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A Facile Synthesis of Pyrazole, Isoxazole and Pyrimidine *ortho*-Dicarboxylic Acid Derivatives *via* β-Enaminoketoesters

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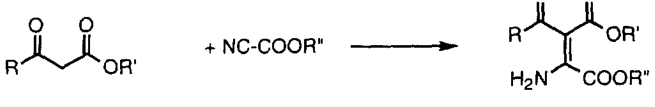
Abstract: β-Alkoxycarbonyl-β-enaminoketoesters **1a,b** react with hydrazines to give pyrazole *ortho*-dicarboxylic acid derivatives **3**, **4** and **5**. Similarly **1a** reacts with hydroxylamine to give isoxazole **6** and with amidines and guanidine to give pyrimidine *ortho*-dicarboxylic acid monoesters **7a-c**.
The total or partial hydrolysis of selected heterocycles afforded the dicarboxylic acids **8** , **9** and **10** and the dicarboxylic acid monoesters **11** and **12**. © 1997 Elsevier Science Ltd.

The metal promoted reactions of β-dicarbonyl compounds with nitriles give β-enaminodione derivatives as a result of the formation of a new C-C bond between the methylene group of the dicarbonyl and the cyano group of the nitrile.[1-4] This reaction was applied to the synthesis of heterocycles such as amino pyridines,[5] quinolines and tetronic acid derivatives.[6]

Alkyl acetoacetates and malonates react in particular with ethyl cyanoformate, in the presence of catalytic amounts of metal acetylacetonates under very mild conditions, to give β-ethoxycarbonyl-β-enaminodiones **1** having the structure of dehydroamino acids.[7] Due to the presence of a number of functional groups, compound of type **1** can be useful intermediates for the synthesis of heterocycles, of aminoacid derivatives and of other multifunctional derivatives.



1

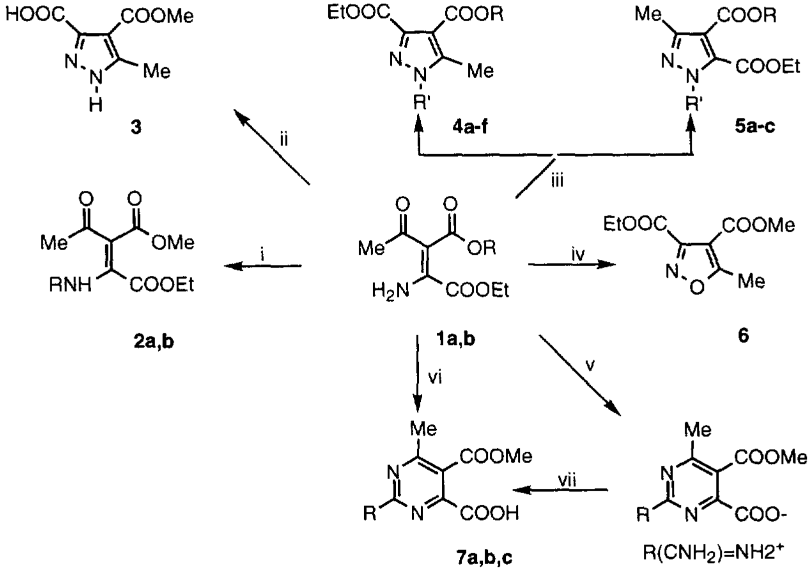
In order to investigate the reactivity of compounds **1**, the convenient derivatives **1a,b** were allowed to react with a series of amino nucleophiles (scheme). The reaction of **1a** with benzylamine or ethylamine afforded as the only reaction products the derivatives **2a,b**, in which the amino group was replaced by the ethylamino or the benzylamino group.

These reactions prompted us to investigate the reactivity of compounds **1** toward a series of ambident nucleophiles and in this paper we report the reactions of **1a** with hydrazine, alkyl and aryl hydrazines, hydroxylamine and amidines.

RESULTS AND DISCUSSION

Synthesis of heterocycles

The reaction of **1a** with hydrazine hydrate afforded the pyrazole dicarboxylic acid methyl ester **3**, in which the ester group in the position 3 was selectively hydrolysed. In the reactions of **1a** with *tert*-butylhydrazine and of **1b** with phenylhydrazine only one compound was obtained, while in the reaction of **1a** with methyl, ethyl, and phenylhydrazine two compounds were obtained one of which in high yield (70-80%) and the other in lower yield (1-10%). The two series of compounds showed similar analytical and ^{1}H-NMR spectroscopic data, which agreed with the structure of the isomeric pyrazole derivatives **4** and **5** bearing two *ortho* ester groups. ^{1}H-NMR spectra of all compounds showed singlets at *ca.* 2.3 ppm (Me), 3.80 ppm (OMe), a quartet at *ca.* 4.0 ppm (OCH_2) and a triplet at 1.3 ppm (OCH_2CH_3) together with the signals attributable to N-substituents.



i: $R\text{-}NH_2$; ii: $NH_2NH_2.H_2O$; iii: $R\text{-}NH\text{-}NH_2$; iv:NH_2OH; v: $R\text{-}C(NH_2)=NH$;
vi: a) $R\text{-}C(NH_2)=NH$, b) HCl; vii: HCl

1 **a**: R=Me; **b**:R=CH_2Ph
2 **a**:R=CH_2Ph; **b**:R=Et
4,5 **a**:R=Me, R'=Me; **b**:R=Me, R'=Et; **c**:R=Me, R'=Ph;
d:R=Me, R'=t.Bu; **e**:R=CH_2Ph, R'=Me; **f**:R=CH_2Ph,R'=Ph;
7 **a**:R=Me; **b**:R=Ph; **c**:R=NH_2

Scheme

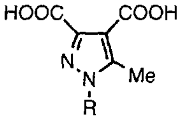
While the ^1H-NMR spectra were very similar and were useless to establish the structures of these isomers, the ^{13}C-NMR spectra showed significant differences in the absorptions between 130 and 150 ppm for both series of compounds. Compunds obtained as the only or the major reaction product showed two absorptions at *ca.* 142 ppm and *ca.* 143 ppm attributable to C-3 and to C-5 of the pyrazole ring. Compounds obtained in lower yield showed instead two absorptions attributable to the same carbon atoms at *ca.* 135 and *ca.* 150 ppm. Basing on these differences of absorption for C-3 and C-5 for the two series of pyrazole derivatives and on the data reported in the literature for compounds with similar structures,[8-10] the structure **4** was assigned to the compounds obtained as the only or the major reaction product and the structure **5** to the compounds obtained in lower yields.

Only one compound was instead obtained in the reactions of **1a** with hydroxylamine, amidines and guanidine. The reaction of **1a** with hydroxylamine afforded isoxazole-3,4-dicarboxylic acid diester **6**.

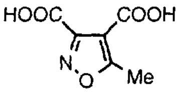
In the reactions of **1a** with amidines and guanidine, pyrimidine derivatives **7** in which the ethyl ester was selectively hydrolyzed to carboxylic acid were obtained. When **1a** was reacted with methyl amidine (molar ratio 1:2) in tetrahydrofuran at room temperature the salt between **7a** and amidine was isolated. Treatment of this salt with hydrochloric acid afforded the free pyrimidine-5,6-dicarboxylic acid 5-methyl ester **7a** in good yield. 2-Phenyl and 2-amino-pyrimidine derivatives **7b,c** were obtained by treatment of **1a** with phenyl amidine and guanidine in similar experimental conditions, followed by treatment with hydrochloric acid.

Hydrolysis of obtained heterocycles

When selected heterocycles were treated with an excess of NaOH or KOH at room temperature for 24-48 h the corresponding dicarboxylic acids were obtained in high yields. In particular the pyrazole 3,4-dicarboxylic acids **8a-e**, the isoxazole 3,4-dicarboxylic acid **9** and the pyrimidine 4,5 dicarboxylic acids **10** were obtained starting from the pertinent pyrazoles **3** and **4**, isoxazole diester **6** and pyrimidine monoesters **7**.



8 **a**: R=H
b: R=Me
c: R=Et
d: R=t.Bu
e: R=Ph



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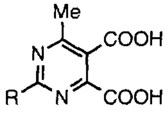
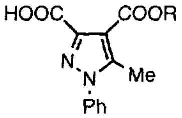
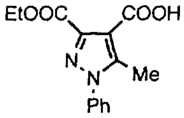


10 **a**: R=Me
b: R=Ph



11 **a**: R=Me
b: R=CH_2Ph



12

In order to selectively hydrolyse the two different ester groups of pyrazole-3,4-diesters **4**, we tried the hydrolysis under different experimental conditions.

Treatment of diesters **4** with sulphuric acid, according to a method described in the literature for the selective hydrolysis of pyrazole-3,5-diesters,[11] afforded only dicarboxylic acid derivatives. The selective hydrolysis of ester groups in the position 3 was achieved by treatment of compounds **4c** and **4f** with one equivalent of KOH in methanol or acetone at 0°C for 24 h to give the dicarboxylic acid monoesters **11a,b** as major products together with small amounts of the corresponding dicarboxylic acids.

The selective hydrolysis of the ester group in the position 4 was instead achieved by hydrogenolysis of the pyrazole-3-ethyl-4-benzyl diester **4f** to give the dicarboxylic acid monoester **12** in high yield.

The obtained results indicate that the β-ethoxycarbonyl-β-enaminoketoesters **1**, easily prepared from β-ketoesters and alkyl cyanoformates, react with ambident nucleophiles, such as hydrazines, hydroxylamine, amidines and guanidine to give pyrazole, isoxazole and pyrimidine derivatives bearing two carboxylic acid groups in *ortho* position.

The formation of these compounds can be explained by a Michael-type reaction in which the amino group attacks on the *beta*-carbon atom with elimination of ammonia followed by intramolecular attack of the second amino (or oxygen) group on the ketonic carbonyl group and subsequent ring clousure.

All these reactions are carried out at room temperature under very mild experimental conditions with respect to the ones reported in literature for similar compounds[12] and this can be explained by the presence of the alkoxycarbonyl group linked to the *beta*-position which allows an easy attack of nucleophiles on the *beta* carbon atom.

In many cases only one compound was obtained corresponding to that derived from the attack of the primary amino group on the *beta*-carbon atom. In the reactions of **1a** with methyl, ethyl and phenyl hydrazines two pyrazoles (**4** and **5**) were obtained due to the possibility of both the nitrogen atoms of these hydrazines to attack the *beta*-position. Also in these reactions the major product **4** derives from the attack of the primary amino group on the *beta*-carbon atom of **1**.

The obtained heterocycles were isolated in some cases as diesters as the pyrazoles **4**, **5** and the isoxazole **6**, in other cases as monoesters as the pyrazole **3** and the pyrimidines **7**. In these last cases only the ester group linked to the carbon atom adjacent to the nitrogen atom of the heterocycle was hydrolysed thus demonstrating that this ester group is more reactive than the other one.

The total hydrolysis of selected heterocyclic esters afforded dicarboxylic acids **8**, **9** and **10**, while the partial hydrolysis or hydrogenolysis afforded the dicarboxylic acid monoesters **11** and **12**, thus allowing a possible selective functionalization of these moieties.

EXPERIMENTAL

Melting points were determined in open capillary tubes on a Buchi apparatus and are uncorrected. IR spectra were recorded on Perkin-Elmer 288 spectrometer (values in cm^{-1}). NMR spectra were recorded on Brucker AC (200 MHz) spectrometer. Chemical shifts are given in ppm (δ) with respect to tetramethylsilane and coupling constants (J) are in Hertz. Merck Kieselgel (type 60) coated on glass plates was used for thin layer chromatography. Merck "Kieselgel 60" (70-230 mesh) was used for column chromatography.

Compound **1a** was prepared according to the literature.[7]

2-Amino-3-benzyloxycarbonyl-4-oxo-2-pentenoic acid ethyl ester 1b

To a solution of benzyl acetoacetate (4.5 ml, 25 mmol) and ethyl cyanoformate (3 ml, 30 mmol) in dry dichloromethane (5 ml) [Zn(acac)$_2$] (315 mg, 1.25 mmol) was added and the mixture was stirred at room temperature for 1.5 h. The solvent was evaporated under reduced pressure, the residue was dissolved in ethyl acetate and the suspension was filtered through celite. After evaporation of the solvent under reduced pressure, the product obtained was crystallized from ethyl acetate and light petroleum to give colourless crystals, 6.46 g (yield 88.7%), m.p. 56-58°C.

IR (KBr): 3350, 1730, 1590, 1480, 1280, 1200. ^{1}H-NMR ($CDCl_3$): two species are present in 85:15 ratio. Major isomer: 1.20 (t, 3H, J=7.1 Hz, Me), 2.34 (s, 3H, Me), 4.06 (q, 2H, J=7.1 Hz, OCH_2), 5.17 (s, 2H, OCH_2Ph), 6.3 (br, 1H, NH), 7.31-7.39 (m, 5H, Ph), 10.5 (br, 1H, NH). Minor isomer shows absorptions at 1.28 (t, 3H, J=7.1 Hz, Me), 2.39 (s, 3H, Me), 4.30 (q, 2H, J=7.1 Hz, OCH_2), 5.24 (s, 2H, OCH_2Ph). ^{13}C-NMR ($CDCl_3$): two species are present. Major isomer: 13.67 (q, J=126 Hz, Me), 30.20 (q, J=127 Hz, Me), 62.82 (t, J=148 Hz, OCH_2), 66.85 (t, J=146 Hz, OCH_2Ph), 101.95 (s, C-3), 128.26 (d, J=152 Hz, Ph), 128.38 (d, J=152 Hz, Ph), 135.48 (s, Ph), 155.96 (s, C-2), 163.88 (s, COO), 167.59 (s, COO), 198.61 (s, CO). Minor isomer: 31.25 (q, J=127 Hz, Me) , 62.72 (t, J=148 Hz, CH_2), 66.13 (t, J=146 Hz, OCH_2Ph), 101.43 (s, C-3), 135.74 (s, Ph), 157.83 (s, C-2), 164.94 (s, COO), 167.96 (s, COO), 197.19 (s, CO). Found: C, 61.93; H, 5.81; N, 4.94. $C_{15}H_{17}NO_5$ requires C, 61.85; H, 5.88; N, 4.81.

2-Benzylamino-3-methyloxycarbonyl-4-oxo-2-pentenoic acid ethyl ester 2a

To a solution of **1a** (2.15 g, 10 mmol) in chloroform (10 ml) benzylamine (1.08 ml, 10 mmol) was added. The reaction mixture was stirred at room temperature for 4 h, concentrated under reduced pressure and the residue obtained was treated with a mixture of diethyl ether and hexane to give colourless crystals, 2,7 g (90%), m.p. 55-57°C. IR (KBr): 3300, 2800, 1730, 1680, 1590, 1550. ^{1}H-NMR ($CDCl_3$): two ismers are present in 4:1 ratio. Major isomer : 1.20 (t, J=7.2 Hz, 3H, Me), 2.42 (s, 3H, Me), 3.71 (s, 3H, OMe), 4.33 (q, J=7.2 Hz, 2H, OCH_2), 4.44 (d, J= 6.2 Hz, 2H, NCH_2), 7.2-7.4 (m, 5H, Ph), 12.5 (br, 1H, NH). Minor isomer shows absorptions at : 2.38 (s, Me), 3.76 (s, OMe), 11.4 (br, 1H, NH). Found: C, 62.85; H, 6.36; N, 4.51. $C_{16}H_{19}NO_5$ requires C, 62.94; H, 6.27; N, 4.59.

2-Ethylamino-3-methyloxycarbonyl-4-oxo-2-pentenoic acid ethyl ester 2b

The reaction of **1a** with ethylamine carried out using similar experimental conditions afforded compound **2b** as a colourless oil (yield 95%). IR (neat): 3300, 1740, 1700, 1670, 1630, 1600, 1500. ^{1}H-NMR ($CDCl_3$): two isomers are present in a 4:1 ratio. Major isomer: 1.2 (t, J=7.3 Hz, 3H, Me), 1.3 (t, J=7.1 Hz, 3H, Me), 2.4 (s, 3H, Me), 3.3 (q, J=7.3 Hz, 2H, NCH_2), 3.7 (s, 3H, OMe), 4.4 (q, J=7.1 Hz, 2H, OCH_2), 12.3 (br, 1H, NH). Minor isomer shows absorptions at 2.35 (s, 3H, Me), 3.8 (s, 3H, OMe), 10.3 (br, 1H, NH). Found: C, 54.45; H, 7.14; N, 5.73. $C_{11}H_{17}NO_5$ requires C, 54.31; H, 7.04; N, 5.76.

Reactions with hydrazines

5-Methylpyrazole-3,4-dicarboxylic acid-4-methyl ester 3

To a solution of compound **1a** (1 g, 4.6 mmol) in ethanol (10 ml) cooled at 0°C hydrazine hydrate was added (0.7 g, 13.9 mmol). The reaction mixture was stirred at the same temperature for 3 h. The separated colourless crystals were filtered, washed with diethyl ether and dried (P_2O_5). The mother liquor was treated with 1N HCl (10 ml, pH *ca.*3). The colourless crystals obtained were filtered, washed with water and dried (P_2O_5). The two crops of crystals have the same m.p. and identical IR, corresponding to compound **3**: 0.42 g (49%), m.p. 215-218°C. IR (KBr): 3520, 3200-2500, 1720, 1650, 1510, 1260. ^{1}H-NMR (DMSO-d_6): 2.42 (s, 3H, Me), 3.77 (s, 3H, OMe), 6-10 (2H, NH + COOH). ^{13}C-NMR (DMSO-d_6): 10.91 (q, J=129 Hz, Me), 51.53 (q, J=146 Hz, OMe), 109.64 (s, C-4), 144.27 (s, C-3), 144.59 (s, C-5), 163.33 (s, COO), 163.75 (s, COO). Found: C, 45.28; H, 4.56; N, 15.14. $C_7H_8N_2O_4$ requires C, 45.66; H, 4.38; N, 15.21.

1,5-Dimethylpyrazole-3,4-dicarboxylic acid-3-ethyl-4-methyl ester 4a

1,3-Dimethylpyrazole-4,5-dicarboxylic acid-5-ethyl-4-methyl ester 5a

To a cooled (0°C) solution of **1a** (3 g, 13.8 mmol) in dichloromethane (25 ml) methyl hydrazine (1.1 ml, 20.7 mmol) was added. The reaction mixture was stirred at 0°C for 3h, treated with 1N HCl (20 ml, pH *ca.*3) and extracted with dichloromethane (20 ml). The organic layer was washed with water, dried (Na_2SO_4) and concentrated under reduced pressure to give a pale yellow oil which was purified by column chromatography (SiO_2, ethyl acetate/light petroleum 1:1). Two products were obtained:

4a: Rf: 0.6, pale yellow oil (2.56 g, 81.3%). IR (neat): 1720, 1550, 1430, 1210, 1080, 1030. ^1H-NMR ($CDCl_3$): 1.39 (t, J=7.2 Hz, 3H, Me), 2.48 (s, 3H, Me), 3.83, 3.84 (2s, 3H + 3H, OMe + NMe), 4.40 (q, J=7.2 Hz, 2H, OCH_2). ^{13}C-NMR ($CDCl_3$): δ 10.72 (q, J=129 Hz, Me), 14.22 (q, J=126 Hz, Me), 36.88 (q, J=140 Hz, N-Me), 51.62 (q, J=146 Hz, OMe), 61.62 (t, J=148 Hz, OCH_2), 112.04 (s, C-4), 143.13 (s, C-3), 143.63 (s, C-5), 162.46 (s, COO), 163.50 (s, COO). Found: C, 53.31; H, 6.42; N, 12.53. $C_{10}H_{14}N_2O_4$ requires C, 53.09; H, 6.24; N, 12.38.

5a: Rf: 0.8, pale yellow oil (0.04 g, 1.3%). IR (neat): 1720, 1530, 1250, 1100. ^1H-NMR ($CDCl_3$): 1.39 (t, J=7.2 Hz, 3H, Me), 2.40 (s, 3H, Me), 3.82 (s, 3H, NMe), 3.93 (s, 3H, OMe), 4.41 (q, J=7.2 Hz, 2H, OCH_2). ^{13}C-NMR ($CDCl_3$): δ 13.07 (q, J=135 Hz, Me), 14.03 (q, J=140 Hz, Me), 38.35 (q, J=140 Hz, NMe), 51.57 (q, J=146 Hz, OMe), 62.17 (t, J=143 Hz, OCH_2), 113.08 (s, C-4), 135.98 (s, C-5), 149.44 (s, C-3), 160.50 (s, COO), 163.53 (s, COO). Found: C, 53.24; H, 6.28; N, 12.29. $C_{10}H_{14}N_2O_4$ requires C, 53.09; H, 6.24; N, 12.38.

1-Ethyl-5-methylpyrazole-3,4-dicarboxylic acid-3-ethyl-4-methyl ester 4b
1-Ethyl-3-methylpyrazole-4,5-dicarboxylic acid-5-ethyl-4-methyl ester 5b

The reaction of **1a** with ethyl hydrazine carried out using the same experimental conditions afforded two products:

4b: Rf: 0.6, pale yellow oil (79.9%). IR (neat): 1720, 1550, 1440, 1210, 1080. ^1H-NMR ($CDCl_3$): 1.30 (q, J=7.1 Hz, Me), 1.41 (q, J=7.3 Hz, Me), 2.50 (s, 3H, Me), 3.83 (s, 3H, OMe), 4.17 (q, J=7.3 Hz, NCH_2), 4.40 (q, J=7.1 Hz, OCH_2). ^{13}C-NMR ($CDCl_3$): δ 10.47 (q, J=129 Hz, Me), 14.23 (q, J=126 Hz, Me), 15.01 (q, J=124 Hz, Me), 44.86 (t, J=139 Hz, NCH_2), 51.56 (q, J=146 Hz, OMe), 61.46 (t, J=147 Hz, OCH_2), 111.90 (s, C-4), 142.66 (s, C-5), 143.33 (s, C-3), 162.73 (s, COO), 163.60 (s, COO). Found: C, 54.82; H, 6.66; N, 11.55. $C_{11}H_{16}N_2O_4$ requires C, 54.99; H, 6.71; N, 11.66.

5b: Rf: 0,7, pale yellow oil (1.7%). IR (neat): 1720, 1540, 1480, 1240, 1100. ^1H-NMR ($CDCl_3$): 1.41 (q, J=7.2 Hz, Me), 1.42 (q, J=7.2 Hz, Me), 2.41 (s, Me), 3.82 (s, OMe), 4.24 (q, J=7.2 Hz, NCH_2), 4.41 (q, J=7.2 Hz, OCH_2). ^{13}C-NMR ($CDCl_3$): 13.18 (q, J=125 Hz, Me), 14.03 (q, J=126 Hz, Me), 15.69 (q, J=128 Hz, Me), 46.44 (t, J=140 Hz, NCH_2), 51.54 (q, J=146 Hz, OMe), 62.21 (t, J=147 Hz, OCH_2), 112.64 (s, C-4), 135.62 (s, C-5), 149.56 (s, C-3), 160.70 (s, COO), 163.58 (s, COO). Found: C, 54.82; H, 6.93; N, 11.56. $C_{11}H_{16}N_2O_4$ requires C, 54.99; H, 6.71; N, 11.66.

5-Methyl-1-phenylpyrazole-3,4-dicarboxylic acid-3-ethyl-4-methyl ester 4c
1-Phenyl-3-methylpyrazole-4,5-dicarboxylic acid-5-ethyl-4-methyl ester 5c

The reaction of **1a** with phenyl hydrazine carried out under the same experimental conditions gave two products:

4c: Rf:. 0.6, yellow oil (70.5%). IR (neat): 1740, 1720, 1550, 1220, 1100. ^1H-NMR ($CDCl_3$): 1.39 (t, J=7.2 Hz, 3H, Me), 2.49 (s, 3H, Me), 3.87 (s, 3H, OMe), 4.43 (q, J=7.2 Hz, 2H, OCH_2), 7.43-7.51 (m, 5H, Ph).^{13}C-NMR ($CDCl_3$): 11.87 (q, J=129 Hz, Me), 14.09 (q, J= 126 Hz, Me), 51.62 (q, J=146 Hz, OMe), 61.57 (t, J=143 Hz, OCH_2), 112.4 (s, C-4), 125.7 (d, J=168 Hz, Ph), 129.1 (d, J=160 Hz, Ph), 129.2 (d, J=160 Hz, Ph), 138.0 (s, Ph), 144.0 (s, C-5), 144.6 (s, C-3), 162.6 (s, COO), 163.3 (s, COO). Found: C, 62.62; H, 5.73; N, 9.69. $C_{15}H_{16}N_2O_4$ requires C, 62.49; H, 5.59; N, 9.72.

5c: (Rf:. 0.8: yellow oil, (10.9%) IR (neat): 1720, 1540, 1240, 1110. ^1H-NMR ($CDCl_3$): 1.22 (t, J=7.2 Hz, 3H, Me), 2.52 (s, 3H, Me), 3.84 (s, 3H, OMe), 4.32 (q, J=7.2 Hz, 2H, OCH_2), 7.3-7.5 (m, 5H, Ph). ^{13}C-NMR ($CDCl_3$): 13.51 (q, J=128 Hz, Me), 14.82 (q, J=126 Hz, Me), 51.68 (q, J=146 Hz, OMe), 62.65 (t, J=147 Hz, OCH_2), 113.03 (s, C-4), 123.09 (d J=163 Hz, Ph), 128.33 (d, J=161 Hz, Ph), 129.36 (d, J=160 Hz, Ph), 138.01 (s, Ph), 138.84 (s, C-5), 151.27(s, C-3), 161.21 (s, COO), 163.57 (s, COO). Found: C, 62.62; H, 5.43; N, 9.65. $C_{15}H_{16}N_2O_4$ requires C, 62.49; H, 5.59; N, 9.72.

1-*tert*-Butyl-5-methylpyrazole-3,4-dicarboxylic acid-3-ethyl-4-methyl ester 4d

The reaction of **1a** with *tert*-butyl hydrazine was carried out using the same experimental conditions and gave compound **4d**: yellow crystals (76.3%), m.p. 70-75°C. IR (KBr): 1720, 1540, 1210. ^{1}H-NMR ($CDCl_3$): 1.37 (t, J=7.1 Hz, Me), 1.67 (s, 9H, 3Me), 2.66 (s, 3H, Me), 3.82 (s, 3H, OMe), 4.4 (q, J=7.1 Hz, OCH_2). ^{13}C-NMR ($CDCl_3$): 13.18 (q, J=129 Hz, Me), 14.20 (q, J=126 Hz, Me), 29.82 (q, J=126 Hz, Me), 51.56 (q, J=146 Hz, OMe), 61.34 (t, J=142 Hz, OCH_2), 113.47 (s, C-4), 141.43 (s, C-3), 142.51 (s, C-5), 163.40 (s, COO), 164.14 (s, COO). Found: C, 58.11; H, 7.32; N, 10.30. $C_{13}H_{20}N_2O_4$ requires C, 58.19; H, 7.51; N, 10.44.

1,5-Dimethylpyrazole-3,4-dicarboxylic acid-3-ethyl-4-benzyl ester 4e

To a cooled (0°C) solution of compound **1b** (1.46 g, 5 mmol) in dry dichloromethane (10 ml) methylhydrazine (0.3 ml, 5.5 mmol) was added. The reaction mixture was stirred at 0°C for 2 h. The solvent was evaporated under reduced pressure to give a residue which was dissolved in ethyl acetate, washed with 1N HCl, a saturated solution of sodium carbonate and with brine. The organic layer was separated, dried over sodium sulphate and evaporated under reduced pressure to give **4e** as an yellow oil (1.337 g, yield 88%). IR (neat) 1740, 1710, 1540, 1380, 1220, 1200. ^{1}H-NMR ($CDCl_3$): 1.25 (t, J=7.1 Hz, 3H, Me), 2.44 (s, 3H, Me), 3.77 (s, 3H, NMe), 4.24 (q, J=7.2 Hz, 2H, OCH_2), 5.26 (s, 2H, OCH_2-Ph), 7.31-7.39 (m, 5H, Ph). ^{13}C-NMR ($CDCl_3$): 10.44 (q, J=129 Hz, Me), 13.80 (q, J=126 Hz, Me), 36.52 (q, J=140 Hz, NMe), 61.26 (t, J=147 Hz, OCH_2), 66.12 (t, J=146 Hz, OCH_2Ph), 111.21 (s, C-4), 127.93 (d, J=159 Hz, Ph), 128.23 (d, J=159 Hz, Ph), 135.57 (s, Ph), 143.23 (s, C-3), 143.59 (s, C-5), 162.42 (s, COO), 162.42 (s, COO). Found: C, 63.71; H, 6.16; N, 9.32. $C_{16}H_{18}N_2O_4$ requires C, 63.57; H, 6.00; N, 9.27.

5-Methyl-1-phenylpyrazole-3,4-dicarboxylic acid-3-ethyl-4-benzyl ester 4f

To a solution of **1b** (874 mg, 3 mmol) in dry dichloromethane (6 ml) phenyl hydrazine (0.325 ml, 3.3 mmol) was added. The mixture was stirred at room temperature for 8 h. The solvent was evaporated under reduced pressure to give a residue which was dissolved in ethyl acetate. The organic solution was washed with 1N HCl and with brine. The organic layer was separated and dried (Na_2SO_4). The product was purified by flash column chromatography (eluent ethyl acetate-light petroleum 1:3) to give **4f** as yellow oil (928 mg, yield 84.6%). IR (neat) 1750, 1730, 1510, 1440, 1310, 1220. ^{1}H-NMR ($CDCl_3$): 1.26 (t, 3H, J=7.1 Hz, Me), 2.50 (s, 3H, Me), 4.27 (q, 2H, J=7.1 Hz, CH_2), 5.32 (s, 2H, OCH_2-Ph), 7.34-7.51 (m, 10H, 2Ph). ^{13}C-NMR ($CDCl_3$): 11.97 (Me), 13.97 (Me), 61.66 (CH_2), 66.49 (CH_2), 111.98 (C-4), 125.69 (Ph) 128.20 (Ph), 128.45 (Ph), 129.17 (Ph), 129.25 (Ph), 135.65 (Ph), 138.00 (Ph), 144.27 (C-3), 145.01 (C-5), 162.59 (COO), 162.80 (COO). Found: C, 69.11; H, 5.59; N, 7.83. $C_{21}H_{20}N_2O_4$ requires C, 69.22; H, 5.53; N, 7.69.

Reaction of 1a with hydroxylamine:

5-Methylisoxazole-3,4-dicarboxylic acid-3-ethyl-4-methyl ester 6

To a solution of **1a** (1 g, 10 mmol) in chloroform (3 ml) hydroxylamine hydrocloride (0.9 g, 13 mmol) and triethylamine (1.8 ml, 13 mmol) were added. The reaction mixture was stirred at room temperature for 12 h, treated with 1N HCl (pH *ca.* 3) and extracted with chloroform (10 ml). The organic layer was dried (Na_2SO4), concentrated under reduced pressure to give a colourless oil, 0.40 g (41%). IR (neat): 1740, 1610, 1460, 1210, 1100. ^{1}H-NMR ($CDCl_3$): 1.40 (t, J=7.2 Hz, 3H, Me), 2.71 (s, 3H, Me), 3.88 (s, 3H, OMe), 4.46 (q, J=7.2 Hz, 2H, OCH_2). ^{13}C-NMR ($CDCl_3$): 12.80 (q, J=131 Hz, Me), 14.00 (q, J= 126 Hz, Me), 51.14 (q, J=147 Hz, OMe), 62.72 (t, J=148 Hz, OCH_2), 108.44 (s, C-4), 155.63 (s, C-3), 160.06 (s, COO), 160.95 (s, COO), 175.29 (s, C-5). Found: C, 50.51; H, 5.13; N, 6.61. $C_9H_{11}NO_5$ requires C, 50.71; H, 5.20; N, 6.57.

Reactions of 1a with amidines and guanidine

2,6-Dimethylpyrimidine-4,5-dicarboxylic acid-5-methyl ester 7a

To a solution of **1a** (1.0 g, 4.6 mmol) in ethanol (3 ml) acetamidine hydrochloride (1.3 g, 14 mmol) and

1,1,3,3-tetramethylguanidine (1.75 ml, 14 mmol) were added. The reaction mixture was stirred at room temperature for 24 h, treated with 1N HCl (10 ml, pH *ca.* 2) and extracted with ethyl acetate (3 x 20 ml). The organic layer was dried (Na_2SO_4), concentrated under reduced pressure to give brown crystals, m.p. 142-145°C: 0.92 g (94%). IR (KBr): 3200-2500, 1725, 1560, 1230, 1100. ^{1}H-NMR (DMSO-d_6): 2.54 (s, 3H, Me), 2.67 (s, 3H, Me), 3.84 (s, 3H, OMe), 14.00 (br, 1H, COOH). Found: C, 51.52; H, 4.66; N, 13.46. $C_9H_{10}N_2O_4$ requires C, 51.43; H, 4.8; N, 13.33.

6-Methyl-2-phenylpyrimidine-4,5-dicarboxylic acid-5-methyl ester 7b

To a solution of **1a** (0.65 g, 3 mmol) in anydrous tetrahydrofuran (5 ml) benzamidine (0.72 g, 6 mmol) was added. The reaction mixture was stirred at room temperature for 24 h. The separated bright orange crystals were filtered, washed with ethyl ether and dried (P_2O_5): pink crystals, m.p. 160-163°C, 0.88 g (75%) of a salt of **7b** with benzamidine IR (KBr):3400 (br), 1720, 1680, 1610, 1550, 1260.

The pink crystals (0.784 g, 2 mmol) were dissolved in water (7 ml) and treated with 1N HCl (3 ml, pH *ca.* 2). The obtained suspension was stirred at room temperature for 1 h to give crystals which were filtered, washed with water (10 ml) and extracted with ethyl ether. The dried extracts were concentrated under reduced pressure to give colourless crystals, m.p. 125-128°C, 0.44 g (79%). IR (neat): 3400-2500, 1760 (br), 1600, 1300 (br). ^{1}H-NMR (DMSO-d_6): 2.66 (s, 3H, Me), 3.87 (s, 3H, OMe), 7.55-7.50 (m, 3H, Ph), 8.40-8.45 (m, 2H, Ph), 14.00 (br, 1H, COOH). Found: C, 61.72; H, 4.59; N, 10.42. $C_{14}H_{12}N_2O_4$ requires C, 61.76; H, 4.44; N, 10.29.

2-Amino-6-methylpyrimidine-4,5-dicarboxylic acid-5-methyl ester 7c

To a solution of **1a** (0.50 g, 2.3 mmol) in ethanol (3 ml) guanidine hydrochloride (0.660 g, 6.9 mmol) and tetramethylguanidine (0.86 ml, 6.9 mmol) were added. The reaction mixture was stirred at room temperature for 24 h and treated with 1N HCl (pH *ca.* 3). The obtained supension was extracted with ethyl acetate, the organic layer was dried (Na_2SO_4) and concentrated under reduced pressure to give colourless crystals, m.p. 207-209°C (EtOH), 0.2 g (40%). IR (KBr): 3200 (br), 3000 (br), 1740, 1690, 1610, 1240. ^{1}H-NMR (DMSO-d_6): 2.43 (s, 3H, Me), 3.72 (s, 3H, OMe), 7.49 (br, 2H, NH_2). ^{13}C-NMR (DMSO-d_6): 23.41 (Me), 51.76 (OMe), 109.77 (s, C-5), 161.28, 162.57 (2s, C-4 and C-6), 165.77 (COOH), 166.84 (COO), 169.02 (C-2). Found: C, 45.63; H, 4.25; N, 19.73. $C_8H_9N_3O_4$ requires C, 45.50; H, 4.30; N, 19.90.

Synthesis of dicarboxylic acids

5-Methylpyrazole-3,4-dicarboxylic acid 8a

To a solution of **3** (0.417 g, 2.26 mmol) in methanol NaOH 1N (6.8 ml, 6.8 mmol) was added. The reaction mixture was stirred at room temperature for 24 h., treated with 1N HCl (7 ml, pH *ca.* 3) and stirred at room temperature for 1 h. The obtained suspension was filtered to give colourless crystals, m.p. 235-240°C, 0.18 g (47%). IR (KBr): 3500, 3180(br), 2450(br), 1740, 1630, 1500, 1210, 1130. ^{1}H-NMR (DMSO-d_6): 2.54 (s, 3H, Me), 9.45 (br, 3H, 2COOH + NH). ^{13}C-NMR (DMSO-d_6): 11.76 (q, J=129 Hz, Me), 110.81 (s, C-4), 142.17 (s, C-3), 146.93 (s, C-5), 163.65 (s, COO), 165.58 (s, COO). Found: C, 42.53; H, 3.68; N, 16.36. $C_6H_6N_2O_4$ requires C, 42.36; H, 3.55; N, 16.47.

Following the same procedure the following diacid derivatives were prepared:

1,5-Dimethylpyrazole-3,4-dicarboxylic acid 8b

Otained from **4a** as colourless crystals, m.p. 234-237°C (64%). IR (KBr): 3400 (br), 2400 (br), 1715 (br), 1250 (br). ^{1}H-NMR (DMSO-d_6): 2.50 (s, 3H, Me), 3.84 (s, 3H, Me), 12.0 (br, 2H, 2COOH). ^{13}C-NMR (DMSO-d_6): 10.63 (q, J=129 Hz, Me), 36.85 (q, J=140 Hz, NMe), 111.46 (s, C-4), 141.82 (s, C-3), 145.19 (s, C-5), 164.43 (s, COO), 164.59 (s, COO). Found: C, 45.72; H, 4.21; N, 15.18. $C_7H_8N_2O_4$ requires C, 45.66; H, 4.38; N, 15.21.

1-Ethyl-5-methylpyrazole-3,4-dicarboxylic acid 8c

Obtained from **4b** as colourless crystals, m.p.240-243°C (44%). IR (KBr): 3200-2200, 1710, 1600, 1500 (br), 1230, 1020. ^{1}H-NMR (DMSO-d_6): 1.34 (t, J=7.1 Hz, 3H, Me), 2.53 (s, 3H, Me), 4.18 (q, J=7.1 Hz, 2H, NCH_2), 12.0 (br, 2H, 2 COOH). ^{13}C-NMR (DMSO-d_6): 10.58 (q, J=131 Hz, Me), 14.49 (q, J=126 Hz, Me), 44.37 (t, J=140 Hz, NCH_2), 111.57 (s, C-4), 142.17 (s, C-5), 144.31 (s, C-3), 164.65 (s, 2 COO). Found: C, 48.52; H, 5.26; N,14.32. $C_8H_{10}N_2O_4$ requires C, 48.49; H, 5.09; N, 14.14.

1-*tert*-Butyl-5-methylpyrazole-3,4-dicarboxylic acid 8d

Obtained from **4d** as colourless crystals, m.p.198-199°C (70%). IR (KBr): 3000 (br), 2480 (br), 1720, 1630, 1500 (br), 1220. ^{1}H-NMR (DMSO-d_6): 1.62 (s, 9H, 3Me), 2.88 (s, 3H, Me), 12.05 (br, 2H, COOH). ^{13}C-NMR (DMSO-d_6): 12.84 (q, J=129 Hz, Me), 29.31 (q, J=126 Hz, Me), 61.76 (s, $\underline{C}Me_3$), 113.48 (s, C-4), 140.77 (s, C-3), 143.42 (s, C-5), 164.59 (s, COO), 164.71 (s, COO). Found: C, 53.27; H, 6.14; N, 12.52. $C_{10}H_{14}N_2O_4$ requires C, 53.09; H, 6.24; N, 12.38.

5-Methyl-1-phenylpyrazole-3,4-dicarboxylic acid 8e

Obtained from **4c** as colourless crystals, m.p. 245-247°C, (83.3%). IR (KBr): 3400(br), 1700, 1620, 1600, 1500, 1240. ^{1}H-NMR (DMSO-d_6): 2.49 (s, 3H, Me), 7.60 (m, 5H, Ph), 12.00 (br, 2H, 2COOH). ^{13}C-NMR (DMSO-d_6): 11.25 (q, J=129 Hz, Me), 111.72 (s, C-4), 125.00 (d, J=163 Hz, Ph), 128.54 (d, J=162 Hz, Ph), 128.73 (d, J=162 Hz, Ph), 137.25 (s, Ph), 143.86 (s, C-3), 144.00 (s, C-5), 163.60 (s, 2 COO). Found: C, 58.32; H, 4.26; N,11.21. $C_{12}H_{10}N_2O_4$ requires C, 58.54; H, 4.09; N, 11.38.

5-Methylisoxazole-3,4-dicarboxylic acid 9

Obtained from **6** as colourless crystals, m.p. 183-188°C, (76%). IR (KBr): 3200-2400, 1730, 1610 (br), 1510, 1240. ^{1}H-NMR (DMSO-d_6): 2.67 (s, 3H, Me), 11.94 (br, 2H, 2COOH). ^{13}C-NMR (DMSO-d_6): 12.35 (q, J=131 Hz, 3H, Me), 108.35 (s, C-4), 156.88 (s, C-3), 161.55 (s, COO), 161.77 (s, COO), 174.85 (s, C-5). Found: C, 42.23; H, 3.12; N, 8.24. $C_6H_5NO_5$ requires C, 42.12; H, 2.95; N, 8.19.

2,6-Dimethylpyrimidine-4,5-dicarboxylic acid 10a

Obtained from **7a** as pink crystals, m.p. 185-88°C, (70%). IR (KBr): 3350 (br), 2450 (br), 1960 (br), 1730, 1650, 1610, 1290. ^{1}H-NMR (DMSO-d_6): 2.59 (s, 3H, Me), 2.67 (s, 3H, Me), 12.00 (br, 2H, 2COOH). ^{13}C-NMR (DMSO-d_6): 22.61 (q, J=128 Hz, Me), 25.35 (q, J=127 Hz, Me), 122.34 (s, C-5), 156.08 (s, C-4), 166.08, 166.19, 167.03 (3 s, 2 COO and C-6), 167.47 (s, C-2). Found: C, 49.10; H, 4.23; N, 14.46. $C_8H_8N_2O_4$ requires C, 48.98; H, 4.11; N, 14.28.

6-Methyl-2-phenylpyrimidine-4,5-dicarboxylic acid 10b

Obtained from **7b** as yellow crystals, m.p. 138-143°C, (79%). IR (KBr): 3400-2500, 1740, 1690, 1550, 1380, 1280, 1220. ^{1}H-NMR (DMSO-d_6): 2.71 (s, 3H, Me), 7.50-7.60 (m, 3H, Ph), 8.40-8.47 (m, 2H, Ph), 13.5 (br, 2H, 2 COOH). ^{13}C-NMR (DMSO-d_6): 23.08 (q, J=128 Hz, Me), 122.89 (s, C-5), 128.19 (d, J=161 Hz, Ph), 128.78 (d, J=158 Hz, Ph), 131.65 (d, J=146 Hz, Ph), 135.70 (s, Ph), 156.68 (s, C-4), 162.76 (s, C-6), 166.14, 166.79, 166.79 (3 s, 2 COO and C-2). Found: C, 60.66; H, 3.72; N, 10.76. $C_{13}H_{10}N_2O_4$ requires C, 60.47; H, 3.90; N, 10.85.

Synthesis of monocarboxylic acids

5-Methyl-1-phenylpyrazole-3,4-dicarboxylic acid-4-methyl ester 11a

To a solution of pyrazole diester **4c** (865 mg, 3 mmol) in methanol (8 ml) cooled at 0°C, 3 ml of 1N solution of KOH (3 mmol) were added and the mixture was stirred at 0°C for 24 h. The reaction mixture was concentrated under reduced pressure to a volume of 2 ml, diluted with ethyl acetate and extracted with water. The aqueous layer was separated, acidified with 6N HCl to pH *ca.* 2 and stirred for 2 h to give **11a** as a yellow solid (350 mg, 44%), m.p. 189-191°C. IR (KBr) 2700, 1750, 1640, 1500, 1230. ^{1}H-NMR (DMSO-d_6): 2.43 (s, 3H, Me), 3.77 (s, 3H, OMe), 7.57 (m , 5H, Ph), 13.35 (br, 1H, COOH). Found: C, 60.12; H, 4.56; N, 10.63. $C_{13}H_{12}N_2O_4$ requires C, 60.00; H, 4.65; N, 10.76.

5-Methyl-1-phenylpyrazole-3,4-dicarboxylic acid-4-benzyl ester 11b

To a solution of pyrazole diester **4f** (730 mg, 2 mmol.) in acetone (5 ml) cooled at 0° C, 118 mg (2.1 mmol) of KOH in water (1 ml) were added and the mixture was stirred at 0°C for 36 h. The reaction mixture was concentrated under reduced pressure, the residue was diluted with ethyl acetate and extracted several times with water. The aqueous layer was separated, acidified with 1N HCl (2.1 ml) and extracted with ethyl acetate (3 x 20 ml). The organic layers were washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure to give a residue which was crystallized from tetrahydrofuran/hexane to give a white solid (420 mg, 58 %) of pyrazole monoester **11b**. IR (KBr) 3000 br, 2650 br, 1750, 1640, 1500, 1240. ^{1}H-NMR (DMSO-d_6): 2.44 (s, 3H, Me), 5.29 (s, 2H, CH_2), 7.35-7.44 (m, 5H, Ph), 7.56 (s, 5H, Ph), 13.4 (br, 1H, COOH). ^{13}C-NMR (DMSO-d_6): 11.66 (q, J=129 Hz, Me), 65.92 (t, J=147 Hz, CH_2), 111.19 (s, C-4), 125.58 (d, Ph), 127.83 (d, Ph), 127.96 (d, Ph), 128.41 (d, Ph), 129.13 (d, Ph), 129.39 (d, Ph), 135.99 (s, Ph), 137.90 (s, Ph), 143.90 (s, C-5), 145.56 (s, C-3), 162.37 (s, COO), 163.85 (s, COO). Found: C, 67.78; H, 4.93; N, 8.21. $C_{19}H_{16}N_2O_4$ requires C, 67.85; H, 4.79; N, 8.33.

5-Methyl-1-phenylpyrazole-3,4-dicarboxylic acid-3-ethyl ester 12

To a solution of **4f** (730 mg, 2 mmol) in dimethoxyethane (15 ml) ammonium formate (650 mg, 10 mmol) and palladised charcoal (700 mg, 10% Pd) were added and the suspension was heated under reflux for 3 h. The charcoal was filtered off and the solution was concentrated under reduced pressure to give a residue which was dissolved in ethyl acetate. The solution was extracted with a 5% solution of sodium hydrogen carbonate (15 ml x 3), the aqueous layer was acidified to pH *ca.* 1 and stirred at room temperature for 3 h. The crystals obtained were filtered, washed with cool water and dried in vacuo (P_2O_5): colourless crystals, 410 mg (yield 75%), m.p. 89-91°C. IR (KBr) 2790, 1740, 1660, 1630, 1540, 1250. ^{1}H-NMR ($CDCl_3$): 1.47 (t, 3H, J=7.2 Hz, Me), 2.63 (s, 3H, Me), 4.57 (q, 2H, J=7.2 Hz, CH_2), 7.41-7.46 (m, 2H, Ph), 7.54-7.57 (m, 3H, Ph), 13.51 (br., 1H, COOH). ^{13}C-NMR ($CDCl_3$): 12.75 (q, J=130 Hz, Me), 13.99 (q, J=127 Hz, Me), 63.64 (t, J=148 Hz, CH_2), 114.34 (s, C-4), 125.98 (d, J=183 Hz, Ph), 129.44 (d, J=170 Hz, Ph), 129.80 (d, J=155 Hz, Ph), 137.63 (s, Ph), 139.57 (s, C-3), 148.95 (s, C-5), 161.88 (s, COO), 166.36 (s, COO). Found: C, 61.20; H, 5.33; N,10.11. $C_{14}H_{14}N_2O_4$ requires C, 61.31; H, 5.14; N, 10.21.

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