Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron
Tetrahedron 63 (2007) 9741–9745

Three multicomponent reactions of 3,5-dimethyl-4-nitroisoxazole

Mauro F. A. Adamo,[a,*] Vivekananda R. Konda,[a] Donato Donati,[b] Piero Sarti-Fantoni[c] and Tomas Torroba[d]

[a]*Centre for Synthesis and Chemical Biology (CSCB), Department of Pharmaceutical and Medicinal Chemistry, The Royal College of Surgeons in Ireland, 123 St. Stephen's Green, Dublin 2, Dublin, Ireland*
[b]*Dipartimento di Chimica, Università di Siena, Via Aldo Moro, Siena 53100, Italy*
[c]*Dipartimento di Chimica Organica 'U. Schiff', Università di Firenze, Via della Lastruccia, Sesto Fiorentino 50019, Italy*
[d]*Quìmica Organica, Facultad de Ciencias, Universidad de Burgos, 09001 Burgos, Spain*

Received 17 April 2007; revised 21 June 2007; accepted 6 July 2007
Available online 13 July 2007

Abstract—The title compound is used to prepare 3-arylglutaric acids, bis-isoxazoles and bis-pyrazoles from commercially available materials. The methodologies described have afforded important synthetic intermediates in high yields and without the use of chromatography.

1. Introduction

Glutaric acid and its derivatives are important constituents in several pharmaceutically significant natural products and have a wide variety of uses in medicinal chemistry.[1–5] The most prominent examples are (*R*)-Baclofen, a selective $GABA_B$ receptor agonist,[1–3] and some NK-receptor antagonists.[4,5] As a part of our ongoing studies regarding the use of 3,5-dimethyl-4-nitroisoxazole **1** (Fig. 1) for the development of multicomponent syntheses, we envisaged a novel fast synthesis of 3-arylglutaric acids. Our approach to the development of diversity orientated synthesis is based on the optimisation of multicomponent procedures that allow the preparation of compounds in a modular fashion and under homogeneous reaction conditions.[6–12] For example, we have shown that **1** could be employed efficiently for the preparation of spiroisoxazolines,[6,7] heteroarylpropionic acids[8–10] or 3-indolepropionic acids.[11]

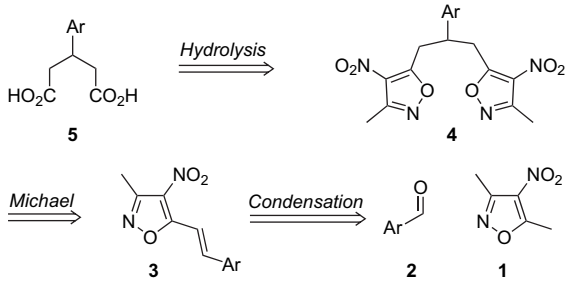


Figure 1. Retrosynthetic analysis of target **5**.

A retrosynthetic analysis of target **5** showed that 3,5-dimethyl-4-nitroisoxazole **1** could be employed as a starting material (Fig. 1).

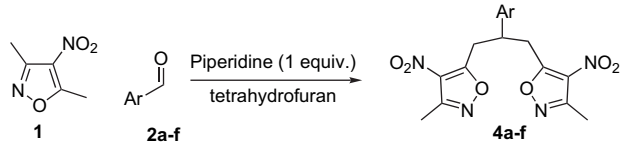
We have extensively studied the condensation of isoxazole **1** with aromatic aldehydes, as a means of generating compounds **3**.[12] During these studies we found that when isoxazole **1** and an aldehyde **2** were reacted in the presence of stoichiometric amounts of piperidine base, compound **4** was obtained as a side product.[13] Therefore, it was thought that compound **4** could be obtained as the major product of the reaction by adjusting the ratio of reactants **1** and **2**. Once prepared, compound **4** would then serve as a precursor to generate the desired 3-arylglutaric acid **5**.

2. Results and discussion

We started our investigation from the preparation of compound **4d** (Scheme 1). In a test experiment we reacted 1.0 equiv of benzaldehyde with 2.2 equiv of isoxazole **1** in the presence of 1.0 equiv of piperidine base. We were delighted to observe that under these conditions compound **4d** was obtained as the sole product of the reaction. The generality of this process was demonstrated by the preparation of a small family of compounds **4a–f** obtained by variation of the aldehyde component (Scheme 1 and Table 1). We have tried to implement this procedure by decreasing the amount of base employed, but when less than 1 equiv of piperidine was used the reaction failed to reach completion

Keywords: Isoxazoles; Polyfunctional scaffold; Pyrazoles; Glutaric acid derivatives.
* Corresponding author. Tel.: +353 1 4022208; fax: +353 1 4022168; e-mail: madamo@rcsi.ie

0040–4020/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2007.07.015



Scheme 1. Novel synthesis of di-isoxazoles **4a–f**.

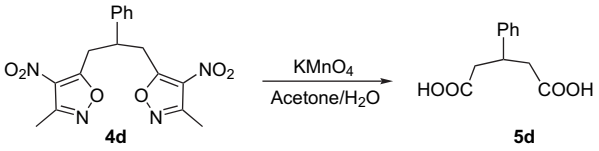
Table 1. One-pot synthesis of bis-isoxazoles **4a–f**

Entry	Compound	Ar	Yield[a] %
1	**4a**	*p*-Tolyl	63
2	**4b**	*p*-OMe–C_6H_4	68
3	**4c**	*p*-Cl–C_6H_4	61
4	**4d**	Ph	65
5	**4e**	*p*-NO_2–C_6H_4	51
6	**4f**	*p*-CN–C_6H_4	54

[a] Isolated yields after chromatography.

and variable amounts of compound **3d** (Ar=Ph) appeared as the side product.

With compound **4d** in hand, we studied its conversion to 3-phenylglutaric acid **5d** (Scheme 2). We firstly tried to hydrolyse the isoxazole cores using NaOH. It was hoped that under the reaction conditions the isoxazole core would have revealed a carboxylate, a reaction we have employed before.[8–11] Therefore, compound **4d** was reacted with NaOH under a wide number of reaction conditions. We have investigated the effect of temperature, reaction time, solvent (mixtures of tetrahydrofuran, 1,4-dioxane or acetonitrile and water) and amount of NaOH. However, compound **5d** could never be isolated. Although in these reactions compound **4d** was rapidly consumed, desired acid **5d** was not formed. Considering that 4-nitroisoxazoles could be converted to carboxylates also by treatment with $KMnO_4$, we reacted compound **4d** with a diluted solution of this oxidant in an acetone/water mixture (Scheme 2). We were delighted to observe that by using this procedure compound **5d** could be



Scheme 2. Synthesis of 3-phenylglutaric acid **5d**.

isolated in 71% yield. We have attempted the transformation of **4d** to **5d** using milder oxidising agents including Oxone®, ^{t}BuOOH or *m*-CPBA, but no acid **5d** could be detected in these experiments.

We also established a one-pot procedure for the synthesis of compounds **5a–f** (Scheme 3 and Table 2). Generally **1** (2.2 equiv) and **2a–f** (1.0 equiv) were reacted with piperidine (1.0 equiv) in tetrahydrofuran (10 mL) at 70 °C for 12 h. Then a solution of potassium permanganate (12 equiv) in a mixture of water (30 mL) and acetone (10 mL) was added. After 5 h the mixture was worked up, the solvent evaporated and the solid compounds **5a–f** so obtained were filtered and recrystallised from an ethyl acetate/toluene mixture (1:1). Importantly, compounds **5a–f** were obtained pure and in good yields without the use of chromatography (Table 2).

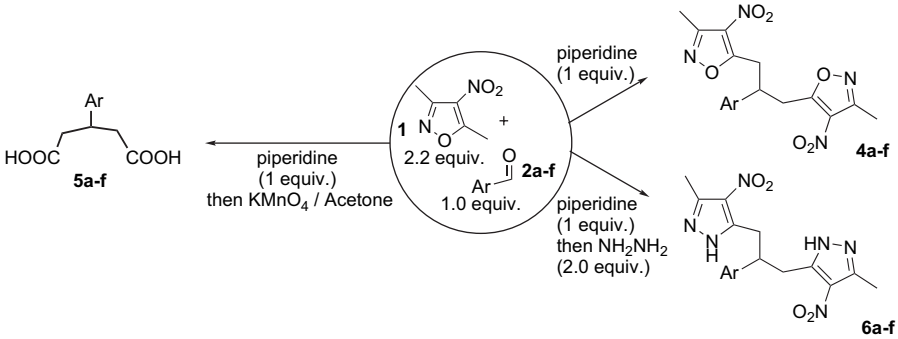
One important feature of 4-nitroisoxazoles is their ability to undergo conversion to a 4-nitropyrazolyl group when reacted with hydrazines.[9,10,14] This is a very efficient process that furnished 4-nitropyrazoles in excellent yields using just 1 equiv of hydrazine.[9,10] In order to expand the range of compounds obtainable from isoxazole **1**, we reacted **4d** with hydrazine hydrate. We were delighted to observe that a di-pyrazole **6d** was formed in high yields. We also demonstrated that compounds **6a–f** could be prepared in a one-pot fashion directly from component **1**, **2a–f** and hydrazine (Scheme 3 and Table 3).

In conclusion we have expanded the range of compounds obtainable from isoxazole **1**. The reported methodologies are simple to execute, rely on inexpensive starting materials and the products are obtained in good to excellent yields without the use of chromatography. Therefore, they constitute useful tools for those studies in which the rapid generation of families of compounds is required.

Table 2. One-pot synthesis of compounds **5a–f**

Entry	Compound	Ar	Yield[a] %
1	**5a**	*p*-Tolyl	61
2	**5b**	*p*-OMe–C_6H_4	59
3	**5c**	*p*-Cl–C_6H_4	63
4	**5d**	Ph	60
5	**5e**	*p*-NO_2–C_6H_4	54
6	**5f**	*p*-CN–C_6H_4	58

[a] Isolated yields after crystallisation from ethyl acetate/toluene.



Scheme 3. Three one-pot syntheses using isoxazole **1**.

Table 3. One-pot synthesis of compounds **6a–f**

Entry	Compound	Ar	Yield[a] %
1	**6a**	*p*-Tolyl	92
2	**6b**	*p*-OMe–C_6H_4	90
3	**6c**	*p*-Cl–C_6H_4	94
4	**6d**	Ph	91
5	**6e**	*p*-NO_2–C_6H_4	96
6	**6f**	*p*-CN–C_6H_4	95

[a] Isolated yields after crystallisation.

3. Experimental section

3.1. General experimental

^{1}H and ^{13}C NMR spectra were recorded on a 200 or a 400 MHz spectrometer at ambient temperatures. ^{1}H NMR spectral assignments are supported by ^{1}H–^{1}H COSY and ^{13}C–^{1}H COSY where necessary. For ^{1}H NMR recorded in $CDCl_3$ chemical shifts (δ_H) are quoted in parts per million (ppm) and are referenced to the residual solvent peak. The following abbreviations are used: s, singlet; d, doublet; t, triplet; dd, doublet of doublets; dt, doublet of triplets; tt, triplet of triplets; m, multiplet and br, broad. Coupling constants (*J*) were recorded in hertz (Hz) to the nearest 0.5 Hz. Carbon spectra are supported by DEPT analysis where necessary. Infrared (IR) spectra were recorded as thin films between NaCl plates. Absorption maximum (ν_{max}) is reported in wave numbers (cm^{-1}) and only selected peaks are reported. The following abbreviations are used: w, weak; m, medium; s, strong and br, broad. High resolution mass spectra were obtained on a Waters Micro mass LCT and low resolution mass spectra were recorded on Waters Micro mass Quattro LCMS spectrometers at 70 eV. Flash chromatography was carried out using silica gel 60 (0.040–0.063 mm, 230–400 mesh) as the stationary phase. Thin layer chromatography was carried out on aluminium backed plates pre-coated with silica gel 60, which were visualised by quenching of UV fluorescence (λ_{max}=254 nm) or by staining with either 10% w/v ammonium molybdate in 2 M sulfuric acid or basic potassium permanganate solution (followed by heat) as appropriate. Retention factors (R_f) are reported to ±0.05.

3.2. General procedure for the preparation of compounds 4a–f (Table 1)

To a stirred solution of 3,5-dimethyl-4-nitroisoxazole **1** (1.3 g, 9.16 mmol, 2.2 equiv) in ethanol (20 mL), were added piperidine (354 mg, 4.16 mmol, 1.0 equiv) and an aromatic aldehyde **2a–f** (4.16 mmol). The resulting solution was reacted at 70–80 °C for 12 h. At the end of this time the reaction mixture was cooled to room temperature and the solvent evaporated to reveal a solid that was purified by column chromatography.

3.2.1. 2-(*p*-Tolyl)-1,3-di(3-methyl-4-nitroisoxazole-5-yl) propane 4a. Colourless solid (244 mg, 0.63 mmol, 63% yield), mp: 74–76 °C (ethanol); R_f=0.3 (10% ethyl acetate in petroleum spirits); ν_{max} (KBr)/cm^{-1}: 3264, 1390, 1217; δ_H (400 MHz, $CDCl_3$) 7.11–7.07 (4H, m, *Ar*), 3.90–3.86 (1H, m, CH_2CHCH_2), 3.71 (2H, dd, *J*=15.0, *J*=8.0, $CHCH_2$), 3.54 (2H, dd, *J*=15.0, *J*=8.0, $CHCH_2$), 2.51 (6H, s, CH_3C=N), 2.30 (3H, s, CH_3–Ar); δ_C (100.6 MHz, $CDCl_3$) 171.6, 155.1, 137.3, 135.9, 130.5, 129.2, 126.2, 40.6, 33.4, 20.6, 11.2; HRMS found: [M−H$^+$] 385.1159, $C_{18}H_{17}N_4O_6$ requires 385.1148; *m/z*: 385 (100%, M−H$^+$).

3.2.2. 2-(4-Methoxyphenyl)-1,3-di(3-methyl-4-nitroisoxazole-5-yl) propane 4b. Colourless solid (200 mg, 0.68 mmol, 68% yield), mp: 81–88 °C (ethanol); R_f=0.2 (10% ethyl acetate in petroleum spirits); ν_{max} (KBr)/cm^{-1}: 3346, 1433, 1247; δ_H (400 MHz, $CDCl_3$) 7.12 (2H, d, *J*=8.0, *Ar*), 6.80 (2H, d, *J*=8.0, *Ar*), 3.87–3.85 (1H, m, CH_2CHCH_2), 3.76 (3H, s, CH_3O–Ar), 3.70 (2H, dd, *J*=15.0, *J*=6.0, $CHCH_2$), 3.53 (2H, dd, *J*=15.0, *J*=6.0, $CHCH_2$), 2.50 (6H, s, CH_3C=N); δ_C (100.6 MHz, $CDCl_3$) 171.6, 155.1, 130.8, 130.1, 127.5, 127.1, 113.9, 54.7, 40.3, 33.5, 11.3 (CH_3C=N); HRMS found: [M−H$^+$] 401.3615, $C_{18}H_{17}N_4O_7$ requires 401.3623; *m/z*: 293 (100%, M−H$^+$).

3.2.3. 2-(4-Chlorophenyl)-1,3-di(3-methyl-4-nitroisoxazole-5-yl) propane 4c. Colourless solid (248 mg, 0.61 mmol, 61% yield), mp: 91–93 °C (ethanol); ν_{max} (KBr)/cm^{-1}: 3369, 1429, 1371; R_f=0.3 (10% ethyl acetate in petroleum spirits); δ_H (400 MHz, $CDCl_3$) 7.28 (2H, d, *J*=8.0, *Ar*), 7.17 (2H, d, *J*=8.0, *Ar*), 3.94–3.90 (1H, m, CH_2CHCH_2), 3.72 (2H, dd, *J*=14.0, *J*=6.0, $CHCH_2$), 3.54 (2H, dd, *J*=14.0, *J*=6.0, $CHCH_2$), 2.52 (6H, s, CH_3C=N); δ_C (100.6 MHz, $CDCl_3$) 171.2, 155.2, 137.4, 133.5, 130.8, 128.8, 127.8, 40.3, 33.2, 11.2; HRMS found: [M−H$^+$] 405.0591, $C_{17}H_{14}N_4O_6Cl$ requires 405.0602; *m/z*: 405 (100%, M−H$^+$).

3.2.4. 2-Phenyl-1,3-di(3-methyl-4-nitroisoxazole-5-yl) propane 4d. Colourless solid (242 mg, 0.65 mmol, 65% yield), mp: 89–91 °C (ethanol); R_f=0.4 (10% ethyl acetate in petroleum spirits); ν_{max} (KBr)/cm^{-1}: 3006, 1412, 1396; δ_H (400 MHz, $CDCl_3$) 7.32–7.25 (3H, m, *Ar*), 7.23–7.21 (2H, m, *Ar*), 3.94–3.90 (1H, m, CH_2CHCH_2), 3.74 (2H, dd, *J*=14.0, *J*=6.0, $CHCH_2$), 3.56 (2H, dd, *J*=14.0, *J*=6.0, $CHCH_2$), 2.51 (6H, s, CH_3C=N); δ_C (100.6 MHz, $CDCl_3$) 171.4, 155.1, 138.9, 131.0, 128.6, 127.6, 126.4, 41.0, 33.3, 11.1; HRMS found: [M−H$^+$] 371.1064, $C_{17}H_{15}N_4O_6$ requires 371.1070; *m/z*: 371.0 (100%, M−H$^+$).

3.2.5. 2-(4-Nitrophenyl)-1,3-di(3-methyl-4-nitroisoxazole-5-yl) propane 4e. Colourless solid (213 mg, 0.51 mmol, 51% yield), mp: 79–83 °C (ethanol); R_f=0.2 (10% ethyl acetate in petroleum spirits); ν_{max} (KBr)/cm^{-1}: 3691, 1421, 1217; δ_H (400 MHz, $CDCl_3$) 8.10 (2H, d, *J*=9.0, *Ar*), 7.37 (2H, d, *J*=9.0, *Ar*), 4.01–3.97 (1H, m, CH_2CHCH_2), 3.69 (2H, dd, *J*=15.0, *J*=8.0, $CHCH_2$), 3.54 (2H, dd, *J*=15.0, *J*=8.0, $CHCH_2$), 2.43 (6H, s, CH_3C=N); δ_C (100.6 MHz, $CDCl_3$) 170.8, 155.8, 147.6, 146.7, 130.5, 128.1, 124.4, 41.0, 33.4, 11.5; HRMS found: [M−H$^+$] 416.0828, $C_{17}H_{14}N_5O_8$ requires 416.0842; *m/z*: 416 (100%, M−H$^+$).

3.2.6. 2-(4-Cyanophenyl)-1,3-di(3-methyl-4-nitroisoxazole-5-yl) propane 4f. Colourless solid (214 mg, 0.54 mmol, 54% yield), mp: 79–83 °C (ethanol); R_f=0.2 (10% ethyl acetate in petroleum spirits); ν_{max} (KBr)/cm^{-1}: 3269, 2226, 1417; δ_H (400 MHz, $CDCl_3$) 7.63 (2H, d, *J*=8.0, *Ar*), 7.38 (2H, d, *J*=8.0, *Ar*), 4.02–3.90 (1H, m, CH_2CHCH_2), 3.74 (2H, dd, *J*=15.0, *J*=8.0, $CHCH_2$), 3.60 (2H, dd, *J*=15.0, *J*=8.0, $CHCH_2$), 2.53 (6H, s, CH_3C=N);

δ_C (100.6 MHz, $CDCl_3$) 170.4, 155.3, 134.2, 132.5, 130.9, 127.4, 116.8, 112.3, 40.8, 32.9, 11.2; HRMS found: [M−H$^+$] 396.0932, $C_{18}H_{14}N_5O_6$ requires 396.0944; *m/z*: 396 (100%, M−H$^+$).

3.3. General procedure for the preparation of compounds 5a–f (Table 2)

To a stirred solution of 3,5-dimethyl-4-nitroisoxazole **1** (0.23 g, 1.6 mmol) in tetrahydrofuran (10 mL), were added piperidine (138 mg, 1.6 mmol, 1.0 equiv) and an aromatic aldehyde **2a–f** (3.2 mmol, 2.0 equiv). The resulting solution was reacted at 70–80 °C for 12 h. The reaction mixture was then cooled to room temperature and treated with a solution made of potassium permanganate (0.850 g, 5.4 mmol, 12 equiv), water (30 mL) and acetone (10 mL), which was added dropwise. The addition required 5 h. After this time, the reaction mixture was treated with saturated solution of aqueous sodium sulfite (40 mL) and acidified with concentrated hydrochloric acid (8.0 mL) to reach pH 1–2. The reaction mixture was then concentrated and the solid obtained was filtered and crystallised from mixtures of ethyl acetate/toluene.

3.3.1. 3-*p*-Tolyl-pentanedioic acid 5a. Colourless solid (136 mg, 0.61 mmol, 61% yield), mp: 118–121 °C (ethyl acetate/toluene 1:1); R_f=0.3 (40% ethyl acetate in petroleum spirits); ν_{max} (KBr)/cm^{-1}: 3564, 1744, 1271; δ_H (400 MHz, $CDCl_3$) 12.05 (2H, br, CO_2H), 7.14 (2H, d, *J*=8.0, *Ar*), 7.07 (2H, *J*=8.0, *Ar*), 3.37 (1H, m, CH_2CHCH_2), 2.64–2.58 (2H, m, CH_2CH), 2.51–2.44 (2H, m, $CHCH_2$), 2.25 (3H, s, CH_3–Ar); δ_C (100.6 MHz, $CDCl_3$) 172.8, 140.3, 135.3, 128.7, 127.2, 37.5, 20.5; HRMS found: [M−H$^+$] 221.0886, $C_{12}H_{13}O_4$ requires 221.0892; *m/z*: 221 (100%, M−H$^+$).

3.3.2. 3-(4-Methoxyphenyl)-pentanedioic acid 5b. Colourless solid (140 mg, 0.59 mmol, 59% yield), mp: 103–106 °C (ethyl acetate/toluene 1:1); R_f=0.4 (40% ethyl acetate in petroleum spirits); ν_{max} (KBr)/cm^{-1}: 3563, 1685, 1298; δ_H (400 MHz, $CDCl_3$) 12.10 (2H, br, CO_2H), 7.76 (2H, d, *J*=8.0, *Ar*), 7.49 (2H, *J*=8.0, *Ar*), 3.85 (3H, s, –OCH_3), 3.50–3.41 (1H, m, CH_2CHCH_2), 2.69–2.64 (2H, m, CH_2CH), 2.62–2.56 (2H, m, $CHCH_2$); δ_C (100.6 MHz, $CDCl_3$) 174.4, 159.0, 141.8, 128.7, 121.6, 61.3, 35.7, 20.8; HRMS found: [M−H$^+$] 237.0839, $C_{12}H_{13}O_5$ requires 237.0841; *m/z*: 237 (100%, M−H$^+$).

3.3.3. 3-(4-Chlorophenyl)-pentanedioic acid 5c. Colourless solid (153 mg, 0.63 mmol, 63% yield), mp: 136–141 °C (ethyl acetate/toluene 1:1); R_f=0.3 (40% ethyl acetate in petroleum spirits); ν_{max} (KBr)/cm^{-1}: 3469, 1684, 1286; δ_H (400 MHz, $CDCl_3$) 12.15 (2H, br, CO_2H), 7.33 (2H, d, *J*=8.0, *Ar*), 7.29 (2H, *J*=8.0, *Ar*), 3.44–3.37 (1H, m, CH_2CHCH_2), 2.68–2.62 (2H, m, CH_2CH), 2.55–2.48 (2H, m, $CHCH_2$); δ_C (100.6 MHz, $CDCl_3$) 172.6, 142.4, 130.9, 129.4, 128.0, 37.3, 20.1; HRMS found: [M−H$^+$] 241.0349, $C_{11}H_{10}ClO_4$ requires 241.0346; *m/z*: 241 (100%, M−H$^+$).

3.3.4. 3-Phenyl-pentanedioic acid 5d. Colourless solid (125 mg, 0.60 mmol, 60% yield), mp: 105–108 °C (ethyl acetate/toluene 1:1); R_f=0.4 (40% ethyl acetate in petroleum spirits); ν_{max} (KBr)/cm^{-1}: 3669, 1741, 1289; δ_H (400 MHz, $CDCl_3$) 12.07 (2H, br, CO_2H), 7.21 (5H, s, *Ar*), 3.37–3.33 (1H, m, CH_2CHCH_2), 2.61–2.59 (2H, m, CH_2CH), 2.50–2.47 (2H, m, $CHCH_2$); δ_C (100.6 MHz, $CDCl_3$) 175.3, 141.2, 135.9, 128.1, 126.2, 36.4, 20.6; HRMS found: [M−H$^+$] 207.0741, $C_{11}H_{11}O_4$ requires 207.0736; *m/z*: 207.2 (100%, M−H$^+$).

3.3.5. 3-(4-Nitrophenyl)-pentanedioic acid 5e. Colourless solid (137 mg, 0.54 mmol, 54% yield), mp: 141–144 °C (ethyl acetate/toluene 1:1); R_f=0.3 (40% ethyl acetate in petroleum spirits); ν_{max} (KBr)/cm^{-1}: 3561, 1699, 1481; δ_H (400 MHz, $CDCl_3$) 12.22 (2H, br, CO_2H), 8.14 (2H, d, *J*=8.0, *Ar*), 7.67 (2H, *J*=8.0, *Ar*), 3.69–3.66 (1H, m, CH_2CHCH_2), 2.71–2.68 (2H, m, CH_2CH), 2.59–2.54 (2H, m, $CHCH_2$); δ_C (100.6 MHz, $CDCl_3$) 178.1, 154.6, 145.9, 131.9, 129.5, 37.9, 20.0; HRMS found: [M−H$^+$] 252.0581, $C_{11}H_{10}NO_6$ requires 252.0586; *m/z*: 252.1 (100%, M−H$^+$).

3.3.6. 3-(4-Cyanophenyl)-pentanedioic acid 5f. Pale yellow solid (135 mg, 0.58 mmol, 58% yield), mp: 128–134 °C (ethyl acetate/toluene 1:1); R_f=0.3 (40% ethyl acetate in petroleum spirits); ν_{max} (KBr)/cm^{-1}: 3561, 2262, 1681; δ_H (400 MHz, $CDCl_3$) 12.12 (2H, br, CO_2H), 7.59 (2H, d, *J*=8.0, *Ar*), 7.32 (2H, *J*=8.0, *Ar*), 3.59–3.54 (1H, m, CH_2CHCH_2), 2.68–2.64 (2H, m, CH_2CH), 2.61–2.58 (2H, m, $CHCH_2$); δ_C (100.6 MHz, $CDCl_3$) 173.8, 142.1, 130.8, 129.6, 127.4, 118.1, 37.1, 21.2; HRMS found: [M−H$^+$] 232.0682, $C_{12}H_{10}NO_4$ requires 232.0688; *m/z*: 232.1 (100%, M−H$^+$).

3.4. General procedure for the preparation of compounds 6a–f (Table 3)

To a stirred solution of 3,5-dimethyl-4-nitroisoxazole **1** (0.23 g, 1.6 mmol) in ethanol (10 mL), were added piperidine (138 mg, 1.6 mmol, 1.0 equiv) and an aromatic aldehyde **2a–f** (3.2 mmol, 2.0 equiv). The resulting solution was reacted at 70–80 °C for 12 h, then hydrazine hydrate (60% in water, 1.1 mmol, 1.1 equiv) was added and the reaction mixture was reacted at 80 °C for 4 h. At the end of this time the reaction mixture was allowed to reach room temperature, diluted with water (20 mL) and extracted with ethyl acetate (25 mL×2). The combined organic layer was washed with water (10 mL×2), then brine (10 mL), dried over Na_2SO_4 and finally concentrated under reduced pressure. The crude product was triturated with 10% ethyl acetate in petroleum ether to afford the pure products **6a–f**.

3.4.1. 2-(*p*-Tolyl)-1,3-di(3-methyl-4-nitro 1*H*-pyrazol-5-yl) propane 6a. Colourless solid (353 mg, 0.92 mmol, 92% yield), mp: 191–193 °C (ethanol); ν_{max} (KBr)/cm^{-1}: 3291, 1572, 1439; δ_H (400 MHz, $CDCl_3$) 13.50 (2H, br, N–N*H*), 7.14–7.13 (4H, m, *Ar*), 3.75–3.72 (1H, m, CH_2CHCH_2), 3.35 (4H, dd, *J*=8.0, *J*=14.5, $CHCH_2$), 2.56 (6H, s, CH_3C=N), 2.30 (3H, s, CH_3–Ar); δ_C (100.6 MHz, $CDCl_3$) 157.3, 145.5, 142.8, 135.3, 129.8, 128.8, 127.0, 41.3, 33.4, 20.5, 11.6; HRMS found: [M−H$^+$] 383.1463, $C_{18}H_{19}N_6O_4$ requires 383.1468; *m/z*: 383 (100%, M−H$^+$).

3.4.2. 2-(4-Methoxyphenyl)-1,3-di(3-methyl-4-nitro 1*H*-pyrazol-5-yl) propane 6b. Colourless solid (360 mg, 0.90 mmol, 90% yield), mp: 179–185 °C (ethanol); ν_{max} (KBr)/cm^{-1}: 3162, 1451, 1237; δ_H (400 MHz, $CDCl_3$)

13.70 (2H, br, N–N*H*), 7.17 (2H, d, *J*=8.0, *Ar*), 6.84 (2H, d, *J*=8.0, *Ar*), 3.78 (3H, s, C*H*$_3$O–), 3.74–3.71 (1H, m, CH$_2$C*H*CH$_2$), 3.37–3.34 (4H, m, CHC*H*$_2$), 2.57 (6H, s, C*H*$_3$C═N); δ_C (100.6 MHz, $CDCl_3$) 158.6, 145.6, 143.9, 139.8, 130.8, 128.0, 114.2, 55.2, 41.3, 33.1, 13.1; HRMS found: [M−H$^+$] 399.1406, $C_{18}H_{19}N_6O_5$ requires 399.1417; *m*/*z*: 399 (100%, M−H$^+$).

3.4.3. 2-(4-Chlorophenyl)-1,3-di(3-methyl-4-nitro 1*H*-pyrazol-5-yl) propane 6c. Colourless solid (379 mg, 0.94 mmol, 94% yield), mp: 198–203 °C (ethanol); ν_{max} (KBr)/cm^{-1}: 3316, 1509, 1439; δ_H (400 MHz, $CDCl_3$) 13.10 (2H, br, N–N*H*), 7.28 (2H, d, *J*=8.0, *Ar*), 7.19 (2H, d, *J*=8.0, *Ar*), 3.80–3.75 (1H, m, CH$_2$C*H*CH$_2$), 3.35 (4H, d, *J*=7.0, CHC*H*$_2$), 2.57 (6H, s, C*H*$_3$C═N); δ_C (100.6 MHz) 152.7, 142.3, 141.9, 136.8, 129.8, 129.2, 128.1, 40.2, 33.3, 11.7; HRMS found: [M−H$^+$] 403.0920, $C_{17}H_{16}N_6O_4Cl$ requires 403.0922; *m*/*z*: 403 (100%, M−H$^+$).

3.4.4. 2-Phenyl-1,3-di(3-methyl-4-nitro 1*H*-pyrazol-5-yl) propane 6d. Colourless solid (336 mg, 0.91 mmol, 91% yield), mp: 206–207 °C (ethanol); ν_{max} (KBr)/cm^{-1}: 3241, 1409, 1271; δ_H (400 MHz, $CDCl_3$) 13.29 (2H, br s, N–N*H*), 7.23–7.16 (5H, m, *Ar*), 3.66–3.61 (1H, m, CH$_2$C*H*CH$_2$), 3.26 (4H, dd, *J*=8.0, *J*=14.5, CHC*H*$_2$), 2.44 (6H, s, C*H*$_3$C═N); δ_C (100.6 MHz, $CDCl_3$) 152.9, 142.8, 140.9, 139.8, 128.2, 127.2, 126.4, 41.8, 33.7, 11.8; HRMS found: [M−H$^+$] 369.1386, $C_{17}H_{17}N_6O_4$ requires 369.1390; *m*/*z*: 369.1 (100%, M−H$^+$).

3.4.5. 2-(4-Nitrophenyl)-1,3-di(3-methyl-4-nitro 1*H*-pyrazol-5-yl) propane 6e. Colourless solid (399 mg, 0.96 mmol, 96% yield), mp: 209–213 °C (ethanol); ν_{max} (KBr)/cm^{-1}: 3330, 1521, 1506; δ_H (400 MHz, $CDCl_3$) 13.30 (2H, br, N–N*H*), 8.10 (2H, d, *J*=6.0, *Ar*), 7.48 (2H, d, *J*=6.0, *Ar*), 3.84–3.78 (1H, m, CH$_2$C*H*CH$_2$), 3.26 (4H, m, CHC*H*$_2$), 2.44 (6H, s, C*H*$_3$C═N); δ_C (100.6 MHz, $CDCl_3$) 156.0, 152.9, 142.8, 140.9, 141.3, 129.8, 127.4, 123.3, 41.8, 33.1, 11.6; HRMS found: [M−H$^+$] 414.1236, $C_{17}H_{16}N_7O_6$ requires 414.1240; *m*/*z*: 414 (100%, M−H$^+$).

3.4.6. 2-(4-Cyanophenyl)-1,3-di(3-methyl-4-nitro 1*H*-pyrazol-5-yl) propane 6f. Colourless solid (375 mg, 0.95 mmol, 95% yield), mp: 191–194 °C (ethanol); ν_{max} (KBr)/cm^{-1}: 3016, 2251, 1487; δ_H (400 MHz, $CDCl_3$) 13.30 (2H, br s, NH), 7.27 (2H, m, *Ar*), 7.19 (2H, m, *Ar*), 3.63–3.61 (1H, m, CH$_2$C*H*CH$_2$), 3.19–3.17 (4H, m, CHC*H*$_2$), 2.44–2.20 (6H, s, C*H*$_3$C═N); δ_C (100.6 MHz, $CDCl_3$) 153.8, 146.9, 142.7, 142.3, 130.9, 129.8, 128.1, 118.9, 41.3, 33.3, 11.7; HRMS found: [M−H$^+$] 394.1349, $C_{18}H_{16}N_7O_4$ requires 394.1342; *m*/*z*: 394 (100%, M−H$^+$).

References and notes

1. Karla, R.; Ebert, B.; Thorkildsen, C.; Herdeis, C.; Johansen, T. N.; Nielsen, B.; Krogsgaard-Larsen, P. *J. Med. Chem.* **1999**, *42*, 2053.
2. Chenevert, R.; Desjardins, M. *Tetrahedron Lett.* **1991**, *32*, 4249.
3. Chenevert, R.; Desjardins, M. *Can. J. Chem.* **1994**, *72*, 2312.
4. Homann, M. J.; Vail, R.; Morgan, B.; Sabesan, V.; Levy, C.; Dodds, D. R.; Zaks, A. C. *Adv. Synth. Catal.* **2001**, *343*, 744.
5. Reichard, G. A.; Ball, Z. T.; Aslanian, R.; Anthes, J. C.; Shih, Y.; Piwinski, J. J. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2329.
6. Adamo, M. F. A.; Chimichi, S.; De Sio, F.; Donati, D.; Sarti-Fantoni, P. *Tetrahedron Lett.* **2002**, *43*, 4157.
7. Adamo, M. F. A.; Donati, D.; Duffy, E. F.; Sarti-Fantoni, P. *J. Org. Chem.* **2005**, *70*, 8395.
8. Adamo, M. F. A.; Duffy, E. F. *Org. Lett.* **2006**, *8*, 5157.
9. Adamo, M. F. A.; Donati, D.; Duffy, E. F.; Sarti-Fantoni, P. *Tetrahedron* **2007**, *63*, 2047.
10. Adamo, M. F. A.; Donati, D.; Duffy, E. F.; Sarti-Fantoni, P. *Tetrahedron* **2007**, *63*, 2684.
11. Adamo, M. F. A.; Konda, V. R. *Org. Lett.* **2007**, *9*, 303.
12. Adamo, M. F. A.; Duffy, E. F.; Konda, V. R.; Murphy, F. *Heterocycles* **2007**, *71*, 1173.
13. The Michael reaction of **2** and **1** was noted before: Rao, C. J.; Reddy, K. M.; Murthy, A. K. *Indian J. Chem., Sect. B* **1981**, *20*, 997.
14. Musante, C. *Gazz. Chim. Ital.* **1942**, *72*, 537.