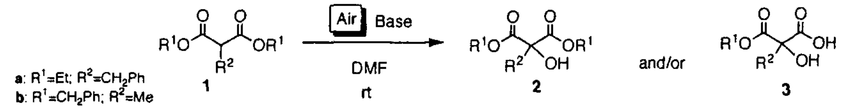
Entry	Base (2 Meq.)	Time	Products ratio[a]			
			2a	**3a**	**4**	**1a** (recov.)
1	CsF	31 h	$\boxed{99}$	0	0	1
2	Cs_2CO_3	30 h	25	$\boxed{75}$	0	trace
3	K_2CO_3	30 h	7	25	2	66
4	KF	9 d	0	0	0	100
5	NaH	30 h	trace	11	10	79
6[b]	KOH	30 h	0	~30	~15	~9

[a] The combined yields of the products were essentially quantitative, and the ratio was estimated by ^{1}H-NMR.

[b] Unidentified compound was formed (*ca.* 46%).

Although partial hydrolysis of aryl diesters with Cs_2CO_3 under non-aqueous conditions is known,[7] present findings suggest a possibility of controlling oxygenation and/or hydrolysis of malonate derivatives. We next examined the effect of molar ratio of these cesium salts on air-oxidation (Table 2).

Table 2. Air-Oxidation of Malonates (1); Effect of Molar Ratio



Entry	Substrate	Base	(Meq.)	Time (h)	Products ratio[a]		
					2	**3**	**1** (recov.)
1	**1a**	CsF	(2.0)	31	$\boxed{99}$	0	1
2[b]	**1a**		(0.1)	30	23	0	77
3	**1a**	Cs_2CO_3	(2.0)	30	25	$\boxed{75}$	trace
4	**1a**		(1.0)	30	62	38	trace
5	**1a**		(0.5)	33	74	26	trace
6	**1a**		(0.1)	30	$\boxed{73}$	trace	27
7	**1b**	CsF	(2.0)	4[c]	$\boxed{92}$	5	3
8	**1b**		(0.1)	30	57	0	43
9	**1b**	Cs_2CO_3	(2.0)	30	0	$\boxed{100}$	0
10	**1b**		(0.1)	30	$\boxed{73}$	3	24

[a] The combined yields of the products were essentially quantitative, and the ratio was estimated by ^{1}H-NMR.

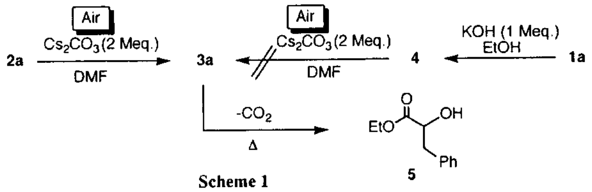
[b] Similar result was obtained at higher temperature (50 °C, 4 h). (**2a** : **3a** : **1a** = 18 : 82 : 0)

[c] Slightly increased **3b** was obtained on prolonged reaction (34 h). (**2b** : **3b** : **1b** = 86 : 14 : 0)

In the case of CsF, a catalytic amount of reagent led to low yield of α-hydroxy product (**2a**) (Table 2, entry 2). However, with Cs_2CO_3, less reagent gave a lower yield of half ester (**3a**) and a higher yield of α-hydroxy product (**2a**) (Table 2, entries 3-6). Similar results dependent upon reagents and molar ratio were also obtained in another malonate derivative (**1b**)[8] (Table 2, entries 7-10). These findings showed that oxygenation at the α-position of the carbonyl group occurred sufficiently with a catalytic amount of Cs_2CO_3, and an excess amount of carbonate is required for partial hydrolysis. Reaction temperature and time with Cs_2CO_3 did not affect the distribution of oxygenated products. Thus, it is noteworthy that the controlling factor for the distribution of products is only the quantity of Cs_2CO_3.

To clarify the correlation between these products, α-hydroxy product (**2a**) was hydrolyzed under the original condition [Cs_2CO_3 (2 Meq.) / DMF][9] to afford half-ester (**3a**) quantitatively. However, oxidation of the half-ester (**4**), prepared from the diester (**1a**) by partial hydrolysis with KOH (1 Meq.) / EtOH, was not oxidized by Cs_2CO_3 (Scheme 1). These findings suggest that the supposed intermediate to α-hydroxy half-ester (**3a**) is not the half-ester (**4**) but α-hydroxy product (**2a**); *i.e.* the initial step is oxygenation[10] at the α-position, followed by partial hydrolysis.

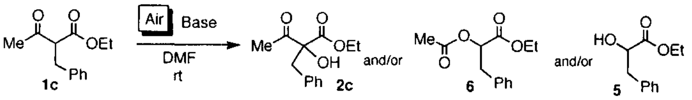
Furthermore, as the hydroxylated half-ester (**3a**) had the potential in its structure to lead synthetically useful α-hydroxy acid, decarboxylation of **3a** was attempted.[11] Heating at 170 °C under reduced pressure (15 mmHg) for 3 h afforded desired lactic acid derivative (**5**) in 93% conversion yield (60% recovery of **3a**),[12] which was identical to the side product obtained by air-oxidation of the acetoacetate (**1c**) described later (Scheme 1).



Scheme 1

To examine further nature of this air-oxidation with cesium salts, the reaction of ethyl 2-benzylacetoacetate (**1c**) was studied. Table 3 lists the results of **1c** reacted with varying quantities of CsF and Cs_2CO_3. When 2 Meq. of CsF was used (Table 3, entry 1) two products were formed. The minor product was the 2-hydroxy compound (**2c**), and the major product was also oxygenated, but without a hydroxy group by ^{1}H-NMR. Recently, Davis *et al.*[5] reported asymmetric oxidation of the enolate of **1c** using (camphorylsulfonyl)oxaziridines, in which they obtained acetate (**6**) and lactate (**5**) *via* Baeyer-Villiger type rearrangement other than the desired 2-hydroxy compound (**2c**). The major product was identified with rearranged product (**6**).[5] With a catalytic amount of CsF the reaction afforded only a moderate yield of hydroxy compound (**2c**) (Table 3, entry 2). Oxidation with Cs_2CO_3 (2 Meq.) resulted in no formation of **2c**, only a rearranged product (**6**) accompanied by a lactate derivative (**5**)[5] assumed to come from **6** (Table 3, entry 3). Interestingly, with a catalytic amount of Cs_2CO_3, the reaction proceeded cleanly to give 2-hydroxy compound (**2c**) in good yield (Table 3, entry 4).

Table 3. Air-Oxidation of Ethyl 2-Benzylacetoacetate (**1c**); Effect of Molar Ratio



Entry	Base	(Meq.)	Time	Products ratio[a]			
				2c	6	5	1c (recov.)
1	CsF	(2.0)	31 h	30	69	0	1
2		(0.1)	3 d	50	0	0	50
3	Cs_2CO_3	(2.0)	5 d	0	24[b]	15[b]	trace
4		(0.1)	65 h	$\boxed{75}$	0	0	25

[a] The combined yields of the products were essentially quantitative, and the ratio was estimated by ^{1}H-NMR.
[b] Isolated yield.

Finally, we examined the oxidation of cyclic 1,3-dicarbonyl compound, 2-acetyl-1-tetralone with cesium salts. The resulting reaction mixture was an inseparable complex mixture even with KF, the reagent for α-hydroxylation of cyclic β-keto-esters.[13]

In summary, we found novel oxidation of 1,3-dicarbonyl compounds with cesium salts. The ratio of oxidation products of malonates (**1a, b**) varied depending on the quantity of Cs_2CO_3. The present findings suggest that three compounds, **2**, **3**, and **4**, were selectively available from **1** by choice of reagent or amount of reagent. Alternatively, the oxidation of acetoacetate (**1c**) with Cs_2CO_3 proceeded to yield 2-hydroxy compound (**2c**) exclusively, in higher yield than previously reported.[5] Current studies are aimed at broadening the scope and efficiency of this air-oxidation with cesium salts, as well as mechanistic consideration.

References and Notes

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8. a) Preparation of **1b**: Kametani, T.; Taub, W.; Ginsburg, D., *Bull. Chem. Soc. Jpn.*, **1958**, *31*, 857-859. b) Dibenzyl 2-hydroxy-2-methylmalonate (**2b**): A colorless oil. HRFABMS *m/z*: Calcd for $C_{18}H_{19}O_5$: 315.1232 (M^++1). Found: 315.1231. IR ν_{max} (neat) cm^{-1}: 3489 (OH), 1741 (C=O). ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.67 (3H, s, CCH_3), 3.79 (1H, s, OH), 5.19 (4H, s, 2 x CH_2Ph), 7.23-7.34 (10H, m, ArH). Benzyl hydrogen 2-hydroxy-2-methylmalonate (**3b**): A colorless oil. HRFABMS *m/z*: Calcd for $C_{11}H_{13}O_5$: 225.0763 (M^++1). Found: 225.0754. IR ν_{max} (neat) cm^{-1}: 3448 (OH), 1736 (C=O). ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.70 (3H, s, CCH_3), 2.51 (2H, br s, 2 x OH), 5.25 (1H, d, *J* = 12.2 Hz, C-C$\underline{\mathrm{Ha}}$CHb-Ph), 5.28 (1H, d, *J* = 12.2 Hz, C-CHaC$\underline{\mathrm{Hb}}$-Ph), 7.32-7.40 (5H, m, ArH).
9. Alternatively the half-ester (**3a**) was given by treatment with KOH (1 Meq.)/EtOH.
10. When the reaction was carried out under oxygen atmosphere, a remarkable acceleration of oxygenation was observed. On the other hand, under strictly deoxygenated condition (argon gas bubbling) the reaction was completely inhibited.
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