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SYNTHESIS OF DEUTERIUM LABELLED ACIDS

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SUMMARY

Knoevenagel condensation of Meldrum's acid (**1**) with benzaldehyde, anisaldehyde, furfural, cinnamaldehyde and acetone gave the corresponding alkylidene derivatives (**3**) which were reduced with sodium borohydride to yield alkyl Meldrum's acids (**4**). Reaction of (**4**) with pyridine-D_2O at high temperature furnished α-dideuterated acids (**6**). The reduction of alkylidene derivatives (**3**) with sodium borodeuteride yielded β-deuterated alkyl Meldrum's acids (**7**) which on hydrolysis and decarboxylation yielded β-deuterated acids (**9**). α,α,β-Trideuterated acids (**11**) were prepared by hydrolysis and decarboxylation of (**7**) with pyridine-D_2O.

Keywords :Meldrum's acid, Knoevenagel condensation, sodium borodeuteride reduction, α-dideuterated, β-monodeuterated and α,α,β- trideuterated acids.

INTRODUCTION

Meldrum's acid (2,2-dimethyl-1,3-dioxane-4,6-dione), also known as isopropylidene malonate (1)(1) is a versatile reagent which has attracted considerable attention (2,3). Being a strong carbon acid with a pK_a (5.0) comparable to that of acetic acid, it is easy to generate the carbanion from this molecule. In the present paper we report a highly efficient method for the synthesis of deuterated acids using this acid.

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Knoevenagel condensation of Meldrum's acid (**1**) with benzaldehyde, anisaldehyde, furfural, cinnamaldehyde and acetone furnished the corresponding alkylidene derivatives (**3**) (4,5).Sodium borohydride reduction (6) of the alkylidene derivatives (**3**) yielded the corresponding mono alkyl Meldrum's acids (**4**) in high yields. The double bond in alkylidene Meldrum's acid is highly electrophilic and therefore reduction with sodium borohydride by conjugate addition is facilitated. The alkyl Meldrum's acids have a highly acidic α-hydrogen which can exchange with deuterium very easily. The hydrolysis and decarboxylation of (4) with pyridine and D_2O resulted in the formation of the corresponding α-deuterated alkyl malonic acids (**5**) which underwent decarboxylation to yield α-dideuterated carboxylic acids (**6**). The incorporation of deuterium was in the range 90-95%.

Sodium borodeuteride reduction of the alkylidene Meldrum's acid derivatives (**3**) yielded the corresponding β-monodeuterated alkyl Meldrum's acids (7) in high yields. The hydrolysis and decarboxylation of (7) with pyridine-H_2O furnished the corresponding β-monodeuterated acids (**9**). The ^1H NMR spectra of the products indicated virtually complete monodeuteration (~98%) of the β-position. The hydrolysis and decarboxylation of (7) with pyridine-D_2O yielded the corresponding α,α,β-trideuterated acids (**11**).

EXPERIMENTAL

Methanol (Qualigens) distilled, sodium borohydride (Merck), sodium borodeuteride (98%, Aldrich), deuterium oxide (99.8%, Merck), and pyridine (BDH), distilled over KOH pellets, were used. The ether extracts were dried over anhydrous sodium sulphate. Melting and boiling points are uncorrected. The ^1H NMR spectra were recorded on a FX 90Q FT-NMR spectrometer. The chemical shifts are expressed in δ-units.

β-Monodeuterated alkyl Meldrum's acids (7).

General procedure

The alkylidene derivative (**3** a-e) (5 mmol) was stirred in methanol (30 ml) and sodium borodeuteride (5 mmol) was added slowly over a period of 10 min with external cooling as necessary to keep the temperature between 15-20°C. After stirring for an additional 5 min, 1 N hydrochloric acid (15 ml) was added and resulting suspension chilled. The crystalline product was filtered , washed with cold water, dried and crystallised (usually hexane-toluene) to give the pure product (7 a-e). The deuterium incorporation as determined from the ^{1}H NMR spectra was greater than 95%. The following β-monodeuterated alkyl Meldrum's acids were prepared.

1) β-Monodeuterated benzyl Meldrum's acid (7a).

Yield 1.0 g (85%), m.p. 80°C(hexane) (lit.(6) m.p. 81°C);^{1}H NMR ($CDCl_3$,): 1.6 and 1.82 (3H each, s, 2xCH_3), 3.75 (1H, bd, J= 6 Hz,Ar-CH), 4.06 (1H, d, J= 6 Hz, CH), 7.85 (5H, s, Ar-H).

2) β-Monodeuterated 4-methoxyphenyl Meldrum's acid (7b).

Yield 1.2 g (83%), m.p. 65° C(hexane); ^{1}H NMR ($CDCl_3$) : 1.57 and 1.82 (3H each, s, 2xCH_3), 3.62 (1H, bd, J= 6 Hz, Ar-CH), 3.95 (1H, d,J= 6 Hz, CH), 4.0(3H, s, Ar-OCH_3), 7.23 (2H, d. J= 8 Hz, Ar-H) and 7.72 (2H, d, J= 8 Hz, Ar-H).

3) β-Monodeuterated furfuryl Meldrum's acid (7c).

Yield 0.95 g (84%), m.p. 91° C(hexane-toulene) (lit.(6) m.p.92-93°C); ^{1}H NMR ($CDCl_3$): 1.78 and 1.86 (3H each, s, 2xCH_3), 3.72 (1H, bd,J= 6 Hz, CH), 4.1 (1H, d, J= 6Hz,CH of Meldrum's acid), 6.62, 6.8 and 7.84 (1H each, three furan protons).

4) β-Monodeuterated cinnamyl Meldrum's acid (7d).

Yield 1.0 g (80%), m.p.107°C(hexane-toluene) (lit.(6) m.p.108-109°C); ^{1}H NMR ($CDCl_3$) : 1.89 and 1.94 (3H each, s, 2xCH_3), 3.24 (1H, bt, allylic proton), 3.94 (1H, d, J=6 Hz, CH of Meldrum's acid), 6.75 (1H, dd, J= 16.5 and 7 Hz, CH) 7.08 (1H, d, J=16.5 Hz, CH), 7.9 (5H, m, Ar-H).

5) β-Monodeuterated isopropyl Meldrum's acid (7e).

Yield 0.65 g (70%), m.p. 103° C(hexane-toluene) (lit.(6) m.p. 104-105°C); ^{1}H NMR ($CDCl_3$): 1.28 (6H, s, 2xCH_3), 1.86 (6H, s, 2xCH_3 of Meldrum's acid), 3.6 (1H, s,CH).

α-Dideuterated acids (6).

A mixture of the alkyl Meldrum's acid (4 a-e) (3 mmol), dry pyridine (3.5 ml,43.4 mmol) and deuterium oxide (1.0 ml,55 mmol) was kept at room temperature for 1 hr and then heated on a water bath for 3 hr. The reaction mixture was cooled, diluted with water, acidified with 10% hydrochloric acid and extracted with ether. The ether extract was washed with water and dried. Removal of solvent gave the desired α-dideuterated product (**6** a-e). The ^1H NMR spectra of the products showed very small broad peaks corresponding to the α-methylene position of the acids which indicates almost complete deuteration. A broad singlet was observed for the β-methylene hydrogen. The deuterium incorporation was in the range 90-95%.The following α-dideuterated acids were prepared.

1) α-Dideuterated 3-phenyl propionic acid (6a).

Yield 0.41 g (89%), m.p. 48°C(petroleum ether) (lit. (7) m.p. 47-49°C); ^1H NMR ($CDCl_3$): 2.93 (2H, s, Ar-CH_2), 7.2 (5H, s, Ar-H), 9.1 (1H, bs, COOH).

2) α-Dideuterated 3-(4'-methoxyphenyl) propionic acid (6b).

Yield 0.5 g (91%), m.p. 97°C(petroleum ether) (lit.(7) m.p. 98-100°C); ^1H NMR ($CDCl_3$): 3.05 (2H, s, Ar -CH_2) 4.02 (3H, s, Ar-OCH_3), 7.3 (2H, d, J= 8 Hz, Ar-H),7.7 (2H, d, J= 8 Hz, Ar-H), 10.5 (1H, bs, COOH).

3) α-Dideuterated 2-furan propionic acid (6c).

Yield 0.37g (86%), m.p. 57°C(chloroform-petroleum ether) (lit.(7) m.p. 58°C); ^1H NMR ($CDCl_3$); 2.95 (2H, s, CH_2), 6.62,6.8 and 7.8 (1H each, three furan protons), 10.2 (1H, s, COOH).

4) α-Dideuterated 5-phenyl-4-pentenoic acid (6d). Yield 0.48 g (85%), m.p. 90°C(petroleum ether) (lit.(7) m.p. 90-91°C); ^1H NMR ($CDCl_3$):2.6 (2H, broad s , CH =CH-$\underline{CH_2}$), 6.25 (1H, dt, CH), 6.5 (1H, d, J=16.5 Hz, CH), 7.35 (5H, m, Ar-H), 10.82 (1H, bs, COOH).

5) α-Dideuterated 3-methyl butanoic acid (6e).

Yield 0.26 g (85%) b.t. 170-172° C(lit.(7) b.p.175°C); ^{1}H NMR ($CDCl_3$): 0.96 (6H, d, J= 6Hz, 2 x CH_3), 2.0 (1H, m, CH_3-<u>CH</u>-CH_3), 10.1 (1H bs, COOH).

β-Monodeuterated acids (9).

A mixture of β-monodeuterated alkyl Meldrum's acid (7 a-e) (2.12 mmol), pyridine (3.0 ml,37.61 mmol) and water (1.0 ml,55.55 mmol) was heated on a water bath for 3 hr and the reaction was carried out as described above to furnish β-monodeuterated acids (9) The ^{1}H NMR spectra of the products indicated deuterium incorporation between 90 to 95%. The following β-monodeuterated acids were prepared.

1) β-Monodeuterated 3-phenyl propionic acid (9a).

Yield (84%) ; ^{1}H NMR ($CDCl_3$) :2.86 (2H, d, J= 6 Hz, CH_2), 3.14 (1H, bt, CH), 7.8 (5H, s, Ar-H), 10.71 (1H, bs, COOH).

2) β-Monodeuterated 3-(4'-methoxyphenyl)propionic acid (9b).

Yield (89%); ^{1}H NMR ($CDCl_3$) : 2.83 (2H, d, J= 6 Hz, CH_2), 3.04 (1H, bt, CH), 4.02 (3H, s, Ar-OCH_3), 7.33 (2H, d, J= 8 Hz, Ar-H), 7.7 (2H, d, J= 8 Hz, Ar-H), 10.9 (1H, bs, COOH).

3) β-Monodeuterated 2-furan propionic acid (9c).

Yield (84%); ^{1}H NMR ($CDCl_3$) : 2.68 (2H, d, J= 6Hz, CH_2), 2.96 (2H, bt, CH),6.6, 6.7 and 7.7 (1H each, three furan protons), 10.2 (1H, bs, COOH).

4) β-Monodeuterated 5-phenyl-4-pentenoic acid (9d).

Yield (80%); ^{1}H NMR ($CDCl_3$): 2.62 (2H, d, J= 6 Hz, CH_2), 2.58 (1H, bt, CH), 6.25 (1H, dt, CH), 6.5 (1H, d, J= 16.5 Hz, CH), 7.35 (5H, *m*, Ar-H), 10.82 (1H, bs, COOH).

5) β-Monodeuterated 3-methyl butanoic acid (9e).

Yield (77%); ^{1}H NMR($CDCl_3$) : 0.96 (6H, *s*, 2xCH_3), 2.2 (2H, bs, CH_2), 10.1 (1H, bs, COOH).

α,α,β-Trideuterated acids (11).

A mixture of β-monodeuterated alkyl Meldrum's acid (7 a-e) (2.12 mmol), dry pyridine (3.0 ml,37.61 mmol) and deuterium oxide (0.9 ml,49.5 mmol) were kept at room temperature for 1 hr and then the reaction was carried out in the manner described above to furnish α,α,β-trideuterated acids (11). The ^{1}H NMR spectra of the products indicated deuterium incorporation between 90-95%. The following α,α,β-trideuteriated acids were prepared.

1) α,α,β-Trideuterated 3-phenyl propionic acid (11a).

Yield (84%); ^{1}H NMR ($CDCl_3$): 3.1 (1H, bs, Ar-CH), 7.8 (5H, s, Ar-H), 10.5 (1H, bs, COOH).

2) α,α,β-Trideuterated 3-(4'-methoxyphenyl)propionic acid (11b).

Yield (89%); ^{1}H NMR ($CDCl_3$) 3.04 (1H, bs, Ar-CH), 4.02 (3H, s, Ar-OCH_3), 7.33 (2H, d, J= 8 Hz, Ar-H), 7.7 (2H, d, J= 8 Hz, Ar-H), 10.5 (1H, bs, COOH).

3) α,α,β-Trideuterated 2-furan propionic acid (11c).

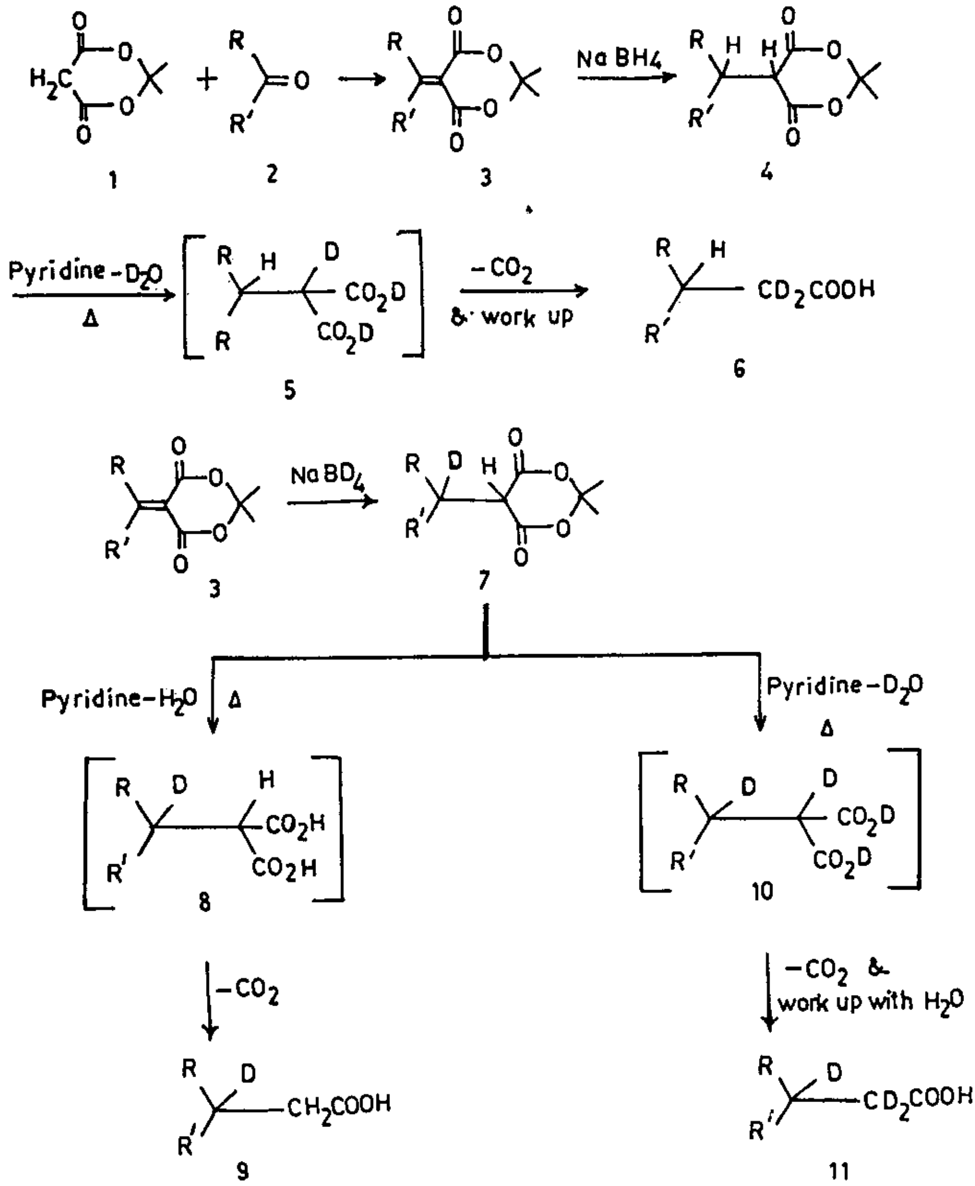
Yield (84%); ^{1}H NMR ($CDCl_3$) : 2.96 (1H, bs, CH), 10.2 (1H,bs,COOH).

4) α,α,β-Trideuterated 5-phenyl-4-pentenoic acid (11d).

Yield (80%); ^{1}H NMR ($CDCl_3$) : 2.58 (1H, bd, CH=CH - $\underline{CH}$), 6.25 (1H, dd, CH), 6.5 (1H, d, J= 16.5 Hz CH), 7.35 (5H, m, Ar-H).

5) α,α,β-Trideuterated 3-methyl butanoic acid (11e).

Yield (77%); ^{1}H NMR ($CDCl_3$) : 0.96 (6H, bs, 2x CH_3), 10.1 (1H, bs, COOH).



a, R = Ph, R' = H

b, R = p-OMe-Ph, R' = H

c, R =  , R' = H

d, R = Ph-CH=CH, R' = H

e, R = CH_3, R' = CH_3

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