HETEROCYCLES, Vol. 53, No. 6, 2000, pp. 1285 - 1292, Received, 9th February, 2000

CHEMOSELECTIVE SYNTHESIS OF 3- AND 5-PYRAZOLYLACETATES

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Abstract - Methyl 3,5-dioxohexanoate (**1**) reacts with hydrazines (**2**) in methanol or acetic acid to give a mixture of the isomeric pyrazolylacetates (**3**) and (**4**), whose molar ratio depends on the solvent and hydrazine. 2,2-Dimethyl-5-(1-hydroxy-3-oxobutylidene)-1,3-dioxane-4,6-dione (**5**) reacts chemoselectively with hydrazines to give the 5-pyrazolylacetates (**3**) as the only reaction products.

Pyrazole derivatives are of special interest owing to their potential biological properties as agrochemicals and pharmacological agents.[1-6] A series of heteroaryl acetic acid derivatives, and in particular of benzo-pyrazolyl-acetic acids, have been patented and employed in agriculture as herbicides and plant growth regulators.[6]

In the course of our researches on the synthesis of new agrochemicals, we were interested in the preparation of new pyrazolylacetic acid derivatives. A survey of literature revealed that the synthetic approaches to this class of compounds are restricted to the following: i) the reaction of 3-pyrazolylcarboxylic acid chloride with diazomethane followed by treatment of obtained diazo ketone with alcohols,[7] ii) the hydrolysis of the 3- or 5-pyrazolylacetonitriles obtained in a few steps from the corresponding alkyl pyrazolylcarboxylates[4,8] or pyrazolylethers,[5] iii) the reactions of ethyl 3,5,5-triethoxy-2-pentenoates with hydrazines.[9]

Pyrazolylacetates could *a priori* be obtained straightforwardly by the reactions of methyl 3,5-dioxo-hexanoate (**1**)[10] with hydrazines. While the reaction of hydrazine hydrate (**2a**) with compound (**1**) can afford only one derivative, the reactions with alkyl- and arylhydrazines could give two isomeric 3- and 5-pyrazolylacetates depending on the possibility of attack of two nitrogen group of hydrazine on the two carbonyl groups of dioxohexanoate (**1**).

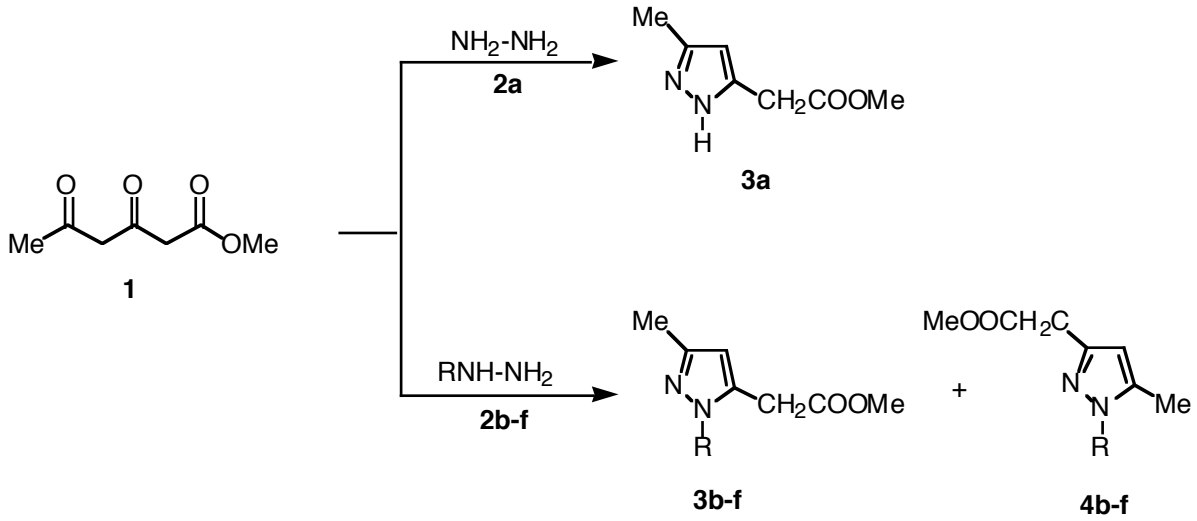
In this paper we report the results obtained in the reactions of **1** with alkyl- and arylhydrazines carried out in two different solvents, methanol and acetic acid, in order to investigate the effect of these solvents on the distribution of the compounds. Furthermore we investigated the possibility of obtaining pyrazolylacetates *via* an alternative route involving the reactions of hydrazines with 2,2-dimethyl-5-(1-hydroxy-3-oxobutylidene)-1,3-dioxane-4,6-dione (**5**), prepared by reaction of Meldrum acid with diketene,[11] and we report here on the results obtained.

RESULTS

Methyl 3,5-dioxo-hexanoate (**1**) reacts with hydrazine (**2a**) in acetic acid to give methyl pyrazolylacetate (**3a**) in high yield (**Scheme 1**, Entry 1).

The reactions of **1** with alkyl- and arylhydrazines were carried out using methanol or acetic acid as solvents at room temperature. In the reaction of **1** with methylhydrazine (**2b**) in methanol two isomeric pyrazolylacetates (**3b**) and (**4b**) were obtained in *ca*. 2:1 molar ratio and 80% of total yield (Entry 2). When the same reaction was carried out under the same experimental conditions but using acetic acid as solvent isomer (**4b**) was isolated in 70% yield as the only reaction product (Entry 3).

Different results in the two solvents have been obtained also in the reaction of **1** with *tert*-butylhydrazine (**2c**).

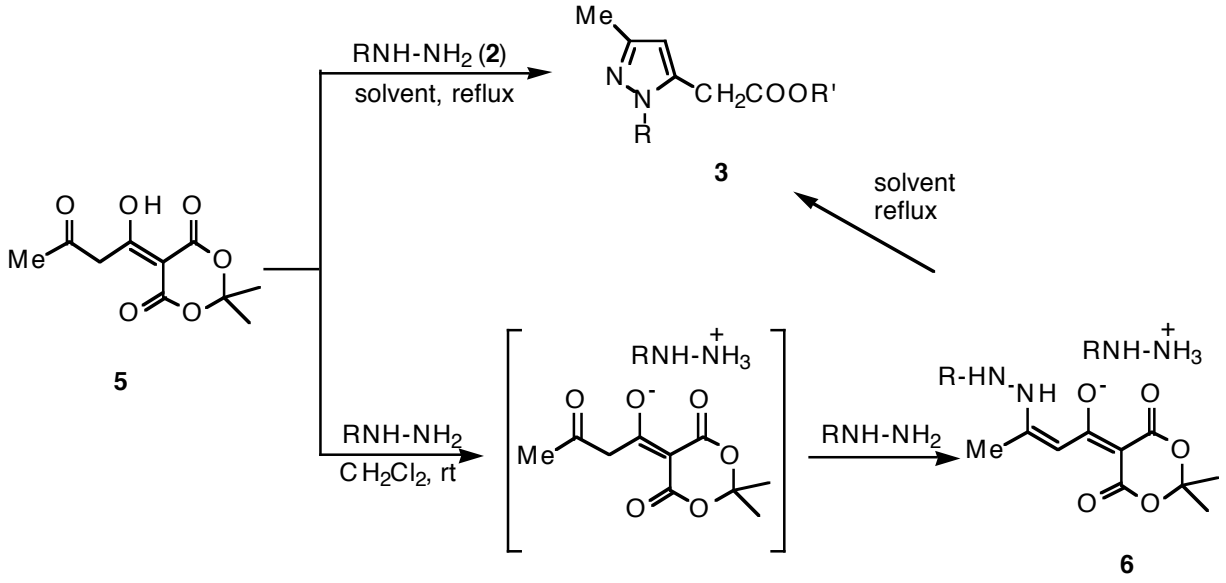


Entry	R	Solvent	time/temp.	Products	Yield of **3** (%)	Yield of **4** (%)	Total Yield (%)
1	H	AcOH	1 h/rt	**3a**	97	-	
2	Me	MeOH	1 h/rt	**3b+4b**	53	27	80
3	Me	AcOH	1 h/rt	**4b**	-	70	
4	*t*-Bu	MeOH	1 h/rt	**3c**	88	-	
5	*t*-Bu	AcOH	1 h/rt	**-**	-	-	
6	Ph	MeOH	1 h/rt	**3d+4d**	55	28	83
7	Ph	AcOH	1 h/rt	**3d+4d**	55	28	83
8	*p*-$NO_2C_6H_4$	MeOH	24 h/rt	**3e+4e**	19	19	38
9	*p*-$NO_2C_6H_4$	AcOH	1 h/rt	**3e+4e**	60	30	90
10	*p*-ClC_6H_4	MeOH	1 h/rt	**3f+4f**	68	17	85
11	*p*-ClC_6H_4	AcOH	1 h/rt	**3f+4f**	56	29	85

The reaction of **1** with **2c** in methanol afforded 5-pyrazolylacetate (**3c**) as the only reaction product in 88% yield (Entry 4), while when the same reaction was carried out in acetic acid no reaction product was isolated (Entry 5).

The reactions of **1** with phenylhydrazine (**2d**), *p*-nitrophenylhydrazine (**2e**) and *p*-chlorophenylhydrazine (**2f**) carried out in methanol and in acetic acid afforded a mixture of the two isomeric pyrazole derivatives (**3d**,**e**,**f**) and (**4d**,**e**,**f**,) the isomer (**3**) being isolated generally in higher yield (Entries 6-11).

In the alternative approach 2,2-dimethyl-5-(1-hydroxy-3-oxobutylidene)-1,3-dioxane-4,6-dione (**5**) was reacted with alkyl- and arylhydrazines in methanol or ethanol and in methylene chloride (**Scheme 2**).



Entry	reagents	molar ratio **5:2**	R	R'	solvent	time/temp.	product	yield (%)
1	**5+2b**	1:1	Me	Me	MeOH	3 h/60°C	**3b**	90
2	**5+2c**	1:1	*t*-Bu	Me	MeOH	3 h/60°C	**3c**	71
3	**5+2d**	1:1	Ph	Me	MeOH	3 h/60°C	**3d**	74
4	**5+2d**	1:1	Ph	Et	EtOH	3 h/60°C	**3g**	76
5	**5+2e**	1:1	*p*-$NO_2C_6H_4$	Me	MeOH	3 h/60°C	**3e**	88
6	**5+2b**	1:1	Ph		CH_2Cl_2	1 h/rt	**6**	35
7	**5+2b**	1:2	Ph		CH_2Cl_2	1 h/rt	**6**	88
8	**6**	-	Ph	Me	MeOH	3 h/60°C	**3d**	98

Scheme 2

When compound (**5**) was heated at 60°C in methanol or ethanol with methyl-, *tert*-butyl-, phenyl- and *p*-nitrophenylhydrazines methyl or ethyl 5-pyrazolylacetates (**3b**), (**3c**), (**3d**), (**3g**) and (**3e**) were obtained as the only reaction product in good to high yield (**Scheme 2**, Entries 1-5).

The reactions of **5** with phenylhydrazine carried out in methylene chloride at room temperature afforded compound (**6**) in *ca*. 35% yield when the molar ratio of the two reagents was 1:1 (Entry 6) and in 85% yield when the molar ratio was 1:2 (Entry 7).

When compound (**6**) was heated in methanol at 60°C for 3 h, the pyrazole (**3d**) was isolated as the only reaction product in quantitative yield (Entry 8).

The high chemoselectivity observed in these reactions can be explained by the formation of an intermediate salt which undergoes a fast attack of the second hydrazine molecule on the acetyl carbonyl group affording compounds analogous to (**6**), which react with alchools to give compounds (**3**).

The structure of the two isomeric pyrazolylacetates (**3**) and (**4**) was determined by spectral data. While IR and ^{1}H-NMR spectra of two isomers are very similar and did not allow us to assign the relative structure, the ^{13}C-NMR spectra show for the two isomers interesting differences in the absorptions of the C-3 and C-5 carbon atoms of pyrazole ring.

In particular all compounds (**3**) show absorptions in the range 145-150 and 134-136 ppm attributable to the C-3 and C-5 respectively.[12-14] In the coupled ^{13}C-NMR spectra the absorptions attributable at C-3 carbon atoms are detected as a double quartet, due to the long range coupling ($^{2}J_{CCH}$) of the C-3 carbon atom with the hydrogen of the methyl group and the hydrogen linked to C-4 carbon atom of the ring. The absorptions attributable to C-5 carbon atom are detected as a double triplet, due to the long range coupling of the C-5 carbon atom with the hydrogens of methylene group of acetic chain and the hydrogen linked to the ring C-4 carbon atom.

All compounds (**4**) show instead absorptions in the range 143-150 ppm and 139-140 ppm for the C-3 and C-5 carbon atoms respectively. In the coupled spectra the C-3 absorptions are detected as double triplet while the C-5 absorptions are detected as a double quartet showing that the C-3 is coupled with the methylene group while the C-5 is coupled with the methyl group and these data confirm the proposed structure.

The results obtained demonstrate that the two synthetic approaches are complementary. In particular the route involving the reaction of compound (**5**) with hydrazines represents a simple way to obtain the 5-pyrazolylacetates (**3**) chemoselectively and in good yield.

EXPERIMENTAL

Melting points were determined in open capillary tubes on a Büchi apparatus and are uncorrected. IR spectra were recorded on Perkin-Elmer Paragon 500 FT-IR spectrophotometer (values in cm^{-1}). NMR spectra were recorded on Bruker AC (200 MHz) spectrometer. Chemical shifts are given in ppm (δ) with respect to tetramethylsilane and coupling constants (J) are in Hertz. Flash column chromatography was performed using Merck silica gel (230-400 mesh).

Compounds (**1**) and (**5**) were prepared according to the literature.[10, 11]

Reaction of methyl 3,5-dioxohexanoate (1) with hydrazines

General procedures

To a solution of **1** (1 mmol) in methanol or acetic acid (1 mL) a solution of the pertinent hydrazine (1 mmol) in methanol (3 mL) or in acetic acid (2 mL) was added. The reaction mixture was stirred at rt for 1-24 h (see **Scheme 1**), concentrated under reduced pressure to give a residue which was purified by flash column

chromatography (eluent ethyl ether/light petroleum 4.5:5.5).

Methyl (3-methylpyrazol-5-yl)acetate (3a)

This product was obtained from **1** and hydrazine hydrate using acetic acid as solvent: pale yellow oil (97% yield). IR (neat): 3203, 1742, 1579, 1437. ^{1}H-NMR ($CDCl_3$): 2.27 (s, 3H, Me), 3.66 (s, 2H, CH_2), 3.70 (s, 3H, OMe), 5.99 (s, 1H, CH), 9.49 (s, 1H, NH); ^{13}C-NMR ($CDCl_3$): 11.39 (q, J=127.3 Hz, Me), 33.36 (t, J=129.2 Hz, CH_2), 52.14 (q, J=146.2 Hz, OMe), 104.50 (d, J=173.3 Hz, CH), 142.24 (dq, ^{2}J=6.8 Hz, C-3), 142.94 (dt, ^{2}J=6.6 Hz, C-5), 171.09 (s, COO). *Anal*. Calcd for $C_7H_{10}N_2O_2$: C, 54.54; H, 6.54; N, 18.17. Found: C, 54.45; H, 6.48; N, 18.05.

Methyl (1,3-dimethylpyrazol-5-yl)acetate (3b)

Methyl (1,5-dimethylpyrazol-3-yl)acetate (4b)

These compounds were obtained in the reactions of **1** with methylhydrazine. Using methanol as solvent compounds (**3b**) and (**4b**) were obtained in 53% and 27% yields respectively while in acetic acid compound (**4b**) was obtained in 70% yield as the only reaction product.

3b: pale yellow oil, IR (neat): 1742, 1552. ^{1}H-NMR ($CDCl_3$): 2.21 (s, 3H, Me), 3.63 (s, 2H, CH_2), 3.72 (s, 3H, NMe or OMe), 3.74 (s, 3H, NMe or OMe), 5.95 (s, 1H, CH). ^{13}C-NMR ($CDCl_3$): 13.28 (q, J=124.5 Hz, Me), 31.47 (t, J=129.5 Hz, CH_2), 36.01 (q, J=129.1 Hz, NMe), 52.29 (q, J=144.7 Hz, OMe), 105.95 (d, J=171.2 Hz, CH), 135.13 (dt, ^{2}J=7.9 Hz, C-5), 147.26 (dq, ^{2}J=5.5 Hz, C-3), 169.45 (s, COO). *Anal*. Calcd for $C_8H_{12}N_2O_2$: C, 57.13; H, 7.19; N, 16.66. Found: C, 57.02; H, 7.23; N,16.54.

4b: pale yellow oil; IR (neat): 1741, 1552; ^{1}H-NMR ($CDCl_3$): 2.23 (s, 3H, Me), 3.61 (s, 2H, CH_2), 3.69 and 3.74 (two s, 3H + 3H, N-Me and O-Me), 5.96 (s, 1H, CH). ^{13}C-NMR ($CDCl_3$): 11.01, (q, J=123.3 Hz, Me), 33.97 (t, J=128.6 Hz, CH_2), 35.70 (q, J=128.3 Hz, N-Me), 51.87 (q, J=146.5 Hz, OMe), 104.94 (d, J=173.0 Hz, CH), 139.34 (m, C-5), 143.49 (dt, ^{2}J=4.9 Hz, C-3), 171.40 (COO). *Anal*. Calcd for $C_8H_{12}N_2O_2$: C, 57.13; H, 7.19; N, 16.66. Found: C, 57.18; H, 7.15; N, 16.52.

Methyl (1-*tert*-butyl-3-methylpyrazol-5-yl)acetate (3c)

This compound was obtained in the reactions of **1** with *tert*-butylhydrazine. Using methanol as solvent compound (**3c**) was obtained in 88% yield while in acetic acid no compound was obtained.

3c: pale yellow oil; IR (neat): 1746, 1550, 1258; ^{1}H-NMR ($CDCl_3$): 1.59 (s, 9H, *t*-Bu), 2.21 (s, 3H, Me), 3.72 (s, 3H, OMe), 3.83 (s, 2H, CH_2), 5.96 (s, 1H, CH). ^{13}C-NMR ($CDCl_3$): 13.30 (q, J=126.1 Hz, Me), 30.25 (q, J=128.8 Hz, *t*-Bu), 33.76 (t, J=128.8 Hz, CH_2), 52.10 (q, J=146.3 Hz, OMe), 59.48 (s, *C*(Me)$_3$), 108.64 (d, J=170.8 Hz, CH), 134.41 (dt, ^{2}J=6.9 Hz, C-5), 145.00 (dq, ^{2}J=5.5 Hz, C-3), 170.26 (COO). *Anal*. Calcd for $C_{11}H_{18}N_2O_2$: C, 62.83; H, 8.63; N, 13.32. Found: C, 62.88; H, 8.68; N, 13.21.

Methyl (3-methyl-1-phenylpyrazol-5-yl)acetate (3d)

Methyl (5-methyl-1-phenylpyrazol-3-yl)acetate (4d)

These compounds were obtained in the reactions of **1** with phenylhydrazine. Using methanol or acetic acid as solvent compounds (**3d**) and (**4d**) were obtained in 55% and 28% yields respectively.

3d: pale yellow oil; IR (neat): 1742, 1598, 1503. ^{1}H-NMR ($CDCl_3$): 2.32 (s, 3H, Me), 3.66 (s, 3H, OMe), 3.67 (s, 2H, CH_2), 6.19 (s, 1H, CH), 7.40-7.43 (m, 5H, Ph). ^{13}C-NMR ($CDCl_3$): 13.55 (q, J=127.3 Hz, Me), 31.99 (t, J=130.3 Hz, CH_2), 52.31 (q, J=147.4 Hz, OMe), 107.54 (d, J=174.1 Hz, CH), 125.40 (d, Ph), 127.98 (d, Ph), 129.15 (d, Ph), 135.84 (dt, ^{2}J=7.7 Hz, C-5), 139.30 (s, Ph), 149.19 (dq, ^{2}J=6.4 Hz, C-3),

169.84 (s, COO). *Anal*. Calcd for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.17. Found: C, 67.89; H, 6.11; N, 12.27.

4d: pale yellow oil. IR (neat): 1740, 1595, 1505. ^{1}H-NMR ($CDCl_3$): 2.31(s, 3H, Me), 3.67 (s, 3H, OMe), 3.75 (s, 2H, CH_2), 6.18 (s, 1H, CH), 7.41 (s, 5H, Ph). ^{13}C-NMR ($CDCl_3$): 12.31 (Me), 34.04 (CH_2), 106.80 (CH), 124.70 (Ph), 127.40 (Ph), 128.87 (Ph), 139.50 (Ph), 139.72 (C-5), 145.47 (C-3), 171.23 (COO). *Anal*. Calcd for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.17. Found: C, 67.69; H, 6.19; N, 12.08.

Methyl (3-methyl-1-*p*-nitrophenylpyrazol-5-yl)-acetate (3e)

Methyl (5-methyl-1-*p*-nitrophenylpyrazol-3-yl)acetate (4e)

These compounds were obtained in the reactions of **1** with *p*-nitrophenylhydrazine. Using methanol as solvent compounds (**3e)** and (**4e**) were obtained in 19% and 19% yields respectively while in acetic acid these compounds were obtained in 60% and 30% yields respectively.

3e: yellow crystals, mp 103-104°C (chloroform/light petroleum). IR (KBr): 1729, 1595, 1522. ^{1}H-NMR ($CDCl_3$): 2.32 (s, 3H, Me), 3.70 (s, 3H, OMe), 3.77 (s, 2H, CH_2), 6.27 (s, 1H, CH), 7.64-8.34 (A_2B_2 system, J=8.0 Hz, 4H, Ph). ^{13}C-NMR ($CDCl_3$): 13.44 (q, J=126.8 Hz, Me), 32.09 (t, J=129.7 Hz, CH_2), 52.52 (q, J=146.7 Hz, OMe), 109.82 (d, J=174.1 Hz, CH), 124.57 (d, Ph), 124.72 (d, Ph), 136.00 (dt, ^{2}J=8.0 Hz, C-5), 144.45 (s, Ph), 146.16 (s, Ph), 150.86 (dq, ^{2}J=6.5 Hz, C-3) 169.36 (s, COO). *Anal*. Calcd for $C_{13}H_{13}N_3O_4$: C, 56.73; H, 4.76; N, 15.27. Found: C, 56.58; H, 4.68; N, 15.36.

4e: yellow crystals, mp 89-91°C (chloroform/light petroleum). IR (KBr): 1737, 1595, 1512. ^{1}H-NMR ($CDCl_3$): 2.45 (s, 3H, Me), 3.73 (s, 3H, OMe), 3.74 (s, 2H, CH_2), 6.29 (s, 1H, CH), 7.69 and 8.33 (A_2B_2 system, J=8.0 Hz, 4H, Ph). ^{13}C-NMR ($CDCl_3$): 13.15 (q, J=127.0 Hz, Me), 34.05 (t, J=129.1 Hz, CH_2), 52.19 (q, J=146.7 Hz, OMe), 109.16 (d, J=171.2 Hz, CH), 123.87 (d, Ph), 124.68 (d, Ph), 140.34 (dq, ^{2}J=7.0 Hz, C-5), 144.71 (s, Ph), 145.87 (s, Ph), 147.42 (dt, ^{2}J=6.0 Hz, C-3), 170.93 (COO). *Anal*. Calcd for $C_{13}H_{13}N_3O_4$: C, 56.73; H, 4.76; N, 15.27. Found: C, 56.64; H, 4.78; N, 15.38.

Methyl (1-*p*-chlorophenyl-3-methylpyrazol-5-yl)acetate (3f)

Methyl (1-*p*-chlorophenyl-5-methylpyrazol-3-yl)acetate (4f)

These compounds were obtained in the reactions of **1** with *p*-chlorophenylhydrazine. Using methanol as solvent compounds (**3f)** and (**4f)** were obtained in 68% and 17% yields while in acetic acid these compounds were obtained in 56% and 29% yields respectively.

3f: pale yellow oil. IR (neat): 1742, 1554, 1500. ^{1}H-NMR ($CDCl_3$): 2.30 (s, 3H, Me), 3.65 (s, 2H, CH_2), 3.67 (s, 3H, OMe), 6.18 (s, 1H, CH), 7.37-7.44 (m, 4H, Ph). ^{13}C-NMR ($CDCl_3$): 15.47 (q, J=126.6 Hz, Me), 31.67 (t, J=139.5 Hz, CH_2), 52.38 (q, J=146.6 Hz, Me), 107.98 (d, J=176.2 Hz, CH), 126.53 (d, J=137.1 Hz, Ph), 129.30 (d, J=140.1 Hz, Ph), 131.18 (s, Ph), 135.93 (dt, ^{2}J=7.6 Hz, C-5), 137.81 (s, Ph), 145.94 (m, C-3), 169.65 (COO). *Anal*. Calcd for $C_{13}H_{13}ClN_2O_2$: C, 58.99; H, 4.95; N, 10.58; Cl, 13.39. Found: C, 58.85; H, 4.89; N, 10.65; Cl, 13.31.

4f: yellow oil. IR (neat): 1743, 1555, 1500. ^{1}H-NMR ($CDCl_3$): 2.30 (s, 3H, Me), 3.70 (s, 2H, CH_2), 3.72 (s, 3H, OMe), 6.18 (s, 1H, CH), 7.39 (s, 4H, Ph). ^{13}C-NMR ($CDCl_3$): 12.46 (q, J=128.2 Hz, Me), 31.08 (t, J=141.1 Hz, CH_2), 52.08 (q, J=146.4 Hz, OMe), 107.34 (d, J=173.9 Hz, CH), 125.90 (d, Ph), 129.15 (d, Ph), 133.19 (s, Ph), 139.90 (dq, ^{2}J=7.1 Hz, C-5), 145.97 (dt, ^{2}J=4.9 Hz, C-3), 171.23 (COO). *Anal*. Calcd for $C_{13}H_{13}ClN_2O_2$: C, 58.99; H, 4.95; N, 10.58; Cl, 13.39. Found: C, 58.88; H, 4.88; N, 10.55;

Cl, 13.21.

Reaction of compound (5) with hydrazines in methanol or ethanol

General procedure

To a solution of **5** (228 mg, 1 mmol) in methanol (1.5 mL) the pertinent hydrazine (1.1 mmol) was added. The reaction mixture was heated at 60°C for 3 h and concentrated under reduced pressure to give a residue which was purified by flash chromatography (eluent: ethyl acetate/light petroleum 1:1) to give compound (**3**) as the only reaction product.

Following this general procedure the reaction of **5** with methylhydrazine in methanol gave compound (**3a**) in 90% yield, the reaction with phenylhydrazine gave compound (**3d**) in 74% yield and the reaction with *p*-nitrophenylhydrazine afforded compound (**3e**) in 88% yield.

The reaction of **5** with phenylhydrazine, carried out in the same experimental conditions but using ethanol as solvent, afforded compound (**3g**) as a brown oil (76% yield). IR (neat): 1739, 1596,1506. ^{1}H-NMR: 1.18 (t, J=7.1 Hz, 3H, Me), 2.31 (s, 3H, Me), 3.65 (s, 2H, CH_2), 4.10 (q, J=7.1 Hz, 2H, CH_2), 6.18 (s, 1H, CH), 7.34-7.48 (m, 5H, Ph). ^{13}C-NMR: 13.41 (q, Me), 13.92 (q, Me), 32.15 (t, CH_2), 61.17 (d, CH_2), 107.47 (d, CH), 125.31 (d, Ph), 127.84 (d, Ph), 129.03 (d, Ph), 135.97 (s, C-5), 139.24 (s, Ph), 149.05 (s, C-3), 169.27 (s, COO). *Anal*. Calcd for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; N, 11.47. Found: C, 68.72; H, 6.45; N, 11.55.

Reaction of compound (5) with *tert*-butylhydrazine

To a solution of **5** (228 mg, 1 mmol) in methanol (1.5 mL) a solution of *tert*-butylhydrazine hydrochloride (137 mg, 1.1 mmol) and triethylamine (0.153 mL, 1.1 mmol) in methanol (1.5 mL) was added. The reaction mixture was heated at 60°C for 3 h and concentrated under reduced pressure. The residue was treated with tetrahydrofuran to give crystals of triethylamine hydrochloride which were filtered off. The filtrate was concentrated under reduced pressure to give a residue which was purified by flash chromatography (eluent ethyl acetate: light petroleum 1:1) to give compound (**3c**) as the only reaction product in 71% yield.

Reaction of compound (5) with phenylhydrazine in methylene chloride

1:2 molar ratio

To a solution of **5** (228 mg, 1 mmol) in methylene chloride (1 mL) phenylhydrazine (0.2 mL, 2 mmol) was added. The reaction mixture was stirred at rt for 1 h to give compound (**6**): 365 mg (88% yield), colourless crystals, mp 103-106°C (chloroform/light petroleum). IR (KBr): 3200-1800 (br), 1574, 1519, 1265. ^{1}H-NMR ($CDCl_3$): 1.42 (s, 6H, 2 Me), 2.16 (s, 3H, Me), 3.3 (br, 3H, NH_3^+), 5.88 (s, 1H, CH), 6.90-6.96 (m, 2H, Ph), 7.18-7.45 (m, 8H, Ph), 8.2 (br, 1H, NH), 9.8 (br, 2H, two NH). ^{13}C-NMR ($CDCl_3$): 13.46 (q, Me), 26.05 (q, Me), 67.71(s, $C(Me)_2$), 99.59 (s, $C(CO)_2$), 109.09 (d, CH), 114.22 (d, Ph), 121.51 (d, Ph), 125.62 (d, Ph), 128.00 (d, Ph), 128.98 (d, Ph), 140.96 (s, Ph), 141.28 (s, Ph), 145.43 (s, NH-C=), 146.47 (s, O-*C*=C), 163.94 (s, COO). *Anal*. Calcd for $C_{22}H_{26}N_4O_5$: C, 61.96; H, 6.15; N, 13.14. Found: C, 61.80; H, 6.05; N, 13.23.

1:1 molar ratio

To a solution of **5** (456 mg, 2 mmol) in methylene chloride (2 mL) phenylhydrazine (0.22 mL, 2.2 mmol) was added. The reaction mixture was stirred at rt for 1 h and concentrated under reduced pressure to give an oil, which slowly separated colourless crystals corresponding to compound (**6**) (35% yield).

Reaction of compound (6) with methanol

Compound (**6**) (430 mg, 1 mmol) was dissolved in methanol (5 mL) and the solution was heated at 60°C for 3 h. The reaction mixture was concentrated under reduced pressure to give a residue which was purified by flash chromatography: pale yellow oil (225 mg, 98% yield) corresponding to pyrazolyl ester (**3d**) described before.

ACKNOWLEDGEMENTS

The Authors are grateful to Dr. A. Casolari and Ms. P. Orlandini for recording the NMR spectra.

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