Tetrahedron Letters No.43, pp. 3851-3860, 1965. Pergamon Press Ltd.
Printed in Great Britain.

ALKYLATIONS OF SOME CYCLIC β-KETO ESTERS WITH α-HALO ESTERS

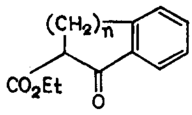
Amareshwar Chatterjee, Dilip Banerjee
and Somenath Banerjee (in part)

Department of Chemistry
Jadavpur University, Calcutta-32, India

(Received 27 August 1965)

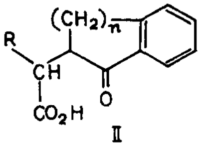
In connection with some other problems, we required the ketoacids II (R=Me or H; n=1,2 and 3) in quantity. These were obtained by alkylations of the β-keto esters I (n=1,2 and 3) with α-bromo esters III (R=Me or H) and subsequent hydrolysis of the alkylated products. In view of recent interests in the acylations[1] and alkylations[2] of cyclic β-keto esters, we like to report our own work. It was found that a change in the metal cation leads to interesting results.

The β-keto ester I (n=1) was prepared[3] by carbethoxylation of 1-indanone with diethyl carbonate using sodium hydride under high dilution condition. The esters I (n=2) and (n=3) were available essentially by the procedures reported in the literature.[4,5]



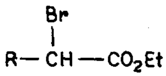
I

(n = 1, 2 and 3)



II

(R=Me or H; N=1,2 and 3)



$$\mathrm{R-\overset{Br}{\overset{|}{C}}H-CO_2Et}$$

III

(R = Me or H)

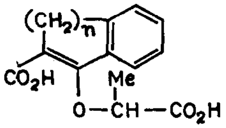
General method for alkylation

Sodium and potassium were used in the molecularised states. Lithium amide and ethoxide were employed in the powdered form.

To the metal (0.042 g. atom) under dry benzene (60 ml.), kept slightly below room temperature, was added dropwise with stirring (N_2 atmosphere) a solution of the β-keto ester (0.039 mole) in benzene (12.8 ml.). The stirring was continued for 6 hours and after 16 hours at room temperature, the α-bromo ester (0.08 mole) and anhydrous DMF (29 ml.) were added all at a time. The resulting mixture was stirred for 7 hours and after 16 hours at room temperature refluxed for 8 hours to complete the reaction. The resulting mixture was then poured into ice-water, organic layer separated and the aqueous portion was extracted 3 times with ether. The combined extract was washed repeatedly with water, dried and evaporated. The oily residue was then carefully fractionated under vacuum to furnish the high boiling alkylated product (mixture).

The separation of the c and o-alkylated products by distillation was not possible. With the limited facility available in our laboratory, the percentages of c and o-alkylated products were calculated on the basis of the ketoacid (solid except in one case) and the 1,2-benzocyclenone (purified by distillation) obtained after acid hydrolysis (HCl-AcOH, 6-7 hours reflux) of the total alkylated product. Though this method is semiquantitative one, duplicate experiments in most of the cases gave results within 2-3%. The results are summarised in Tables 1 and 2.

The total alkylated product was also hydrolysed in some cases by alcoholic KOH or $Ba(OH)_2$ to furnish at least some of the pure o-alkylated acids IV(n=1,2 and 3). The acid IV(n=3), which was available in quantity, on acid hydrolysis afforded quantitatively the expected ketone.



IV
(n = 1, 2 and 3)

A few properties of the o-alkylated acids and the ketoacids II are tabulated in Tables 3 and 4 respectively.

TABLE 1

Alkylation[a] of the β-keto esters with III(R=Me)

β-keto ester	Base used	Alkylated total yield[b] %	Products composition		Ratio O : C
			O,%	C,%	
I, n=1	Na[d]	83.62	7.9	82.39	1 : 10.60
I, n=1	K[d]	74.17[c]	28.32	55.13	1 : 2.00
I, n=2	Na[e]	74.80[c]	45.36	52.24	1 : 1.15
I, n=2	K[e]	81.34[c]	59.00	36.00	1 : 0.61
I, n=2	$LiNH_2$[f]	39.87	22.59	68.39	1 : 3.02
I, n=2	LiOEt[f]	51.59	23.92	68.23	1 : 2.85
I, n=3	Na[g]	77.98	56.54	18.63	1 : 0.33
I, n=3	K[g]	79.68[c]	64.71	11.63	1 : 0.18

[a] Performed in benzene : DMF(5:2). [b] In each experiment the alkylated product (mixture) was analysed to give the expected analytical results. [c] From duplicate experiments. [d] Heterogeneous throughout. [e] By the addition of DMF and the haloester, the enolate went into solution but solid separated on stirring for sometime. [f] The enolate went into solution by adding DMF and haloester, then the reaction mixture was homogeneous throughout. [g] The enolate was soluble in benzene, by the addition of DMF and haloester the reaction mixture became turbid.

In this and subsequent tables O and C represents o-alkylated and c-alkylated products respectively.

TABLE 2

Alkylation[a] of the β-keto esters with III(R=H)

β-keto ester	Base used	Alkylated total yield[b]	Products composition		Ratio
		%	O,%	C,%	O : C
I, n=1	K[c]	80.44	7	84.82	1 : 12.11
I, n=2	Na[c]	90.36	2	93.76	1 : 46.85
I, n=2	K[d]	93.22	7.47	84.43	1 : 11.85
I, n=3	Na[e]	74.71[f]	7.09	85.15	1 : 12.01

[a] Performed in benzene:DMF (5:2). [b] In each experiment, the alkylated product was analysed to give satisfactory results. [c] Heterogeneous throughout. [d] Enolate dissolved on addition of DMF and haloester and after sometime solid separated. [e] Enolate was soluble in benzene, turbidity developed on addition of DMF and haloester. [f] The analytical sample showed IR bands at 1730 and 1684 cm^{-1} in chloroform.

TABLE 3

Properties of the O-alkylated acids

Acids	M.P.[a]	UV $\lambda_{\max}^{\mathrm{EtOH}}$ in mμ	Found		Calc.	
			% C	% O	% C	% O
IV,n=1	164-165°	226(ϵ 8,913) 281(ϵ14,420)	62.47	4.97	62.90	4.87
IV,n=2	136-137°	222(ϵ11,310) 285(ϵ10,910)	64.46	5.68	64.12	5.38
IV,n=3	167-168°	275(ϵ11,300)	65.41	5.84	65.21	6.13

[a] All the acids melt with decomposition.

TABLE 4

Properties of the ketoacids

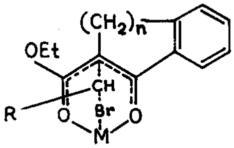
Ketoacids	M.P. in °C	UV λ_{max}^{EtOH} in mμ	Found %C	Found %H	Calc. %C	Calc. %H
II,n=1,R=Me	123-132[a]	244(ε12,020) 288(ε 2,455)	70.67	6.14	70.58	5.92
	140[b]	244(ε11,850) 288(ε 2,455)	70.36	5.88		
II,n=1,R=H	149-150[c]		69.43	5.27	69.46	5.30
II,n=2,R=Me	121-132[d]		71.38	6.77	71.54	6.47
	132[e]	247(ε11,320) 291(ε 1,576)	71.87	6.72		
	108-109[e]	247(ε12,880) 288(ε 1,931)	71.61	6.55		
II,n=2,R=H	107-108[f]		70.47	5.73	70.58	5.92
II,n=3,R=Me	Oil[g]	246(ε 2,674)				
II,n=3,R=H	108[h]	245(ε 7,912) 283(ε 1,205)	71.82	6.48	71.54	6.47
	132-133[i]	245(ε 7,951) 283(ε 1,256)	71.56	6.18		

[a] Probably a mixture of diastereoisomers. [b] A pure isomer, semicarbazone, m.p. 190°, reported[6] m.p. 190-191°. [c] Lit.[7] m.p. 150-151°. [d] Probably a mixture of diastereoisomers, cf. Puterbaugh et al.[8] [e] Pure isomers, cf. Bergs[9]; these isomers showed identical and expected IR bands in chloroform. [f] Lit.[10] m.p. 106-108°. [g] Could not be obtained in the pure state. [h] Labile form. [i] Stable form, reported[11] m.p. 131-131.5° showed IR bands at 1722 and 1684 cm^{-1} in chloroform.

Discussion

The advantages of using DMF (dimethylformamide) in combination with benzene for these alkylations has already been pointed out.[12]

Using Brandstrom's model[13], the transition state for the c-alkylation of the β-keto esters is best represented by V. If c-alkylation is due primarity to the reaction of ion aggregate or chelates, it would be anticipated that even a minor change in the nature of the metal ion might change the ratio of c and o-alkylated products and this has actually been realised (see especially Table 1). Such effects have also been observed with other reactions.[14] The potassium salts reacted to give a significantly larger fraction of the o-alkylated products (see Table 1) and this may possibly be due to increased dissociation[15] of the potassium salts with the dissociated ion reacting to give largely o-alkylated products. The increase of o-alkylated products (compare Tables 1 and 2) in passing from the haloester III (R=H) to III (R=Me) may be explained by growing of steric hindrances in the formation of c-alkylated products.[16] The effect of changing the ring size of the



V

(M stands for the metal atom)

β-keto ester on the proportion of c and o-acylated products has been pointed out[1] and this probably can account the greater preference for c-alkylation in the case of I(n=1) compared to I (n=2).

The lithium salt of I (n=2)favoured c-alkylation most (Table 1) and this is probably due to the greater coordinating ability of lithium ion.[14b,17] The poor yield of the total alkylated product in this case however, is presumably due to the unreactivity of the lithium salt. The relative unreactivity of associated lithium salts has been noted in other reactions.[14a,18]

The alkylation of the β-keto ester I(n=3) with III (R=Me) needs special comment. Even when sodium is the cation (favouring c-alkylation in other cases), o-alkylated product is the major one. This behaviour most probably indicates greater steric requirement of the anion of I (n=3) in the transition state for c-alkylation.

Whether the o-alkylation observed in the present study proceeds through a different mechanism other than S_N2 will of special interest. The study for the effects of some strictly polar (protic and aprotic) and nonpolar solvents in these alkylations is in progress.

Acknowledgements

The authors are indebted to Prof. B. K. Bhattacharyya for valuable discussion, to East India Pharmaceutical Works Limited for awarding a fellowship (to D. B. and S. B.), to

Dr. M. M. Dhar for I. R. Spectra of some of the compounds, and to Mr. B. B. Bhattacharyya for microanalysis.

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