

## 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<sub>2</sub>O at high temperature furnished  $\alpha$ -dideuterated acids (6). The reduction of alkylidene derivatives (3) with sodium borodeuteride yielded  $\beta$ -deuterated alkyl Meldrum's acids (7) which on hydrolysis and decarboxylation yielded  $\beta$ -deuterated acids (9).  $\alpha,\alpha,\beta$ -Trideuterated acids (11) were prepared by hydrolysis and decarboxylation of (7) with pyridine-D<sub>2</sub>O.

**Keywords:** Meldrum's acid, Knoevenagel condensation, sodium borodeuteride reduction,  $\alpha$ -dideuterated,  $\beta$ -monodeuterated and  $\alpha,\alpha,\beta$ -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  $\alpha$ -hydrogen which can exchange with deuterium very easily. The hydrolysis and decarboxylation of (4) with pyridine and D<sub>2</sub>O resulted in the formation of the corresponding  $\alpha$ -deuterated alkyl malonic acids (5) which underwent decarboxylation to yield  $\alpha$ -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  $\beta$ -monodeuterated alkyl Meldrum's acids (7) in high yields. The hydrolysis and decarboxylation of (7) with pyridine-H<sub>2</sub>O furnished the corresponding  $\beta$ -monodeuterated acids (9). The <sup>1</sup>H NMR spectra of the products indicated virtually complete monodeuteration (~98%) of the  $\beta$ -position. The hydrolysis and decarboxylation of (7) with pyridine-D<sub>2</sub>O yielded the corresponding  $\alpha,\alpha,\beta$ -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 <sup>1</sup>H NMR spectra were recorded on a FX 90Q FT-NMR spectrometer. The chemical shifts are expressed in  $\delta$ -units.

### **$\beta$ -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  $^1\text{H}$  NMR spectra was greater than 95%. The following  $\beta$ -monodeuterated alkyl Meldrum's acids were prepared.

**1)  $\beta$ -Monodeuterated benzyl Meldrum's acid (7a).**

Yield 1.0 g (85%), m.p. 80°C(hexane) (lit.(6) m.p. 81°C);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 1.6 and 1.82 (3H each, s,  $2\times\text{CH}_3$ ), 3.75 (1H, bd,  $J=6$  Hz, Ar-CH), 4.06 (1H, d,  $J=6$  Hz, CH), 7.85 (5H, s, Ar-H).

**2)  $\beta$ -Monodeuterated 4-methoxyphenyl Meldrum's acid (7b).**

Yield 1.2 g (83%), m.p. 65°C(hexane);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 1.57 and 1.82 (3H each, s,  $2\times\text{CH}_3$ ), 3.62 (1H, bd,  $J=6$  Hz, Ar-CH), 3.95 (1H, d,  $J=6$  Hz, CH), 4.0(3H, s, Ar- $\text{OCH}_3$ ), 7.23 (2H, d,  $J=8$  Hz, Ar-H) and 7.72 (2H, d,  $J=8$  Hz, Ar-H).

**3)  $\beta$ -Monodeuterated furfuryl Meldrum's acid (7c).**

Yield 0.95 g (84%), m.p. 91°C(hexane-toluene) (lit.(6) m.p.92-93°C);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 1.78 and 1.86 (3H each, s,  $2\times\text{CH}_3$ ), 3.72 (1H, bd,  $J=6$  Hz, CH), 4.1 (1H, d,  $J=6$  Hz, CH of Meldrum's acid), 6.62, 6.8 and 7.84 (1H each, three furan protons).

**4)  $\beta$ -Monodeuterated cinnamyl Meldrum's acid (7d).**

Yield 1.0 g (80%), m.p.107°C(hexane-toluene) (lit.(6) m.p.108-109°C);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 1.89 and 1.94 (3H each, s,  $2\times\text{CH}_3$ ), 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)  $\beta$ -Monodeuterated isopropyl Meldrum's acid (7e).**

Yield 0.65 g (70%), m.p. 103°C(hexane-toluene) (lit.(6) m.p. 104-105°C);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 1.28 (6H, s,  $2\times\text{CH}_3$ ), 1.86 (6H, s,  $2\times\text{CH}_3$  of Meldrum's acid), 3.6 (1H, s, CH).

**$\alpha$ -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  $\alpha$ -dideuterated product (6 a-e). The  $^1\text{H}$  NMR spectra of the products showed very small broad peaks corresponding to the  $\alpha$ -methylene position of the acids which indicates almost complete deuteration. A broad singlet was observed for the  $\beta$ -methylene hydrogen. The deuterium incorporation was in the range 90-95%.The following  $\alpha$ -dideuterated acids were prepared.

**1)  $\alpha$ -Dideuterated 3-phenyl propionic acid (6a).**

Yield 0.41 g (89%), m.p. 48°C(petroleum ether) (lit. (7) m.p. 47-49°C);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 2.93 (2H, s, Ar- $\text{CH}_2$ ), 7.2 (5H, s, Ar-H), 9.1 (1H, bs, COOH).

**2)  $\alpha$ -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);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 3.05 (2H, s, Ar - $\text{CH}_2$ ) 4.02 (3H, s, Ar- $\text{OCH}_3$ ), 7.3 (2H, d,  $J=8$  Hz, Ar-H ),7.7 (2H, d,  $J=8$  Hz, Ar-H ), 10.5 (1H, bs, COOH).

**3)  $\alpha$ -Dideuterated 2-furan propionic acid (6c).**

Yield 0.37g (86%), m.p. 57°C(chloroform-petroleum ether) (lit.(7) m.p. 58°C);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 2.95 (2H, s,  $\text{CH}_2$  ), 6.62,6.8 and 7.8 (1H each, three furan protons ), 10.2 (1H, s, COOH).

**4)  $\alpha$ -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);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):2.6 (2H, broad s,  $\text{CH}=\text{CH}-\text{CH}_2$ ), 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)  $\alpha$ -Dideuterated 3-methyl butanoic acid (6e).**

Yield 0.26 g (85%) b.t. 170-172° C(lit.(7) b.p.175°C);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 0.96 (6H, d,  $J = 6\text{ Hz}$ ,  $2 \times \text{CH}_3$ ), 2.0 (1H, m,  $\text{CH}_3\text{-}\underline{\text{CH}}\text{-CH}_3$ ), 10.1 (1H bs, COOH).

 **$\beta$ -Monodeuterated acids (9).**

A mixture of  $\beta$ -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  $\beta$ -monodeuterated acids (9) The  $^1\text{H}$  NMR spectra of the products indicated deuterium incorporation between 90 to 95%. The following  $\beta$ -monodeuterated acids were prepared.

**1)  $\beta$ -Monodeuterated 3-phenyl propionic acid (9a).**

Yield (84%);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 2.86 (2H, d,  $J = 6\text{ Hz}$ ,  $\text{CH}_2$ ), 3.14 (1H, bt, CH), 7.8 (5H, s, Ar-H), 10.71 (1H, bs, COOH).

**2)  $\beta$ -Monodeuterated 3-(4'-methoxyphenyl)propionic acid (9b).**

Yield (89%);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 2.83 (2H, d,  $J = 6\text{ Hz}$ ,  $\text{CH}_2$ ), 3.04 (1H, bt, CH), 4.02 (3H, s, Ar-OCH<sub>3</sub>), 7.33 (2H, d,  $J = 8\text{ Hz}$ , Ar-H), 7.7 (2H, d,  $J = 8\text{ Hz}$ , Ar-H), 10.9 (1H, bs, COOH).

**3)  $\beta$ -Monodeuterated 2-furan propionic acid (9c).**

Yield (84%);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 2.68 (2H, d,  $J = 6\text{ Hz}$ ,  $\text{CH}_2$ ), 2.96 (2H, bt, CH), 6.6, 6.7 and 7.7 (1H each, three furan protons), 10.2 (1H, bs, COOH).

**4)  $\beta$ -Monodeuterated 5-phenyl-4-pentenoic acid (9d).**

Yield (80%);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 2.62 (2H, d,  $J = 6\text{ Hz}$ ,  $\text{CH}_2$ ), 2.58 (1H, bt, CH), 6.25 (1H, dt, CH), 6.5 (1H, d,  $J = 16.5\text{ Hz}$ , CH), 7.35 (5H, m, Ar-H), 10.82 (1H, bs, COOH).

**5)  $\beta$ -Monodeuterated 3-methyl butanoic acid (9e).**

Yield (77%);  $^1\text{H}$  NMR( $\text{CDCl}_3$ ) : 0.96 (6H, s,  $2\times\text{CH}_3$ ), 2.2 (2H, bs,  $\text{CH}_2$ ), 10.1 (1H, bs, COOH).

 **$\alpha,\alpha,\beta$ -Trideuterated acids (11).**

A mixture of  $\beta$ -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  $\alpha,\alpha,\beta$ -trideuterated acids (11). The  $^1\text{H}$  NMR spectra of the products indicated deuterium incorporation between 90-95%. The following  $\alpha,\alpha,\beta$ -trideuterated acids were prepared.

**1)  $\alpha,\alpha,\beta$ -Trideuterated 3-phenyl propionic acid (11a).**

Yield (84%);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 3.1 (1H, bs, Ar-CH), 7.8 (5H, s, Ar-H), 10.5 (1H, bs, COOH).

**2)  $\alpha,\alpha,\beta$ -Trideuterated 3-(4'-methoxyphenyl)propionic acid (11b).**

Yield (89%);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) 3.04 (1H, bs, Ar-CH), 4.02 (3H, s, Ar-OCH<sub>3</sub>), 7.33 (2H, d,  $J = 8$  Hz, Ar-H), 7.7 (2H, d,  $J = 8$  Hz, Ar-H), 10.5 (1H, bs, COOH).

**3)  $\alpha,\alpha,\beta$ -Trideuterated 2-furan propionic acid (11c).**

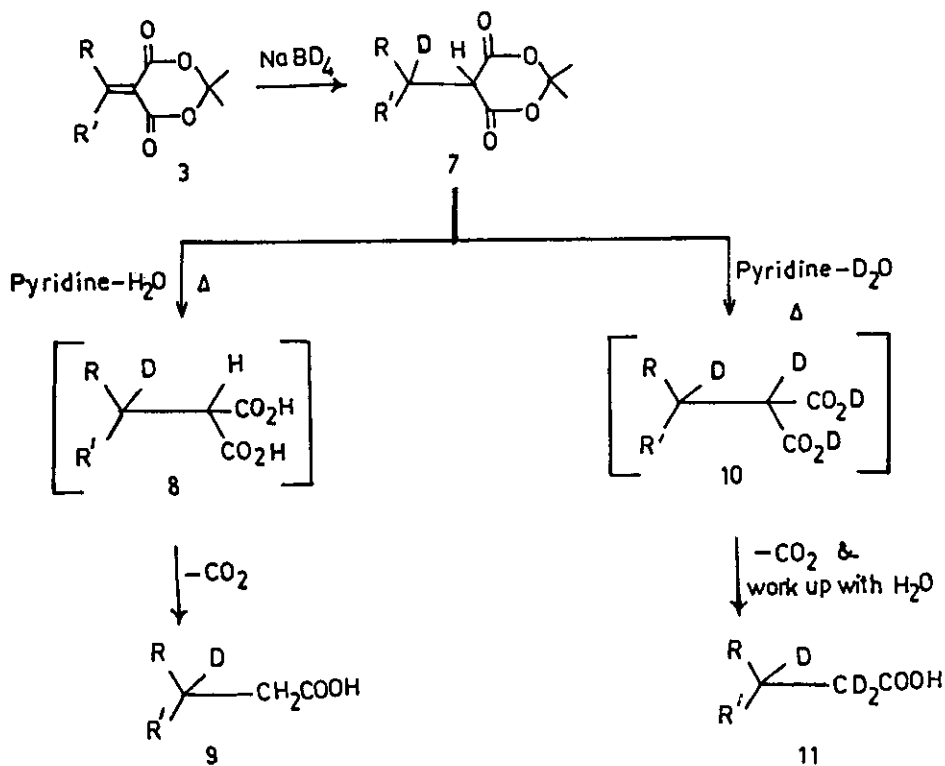
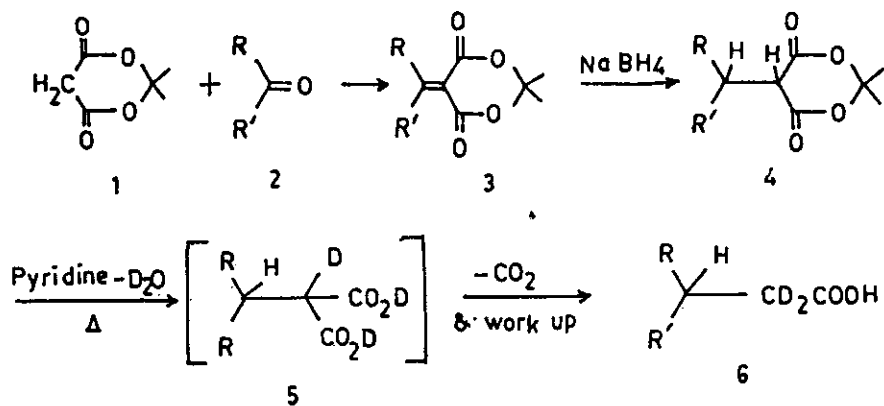
Yield (84%);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) : 2.96 (1H, bs, CH), 10.2 (1H, bs, COOH).

**4)  $\alpha,\alpha,\beta$ -Trideuterated 5-phenyl-4-pentenoic acid (11d).**

Yield (80%);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) : 2.58 (1H, bd,  $\text{CH}=\text{CH}-\underline{\text{CH}}$ ), 6.25 (1H, dd, CH), 6.5 (1H, d,  $J = 16.5$  Hz CH), 7.35 (5H, m, Ar-H).


**5)  $\alpha,\alpha,\beta$ -Trideuterated 3-methyl butanoic acid (11e).**

Yield (77%);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) : 0.96 (6H, bs,  $2\times\text{CH}_3$ ), 10.1 (1H, bs, COOH).



a, R = Ph, R' = H

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

 c, R = , R' = H

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

 e, R = CH<sub>3</sub>, R' = CH<sub>3</sub>

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#### REFERENCES

1. Davidson D. and Bernhard S.A.-J. Amer. Chem. Soc. 70: 3426 (1942)
2. McNab H.-Chem. Soc. Revs. 7: 345 (1978)
3. Bang-Chi-Chen.- Heterocycles 32: 529 (1991)
4. Swoboda G., Swoboda H. and Wessely F.-Monatsch. Chem. 95: 1283 (1964)
5. Schuster P., Polansky O. E. and Wessely F. -Monatsch. Chem. 95: 53 (1964)
6. Wright A.D., Haslego M. L. and Smith F. X.-Tetrahedron Lett. 25: 2325 (1979)
7. Dictionary of Organic Compounds, 5<sup>th</sup> Edtn. 1982, Chapman and Hall.