Mn(III)-Promoted Homolytic Methylmalonylation of Pyrrole and Indole Derivatives. A Simple Route to α-Methyl-2-Pyrrole- and α-Methyl-3-Indoleacetic Acids

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The Mn(III)- and Ce(IV)-induced homolytic malonylation of homocyclic aromatic compounds have been extensively studied.[1] Very likely these reactions occur as described in Scheme I (R = H, alkyl, R′ = alkyl). As expected, they are more efficient with electron-rich substrates (toluene, anisole, methoxynaphthalene) than with benzene. So far, however, the logical extension of these reactions to the electron-rich pentatomic heteroaromatics has been possible only for furan and thiophene derivatives.[1a,b,2] With the still more electron-rich pyrrole the procedure has been unsuccessful, due to the fact that the oxidative conditions of these reactions are not compatible with this substrate.

Recently, the homolytic alkylation of pyrrole with electrophilic carbon radicals has been accomplished under milder conditions such as H_2O_2/Fe^{+2}/alkyl iodide in DMSO[3a] and BEt_3/O_2/alkyl halides in DMSO.[3b] These are very efficient procedures which, however, to generate the malonyl radical require the use of the halomalonates. We have felt, therefore, it worthwhile to explore the possibility that the oxidative conditions of Mn^{+3}- and Ce^{+4}-promoted reactions could at least be applied to pyrroles and indoles substituted by strong electron-withdrawing groups,[4] which are expected to be less easily oxidizable than unsubstituted pyrrole. We have mainly concentrated our attention on the methylmalonyl radical, since the methylmalonyl group can easily be converted into the α-methylacetic group by one-pot hydrolysis and decarboxylation. Thus, this approach could provide us with a simple method for the synthesis of a number of α-methyl-2-pyrroleacetic acids, directly starting from a dialkyl methylmalonate.

The results of this study are reported herewith.

Results and Discussion

Pyrroles 1–7, when reacted with diethyl methylmalonate (5-fold excess), $Mn(OAc)_3 \cdot 2H_2O$, and sodium acetate in AcOH at 70 °C, gave the methylmalonyl derivatives 8–14 (eq 1). The results are reported in Table I. When starting from 2-substituted pyrroles 1–5, the methylmalonyl derivatives 8–12 were obtained, as the exclusive reaction products, in good yields. The reaction proceeds well with both pyrrole and *N*-methylpyrrole derivatives.

Lower yields were instead observed in the corresponding reactions of the 3-substituted pyrroles 6 and 7. With 6, the reaction occurred exclusively at the 2-position whereas from 7, in addition to 14, also the isomeric product substituted at the 5-position (15) was obtained. The relative ratio of the two isomers is 3.4.

The preference for attack at the position adjacent to the electron-withdrawing group can be justified, since it leads to the most stable intermediate σ-radical (structure 16, W = $COCH_3$ or CO_2CH_3).

It is not clear, however, why this preference is much larger in the reaction of 6 than in that of 7.

Scheme I

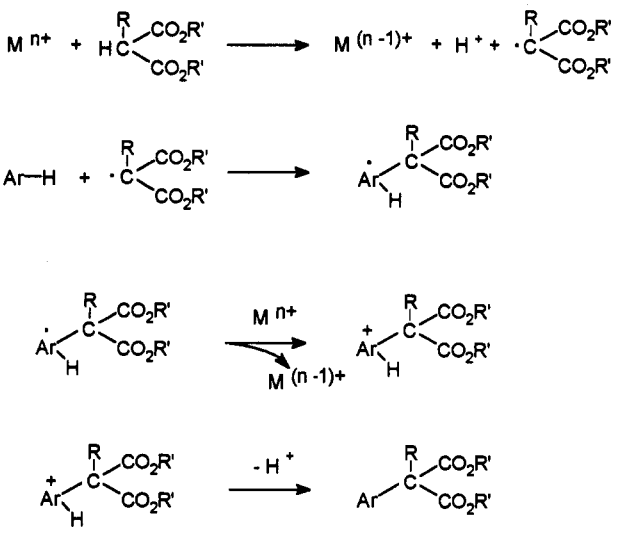
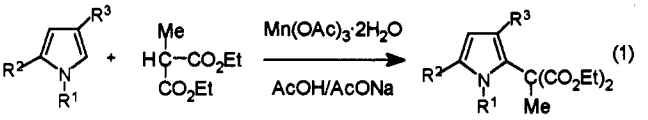


Table I. Mn^{+3}-Promoted Methylmalonylation of Substrates 1–7

substrate	product	yield (%)[a]
1	8	80
2	9	60
3	10	64
4	11	70
5	12	83
6	13	19
7	14	24[b]

[a] Isolated yield, determined with respect to the substrate used. [b] Together with 2-substitution (product 14), partial 5-substitution (12% of isolated yield) was also observed (product 15). The isomeric ratio was 3.4 (see Experimental Section).



(1)

1: R¹=H, R²=CHO, R³=H
2: R¹=Me, R²=CO_2Me, R³=H
3: R¹=Me, R²=COMe, R³=H
4: R¹=Me, R²=*p*-MePhCO, R³=H
5: R¹=H, R²=PhCO, R³=H
6: R¹=Me, R²=H, R³=COMe
7: R¹=H, R²=H, R³=CO_2Me

8: R¹=H, R²=CHO, R³=H
9: R¹=Me, R²=CO_2Me, R³=H
10: R¹=Me, R²=COMe, R³=H
11: R¹=Me, R²=*p*-MePhCO, R³=H
12: R¹=H, R²=PhCO, R³=H
13: R¹=Me, R²=H, R³=COMe
14: R¹=H, R²=H, R³=CO_2Me

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(3) (a) Baciocchi, E.; Muraglia, E.; Sleiter, G. *J. Org. Chem.* **1992**, *57*, 6817; Ital. Patent 001405A/92. (b) Baciocchi, E.; Muraglia, E. *Tetrahedron Lett.* **1993**, *34*, 5015.

(4) While this work was under way it has been reported that 2-benzoylpyrrole reacts with diethyl malonate/Mn^{+3}/AcOH to give diethyl α-acetoxy-2-benzoyl-2-pyrrolemalonate (Artis, D. R.; Cho, I.-S.; Muchowski, J. M. *Can. J. Chem.* **1992**, *70*, 1838). Muchowski and Cho have also reported that the reaction of 2-acylpyrroles with triethyl methanetricarboxylate and Mn^{+3} leads to the corresponding triethyl (5-acylpyrrol-2-yl)methanetricarboxylates. Under the same conditions, pyrrole itself was rapidly destroyed. (Cho, I.-S.; Muchowski, J. M. *Synthesis* **1991**, 567; Muchowski, J. M.; Cho, I.-S. U.S. Patent, 5,082,950 (1992) [*Chem. Abstr.* **1992**, *116*, 255473n]).

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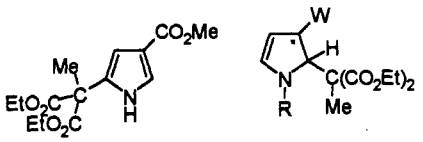
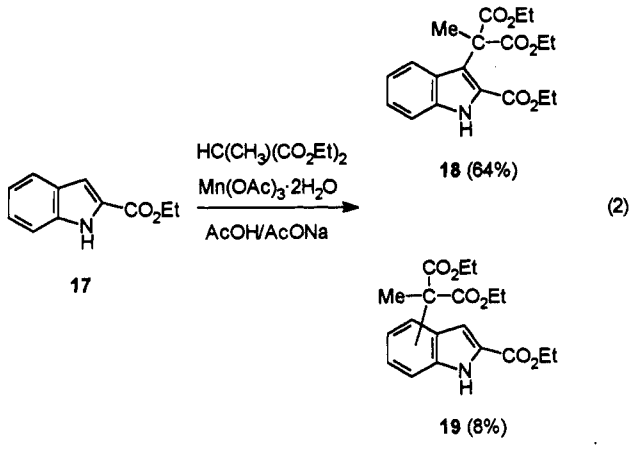


15 16

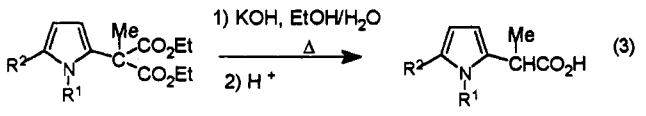
Ethyl 2-indolecarboxylate (17) was also reacted under the above conditions (eq 2). The major product was the



17 18 (64%) 19 (8%) (2)

expected 3-methylmalonyl derivative 18, which forms in 64% yield. However, another product was also isolated from the reaction mixture, which showed a ^{1}H NMR pattern similar to 18 and a mass spectrum corresponding to a diethyl α-methyl-2-(ethoxycarbonyl)-2-indolemalonate. On the basis of this spectroscopic evidence, it is suggested to be a product of substitution on the benzenoid ring of 17 (19). The ratio of 18/19 was 6.4:1 (see Experimental Section).

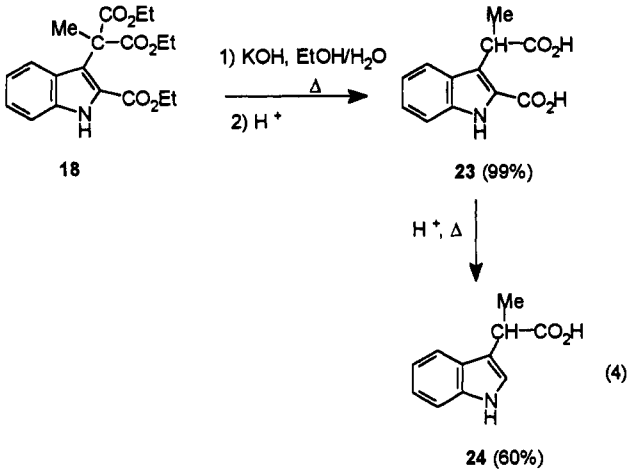
In order to demonstrate the effectiveness of the methylmalonylation as a synthetic tool for the preparation of α-methylpyrroleacetic acids, products 8, 10, and 11 were refluxed with KOH in EtOH/H_2O to give, after acidification, the corresponding α-methylpyrroleacetic acids 20, 21, and 22 (eq 3), with yields above 80%.



(3)

		Yield (%)
8	20: R^1=H, R^2=CHO	83
10	21: R^1=Me, R^2=COMe	81
11	22: R^1=Me, R^2=p-MePhCO	95

When 18 was reacted under the above conditions, a solid was obtained (23) which, after 30 min of refluxing in HCl 1:1, gave α-methyl-3-indoleacetic acid (24),[5] a plant growth regulator[6] and a key intermediate for the synthesis of the antitumor alkaloid ellipticine.[7] The synthesis of this compound is generally achieved under much more drastic



18 23 (99%) 24 (60%) (4)

conditions (reaction of indole, lactic acid and KOH at 250 °C in autoclave for ca. 20 h).[5]

Experimental Section

^{1}H NMR spectra were recorded on a Bruker instrument at 80 MHz in $CDCl_3$ solution, unless otherwise indicated. ^{13}C NMR spectra were recorded on a Varian XL 300 in $CDCl_3$ solution. Mass spectra were obtained on a Hewlett-Packard 5970 mass-selective detector, operating at 70 eV, coupled with a 5890 GC. GC analyses were performed with a Hewlett-Packard GC 5859 (capillary column, 30 m × 0.25 mm i.d. FSOT SE-54 0.25 m). Melting points are uncorrected. 2-Formylpyrrole (1), 2-acetyl-1-methylpyrrole (3), 3-acetyl-1-methylpyrrole (6), and ethyl 2-indolecarboxylate (17) were commercially available (Aldrich). Methyl 3-pyrrolecarboxylate (7) was obtained by reacting methyl acrylate and tosylmethyl isocyanide (TosMIC) with NaH.[8] 2-Benzoylpyrrole (5) was prepared by Vilsmeier aroylation of pyrrole, according to the literature.[9] 2-Toluoylpyrrole[9] and 1-methylpyrrole-2-carboxylate (Aldrich) were methylated with CH_3I/KOH/DMSO[10] to give, respectively, 2-toluoyl-1-methylpyrrole (4) and methyl 1-methylpyrrole-2-carboxylate (2). All reagents and solvents were used as purchased, without any further purification.

Mn(OAc)$_3$-Promoted Methylmalonylation. General Procedure. $Mn(OAc)_3 \cdot 2H_2O$ (12 mmol) was added, under argon, to a stirred mixture of the substrate (5 mmol), AcONa (25 mmol), and diethyl methylmalonate (25 mmol) in 25 mL of glacial acetic acid. The mixture was stirred at 70 °C until $Mn(OAc)_3 \cdot 2H_2O$ had been consumed (4–6 h), diluted with brine, and extracted with diethyl ether. The organic layer was washed with a saturated solution of $NaHCO_3$ and then with brine, dried over Na_2SO_4, and evaporated. The residue was purified by column chromatography (SiO_2/diethyl ether–petroleum ether (bp 40–70 °C)) to give the methylmalonyl derivatives. With the substrates 1–6 only one product was obtained (see Table I). With 7, two products were obtained, 14 and 15, in a 3.4:1 ratio (determined by GC). Likewise, in the methylmalonylation of 17, together with 18 another product was isolated from the reaction mixture. It showed ^{1}H NMR similar to 18 and a mass spectrum compatible with a diethyl α-methyl-2-(ethoxycarbonyl)indolemalonate. On this spectroscopic evidence it was supposed to be a product of substitution on the benzenoid ring of 17 (19). The isomer ratio 18/19 was 6.4 (determined by GC).

The reaction products were characterized as follows.

Diethyl α-methyl-5-formyl-2-pyrrolemalonate (8): oil; MS (rel inten) 267 (M^+, 35), 194 ($M^+ - CO_2Et$, 100), 148 (77), 120 (50), 92 (33), 65 (33); ^{1}H NMR δ (ppm) 1.20 (t, J = 7.1 Hz, 6 H), 1.80 (s, 3 H), 4.18 (q, J = 7.1 Hz, 4 H), 6.1–6.2 (m, 1 H), 6.79–6.86 (m, 1 H), 9.43 (s, 1 H), 10.1 (bs, 1 H); ^{13}C NMR δ (ppm) 13.75, 21.08, 53.82, 62.26, 109.79, 120.26, 132.79, 136.17, 169.35, 178.92. 8 was characterized as the corresponding α-methylacetic acid 20.

(5) Johnson, H. E.; Crosby, D. G. *J. Org. Chem.* **1963**, *28*, 1246.
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(9) White, J.; McGillivray, G. *J. Org. Chem.* **1977**, *42*, 4248.
(10) Johnstone, R. A. W.; Rose, M. E. *Tetrahedron* **1979**, *35*, 2169.

Diethyl α-methyl-5-(methoxycarbonyl)-1-methyl-2-pyrrolemalonate (9): oil; MS (rel inten) 311 (M^+, 27), 238 ($M^+ - CO_2Et$, 100), 164 (32), 150 (6). ^1H NMR δ (ppm) 1.22 (t, J = 7.1 Hz, 6 H), 1.85 (s, 3 H), 3.74 (s, 3 H), 3.78 (s, 3 H), 4.19 (q, J = 7.1 Hz, 4 H), 6.05 (d, J = 4.2 Hz, 1 H), 6.86 (d, J = 4.2 Hz, 1 H); ^{13}C NMR δ (ppm) 13.75, 22.58, 34.51, 50.82, 54.48, 60.01, 108.08, 116.51, 123.96, 136.52, 161.46, 169.93.

Diethyl α-methyl-5-acetyl-1-methyl-2-pyrrolemalonate (10): oil; MS (rel inten) 295 (M^+, 41), 222 ($M^+ - CO_2Et$, 100), 176 (11), 148 (31), 106 (53); ^1H NMR δ (ppm) 1.22 (t, J = 7.0 Hz, 6 H), 1.85 (s, 3 H), 2.38 (s, 3 H), 3.78 (s, 3 H), 4.20 (q, J = 7.0 Hz, 4 H), 6.07 (d, J = 4.3 Hz, 1 H), 6.88 (d, J = 4.3 Hz, 1 H); ^{13}C NMR δ (ppm) 13.77, 22.55, 27.35, 35.29, 54.46, 62.12, 108.14, 118.60, 132.16, 137.91, 169.78, 188.54. **10** was characterized as the corresponding α-methylacetic acid **21**.

Diethyl α-methyl-5-(4-methylbenzoyl)-1-methyl-2-pyrrolemalonate (11): oil; MS (rel inten) 371 (M^+, 30), 298 ($M^+ - CO_2Et$, 100), 119 (CH_3PhCO^+, 62), 106 (10); ^1H NMR δ (ppm) 1.27 (t, J = 7.1 Hz, 6 H), 1.91 (s, 3 H), 2.38 (s, 3 H), 3.88 (s, 3 H), 4.25 (q, J = 7.1 Hz, 4 H), 6.11 (d, J = 4.3 Hz, 1 H), 6.63 (d, J = 4.3 Hz, 1 H), 7.1–7.8 (AB system, 4 H); ^{13}C NMR δ (ppm) 13.88, 21.43, 22.67, 35.06, 54.70, 62.25 (OCH_2CH_3), 108.27, 121.40, 128.58, 129.40, 132.40, 137.23, 138.30, 141.88, 169.95, 186.11. **11** was characterized as the corresponding -methylacetic acid **22**.

Diethyl α-methyl-5-benzoyl-2-pyrrolemalonate (12): mp (°C) 90.5–91.5 (hexane); MS (rel inten) 343 (M^+, 26), 270 ($M^+ - CO_2Et$, 100), 224 (23), 105 ($PhCO^+$, 62); ^1H NMR δ (ppm) 1.24 (t, J = 7.1 Hz, 6 H), 1.84 (s, 3 H), 4.22 (q, J = 7.1 Hz, 4 H), 6.16–6.24 (m, 1 H), 6.70–6.79 (m, 1 H), 7.4–7.9 (m, 5 H), 10.2 (bs, 1 H). Anal. Found (calcd): C, 65.95 (66.44); H, 6.64 (6.17); N, 4.07 (4.08).

Diethyl α-methyl-3-acetyl-1-methyl-2-pyrrolemalonate (13): mp (°C) 85.5-87.5 (Et_2O–pentane); MS (rel inten) 295 (M^+, 57), 250 (18), 222 ($M^+ - CO_2Et$, 20), 206 (38), 180 (31), 176 (100), 148 (86), 106 (68); ^1H NMR δ (ppm) 1.22 (t, J = 7.1 Hz, 6 H), 1.78 (s, 3 H), 2.34 (s, 3 H), 3.46 (s, 3 H), 4.03–4.40 (m, 4 H), 6.4–6.5 (AB system, ν_1 = 6.44, ν_2 = 6.48, J = 3.1 Hz, 2 H). Anal. Found (calcd): C, 61.35 (60.99); H, 6.83 (7.17); N, 4.99 (4.74).

Diethyl α-methyl-3-(methoxycarbonyl)-2-pyrrolemalonate (14): oil; MS (rel inten) 297 (M^+, 39), 224 ($M^+ - CO_2Et$, 22), 192 (100), 164 (42), 150 (23), 136 (40); ^1H NMR δ (ppm) 1.18 (t, J = 7.1 Hz, 6 H), 1.80 (s, 3 H), 3.67 (s, 3 H), 4.18 (q, J = 7.1 Hz, 4 H), 6.54 (s, 1 H), 6.58 (s, 1 H), 10.2 (bs, 1 H); ^{13}C NMR δ (ppm) 13.67, 23.82, 50.58, 54.47, 61.91, 111.24, 111.45, 117.20, 134.14, 164.67, 170.65.

Diethyl α-methyl-4-(methoxycarbonyl)-2-pyrrolemalonate (15): mp (°C) 77.0–80.0 (hexane); MS (rel inten) 297 (M^+, 22), 224 ($M^+ - CO_2Et$, 100), 192 (4), 178 (50), 164 (5), 150 (17); ^1H NMR δ (ppm) 1.25 (t, J = 7.1 Hz, 6 H), 1.80 (s, 3 H), 3.67 (s, 3 H), 4.19 (q, J = 7.1 Hz, 4 H), 6.50–6.55 (m, 1 H), 7.35–7.41 (m, 1 H), 9.4 (bs, 1 H); ^{13}C NMR (ppm) 13.90, 20.50, 51.01, 53.53, 62.19, 108.35, 115.68, 123.94, 128.83, 165.17, 170.25. Anal. Found (calcd): C, 56.84 (56.54); H, 6.42 (6.44); N, 4.88 (4.71).

Diethyl α-methyl-2-(ethoxycarbonyl)-3-indolemalonate (18): mp (°C) 114.0–114.5 (diethyl ether); MS (rel inten) 361 (M^+, 24), 288 ($M^+ - CO_2Et$, 14), 242 ($M^+ - (CO_2Et + EtOH)$, 100), 214 (98), 186 (95), 168 (44), 115 (49); ^1H NMR δ (ppm) 1.1–1.4 (m, 9 H), 1.95 (s, 3 H), 4.0–4.5 (m, 6 H), 6.9–7.5 (m, 4 H), 9.2 (bs, 1 H). Anal. Found (calcd): C, 63.43 (63.15); H, 6.69 (6.42); N, 4.02 (3.88).

Diethyl α-methyl-2-(ethoxycarbonyl)indolemalonate (19): oil; MS (rel inten) 361 (M^+, 33), 288 ($M^+ - CO_2Et$, 72), 242 ($M^+ - (CO_2Et + EtOH)$, 17), 214 (100), 186 (65), 168 (31), 115 (47); ^1H NMR (ppm) 1.1–1.5 (m, 9 H), 1.99 (s, 3 H), 4.1–4.5 (m, 6 H), 6.9–7.4 (m, 4 H), 9.4 (bs, 1 H).

α-Methylacetic Acid Derivatives 20–22 and 24. The methylmalonate derivative (1 mmol) is added to a mixture of KOH (5 mmol) in 2.5 mL of EtOH and 0.5 mL of H_2O and refluxed for 3 h. After cooling, the solution is acidified to pH 2 and extracted with ethyl acetate. The organic layer is dried over Na_2SO_4 and evaporated to give the propionic acid derivative (**20–22**). When the substrate is **18**, the residue obtained following the above procedure is **23**. **23** is refluxed for 30 min in HCl 1:1, and the solution is diluted with brine and extracted with ethyl acetate. The organic layer is dried over Na_2SO_4 and evaporated to give **24** (mp 103–104.5 °C from benzene–petroleum ether, lit.[5] 102 °C, 105–110 °C).

The reaction products were characterized as follows.

α-Methyl-5-formyl-2-pyrroleacetic acid (20): mp (°C) 96.0–97.0 (Et_2O–pentane); ^1H NMR (ppm) (acetone-d_6) 1.53 (d, J = 7.3 Hz, 3 H), 3.96 (q, J = 7.3 Hz, 1 H), 6.2–6.3 (m, 1 H), 6.9–7.0 (m, 1 H), 9.43 (s, 1 H), 10.0 and 11.0 (bs, 2 H). Anal. Found (calcd): C, 58.02 (57.48); H, 5.51 (5.43); N, 8.15 (8.38).

α-Methyl-5-acetyl-1-methyl-2-pyrroleacetic acid (21): mp (°C) 83.5–85.0 (Et_2O–pentane); ^1H NMR (ppm) (acetone-d_6) 1.50 (d, J = 7.2 Hz, 3 H), 2.34 (s, 3 H), 3.90 (s, 3 H), 3.96 (q, J = 7.2 Hz, 1 H), 6.09 (d, J = 4.1 Hz, 1 H), 6.99 (d, J = 4.1 Hz, 1 H), 9.6 (bs, 1 H). Anal. Found (calcd): C, 62.01 (61.51); H, 6.59 (6.72); N, 7.34 (7.18).

α-Methyl-5-(4-methylbenzoyl)-1-methyl-2-pyrroleacetic acid (22): mp (°C) 165.0–166.5 (Et_2O–pentane); ^1H NMR δ (ppm) (acetone-d_6) 1.54 (d, J = 7.2 Hz, 3 H), 2.39 (s, 3 H), 3.98 (s, 3 H), 4.00 (q, J = 7.2 Hz, 1 H), 6.14 (d, J = 4.1 Hz, 1 H), 6.62 (d, J = 4.1 Hz, 1 H), 7.2–7.7 (AB system, 4 H), 9.2 (bs, 1 H). Anal. Found (calcd): C, 71.44 (70.83); H, 6.56 (6.32); N, 5.09 (5.16).

α-Methyl-2-carboxy-3-indoleacetic acid (23): mp (°C) 205.0–210.0 (acetone); ^1H NMR δ (ppm) (DMSO-d_6) 1.65 (d, J = 7.1 Hz, 3 H), 6.05 (q, J = 7.1 Hz, 1 H), 7.0-7.8 (m, 4 H), 12.8 (bs, 2 H). The compound **23** was identified by comparison with an authentic sample syntesized by a different procedure.[11]

Acknowledgment. This work was carried out into the framework of the Progetto Finalizzato CNR Chimica Fine II.

Supplementary Material Available: Copies of ^1H NMR spectra of **9**, **14**, and **19**; ^1H NMR data, complete with peak assignments, of **8–15**, **18–23**; ^{13}C NMR data, complete with peak assignments, for **8-11**, **14**, **15** (6 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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