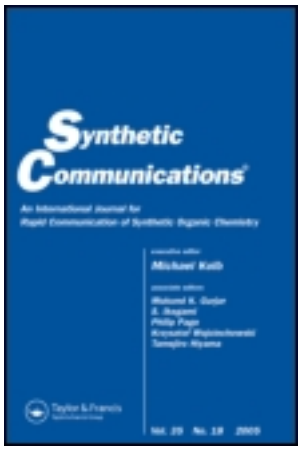


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

EFFICIENT SYNTHESIS OF 4-ETHOXYCARBONYL PYRAZOLIN-5-ONE DERIVATIVES

Jae C. Jung [a] , E. Blake Watkins [a] & Mitchell A. Avery [b]

[a] Department of Medicinal Chemistry, School of Pharmacy, University of Mississippi, P.O. Box 1848, University, MS, 38677-1848, U.S.A.

[b] Department of Chemistry, University of Mississippi, P.O. Box 1848, University, MS, 38677-1848, U.S.A.

Published online: 23 Aug 2006.

To cite this article: Jae C. Jung , E. Blake Watkins & Mitchell A. Avery (2002): EFFICIENT SYNTHESIS OF 4-ETHOXYCARBONYL PYRAZOLIN-5-ONE DERIVATIVES, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 32:24, 3767-3777

To link to this article: http://dx.doi.org/10.1081/SCC-120015395

MARCEL DEKKER, INC. • 270 MADISON AVENUE • NEW YORK, NY 10016

SYNTHETIC COMMUNICATIONS
Vol. 32, No. 24, pp. 3767–3777, 2002

EFFICIENT SYNTHESIS OF 4-ETHOXYCARBONYL PYRAZOLIN-5-ONE DERIVATIVES

Jae C. Jung,[1] E. Blake Watkins,[1] and Mitchell A. Avery[1,2,3,*]

[1]Department of Medicinal Chemistry, School of Pharmacy
[2]Department of Chemistry, and [3]National Center for Natural Products Research, University of Mississippi, P.O. Box 1848, University, MS 38677-1848, USA

ABSTRACT

Concise and efficient methods for the preparation of 3-substituted 4-ethoxycarbonylpyrazolin-5-ones are described. The synthetic strategies involve carbon-acylation in the presence of base, followed by ring cyclization with hydrazine or hydrazine monohydrochloride.

Key Words: Pyrazolin-5-ones; Cyclocondensation; Acyl Diethylmalonates

Derivatives of pyrazolin-5-one posses important pharmacological properties including analgesic, antipyretic, and antiinflammatory properties.[1] They are also useful intermediates for many industrial products,

*Corresponding author. E-mail: mavery@olemiss.edu

DOI: 10.1081/SCC-120015395 0039-7911 (Print); 1532-2432 (Online)

e.g., color photography[2] and liquid crystals.[3] Several syntheses of these compounds, based on 1,3-diketone ring cyclization with hydrazine, have been reported in the literature.[4–6] Unfortunately, most of these methods require tedious isolation and give only poor to moderate yields. During our study on cycloaddition reaction of azo dienophiles, we realized that a more efficient method of preparing derivatives of pyrazolin-5-ones was needed. In this paper, we present simple and improved methods for the preparation of α-acylated diethylamalonates and 4-ethoxy-carbonylpyrazolin-5-ones.

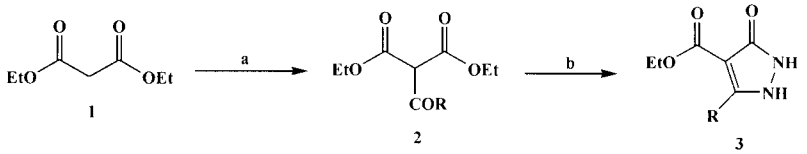
Our synthesis of substituted pyrazolin-5-ones required suitably substituted acyl malonates. We chose to prepare these acyl malonates from diethyl malonate and the corresponding acyl chloride by treatment with a suitable base (Sch. 1). To determine the best method for preparing the desired acyl malonates, the reaction was performed in the presence of various bases. The bases used included *n*-BuLi, NaH, NaOEt, $Mg(OEt)_2$, and *t*-BuOK. The results are shown in Table 1.

Magnesium ethoxide proved to be the superior base and consistently gave 10–25% higher yields than the other bases studied, even when sterically hindered acyl chlorides were used (Table 1, Entry 9). It seems probable that the effectiveness of magnesium ethoixde can be explained in part by a magnesium(II) chelation effect.[7]

Having determined the optimum reaction conditions, the remaining acyl malonates were synthesized in excellent yields (Table 2). This method proved effective for both short and long chain, as well as aryl, acyl chlorides.

With the acyl malonates in hand, we turned our attention to formation of the desired pyrazolin-5-ones. Cyclization of α-acylated diethylmalonates **2a–j** was achieved by treatment with hydrazine solution (pH 7), hydrazine monohydrochloride or hydrazine (55%) in acetic acid to give 4-ethoxycarbonyl pyrazolin-5-ones in 80–90% yield with varying substitution in the 3-position (Sch. 1). The results of the cyclization reactions are shown in Table 3.

Similarly, we found that ethyl 3-amino-2-ethoxycarbonyl-2-butenoate (**4**)[8] or ethyl 3-amino-2-phenylaminocarbonyl-2-butyrate (**5**)[9] underwent



(a) 1) Mg, EtOH, CCl_4/toluene, ii) RCOCl; (b) Method A: H_2NNH_2 (pH = 7), $EtOH/H_2O$; Method B: $H_2NNH_2HCl/EtOH$; Method C: H_2NNH_2 (55%)/HOAc.

Scheme 1.

Table 1. Acylation of Diethyl Malonate with Acyl Chlorides Using Various Bases

Entry	*R*	Base/Solvent	Time (h)	Yield[a] (%)	Product
1		*n*-BuLi/THF	2	74	
2		NaOEt/EtOH	3	50	
3	Me	NaH/THF	3	66	**2a**
4		$Mg(OEt)_2$/toluene	1	82	
5		*t*-BuOK/THF	3	54	
6		*n*-BuLi/THF	2	70	
7		NaOEt/EtOH	3	61	
8	*t*-Bu	NaH/THF	3	66	**2c**
9		$Mg(OEt)_2$/toluene	1	88	
10		*t*-BuOK/THF	3	65	
11		*n*-BuLi/THF	2	59	
12		NaOEt/EtOH	3	56	
13	Ph	NaH/THF	3	71	**2g**
14		$Mg(OEt)_2$/toluene	1	89	
15		*t*-BuOK/THF	3	65	
16		*n*-BuLi/THF	2	52	
17		NaOEt/EtOH	3	60	
18	4-$MeOC_6H_4$	NaH/THF	3	73	**2h**
19		$Mg(OEt)_2$/toluene	1	86	
20		*t*-BuOK/THF	3	75	

[a]Isolated yields.

Table 2. Synthesis of Acyl Malonates from Diethyl Malonate and Acyl Chlorides

Entry	*R*	Yield[a] (%)	Product
1	Et	88	**2b**
2	*c*-C_5H_9	87	**2d**
3	$(CH_2)_4CH_3$	87	**2e**
4	$(CH_2)_8CH_3$	89	**2f**
5	Bz	90	**2i**
6	CH_2-Bz	84	**2j**

[a]Isolated yield.

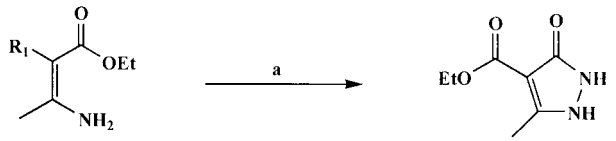
ring cyclization with hydrazine monohydrochloride or hydrazine (55%) in acetic acid to give 3-methyl-4-ethoxycarbonylpyrazolin-5-one (**3a**) in 86% and 91% yields, respectively (Sch. 2).

Cyclization was achieved in all cases where steric hindrance was not present. In the case of **2c**, **2d**, **2g**, and **2h** the bulkiness of the substituents

Table 3. Cyclization of Acyl Malonates

Entry	*R*	Method	Yield[a] (%)	Product
1	Me	A	85 (86)[b] (91)[c]	**3a**
2	Et	C	81	**3b**
3	*t*-Bu	B, C	NR[d]	–
4	*c*-C_5H_9	B, C	NR[d]	–
5	$(CH_2)_4CH_3$	B	80	**3c**
6	$(CH_2)_8CH_3$	C	86	**3d**
7	Ph	B, C	NR[d]	–
8	4-OMe-Ph	B, C	NR[d]	–
9	Bz	C	81	**3e**
10	CH_2-Bz	B	80	**3f**

[a]Isolated pure yield.
[b]Method B.
[c]Method C.
[d]No reaction.



4 $R_1 = CO_2Et$
5 R_1 = NH-Ph

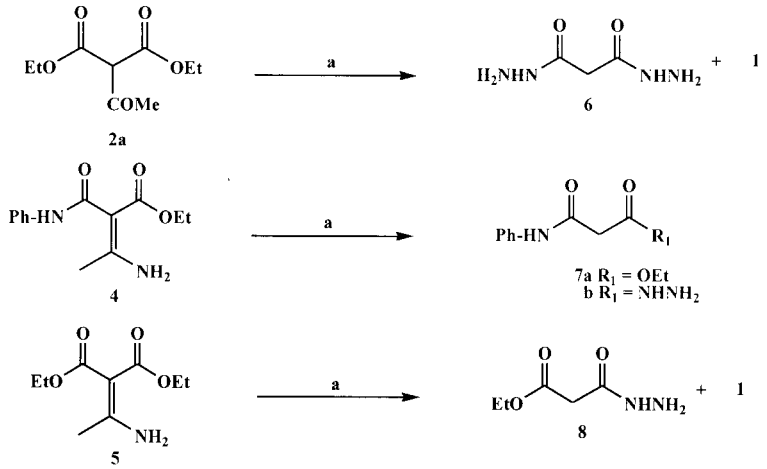
3a

(a) Method A: H_2NNH_2 (pH = 7), $EtOH/H_2O$; Method B: $H_2NNH_2HCl/EtOH$; Method C: H_2NNH_2 (55%)/HOAc.

Scheme 2.

prohibited ring closure. Cyclization failed when *R* was a phenyl group (Entry 7, Table 3) but was successful when *R* was a benzyl group (Entry 9, Table 3). The addition of a methylene undoubtedly allows clearance for the hydrazine to add and for cyclization to take place.

Unfortunately, when diethyl acetylmalonate (**2a**) was treated with hydrazine (98%) in ethanol, a mixture of diethyl malonate (**1**) and malonyldihydrazide (**6**), due to β-carbon cleavage, was isolated in 24% and 45% yields, respectively. Furthermore, the β-enamino carbonyl compounds **4** and **5** were converted to malonanilic acid ethyl ester (**7a**), malonanilic acid hydrazide (**7b**), ethoxycarbonylacetohydrazide (**8**), and diethyl malonate (**1**),



(a) H_2NNH_2 (80%)/EtOH.

Scheme 3.

as β-carbon cleavage products, upon treatment with hydrazine (80%) in ethanol (Sch. 3).

In conclusion, we report the efficient synthesis of α-acylated diethyl malonates and 4-ethoxycarbonylpyrazolin-5-ones in high yield. The operational simplicity, inexpensive and readily available materials make this procedure a useful alternative to the currently available methods.

EXPERIMENTAL

Reactions requiring anhydrous conditions were performed with the usual precautions for rigorous exclusion of air and moisture. Tetrahydrofuran was distilled from sodium bezophenone ketyl prior to use. Thin layer chromatography (TLC) was performed on precoated silica gel 60 F_{254} plates from EM reagents and visualized with a 254-nm UV light. Flash chromatography was carried out on silica gel 60 (E.M. Merck, particle size 0.040–0.063 mm, 230–400 mesh ASTM). ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker DPX 300 at 300 MHz and 76 MHz, respectively. The chemical shifts were reported in parts per million (ppm) downfield from tetramethylsilane, and *J*-values were in Hz. IR spectra were obtained on an ATI Mattson FT/IR spectrometer. Mass spectra were recorded on a Bruker BioApex FTMS system. All m.p.s were uncorrected.

When necessary, chemicals were purified according to the reported procedures.[10]

General Procedure for the Preparation of α-Acylated Diethyl Malonates (2a–f) with Magnesium Ethoxide

A mixture of diethyl malonate (**1**, 10.0 mmol), magnesium (10.0 mmol), ehtanol (33.0 mmol), CCl_4 (0.25 mL) and anhydrous toluene (22 mL) was stirred under argon at room temperature for 30 min. The mixture was refluxed for 1 h and then cooled to 0–5°C. The acylating reagent (10.0 mmol) was added dropwise to the solution at 0–5°C for 30 min, and the reaction mixture was stirred at room temperature for 1 h. The resulting mixture was recooled to 0–5°C and washed with cold 5% aq. HCl solution (20 mL), sat'd $NaHCO_3$ solution (20 mL) and brine (20 mL). The organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to give pale yellow liquids. The product was purified by column chromatography (10% ethyl acetate : hexane) to give a colorless oil.

General Procedure for the Preparation of α-Acylated Diethyl Malonates (2a, c, g, h) with Various Bases

To a stirred suspension o diethyl malonate (**1**, 12.0 mmol) and base (12.0 mmol) in anhydrous solvents, the acylating agent (12.0 mmol) was added dropwise at 0–10°C for 30 min. The reaction mixture was stirred for 1–3 h. After removal of the solvent, the residue was treated with ethyl acetate (20 mL) and washed with cold 5% aq. HCl solution (20 mL), sat'd $NaHCO_3$ solution (20 mL) and brine (20 mL). The organic layer was dried over anhydrous $MgSO_4$ and concentrated to give pale yellow liquids.

Diethyl acetylmalonate (2a): $R_f = 0.45$ (20% ethyl acetate in hexanes); IR (neat, NaCl) 2984, 1729, 1650, 1469, 1090 cm^{-1}; ^1H NMR[11a] ($CDCl_3$) δ 13.45, 4.38 (br s, br s, total 1H), 4.23–4.13 (m, 4H), 2.27, 2.13 (s, s, total 3H), 1.27–1.19 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 197.04, 171.55, 166.41, 100.19, 62.19, 61.40, 21.01, 14.39, 14.30; MS (ESI) (m/z) 203 $[M+H]^+$, 179, 157 (base peak); 225 $[M+Na]^+$.

Diethyl propionylmalonate (2b): $R_f = 0.55$ (20% ethyl acetate in hexanes); IR (neat, NaCl) 3443, 2984, 1734, 1604, 1034 cm^{-1}; ^1H NMR[11b] ($CDCl_3$) δ 13.31, 4.37 (br s, br s, total 1H), 4.17–4.07 (m, 4H), 2.53 (q, $J = 7.13$, 1H), 2.35 (q, $J = 7.13$, 1H), 1.21–1.15 (m, 6H), 1.08 (t, $J = 7.13$, 1.5H), 0.98 (t, $J = 7.13$, 1.5 H); ^{13}C NMR ($CDCl_3$) δ 199.80, 171.52, 164.98,

99.49, 62.45, 61.33, 27.57, 14.27, 14.17, 7.79; MS (ESI) (m/z) 217 $[M+H]^+$, 161, 133, 104 (base peak); 239 $[M+Na]^+$.

Diethyl pivaloylmalonate (2c): $R_f = 0.50$ (10% ethyl acetate in hexanes); IR (neat, NaCl) 3654, 2978, 1736, 1478, 1038 cm^{-1}; ^1H NMR[11c] ($CDCl_3$) δ 4.83 (br s, 1H), 4.15 (q, $J = 7.12$, 4H), 1.19 (q, $J = 7.12$, 6H), 1.10 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 203.88, 165.01, 62.47, 60.05, 45.82, 26.13, 14.22; MS (m/z) 245 $[M+H]^+$, 161, 84 (base peak); 267 $[M+Na]^+$.

Diethyl cyclopentanecarbonylmalonate (2d): $R_f = 0.60$ (15% ethyl acetate in hexanes); IR (neat, NaCl) 3583, 2963, 1730, 1601, 1241, 1035 cm^{-1}; ^1H NMR[11d] ($CDCl_3$) δ 13.28, 4.52 (br s, br s, total 1H), 4.22–4.23 (m, 4H), 3.05–2.90 (m, 1H), 1.78–1.52 (m, 8H), 1.27–1.18 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 202.13, 171.43, 165.00, 99.54, 62.49, 61.48, 43.09, 31.34, 29.90, 26.74, 26.32, 14.56, 14.28; MS (ESI) (m/z) 257 $[M+H]^+$, 202, 115, 96. 55 (base peak); 279 $[M+Na]^+$.

Diethyl caproylmalonate (2e): $R_f = 0.50$ (10% ethyl acetate in hexanes); IR (neat, NaCl) 3584, 2959, 1734, 1602, 1243, 1040 cm^{-1}; ^1H NMR ($CDCl_3$) δ 13.36, 4.43 (br s, br s, total 1H), 4.26–4.19 (m, 4H), 2.58 (t, $J = 7.30$, 1H), 2.40 (t, $J = 7.30$, 1H), 1.64–1.57 (m, 2H), 1.30–1.22 (m, 10H), 0.86 (t, $J = 6.76$, 3H); ^{13}C NMR ($CDCl_3$) δ 199.37, 171.56, 165.04, 100.08, 62.59, 61.60, 34.11, 31.77, 26.83, 22.69, 14.45, 14.34, 14.21; MS (ESI) (m/z) 259 $[M+H]^+$, 180, 135 (base peak); 281 $[M+Na]^+$.

Diethyl decanoylmalonate (2f): $R_f = 0.30$ (15% ethyl acetate in hexanes); IR (neat, NaCl) 2927, 1735, 1602, 1243, 1037 cm^{-1}; ^1H NMR ($CDCl_3$) δ 13.36, 4.43 (br s, br s, total 1H), 4.28–4.19 (m, 4H), 2.59 (t, $J = 7.29$, 1H), 2.41 (t, $J = 7.29$, 1H), 1.64–1.57 (m, 2H), 1.31–1.21 (m, 18H), 0.86 (t, $J = 6.87$, 3H); ^{13}C NMR ($CDCl_3$) δ 199.39, 171.58, 165.05, 100.08, 62.61, 61.45, 34.19, 32.22, 29.77, 29.63, 27.17, 25.36, 23.76, 23.02, 14.61, 14.43, 14.33; MS (ESI) (m/z) 315 $[M+H]^+$, 202, 161 (base peak); 104; 337 $[M+Na]^+$.

Diethyl benzoylmalonate (2g): $R_f = 0.45$ (20% ethyl acetate in hexanes); IR (neat, NaCl) 3463, 3063, 1734, 1692, 1294, 1037 cm^{-1}; ^1H NMR[11a] ($CDCl_3$) δ 13.41, 5.28 (br s, br s, total 1H), 7.89–7.42 (m, 5H), 4.23 (q, $J = 7.13$, 4H), 1.23 (t, $J = 7.13$, 6H); ^{13}C NMR ($CDCl_3$) δ 189.36, 165.26, 135.80, 134.41, 129.07, 128.69, 62.75, 61.94, 14.40, 14.03; MS (ESI) (m/z) 265 $[M+H]^+$, 219, 104 (base peak); 287 $[M+Na]^+$.

Diethyl 4-methoxybenzoylmalonate (2h): $R_f = 0.50$ (20% ethyl acetate in hexanes); IR (neat, NaCl) 3651, 2983, 1735, 1600, 1028 cm^{-1}; ^1H ^1H NMR ($CDCl_3$) δ 13.35, 5.23 (br s, br s, total 1H), 7.83 (d, $J = 8.92$, 2H), 6.88 (d, $J = 8.92$, 2H), 4.20 (q, $J = 7.08$, 4H), 3.78 (s, 3H), 1.19 (t, $J = 7.08$, 6H); ^{13}C NMR ($CDCl_3$) δ 187.78, 165.43, 164.64, 134.33, 131.26, 125.65, 114.50, 62.58, 61.95, 55.90, 14.26; MS (ESI) (m/z) 295 $[M+H]^+$, 249, 135 (base peak); 317 $[M+Na]^+$.

Diethyl 3-phenylpropionylmalonate (2i): $R_f = 0.50$ (33% ethyl acetate in hexanes); IR (neat, NaCl) 3584, 3031, 1731, 1650, 1243, 1037 cm^{-1}; ^1H NMR[11c] ($CDCl_3$) δ 13.40, 4.58 (br s, br s, total 1H), 7.34–7.19 (m, 5H), 4.29–4.21 (m, 4H), 3.94, 3.80 (s, s, total 2H), 1.34–1.25 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 197.08, 171.53, 164.91, 135.90, 130.16, 129.51, 129.05, 128.62, 127.64, 100.78, 63.77, 61.70, 39.97, 14.50, 14.37; MS (ESI) (m/z) 279 $[M+H]^+$, 202, 161 (base peak); 104, 90; 301 $[M+Na]^+$.

Diethyl hydrocinnamoylmalonate (2j): $R_f = 0.50$ (20% ethyl acetate in hexanes); IR (neat, NaCl) 3449, 3063, 1733, 1604, 1245, 1039 cm^{-1}; ^1H NMR ($CDCl_3$) δ 13.50, 4.44 (br s, br s, total 1H), 7.31–7.17 (m, 5H), 4.28–4.17 (m, 4H), 2.99–2.59 (m, 4H), 1.33–1.21 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 198.45, 171.64, 164.93, 140.99, 140.90, 140.79, 128.89, 128.72, 126.66, 100.42, 62.72, 61.36, 36.34, 31.38, 14.59, 14.33; MS (ESI) (m/z) 293 $[M+H]^+$, 247, 161 (base peak); 104; 315 $[M+Na]^+$.

Malonyldihydrazide (6): To a stirred solution of diethyl acetylmalonate (**3a**, 5.0 g, 24.7 mmol) in ethanol, hydrazine (98%, 1.2 g, 36.7 mmol) was added dropwise at room temperature. The reaction mixture was heated at reflux for 3 h. After cooling, the solvent was evaporated, and the residue was treated with diethyl ether (36 mL). The resulting solid was filtered and washed with diethyl ether and then recrystallized from ethanol in diethyl ether (v/v: 1/10) to give white crystals (1.5 g, 45%). $R_f = 0.25$ (10% methanol in dichlorohexane); m.p. 153°C (lit.[12] m.p. 154°C); IR (Nujol, NaCl) 3305, 2923, 1681, 1461, 1052 cm^{-1}; ^1H NMR (DMSO-d_6) δ 9.04 (br s, 2H), 4.22 (br s, 4H), 2.88 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 166.91, 39.68; MS (ESI) (m/z) 133 $[M+H]^+$, 100 (base peak); 155 $[M+Na]^+$, also isolated was diethyl malonate (**1**, 0.95 g, 24%).

General Procedure for the Preparation of 4-Ethoxycarbonylpyrazolin-5-one Derivatives (3a–f)

Method A: To a stirred solution of α-acylated diethyl malonate (**2**, 20.0 mmol) in ethanol was added dropwise aqueous hydrazine solution (pH = 7, 30.0 mmol), [prepared by neutralizing hydrazine (55% aq. solution) with 1 N HCl], at room temperature. The reaction mixture was heated at reflux for 3–16 h. After cooling, the solvent was evaporated, and the residue was treated with diethyl ether (35 mL). The resulting solid was filtered and washed with diethyl ether and recrytallized from ethanol in diethyl ether (v/v; 1/10) to give white crystals.

Method B: To a stirred solution of α-acylated diethyl malonates (**2**, 20.0 mmol) in ethanol, hydrazine monohydrochloride (30.0 mmol) was added portionwise at room temperature. The reaction mixture was heated

at reflux for 3–16 h. After cooling, the solvent was evaporated, and the residue was treated with diethyl ether (35 mL). The resulting solid was filtered and washed with a small amount of water and diethyl ether and then recrystallized from ethanol in diethyl ether (v/v; 1/10) to give white crystals.

Method C: To a stirred solution of α-acylated diethyl malonates (**2**, 30.0 mmol) in acetic acid (16 mL), hydrazine (55%, 45.0 mmol) was added dropwise at 10°C. The reaction mixture was heated at reflux for 3 h. After cooling, the solvent was evaporated, and the residue was treated with diethyl ether (50 mL). The resulting solid was filtered and washed with diethyl ether and then recrystallized from ethanol in diethyl ether (v/v; 1/10) to give white crystals.

4-Ethoxycarbonyl-3-methylpyrazolin-5-one (3a): $R_f = 0.12$ (5% methanol in dichloromethane); m.p. 202°C (lit.[6] 206–207°C); IR (Nujol, NaCl) 3256, 2923, 1682, 1538, 1456, 1131 cm^{-1}; ^1H NMR (DMSO-d_6) δ 11.03 (br s, 2H), 4.12 (q, $J = 7.05$, 2H), 2.28 (s, 3H), 1.21 (t, $J = 7.05$, 3H); ^{13}C NMR (DMSO-d_6) δ 164.43, 161.91, 144.93, 95.65, 59.59, 15.19, 12.96; MS (ESI) (m/z) 171 $[M+H]^+$, (base peak), 157, 143, 125.

4-Ethoxycarbonyl-3-ethylpyrazolin-5-one (3b): $R_f = 0.10$ (5% methanol in dichloromethane); m.p. 152°C; IR (Nujol, NaCl) 3244, 2923, 1683, 1462, 1130 cm^{-1}; ^1H NMR (DMSO-d_6) δ 11.84 (br s, 2H), 4.13 (q, $J = 6.85$, 2H), 2.70 (q, $J = 7.22$, 2H), 1.20 (t, $J = 6.85$, 3H), 1.11 (t, $J = 7.22$, 3H); ^{13}C NMR (DMSO-d_6) δ 163.38, 161.98, 150.42, 94.72, 59.63, 20.37, 15.12, 13.76; MS (ESI) (m/z) 185 $[M+H]^+$, 171, 157, 139 (base peak), 104; 207 $[M+Na]^+$.

4-Ethoxycarbonyl-3-pentylpyrazolin-5-one (3c): $R_f = 0.12$ (10% methanol in dichloromethane); m.p. 115–116°C; IR (Nujol, NaCl) 3208, 2924, 1690, 1461, 1106 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.00 (br s, 2H), 4.12 (q, $J = 7.10$, 2H), 2.69 (t, $J = 7.56$, 2H), 1.53 (t, $J = 6.77$, 2H), 1.23–1.18 (m, 7H), 0.83 (t, $J = 2.50$, 3H); ^{13}C NMR (DMSO-d_6) δ 164.14, 161.55, 149.48, 95.13, 59.74, 31.70, 28.77, 26.64, 22.58, 15.11, 14.66; MS (ESI) (m/z) 227 $[M+H]^+$, (base peak), 181, 135; 249 $[M+Na]^+$.

4-Ethoxycarbonyl-3-nonylpyrazolin-5-one (3d): $R_f = 0.10$ (5% methanol in dichloromethane); m.p. 136°C; IR (Nujol, NaCl) 3287, 2942, 1688, 1460, 1103 cm^{-1}; ^1H NMR (DMSO-d_6) δ 6.52 (br s, 2H), 4.13 (q, $J = 7.07$, 2H), 2.68 (t, $J = 7.79$, 2H), 1.53 (d, $J = 6.36$, 2H), 1.23 ~ 1.19 (m, 15H), 0.82 (t, $J = 6.75$, 3H); ^{13}C NMR (DMSO-d_6) δ 164.32, 161.89, 149.17, 95.02, 59.64, 32.12, 29.74, 29.49, 29.13, 26.72, 22.93, 15.12, 14.76; MS (ESI) (m/z) 283 $[M+H]^+$, (base peak), 255, 161, 104; 305 $[M+Na]^+$.

4-Ethoxycarbonyl-3-benzylpyrazolin-5-one (3e): $R_f = 0.16$ (10% methanol in dichloromethane); m.p. 146°C; IR (Nujol, NaCl) 3203, 3062, 1725, 1685, 1461, 1107 cm^{-1}; ^1H NMR (DMSO-d_6) δ 8.87 (br s, 2H), 7.20–7.15 (m,

5H), 4.09 (q, $J = 7.10$, 2H), 4.06 (s, 2H), 1.14 (t, $J = 7.10$, 3H); ^{13}C NMR (DMSO-d_6) δ 163.80, 161.02, 147.93, 138.98, 129.15, 127.16, 95.37, 59.90, 32.23, 15.08; MS (ESI) (m/z) 247 $[M+H]^+$, 201, 133 (base peak), 89; 269 $[M+Na]^+$.

4-Ethoxycarbonyl-3-methylbenzylpyrazolin-5-one (3f): $R_f = 0.11$ (5% methanol in dichloromethane); m.p. 131–132°C; IR (Nujol, NaCl) 3329, 2923, 1686, 1456, 1102 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 7.28–7.13 (m, 5H), 6.96 (br s, 2H), 4.15 (q, $J = 7.07$, 2H), 2.99 (dd, $J = 6.77$, $J = 4.89$, 2H), 2.85 (dd, $J = 5.28$, $J = 6.57$, 2H), 1.21 (t, $J = 7.07$, 3H); ^{13}C NMR (DMSO-d_6) δ 164.07, 162.73, 161.27, 148.79, 141.63, 129.19, 129.02, 126.90, 95.28, 59.86, 35.11, 28.82, 15.20; MS (ESI) (m/z) 261 $[M+H]^+$, (base peak), 215, 161, 133; 283 $[M+Na]^+$.

Malonanilic acid ethyl ester (7a) and malonanilic acid hydrazide (7b): To a stirred solution of ethyl 3-amino-2-phenylaminocarbonyl-2-butyrate (**8**, 1.7 g, 6.9 mmol) in ethanol was added dropwise hydrazine (80%, 0.4 g, 10.0 mmol) at room temperature. The reaction mixture was heated at reflux for 3 h. After cooling, the solvent was evaporated, and the mixture was separated by column chromatography on silica gel using 5% methanol in dichloromethane to afford malonanilic acid ethyl ester (**7a**, 0.31 g, 22%) and malonanilic acid hydrazide (**7b**, 0.83 g, 63%), respectively. Compound **7a:** $R_f = 0.55$ (3% methanol in dichloromethane); m.p. 38°C (lit.[13] m.p. 38–39°C); IR (Nujol, NaCl) 3286, 2951, 1640, 1461, 1376 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.38 (s, 1H), 7.51–7.03 (m, 5H), 4.10 (q, $J = 7.12$, 2H), 3.42 (s, 2H), 1.17 (t, $J = 7.12$, 3H); ^{13}C NMR ($CDCl_6$) δ 164.47, 159.97, 133.37, 124.50, 120.20, 115.97, 57.28, 38.41, 9.63. Compound **7b:** m.p. 184°C (lit.[14] m.p. 183°C); $R_f = 0.32$ (5% methanol in dichloromethane); IR (Nujol, NaCl) 3290, 2923, 1640, 1462, 1376, 1004 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 10.07 (br s, 1H), 9.18 (br s, 1H), 7.57–7.00 (m, 5H), 4.38 (s, 2H), 3.17 (s, 2H); ^{13}C NMR ($CDCl_6$) δ 166.83, 166.30, 139.80, 129.60, 124.20, 119.91, 43.82.

Ethoxycarbonylacetohydrazide (8): To a stirred solution of ethyl 3-amino-2-ethoxycarbonyl-2-butyrate (**5**, 2.0 g, 10.0 mmol) in ethanol, hydrazine (80%, 0.6 g, 15.0 mmol) was added dropwise at room temperature. The reaction mixture was heated at reflux for 3 h. After cooling, the solvent was evaporated, and the mixture was separated by column chromatography on silica gel using 2% methanol in dichloromethane to give a pale yellow solid (0.45 g, 31%). $R_f = 0.33$ (5% methanol in dichloromethane); m.p. 70°C (lit.[15] m.p. 68–69°C); IR (Nujol, NaCl) 3299, 3044, 1731, 1462, 1004 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.20 (br s, 1H), 4.18 (q, $J = 7.11$, 2H), 3.69 (br s, 2H), 3.31 (br s, 2H), 1.27 (t, $J = 7.11$, 3H); ^{13}C NMR ($CDCl_3$) δ 169.90, 166.35, 62.16, 40.62, 14.41, also isolated was diethyl malonate (**1**, 0.22 g, 14%).

ACKNOWLEDGMENT

This publication was supported by Grant/Cooperative Agreement Number UR3/CCU418652 from The Centers for Disease Control and Prevention (CDC).

REFERENCES

1. Sugiura, S.; Ohno, S.; Ohtani, O.; Izumi, K.; Kitamikado, H.; Asai, H.; Kato, K.; Hori, M.; Fujimura, H. J. Med. Chem. **1977**, *20*, 80.
2. (a) Kendall, J. D.; Duffin, G.F. U.S.P. **1955**, *2*, 704,762; (b) Reynolds, G.A. U.S.P. **1954**, *2*, 688, 548.
3. Cativiela, C.; Serrano, J.L.; Zurbano, M.M. J. Org. Chem. **1995**, *60*, 3074.
4. Missio, L.J.; Braibante, H.S.; Braibante, M.E.F. J. Heterocyclic Chem. **1996**, *33*, 1243.
5. Al-Jallo, H.N.; Al-Khashab, A.; Sallomi, I.G. J. Chem. Soc. Perkin Trans. 1 **1972**, 1022.
6. Jursic, B.; Bregant, N. Synth. Commun. **1989**, *19*, 2087.
7. Little, R.D.; Russu, W.A. J. Org. Chem. **2000**, *65*, 8096.
8. Braibante, M.E.F.; Braibante, H.S.; Missio, L.; Andricopulo, A. Synthesis **1994**, *9*, 898.
9. Scavo, F.; Helquist, P. Tetrahedron Lett. **1985**, *26*, 2603.
10. Perrin, D.D.; Armarego, L.F.; Perrin, D.R. *Purification of Laboratory Chemicals*, 2nd Ed.; Peragmon Press: New York, 1980.
11. (a) Rathke, M.W.; Cowan, P.J. J. Org. Chem. **1985**, *50*, 2622; (b) Bohman, O.; Allenmark, S. Acta Chem. Scand. **1968**, *22*, 2716; (c) Skarzewski, J. Tetrahedron **1989**, *45*, 4593; (d) Sakai, T.; Amano, E., Kawabata, A.; Takeda, A. J. Org. Chem. **1980**, *45*, 43; (e) Schweizer, E.E.; Lee, K.J. J. Org. Chem. **1982**, *47*, 2768.
12. Amanulla, S.; Jain, S.R. Indian J. Chem. **1997**, *36B*, 687.
13. Ukrainets, I.V.; Bezugly, P.A.; Treskach, V.I.; Taran, S.G.; Gorokhova, O.V. Tetrahedron **1994**, *50*, 10331.
14. Ziegler, E.; Brus, G. Monatsh. Chem. **1967**, *98*(3), 1100; Chem. Abstr. *67*, 73567h.
15. Gallagher, M.J.; Jenkins, I.D. J. Chem. Soc., Perkin Trans. 1 **1971**, 208.

Received in the USA December 7, 2002

MARCEL DEKKER, INC. • 270 MADISON AVENUE • NEW YORK, NY 10016