Metal–Ammonia Reduction and Reductive Alkylation of Conjugated Dienoic Acids

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Abstract

Conjugated dienoic acids are readily reduced or reductively alkylated with lithium–ammonia to their *trans*-β,γ-unsaturated and *trans*-α-alkyl-β,γ-unsaturated derivatives respectively. Competing protonation in the latter reaction detracts from its general use in synthesis; the origin of this side reaction is briefly discussed.

The first preparations of dienolate and trienolate dianions of carboxylic acids were performed by treating unsaturated acids such as crotonic and sorbic acids with potassium amide in liquid ammonia.[1] The nature and reactivities of the anions were demonstrated by methylation or kinetically controlled protonations in the 2-positions. More recently similar anions have been generated by base-catalysed abstraction of a proton under a variety of conditions.[2]

Their alternative generation by a reduction process has been noted,[3] and we have now examined the lithium–ammonia reduction of several conjugated dienoic acids. Reductions of α,β-unsaturated acids in ammonia have received little attention[4] and alkylations of the products do not appear to have been attempted although successful alkylations have been reported in hexamethylphosphoramide systems.[5] Only isolated examples of reductions of conjugated dienoic acids with metal–ammonia have been reported,[6] although their reduction with sodium amalgam has long been known.[7]

(1)	R = H	(3)	R = H	(5)	R = H	(7)	R = H
(2)	R = Me	(4)	R = Me	(6)	R = Me	(8)	R = Me
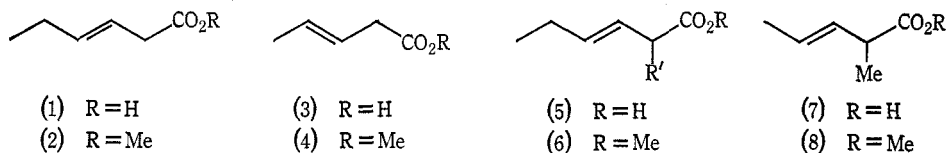
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The anions generated by reduction are identical with those generated by the base-catalysed process on acids with one less double bond.

Sorbic acid with lithium–ammonia gave the expected dienolate dianion, since kinetic protonation (cf.[8]) produced the *trans-β,γ*-unsaturated acid (1) (85%), characterized as its methyl ester (2). Examination by g.l.c. and n.m.r. showed no sign of the *cis*-isomer, the *trans* nature of the double bond was indicated by strong absorption at 970 cm^{-1} and the absence of absorption between 1600 and 1700 cm^{-1} in the i.r. spectrum[9] of (2). Similarly, penta-2,4-dienoic acid gave (E)-pent-3-enoic acid (3) (90%), converted into the ester (4).

Table 1. Some reductive alkylations of alka-2,4-dienoic acids

Sub-strate	Alkyl halide	2-Alkyl product	Total yield (crude) (%)	By-product (R' = H) (%) N.m.r.	G.l.c.
C_6 acid	methyl iodide	(5; R' = Me)	90	—	31
C_6 acid	isopropyl bromide	(5; R' = Pr^i)	95	25	26
C_6 acid	allyl bromide	(5; R' = CH$_2$CH=CH$_2$)	90	29	38
C_5 acid	methyl iodide	(7)	90	18	24

Reductive alkylation of sorbic acid with representative alkyl halides (Table 1) gave (E)-2-alkylhex-3-enoic acids (5) purified through their methyl esters (6). The *trans* nature of the double bond was supported by absorption at 970 cm^{-1}; g.l.c. and n.m.r. indicated the presence of only one isomer. Comparison with published n.m.r. spectra[10] in the case of (6; R' = Me) also showed no sign of peaks reported for the *cis*-isomer. Reductive methylation of penta-2,4-dienoic acid similarly gave the known (E)-2-methylpent-3-enoic acid (7)[11] purified as the methyl ester (8) and characterized through its spectral data [for the n.m.r. spectrum of the (presumed) *trans* ethyl ester, see ref.[12]].

A major by-product (Table 1) in all cases was the product of protonation (1) or (3), which could be separated by g.l.c. on 20% SE-30 columns. This is probably formed by reaction of the dianions with the solvent. The reductive alkylation of crotonic acid indeed gave less than 10% of alkylation product, protonation being dominant as might be expected from the less stabilized nature of the enolate salt. An attempt to eliminate the by-product by addition of the acid to the metal solution at $-78°$, followed by rapid addition of alkyl halide, the superior method with furoic acid,[3] led only to minor improvement.

No dialkylation was observed in any example, although it occurs under forcing conditions with excess base,[1] so anion interchange with the first alkylation product does not occur.

Despite the probable generality of the alkylation process with dienoic acids, the formation of a significant proportion of reduction product is a drawback in synthesis. A favourable feature, however, is the apparently exclusive formation of α-alkylated *trans* products, and the absence of dialkylated products in contrast to the alternative procedures.[2,10]

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Experimental

The main details are described elsewhere.[13] For g.l.c. a 6 ft by ¼ in. o.d. steel column packed with 20% SE-30 on 60/80 Chromosorb W with a range of temperatures 70–115° and a gas flow of 120 ml helium/min was used.

Reduction Procedure

The experimental procedures employed were essentially the reduction method D, and the reductive alkylation method III of van Bekkum *et al.*;[8] only enough metal (about 2·5 equiv.) was added to establish a permanent blue colour. The acids (0·01–0·015 mol per 100 ml NH_3) were insoluble but dissolved as the reaction proceeded. A slightly modified workup procedure[13] was employed. Continuous extraction was not required. The products were analysed and separated (where needed) by g.l.c. as their methyl esters; known products were identified as described in the text; further data are:

(*E*)-Hex-3-enoic acid (1), b.p. 75–80°/2 mm (lit.[14] 81–82°/2 mm); methyl ester (2), b.p. 65–70°/35 mm (lit.[14] 67–68°/34 mm).

Methyl (E)-*2-isopropylhex-3-enoate* (6; R′ = Pr^i), b.p. 80°/20 mm (Found: C, 70·7; H, 10·8. $C_{10}H_{18}O_2$ requires C, 70·5; H, 10·7%). ν_{max} 1735 (methyl ester) and 970 cm^{-1} (*trans* disubstituted double bond); δ (CDCl$_3$) 2·70, t, J 7·5 Hz, 1H, C$_\alpha$H; 3·72, s, CO$_2$CH$_3$; 5·58, m, 2H, vinyl H.

Methyl (E)-*2-(prop-2-enyl)hex-3-enoate* (6; R′ = CH$_2$CH=CH$_2$), b.p. 85°/20 mm (Found: C, 71·8; H, 9·9. $C_{10}H_{16}O_2$ requires C, 71·4; H, 9·6%). ν_{max} 1735 (methyl ester), 1640 (monosubstituted double bond) and 970 cm^{-1} (*trans* disubstituted double bond); δ (CDCl$_3$) 0·97, t, J 6·5 Hz, CH$_2$CH$_3$; 3·08, q, J 7 Hz, 1H, C$_\alpha$H; 3·68, s, CO$_2$CH$_3$.

(*E*)-Pent-3-enoic acid (3), b.p. 80–85°/12 mm (lit.[14] 93·5–95°/16 mm); methyl ester (4), b.p. 45–50°/20 mm (lit.[14] 42–43°/18 mm).

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