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

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Abstract: 1,3-Dicarbonyl compounds (1) were efficiently oxygenated at the  $\alpha$ -position with cesium salts, such as CsF or Cs<sub>2</sub>CO<sub>3</sub> (0.1 Meq) in DMF at room temperature. Reaction of malonate derivatives (1a, b) with excess amount (2 Meq) of Cs<sub>2</sub>CO<sub>3</sub> gave  $\alpha$ -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  $\alpha$ -position to carbonyl are known.<sup>1</sup> 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.<sup>2, 3</sup> 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.<sup>4</sup> The solvent used was *N*,*N*-dimethylformamide (DMF), and with other solvents (CHCl<sub>3</sub>, 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.<sup>5</sup> However, the major product of the reaction with cesium carbonate (Cs<sub>2</sub>CO<sub>3</sub>) (Table 1, entry 2) was not 2a, but an acidic compound. The <sup>1</sup>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).<sup>6</sup> 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<sub>2</sub>CO<sub>3</sub> in EtOH gave no oxidized products (2a or 3a), only half-ester (4) exclusively.

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EtO 1a	OEt DMF Ph rt	-→ EtO´		EtC and/or	о о он он Рћ за	and/or Et			
Entry	Base (2 Meg.)			Products ratio <sup>a</sup>					
	Dase (2 Meq.)	1 me		2a	<u> 3a</u>	4	la (recov.)		
1	CsF	31 h		99	0	0	1		
2	Cs <sub>2</sub> CO <sub>3</sub>	30 h		25	75	0	trace		
3	K <sub>2</sub> CO <sub>3</sub>	30 h		7	25	2	66		
4	KF	9 d		0	0	0	100		
5	NaH	30 h		trace	11	10	79		
6 <sup>b</sup>	КОН	30 h		0	~30	~15	~9		

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

<sup>a</sup> The combined yields of the products were essentially quantitative, and the ratio was estimated by <sup>1</sup>H-NMR.
<sup>b</sup> Unidentified compound was formed (ca. 46%).

Although partial hydrolysis of aryl diesters with Cs<sub>2</sub>CO<sub>3</sub> under non-aqueous conditions is known,<sup>7</sup> 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
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	a: R¹=Et; Rª b: R¹=CH₂P	²=CH₂Ph 'h; R²=Me	0 R <sup>1</sup> 0 F	OR <sup>1</sup>	Ai	DMF	ر الر R <sup>1</sup> O	2 2 2 2	)R <sup>1</sup>	and/or	ر R <sup>1</sup> O F	) - ОН -2 ОН 3			
	C. hataata	D	() <b>(</b> ) ( )	T: (1)		Products r	atio <sup>a</sup>			_			Pr	oducts r	atio <sup>a</sup>
Entry	Substrate	Base	(Meq.)	Time (h)	2	3	1 (recov.)	Entry	Substrat	e Base	(Meq.)	Time (h)	2	3	1 (recov.)
1	la	CsF	(2.0)	31	99	0	1	7	1b	CsF	(2.0)	4 <sup>c</sup>	92	5	3
2 <sup>6</sup>	1a		(0.1)	30	23	0	77	8	1b		(0.1)	30	57	0	43
3	1a	Cs <sub>2</sub> CO <sub>3</sub>	(2.0)	30	25	75	trace	9	1b	Cs <sub>2</sub> CO	3 (2.0)	30	0	100	0
4	1a		(1.0)	30	62	38	trace	10	16		(0.1)	30	73	3	24
5	1a		(0.5)	33	74	26	trace								
6	1a	_	(0.1)	30	73	trace	27	<sup>b</sup> Sin (2a	nilar result 1 : 3a : 1a :	was obta = 18 : 82 :	ned at hi 0)	gher tempera	ature (50 °	'C. 4 h).	

<sup>a</sup> The combined yields of the products were essentially quantitative, and the ratio was estimated by <sup>1</sup>H-NMR. <sup>c</sup> 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  $\alpha$ -hydroxy product (**2a**) (Table 2, entry 2). However, with Cs<sub>2</sub>CO<sub>3</sub>, less reagent gave a lower yield of half ester (**3a**) and a higher yield of  $\alpha$ -hydroxy product (**2a**) (Table 2, entries 3-6). Similar results dependent upon reagents and molar ratio were also obtained in another malonate derivative (**1b**)<sup>8</sup> (Table 2, entries 7-10). These findings showed that oxygenation at the  $\alpha$ -position of the carbonyl group occurred sufficiently with a catalytic amount of Cs<sub>2</sub>CO<sub>3</sub>, and an excess amount of carbonate is required for partial hydrolysis. Reaction temperature and time with Cs<sub>2</sub>CO<sub>3</sub> 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<sub>2</sub>CO<sub>3</sub>.

To clarify the correlation between these products,  $\alpha$ -hydroxy product (2a) was hydrolyzed under the original condition [Cs<sub>2</sub>CO<sub>3</sub> (2 Meq.) / DMF]<sup>9</sup> 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<sub>2</sub>CO<sub>3</sub> (Scheme 1). These findings suggest that the supposed intermediate to  $\alpha$ -hydroxy half-ester (3a) is not the half-ester (4) but  $\alpha$ -hydroxy product (2a); *i.e.* the initial step is oxygenation<sup>10</sup> at the  $\alpha$ -position, followed by partial hydrolysis.

Furthermore, as the hydroxylated half-ester (3a) had the potential in its structure to lead synthetically useful  $\alpha$ -hydroxy acid, decarboxylation of 3a was attempted.<sup>11</sup> 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),<sup>12</sup> which was identical to the side product obtained by air-oxidation of the acetoacetate (1c) described later (Scheme 1).



To examine further nature of this air-oxidation with cesium salts, the reaction of ethyl 2benzylacetoacetate (1c) was studied. Table 3 lists the results of 1c reacted with varying quantities of CsF and Cs<sub>2</sub>CO<sub>3</sub>. 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 <sup>1</sup>H-NMR. Recently, Davis *et al.*<sup>5</sup> 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).<sup>5</sup> With a catalytic amount of CsF the reaction afforded only a moderate yield of hydroxy compound (2c) (Table 3, entry 2). Oxidation with Cs<sub>2</sub>CO<sub>3</sub> (2 Meq.) resulted in no formation of 2c, only a rearranged product (6) accompanied by a lactate derivative (5)<sup>5</sup> assumed to come from 6 (Table 3, entry 3). Interestingly, with a catalytic amount of Cs<sub>2</sub>CO<sub>3</sub>, 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

Me 1c	OEt Ai	DMF rt		t Me and/or (		Et ⊢ and/or				
Entry	Basa	(Meq.)	Time		Products ratio <sup>a</sup>					
y	Dase			2c	6	5	lc (recov.)			
1	CsF	(2.0)	31 h	30	69	0	1			
2		(0.1)	3 d	50	0	0	50			
3	Cs <sub>2</sub> CO <sub>3</sub>	(2.0)	5 d	0	24 <sup>b</sup>	15 <sup>6</sup>	trace			
4		(0.1)	65 h	75	0	0	25			

<sup>a</sup> The combined yields of the products were essentially quantitative, and the ratio was estimated by <sup>1</sup>H-NMR. <sup>b</sup> 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  $\alpha$ -hydroxylation of cyclic  $\beta$ -keto-esters.<sup>13</sup>

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.<sup>5</sup> 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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- 4. General procedure for air-oxidation of 1,3-dicarbonyl compounds: a solution of 1,3-dicarbonyl compound (1) (1 mmol) in DMF (2.5 mL/1mmol of 1) was added to the base (0.1-2 mmol), and the whole was stirred at room temperature. The reaction mixture was diluted with water (20 mL), acidified with 10%HCl aq., and extracted with AcOEt (3 x 20 mL). The organic layer was washed with water (5 x 10 mL) and brine (15 mL), dried over MgSO4 and evaporated to dryness *in vacuo*.
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- Ethyl hydrogen 2-benzyl-2-hydroxymalonate (3a): Colorless prisms, mp 63-64 <sup>o</sup>C (recryttallized from ether-pentane). Anal. Calcd for C<sub>12</sub>H<sub>14</sub>O<sub>5</sub>: C, 60.50; H, 5.92. Found: C, 60.64; H, 5.89. IR ν<sub>max</sub> (Nujol) cm<sup>-1</sup>: 3387 (OH), 1756 and 1735 (C=O). <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>) & 1.30 (3H, t, J = 7.1 Hz, CH<sub>2</sub>CH<sub>3</sub>), 3.34 (1H, d, J = 14.0 Hz, C-CHaCHb-Ph), 3.38 (1H, d, J = 14.0 Hz, C-CHaCHb-Ph), 4.27 (2H, q, J = 7.1 Hz, OCH<sub>2</sub>CH<sub>3</sub>), 4.74 (2H, broad, C-OH and COOH), 7.23-7.29 (5H, m, ArH). <sup>13</sup>C-NMR (125 MHz, CDCl<sub>3</sub>) & 13.9 (q, CH<sub>3</sub>), 41.1 (t, CH<sub>2</sub>Ph), 63.3 (t, OCH<sub>2</sub>), 79.3 (s, C-2), 127.3, 128.2, 130.4 (each d, ArCH), 134.1 (s, ArC), 169.9 (s, C=O), 171.8 (s, C=O). FABMS m/z: 239 (M<sup>+</sup>+1).
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- 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 C18H19O5: 315.1232 (M<sup>+</sup>+1). Found: 315.1231. IR v<sub>max</sub> (neat) cm<sup>-1</sup>: 3489 (OH), 1741 (C=O). <sup>1</sup>H-NMR (500 MHz, CDCl3) & 1.67 (3H, s, CCH3), 3.79 (1H, s, OH), 5.19 (4H, s, 2 x CH2Ph), 7.23-7.34 (10H, m, ArH). Benzyl hydrogen 2-hydroxy-2-methylmalonate (3b): A colorless oil. HRFABMS m/z: Calcd for C11H13O5: 225.0763 (M<sup>+</sup>+1). Found: 225.0754. IR v<sub>max</sub> (neat) cm<sup>-1</sup>: 3448 (OH), 1736 (C=O). <sup>1</sup>H-NMR (500 MHz, CDCl3) & 1.70 (3H, s, CCH3), 2.51 (2H, br s, 2 x OH), 5.25 (1H, d, J = 12.2 Hz, C-CHaCHb-Ph), 5.28 (1H, d, J = 12.2 Hz, C-CHaCHb-Ph), 5.28 (1H, d, J = 12.2 Hz, C-CHaCHb-Ph), 5.27 (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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