Highly Efficient Synthesis of Alkyl Pyrrolylacetates and Dialkyl Pyrrolylmalonates[1]

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N-Pyrrolylmagnesium halides (**1**, **2**) react with alkyl bromoacetates (**3a–d**) in THF solution to give alkyl 2-pyrrolylacetates (**5a–d**) in good yields and with very high positional selectivity (C-2:C-3 ≥ 25). The high regioselectivity is rationalized in terms of an increased propinquity between C-2 and the bromoacetate methylene group as a consequence of coordination between magnesium and the carbonyl oxygen of the alkylating agent. (2,5-Dimethylpyrrol-*N*-yl)magnesium chloride (**9**) and isopropyl bromoacetate (**3c**) gave the 3-pyrrolylacetate **10** exclusively. Alkoxycarbonylation of the dianions of the above alkyl pyrrolylacetates with alkyl chloroformates gave the corresponding dialkyl pyrrolylmalonates, two of which (**16a** and **19**) were transformed into the dialkyl 1,2-dihydro-3*H*-pyrrolo[1,2-*a*]pyrrole-1,1-dicarboxylates (**22** and **20**, respectively) with 1,2-dichloroethane under phase transfer conditions. Compound **20** was converted into the powerful nonaddicting analgesic ketorolac (**21**).

Introduction

Pyrrole acetic acid esters, especially the 2-pyrrolyl congeners, are valuable intermediates for the synthesis of certain antiinflammatory and analgesic agents of clinical utility.[2–4] Pyrrole acetic acid esters have been prepared by Hantzsch[4–6] or Knorr[7] type syntheses, by the copper-catalyzed reaction of diazoacetic esters with pyrroles,[8,9] from the readily available (see ref 9, pp 360–361) acetonitriles,[10] by the reduction of α-hydroxyacetic acids[11] or esters[6] and related compounds,[13,14] by reduction of α-oxoacetic acid esters and derivatives thereof,[6,15] from pyrrolidine-2-thiones,[16] via condensation of pyrrole-2-carboxaldehydes with methyl methylsulfinylmethyl sulfide,[17] and by the oxidative rearrangement of acetylpyrroles with thallium(III) nitrate.[18] Each of these syntheses has positive features, but few of them have appreciable generality. Recently, Baciocchi et al.[19] have efficiently generated alkyl 2-pyrrolylacetates by the oxidative addition of (alkoxycarbonyl)methyl radicals (from the iodoacetates) to pyrrole and derivatives thereof under Fenton-type conditions. The synthetic utility of this process is, however, considerable diminished by the high pyrrole: iodoacetate ratios (15–20:1) which were used. Dialkyl 2-pyrrolylmalonates (see below) were synthesized in the same manner from pyrroles and dialkyl iodomalonates.

Dialkyl pyrrolylmalonates have considerable synthetic potential. Indeed, we have demonstrated that diethyl (5-benzoylpyrrol-2-yl)malonate is efficiently converted into the powerful analgesic ketorolac in two steps.[20] This malonate ester was generated by the oxidative addition of various dialkoxymalonyl radicals to 5-benzoylpyrrole.[20] 2-Pyrrolylmalonates have also been obtained by the reaction of bis(methoxycarbonyl)carbene with pyrrole[21] and by the base-catalyzed reaction of di-*tert*-butyl dicarbonate with a [bis(alkoxycarbonyl)pyrrol-2-yl]acetic acid ester.[22] This latter process is likely to be limited to pyrrole acetic acid esters bearing one or more electron-attracting substituents in the pyrrole nucleus.

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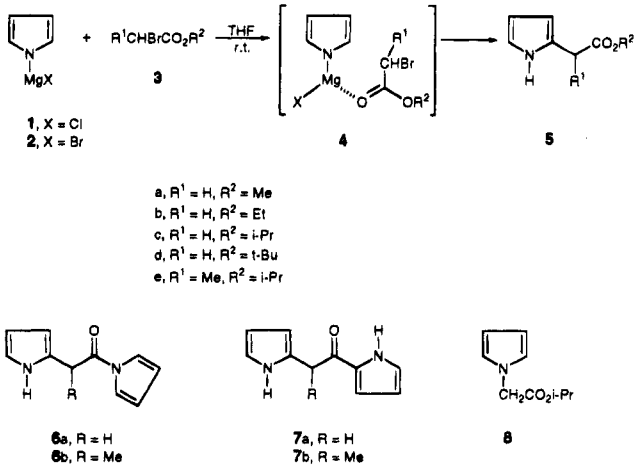
Table 1. Synthesis of Alkyl Pyrrolylacetates

grignard reagent (mole)[a,b]	bromo-acetate	product	purification method[c]	% yield	bp °C/mm
1 (2.44)[d]	**3a**	**5a**	CC[e]	48	ND[f]
1 (3.72)	**3b**	**5b**	D	55	65–7/1[g]
1 (3.77)	**3c**	**5c**	D	64	90/1
2 (3.76)[h]	**3c**	**5c**	D	76	90/1
1 (3.80)[i]	**3c**	**8**	D	21	75/1
1 (4.18)	**3d**	**5d**	D	77	89/1
9 (3.76)	**3c**	**10**	D	46	115/1
2 (4.03)[j]	**3e**	**5e**	D	17	115/1

[a] Prepared from MeMgCl unless specified otherwise. [b] 1.06 mol of the pyrrole/mole of Grignard was used unless indicated otherwise. [c] CC = column chromatography on silica gel; D = distillation *in vacuo*. [d] Prepared from *n*-BuMgCl and 1.02 mol of pyrrole/mole of Grignard reagent. [e] Eluting solvent = ether–hexane (1:1). [f] ND = not distilled. Literature[29] bp 59–60 °C/1.2 mm. [g] Literature[30] bp 129 °C/15 mm. [h] Grignard prepared from EtMgBr. [i] Reaction effected in the presence of 2 mol of HMPA/mole of Grignard reagent. [j] Grignard prepared from MeMgBr.

Scheme 1

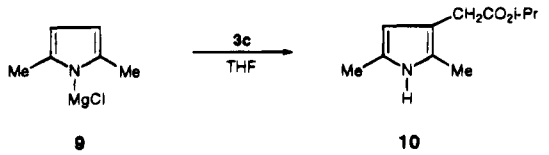


This publication shows that N-unsubstituted pyrrole acetic acid esters can be efficiently synthesized from pyrrole Grignard reagents and alkyl bromoacetates and that the dianions derived therefrom are easily converted into pyrrolylmalonates.

Results and Discussion

A. Synthesis of Alkyl Pyrrolylacetates. The reaction of pyrrolyl Grignard reagents with alkylating agents is well known[23] to produce a mixture, consisting mainly of 2- and 3-alkylpyrroles, in which the 2-isomer usually predominates by a factor of 2–3. Bromoacetic acid esters apparently have not been examined in this reaction,[24] and it was of interest to determine if these bromo compounds would give a product distribution analogous to that of other alkyl halides. The addition of various alkyl bromoacetates (**3a–d**, Scheme 1) to a 2.5–4 molar excess of a suspension of pyrrolylmagnesium chloride (**1a**) in THF at ice bath temperature resulted in a mildly exothermic reaction from which the alkyl 2-pyrrolylacetates (**5a–d**) were isolated, usually by distillation, as the major products in preparatively significant yields (Table 1). An excess of the Grignard reagent was utilized to minimize

Scheme 2



polyalkylation. Reduction of the Grignard:bromoacetate ratio below 2.5 resulted in a significant diminution in 2-pyrrolylacetate yields and an increase in the complexity of the reaction mixture. Whereas there was little difference in product yield and purity between pyrrolylmagnesium chloride (**1**) and bromide (**2**), the size of the ester alkyl group had a significant impact on both. In general, the more sterically demanding isopropyl **3c** and *tert*-butyl **3d** esters gave alkyl 2-pyrrolylacetates in optimal yields and of the highest purity. Several minor byproducts, two of which (**6**, **7**) were characterized, were formed in these reactions, but they were eliminated by distillation (pot residues).

The most striking feature of these coupling reactions is the regiochemical purity of the distilled product. In all the cases examined, the alkyl 2-pyrrolylacetates constituted much greater than 95% of the distillate as determined by ^{1}H NMR spectroscopy.[25] This favorable α:β coupling ratio was maintained with isopropyl 2-bromopropionate (**3e**), although the reaction mixture was considerably more complex (see Experimental Section) and the yield of the desired product **5e** was lower (Table I) than for the bromoacetates. We attribute this high regioselectivity to coordination of the magnesium atom of the Grignard reagent with the carbonyl oxygen of the bromo ester, the result being that the bromo ester is positioned favorably (**4**, Scheme I) for reaction at the α-carbon of the pyrrole nucleus. Consistent with this proposal is that when the coupling reaction is effected with **2c** in the presence of the strongly coordinating solvent HMPA (2 mol/mol of Grignard), only N-alkylation is observed (i.e., **8**).[26,27]

As expected, when both α-positions of the pyrrole nucleus are occupied, as in Grignard reagent **9** (Scheme 2) derived from 2,5-dimethylpyrrole, the β-substituted product **10** is obtained exclusively.

This is the shortest and most efficient of all the alkyl pyrrolylacetate syntheses reported to date.

B. Synthesis of Dialkyl Pyrrolylmalonates. In the very early phase of the development of the potent analgesic ketorolac, attempts were made to prepare alkyl 1,2-dihydro-3*H*-pyrrolo[1,2-*a*]pyrrole-1-carboxylates (e.g., **12**, Scheme 3) by the base-induced reaction of the (5-thien-2-yl-2-pyrrolyl)acetate **11** with bidentate alkylating agents such as 1,2-dibromoethane (ref 4, pp 111–112). Although small amounts of the desired compound were formed, the majority of the complex mixture consisted of products derived from initial carbon alkylation (one of which was the cyclopropane **13**), even for reactions which proceeded via the dianion **14**. It was therefore assumed that, if preferential attack of electrophilic reagents at the carbon site of such anions, e.g., **15**

(23) Anderson, H. J.; Loader, C. E. In *Pyrroles*; by Jones, R. A., Ed.; John Wiley & Sons: New York, 1990; Part 1, pp 427–429.

(24) The report that a pyrrole Grignard reagent reacted with an ethyl haloacetate to produce ethyl 2-pyrrolylacetate in unspecified yield (ref 23, p 429, Table 3.4.9.) would seem to be an abstraction error. The coupling process described herein was first conceived and executed by G.C.S. in the Boulder Laboratories.

(25) The presence of the alkyl 2-pyrrolylacetates is easily ascertained by two characteristic single proton multiplets for H-3 and H-4 at δ 6.0 and 6.1 respectively, which show a $J_{3,4}$ of 3–4 Hz (see ref 9, pp 472–6) as well as an 0.8 Hz long-range coupling between H-3 and the acetate methylene group (see Experimental Section).

(26) This change from predominant C-alkylation to predominant N-alkylation in the presence of HMPA has been observed previously.[23]

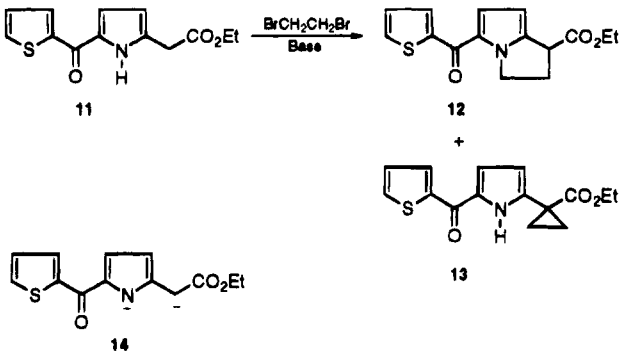
(27) These observations would also seem to favor an S_N2 like process for the coupling reactions rather than one initiated by electron transfer from the pyrrolyl Grignard to bromoacetate.

Table 2. Synthesis of Dialkyl Pyrrolylmalonates

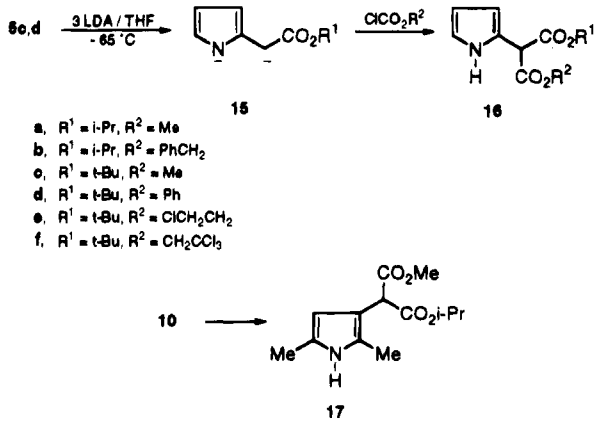
starting material	reaction temp, °C	reaction time, h	product	purification method[a]	% yield
5c	−70	1	**16a**	D	96
5c	−65	1	**16b**	CC[b]	25
5d	−65	0.33	**16c**	CC[b]	95
5d	−70 to −60	1	**16d**	CC[c]	28
5d	−60	0.33	**16e**	CC[b]	58
5d	−75	1	**16f**	CC[c]	22
10	−60[d]	0.17	**17**[e]	CC[f]	45
18	−65 to 0	~0.5	**19**	CC[g]	97

[a] D = distillation *in vacuo*; CC = column chromatography on silica gel. [b] Eluting solvent = hexane−ethyl acetate (95:5 then 9:1). [c] Eluting solvent = hexane−ethyl acetate (95:5). [d] See Experimental Section for conditions. [e] The *N*-methoxycarbonyl derivative of **17** was also formed (19%). [f] Hexane−ethyl acetate (9:1) eluted the *N*-methoxycarbonyl derivative of **17** and hexane−ethyl acetate (4:1) eluted **17**. [g] Eluting solvent = hexane−ethyl acetate (95:5 and then 85:15).

Scheme 3



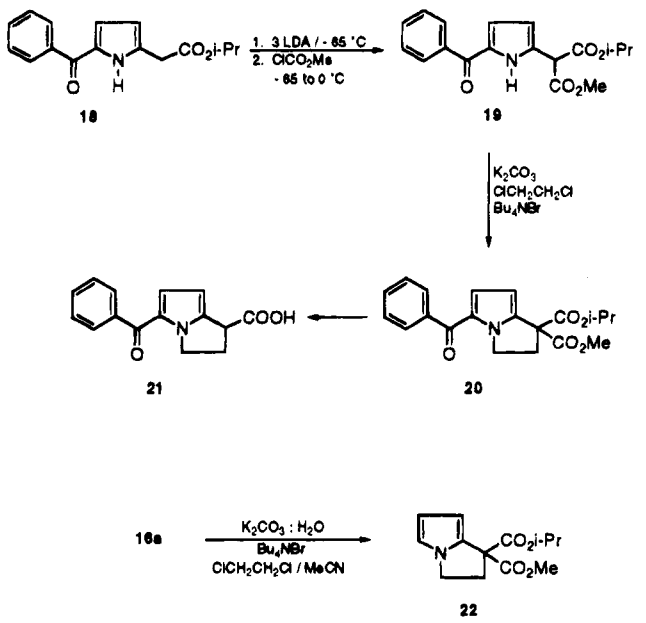
Scheme 4



(Scheme 4), was a general phenomenon, then reaction with alkyl chloroformates would provide access to dialkyl 2-pyrrolylmalonates **16**, which have recently been shown to undergo efficient potassium carbonate-induced formation of the desired bicyclic systems with 1,2-dichloroethane under phase transfer conditions.[20] Indeed, addition of 3.35 mol equiv of LDA to a THF solution of isopropyl 2-pyrrolylacetate (**5c**) at −65 °C generated the putative dianion **15a** which reacted rapidly with methyl chloroformate to produce the malonate ester **16a** in 96% yield. The malonate esters **16b**−**f** were obtained in the same manner in modest to excellent yields (unoptimized, Table 2). The 3-pyrrolylmalonate derivative **17** was also prepared in the same way from **10** and methyl chloroformate.

Of particular importance with regard to the synthesis of ketorolac **21** is that acylation of the deep red-orange dianion corresponding to **18** (Scheme 5), for synthesis see Experimental Section) with methyl chloroformate gave

Scheme 5



the 5-benzoyl-2-pyrrolylmalonate ester **19** in virtually quantitative yield (Table 2). This compound could also be prepared (72% yield) by benzoylation of **16a** under Vilsmeier−Haack[28] conditions (See Experimental Section). The cyclization of **19** to **20** with 1,2-dichloroethane occurred under the phase transfer conditions previously reported,[20] and alkaline hydrolysis of **20** gave ketorolac **21** after acidification in an uneventful manner. In contrast, the cyclization of **16a** to **22** (Scheme 5) was more difficult, but could be accomplished (58% yield) under modified phase transfer conditions using water-doped potassium carbonate as the base. This difficulty must, at least in part, be associated with the expected higher pK_as for the malonate CH and especially the pyrrole NH in **16a** versus those for the corresponding protons in **19**.

In summary, short, efficacious syntheses of alkyl pyrrolylacetates and dialkyl pyrrolylmalonates have been devised. This methodology is likely to have significant applications beyond those described herein.

Experimental Section

The physical constants of the compounds described herein were obtained as described previously.[20] The ^{1}H NMR spectra (300 MHz) were measured in $CDCl_3$; the spectra of compounds with exchangeable hydrogens are those taken after D_2O exchange. High-resolution mass spectra were obtained on samples which were at least of 95% purity as judged by ^{1}H NMR spectroscopy.

Synthesis of the Alkyl Pyrrolylacetates. All of these compounds, except methyl 2-pyrrolylacetate (**5a**), isopropyl 2-(2-pyrrolyl)propionate (**5e**), and isopropyl 1-pyrrolylacetate (**8**) were prepared by the following general procedure. The Grignard reagent, (e.g., 3 M MeMgCl in THF; 2.44−4.13 mol/mol of bromoacetate; see Table 1) was added to a stirred solution of the pyrrole (1.06 mol/mol of the Grignard reagent) in freshly distilled dry THF (1.5 mL/mmol of pyrrole; 5.5 mL/mmol of 2,5-dimethylpyrrole) cooled in an ice−sodium chloride−2-propanol bath (−15 to −20 °C bath temperature) maintained in an atmosphere of nitrogen, over a 10−50 min period. The cooling bath was removed, and the suspension was stirred at room temperature for 0.5 h (usually the Grignard reagent dissolved by this time). The reaction temperature was then lowered to −10 °C, and the bromoacetate (1 mol) was added rapidly (small exotherm). The stirred reaction mixture was left to reach room temperature, and stirring was continued for 0.5−2 h. Ether and excess saturated aqueous ammonium chloride were added. The organic phase was separated,

washed with saturated ammonium chloride solution, and dried over magnesium sulfate. The solvent was removed at reduced pressure, and the residual oil was fractionally distilled *in vacuo* using a short path distillation head. The excess pyrrole distills at *ca.* 30 °C/1 mM and is followed by the alkyl pyrrolylacetate which distills at a considerably higher temperature (See Table 1).

Isopropyl 2-pyrrolylacetate (5c): IR (film) 3387, 1725 cm^{-1}; ^1H NMR δ 1.25 (d, 6H, J = 6.26 Hz, Me_2CH), 3.63 (d, 2H, J_{3,CH_2} = 0.80 Hz, CH_2), 5.03 (sept, 1H, J = 6.26 Hz, Me_2CH), 6.00 (m, 1H, J_{3,CH_2} = 0.80 Hz, $J_{3,4}$ = 3.34 Hz, $J_{3,5}$ = 1.54 Hz, H-3), 6.13 (t, 1H, H-4), 6.74 (dd, 1H, $J_{3,5}$ = 1.54 Hz, $J_{4,5}$ = 2.79 Hz, H-5); mass spectrum *m/z* 167 (38), 125 (8), 80 (100). Anal. Calcd for $C_9H_{13}NO_2$: C, 64.65; H, 7.84; N, 8.38. Found: C, 64.38; H, 8.13; N, 8.81.

***tert*-Butyl 2-pyrrolylacetate (5d)**: IR (film) 3387, 1721 cm^{-1}; ^1H NMR δ 1.46 (s, 9H, Me_3C), 3.57 (d, 2H, $J_{3,CH}$ = 0.81 Hz, CH_2), 5.99 (m, 1H, $J_{3,CH}$ = 0.81 Hz, $J_{3,4}$ = 3.35 Hz, $J_{3,5}$ = 1.53 Hz, H-3), 6.13 (t, 1H, H-4), 6.72 (dd, 1H, $J_{3,5}$ = 1.53 Hz, $J_{4,5}$ = 2.77 Hz, H-5); mass spectrum *m/z* 181 (8), 125 (23), 80 (100). Anal. Calcd for $C_{10}H_{15}NO_2$: C, 67.22; H, 8.34; N, 7.73. Found: C, 65.96; H, 8.59; N, 8.18.

Isopropyl 2,5-dimethyl-3-pyrrolylacetate (10): IR (film) 3376, 1721 cm^{-1}; ^1H NMR δ 1.27 (d, 6H, J = 6.28 Hz, Me_2CH), 2.18 (s, 3H, C-2 or C-5 Me), 2.22 (s, 3H, C-5 or C-2 Me), 3.36 (s, 2H, CH_2), 5.03 (sept, 1H, J = 6.28 Hz, Me_2CH), 5.78 (s, 1H, H-4). Anal. Calcd for $C_{11}H_{17}NO_2$: C, 67.66; H, 8.78; N, 7.17. Found: C, 67.40; H, 8.88; N, 6.94.

Synthesis of Methyl 2-Pyrrolylacetate 5a. Pyrrole (3.0 g, 44.7 mmol) was added dropwise at 35 °C to a stirred solution of *n*-butylmagnesium chloride in THF (2.2 M, 20 mL, 44 mmol). The suspension thus obtained was stirred at 25 °C for 40 min and then methyl bromoacetate (2.75 g, 18 mmol) dissolved in anhydrous THF (30 mL) was added rapidly (5 °C exotherm). The reaction mixture was stirred for 6 h at 25 °C and then poured into cold 2% hydrochloric acid. The product was extracted into toluene and dried, and the solvent was removed *in vacuo*. The residual oil was subjected to column chromatographic separation on silica gel using hexane–ether (1:1) to elute the product (1.5 g, 48% yield) as an oil which had a ^1H NMR spectrum consistent with that of known compound **5a**.[29]

Synthesis of Isopropyl 2-(2-Pyrrolyl)propionate (5e). *N*-Pyrrolylmagnesium bromide was prepared as described in the general procedure by adding a 1.4 M solution (THF: toluene; 3:1) of MeMgBr to a solution of pyrrole. The reaction mixture was warmed to room temperature and a solution of isopropyl 2-bromopropionate (see Table 1 for molar ratios) in THF was added rapidly to the stirred Grignard solution. Stirring was continued for 3.5 h, at which time TLC showed that the bromopropionate had been consumed. The reaction was worked up in the usual manner to give an oil which by TLC analysis consisted of two major and several minor products. To eliminate N-acylated materials (e.g., **6b**), the oil was dissolved in a small amount of dry 2-propanol, added to a solution of sodium 2-propoxide (2.6 mol/mol isopropyl 2-bromopropionate) in dry 2-propanol (2 mL/mmol of 2-propoxide), and the solution was heated at 60 °C for 0.33 h. The solvent was removed *in vacuo*, ether was added to the residue, and the solution was washed successively with 10% hydrochloric acid and saturated sodium bicarbonate solution. The solution was dried over magnesium sulfate, and the solvent was removed *in vacuo*, giving an oil [2 major products (**5e** and **7b**) by TLC] which on distillation *in vacuo* gave pure **5e**: IR (film) 3387, 1717 cm^{-1}; ^1H NMR δ 1.22 (d, 3H, J = 6.25 Hz, Me_2CH), 1.25 (d, 3H, J = 6.25 Hz, Me_2CH), 1.49 (d, 3H, J = 7.18 Hz, $MeCH$), 3.74 (m, 1H, J = 7.18 Hz, $J_{3,CH}$ = 0.72 Hz, $MeCH$), 5.01 (sept, 1H, J = 6.25 Hz, Me_2CH), 6.01 (m, 1H, $J_{3,CH}$ = 0.72 Hz, $J_{3,4}$ = 3.38 Hz, $J_{3,5}$ = 1.56 Hz, H-3), 6.15 (dd, 1H, $J_{3,4}$ = 3.38 Hz, $J_{4,5}$ = 2.82 Hz, H-4), 6.70 (dd, 1H, $J_{3,5}$ = 1.56 Hz, $J_{4,5}$ = 2.82 Hz, H-5); HRMS calcd for $C_{10}H_{15}NO_2$ 181.1103, found 181.1101. Anal. Calcd for $C_{10}H_{15}N_2$: C, 66.27; H, 8.34; N, 7.73. Found: C, 65.64; H, 8.23; N, 7.54.

***N*-(2-Pyrrolylacetyl)pyrrole (6a).** The pot residue from the synthesis of **3c** contained a small amount of a crystalline solid which was recrystallized from hexane to give pure **6a**: mp 122–124 °C; IR (KBr) 3435, 3355, 1709, 1634w cm^{-1}; ^1H NMR δ 4.19 (d, 2H, $J_{3,CH_2} \approx$ 0.8 Hz, CH_2), 6.09 (m, 1H, $J_{3,CH_2} \approx$ 0.8 Hz, $J_{3,4}$ = 3.37 Hz, $J_{3,5}$ = 1.54 Hz, H-3), 6.16 (t, 1H, H-4), 6.32 (q, 2H, H-3′,4′), 6.78 (dd, 1H, $J_{3,5}$ = 1.54 Hz, $J_{4,5}$ = 2.89 Hz, H-5), 7.36 (t, 2H, H-2′,5′); HRMS calcd for $C_{10}H_{10}N_2O$ 174.0793, found 174.0796. Anal. Calcd for $C_{10}H_{10}N_2O$: C, 68.95; H, 5.97; N, 16.08. Found: C, 68.41; H, 5.81; N, 15.65.

2-(2-Pyrrol-2-ylpropionyl)pyrrole (7b). Isopropyl 2-(2-pyrrolyl)propionate (**5e**) was synthesized in the usual manner except that the reaction time was 15 h and the crude product was not subjected to alcoholysis with 2-propanol. Instead, the crude mixture was separated by column chromatography on silica gel. Elution with methyl acetate–hexane (1:9) gave an oil (mainly **5e**) and elution with ethyl acetate–hexane (3:7) gave a mixture containing **7b**. The latter mixture was purified further by column chromatography on silica, eluting **7b** as an unstable, low-melting solid (10% yield) with ethyl acetate–hexane (1:9 to 3:7). Flash distillation of this material at 1.0 mm gave the analytical specimen: IR (film) 3351, 1632 cm^{-1}; ^1H NMR δ 1.54 (d, 3H, J = 7.14 Hz, Me), 4.53 (q, 1H, J = 7.14 Hz, CH), 6.05 (m, 1H, H-3), 6.11 (m, 1H, H-4), 6.27 (dd, 1H, $J_{3',4'}$ = 3.90 Hz, $J_{4',5'}$ = 2.52 Hz, H-4′), 6.70 (m, 1H, H-5), 7.01 (dd, 1H, $J_{3',4'}$ = 3.90 Hz, $J_{3',5'}$ = 1.33 Hz, H-4′), 7.04 (dd, 1H, $J_{3',5'}$ = 1.33 Hz, $J_{4',5'}$ = 2.52 Hz, H-5′); HRMS calcd for $C_{11}H_{12}N_2O$ 188.0950, found 188.0946.

Isopropyl 1-Pyrroylacetate (8). This reaction was carried out as described for the synthesis of the alkyl 2-pyrrolylacetates except that the THF contained HMPA (2 mol/mol of Grignard reagent). IR (film) 1750 cm^{-1}; ^1H NMR δ 1.25 (d, 6H, J = 6.25 Hz, Me_2CH), 4.56 (s, 2H, CH_2), 5.06 sept, 1H, J = 6.25 Hz, Me_2CH), 6.18 (t, 2H, H-3,4), 6.65 (t, 2H, H-2, 5); HRMS calcd for $C_9H_{13}NO_2$ 167.0946, found 167.0947.

Synthesis of Dialkyl Pyrrolylmalonates. A solution of the pyrrolylacetate in anhydrous THF (*ca.* 1 mL/mmol of ester) was added to a stirred solution of lithium diisopropylamide [3.35 mmol/mmol of ester; prepared from diisopropylamine (4.1–4.4 mmol/mmol of ester) and *n*-BuLi (2.5 M) in THF] in anhydrous THF (*ca.* 15 mL/mmol of ester) cooled to −60 to −75 °C, and in a nitrogen atmosphere, over a 5–10 min period. Stirring was continued at this temperature for 0.25–1 h and then a solution of the alkyl chloroformate (1.1–1.3 mmol/mmol of ester; except for compound **18** where 6.5 mmol/mmol of ester was used) in dry THF (1–2 mL/mmol of chloroformate) was added slowly at the temperature indicated in Table 2. The solution was stirred for the time and temperature indicated in Table 2 and then excess saturated aqueous ammonium chloride solution was added. The mixture was diluted with ether, and the organic phase was separated and washed successively with saturated aqueous solutions of ammonium chloride and sodium chloride. The organic phase was dried over magnesium sulfate and the solvent was removed *in vacuo*. The residue was then purified by the method indicated in Table 2.

Methyl Isopropyl 2-pyrrolylmalonate (16a): bp 114–116°/1 mm; IR (film) 3401, 1732 cm^{-1}; ^1H NMR δ 1.24 (d, 3H, J = 6.25 Hz, Me_2CH), 1.27 (d, 3H, J = 6.25 Hz, Me_2CH), 3.75 (s, 3H, Me), 4.73 (s, 1H, CH), 5.06 (sept, 1H, J = 6.25 Hz, Me_2CH), 6.15 (m, 2H, H-3, 4), 6.80 (dd, 1H, $J_{3,5}$ = 1.69 Hz, $J_{4,5}$ = 2.69 Hz, H-5). Anal. Calcd for $C_{11}H_{15}NO_4$: C, 58.65; H, 6.71; N, 6.22. Found: C, 58.69; H, 6.81; N, 6.27.

Benzyl Isopropyl 2-Pyrrolylmalonate (16b): oil; IR (film) 3403, 1732 cm^{-1}; ^1H NMR δ 1.18 (d, 6H, J = 6.28 Hz, Me_2CH), 4.77 (s, 1H, CH), 5.02 (sept, 1H, J = 6.28 Hz, Me_2CH), 5.18 (q, 2H, J_{AB} = 12.35 Hz, CH_2), 6.15 (m, 2H, H-3,4), 6.80 (dd, 1H, $J_{3,5}$ = 1.79 Hz, $J_{4,5}$ = 2.59 Hz, H-5), 7.33–7.38 (m, 5H, C_6H_5); HRMS calcd for $C_{17}H_{19}NO_4$ 301.1314, found 301.1318.

Methyl *tert*-Butyl 2-Pyrrolylmalonate (16c): oil; IR (film) 3403, 1732 cm^{-1}; ^1H NMR δ 1.46 (s, 9H, Me_3C), 3.75 (s, 3H, Me), 4.68 (d, 1H, $J_{3,CH}$ = 0.4 Hz, CH), 6.11 (m, 1H, $J_{3,CH}$ = 0.4 Hz, $J_{3,4}$ = 3.41 Hz, $J_{3,5}$ = 1.61 Hz, H-3), 6.14 (dd, 1H, $J_{3,4}$ = 3.41 Hz, $J_{4,5}$ = 2.78 Hz, H-4), 6.78 (dd, 1H, $J_{3,5}$ = 1.61 Hz, $J_{4,5}$ = 2.78 Hz, H-5); HRMS calcd for $C_{12}H_{17}NO_4$ 239.1158,

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found 239.1161. Anal. Calcd for $C_{12}H_{17}NO_4$: C, 60.23; H, 7.16; N, 5.85. Found: C, 59.96; H, 7.54; N, 5.96.

Phenyl *tert*-Butyl 2-Pyrrolylmalonate (16d): mp 93.3–97.6 °C dec (ethyl acetate–hexane); IR (KBr) 3426, 3397, 1763w, 1738 cm^{-1}; ^1H NMR δ 1.51 (s, 9H, Me_3C), 4.91 (s, 1H, CH), 6.19 (dd, 1H, $J_{3,4}$ = 3.44 Hz, $J_{4,5}$ = 2.81 Hz, H-4) 6.23 (dd, 1H, $J_{3,4}$ = 3.44 Hz, $J_{3,5}$ = 1.57 Hz, H-3), 6.83 (dd, 1H, $J_{3,5}$ = 1.57 Hz, $J_{4,5}$ = 2.81 Hz, H-5), 7.08 (m, 2H, H-3′,5′), 7.25 (m, 1H, H-4′), 7.38 (m, 2H, H-2′,6′). Anal. Calcd for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.36; N, 4.65. Found: C, 67.62; H, 6.49; N, 4.75.

1-(2-Chloroethyl) *tert*-Butyl 2-Pyrrolylmalonate (16e): mp 79.5–80.2 °C (ether–hexane); IR (KBr) 3384, 1759, 1716 cm^{-1}; ^1H NMR δ 1.49 (s, 9H, Me_3C), 3.71 (t, 2H, J = 5.69 Hz, CH_2Cl), 4.35–4.50 (m, 2H, OCH_2), 4.75 (s, 1H, CH), 6.17–6.20 (m, 2H, H-3, 4), 6.84 (dd, 1H, $J_{3,5}$ = 1.69 Hz, $J_{4,5}$ = 2.71 Hz, H-5). Anal. Calcd for $C_{13}H_{18}ClNO_4$: C, 54.26; H, 6.31; N, 4.87. Found: C, 54.53; H, 6.44; N, 4.69.

1-(2,2,2-Trichloroethyl) *tert*-Butyl 2-Pyrrolylmalonate (16f): mp 76.3–78.5 °C; IR (KBr) 3432, 1754 cm^{-1}; ^1H NMR δ 1.48 (s, 9H, Me_3C), 4.78 (q, 2H, J_{AB} = 11.80 Hz, OCH_2), 4.82 (s, 1H, CH), 6.16 (dd, 1H, $J_{3,4}$ = 3.47 Hz, $J_{4,5}$ = 2.67 Hz, H-4), 6.18 (dd, 1H, $J_{3,4}$ = 3.47 Hz, $J_{3,5}$ = 1.63 Hz, H-3), 6.82 (dd, $J_{3,5}$ = 1.63 Hz, $J_{4,5}$ = 2.67 Hz, H-5); mass spectrum *m/z* 359 (1), 357 (3), 355 (2), 256 (9), 181 (10), 124 (28), 106 (25), 79 (7), 57 (100); HRMS calcd for $C_{13}H_{16}Cl_3NO_4$ 355.0145, found 355.0144. Anal. Calcd for $C_{13}H_{16}Cl_3NO_4$: C, 43.78; H, 4.52; N, 3.93. Found: C, 45.26; H, 4.72; N, 4.07.

Methyl Isopropyl 2,5-Dimethyl-3-pyrrolylmalonate (17). This reaction was carried out as described above except that the following reagent ratios were used: compound **10** (1 mol), lithium diisopropylamide (2.4 mol), and methyl chloroformate (1 mol). The product consisted of a mixture of the **17** and its *N*-methoxycarbonyl derivative which was separated by column chromatography on silica gel. Elution with hexane–ethyl acetate (9:1) gave a 4:1 mixture of starting material and the *N*-methoxycarbonyl derivative of **17** (19%). A pure sample of this material was obtained by effecting the methoxycarbonylation by the standard technique except that 2 mol of methyl chloroformate was used. This material was an oil: IR (film) 1748 cm^{-1}; NMR δ 1.23 (d, 3H, J = 6.29 Hz, Me_2CH), 1.26 (d, 3H, J = 6.29 Hz, Me_2CH), 2.34 (s, 3H, Me), 2.37 (s, 3H, Me), 3.73 (s, 3H, OMe), 3.90 (s, 3H, OMe), 4.50 (s, 1H, CH), 5.05 (sept, 1H, J = 6.29 Hz, Me_2CH), 6.03 (s, 1H, H-4); HRMS calcd for $C_{15}H_{21}NO_6$ 311.1369, found 311.1373.

The desired product **17** was eluted from the column with hexane–ethyl acetate (4:1) in 45% yield as an oil: IR (film) 3584w, 3386, 1732 cm^{-1}; ^1H NMR δ 1.21 (d, 3H, J = 6.27 Hz, Me_2CH), 1.24 (d, 3H, J = 6.27 Hz, Me_2CH), 2.11 (s, 3H, Me), 2.12 (s, 3H, Me), 3.68 (s, 3H, OMe), 4.47 (s, 1H, CH), 5.03 (sept, 1H, J = 6.27 Hz, Me_2CH), 5.84 (s, 1H, H-4); HRMS calcd for $C_{13}H_{19}NO_4$ 253.1314, found 253.1318.

Isopropyl (5-Benzoylpyrrol-2-yl)acetate (18). Oxalyl chloride (1.0 mL, 1.33 g, 10.4 mmol) was added to a stirred solution of *N,N*-dimethylbenzamide (1.0 g, 6.70 mmol) in anhydrous ether (25 mL) cooled in an ice bath. A solid began to precipitate immediately accompanied by gas evolution. When gas evolution had ceased (0.75 h), the solvent was removed *in vacuo* (protection from moisture) and the residue was maintained *in vacuo* to remove excess oxalyl chloride. The solid residue was dissolved in anhydrous dichloromethane (5 mL), and a solution of *i*-propyl 2-pyrrolylacetate (**5c**, 1.0 g, 5.99 mmol) in dry dichloromethane (5 mL) was added. The solution was stirred at room temperature for 40 h (The true reaction time is much shorter.) and then a solution of sodium acetate trihydrate (2.0 g) in water (10 mL) was added and the two-phase mixture was agitated vigorously for 15 h. The organic phase was separated and dried over magnesium sulfate, and the solvent was then removed *in vacuo*. The oily residue was dissolved in the minimum amount of dichloromethane and applied to a dry-packed column of silica gel. The column was developed with ethyl acetate–hexane (1:9 then 1:4) mixtures, the more polar mixture eluting the solid product (1.17 g, 72% yield) which, on crystallization from ether had mp 131–132 °C; IR (KBr) 3441, 3266, 1734, 1608 cm^{-1}; ^1H NMR δ 1.30 (d, 6H, J = 6.28 Hz, Me_2CH), 3.75 (s, 2H, CH_2), 5.10 (sept, 1H, J = 6.28 Hz, CH), 6.20 (d, 1H, J = 3.69 Hz, H-3), 6.83 (d, 1H, $J_{3,4}$ = 3.69 Hz, H-4), 7.47–7.61 (m, 3H, H-3′–6′), 7.90 (dd, 2H, J_0 = 8.3 Hz, J_m = 1.3 Hz, H-2′,6′). Anal. Calcd for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32; N, 5.16. Found: C, 70.93; H, 6.32; N, 5.16.

Methyl Isopropyl (5-Benzoyl-2-pyrrolyl)malonate (19) by Vilsmeier–Haack Reaction on (16a). This reaction was carried out on the same scale and in exactly the same manner as described for the synthesis of **18** except that the Vilsmeier–Haack reaction was worked up after 15 h and the iminium salt hydrolysis was carried out for 24 h. The chromatographically pure product **19** was obtained as an oil (1.42 g, 72% yield) identical in all respects to material prepared by the methoxycarbonylation of **18** (See Table 2 for conditions); IR (KBr) 3264, 1736, 1611 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.28 (d, 3H, J = 6.29 Hz, Me_2CH), 1.30 (d, 3H, J = 6.29 Hz, Me_2CH), 3.81 (s, 3H, Me), 4.80 (s, 1H, CH), 5.11 (sept, 1H, J = 6.29 Hz, Me_2CH), 6.29 (d, 1H, $J_{3,4}$ = 3.78 Hz, H-3), 6.81 (d, 1H, $J_{3,4}$ = 3.78 Hz, H-4), 7.45–7.59 (m, 3H, H-3′–5′), 7.88 (d, 2H, J_0 = 7.4 Hz, H-2′,6′); HRMS calcd for $C_{18}H_{19}NO_5$ 329.1263, found 329.1260.

Methyl Isopropyl 5-Benzoyl-1,2-dihydro-3*H*-pyrrolo[1,2-*a*]pyrrole-1,1-dicarboxylate (20). A mixture of compound **19** (4.00 g, 1.22 mmol), potassium carbonate (2.0 g), tetra-*n*-butylammonium bromide (0.400 g), and 1,2-dichloroethane (25 mL) was stirred vigorously at reflux temperature for 44 h. The mixture was filtered, and the filtrate was combined with a dichloromethane washing of the solid and evaporated to dryness *in vacuo*. The residue was dissolved in ether, washed successively with 10% HCl and saturated sodium bicarbonate solutions, and dried over magnesium sulfate, and the solvent was removed *in vacuo*. The residue was subjected to column chromatographic purification on silica gel using hexane–ethyl acetate [9:1 then 4:1 (product)] giving compound **20** as an oil (0.292 g, 68% yield); IR (film) 1738, 1626 cm^{-1}; ^1H NMR δ 1.26 (d, 3H, J = 6.28 Hz, Me_2CH), 1.28 (d, 3H, J = 6.38 Hz, Me_2CH), 3.04–3.21 (m, 2H, 2-CH_2), 3.80 (s, 3H, OMe), 4.49–4.59 (m, 2H, NCH_2), 5.10 (sept, 1H, J = 6.28 Hz, Me_2CH), 6.26 (d, 1H, $J_{6,7}$ = 4.05 Hz, H-7), 6.84 (d, 1H, $J_{6,7}$ = 4.05 Hz, H-6), 7.43–7.57 (m, 3H, H-3′–5′), 7.82 (m, 2H, H-2′,6′); HRMS calcd for $C_{20}H_{21}NO_5$ 355.1420, found 355.1427.

5-Benzoyl-1,2-dihydro-3*H*-pyrrolo[1,2-*a*]pyrrole-1-carboxylic Acid (21, ketorolac). A solution of the diester (0.269 g, 0.76 mmol) in methanol (25 mL) containing 1 N NaOH (1.55 mL, 1.5 mmol) was left at room temperature overnight. Most of the solvent was removed *in vacuo*, water was added to the residue, and the solution was extracted with ethyl acetate. The aqueous phase was made acidic with 10% hydrochloric acid, the product was extracted into ethyl acetate, and the extract was dried over magnesium sulfate and evaporated *in vacuo*. A crystalline solid (0.190 g, 99% yield) was obtained which on recrystallization from ethyl acetate gave material with mp 157–158 °C (lit.[31] mp 160–161 °C) and a ^1H NMR spectrum identical to that reported.[31]

Methyl Isopropyl 1,2-Dihydro-3*H*-pyrrolo[1,2-*a*]pyrrole-1,1-dicarboxylate (22). A mixture of the malonate ester **16a** (1.00 g, 4.44 mmol), acetonitrile (30 mL), 1,2-dichloroethane (10 mL), tetra-*n*-butylammonium bromide (1.00 g), and anhydrous potassium carbonate (2.0 g) was vigorously stirred at reflux temperature. At the end of 5.25 h the reaction was accelerated by the addition of water (100 μL). A further 100 μL of water was added at 6.5 h followed by 300 μL of water and potassium carbonate (8.0 g) at 7 h. The reaction mixture was stirred for a total of 22 h. After workup as described for **20**, the crude product was dissolved in dichloromethane and flushed through a column of neutral alumina (act. II). Removal of the solvent gave an oil which was purified by column chromatography on silica gel using hexane–ethyl acetate (9:1) to elute the product (0.646 g, 58% yield) as an oil: IR (film) 1732 cm^{-1}; ^1H NMR δ 1.24 (d, 3H, J = 6.26 Hz, Me_2CH), 1.26 (d, 3H, J = 6.26 Hz, Me_2CH), 2.95–3.12 (m, 2H, CCH_2), 3.76 (s, 3H, OMe), 4.07 (t, 2H, J = 6.88 Hz, NCH_2), 5.06 (s, 1H, J = 6.26 Hz, Me_2CH), 6.14 (dd, 1H, $J_{5,7}$ = 1.31 Hz, $J_{6,7}$ = 3.52 Hz, H-7), 6.25 (dd, 1H, $J_{5,6}$ = 2.63 Hz, $J_{6,7}$ = 3.52 Hz, H-6), 6.63 (dd, 1H, $J_{5,6}$ = 2.63 Hz, $J_{5,7}$ = 1.31 Hz, H-5); HRMS calcd for $C_{13}H_{17}NO_4$ 251.1156, found 251.1162.

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