Alkali-catalysed Alkoxy Exchange, Alcohol Elimination, and Hydrolysis of Acetals Having a Dissociable α-Proton

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Summary Some acetals with strong anionic activation in the α-position are prone to alkali-catalysed acetal exchange and/or alcohol elimination or, in the presence of water, to hydrolysis.

IT is generally accepted and invariably pointed out in textbooks and monographs[1] that acetals are stable towards alkali. In view of the known reversibility of the Michael addition, we feel that this statement should be qualified for acetals which tend to undergo anionic dissociation in the α-position. According to the equilibrium $(RO)_2CH-\bar{C}< \rightleftharpoons ROCH=C< + RO^-$, these may undergo, under alkaline conditions, (a) alkoxy exchange, (b) elimination of alcohol, or (c), in the presence of water, hydrolysis. Compounds of

types (**1**)—(**6**) have been examined and the following examples of all three expected changes have been found.

$(R^1O)_2CH–CHR^2R^3$

(**1**); R^2=MeCO, R^3=H
(**2**); R^2=CN, R^3=H
(**3**); R^2=R^3=CO_2R
(**4**); R^2=Aryl, R^3=MeCO
(**5**); R^2=Aryl, R^3=CO_2R
(**6**); R^2=Aryl, R^3=Aryl–CO

(a) Transacetalisation: alkoxide-catalysed alkoxide exchange with primary alcohols takes place with all compounds (**1**)—(**6**); the rate of exchange decreases in the order (**1**) ~ (**4**) ~ (**6**) > (**5**) ~ (**3**) > (**2**).[2] For example (**1**; R^1 = Me) in 0·1N NaOEt at room temperature exchanged quantitatively to give (**1**; R^1 = Et) in 24 h, whereas (**2**; R^1 = Et) required refluxing for 8 h in 0·1N $NaOBu^n$ for complete conversion into (**2**, R^1 = Bu^n). Reaction with Pr^iOH was slow; (**1**; R^1 = Me) with 0·1N $NaOPr^i$ at room temperature gave, after 80 h, the mixed acetal (**1**; R^1 = Me and Pr^i) which yielded, on repeated treatment, a mixture of (**1**; R^1 = Pr^i) and (**7**). Transacetalisation with tertiary alcohols and transacetalization of $BrCH_2CH(OEt)_2$ and PhCH–CH$(OMe)_2$ did not take place.

$R^1OCH=CR^2R^3$

(**7**); R^1=Pr^i, R^2 = MeCO, R^3=H
(**8**); R^1=Et, R^2=2-benzyloxy-4,5-methylenedioxyphenyl, R^3=COMe
(**9**); R^1 = Et, R^2=4-$MeOC_6H_4$, R^3 = CO_2Bu^t
(**10**); R^1=n-Alkyl, R^2=R^3=CN

(b) Alcohol elimination: the postulated vinyl ether intermediate in the exchange reaction was isolated in some cases. Thus (**4**; R^1 = Me, R^2 = 2-benzyloxy-4,5-methylenedioxyphenyl) afforded, in 0·1N NaOEt at room temperature, the sparingly soluble vinyl ether (**8**); (**5**; R^1 = Me, R^2 = 4-$MeOC_6H_4$, R^3 = CO_2Bu^t) gave (**9**) on brief boiling with 10% KOH in 50% aq. EtOH and, as already mentioned, (**1**; R^1 = Me) gave (**7**) with 0·1N $NaOPr^i$.

Compounds (**10**) undergo alkyl exchange (R^1: Et → Me, Me → Et, Me → Bu^n), without alkoxide catalysis, on heating to reflux with a primary alcohol. Here the corresponding nonisolable acetal is assumed to be an intermediate.

(c) Hydrolysis: the acetals (**1**), (**3**), and (**6**) give, with KOH–EtOH diluted with Et_2O at 0 °C, the corresponding potassium enolates, identified by the n.m.r. spectra of the salts in D_2O or of the unstable enols liberated with CO_2. Heating with 10% KOH in EtOH effected hydrolysis and subsequent deformylation. (**4**; R^1 = Me, R^2 = 2-benzyloxy-4,5-methylenedioxyphenyl) gave 1-(2-benzyloxy-4,5-methylenedioxyphenyl)propan-2-one, m.p. 75—77 °C, (**6**; R^1 = Me, R^2 = 4-$MeOC_6H_4$, R^3 = 2-$PhCH_2O$,4-$MeOC_6H_3$-CO) gave 2′-benzyloxy-4′-methoxy-2-(4-methoxyphenyl)-acetophenone, and (**5**; R^1 = Me, R^2 = 4-$MeOC_6H_4$, R^3 = CO_2Bu^t) gave 4-methoxyphenylacetic acid.

Intramolecular alkali-catalysed alkyl exchange and alcohol elimination provides a novel non-acetic method of cyclisation. Thus in 0·1N NaOMe at room temperature (**4**; R^1 = Me, R^2 = 2-hydroxy-4,5-methylenedioxyphenyl) gave 3-acetyl-5,6-methylenedioxybenzofuran, m.p. 88—89 °C, and (**6**; R^1 = Me, R^2 = 4-$MeOC_6H_4$, R^3 = 2-HO-4-$MeOC_6H_3$CO)[3] gave 4′,7-dimethoxyisoflavone.[3]

The structure of all new compounds has been confirmed by ^1H n.m.r. spectroscopy, elemental analyses, and/or accurate mass measurement.

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[2] Transacetalisation of (**3**) had been observed before but not commented on: J. E. Vik, *Acta Chem. Scand.*, 1973, **27**, 239.
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