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SODIUM AMALGAM REDUCTION OF 3-BROMOPROPENOIC ACIDS: A CONVENIENT STEREOSPECIFIC SYNTHESIS OF [3-$^{3}H_{1}$] and [3-$^{2}H_{1}$] ACRYLIC ACIDS

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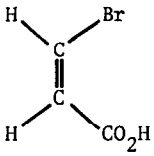
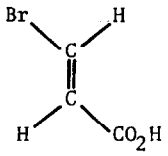
A variety of methods have been used to synthesise acrylates labelled in the β-position with isotopic hydrogen. Catalytic deuteration of propiolic esters or hydrogenation of deuteriopropiolic esters using the Lindlar catalyst suffered from low stereospecificity and over-reduction[1,2]. Reduction of propiolates in D_2O with chromous ion gave exclusively trans addition of deuterium but in low yield[3,4]. Addition of DCl to acetylene followed by conversion into the Grignard reagent and carbonation proceeded with very low stereospecificity[1b]. Nickel carbonyl-mediated carbonation of methyl acetylene in the presence of deuterioethanol or deuteriomethanol and DCl in D_2O gave (Z)-[3-$^{2}H_{1}$]acrylates stereospecifically[4]. Catalytic deuteration of the Diels-Alder adduct of methyl propiolate and anthracene followed by pyrolysis gave methyl (E)-[1,2-$^{2}H_{2}$]methacrylate stereospecifically and in good yield[2]. A similar hydrogenation and pyrolysis of the adduct with methyl [3-$^{2}H_{1}$]propiolate gave methyl (Z)-[3-$^{2}H_{1}$]methacrylate[2].

We describe here a simple procedure for the preparation of stereospecifically deuterated or tritiated acrylic acids which offers the following advantages over some or all of these methods: the preparation takes place in one step; the reaction is stereospecific; the label is derived from the least expensive and most convenient source of isotopic hydrogen, D_2O or THO; the label is confined to the β-carbon; the method is applicable to the preparation of α-substituted acrylates. The method consists in the sodium amalgam reduction[5] of readily available 3-bromoacrylates[6] in the presence of D_2O or THO, which takes place with retention of configuration. Thus the (Z)- and (E)-3-bromoacrylic acids[7] ((1) and (2) respectively) were reduced to the sodium (Z)- and (E)-[3-^{2}H]acrylates ((3) and (4)) respectively. The stereochemical integrity of the products was evident from the olefinic region of their n.m.r. spectra (Table).

(E)-[3-$^{2}H_{1}$]-2-Methylpropenoic acid (methacrylic acid) was similarly produced from (E)-3-bromo-2-methylpropenoic acid[8] and (Z)-3-[3-^{2}H]-2-methyl-2-butenoic acid (angelic acid) from (E)-3-bromo-2-methyl-2-butenoic acid (β-bromoangelic acid)[5]. The method was also applied to

the synthesis of the corresponding tritiated methacrylic and angelic acids.


(1)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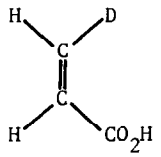
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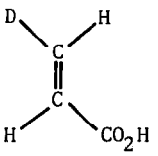
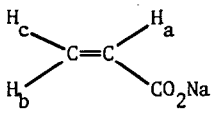

(4)

Table

NMR Spectra of Sodium Acrylate and the Stereoisomers of Sodium [3-$^2H_2$]Acrylate

	H_a	H_b	H_c
Sodium acrylate	Complex multiplet δ 5.9-6.1		δ 5.56, dd, J 9 Hz, 4 Hz
Sodium(Z)-[3-$^2H_1$]acrylate	δ 6.02, dt J 9 Hz, 2 Hz	-	δ 5.54, d, J 9 Hz
Sodium(E)-[3-$^2H_1$]acrylate	δ 5.96, 6.01, each apparent s		-

The only significant disadvantage of the method is that reduction of the bromoacrylate and bromomethacrylate was attended by a degree of over-reduction to the corresponding propionates, typically to the extent of 10-15%. To facilitate the isolation and purification of the products we have accordingly devised a simple work-up which furnishes the pure acrylates as their crystalline dicyclohexylammonium salts, as in the following illustrative procedures.

Synthesis of (E)-[3-$^2H_1$]-2-Methylpropenoic Acid

To a slowly stirred solution of (E)-3-bromo-2-methylpropenoic acid (0.27 g, 1.4 mmol) in D_2O (99.7 atom %) at 5 °C was added, in aliquots over 48 hours, sodium amalgam (2.5%, 5.5 g). The mixture was stirred for a further 25 hours at 0-5 °C [9]. The aqueous solution was separated by decantation, the mercury was washed with water (3 x 1 cm^3) and the combined aqueous solutions were acidified (Congo Red) with hydrochloric acid (1 M). The solution was extracted with ether (3 x 3 cm^3), dried ($MgSO_4$), and evaporated to give (E)-[3-$^2H_1$]-2-methylpropenoic acid (0.082 g, 68%) contaminated by [2,3,3-$^2H_3$]-2-methylbutanoic acid (0.014 g) (n.m.r.).

Purification of (E)-[3-$^2H_1$]Propenoic Acid as the Dicyclohexylammonium Salt

The aqueous supernatant from the reduction of (E)-3-bromopropenoic acid (0.070 g, 0.5 mmol) in D_2O (0.5 cm^3) was lyophilised, the residue was dissolved in 90% aqueous ethanol (2 cm^3), treated with dicyclohexylammonium chloride (108 mg, 0.5 mmol), warmed briefly to bring all the solids into solution, evaporated to dryness and dried over P_2O_5 *in vacuo* at 70 °C for 12 hours. The residue was extracted with dry acetone for 12 hours, the acetone extract was evaporated and the residue was twice recrystallised from ether to give dicyclohexylammonium (E)-[3-$^2H_1$]propenoate, 83 mg (58%), m.p. 131-132 °C. The corresponding salt of methacrylic

acid had m.p. 151.5-153 °C. Satisfactory elemental analyses for these compounds were obtained. [3-^{2}H]-Angelic acid, m.p. 42-43 °C, was obtained in 86% yield unaccompanied by significant amounts of 2-methylbutanoic acid.

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References

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4. W. Powells, C. Schuerch, F. A. Bovey and F. P. Hood, J. Amer. Chem. Soc., 89, 1396 (1967).

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6. (E)- and (Z)- 3-Bromopropenoic acids were readily obtained by the following modification of the published procedure[8]. Propiolic acid (1 g) was boiled under reflux with hydrobromic acid (8.8 M, 1.6 cm^{3}) for 8 hours with an oil-bath temperature of 100 °C. Evaporation of the solvent gave the (E)- and (Z)-acids ((1) and (2)) as a 4:1 mixture (n.m.r.) from which the pure (E)-acid (1) (1.6 g, 73%, m.p. 60-1 °C) was obtained after two to three recrystallisations from light petroleum-ether (40:60). Repetition of the preparation, but with an oil bath temperature of 140 °C gave a mixture of the (E)- and (Z)-acids ((1) and (2)) (1:9) from which the pure (Z)-acid (2) (1.5 g, 71%, m.p. 112-3 °C) was obtained after two to three recrystallisations from water.

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9. The reduction procedure was similar to that described by Buckles and Mock[5]. However, the reduction time can be greatly shortened with no significant diminution in yield, by adding the sodium amalgam in one batch and shaking the mixture vigorously for 30 minutes at room temperature.