Straightforward and Regiospecific Synthesis of Pyrazole-5-carboxylates from Unsymmetrical Enaminodiketones

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Abstract: A series of 4-substituted 1*H*-pyrazole-5-carboxylates was prepared from the cyclocondensation reaction of unsymmetrical enaminodiketones [$RC(O)C(=CNMe_2)C(O)CO_2Et$, where R = Ph, 4-$MeOC_6H_4$, 4-$ClC_6H_4$, 4-$FC_6H_4$, 4-$O_2NC_6H_4$, thien-2-yl, benzofur-2-yl, CCl_3 and CF_3] with *tert*-butylhydrazine hydrochloride or carboxymethylhydrazine. The compounds were obtained regiospecifically and in good to excellent yields (73–94%). In addition, 5-carboxyethyl-1-(1,1-dimethylethyl)-1*H*-pyrazole-4-carboxylic acid was synthesized from regiospecific conversion of ethyl 4-(2,2,2-trichloroacetyl)-1-(1,1-dimethylethyl)-1*H*-pyrazole-5-carboxylate. The carbonyl substitution reaction was regiospecific for the trichloroacetyl group and did not affect the ester group.

Key words: enones, cyclizations, regioselectivity, pyrazoles, heterocycles

The synthesis of pyrazole has been the subject of consistent interest because of the wide applications for such heterocycles in the pharmaceutical and agrochemical industries.[1] Among the range of properties, compounds containing a pyrazole scaffold have been shown to exhibit HIV-1 reverse transcriptase and IL-1 synthesis inhibition, as well as antihyperglycemic, antibacterial, sedative-hypnotic, anti-inflammatory, antipyretic and analgesic activities.[2] More specifically, pyrazole-5-carboxylic acid derivatives are compounds of considerable pharmacological relevance[3] and also represent useful synthetic building blocks in organic chemistry.[4] The synthesis of pyrazole derivatives has been well explored using the so-called [3+2]-atom fragments, where β-diketones or α,β-unsaturated ketones are used as 3-atom building blocks and hydrazines as the 2-atom fragment. In the last few decades, our research group has reported the general synthesis of 1,1,1-trihalo-4-alkoxy-3-alken-2-ones, a 3-atom building block, and demonstrated their usefulness in heterocyclic preparations.[5] However, with unsymmetrical 1,3-dicarbonyl substrates this method often suffers from the formation of a regioisomeric mixture of pyrazoles with generally poor selectivity.[6] Moreover, pyrazole regioisomers can often be difficult to separate by chromatography and repeated crystallization may be necessary to remove the undesired regioisomer. Thus, development of effective and efficient methods for synthesis of such compounds, which avoid the use of column chromatography or crystallization in the isolation procedure, is highly desirable from both an environmental and an economic perspective. Data from the literature have demonstrated the application of enaminodiketones, compounds analogous to the 1,3-dicarbonyl, as interesting building blocks for the synthesis of heterocycles such as pyrazoles[7–10] and pyrimidines.[11–13] However, only few examples have been reported in the literature dealing with the use of such building blocks for the regiospecific construction of pyrazoles. Hojo and co-workers reported the reaction of dialkylamino methylenehexafluoroacetylacetone with methylhydrazine, *tert*-butylhydrazine and phenylhydrazine. The reaction with methylhydrazine and *tert*-butylhydrazine resulted in the formation of a sole regioisomer while the reaction with phenylhydrazine led to a mixture of regioisomers.[7] On the other hand, Kascheres and co-workers[9] showed the reactivity of α-acylenamino ketones in reactions with hydrazines under different conditions. In most of the cases, regardless of the solvent and hydrazine used, the products were obtained as a mixture of isomers and the presence of side products was observed. In addition, Mirand and co-workers[10] reported the reaction of trifluoromethylated enaminodiketones with methylhydrazine and phenylhydrazine carried out in MeCN. The result was a mixture of two regioisomers or a mixture of three regioisomers.

We have reported recently the synthesis of a variety of enaminodiketones **1** from C-acylation of enaminones with ethyl oxalyl chloride.[14,15] These precursors are highly attractive for the construction of new heterocycle derivatives. Therefore, we are interested in the reaction of such compounds with hydrazines in a preliminary study on the different electrophilic centers present in the enaminodiketone system (**1**, Scheme 1) in the attempt to find a straightforward and regiospecific method for the synthesis of pyrazole derivatives.

We began our studies with the reaction of enaminodiketone **1** with *tert*-butylhydrazine hydrochloride carried out in ethanol with the aim of determining the relative reactivity of the four electrophilic centers during a nucleophilic attack. Surprisingly, from the preliminary results it was observed that 1-*tert*-butylpyrazole **2** was obtained as the sole regioisomer (**A**, Scheme 1).

The product identified can be explained by an addition–elimination reaction, in which the more reactive amino group of the hydrazine attacks the β-carbon atom of com-

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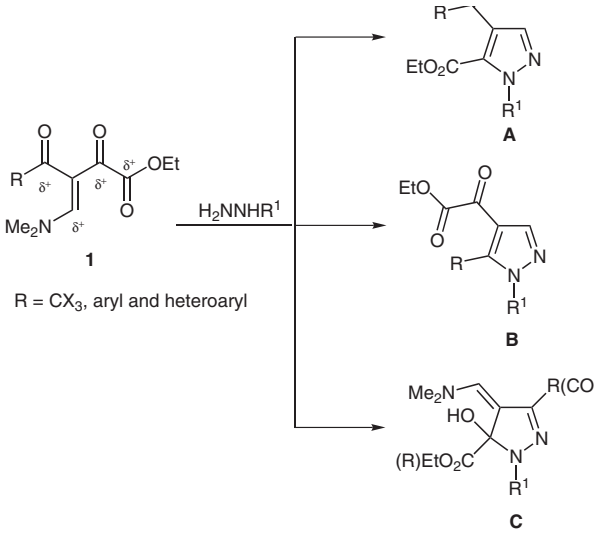
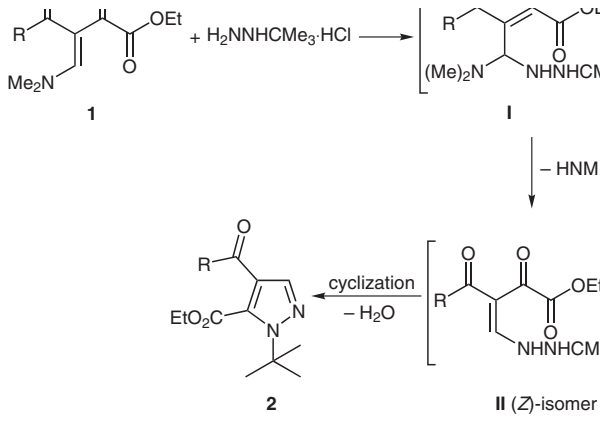


Scheme 1 Enaminodiketone **1** and representation of possible compounds (**A**, **B**, **C**) from reaction with hydrazines

pound **1** to form adduct I, which undergoes an elimination of dimethylamine to form the β-hydrazino unsaturated ketone II (Scheme 2). Then, the subsequent heterocyclization was attained from the attack of the second amino group of hydrazine to the carbonylic carbon neighbor to the ester group. This attack suggests that the intermediate β-hydrazino unsaturated ketone II presents the RCO group *trans* to the hydrazino group[9] that seems to be sterically less hindered in relation to the *tert*-butyl group. The structure of 1-*tert*-butylpyrazole-5-carboxylates **2** was determined by ^{1}H NMR and ^{13}C NMR spectroscopy, GC–MS and elemental analysis and confirmed by crystallographic data (compound **2h**, Figure 1).[16,17]



Scheme 2 Formation of pyrazoles **2** by an addition–elimination reaction

The reaction of enaminodiketones **1a–i** with *tert*-butylhydrazine hydrochloride was regiospecific and afforded a series of pyrazoles in good to excellent yields (73–91%), independently of the structure of the substituent R present in the enaminodiketone (Table 1, entries 1–9). In addition,

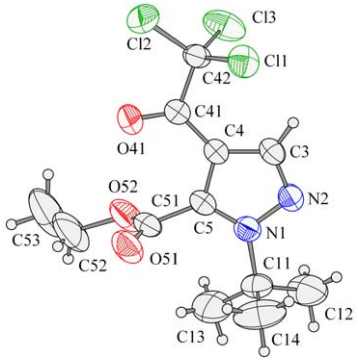
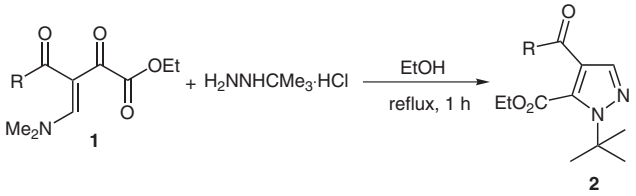


Figure 1 ORTEP diagram of 1-*tert*-butylpyrazole **2h**

Table 1 Regiospecific Synthesis of 4-Substituted 1-*tert*-Butylpyrazole-5-carboxylates **2a–i** from the Reaction of Enaminodiketones **1a–i** with *tert*-Butylhydrazine Hydrochloride



Entry	Enaminodiketone	R	Pyrazole	Yield (%)[a]
1	**1a**	Ph	**2a**	77
2	**1b**	4-MeOC$_6$H$_4$	**2b**	90
3	**1c**	4-ClC$_6$H$_4$	**2c**	73
4	**1d**	4-FC$_6$H$_4$	**2d**	83
5	**1e**	4-O$_2$NC$_6$H$_4$	**2e**	91
6	**1f**	thien-2-yl	**2f**	79
7	**1g**	benzofur-2-yl	**2g**	86
8	**1h**	CCl_3	**2h**	78
9	**1i**	CF_3	**2i**	76

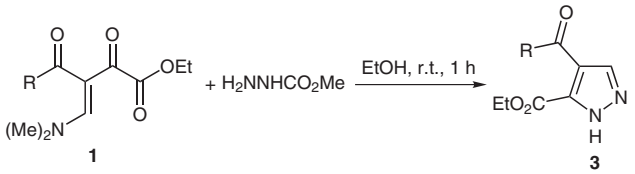
[a] Yield of isolated product.

it is important to mention that an acyl group at the 4-position and a carboxylic acid ethyl ester at the 5-position were present in the structure of the obtained multifunctionalized products **2**.

In the second part of this work, we performed the reaction of enaminodiketones **1a–i** with carboxymethylhydrazine. This reaction was carried out in ethanol at room temperature for one hour. The reaction was regiospecific and furnished only the regioisomer **A** (Scheme 1). The synthesis of these products also can be explained by an addition–elimination reaction as shown in Scheme 2. However, the product was not obtained as carboxymethylpyrazole, but in the form of 1*H*-pyrazoles **3** even under mild conditions (Table 2). Even so, this result was interesting considering that the reaction of compound **1** with monohydrate hydrazine led to a mixture of 1*H*-pyrazole regioisomers. The reaction of enaminodiketones **1a–i** with carboxy-

methylhydrazine was regiospecific and gave good to excellent yields (74–94%), for all substituents present in the enaminodiketone (Table 2, entries 1–7). The exceptions were the reaction of **1h** and **1i**, where the respective products were not identified (Table 2, entries 8 and 9). The pyrazoles **3a–g** (Table 2, entries 1–7) were obtained with a high degree of purity and without an additional step of purification.

Table 2 Regiospecific Synthesis of 4-Substituted 1*H*-Pyrazole-5-carboxylates **3a–g** from the Reaction of Enaminodiketones **1a–i** with Carboxymethylhydrazine



Entry	Enaminodiketone	R	Pyrazole	Yield (%)[a]
1	**1a**	Ph	**3a**	75
2	**1b**	4-$MeOC_6H_4$	**3b**	85
3	**1c**	4-ClC_6H_4	**3c**	86
4	**1d**	4-FC_6H_4	**3d**	88
5	**1e**	4-$O_2NC_6H_4$	**3e**	94
6	**1f**	thien-2-yl	**3f**	74
7	**1g**	benzofur-2-yl	**3g**	89
8	**1h**	CCl_3	–[b]	–
9	**1i**	CF_3	–[b]	–

[a] Yield of isolated product.
[b] Product was not identified.

On the other hand, preliminary results have shown that the reaction of compound **1** with phenylhydrazine and with monohydrate hydrazine led to a mixture of compounds **A** and **B** (ratio 3:1 and 2:1, respectively; Scheme 1), which were difficult to separate. The structures of compounds **3** were also determined by ^{1}H NMR and ^{13}C NMR spectroscopy, GC–MS and elemental analysis.[18] Moreover, X-ray crystallography data confirmed the structure of compound **3d** (Figure 2).[19]

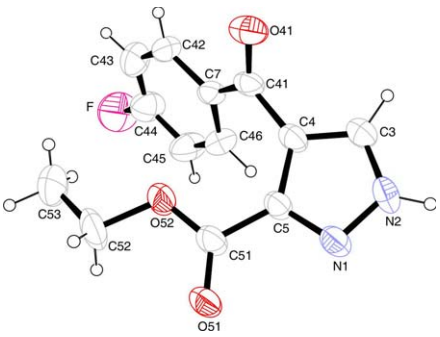
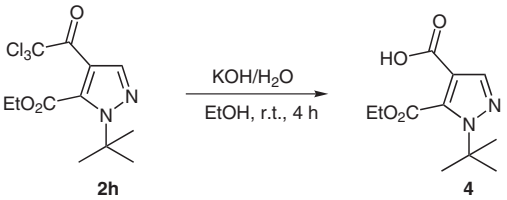


Figure 2 ORTEP diagram of 1*H*-pyrazole **3d**

We also examined the conversion of pyrazole **2h** to pyrazole carboxylic acid[7] and the product obtained was pyrazole-4-carboxylic acid **4**[20] in 76% yield, where the carbonyl substitution reaction was regiospecific for the trichloroacetyl group and did not affect the ester group (Scheme 3).



Scheme 3 Synthesis of pyrazole-4,5-dicarboxylic acid derivative **4** from the regiospecific conversion of the $COCCl_3$ group into carboxylic group.

In summary, we have developed a straightforward and regiospecific method for the synthesis of new pyrazole carboxylic acid derivatives from unsymmetrical enaminodiketones containing different reactivity centers. In addition, we demonstrated that the $COCCl_3$ group can be transformed into the carboxylic acid moiety regiospecifically. Moreover, this new class of pyrazoles comprises versatile precursors for the synthesis of other heterocyclic compounds such as pyrazolopyridazinone derivatives and the carboxylic acid ethyl ester moiety at the 5-position can be easily transformed into other useful functionalities of interest.

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(15) **4-Dimethylamino-3-(4-methoxybenzoyl)-2-oxobut-3-enoic Acid Ethyl Ester (1b)**: yield: 86%; oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.11 (t, 3 H, OCMe), 2.78 (s, 3 H, NMe_2), 3.33 (s, 3 H, NMe_2), 3.85 (s, 3 H, OMe), 3.93 (q, 2 H, OCH_2), 6.91–7.75 (m, 4 H, C_6H_4), 7.85 (s, 1 H, H4). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.5 (OCMe), 42.2 (NMe_2), 47.7 (NMe_2), 55.3 (OMe), 61.3 (OCH_2), 107.8 (C3), 113.5, 131.3, 132.8, 162.9 (C_6H_4), 158.4 (C4), 164.6 (C1), 183.1 (C2), 192.3 (C3′). MS (EI, 70 eV): *m*/*z* (%) = 305 (3) [M$^+$], 232 (29), 135 (100), 107 (4), 77 (10). Anal. Calcd for $C_{16}H_{19}NO_5$: C, 62.94; H, 6.27; N, 4.59. Found: C, 63.15; H, 6.43; N, 4.81.
3-(Benzofuran-2-carbonyl)-4-dimethylamino-2-oxobut-3-enoic Acid Ethyl Ester (1g): yield: 89%; oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.03 (t, 3 H, OCMe), 2.91 (s, 3 H, NMe_2), 3.40 (s, 3 H, NMe_2), 3.94 (q, 2 H, OCH_2), 7.28–7.66 (m, 5 H, benzofur-2-yl), 7.90 (s, 1 H, H4). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.5 (OCMe), 42.8 (NMe_2), 48.2 (NMe_2), 61.7 (OCH_2), 107.6 (C3), 112.1, 113.3, 122.9, 123.7, 126.9, 127.7, 154.2, 155.4 (benzofur-2-yl), 159.5 (C4), 164.0 (C1), 180.8 (C2), 182.5 (C3′). MS (EI, 70 eV): *m*/*z* (%) = 315 (10) [M$^+$], 242 (77), 169 (39), 145 (100), 89 (33). Anal. Calcd for $C_{17}H_{17}NO_5$: C, 64.75; H, 5.43; N, 4.44. Found: C, 64.92; H, 5.56; N, 4.67.

(16) **General Procedure for the Synthesis of Pyrazoles 2**: A mixture of enaminodiketone **1** (5 mmol) and *tert*-butylhydrazine hydrochloride (0.748 g, 6 mmol) was stirred under reflux in anhyd EtOH (20 mL) for 1 h. Then the mixture was cooled to r.t. and the solvent was evaporated under vacuum. The residue was washed with H_2O (20 mL) and extracted with CH_2Cl_2 (3 × 30 mL) and the organic layers were dried over Na_2SO_4, and evaporated under vacuum. Recrystallization from hexane afforded the pure pyrazoles **2a–i**.
Ethyl 4-Benzoyl-1-(1,1-dimethylethyl)-1*H*-pyrazole-5-carboxylate (2a): yield: 1.15 g (77%); oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.34 (t, 3 H, OCMe), 1.69 (s, 9 H, *t*-Bu), 4.37 (q, 2 H, OCH_2), 7.51–7.84 (m, 5 H, Ph), 7.71 (s, 1 H, H3). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.5 (Me), 29.6 (3 × Me), 62.6 (OCH_2), 62.9 [$NC(CH_3)_3$], 122.4 (C4), 128.4, 128.9, 132.4, 138.8 (Ph), 136.9 (C5), 138.3 (C3), 163.0 (CO_2), 188.5 (CO). MS (EI, 70 eV): *m*/*z* (%) = 300(16) [M$^+$], 245 (49), 199 (100), 167 (72), 139 (49), 121 (14), 105 (37), 77 (38). Anal. Calcd for $C_{17}H_{20}N_2O_3$: C, 67.98; H, 6.71; N, 9.33. Found: C, 67.93; H, 6.62; N, 9.15.
Ethyl 4-(4-Methoxybenzoyl)-1-(1,1-dimethylethyl)-1*H*-pyrazole-5-carboxylate (2b): yield: 1.48 g (90%); oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.33 (t, 3 H, OCMe), 1.69 (s, 9 H, *t*-Bu), 3.87 (s, 3 H, OMe), 4.37 (q, 2 H, OCH_2), 6.96–7.86 (m, 4 H, C_6H_4), 7.70 (s, 1 H, H3). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.5 (Me), 29.6 (3 × Me), 55.4 (OMe), 62.6 (OCH_2), 62.8 [$NC(CH_3)_3$], 113.6, 131.0, 131.3, 163.1 (C_6H_4), 122.9 (C4), 136.7 (C5), 138.4 (C3), 163.1 (CO_2), 187.2 (CO). MS (EI, 70 eV): *m*/*z* (%) = 330 (45) [M$^+$], 274 (32), 230 (100), 201 (26), 167 (20), 139 (29), 135 (54), 107 (8), 77 (14). Anal. Calcd for $C_{18}H_{22}N_2O_4$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.52; H, 6.65; N, 8.31.
Ethyl 4-(4-Chlorobenzoyl)-1-(1,1-dimethylethyl)-1*H*-pyrazole-5-carboxylate (2c): yield: 1.22 g (73%); mp 54–56 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.35 (t, 3 H, OCMe), 1.69 (s, 9 H, *t*-Bu), 4.39 (q, 2 H, OCH_2), 7.46–7.79 (m, 4 H, C_6H_4), 7.67 (s, 1 H, H3). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.6 (Me), 29.6 (3 × Me), 62.8 (OCH_2), 63.1 [$NC(CH_3)_3$], 122.1 (C4), 128.7, 130.3, 138.3, 138.6 (C_6H_4), 131.7 (C5), 136.6 (C3), 162.9 (CO_2), 187.2 (CO). MS (EI, 70 eV): *m*/*z* (%) = 334 (15) [M$^+$], 279 (46), 233 (89), 199 (70), 167 (76), 139 (100), 111 (28). Anal. Calcd for $C_{17}H_{19}ClN_2O_3$: C, 60.99; H, 5.72; N, 8.37. Found: C, 60.83; H, 5.57; N, 8.13.
Ethyl 4-(4-Fluorobenzoyl)-1-(1,1-dimethylethyl)-1*H*-pyrazole-5-carboxylate (2d): yield: 1.32 g (83%); mp 53–55 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.35 (t, 3 H, OCMe), 1.69 (s, 9 H, *t*-Bu), 4.40 (q, 2 H, OCH_2), 7.16–7.88 (m, 4 H, C_6H_4), 7.68 (s, 1 H, H3). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.6 (Me), 29.6 (3 × Me), 62.7 (OCH_2), 63.0 [$NC(CH_3)_3$], 115.5 (d, ^2J = 21 Hz, C_6H_4), 122.3 (C4), 131.5 (d, ^3J = 9 Hz, C_6H_4), 134.6 (d, ^4J = 3 Hz, C_6H_4), 136.9 (C5), 138.6 (C3), 162.9 (CO_2), 165.3 (d, ^1J = 254 Hz, C_6H_4), 187.0 (CO). MS (EI, 70 eV): *m*/*z* (%) = 318 (12) [M$^+$], 263 (42), 217 (100), 189 (21), 167 (50), 139 (41), 123 (60), 95 (43). Anal. Calcd for $C_{17}H_{19}FN_2O_3$: C, 64.14; H, 6.02; N, 8.80. Found: C, 63.94; H, 5.99; N, 8.53.
Ethyl 1-(1,1-Dimethylethyl)-4-(4-nitrobenzoyl)-1*H*-pyrazole-5-carboxylate (2e): yield: 1.57 g (91%); mp 84–85 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.39 (t, 3 H, OCMe), 1.70 (s, 9 H, *t*-Bu), 4.43 (q, 2 H, OCH_2), 7.67 (s, 1 H, H3), 8.00–8.34 (m, 4 H, C_6H_4). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.6 (Me), 29.6 (3 × Me), 62.9 (OCH_2), 63.4 [$NC(CH_3)_3$], 121.4 (C4), 123.7, 129.7, 143.3, 149.8 (C_6H_4), 137.3 (C5), 138.8 (C3), 162.7 (CO_2), 186.5 (CO). MS (EI, 70 eV): *m*/*z* (%) = 345 (15) [M$^+$], 290 (96), 244 (100), 198 (22), 167 (57), 150 (20), 139 (54), 104 (19). Anal. Calcd for $C_{17}H_{19}FN_3O_5$: C, 59.12; H, 5.55; N, 12.17. Found: C, 58.75; H, 5.18; N, 11.94.
Ethyl 1-(1,1-Dimethylethyl)-4-(thiophene-2-carbonyl)-1*H*-pyrazole-5-carboxylate (2f): yield: 1.21 g (79%); oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.36 (t, 3 H, OCMe), 1.69 (s, 9 H, *t*-Bu), 4.42 (q, 2 H, OCH_2), 7.17–7.77 (m, 3 H, thien-2-yl), 7.91 (s, 1 H, H3). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.6 (Me), 29.6 (3 × Me), 62.7 (OCH_2), 63.0 [$NC(CH_3)_3$], 122.4 (C4), 127.9, 132.7, 133.3, 143.9 (thien-2-yl), 136.8 (C5), 137.6 (C3), 162.9 (CO_2), 179.4 (CO). MS (EI, 70 eV): *m*/*z* (%) = 306 (28) [M$^+$], 251 (32), 206 (100), 178 (47), 139 (36),

111 (61), 83 (6). Anal. Calcd for $C_{15}H_{18}N_2O_3S$: C, 58.80; H, 5.92; N, 9.14. Found: C, 58.61; H, 6.21; N, 9.26.

Ethyl 4-(Benzofuran-2-carbonyl)-1-(1,1-dimethylethyl)-1*H*-pyrazole-5-carboxylate (2g): yield: 1.46 g (86%); mp 84–85 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.40 (t, 3 H, OCMe), 1.70 (s, 9 H, *t*-Bu), 4.46 (q, 2 H, OCH_2), 7.31–8.32 (m, 5 H, benzofur-2-yl), 7.61 (s, 1 H, H3). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.6 (Me), 29.6 (3 × Me), 62.8 (OCH_2), 63.0 [$NC(CH_3)$], 112.2, 113.6, 123.1, 123.9, 126.9, 128.0, 153.0, 155.5 (benzofur-2-yl), 121.2 (C4), 137.5 (C5), 138.6 (C3), 163.2 (CO_2), 175.8 (CO). MS (EI, 70 eV): *m*/*z* (%) = 340 (100) [M$^+$], 284 (74), 240 (78), 211 (73), 195 (49), 167 (17), 145 (44), 139 (39), 121 (17), 89 (36). Anal. Calcd for $C_{19}H_{20}N_2O_4$: C, 67.05; H, 5.92; N, 8.23. Found: C, 67.44; H, 6.15; N, 8.01.

Ethyl 4-(2,2,2-Trichloroacetyl)-1-(1,1-dimethylethyl)-1*H*-pyrazole-5-carboxylate (2h): yield: 1.33 g (78%); mp 96–98 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.43 (t, 3 H, OCMe), 1.66 (s, 9 H, *t*-Bu), 4.50 (q, 2 H, OCH_2), 8.10 (s, 1 H, H3). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.6 (Me), 29.5 (3 × Me), 63.2 (OCH_2), 63.5 [$NC(CH_3)$], 95.3 (CCl_3), 113.1 (C4), 139.3 (C3), 140.2 (C5), 162.6 (CO_2), 175.2 (CO). MS (EI, 70 eV): *m*/*z* (%) = 297 (2) [M + 2 – OEt], 239 (5), 223 (20), 167 (100), 139 (50), 121 (11). Anal. Calcd for $C_{12}H_{15}Cl_3N_2O_3$: C, 42.19; H, 4.43; N, 8.20. Found: C, 42.39; H, 4.58; N, 8.32.

Ethyl 4-(2,2,2-Tri-fluoroacetyl)-1-(1,1-dimethylethyl)-1*H*-pyrazole-5-carboxylate (2i): yield: 1.11 g (76%); oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.42 (t, 3 H, OCMe), 1.66 (s, 9 H, *t*-Bu), 4.49 (q, 2 H, OCH_2), 7.90 (s, 1 H, H3). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.6 (Me), 29.5 (3 × Me), 63.4 (OCH_2), 63.9 [$NC(CH_3)$], 115.3 (C4), 116.2 (q, ^1J = 290 Hz, CF_3), 138.7 (C5), 138.8 (C3), 162.2 (CO_2), 174.2 (q, ^2J = 37 Hz, CO). MS (EI, 70 eV): *m*/*z* (%) = 292 (4) [M$^+$], 277 (4), 237 (65), 231 (35), 223 (23), 209 (12), 191 (100), 167 (55), 139 (40), 121 (13), 69 (4). Anal. Calcd for $C_{12}H_{15}F_3N_2O_3$: C, 49.32; H, 5.17; N, 9.59. Found: C, 49.09; H, 5.37; N, 9.86.

(17) Crystallographic data for compound **2h**, reported in this paper, have been deposited with the Cambridge Crystallographic Data Centre (CCDC 669661). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: +44(1223)336033 or e-mail: deposit@ccdc.cam.ac.uk.

(18) **General Procedure for the Synthesis of Pyrazoles 3**: A mixture of enaminodiketone **1** (5 mmol) and carboxymethylhydrazine (0.540 g, 6 mmol) was stirred at r.t. in anhyd EtOH (20 mL) for 1 h. Then the product was filtered, washed with EtOH and dried under vacuum affording the pure pyrazoles **3a**–**g**.

Ethyl 4-Benzoyl-1*H*-pyrazole-5-carboxylate (3a): yield: 0.91 g (75%); mp 196–198 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.93 (t, 3 H, OCMe), 4.10 (q, 2 H, OCH_2), 7.47–7.87 (m, 5 H, Ph), 8.24 (s, 1 H, H3), 14.56 (br, 1 H, NH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.3 (Me), 61.4 (OCH_2), 122.1 (C4), 128.3, 129.4, 133.0, 138.6 (Ph), 133.7 (C3), 141.6 (C5), 161.8 (CO_2), 190.2 (CO). MS (EI, 70 eV): *m*/*z* (%) = 244 (18) [M$^+$], 217 (6), 200(45), 171 (11), 167 (41), 139 (52), 121 (29), 105 (43), 77 (100). Anal. Calcd for $C_{13}H_{12}N_2O_3$: C, 63.93; H, 4.95; N, 11.47. Found: C, 64.11; H, 5.33; N, 11.76.

Ethyl 4-(4-Methoxybenzoyl)-1*H*-pyrazole-5-carboxylate (3b): yield: 1.16 g (85%); mp 156–158 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.00 (t, 3 H, OCMe), 3.88 (s, 3 H, OMe), 4.15 (q, 2 H, OCH_2), 6.94–7.85 (m, 4 H, C_6H_4), 8.16 (s, 1 H, H3), 14.34 (br, 1 H, NH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.5 (Me), 55.4 (OMe), 61.3 (OCH_2), 113.6, 131.4, 131.8, 163.6 (C_6H_4), 122.4 (C4), 133.2 (C3), 141.3 (C5), 161.8 (CO_2), 188.9 (CO). MS (EI, 70 eV): *m*/*z* (%) = 274 (100) [M$^+$], 247 (20), 230 (58), 201 (21), 167 (16), 139 (52), 135 (100), 121 (40), 107 (24), 91 (47), 77 (62). Anal. Calcd for $C_{14}H_{14}N_2O_4$: C, 61.31; H, 5.14; N, 10.21. Found: C, 61.10; H, 4.93; N, 9.99.

Ethyl 4-(4-Chlorobenzoyl)-1*H*-pyrazole-5-carboxylate (3c): yield: 1.20 g (86%); mp 190–192 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.98 (t, 3 H, OCMe), 4.14 (q, 2 H, OCH_2), 7.45–7.81 (m, 4 H, C_6H_4), 8.22 (s, 1 H, H3), 14.45 (br, 1 H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 13.6 (Me), 60.7 (OCH_2), 121.1 (C4), 128.8, 130.8, 136.8, 138.0 (C_6H_4), 133.0 (C3), 142.7 (C5), 161.9 (CO_2), 188.2 (CO). MS (NICI, CH_4): *m*/*z* (%) = 278 (100) [M$^+$]. Anal. Calcd for $C_{13}H_{11}ClN_2O_3$: C, 56.03; H, 3.98; N, 10.05. Found: C, 55.77; H, 3.62; N, 9.95.

Ethyl 4-(4-Fluorobenzoyl)-1*H*-pyrazole-5-carboxylate (3d): yield: 1.15 g (88%); mp 189–191 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.98 (t, 3 H, OCMe), 4.15 (q, 2 H, OCH_2), 7.15–7.90 (m, 4 H, C_6H_4), 8.21 (s, 1 H, H3). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 13.6 (Me), 60.7 (OCH_2), 115.7 (d, ^2J = 22 Hz, C_6H_4), 121.3 (C4), 131.9 (d, ^3J = 9 Hz, C_6H_4), 132.7 (C3), 134.8 (d, ^4J = 3 Hz, C_6H_4), 142.7 (C5), 161.8 (CO_2), 165.0 (d, ^1J = 251 Hz, C_6H_4), 187.9 (CO). MS (EI, 70 eV): *m*/*z* (%) = 262 (100) [M$^+$], 218 (76), 189 (13), 167 (67), 139 (71), 123 (64), 107 (7), 95 (82). Anal. Calcd for $C_{13}H_{11}FN_2O_3$: C, 59.54; H, 4.23; N, 10.68. Found: C, 59.17; H, 3.86; N, 10.67.

Ethyl 4-(4-Nitrobenzoyl)-1*H*-pyrazole-5-carboxylate (3e): yield: 1.36 g (94%); mp 177–179 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.02 (t, 3 H, OCMe), 4.15 (q, 2 H, OCH_2), 8.00–8.31 (m, 4 H, C_6H_4), 8.18 (s, 1 H, H3), 13.72 (br, 1 H, NH). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.6 (Me), 61.8 (OCH_2), 121.7 (C4), 123.7, 130.2, 143.3, 150.4 (C_6H_4), 135.1 (C3), 141.0 (C5), 161.1 (CO_2), 188.3 (CO). MS (EI, 70 eV): *m*/*z* (%) = 289 (11) [M$^+$], 262 (13), 245 (21), 199 (21), 167 (66), 139 (100), 122 (72), 104 (30), 76 (18). Anal. Calcd for $C_{13}H_{11}N_3O_5$: C, 53.98; H, 3.83; N, 14.53. Found: C, 53.99; H, 3.59; N, 14.58.

Ethyl 4-(Thiophene-2-carbonyl)-1*H*-pyrazole-5-carboxylate (3f): yield: 0.92 g (74%); mp 140–142 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.11 (t, 3 H, OCMe), 4.25 (q, 2 H, OCH_2), 7.14–7.72 (m, 3 H, thien-2-yl), 8.24 (s, 1 H, H3), 14.31 (br, 1 H, NH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.5 (Me), 61.5 (OCH_2), 122.0 (C4), 128.0, 134.3, 134.4, 145.2 (thien-2-yl), 133.0 (C3), 141.3 (C5), 161.7 (CO_2), 181.7 (CO). MS (NICI, CH_4): *m*/*z* (%) = 250 (100) [M$^+$]. Anal. Calcd for $C_{11}H_{10}N_2O_3S$: C, 52.79; H, 4.03; N, 11.19. Found: C, 52.59; H, 3.77; N, 11.28. **Ethyl 4-(Benzofuran-2-carbonyl)-1*H*-pyrazole-5-carboxylate (3g)**: yield: 1.26 g (89%); mp 158–160 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.08 (t, 3 H, OCMe), 4.23 (q, 2 H, OCH_2), 7.32–7.71 (m, 5 H, benzofur-2-yl), 8.35 (s, 1 H, H3), 13.55 (br, 1 H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 13.6 (Me), 60.7 (OCH_2), 112.1, 114.6, 120.2 (C4), 123.6, 124.0, 126.8, 128.4, 133.1 (C3), 143.3 (C5), 152.5, 155.0 (benzofur-2-yl), 162.1 (CO_2), 177.0 (CO). MS (EI, 70 eV): *m*/*z* (%) = 284 (100) [M$^+$], 257 (4), 240 (27), 211 (33), 184 (16), 167 (12), 145 (38), 139 (53), 89 (68). Anal. Calcd for $C_{15}H_{12}N_2O_4$: C, 63.38; H, 4.25; N, 9.85. Found: C, 63.30; H, 4.21; N, 9.97.

(19) Crystallographic data for compound **3d**, reported in this paper, have been deposited with the Cambridge Crystallographic Data Centre (CCDC 669660). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: +44(1223)336033 or e-mail: deposit@ccdc.cam.ac.uk.

(20) **Procedure for the Synthesis of Pyrazole 4**: To a stirred solution of **2h** (0.341 g, 1 mmol) in EtOH (4 mL) was added sat. aq solution of KOH (2 mL) and stirring was continued at

r.t. for 4 h. The basic solution was acidified with 2 N HCl (20 mL) in an ice-bath. Most of the solvent was removed under reduced pressure and the resulting mixture was diluted with CH_2Cl_2 (20 mL), and dried over Na_2SO_4. Evaporation of the solvent gave pyrazole **4** with a high degree of purity.

5-Carboxyethyl-1-(1,1-dimethylethyl)-1*H*-pyrazole-4-carboxylic Acid (**4**): yield: 0.18 g (76%); mp 99–101 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.36 (t, 3 H, OCMe), 1.64 (s, 9 H, *t*-Bu), 4.44 (q, 2 H, OCH_2), 7.89 (s, 1 H, H3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.6 (Me), 29.5 (3 × Me), 62.8 (OCH_2), 62.9 [$NC(CH)_3$], 113.3 (C4), 137.3 (C5), 139.3 (C3), 162.9 (CO_2), 167.5 (COOH). MS (EI, 70 eV): *mz* (%) = 240 (4) [M$^+$], 225 (4), 207 (19), 195 (6), 185 (30), 167 (90), 139 (100), 121 (9), 68 (12). Anal. Calcd for $C_{11}H_{16}N_2O_4$: C, 54.99; H, 6.71; N, 11.66. Found: C, 55.01; H, 6.88; N, 11.72.