

HYPERVALENT IODINE IN ORGANIC SYNTHESIS.

A NEW ROUTE TO  $\alpha$ -FUNCTIONALIZED CARBOXYLATE ESTERS.

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Summary - Aryl and alkylcarboxylate esters are converted into the corresponding  $\alpha$ -hydroxy acids or  $\alpha$ -alkoxyesters upon treatment with  $C_6H_5I(OAc)_2$  and base in the appropriate solvent.

Recently we reported upon the use of hypervalent iodine compounds such as  $C_6H_5I=O$  and  $C_6H_5I(OAc)_2$  for the direct  $\alpha$ -hydroxylation of ketones<sup>1,2</sup>. This transformation involves addition of the enolate anion of the ketone to the iodine atom of the aryl iodine (III) compound to yield an intermediate which undergoes subsequent intramolecular displacement by addition of a nucleophile to the ketonic carbonyl<sup>2</sup>. It appeared of interest to apply this synthetic process to other potential enolate systems. We now report the reaction of various carboxylate esters with  $C_6H_5I(OAc)_2$  under conditions where either  $\alpha$ -hydroxylation or  $\alpha$ -alkoxylation may occur. The general expression for this reaction is the following:

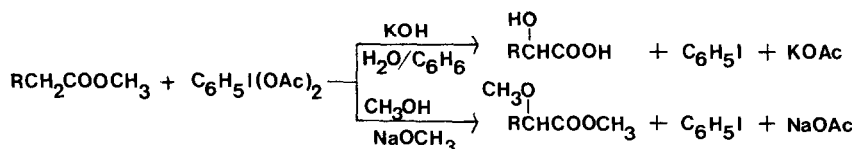


Table 1 presents yields for various carboxylate esters. The  $\alpha$ -functionalization is not restricted to arylacetate esters since ethyl cyclohexane carboxylate reacts to yield the  $\alpha$ -hydroxy acid in 40% yield and the  $\alpha$ -ethoxy acid in 45% yield. The reaction is selective for the enolate since free hydroxyl groups are not oxidized under the above conditions as exemplified in the oxidation of 5 $\beta$ -cholanic acid-3 $\alpha$ -ol methyl ester. Isolated steroidal

double bonds such as C<sub>5-6</sub> unsaturated are also unreactive. The rather low yield with the phenolic system (Table 1, entry 7) may be due to partial ring oxidation.

Table 1 - Reaction of Carboxylate Esters with Phenyliodosodiacetate.

X		R	R'=H			P'=CH <sub>3</sub>		R'=CH <sub>2</sub> CH <sub>3</sub>	
			-OH <sup>§</sup>	m.p.	y <sup>b,c</sup>		-OCH <sub>3</sub> <sup>§</sup>	b.p.	-OCH <sub>2</sub> CH <sub>3</sub> <sup>§</sup>
1.	H	CH <sub>3</sub>	50	131-133°	70	120-121°/10mm	45	e	
2.	H	C <sub>2</sub> H <sub>5</sub>	75	131-133°	75	120-121°/10mm	50	115°/ .2mm	
3.	OCH <sub>3</sub>	CH <sub>3</sub>	66	100-101°	80	d	50	e	
4.	Cl	C <sub>2</sub> H <sub>5</sub>	60	103-105°	80	138-139°/10mm	70	e	
5.	Br	C <sub>2</sub> H <sub>5</sub>	60	117-119°	75	d	60	e	
6.	CH <sub>3</sub>	CH <sub>3</sub>	50	88-89°	70	130-131°/11mm	60	d	
7.	OH	CH <sub>3</sub>	30	149-151°	40	e	30	e	
8.	(C <sub>6</sub> H <sub>5</sub> ) <sub>2</sub> CHCO <sub>2</sub> CH <sub>3</sub>		75	148-150°	65	166-167°/1mm	65	150°/ 1mm	
9.	C <sub>6</sub> H <sub>11</sub> CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>		40	106-107°	65	93-94°/14mm	45		

a) Method A - The preferred procedure for obtaining the  $\alpha$ -methoxy methyl ester (R'=CH<sub>3</sub>, y=OCH<sub>3</sub>) uses C<sub>6</sub>H<sub>5</sub>I(OAc)<sub>2</sub>: NaOCH<sub>3</sub>: ester=1:3:1 in CH<sub>3</sub>OH. The reaction system is stirred at room temperature for 3 days. Work-up involves acidification with dil. HCl at 0°, removal of CH<sub>3</sub>OH in vacuo, addition of H<sub>2</sub>O, extraction with CH<sub>2</sub>Cl<sub>2</sub>, removal of solvent and distillation of the product. Method B involves C<sub>6</sub>H<sub>5</sub>I(OAc)<sub>2</sub>: KOH: ester 1:3:1 in CH<sub>3</sub>OH to yield R'=CH<sub>3</sub>, y=OCH<sub>3</sub>. In Method C, C<sub>6</sub>H<sub>5</sub>I(OAc)<sub>2</sub> and 3 equivalents of KOH to one equivalent of ester react in a two phase system consisting of C<sub>6</sub>H<sub>6</sub>/H<sub>2</sub>O to yield R'=H, y=OH. Using C<sub>2</sub>H<sub>5</sub>OH in either A (NaOC<sub>2</sub>H<sub>5</sub>) or B, yields R'=C<sub>2</sub>H<sub>5</sub>, y=OC<sub>2</sub>H<sub>5</sub>.

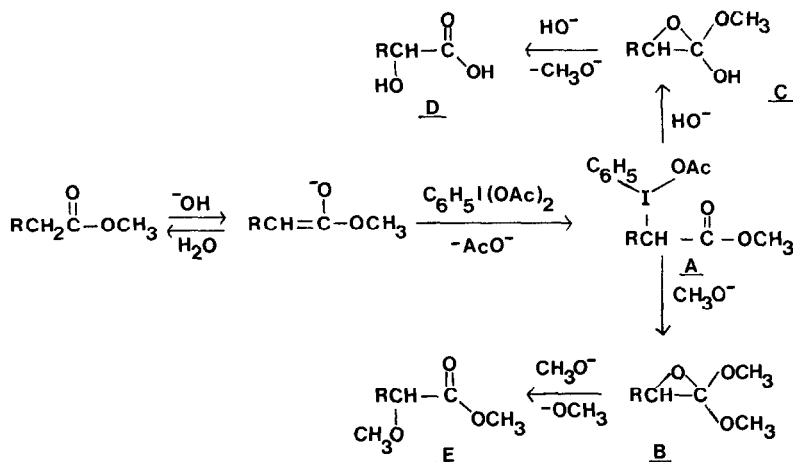
b) Yields are based upon isolated products.

c) Products were compared with literature data where available.

d) Column chromatography.

e) Preparative thin layer chromatography.

We propose that the initial step in the reaction of the various esters is undoubtedly enolate anion formation followed by attack upon the  $C_6H_5I(OAc)_2$  to yield intermediate A. Iodine (III) at the hypervalent state is known to be a good leaving group and in the case of A, C-I cleavage is favorable<sup>3</sup>. In the case of malonate esters, loss of HOAc occurs to yield an iodonium ylid presumably because of stabilization of the anionic part of the ylid<sup>4</sup>. As in the case of ketones<sup>2</sup>, direct displacement at the  $\alpha$ -carbon does not occur but the nucleophile ( $^-OH$  or  $^-OR$ ) is considered to add to the carbonyl group and the alkoxide anion in this tetrahedral intermediate displaces  $C_6H_5I$  and  $^-OAc$ , viz. A  $\rightarrow$  B or A  $\rightarrow$  C. Subsequent attack of  $^-OH$  upon C yields the acid D while attack of  $^-OCH_3$  upon the B yields the  $\alpha$ -methoxy ester E.



As would be expected based on this mechanism, the free acid does not undergo reaction because of the necessity of the initial enolate anion formation. Also a mild sensitivity to steric effects is indicated by the observation that  $CH_3CH_2CH_2OH$  gives poor yields relative to  $CH_3OH$  and  $CH_3CH_2OH$ .

The above mentioned reaction compares very well with other procedures which involve  $\alpha$ -halogenation and displacement (double bonds react)<sup>5</sup>, oxygenation of anions (a reduction step is required)<sup>6</sup>, and  $\alpha$ -acetoxylation using thallium (III) acetate (double bonds react)<sup>7</sup>. The  $\alpha$ -hydroxylation of esters using molybdenum peroxide and the anion generated by LDA in THF-hexane gives results comparable to those obtained in the present study<sup>8,9</sup>.

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## REFERENCES

1. R.M. Moriarty, S.C. Gupta, H.Hu, D.R. Berenschot and K.B. White, J. Am. Chem. Soc., 103, 686 (1981).
2. R.M. Moriarty, H. Hu and S.C. Gupta, Tetrahedron Lett., 000 (1981)
3. Y. Ogata and K. Aoki, J. Org. Chem., 34, 3974 (1969); R.C. Cambie, D. Chambers, B.G. Lindsay, P.S. Rutledge and P.D. Woodgate, J.C.S. Perkin I, 822 (1980)
4. O. Neilands and B. Karele, Zh. Org. Khim., 1, 1854 (1965); 2, 488 (1966); 7, 1611 (1971).
5. C.F. Ward, J. Chem. Soc., 121, 1163 (1922); C.S. Marvel, Syntheses, 20, 106 (1940).
6. H.H. Wasserman and B.H. Lipshutz, Tetrahedron Lett. 1731 (1975); G.W. Moersch and A.R. Burkett, J. Org. Chem., 36, 1149 (1971); G.W. Moersch and M.L. Zwiesler, Synthesis, 647 (1971); P.L. Creger, J. Am Chem. Soc., 89, 25000 (1967); 92, 1396, 1397 (1970); P.E. Pfeffer and L.S. Silbert, J. Org. Chem., 35, 262 (1970)
7. E. C. Taylor, H.W. Altland and G. McGillivray, Tetrahedron Lett., 5285 (1970); E.C. Taylor, R.L. Robey, K.-T. Liu, B. Favre, H.T. Bozimo, R.A. Conley, C.-S. Chiang, A. McKillop and M.E. Ford, J. Am. Chem. Soc., 98, 3037 (1976)
8. E. Vedejs, D.A. Engler and J.E. Telchow, J. Org. Chem., 43, 188 (1978)
9. The superiority of the present method is also reflected in the fact that free hydroxyl groups are not oxidized. Indeed, the reactions are carried in methanol or ethanol. This may appear surprising since the impression is given in the literature that  $C_6H_5I(OAc)_2$  is a good reagent for the oxidation of primary alcohols to aldehydes<sup>10,11</sup>. The essential difference is that under basic condition  $C_6H_5I(OAc)_2$ ,  $C_6H_5I=O$  derived by hydrolysis displays completely different behavior from the neutral system in aprotic solvents.
10. T. Takaya, H. Enyo and E. Imoto, Bull. Chem. Soc. Japan, 41, 1032 (1968)
11. K. Narasaka, A. Morikawa, K. Saigo and T. Mukaijama, ibid., 50, 2773 (1977)

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