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SELECTIVE PREPARATION OF αβ-UNSATURATED ESTERS VIA THE REFORMATSKY REACTION

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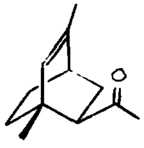
Recent attempts to convert ketone 1 (1) to the unsaturated esters 2 in this laboratory have led to an unexpected and novel fragmentation of the bicyclo-[2.2.2]octene system, and consequently to a new selective preparation of αβ-unsaturated esters via the Reformatsky reaction.

The treatment of 1 with ethyl bromoacetate and zinc under usual Reformatsky conditions (2) afforded alcohol 3 (3) consistently in 85 - 90% yield. We anticipated a reasonable conversion of 3 and 2, although dehydration of β-hydroxy esters is acknowledged to be far from selective (2), but investigation with some acidic dehydrating reagents (Table 1) resulted in only traces of conjugated esters (pmr, uv). The major product "X", formed in up to 60% yield, was an oil whose pmr spectrum showed signals due to two aromatic methyls, an aliphatic secondary methyl, three aromatic protons, and an ethyl ester but no olefinic protons. At first this appeared to be consistent with 6 (R=Et) which could have formed in an unexceptional manner (4) via intermediates 4 and 5, but direct comparison of the acid obtained from X by mild alkaline hydrolysis, with a synthetic sample of 6 (R=H) (5,6) confirmed their non-identity. In particular, the pmr spectrum of X showed no multiplet at 3.4δ characteristic of the benzylic methine proton in 6.

Closer examination of the pmr spectrum of X revealed more aliphatic protons than accounted for by 6, and suggested that X was isomeric with 2. The structure 7 (R=Et) appeared to fit this additional evidence, and was indeed shown to represent X when a synthetic sample of 7 (R=H) (7) was found to be identical with the acid obtained from X. The formation of 7 possibly involves intermediates such as A and B (stereochemistry undefined in the side chain) but the mechanism is currently under investigation.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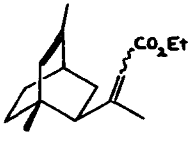

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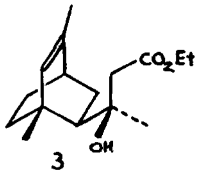

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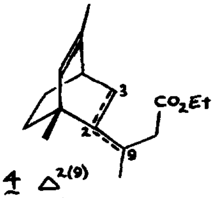
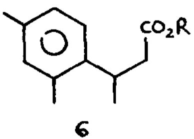


4 $\Delta^{2(9)}$
5 Δ^{2}



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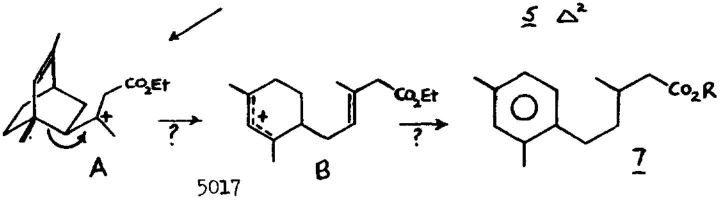
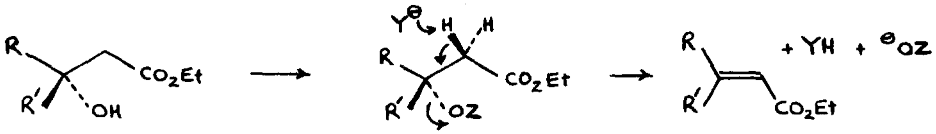


Table 1. Acid-catalysed Dehydration of 3

	Reagent	Time(hr)	Temp.(°C)[a]	% Yield 7 R = Et[b]	 R = H[c]
1)	I_2-benzene	2	80	60	..
2)	$POCl_3$-benzene	1	80	50	..
3)	p-TsOH-benzene[d]	0.75	80	60	..
4)	I_2-acetic acid	1	118	..	57

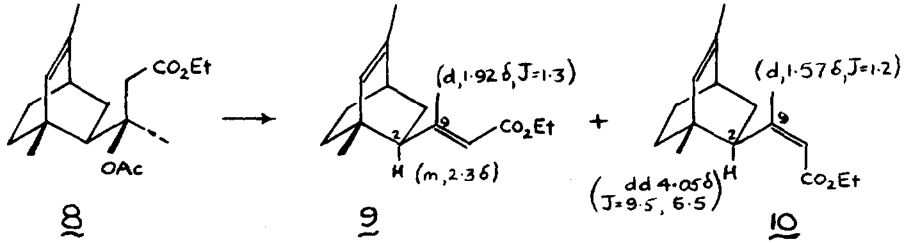
a Refluxing Solvent. b Estimated by pmr of total crude product.
c Isolated by chromatography of the hydrolysed crude product on silica gel.
d With azeotropic removal of water (otherwise much lower yields of 7).

Since this fragmentation appeared to be promoted by conditions which favoured formation of carbonium ions, we anticipated that a base-catalyzed elimination of a sutiable ester of the tertiary alcohol ought to be far more selective in producing an αβ-unsaturated ester.



The alcohol 3 was acetylated with acetyl chloride in refluxing N,N-dimethylaniline and chloroform (8) to give acetate 8 nearly quantitatively (9). A more convenient procedure involved the direct addition of the Reformatsky reaction mixture to acetyl chloride and dimethylaniline in chloroform. After refluxing this mixture until acetylation was complete (pmr), 8 could be isolated in 85-90% yield from 1. A solution of 8 in dry ethanol was treated with ethanolic sodium ethoxide for 1 hour at room temperature to give a mixture of conjugated esters 9 and 10 (3:1) which were isolated in 80% yield by chromatography on neutral alumina. No non-conjugated esters were detected (pmr, ir).

The assignment of stereochemistry to 9 and 10 followed from their pmr spectra. The most striking feature in 10 was the large paramagnetic shift (1.7 ppm) of the signal due to H_2 which was partly obscured by the ethyl ester resonance, but was clearly visible in the spectrum of the corresponding acid obtained by mild alkaline hydrolysis of 10. The shielding of the C_9 methyl groups in the spectra of 9 and 10 also suggested the preferred conformations as shown.



8 9 10

We sought to demonstrate the generality of this sequence with cyclohexanone and diethyl ketone, where the highest percentage of conjugated ester obtained by usual dehydration conditions lies in the range 60-70% (2). The acetates 11 and 12 (R=$COCH_3$) were prepared in 80-85% yield (9) from the respective ketones by direct acetylation of the Reformatsky reaction mixture as described for 8. The results of elimination experiments using sodium ethoxide on these acetates are summarised in Tables 2 and 3.

Table 2. Reaction of 11 (R=Ac)[a] with Sodium Ethoxide[b]

Entry	Equivalents of base	Time (hr)	Temp. (°C)	Ratio of Unsat. Esters[c] 13 (%)	14 (%)
1	1	1	25	99	1
2	1	4	25	95	5
3	1	120	25	77	23
4	1.1	4	25	95	5
5	1.1	16	25	90	10
6	1.1	0.5	80	64	36
7	2.2	0.05	25	95	5
8	2.2	16	25	60	40
9	10	2	25	95	5
10	10	120	25	38	62
11	10	2[d]	80	23	77

Table 3. Reaction of 12 (R=Ac)[a] with Sodium Ethoxide[e]

Entry	Equivalents of base	Time (hr)	Temp. (°C)	Ratio of Unsat. Esters[c] 15 (%)	16 (%)
1[f]	1	0.08	25	98	2
2	1	2	25	97	3
3	1	120	25	92	8
4[f]	2.2	0.08	25	94	6
5	2.2	2	25	91	9
6	2.2	16	25	70	30
7	2.2	1	80	46	54

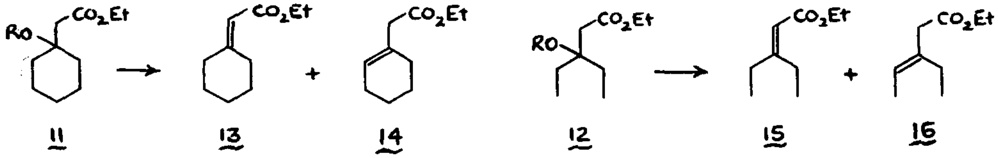
[a] All reactions were carried out in absolute ethanol using 1.0g of acetate.

[b] Molarity of base was 1.44 except with 10 equivalents (0.95).

[c] Products were analysed by vpc (5% Apiezon L on Chromosorb W). The total yield of esters exceeded 90% in each case but included up to 10% of β-hydroxy ester.

[d] Time of refluxing after standing at 25° for 120 hr. (entry 10).

[e] Molarity 1.76. [f] Approx. 5% acetate had not reacted.



The very high ratio of αβ- to βγ-unsaturated ester appeared to be very little affected by excess base at room temperature, provided the reaction times were not prolonged (cf. entries 2,4, and 9 in Table 2). Increased temperatures or long reaction times both caused a marked increase in the more stable βγ-unsaturated esters.

Sodium ethoxide was chosen for general convenience and to avoid complications with transesterification at the ethyl ester function. However, in each experiment up to 10% (vpc) of hydroxy ester 11 or 12 (R=H) was formed, probably by transesterification at the tertiary acetate. This side-reaction was completely avoided using potassium *t*-butoxide/ *t*-butanol under similar conditions, with no sacrifice of the high percentage of αβ-unsaturated ester.

The foregoing results obviously extend the utility of the Reformatsky reaction and indeed make it a very attractive alternative to the Wadsworth-Emmons method[10] for the preparation of αβ-unsaturated esters. In fact, the product we obtained from cyclohexanone by the latter method contained 6% of 14 (vpc). The attractive feature of our sequence lies in the fact that the Reformatsky reaction can be applied to a greater variety of substituted ketones than the phosphonate method[10] which, for example, failed with ketone 1.

Investigations with substituted reagents, e.g. ethyl α-bromopropionate, and with aldehydes and unsymmetrical ketones are being pursued.

References and Footnotes

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(3) This product appeared to be homogeneous by pmr and vpc and is assigned the configuration shown, for reasons to be discussed in a fuller communication.

(4) K. Alder and H.F. Rickert, *Ann. Chem.*, **524**, 180 (1936); *Ber.*, **70**, 1354, 1364 (1937).

(5) I.M. Heilbron and D.G. Wilkinson, *J. Chem. Soc.*, 2537 (1930).

(6) T. Wagner-Jauregg, E. Friess, H. Hippchen, and F. Prier, *Ber.*, **76**, 1157 (1943).

(7) K.C. Mathur and G.S. Saharia, *Chem. Abstracts*, **61**, 4252e (1964). Comparison was made by pmr with the oily acid 7(R=H) and by mixed m.p. with the S-benzylisothiuronium salt (m.p. 153-154°).

(8) cf. J.D. Cocker and T.G. Halsall, *J. Chem. Soc.*, 4262 (1956).

(9) It is noteworthy that no olefinic materials were detected from the acetylation of any of our Reformatsky products under these conditions. The olefinic product reported in reference 8 was likely formed during chromatography on alumina which also gave unsaturated esters from our acetates, but not selectively.

(10) W.S. Wadsworth and W.D. Emmons, *J. Am. Chem. Soc.*, **83**, 1733 (1961).