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Efficient and Versatile Synthesis of 3-substituted Glutaric Acids

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ABSTRACT

An efficient and versatile route to the synthesis of both aromatic and aliphatic 3-subsitituted glutaric acids from the corresponding aldehydes is described by converting the aldehydes to the 2-substituted tetraethyl propane tetracarboxylates through a Knoevenegel condensation followed by Michael addition. The resultant dimalonate are then made to undergo acid hydrolysis and decarboxylation in one pot reaction to obtain the corresponding glutaric acids in moderate yields (50 – 73%).

Keywords: Decarboxylation, Dimalonate, Glutaric acids, Knoevenegel condensation, Michael addition

INTRODUCTION

The 3-substituted pentanedioic acids, the glutaric acids (Scheme 1), are important intermediates for the synthesis of many biologically active natural products and important pharmaceuticals such as paroxetine (Liu *et. al.,* 2001; Yu *et. al*., 2000) and femoxitine, (Johnson *et. al*., 2002) which are selective serotonin uptake inhibitors and used as antidepressants. Glutaric acids can also be readily converted to the corresponding glutaric anhydrides which are highly used for desymmetrisation processes to produce chiral compounds (Heathcock *et. al*., 1993). Although diacids are readily converted to corresponding anhydrides by dehydrative cyclisation, most diacids used in such works are either purchased or synthesized using harsh laboratory conditions. Zimmermann *et al*. (2005) used ruthenium catalysed oxidation of monoenic fatty acids and diols using a combination of two strong oxidizing agents $RuCl_3$ / $NaIO_4$ to synthesize long chain diacids. Hronowski and Szarek (1988) employed oxidative cleavage of norbornene using $KMnO_4$ to produce 1,3-cyclopentanedicarboxylic acid in the synthesis of various nucleosides. In this work, various 3-aryl and 3-alkyl glutaric acids were readily synthesized in 3 steps and in moderate yields starting from the commercially available corresponding aldehydes.

METHODOLOGY

All solvents were obtained dry from a Grubbs dry solvent system and glassware was flame dried and cooled under vacuum before use. ^1H and ^{13}C NMR spectra were measured using $CDCl_3$ or DMSO as solvent unless otherwise stated, on a Brüker 250 or 400 MHz machine with an automated sample changer (unless otherwise stated). Chemical shifts for carbon and hydrogen are given on the δ scale relative to TMS (tetramethylsilane, δ = 0 ppm). Coupling constants were measured in Hz. ^{13}C NMR spectra were recorded using the JMOD method. Infrared spectra were recorded on a Perkin-Elmer 1600 FT-IR machine using 0.5mm NaCl cells and mass spectra were recorded on a Kratos instrument using electrospray technique unless otherwise stated.

General Procedure (A) for the synthesis of 3-(substitutedphenyl)glutaric acids.

A-1 Synthesis of benzylidenemalonate from 3-(o-Substituted)benzaldehydes

$AlCl_3$ (0.1 equiv.) was slowly added to a mixture of 2-substituted benzaldehyde and diethylmalonate (2 equiv.) and stirred at room temperature for 24 h. The mixture was poured into an ice-water / conc. HCl solution mixture (25 : 5 cm^3) and extracted with CH_2Cl_2 (3 × 15 cm^3). The combined organic extracts were dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* and excess diethylmalonate was removed by vacuum distillation (130 ^oC, 9.5 × 10^{-1} mbar) to give the crude diethyl 2-substitutedbenzylidenemalonate which was taken to next step (A-3) without further purification.

A-2 Synthesis of benzylidenemalonate from 3-(p-Substituted)benzaldehydes

A solution of *p*-substituted benzaldehyde in toluene (10 cm^3) was added drop-wise to a mixture of $AlCl_3$ (0.1 equiv.) and diethylmalonate (2 equiv.) in toluene (10 cm^3) and stirred at room temperature for 24 h. The mixture was poured into an ice-water / conc. HCl solution mixture (25 : 5 cm^3) and extracted with CH_2Cl_2 (3 × 25 cm^3). The combined organic extracts were dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* and excess diethylmalonate was removed by vacuum distillation (130 ^oC, 9.5 × 10^{-1} mbar) to give crude diethyl 4-substitutedbenzylidenemalonate as oily residue which was taken to next step (A-3) without further purification.

A-3 Synthesis of substitutedbenzylidene dimalonate

$AlCl_3$ (0.05 equiv.) was slowly added to a mixture of the crude benzylidenemalonate (obtained from procedure A-1 or A-2 above) and diethylmalonate (1 equiv.) and stirred at 60 ^oC for 24 h. Another portion of $AlCl_3$ (0.05 equiv.) was slowly added to the mixture and the reaction temperature was raised to 70 ^oC and further stirred for additional 24 h. The mixture was allowed to cool to room temperature, poured into an ice / conc. HCl solution mixture (25 : 5 cm^3) and extracted with CH_2Cl_2 (3 × 25 cm^3). The combined organic extracts were dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* and excess diethylmalonate was removed by vacuum distillation (130 ^oC, 9.5 × 10^{-1} mbar) to give the crude tetraethyl 2-(*ortho* or *para* substituted phenyl)propane-1,1,3,3-tetracarboxylate as oily residue which was taken to the next synthetic step without further purification.

A-4 Synthesis of 3-(substitutedphenyl) glutaric acids

The crude benzylidene dimalonate (obtained in A-3 above) in conc. HCl (10 cm^3) was heated at reflux for 24 h. The conc. HCl was evaporated to about 4 cm^3 and fresh conc. HCl (10 cm^3) was added and further heated at reflux for additional 24 h. The mixture was allowed to cool to room temperature, the solid was filtered off and recrystallised from EtOAc / petrol (40 – 60 ^oC).

3-Phenylpentan-1,5-dioic acid (4a)

Using general procedure *A-1* starting with (10.00 g, 94.34 mmol) of benzaldehyde and diethylmalonate (28.65 cm^3, 188.68 mmol), the crude diethyl benzylidenemalonate (16.26 g) was obtained as a yellow liquid which was not purified. Selected data; ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 0.91 (3H, t, *J* 7.1, C*H*$_3$), 1.10 (3H, t, *J* 7.1, C*H*$_3$), 4.17 (2H, q, *J* 7.1, C*H*$_2$), 4.23 (2H, q, *J* 7.1, C*H*$_2$), 6.82 – 7.37 (5H, m, ArC*H*), 7.56 (1H, s, =C*H*). The compound was subjected to general procedure *A-3*, and the crude tetraethyl 2-phenylpropane-1,1,3,3-tetracarboxylate (22.59 g) was obtained as a yellow liquid which was not purified at this stage. Selected data; ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 1.01 (6H, t, *J* 7.1, 2 × C*H*$_3$), 1.08 (6H, t, *J* 7.1, 2 × C*H*$_3$), 3.72 (4H, q, *J* 7.1, 2 × C*H*$_2$), 3.91 – 4.12 (7H, m, 2 × C*H*$_2$ and 3 × C*H*), 6.80 – 7.32 (5H, m, ArC*H*). This compound was subjected to procedure *A-4*, to give a brown solid that was purified by recrystallisation using EtOAc / petrol (40 – 60 ^oC) giving the title compound as white crystals (14.280 g, 73% over 3 steps). Mpt 141 – 143 ^oC (Found: 63.36; H, 4.65. $C_{11}H_{12}O_4$ requires C, 63.45; H, 5.81); υ_{max} (ATR)/cm^{-1} 2914 (broad), 2672, 1708, 1509; ^{1}H NMR (400 MHz; DMSO) δ_H 2.51 (2H, dd, *J* 15.8, 8.8, 2 × C*H*), 2.65 (2H, dd, *J* 15.8, 6.2, 2 × C*H*), 3.39 – 3.35 (1H, m, C*H*), 7.31 – 7.52 (5H, m, *J* 8.8, ArC*H*), 12.11 (2H, bs, 2 × O*H*); ^{13}C NMR (100 MHz; DMSO) δ_C 37.7 (*C*H), 40.6 (2 × *C*H$_2$), 117.2 (2 × Ar*C*H), 130.0 (2 × Ar*C*H), 141.0 (Ar*C*H), 161.4 (Ar*C*), 173.4 (2 × *C*=O); *m/z* (TOF MS ES$^+$) 209 (100%, MH^+ $C_{11}H_{13}O_4$).

3-(2-Fluorophenyl)pentan-1,5-dioic acid (4b)

Using general procedure *A-1* starting with (8.250 g, 66.47 mmol) of 2-fluorobenzaldehyde and diethylmalonate (20.20 cm^3, 132.9 mmol), the crude diethyl 2-fluorobenzylidenemalonate (17.00 g) was obtained as a yellow liquid which was not purified. Selected data; ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 1.16 – 1.21 (6H, m, 2 × C*H*$_3$), 4.22 (4H, qd, *J* 7.1, 1.2, 4 × C*H*), 7.00 – 7.07 (2H, m, ArC*H*), 7.28 – 7.34 (1H, m, ArC*H*), 7.38 [1H, (AX)$_2$, ArC*H*], 7.83 (1H, s, =C*H*). This compound when subjected to general procedure *A-3* gave the tetraethyl 2-(2-fluorophenyl)propane-1,1,3,3-tetracarboxylate (23.29 g) as a yellow liquid. ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 0.90 (6H, t, *J* 7.1, 2 × C*H*$_3$), 1.11 (6H, t, *J* 7.1, 2 × C*H*$_3$), 3.82 (4H, q, *J* 7.1, 2 × C*H*$_2$), 3.98 – 4.06 [6H, m, 2 × C*H*$_2$ and 2 × C*H*(CO)$_2$], 4.36 (1H, t, *J* 9.4, C*H*), 6.83 – 6.88 (1H, m, ArC*H*), 6.90 – 6.94 (1H, m, ArC*H*), 7.07 – 7.12 (1H, m, ArC*H*), 7.28 – 7.32 (1H, m, ArC*H*); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 13.7 (2 × *C*H$_3$), 13.9 (2 × *C*H$_3$), 38.3 (*C*H), 54.4 (2 × *C*H), 61.4 (2 × *C*H$_2$), 61.7 (2 × *C*H$_2$), 115.4 (d, $J_{C\text{-}F}$ 22.9, Ar*C*H), 123.8 (d, $J_{C\text{-}F}$ 3.3, Ar*C*H), 124.8 (d, $J_{C\text{-}F}$ 14.6, Ar*C*), 129.5 (d, $J_{C\text{-}F}$ 8.6, Ar*C*H), 131.6 (Ar*C*H), 161.2 (d, $J_{C\text{-}F}$ 248, Ar*C*), 167.4 (2 × *C*=O), 167.8 (2 × *C*=O). The above material was subjected to procedure *A-4* to give a brown solid that was purified by recrystallisation from EtOAc / petrol (40 – 60 ^oC) giving the title compound as white crystals (7.660 g, 51% over 3 steps). Mpt 140 – 142 ^oC; (Found: C, 58.23; H, 4.96. $C_{12}H_{14}O_4$ requires C, 58.41; H, 4.90); υ_{max} (ATR)/cm^{-1} 2890 (broad), 1693, 1585; ^{1}H NMR (400 MHz; DMSO) δ_H 2.58 (2H, dd, *J* 15.9, 8.5, 2 × C*H*), 2.66 (2H, dd, *J* 15.9, 6.6, 2 × C*H*), 3.73 (1H, quintet, *J* 7.0, C*H*), 7.09 – 7.15 (2H, m, ArC*H*), 7.21 – 7.27 (1H, m, ArC*H*), 7.37 (1H, td, *J* 7.7, 1.5, ArC*H*), 12.16 (2H, s, 2 × O*H*); ^{13}C NMR (100 MHz; DMSO) δ_C 31.8 (*C*H), 39.4 (2 × *C*H$_2$), 115.8 (d, $J_{C\text{-}F}$ 22.5, Ar*C*H), 124.7 (d, $J_{C\text{-}F}$ 2.9, Ar*C*H), 128.7 (d, $J_{C\text{-}F}$ 8.4, Ar*C*H), 129.5 (d, $J_{C\text{-}F}$ 4.5, Ar*C*H), 130.4 (d, $J_{C\text{-}F}$ 14.2, Ar*C*), 160.7 (d, $J_{C\text{-}F}$ 244.2, Ar*C*), 173.1 (2 × *C*=O); *m/z* (TOF MS ES$^+$) 227 (70%, MH^+ $C_{11}H_{12}FO_4$), 209 (100).

3-(4-Fluorophenyl)pentan-1,5-dioic acid (4c)

Using general procedure *A-2* starting with (10.00 g, 80.57 mmol) of 4-fluorobenzaldehyde and diethylmalonate (24.50 cm^3, 161.1 mmol), the crude diethyl 4-fluorobenzylidenemalonate (18.22 g) was obtained as a yellow liquid which was not

purified. Selected data; ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 0.90 (3H, t, *J* 7.1, C*H*$_3$), 1.08 (3H, t, *J* 7.1, C*H*$_3$), 4.16 (2H, q, *J* 7.1, C*H*$_2$), 4.21 (2H, q, *J* 7.1, C*H*$_2$), 6.82 [2H, (AX)$_2$, ArC*H*], 7.35 [2H, (AX)$_2$, ArC*H*], 7.56 (1H, s, =C*H*). This material was subjected to general procedure *A-3*, and the crude tetraethyl 2-(4-fluorophenyl)propane-1,1,3,3-tetracarboxylate (23.29 g) was obtained as a yellow liquid which was not purified at this stage. Selected data; ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 0.89 (6H, t, *J* 7.1, 2 × C*H*$_3$), 1.08 (6H, t, *J* 7.1, 2 × C*H*$_3$), 3.82 (4H, q, *J* 7.1, 2 × C*H*$_2$), 3.94 – 4.02 (7H, m, 2 × C*H*$_2$ and 3 × C*H*), 6.80 (2H, app t, *J* 8.7, 2 × ArC*H*), 7.24 [2H, (AX)$_2$, ArC*H*]. It was then subjected to procedure *A-4*, to give a brown solid that was purified by recrystallisation from EtOAc / petrol (40 – 60 ^{o}C) giving the title compound as white crystals (9.881 g, 55% over 3 steps). Mpt 145 – 147 ^{o}C (Liu *et. al*., (2001); Chaubey and Ghosh, (2012) 146 – 147 ^{o}C); (Found: 58.36; H, 4.65. $C_{11}H_{11}FO_4$ requires C, 58.41; H, 4.90); υ_{max} (ATR)/cm^{-1} 2914 (broad), 2672, 1708, 1604, 1509; ^{1}H NMR (400 MHz; DMSO) δ_H 2.51 (2H, dd, *J* 15.8, 8.8, 2 × CH*H*), 2.65 (2H, dd, *J* 15.8, 6.2, 2 × CH*H*), 3.37 – 3.45 (1H, m, C*H*), 7.10 (2H, app t, *J* 8.8, ArC*H*), 7.31 [2H, (AX)$_2$, ArC*H*], 12.11 (2H, bs, 2 × O*H*); ^{13}C NMR (100 MHz; DMSO) δ_C 37.7 (*C*H), 40.6 (2 × *C*H$_2$), 115.3 (d, *J* $_{C-F}$ 21.0, 2 × Ar*C*H), 129.8 (d, *J* $_{C-F}$ 7.8, 2 × Ar*C*H), 140.0 (d, *J* $_{C-F}$ 2.6, Ar*C*), 161.3 (d, *J* $_{C-F}$ 241.9, Ar*C*), 173.2 (2 × *C*=O); *m*/*z* (TOF MS ES$^+$) 227 (30%, MH$^+$ $C_{11}H_{12}FO_4$), 250 (20%, MH$^+$ + Na), 209 (100).

3-(2-Methylphenyl)pentan-1,5-dioic acid (4d)

Using general procedure *A-1* starting with (9.350 g, 77.82 mmol) of 2-methylbenzaldehyde and diethylmalonate (23.60 cm^3, 155.6 mmol), the crude diethyl 2-methylbenzylidenemalonate (17.00 g) was obtained as a yellow liquid, which was not purified. Selected data; ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 1.05 (3H, t, *J* 7.1, C*H*$_3$), 1.22 (3H, t, *J* 7.1, C*H*$_3$), 2.24 (3H, s, C*H*$_3$), 4.10 (2H, q, *J* 7.1, C*H*$_2$), 4.20 (2H, q, *J* 7.1, C*H*$_2$), 7.02 – 7.09 (2H, m, ArC*H*), 7.15 (1H, app td, *J* 7.5, 1.2, ArC*H*), 7.26 (1H, d, *J* 7.5, ArC*H*), 7.87 (1H, s, =C*H*). This compound was then subjected to procedure *A-3* to give the crude tetraethyl 2-(2-methylphenyl)propane-1,1,3,3-tetracarboxylate (15.90 g) as a yellow liquid which was again not purified at this stage. Selected data; ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 0.89 (6H, t, *J* 7.1, 2 × C*H*$_3$), 1.17 (6H, t, *J* 7.1, 2 × C*H*$_3$), 2.42 (3H, s, C*H*$_3$), 3.80 (4H, q, *J* 7.1, 2 × C*H*$_2$), 3.96 [2H, d, *J* 9.5, 2 × C*H*(CO)$_2$], 4.03 – 4.11 (4H, m, 2 × C*H*$_2$), 4.51 (1H, t, *J* 9.5, C*H*), 7.00 – 7.06 (3H, m, ArC*H*), 7.18 (1H, d, *J* 6.8, ArC*H*). Subjecting this compound to the general procedure *A-4* gave a brown solid that was purified by recrystallisation from EtOAc / petrol (40 – 60 ^{o}C) giving the title compound as white crystals (8.942 g, 52% over 3 steps). Mpt 154 – 156 ^{o}C; (Found: 64.71; H, 6.46. $C_{12}H_{14}O_4$ requires C, 64.85; H, 6.35); υ_{max} (ATR)/cm^{-1} 2971 (broad), 1708; ^{1}H NMR (400 MHz; DMSO) δ_H 2.37 (3H, s, C*H*$_3$), 2.49 – 2.63 (4H, m, 2 × C*H*$_2$), 3.69 – 3.76 (1H, m, C*H*), 7.04 – 7.16 (3H, m, ArC*H*), 7.27 (1H, d, *J* 7.6, ArC*H*), 12.60 (2H, s, 2 × O*H*); ^{13}C NMR (100 MHz; DMSO) δ_C 19.7 (*C*H$_3$), 33.2 (*C*H), 40.5 (2 × *C*H$_2$), 126.2 (Ar*C*H), 126.4 (Ar*C*H), 126.5 (Ar*C*H), 130.5 (Ar*C*H), 136.2 (Ar*C*), 142.3 (Ar*C*), 173.4 (2 × *C*=O); *m*/*z* (TOF ES$^-$) 221 (100%, M-H$^-$).

3-(4-Methylphenyl)pentan-1,5-dioic acid (4e)

Using general procedure *A-2* starting with (10.00 g, 83.23 mmol) of 4-methylbenzaldehyde and diethylmalonate (25.30 cm^3, 166.5 mmol), the crude diethyl 4-methylbenzylidenemalonate (17.23 g) was obtained as a yellow liquid, and was subjected to procedure *A-3* to obtain the crude tetraethyl 2-(4-methylphenyl)propane-1,1,3,3-tetracarboxylate (25.20 g) as a yellow liquid which was not purified at this stage. Selected data; ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 0.98 (6H, t, *J* 7.1, 2 × C*H*$_3$), 1.18 (6H, t, *J* 7.1, 2 × C*H*$_3$), 2.22 (3H, s, C*H*$_3$), 3.90 (4H, q, *J* 7.1, 2 × C*H*$_2$), 4.02 – 4.15 (7H, m, 2 × C*H*$_2$ and 3 × C*H*), 7.0 (2H, d, *J* 8.0, 2 × ArC*H*), 7.17 (2H, d, *J* 8.0, 2 × ArC*H*). This crude material was subjected to general procedure *A-4* to give a brown solid that was purified by recrystallisation from EtOAc / petrol (40 – 60 ^{o}C) giving the title compound as white crystals (10.55 g, 57% over 3 steps). Mpt 122 – 124 ^{o}C (Adamo *et. al*., (2007) 118 – 121 ^{o}C); (Found: 64.85; H, 6.13. $C_{12}H_{14}O_4$ requires C, 64.85; H, 6.35); υ_{max} (ATR)/cm^{-1} 2925 (broad), 1704, 1515; ^{1}H NMR (400 MHz; DMSO) δ_H 2.25 (3H, s, C*H*$_3$), 2.48 (2H, dd, *J* 15.7, 8.7, 2 × CH*H*), 2.62 (2H, dd, *J* 15.7, 6.3, 2 × CH*H*), 3.34 – 3.41 (1H, m, C*H*), 7.07 (2H, d, *J* 8.0, 2 × ArC*H*), 7.14 (2H, d, *J* 8.0, 2 × ArC*H*), 12.06 (2H, s, 2 × O*H*); ^{13}C NMR (100 MHz; DMSO) δ_C 21.1 (*C*H$_3$), 38.0 (*C*H), 40.7 (2 × *C*H$_2$), 127.8 (2 × Ar*C*H), 129.2 (2 × Ar*C*H), 135.8 (Ar*C*), 140.8 (Ar*C*), 173.3 (2 × *C*=O); *m*/*z* (TOF MS ES$^+$) 223 (10%, MH$^+$), 205 (100, MH$^+$ - H_2O).

3-(1-Naphthyl)pentan-1,5-dioic acid (4f)

Using general procedure *A-1* starting with (10.35 g, 66.27 mmol) of 1-naphthaldehyde and diethylmalonate 20.12 cm^3 (132.5 mmol), the crude diethyl 1-naphthylidenemalonate (19.25 g) was obtained as a pale yellow liquid, which was not purified. Selected data; ^{1}H NMR (400 MHz; $CDCl_3$) δ_H ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 1.06 (3H, t, *J* 7.1, C*H*$_3$), 1.38 (3H, t, *J* 7.1, C*H*$_3$), 4.18 (2H, q, *J* 7.1, C*H*$_2$), 4.38 (2H, q, *J* 7.1, C*H*$_2$), 7.42 (1H, t, *J* 7.8, ArC*H*), 7.49 – 7.56 (2H, m, ArC*H*), 7.61 (1H, d, *J* 7.8, ArC*H*), 7.83 – 7.87 (2H, m, ArC*H*), 8.00 (1H, d, *J* 7.8, ArC*H*), 8.50 (1H, s, =C*H*). The unpurified compound was subjected to procedure *A-3*, and the crude tetraethyl 2-(1-naphthyl)propane-1,1,3,3-tetracarboxylate (32.56

g) was obtained as dark brown liquid which again was not purified at this stage. Selected data; ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 0.73 (6H, t, *J* 7.1, 2 × C*H*$_3$), 1.17 (6H, t, *J* 7.1, 2 × C*H*$_3$), 3.67 – 3.76 (4H, m, 2 × C*H*$_2$), 4.06 – 4.14 (4H, m, 2 × C*H*$_2$), 4.24 [2H, d, *J* 9.0, 2 × C*H*(CO)$_2$], 5.25 (1H, t, *J* 9.0, C*H*), 7.37 (1H, t, *J* 7.7, ArC*H*), 7.43 (1H, t, *J* 7.7, ArC*H*), 7.51 – 7.56 (2H, m, ArC*H*), 7.70 (1H, d, *J* 8.1, ArC*H*), 7.76 (1H, d, *J* 8.1, ArC*H*), 8.41 (1H, d, *J* 8.1, ArC*H*). This material was subjected to general procedure *A-4* to give a brown solid that was purified by recrystallisation from EtOAc / petrol (40 – 60 ^{o}C) giving the title compound as white crystals (10.20 g, 60% over 3 steps). Mpt 185 – 187 ^{o}C (D. H. Hey and D. H. Kohn, 1949) 181.5 ^{o}C); (Found: C, 69.64; H, 5.39. $C_{15}H_{14}O_4$ requires C, 69.76; H, 5.46); υ_{max} (ATR)/cm^{-1} 2904 (broad), 1707, 1599, 1511; ^{1}H NMR (400 MHz; DMSO) 2.76 (4H, d, *J* 7.2, 2 × C*H*$_2$), 3.39 (1H, quintet, *J* 7.2, C*H*), 7.46 – 7.62 (4H, m, ArC*H*), 7.80 (1H, d, *J* 7.8, ArC*H*), 7.93 (1H, d, *J* 8.1, ArC*H*), 8.21 (1H, d, *J* 8.6, ArC*H*), 12.17 (2H, s, 2 × O*H*); ^{13}C NMR (100 MHz; DMSO) δ_C 38.0 (*C*H), 40.3 (2 × *C*H$_2$), 123.5 (Ar*C*H), 123.7 (Ar*C*H), 125.9 (Ar*C*H), 126.0 (Ar*C*H), 126.6 (Ar*C*H), 127.3 (Ar*C*H), 129.2 (Ar*C*H), 131.5 (Ar*C*), 134.0 (Ar*C*), 140.0 (Ar*C*), 173.4 (2 × *C*=O); *m*/*z* (TOF MS ES$^-$) 257 (100%, M-H$^-$ $C_{15}H_{13}O_4$).

3-Isopropylpentan-1,5-dioic acid (8)

Piperidine (1.180 g, 13.86 mmol) was added to a mixture of isobutyraldehyde (10.00 g, 138.7 mmol) and diethylmalonate (22.21 g, 138.7 mmol) dissolved in pyridine (25 cm^3) and stirred at 70 ^{o}C for 48 h. The mixture was cooled to room temperature and ethyl acetate (150 cm^3) was added, washed with 1M HCl (4 × 20 cm^3), then brine (20 cm^3), dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* to give crude diethyl isopropylidenemalonate (21.53 g) as a yellow oily residue which was subjected to procedure *A-3* to obtain the crude tetraethyl 2-isopropylpropane-1,1,3,3-tetracarboxylate (25.56 g) as an oily residue which again was not purified at this stage. This material was subjected to general procedure *A-4* but the final acidic mixture, after allowing to cool to room temperature, was poured in to ice / water mixture (50 cm^3) and extracted with ether (4 × 30 cm^3). The combined ethereal portions were washed with water, dried over $MgSO_4$, filtered and solvent evaporated *in vacuo* to obtain a dark brown liquid which upon standing in fridge turned to brown solid. Purification by recrystallisation from EtOAc / petrol (40 – 60 ^{o}C) gave the title compound as white crystals (8.211 g, 34% over 3 steps). Mpt 94 – 96 ^{o}C (Irwin and Jones, (1977) 100 – 101 ^{o}C); (Found: 55.14; H, 8.16. $C_8H_{14}O_4$ requires C, 55.16; H, 8.10); υ_{max} (ATR)/cm^{-1} 2966 (broad), 2160, 1692; ^{1}H NMR (400 MHz; DMSO) δ_H 0.82 (6H, d, *J* 6.9, 2 × C*H*$_3$), 1.70 (1H, pent d, *J* 6.9, 3.4, C*H*), 2.10 – 2.15 (3H, m, 2× CH*H* and C*H*), 2.19 – 2.26 (2H, m, 2 × CH*H*), 12.10 (2H, bs, 2 × O*H*); ^{13}C NMR (100 MHz; DMSO) δ_C 19.2 (2 × *C*H$_3$), 29.9 (*C*H), 35.9 (2 × *C*H$_2$), 37.5 (*C*H), 174.5 (2 × *C*=O); *m*/*z* (TOF MS ES$^+$) 198 (40%, M + Na$^+$), 175 (30, MH$^+$ $C_8H_{15}O_4$), 157 (100).

3-*tert*-Butylpentan-1,5-dioic acid (12)

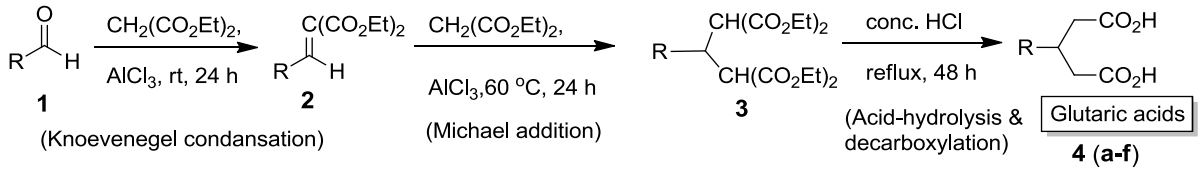
A mixture of trimethylacetaldehyde (10.00 g, 116.3 mmol), ethylcyanoacetate (13.14 g, 116.3 mmol) and piperidine (0.100 cm^3, 1.163 mmol) in toluene (40 cm^3) was heated at reflux for 4 hours and allowed to cool to room temperature. The solvent was removed *in vacuo* and the residue was dissolved in CH_2Cl_2 (30.00 cm^3), dried over $MgSO_4$ and filtered. The solvent was evaporated *in vacuo* to give an orange oily residue (20.70 g) which was added to a solution of dimethylsodiomalonate which was made from dimethylmalonate (15.35 g, 116.3 mmol) and sodium (0.268 g, 11.63 mmol) in dry MeOH (20 cm^3). The mixture was heated at reflux for 17 hours, allowed to cool to room temperature and acidified with 1M HCl (15 cm^3). The mixture was then extracted with ether (5 × 60 cm^3) and the combined ethereal fractions were washed with water (60 cm^3), dried over $MgSO_4$ and filtered. The ether was evaporated under reduced pressure to give the crude cyanotricarboxylate as orange oil (29.60 g). The crude cyanotricarboxylate (29.60 g, ~ 94.57 mmol) in conc. HCl (10 cm^3) was heated at reflux for 24 h. The conc. HCl was evaporated to about 4 cm^3 and fresh conc. HCl (10 cm^3) was added. The reaction mixture was again heated at reflux for additional 24 h. The mixture was allowed to cool to room temperature, poured in to ice / water mixture (50 cm^3) and extracted with ether (5 × 30 cm^3). The combined ethereal portions were washed with water, dried over $MgSO_4$, filtered and solvent evaporated *in vacuo* to obtain a dark brown liquid as crude which upon standing in fridge turned to brown solid. Purification by recrystallisation from EtOAc / hexane gave the title compound as white crystals (12.76 g, 58% over 3 steps). Mpt 146 – 148 ^{o}C (Heathcock and Theisen, (1993) 144.5 – 145.5 ^{o}C); υ_{max} (ATR)/cm^{-1} 2966 (broad), 2671, 1704; ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 0.96 (9H, s, 3 × C*H*$_3$), 2.15 – 2.22 (2H, m, 2 × CH*H*), 2.32 (1H, tt, *J* 9.7, 1.8, C*H*), 2.66 (2H, dd, *J* 14.2, 1.8, 2 × CH*H*), 12.36 (2H, bs, 2 × O*H*); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 27.3 (3 × *C*H$_3$), 33.1 (*C*), 36.1 (2 × *C*H$_2$), 42.4 (*C*H), 180.9 (2 × *C*=O); *m*/*z* (TOF MS ES$^+$) 189.1130 (100%, MH$^+$ $C_9H_{17}O_4$ requires 189.1127). Only melting point and IR were provided in the literature (Heathcock and Theisen (1993); Klein & Stollar, (1973)).

RESULTS AND DISCUSSIONS

The general method for the synthesis of the glutaric acids is represented in Scheme 1. The commercially available aldehyde starting materials were first converted to the corresponding 2-

substituted tetraethyl propane tetracarboxylate (dimalonate) through a Knoevenegel condensation followed by Michael addition. The resultant dimalonate were then made to undergo acid hydrolysis and decarboxylation in one pot, without any purification, to obtain the corresponding glutaric acids in moderate yields.

The 3-arylsubstituted glutaric acids **4a, b, d** & **f** (Table 1) were synthesized from the corresponding aldehydes by first converting the commercially available aldehydes to 2-substituted tetraethyl propane tetracarboxylates through a Knoevenegel condensation followed by Michael addition using a solvent-free condition. However in the case of more reactive *p*-substituted phenyl aldehydes, **4c** & **4e**, the solvent-free condition did not give the required tetracarboxylates but the corresponding benzoic acid readily precipitates instead which might be due to a self-oxidation (Cannizaro) reaction of the aromatic aldehyde starting materials. However a drop-wise addition of the solution of the aldehyde in toluene to the mixture of diethylmalonate and $AlCl_3$ in toluene adopted in the Knoevenegel condensation step led to the formation of the required product. All the resultant dimalonates were smoothly taken to the corresponding glutaric acids, in 50 -74% yields over the three steps without any further purification, by heating the unpurified Michael addition products at reflux for 48 hours.



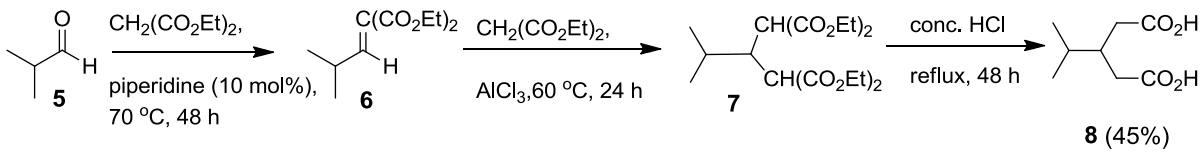
Scheme 1. Route to 3-aryl glutaric acids

Table 1. Synthesis of 3-aryl glutaric acids

Entry	R	Yield
1.	C_6H_5 **(4a)**	73%
2.	2-F-C_6H_4 **(4b)**	52%
3.	4-F-C_6H_4 **(4c)**	57%
4.	2- CH_3-C_6H_4 **(4d)**	51%
5.	4- CH_3-C_6H_4 **(4e)**	50%
6.	1-Naphthyl **(4f)**	60%

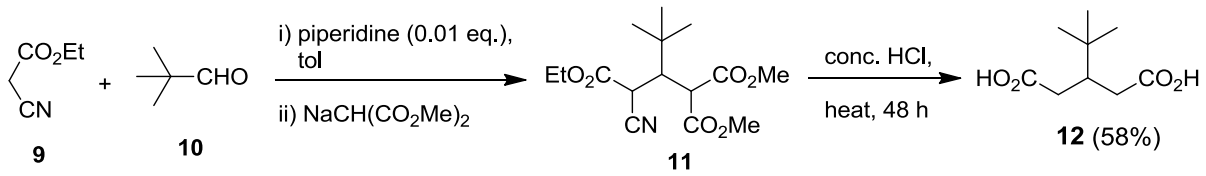
Yield over 3 steps

For the synthesis of 3-alkyl glutaric acids **8** & **12** the above method gave low yield of the corresponding glutaric acid products. The 3-isopropyl glutaric acid **8** was synthesized by slightly adjusting the procedure in the Knoevenegel condensation step (see experimental). A mixture of the isobutyraldehyde starting material and the diethylmalonate in presence of 10 mol% of piperidine was dissolved in pyridine and stirred at 70 °C for 48 hours to give the Knoevenegel condensation product after a work up. The rest of the procedure as shown in Scheme 1 was adopted for the rest of the synthesis to obtain 3-isopropyl glutaric acid **8** in 45% yield over the three steps (Scheme 2).



Scheme 2. Route to 3-isopropylglutaric acid (8)

For the synthesis of 3-*tert*-butyl glutaric acid **12** on the other hand, the method of Theisen *et al*. (1993) which uses ethyl cyanoacetate in the Knoevenegel step and dimethyl sodiomalonate for the Michael addition was adopted (Scheme 3). The resultant cyano dimalonate was then made to undergo acid hydrolysis and decarboxylation in one pot, without any further purification, to obtain the diacid **12** in 58% yield over 3 steps (Scheme 3).



Scheme 3. Route to 3-*tert*-butyl glutaric acid (12)

CONCLUSION

In conclusion, an efficient strategy for the synthesis of 3-substituted glutaric acids was developed. The method is easy to employ and uses common laboratory reaction conditions. Most of the glutaric acids are water insoluble and readily precipitate out. Work is underway to convert these glutaric acids to useful compounds or intermediates for the synthesis of complex organic molecules.

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