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FRAGMENTATION OF HOMOALLYLIC ALKOXIDES. SYNTHESIS OF PROPENYL and 2-METHYLPROPENYL KETONES FROM CARBOXYLIC ESTERS

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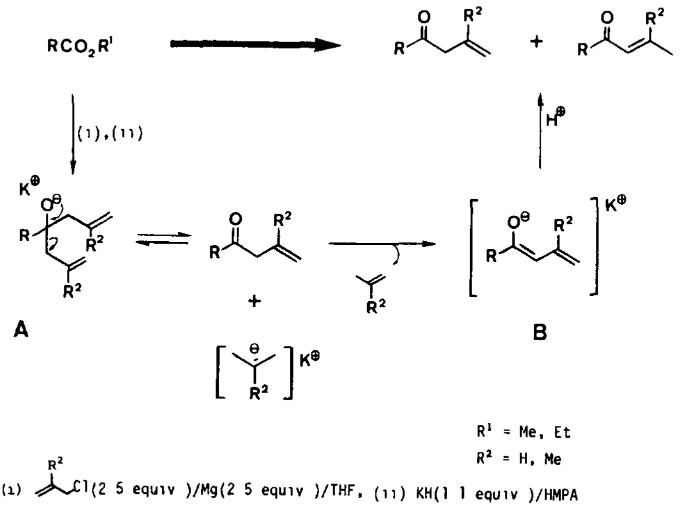
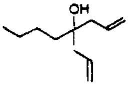
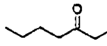
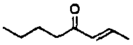
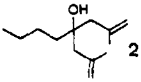
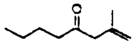
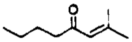
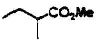
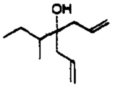
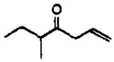
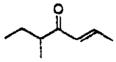
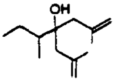
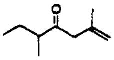
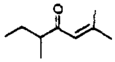
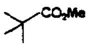
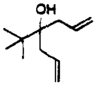
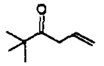
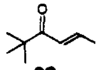
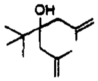
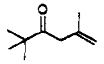
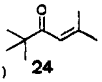
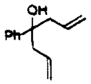
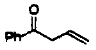
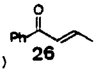
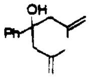
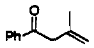
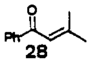
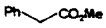
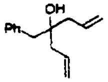
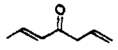
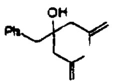
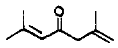
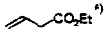
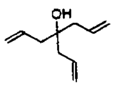
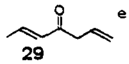
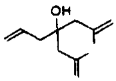
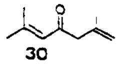
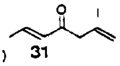
Abstract· An efficient two-step synthesis of propenyl and 2-methylpropenyl ketones from carboxylic esters is described which uses as the key step the fragmentation of a potassium dihomoallylic alkoxide under mild thermolytic conditions.

A practical method for the synthesis of a ketone from a carboxylic ester is a long-standing synthetic problem [1] We report here an efficient two-step synthesis of propenyl and 2-methylpropenyl ketones which involves the fragmentation, in an aprotic solvent, of a dihomoallylic potassium alkoxide A [2] whose parent alcohol [3] is readily prepared from a carboxylic ester by the double addition of allyl or 2-methallyl magnesium chloride (*Scheme 1*). Addition of the appropriate carboxylic ester (RCO_2R^1, R^1 = Me or Et) and allyl or 2-methallyl chloride (2.5 equiv) to magnesium (2.5 equiv.) in THF gave the tertiary alcohols 1 - 12 in excellent yield. Addition of each of these alcohols to a slurry of potassium hydride (1.1 equiv.) in hexamethylphosphoric triamide (HMPA) [4] at 20° under N_2 afforded solutions of the corresponding potassium alkoxides, 1A - 12A, which were heated at 80° during 2 h (gas evolution). Quenching of the cooled mixtures in sat aq. NH_4Cl, extraction (ether) and distillation in *vacuo* furnished mixtures of the β,γ- and α,β-unsaturated ketones 13 - 31 in high yield (Table).

Scheme 1



Table

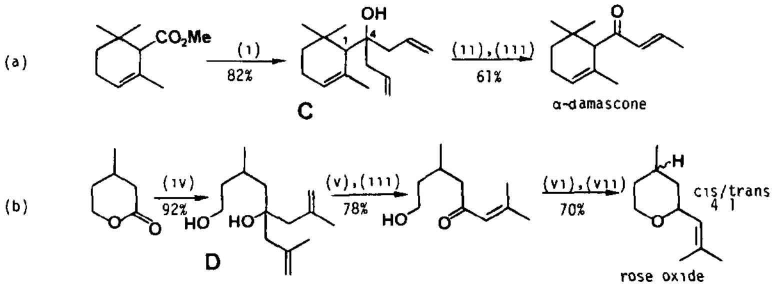
Exp	ESTER a)	ALCOHOL b,c)	Yield d) %	PRODUCTS	Yield d) %
1		 1	83	 13 (4 1) +  14	75
2		 2	84	 15 (2 1) +  16	79
3		 3	80	 17 (4 1) +  18	79
4		 4	82	 19 (3 2) +  20	82
5		 5	85	 21 (3 1) +  22	83
6		 6	86	 23 (3 1) +  24	79
7	$PhCO_2Me$	 7	87	 25 (5 1) +  26	84
8		 8	81	 27 (3 1) +  28	82
9		 9	82	 29 e)	77
10		 10	85	 30 e)	73
11	 f)	 11	77	 29 e)	73
12		 12	79	 30 (4 1) +  31	66

a) commercially available, b) prepared on 0 15 mole scale, c) structures of all new compounds are compatible with their spectral data, b p 1 83-85°/5 Torr, 2 101-102°/15 Torr, 3 88-89°/15 Torr, 4 102-105°/15 Torr, 6 99-101°/15 Torr, 8 73-77°/0 01 Torr, 9 81-84°/0 02 Torr, 10 91-96°/0 01 Torr, 12 94-98°/15 Torr, d) yields, not optimised, refer to pure (GLC) distilled products, e) major component (>90%), f) prepared from allylacetic acid ($EtOH/H^{\oplus}/C_6H_6$ reflux)

The fragmentation mechanism (*Scheme 1*) involves an initial heterolytic cleavage of the allylic C-C bond adjacent to the alkoxide group to form an allylic potassium species and a β,γ-unsaturated ketone. Subsequent irreversible formation of the potassium dienolate B [5] with expulsion of propene (R^2 = H) or isobutene (R^2 = Me) is then followed by protonation either by the solvent or during the aqueous work-up to afford the mixture of enones [6].

Experiments 1 - 8 (Table) demonstrate that this synthetic method is applicable for esters, RCO_2R^1, when R is alkyl (primary, secondary or tertiary) and phenyl [7]. When R is benzyl or allyl (experiments 9 - 12) the products from the fragmentation of these trihomoallylic potassium alkoxides are dependent on the relative benzylic and allylic C-C bond strengths towards heterolytic cleavage For example, on thermolysis both 9A and 10A selectively lose the benzyl group to give exclusively 29 and 30, whereas the 4 · 1 mixture of 30 and 31 resulting from the thermolysis of 12A indicates a preference (*ca* 8 1) for loss of the allyl rather than the 2-methallyl group [8].

Scheme 2



(i) Cl(2 5 equiv)/Mg(2 5 equiv)/THF, (ii) KO^tBu(1 5 equiv)/DMF/40°[10], (iii) HCl aq /THF, (iv) Cl(2 5 equiv)/Mg(2 5 equiv)/THF, (v) KO^tBu(2 2 equiv)/ DMF/40°[10], (vi) $LiAlH_4/Et_2O$, (vii) $KHSO_4/\Delta$

The preparative value of this method is further illustrated by the syntheses of two important perfumery products (*Scheme 2*). The first synthesis (a) is a convenient approach to α-damascone from methyl α-cyclogeraniate which involves the fragmentation of the potassium alkoxide of the trihomoallylic alcohol C followed by treatment with aqueous acid (yield 61% [9]) The second synthesis (b) is an efficient route to rose oxide from 4-methylvalerolactone (overall yield 50%) which uses the fragmentation of the bispotassium alkoxide of the diol D as the key step. Subsequent reduction of the α,β-unsaturated ketone and acid catalysed cyclisation of the resulting enediol completes the synthesis.

References and Notes

[1] For partial solutions to this problem *cf.* I. Kikkawa and T. Yorifuji, *Synthesis*, 877 (1980) and references cited therein.

[2] For a recent synthetic application *cf.* R.L. Snowden and K.H Schulte-Elte, *Helv. Chim. Acta*, in press, when the counterion is Li or MgX (X = halogen) fragmentation occurs less readily *cf.* R.A. Benkeser, M.P. Siklosi & E.C. Mozdzen, *J. Am. Chem. Soc. 100*, 2134 (1978).

[3] Vapour phase thermolysis (>350^0) of the parent dihomoallylic alcohol by a concerted *retro*-ene reaction effects the same transformation *cf* A. Viola & E.J. Iorio, *J. Org. Chem. 35*, 856 (1970) and references cited therein

[4] Other aprotic solvents such as N-methylpyrrolidone and tetramethylurea may also be used.

[5] The enolatisation may be effected by either the allylic potassium or the potassium alkoxide A

[6] This mixture of β,γ- and α,β-enones may be separated by chromatography. The former isomer may be readily converted into the latter by treatment with acid (either TsOH/toluene/Δ or HCl aq./THF/Δ).

[7] This method is often unsatisfactory for α,β-unsaturated esters (R = alkenyl) as the intermediate tertiary alkoxide may also undergo an anionic accelerated oxy-*Cope* rearrangement *cf.* D.A. Evans, D.J. Baillargeon & J.V. Nelson, *J. Am. Chem. Soc. 100*, 2242 (1978).

[8] The selective loss of the benzyl group may be explained by the thermodynamic stability of the benzyl anion. A relative destabilisation of the 2-methallyl anion by the inductive effect of the methyl group may explain the preference for loss of the allyl rather than the 2-methallyl group.

[9] A major side-reaction (*ca.* 30 - 40 %) is cleavage of the C(4)-C(1') allylic bond

[10] Potassium tert-butoxide (1.5 - 2 equiv.) in dimethylformamide (DMF) is a practical alternative for the formation of the potassium tertiary alkoxide.

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