Pyrrole Chemistry. An Improved Synthesis of Ethyl Pyrrole-2-carboxylate Esters from Diethyl Aminomalonate

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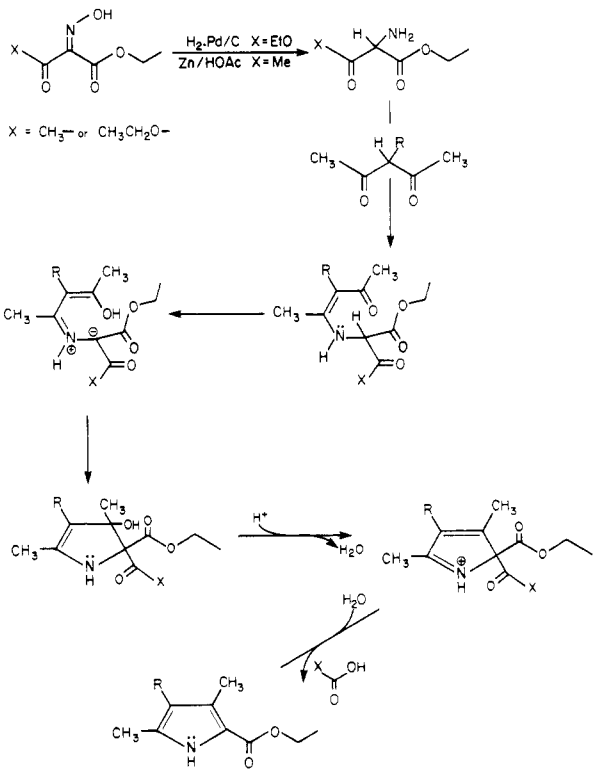
Received July 26, 1984

Ethyl pyrrole-2-carboxylates, versatile precursors for the total synthesis of both synthetic model and naturally occurring tetrapyrroles and porphyrins, can be prepared in greatly improved yields by the addition of 1,3-diketones and *preformed* diethyl aminomalonate to boiling glacial acetic acid. The method is suitable for both small- and large-scale synthesis and has proved far more reliable than the original in situ dissolving zinc reduction of diethyl oximinomalonate discovered by Kleinspehn. Yields range from 60–70% for the dominant product isomer from unsymmetrical diketones to 75–90% for the single product derived from symmetrical diketones. Seventeen examples of alkyl-substituted ethyl pyrrole-2-carboxylates are provided. Improved procedures are given for the preparation of the required precursors.

The laboratory synthesis of porphyrins has long been dependent upon the availability of appropriately substituted 5-methylpyrrole-2-carboxylate esters.[1] Since 1955, these pyrroles have most conveniently been prepared, where possible, by the method of Kleinspehn[2], a dissolving zinc reduction of diethyl oximinomalonate in the presence of a β,β-diketone in acetic acid. This reaction was initially used with 2,4-pentanedione and its 3-alkyl derivatives and then extended to the use of unsymmetrically substituted diketones[3-5] and dibenzyl oximinomalonate.[6,7] 3,5-Disubstituted 2,4-pentanediones were reported to give the 5-methylpyrrole derivatives exclusively.[3-7] Since 1958, ethyl, benzyl, and *tert*-butyl oximinoacetoacetates[8,9] have been similarly employed with 3-alkyl-2,4-pentanediones to give a variety of 4-substituted 3,5-dimethylpyrrole-2-carboxylate esters (Scheme I).

Our interest in unsymmetrical β-diketones followed from the report of Wang and Chang[10] on the direct synthesis of 3-ethyl-2,4-hexanedione from 2-pentanone, propionic anhydride, and BF_3. The *crystalline* BF_2 complex allowed the β-diketone to be readily isolated in an isomerically pure form. In our hands the Kleinspehn[2] procedure using this diketone gave disappointingly low yields of the 3,4-diethyl-5-methylpyrrole (10–20%), unlike the similar Johnson[8,9] syntheses, which even when scaled up gave consistently higher yields (~45%). This is a consequence of a more facile loss of the acetyl group from the 2*H*-pyrrole in the latter procedure, compared to the slower loss of the ethoxycarbonyl moiety in the former procedure, which allows alternative modes of destruction, including possible overreduction of intermediates, consequently lowering the yield. In order to circumvent the problem we have examined the strategy of prereducing the diethyl oximinomalonate in the *absence* of diketone followed by reaction of the diethyl aminomalonate with diketone under carefully controlled conditions. This approach is possible with the Kleinspehn synthesis since diethyl aminomalonate is stable enough even to be distilled[11] under reduced pressure without polymerizing. The aminoacetoacetates used in the Johnson synthesis undergo such facile dimerization that they cannot be used similarly. A similar approach to that described here has already been employed with aryl diketones en route to pyrrolnitrin[12] where the intermediate Schiff bases or enamines were isolated and then cyclized by heating in polyphosphate ester melts.

Scheme I



The reduction of the oximinomalonate proceeds smoothly by catalytic reduction[11] in ethanolic solution (even as concentrated as 40% by volume) using low concentrations (0.4%) of 10% Pd/C. The reaction may be carried out successfully at room temperature and pressure

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on a small scale and at 450 psig on a 10-mol scale in a 10-L high-pressure hydrogenater. An aliquot of the resulting solution of diethyl aminomalonate was assayed by conversion to diethyl acetamidomalonate.[13,14]

Originally, the β-diketone was added to the diethyl aminomalonate before removal of the hydrogenation solvent on a rotary evaporator. The resultant oil was poured into boiling acetic acid as rapidly as the exothermicity would permit. A vigorous evolution of CO_2 and ethanol ensued, and after an hour's boiling the reaction was complete. This procedure (method B) gave excellent yields with symmetric diketones but erratic results with unsymmetric analogues.

This behavior derives from the variable amount of acetic acid in the diethyl aminomalonate resulting from the initial nitrosation procedures (see Experimental Section and Table I). It is likely that conditions which permit reversible formation of the two possible Schiff's bases from an unsymmetric diketone (such as the presence of residual acetic acid) will generate the two pyrroles in ratios reflecting the thermodynamic stability of the imine precursors. However, the required 5-methylpyrrole results from the reaction at the less hindered site and as such it is the kinetically favored product. These considerations led us to adopt method A for unsymmetric β-diketones. Here the diethyl oximinomalonate was rigorously freed from acetic acid prior to reduction and the resulting diethyl aminomalonate concentrated in vacuo. The β-diketone was then added and the mixture added *immediately* to boiling acetic acid as before. Yields have been uniformly good (Table I) provided sufficient solvent was employed. With insufficient solvent the reaction mixture is cooled too much by the addition of the reagents, which slows the cyclization step and permits excessive equilibration of the "Schiff's bases". Best results were obtained at ratios of 1.8–2.1 mol of β-diketone per liter of refluxing acetic acid. At a ratio of 3 mol per liter, yields were dramatically reduced. In addition, a 20–30% excess of diethyl aminomalonate produced the best conversion of β-diketone to pyrrole. The use of aqueous acetic acid (as used in Kleinspehn's original procedure) caused the yields to suffer drastically.

Correlation of β-Diketone Structure with Reaction Selectivity. The conversion of β-diketone to pyrrole under the conditions recommended here often approaches 90%, but unlike most previous workers,[3,4,10] however, we observe considerable formation of the unwanted 3-methylpyrrole isomers as byproducts[15] from the reactions involving the various 2,4-hexanediones and 4,6-dioxoheptanoates. This is not surprising, since previous workers, obtaining yields greatly inferior to those reported here, obtained far more nonpyrrolic byproduct wherein such unwanted isomers could hide. Recrystallization allows the isomerically pure 5-methylpyrrole isomers to be obtained in 60–70% yield from the diketone (Table I). An additional 10–15% of this isomer is lost in the mother liquors along with a comparable amount of the "wrong" isomer. The 60–70% yields obtained with the 3-substituted 2,4-hexanediones represented an improvement in reliability and yield by a factor of 2 or 3 over the traditional zinc reduction. The 75–90% yields obtained from the symmetrical 3-substituted 2,4-pentanediones (Table I) represent at least a doubling of the yield likely to be obtained by the zinc reduction procedures used by either Kleinspehn[2] or Johnson.[8,9] The limited set of symmetrical 3,5-heptanediones we have examined seem to give slightly lower yields, probably due to increased steric hindrance, which gives the diethyl aminomalonate somewhat more time to self-destruct.

Whereas meso-alkylated unsymmetrical β-diketones show considerable selectivity toward Schiff's base formation at the less-hindered carbonyl, thereby affording the 5-methylpyrrole isomer preferentially, such is *not* the case with meso-*unsubstituted* unsymmetrical β-diketones. 2,4-Hexanedione, in fact, favored the formation of the 5-ethylpyrrole isomer[16] at least 2:1 over the 5-methylpyrrole, both under our conditions and with the zinc reduction. Ethyl 4,6-dioxoheptanoate[17] also gave a mixture of both possible products. Only the symmetrical members of this class, which can give but one product, are synthetically useful, and they (2,4-pentanedione and 3,5-heptanedione) seem to give significantly lower yields than their meso-alkylated analogues, especially in the former case. It is not known whether this is related to the greater acidity and enolizability of the unsubstituted diketones compared to their substituted analogues or to possibly different geometric preferences exhibited exhibited by the Schiff's base or enamine intermediates, which may tend to disfavor cyclization relative to decomposition.

A limited number of other β-dicarbonyl-containing substrates were examined under our conditions but these proved disappointing. 2-Methyl-3-oxopentanal gave an intractable mixture of both possible products, with an excess of the 5-ethylpyrrole.[18,19] Acetoacetaldehyde dimethyl acetal gave a low yield of ethyl 5-methylpyrrole-2-carboxylate,[18,20,21] but no significant or useful quantity of pyrroles could be obtained from either methyl 3,5-dioxohexanoate[22] or ethyl 2,4-dioxopentanoate.[23]

Although ethyl oximinoacetoacetate and diethyl oximinomalonate afford the same pyrroles upon reductive condensation with 3-substituted-2,4-pentanediones, this is not necessarily the case for *unsymmetrical* β-diketones. The steric requirements for the two intermediary amines are different, leading to significant differences in regioselectivity.[15] The aminoacetoacetate also has available to it a competing mode of cyclization.[24] The lower yields inherent with acetoacetates compared to malonates, and the inferior purity of any products obtained, make the Johnson[8,9] synthesis unattractive for ethyl esters (from unsymmetrical diketones). Since benzyl or *tert*-butyl esters were not directly available by the "hydroknorr" procedure reported here, we examined the Johnson synthesis[8,9] with *tert*-butyl oximinoacetoacetate and 3-methyl- and 3-ethyl-2,4-hexanedione. In both systems, low (20–30%) yields of pyrroles resulted, with the 5-methylpyrrole isomer dominant but contaminated with the 3-methyl isomer to the extent of 30–40%.

The direct synthesis of benzyl esters is not possible via our hydrogenation procedure, due to their facile hydrogenolysis. Since the benzyl esters are readily obtained[1] by base-catalyzed transesterification[25] of the ethyl esters, this consideration is unimportant. Even when retro-

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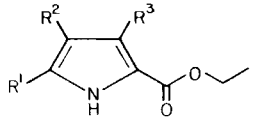
Table I. Reaction Conditions and Yields and Properties of Pyrroles Synthesized



	compound[a]			β-diketone, g (mol)	acetic acid, mL	DEAM,[b] mol	method	yield, g (%)	mp,[c] °C (lit. mp, °C)	^{1}H NMR data ($CDCl_3$),[d] δ		
	R^1	R^2	R^3							R^1	R^2	R^3
1	Me	H	Me	233.7 (2.34)	800	2.33	B	184 (47)	120.5–122 (125)[45]	2.20 (s)	5.74 (d)	2.27 (s)
				200 (2.0)	870	2.15	A	224.6 (67)				
2	Me	Me	Me	315 (2.77)	1038	2.6	A	389.5 (78)	124.5–125.5 (128)[8]	2.18 (s)	1.90 (s)	2.25 (s)
				175.6 (1.54)	600	2.0	B	248 (89)				
3	Me	Et	Me	209 (1.63)	930	1.95	A	272.8 (86)	88–89 (90–91)[2]	2.19 (s)	1.03 (t), 2.37 (q)	2.27 (s)
4	Me	Pr	Me	42.8 (0.30)	202	0.34	A	36.0 (57)	96–96.5 (97.5–98.5)[46]	2.21 (s)	0.90 (t), 1.45 (sx), 2.35 (t)	2.28 (s)
5	Me	$A^{(Me)}$	Me	293.3 (1.7)[51]	1021	1.75	A	298.5 (73)	122.5–124	2.25 (s)	3.41 (s, 2 H), 3.67 (s, 3 H)	2.31 (s)
				294 (1.7)	800	2.06	B	308 (75)				
6	Me	$P^{(Me)}$	Me	372.3 (2.0)[52]	1028	2.06	A	403 (80)	100 (100–102)[25]	2.20 (s)	2.44 (m, 2 H), 2.66 (m, 2 H), 3.63 (s)	2.25 (s)
				288.3 (1.55)	750	2.2	B	302 (77)				
7	Me	Me	Et	216.4 (1.7)	1000	2.16	A	235 (71)	95–96 (96–97)[5]	2.19 (s)	1.93 (s)	1.12 (t), 2.74 (q)
				192 (1.5)	860	2.32	B	210 (72)				
8	Me	Et	Et	210.6 (1.48)	800	1.87	A	196 (63)	73.5–75.2 (74–75)[3]	2.18 (s)	1.06 (t), 2.36 (q)	1.14 (t), 2.70 (q)
				213.6 (1.50)	800	2.2	B	193 (61)				
9	Me	Pr	Et	62.6 (0.40)	305	0.46	A	42 (47)	86.8–89.5	2.22 (s)	0.93 (t), 1.47 (sx), 2.36 (t)	1.15 (t), 2.74 (q)
10	Et	H	Et	38.6 (0.30)	232	0.41	A	48 (82)	47–48.5 (51)[47]	1.25 (t), 2.63 (q)	5.91 (d)	1.20 (t), 2.79 (q)
11	Et	Me	Et	147.4 (1.04)	620	1.0	A	148 (68)	61.5–63.5 (62–63)[48]	1.17 (t), 2.56 (q)	1.91 (s)	1.10 (t), 2.72 (q)
				142.3 (1.00)	550	1.32	B	120 (58)				
12	Et	Et	Et	23.4 (0.15)	150	0.23	A	15 (45)[e]	43–45[f] (47–49)[49]	1.24 (t), 2.61 (q)	1.09 (t), 2.42 (q)	1.16 (t), 2.75 (q)
13	Me	Me	Pr	113.9 (0.80)	504	1.03	A	105 (62)	100–102 (101–104)[49]	2.20 (s)	1.93 (s)	0.95 (t), 1.54 (m), 2.71 (t)
14	Me	Et	Pr	125.6 (0.81)	510	1.04	A	71 (39)	95–96.2	2.20 (s)	1.06 (t), 2.40 (q)	0.97 (t), 1.56 (m), 2.69 (t)
15	Me	Pr	Pr	136.2 (0.80)	500	1.05	A	101 (53)	96–98 (99–101)[42]	2.21 (s)	0.91 (t), 1.47 (m), 2.35 (t)	0.96 (t), 1.56 (m), 2.67 (t)
16	Me	Me	$P^{(Et)}$	100.6 (0.50)	400	0.65	A	82 (61)	87 (88–89)[50]	2.17 (s)	1.93 (s)	1.23 (t), 2.4–2.56 (m), 2.92–3.09 (m), 4.10 (q)
17	Me	$P^{(Me)}$	$P^{(Et)}$	*h*	*h*	*h*	*h*	(21)[g]	50–51	2.24 (s)	3.68 (s), 2.35–3.10 (m, 8 H)	1.26 (t), 4.17 (q)

[a] Satisfactory combustion analytical data for C, H, N (±0.3) were provided for **5**, **9**, **11**, **14**, and **17**. [b] Diethyl aminomalonate. [c] Recrystallized from aqueous ethanol. [d] For all 17 compounds the OCH_2, OCH_2CH_3, and NH protons fall within the narrow ranges δ 4.27–4.34, 1.31–1.36, and 8.70–9.59. [e] The crude second crop was saponified, bringing the total yield of isolated pyrroles to 82%. [f] Prepared by B_2H_6 reduction of the acetylation product of compound **10**. [g] Solubility losses were severe. [h] See Experimental Section.

esterification of vulnerable side-chain esters is required, as with the example provided in the Experimental Section, the overall yield of pyrrole from diketone is still at least double that of the direct Johnson procedure[26] with benzyl oximinoacetoacetate. The transesterification steps allows one to avoid the tedium of preparation of large quantities of either dibenzyl oximinomalonate[27] or of benzyl oximinoacetoacetate.[27]

Related Pyrrole Syntheses. Several reports have appeared recently concerning the conversion of β-diketones or β-diketone analogues to pyrrole esters. Barluenga et al.[28] have shown that the 4-amino-1-azabuta-1,3-diene analogues of some β-diketones react smoothly with glycine ethyl ester hydrochloride or ethyl chloroacetate, in pyridine, to afford regiospecifically, ethyl pyrrole-2-carboxylates. The precursors were prepared from a reaction of aryl Schiff's bases with nitriles and aluminum trichloride.[29]

The first use of glycine ethyl ester in pyrrole synthesis was as early as 1915, when Hale and Hoyt[31] reacted it with the sodium salt of nitromalonaldehyde to obtain ethyl 4-nitropyrrole-2-carboxylate. Treibs and Ohorodnik later[16] found that 2,4-hexanedione gave the 5-ethylpyrrole isomer, when cyclized with sodium ethoxide. The yield was low, and no mention was made of possible presence of the 5-methyl isomer, which is a significant byproduct in the reaction of 2,4-hexanedione with diethyl aminomalonate. The reaction of 2,4-pentanedione with glycine ethyl ester had even earlier been investigated by Fischer and Fink,[18] in work which clearly foreshadowed Kleinspehn's major discovery.

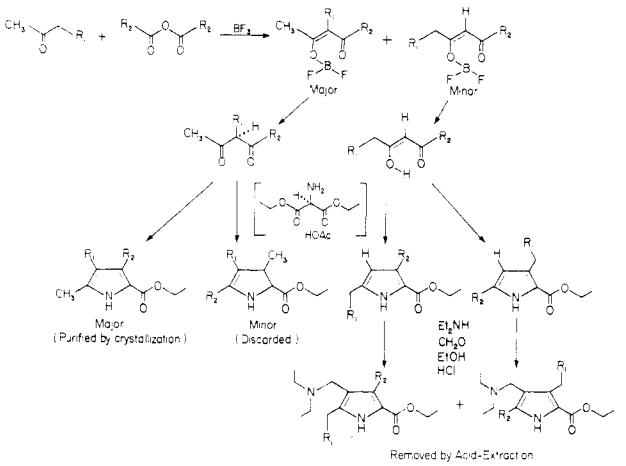
Modest yields of pyrroles, usually aryl substituted, have been reported[30] from β-diketones in refluxing DMF when treated with a very large excess of glycine ethyl ester hydrochloride. Yields of pyrroles from alkyl-substituted diketones were especially poor.

Diketone Synthesis

The reaction[32] between a ketone and 2 equiv of an aliphatic anhydride with BF_3 was found to give the best results when run as rapidly as possible such that despite vigorous external cooling, the temperature reached 80–90 °C until the weight increase corresponded to 3 mol of BF_3 per mol of ketone. The intermediary difluoroboryl complexes were isolated by aqueous dilution and purified if crystalline. The workup has been modified to include a titration with KOH (phenolphthalein indicator) so as to minimize retro-Claisen decomposition of the product as well as to minimize the precipitation of insoluble solids. The product was then isolated by extraction and distillation.

If the difluoroboryl complex was low melting, its purification from isomeric contamination was not attempted. Instead, the crude mixture was hydrolyzed as such, and the mixture of β-diketones reacted with diethyl aminomalonate. Two of the four possible pyrroles produced in this system possessed unsubstituted 4-positions (Scheme II), which left them vulnerable to electrophilic reactions such as the Mannich reaction, with diethylamine and formaldehyde.[33] The pyrrolic bases that resulted from

Scheme II



this quantitative reaction would then be completely removed by extraction into acid. This procedure, which we have employed before,[34] then left only one isomer to be removed by crystallization. This strategy was applied to the synthesis of all of the propyl-substituted pyrroles described herein.

Experimental Section[35]

(3-Ethyl-2,4-hexanedionato)difluoroborane.[10] 2-Pentanone (530 mL, 5 mol) and propionic anhydride (1300 mL, 10.1 mol), in a 3-L Erlenmeyer flask, were stirred magnetically and cooled in an ice bath under a slow stream of N_2 to 5 °C or below. Boron trifluoride gas (diluted with N_2 to prevent back suction) was then introduced as fast as it would dissolve without escaping the flask (hood!). The flow of BF_3 was controlled so as to allow the internal temperature of the reaction mixture to reach 80 °C (but not exceed 90 °C), despite the vigorous ice cooling. Completion of the reaction was signaled by a rapid drop in temperature which occurred even as the BF_3 continued to be absorbed. BF_3 addition was terminated when the temperature fell below 30 °C. Typical reaction times were 120 ± 30 min.

The resulting brown fuming mixture was poured onto crushed ice and diluted to 6 L with H_2O. The solids were filtered off and washed thoroughly with H_2O. The filtrates, containing only traces of oils were discarded. (Too much oil at this stage is indicative of *too slow* an addition of BF_3.) The crude solids were finely divided and then slurried with 70% ethanol–water (v/v). The solids were refiltered and rinsed with 70% ethanol (a total of 2 L being used for both operations) and finally with H_2O (1.5 L). The resulting solids were pale cream to white and completely free of orange-brown oily byproduct. Typical yields ranged from 45% to 55%.

Other Difluoroboryl Complexes. These were prepared on the same scale by the appropriate combinations of acetone (A, 367 mL), 2-butanone (B, 448 mL), 2-pentanone (C, 530 mL), or 3-pentanone (D, 528 mL) with acetic anhydride (E, 950 mL), propionic anhydride (F, 1300 mL), or butyric anhydride (G, 1650 mL). The complexes of 3-methyl-2,4-pentanedione[36] (from B + E), 3-ethyl-2,4-pentanedione[10] (from C + E), and 4-methyl-3,5-heptanedione[37] (from D + F) were all crystalline substances[10,37] and worked up as above.

Smaller scale reactions were employed when using 2-hexanone (H) or 3-hexanone (I). The solid complex of 4-ethyl-3,5-hepta-

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(35) Melting points were determined in a Thomas-Hoover capillary melting point apparatus and are uncorrected. ^1H NMR spectra were measured on a Varian HA-100 or XL-100 spectrometer using saturated solutions in deuteriochloroform containing internal Me_4Si. Combustion analyses were carried out by P. Borda, UBC.
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nedione[36] was only the minor product from F + I.

Most of the other difluoroboryl complexes were low melting and were isolated and hydrolyzed without purification. These included the complexes of 3-methyl-2,4-hexanedione[37] (isomerically pure only from D + E, not B + F), 3-methyl-2,4-heptanedione[37] (from B + G), 3-ethyl-2,4-heptanedione (from C + G), 5-acetyl-4-octanone (from H + G), 4-acetyl-3-heptanone (from H + F), 3-acetyl-2-hexanone (from H + E), and 2,4-hexanedione[36] (from A + F).

3-Ethyl-2,4-hexanedione.[3,10] The moist filter cake from *two* of the above preparations of (3-ethyl-2,4-hexanedionato)difluoroborane was suspended in a mixture of acetone (800 mL), ethanol (100%, 800 mL), phenolphthalein (2–3 g), and propionic acid (100 mL), contained in a 5-L round-bottom flask which was allowed to rest in an ice bath when not being swirled by hand.

Cold concentrated aqueous potassium hydroxide was added in portions, with manual agitation between the additions to discharge the purple indicator color. Addition of base continued until the indicator remained purple despite vigorous shaking of the now two-phase system. Concentrated HCl (ca. 100 mL) was then immediately added to discharge the purple color.

The aqueous phase was removed, back-extracted once with diethyl ether (1 L), and then discarded. The organic phases, *without washing*, were concentrated in several lots on a rotary evaporator. The minor aqueous phase which separated was removed.

The crude product was distilled at 100 °C under high vacuum on the rotary evaporator. If the undistillable residue crystallized (unhydrolyzed difluoroboryl complex), it was saved for future workup; otherwise it was discarded. So prepared, the product is colorless and contains only minor volatiles or water and no isomers which could interfere with pyrrole synthesis. The product (typically obtained in 45% yield from 2-pentanone) was generally employed without further purification.

Diethyl Oximinomalonate.[38,39] Into a 12-L three-neck round-bottom flask equipped with power stirrer and wide-rim long-stem funnel (fume hood) were placed glacial acetic acid (1600 mL) and sodium hydroxide pellets (200 g, 5 mol). Stirring was begun, and over 5 min, the pellets dissolved, bringing the mixture just barely to reflux.[40] Diethyl malonate (1200 mL, 7.9 mol) was added to the hot solution and rinsed in with glacial acetic acid (200 mL); the slow dropwise addition of a solution of sodium nitrite (1100 g, 15.9 mol) in H_2O (1500 mL) was begun immediately. (The long-stem funnel served to direct the nitrite solution into the middle of the stirred reaction mixture.) The addition was complete in 3–5 h.

The homogeneous mixture was allowed to stand and cool overnight. A solution (1500 mL) of NaOH (500 g) in ice–water was added to the stirred mixture in a steady stream, causing separation of oily product. Cold diethyl ether (2 L, USP grade) was added *cautiously* to the warm, *unstirred* mixture. The mixture was agitated gradually so as to prevent violent boiling of the ether, until the organic phases were thoroughly homogenized.

The aqueous phase was removed from the reaction vessel and cold H_2O (2 L) was added to the organic phase. Solid $NaHCO_3$ (450–500 g) was added in portions (effervescence!) with intermittent stirring, until, despite prolonged stirring, some remained undissolved. The aqueous phase was removed and the organic phase washed with H_2O (2 × 2 L).

The organic phase was filtered and concentrated in vacuo (rotary evaporator, bath at 50 °C) to give a pale yellow oil (typically 1600 mL, 1840 g), which became colorless after standing for several days.

Prepared in this manner, diethyl oximinomalonate contained traces of residual diethyl ether and water, but neither diethyl malonate nor acetic acid could be detected by NMR. Kept for a year at room temperature it remained unchanged in appearance or potency: ^{1}H NMR δ 1.33 (3 H, t, J = 7.5 Hz), 1.35 (3 H, t, J = 7.5 Hz), 4.35 (2 H, q, J = 7.5 Hz), 4.39 (2 H, q, J = 7.5 Hz), 7.53 (OH + H_2O); ^{13}C NMR ($CDCl_3$ at 77.39) δ 161.15 and 160.51 (C=O), 144.26 (C=NOH), 62.84 and 62.58 (CH_3CH_2O), 13.94 (2 C, CH_3CH_2O).

Diethyl Aminomalonate. The entire product from the previous preparation (typically 1600 mL), absolute ethanol (3500 mL), and 10% Pd/C (8 g) were rocked gently (0.5 Hz) under H_2 (up to 27 atm) in a custom-built stainless steel bomb of 10-L capacity, until gas uptake ceased (2–3 days). (Temporary cooling through an internal stainless steel coil was applied only if the reaction threatened to get out of hand, since excessive cooling greatly slows the reduction.)

The catalyst was filtered off, rinsed with ethanol and saved. The filtrates were mixed thoroughly and subdivided as the volume (typically around 5500 mL) was measured. This *solution* may be stored at room temperature for several weeks without any decomposition.

An aliquot (100 mL) was treated with acetic anhydride (2 × 25 mL), reacting with noticable exothermicity, as the light yellow color faded to nearly colorless. The solvent was removed in vacuo and chased with H_2O (50 mL). The residue was crystallized from H_2O (10 mL), chilled on ice, and filtered. After a rinse with minimal ice–water, the dense chunky crystals were dried and weighed. Evaporation of the filtrates gave a minor second crop (ca. 10% of first crop).

The yield of solids (diethyl acetamidomalonate, fw 217) established a lower bound for the concentration of diethyl aminomalonate. Typical yields of solids, mp 93–95 °C,[39] ranged from 23 to 26 g, corresponding to overall yields of 73–83% from diethyl malonate: ^{1}H NMR ($CDCl_3$) δ 1.30 (6 H, t, J = 7.5 Hz), 2.08 (3 H, s), 4.29 (4 H, q, J = 7 Hz), 5.22 (1 H, d, J = 7 Hz), 6.90 (1 H, brs); ^{13}C NMR ($CDCl_3$) δ 170.32 (CONH), 166.66 (2, CO_2Et), 62.44 (2, CH_3CH_2O), 56.59 (CH), 22.50 (CH_3CO), 14.01 (2, CH_3CH_2O).

For the purposes of general pyrrole synthesis, the pale yellow mobile oil that resulted when the ethanol was removed on a rotary evaporator (at 50–60 °C) was perfectly satisfactory. By distillation in vacuo as rapidly as possible, at as low a temperature as possible, colorless diethyl aminomalonate could be obtained without excessive loss to polymerization (2-mol scale or less). Purified diethyl aminomalonate is stable for many months at −20 °C: bp 99–103 °C (5.5 torr) or 109–110 °C (10 torr);[11] ^{1}H NMR δ 1.30 (6 H, t, J = 7.5 Hz), 2.01 (2 H, s), 4.21 (1 H, s), 4.27 (4 H, q, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$ at 77.67) δ 169.79 (2, CO), 61.82 (2, CH_3CH_2O), 58.81 ($CHNH_2$), 14.09 (2, CH_3CH_2O).

The Pyrrole Syntheses. Method A. Based on the first crop assay value, diethyl aminomalonate solution equivalent to 2.21 mol was concentrated on the rotary evaporator (bath at 60 °C) until ethanol was removed. β-Diketone (1.7 mol) was added and the mixture added at once, in a steady stream over several minutes, to gently boiling glacial acetic acid (800 mL), contained in a 3-L Erlenmeyer flask atop a magnetic stirrer/hot plate. A vigorous reaction (evolution of CO_2 and ethanol) soon set in and gradually subsided. Gentle boiling was continued for an hour, and some of the solvent was allowed to boil off. (Hood!)

The light brown solution was diluted with ice and water to fill the flask. Product soon solidified; it was filtered off and washed with water. The solids were dissolved in ethanol (steam bath), and the solution was filtered hot to remove remaining traces of Pd/C. The filtrates (ca. 1200 mL) were diluted to near opalescence with water (ca. 250 mL) and seeded. Only after the mixture had gone thick with crystals was it chilled on ice. The solids were filtered off, rinsed with 60% ethanol–water (v/v) (800 mL) and then H_2O, and air-dried. See Table I for details.

Method B. Here, the diketone was added to the diethyl aminomalonate before the removal of ethanol. The oily intermediate was added to boiling acetic acid as before. The precursor diethyl oximinomalonate used for Method B had been partitioned between water and diethyl ether but not treated with excess sodium bicarbonate. Minor volatility losses of diketone during the removal of ethanol occur by this method.

3,5-Heptanedione. A suspension of sodium hydride (50% dispersion in mineral oil, 408.1 g, 8.5 mol) in tetrahydrofuran (1075 mL, distilled from CaH_2) was refluxed with magnetic stirring in a 29/42 4-L heavy-wall Erlenmeyer flask. Ethanol (7.5 mL) was added, followed, slowly dropwise, by a mixture of 2-butanone

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(40) Prebuffering the mixture with sodium acetate greatly stabilizes the nitrous acid. In addition, by using sufficient acetic acid to maintain homogeneity of the reaction mixture until nitrite addition was complete, it was possible to completely nitrosate diethyl malonate with only *2 equiv* of $NaNO_2$.

(371.5 mL, 4.5 mol) and ethyl propionate (501 mL, 4.37 mol), over 90 min. Evolution of H_2 was monitored throughout the reaction and maintained at a vigorous but not threatening rate. The mixture was refluxed until the gas evolution had all but ceased (2 h). The residual NaH was destroyed by adding the reaction mixture cautiously, under a blanket of nitrogen, *to* acetic acid (500 mL) in ice–water (2 L). Indicator paper showed pH values of 7 (aqueous phase) to 8 (organic phase).

The organic phase was separated and treated with acetic acid (50 mL). Hydrochloric acid (12 N, 200 mL) was added to the aqueous phase, which was extracted with ethyl acetate (400 mL). The combined organic phases were concentrated in vacuo (rotary evaporator, water aspirator vacuum, bath at 50 °C). The crude product was then distilled through the rotary evaporator by use of full oil-pump vacuum and boiling water bath. The undistillable residue, mostly mineral oil, was discarded.

The crude product, tainted with the characteristic stench of 3-methyl-2,4-hexanedione, was diluted with ethanol (1 L) and treated with saturated aqueous copper acetate in several portions, with intervening filtration of product, until no more *blue* chelate formed in the filtrates. The sky blue bis(3,5-heptanedionato)-copper was washed with 70% aqueous ethanol and then H_2O to remove any unchelated diketone. The byproduct remained unchelated under these conditions, and its odor was readily apparent in the filtrates. Intermediate cuts from the rotary evaporator were also scavenged with copper acetate, to maximize the yield.

The combined moist filter cakes of the copper chelate were suspended in dichloromethane (1 L) and treated with dilute H_2SO_4 until the organic phase had faded from green to colorless. The organic phase was isolated, concentrated in vacuo, and then distilled through the rotary evaporator as before, yield, 255.9 g (48.1%). The CH_2Cl_2 was recyclized once to extract the aqueous phase, giving minor additional product. The combined oils were distilled (1 atm): bp 168.5–173.5 °C (mostly 170.5–173.5 °C); yield, 256.8 g (48.3%). The foreruns were scavenged with copper acetate, yielding 20.70 g (3.1%) of chelate: ^{1}H NMR δ [enol form] 1.13 (6 H, t, J = 7.5 Hz), 2.32 (4 H, q, J = 7.5 Hz), 5.49 (1 H, s), 15.33 (1 H, v brs), [keto form] 1.06 (6 H, t, J = 7.5 Hz), 2.54 (4 H, q, J = 7.5 Hz), 3.58 (2 H, s).

Ethyl 5-Methyl-4,6-dioxoheptanoate.[4] Ethyl 4,6-dioxoheptanoate[17] (186.3 g, 174 mL, 1 mol), iodomethane (142.5 g, 62.5 mL, 1.00 mol), and anhydrous K_2CO_3 (215.9 g, 1.56 mol) were refluxed in acetone (508 mL, "Spectro") (CO_2/acetone trap condenser) for 18 h. The solids were filtered off and rinsed with acetone; acetic acid (50 mL) was added to the filtrates. The solids were dissolved (effervescence!) in acetic acid (200 mL)–H_2O (250 mL)–acetone (250 mL). The mixture was extracted with diethyl ether (500 mL), and the combined organic phases were concentrated in vacuo.

The oily product was taken into dichloromethane (500 mL), washed with H_2O, and reconcentrated. Distillation through a tall unpacked column led to a main cut, bp 132–136 °C (8.5–9.5 torr) (154.5 g, 77%). The high cut, 17.3 g (8.6%), was also mostly product. By GC, this batch was only 84.3% pure, containing 12.6% of starting material, perhaps due to volatility loss of CH_3I. It was used as such for the syntheses in Table I. The yields in Table I are *uncorrected* for this impurity, whose product pyrroles (known to be a mixture) were undetectable in the recrystallized product: ^{1}H NMR (100 MHz, $CDCl_3$) δ 1.23 (3 H, t, J = 7 Hz), 1.31 (3 H, d, J = 7.5 Hz), 2.17 (3 H, s), 2.56 (2 H, m), 2.77 (2 H, m), 3.72 (1 H, q, J = 7.5 Hz), 4.08 (2 H, q, J = 7.5 Hz), 16.17 (OH). The keto–enol ratio was approximately 8:1, with the impurity mostly enolized also.

5-Acetyl-4-octanone. 2-Hexanone (102.9 g, 127.5 mL, 1.03 mol) (warning: toxic! causes peripheral neuritis)[41] and butyric anhydride (363 mL, 351 g, 2.22 mol), cooled in ice, were treated with a rapid stream of BF_3. The internal temperature reached 95 °C but after 34 min had fallen back to 30 °C, whereupon the BF_3 addition was terminated. An increase in weight of 186.9 g (2.5 mol of BF_3) had occurred to this point. A slow stream of BF_3 for 11 min increased the weight by 19.9 g, for a total of 206.8 g (3.05 mol) of BF_3 consumed. The final temperature was 9 °C. The mixture was poured onto crushed ice and diluted with H_2O. A brown oil, which did not crystallize, separated. This was extracted into diethyl ester (2 × 400 mL). The ethereal phase was diluted with ethanol (500 mL, 100%) and treated with phenolphthalein (2 g), followed by aqueous KOH (353.4 g, 5.36 mol, 85%, dissolved in crushed ice) to a permanent purple end point. Hydrochloric acid (100 mL, 12 N) was added to discharge the purple color. The organic phase was isolated, concentrated in vacuo, diluted with dichloromethane, separated from minor H_2O, reconcentrated, and distilled in vacuo: bp 81–94 °C (6–7.5 torr); yield, 146.3 g (84.8%). By GC, this contained 74.96% of the desired compound and 23.48% of 4,6-decanedione.

The Mannich Reaction Purification Procedure: Ethyl 5-Methyl-3,4-di-*n*-propylpyrrole-2-carboxylate.[42] Crude 5-acetyl-4-octanone (136.2 g, 0.8 mol; 75% pure by GC, containing 23.5% 4,6-decanedione) and crude diethyl aminomalonate (assay 1.05–1.11 mol) were added over 2 min to boiling glacial acetic acid (400 mL) in a 2-L Erlenmeyer flask. Acetic acid (100 mL) was used to rinse the reactants. After 20 min, H_2O (42 mL) was added. After a total of 60 min of boiling, the mixture was diluted to 2 L with ice and water. The crude product soon solidified and was filtered off and washed with H_2O. 4-Unsubstituted pyrrolic byproducts (^{13}C NMR peak at δ 109.39) were evident in the crude product, as were traces of the 3-methylpyrrole isomer (^{13}C NMR peak at δ 10.43).

The moist solids were transferred to a 2-L 29/42 Erlenmeyer flask with ethanol (600 mL, 100%) and treated, in order, with diethylamine (100 mL), aqueous formaldehyde (102 mL, 37%), and 12 N HCl (10.1 mL). The mixture was refluxed for 3 h and then poured onto crushed ice. Diethyl ether (1 L) was added, followed by 12 N HCl to pH 1. The ethereal phase was washed with dilute HCl and then H_2O, then suction filtered, and concentrated in vacuo. The residue was crystallized from ethanol (250 mL)–H_2O (50 mL) and filtered at 0 °C. The solids were washed with 70% ethanol until the rinses were colorless, then 50% ethanol, and finally H_2O. The product formed snow-white sparkling chunks, 100.8 g (53% nominal; 71% based on the estimated content of the appropriate diketone). Impurities were not detected by NMR. The filtrates deposited oils, which were not further investigated.

Ethyl 3-[2-(Ethoxycarbonyl)ethyl]-4-[2-(methoxycarbonyl)ethyl]-5-methylpyrrole-2-carboxylate. Ethyl 4,6-dioxoheptanoate[17] (37.3 g, 0.2 mol), potassium carbonate (3.4 g, anhydrous), and acetone (105 mL) were refluxed overnight after adding methyl acrylate (17.4 g, 18.2 mL, 0.20 mol) through the condenser over 5 min to the boiling solution. The solids were removed and rinsed with CH_2Cl_2(200 mL). The filtrates were rinsed with dilute HCl (8 mL of 12 N in 200 mL of H_2O) and then concentrated in vacuo to afford a crude oil, which was employed without further purification.

Redistilled diethyl aminomalonate (49.9 g, 0.29 mol) was added to the diketone, and both were added to boiling glacial acetic acid (100 mL). The mixture was boiled gently for 1 h and then diluted to 500 mL with ice and water. The resulting oil was isolated by decantation, rinsed with H_2O, and taken into aqueous ethanol. Seeds obtained from ether–hexane at −78 °C were added, and the mixture was kept in a freezer for 10 days. The solids were filtered off and washed with cold 50% (v/v) aqueous ethanol and then H_2O: yield,[43] 14.35 g (21.13% overall); mp 48.5–49.8 °C.

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(51) Methyl 3-acetyl-4-oxopentanoate was prepared via modification of a procedure, using methyl bromoacetate,[26] by using inexpensive chloroacetate, 2,4-pentanedione, excess K_2CO_3, and catalytic KI in refluxing (overnight) 2-butanone.

Benzyl 4-[((Benzyloxy)carbonyl)methyl]-3,5-dimethylpyrrole-2-carboxylate. Ethyl 4-[(methoxycarbonyl)methyl]-3,5-dimethylpyrrole-2-carboxylate (119.6 g, 0.50 mol) and anhydrous benzyl alcohol (300 mL, distilled at 1 atm from K_2CO_3) were heated to boiling under N_2 (2-L 29/42 heavy-wall Erlenmeyer flask, magnetic stirrer/hot plate) until the solvent condensed at the top of the flask and any H_2O, noted as droplets therein, had been expelled. A fresh solution of Na in anhydrous benzyl alcohol was added in 1-mL portions to the boiling mixture, until a vigorous evolution of vapor ensued. When the reaction had subsided, further portions of catalyst were added periodically, until no further effect was noted and the vapor temperature was again in excess of 200 °C.

The hot mixture was then immediately quenched by being added cautiously to a magnetically stirred mixture of methanol (800 mL), H_2O (550 mL), and acetic acid (10 mL) in a 3-L Erlenmeyer flask. The mixture was chilled on ice and then filtered. The solids were washed with 50% aqueous methanol and then H_2O and dried in air, yield, 173.9 g (92.2%). After recrystallization from absolute ethanol (900 mL) (steam bath to ice bath), the first crop weighed 162.55 g (86.2% overall, or 93.5% recovery): mp 110.0–111.0 °C; ^1H NMR ($CDCl_3$) δ 2.15 (3 H, s), 2.29 (3 H, s), 3.42 (2 H, s), 5.11 (2 H, s), 5.31 (2 H, s), 7.31–7.39 (10 H, m), 9.36 (1 H, br); ^{13}C NMR ($CDCl_3$ at 77.12) δ 171.52 (CH_2CO), 161.65 (2-CO), 136.59 (2-Ar, 1), 136.02 (4-Ar, 1), 131.77 (5), 128.48 and 128.01 (11 C, 10 Ar + 3), 116.85 (2), 114.50 (4), 66.41 (4-Ar CH_2), 65.49 (2-Ar CH_2), 30.18 (CH_2CO), 11.41 (5-CH_3), 10.85 (3-CH_3). Anal. Calcd for $C_{23}H_{23}NO_4$: C, 73.19; H, 6.14; N, 3.71. Found: C, 73.00, H, 6.16, N, 3.65.

Benzyl 4-[(Methoxycarbonyl)methyl]-3,5-dimethylpyrrole-2-carboxylate. Benzyl 4-[(benzyloxycarbonyl)-methyl]-3,5-dimethylpyrrole-2-carboxylate (75.5 g, 0.20 mol) was dissolved in tetrahydrofuran (300 mL, distilled from CaH_2) and added, at room temperature, to a solution of sodium (2 g) in anhydrous methanol (500 mL). The mixture was monitored by TLC (CH_2Cl_2–silica) until the starting material was consumed (ca. 20 min). Acetic acid (50 mL) was added, and the solution was filtered, before removal of solvent in vacuo.

The residue was taken into ethanol (250 mL, 100%) and diluted to opalescence with H_2O (143 mL). After 4 h at room temperature, the solids were filtered off, rinsed with aqueous ethanol (70% and then 50%, v/v) and then H_2O, and dried in air. The first crop yield was 47.73 g (79.2%). A second crop crystallized readily, upon further aqueous dilution of the filtrates, 10.33 g (17.1%): total recovery, 58.1 g (96.3%); overall yield from methyl 3-acetyl-4-oxopentanoate,[51] 66.8%, in successive steps of 75.3%, 92.2%, and 96.3%; mp 95.5–96.5 °C (lit.[26] mp 93–94 °C); ^1H NMR ($CDCl_3$) δ 2.18 (3 H, s), 2.31 (3 H, s), 3.38 (2 H, s), 3.64 (3 H, s), 5.32 (2 H, s), 7.37 (5 H m), 9.63 (H, br); ^{13}C NMR ($CDCl_3$ at 77.19) [of the above second crop, found to be pure] δ 172.23 (CH_2CO), 161.78 (2-CO), 136.63 (Ar, 1), 131.91 (5), 128.51 and 127.91 (6, 5 Ar + 3), 116.82 (2), 114.50 (4), 65.50 (Ar CH_2O), 51.81 (CH_3O), 29.95 (CH_2CO), 11.34 (5-CH_3), 10.84 (3-CH_3).

(52) Methyl 4-acetyl-5-oxohexanoate was prepared from 2,4-pentanedione, methyl acrylate, and catalytic K_2CO_3 in boiling 2-butanone.[53]

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Acknowledgment. This work was supported by the United States National Institutes of Health (GM 29198) and the Canadian Natural Sciences and Engineering Research Council.

Registry No. **1**, 2199-44-2; **2**, 2199-46-4; **3**, 2199-47-5; **4**, 4758-64-9; **5**, 99017-93-3; **6**, 2386-37-0; **7**, 34549-93-4; **8**, 16200-50-3; **9**, 99017-94-4; **10**, 99017-95-5; **10** (R_2 = Ac), 99018-01-6; **11**, 4989-26-8; **12**, 35011-45-1; **13**, 35030-47-8; **14**, 99017-96-6; **15**, 94827-35-7; **16**, 17266-77-2; **17**, 99017-97-7; A, 67-64-1; B, 78-93-3; D, 96-22-0; E, 108-24-7; G, 106-31-0; PrCOMe, 107-87-9; $EtCO_2COEt$, 123-62-6; MeCOCH(Me)COMe, 815-57-6; MeCOCH(Et)COMe, 1540-34-7; EtCOCH(Me)COEt, 1187-04-8; $Me(CH_2)_3COMe$, 591-78-6; $Me(CH_2)_2COEt$, 589-38-8; EtCOCH(Et)COEt, 55552-65-3; EtCOCH(Me)COMe, 4220-52-4; PrCOCH(Me)COMe, 13152-54-0; PrCOCH(Et)COMe, 34581-50-5; PrCH(Ac)COPr, 94827-34-6; PrCH(Ac)COEt, 99017-98-8; PrCH(Ac)COMe, 1540-35-8; $EtCOCH_2COMe$, 3002-24-2; MeCOCH(Et)COEt, 71703-50-9; $EtOCOCH_2CO_2Et$, 105-53-3; $EtOCOCH(NH_2)CO_2Et$, 6829-40-9; $EtCOCH_2COEt$, 7424-54-6; $EtCO_2Et$, 105-37-3; $MeCOCH(Me)CO(CH_2)_2CO_2Et$, 17266-65-8; $MeCOCH_2CO(CH_2)_2CO_2Et$, 20754-03-4; $Me(CH_2)_3COCH_2COPr$, 13882-02-5; $H_2C{=}CHCO_2Me$, 96-33-3; $MeOCO(CH_2)_2CH(Ac)CO(CH_2)_2CO_2Et$, 99017-99-9; $MeCOCH(Ac)CH_2CO_2Me$, 39265-95-7; $MeCOCH_2COMe$, 123-54-6; $MeCOCH(Ac)(CH_2)_2CO_2Me$, 13984-53-7; $MeCOC(Me){=}C(Me)OBF_2$, 367-16-8; $MeCOC(Et){=}C(Me)OBF_2$, 71896-31-6; $EtCOC(Me){=}C(Et)OBF_2$, 1549-46-8; $EtCOC(Et){=}C(Et)OBF_2$, 99018-03-8; $MeCOC(Pr){=}C(Me)OBF_2$, 99018-02-7; (3-ethyl-2,4-hexanedionato)difluoroborane, 71736-28-2; (3-methyl-2,4-pentanedionato)difluoroborane, 14947-58-1; (3-ethyl-2,4-pentanedionato)difluoroborane, 71736-26-0; (4-methyl-3,5-heptanedionato)difluoroborane, 14643-73-3; (4-ethyl-3,5-heptanedionato)difluoroborane, 15130-21-9; (3-methyl-2,4-hexanedionato)difluoroborane, 15130-19-5; (3-methyl-2,4-heptanedionato)difluoroborane, 15130-18-4; (3-ethyl-2,4-heptanedionato)difluoroborane, 99018-04-9; (3-propyl-2,4-heptanedionato)difluoroborane, 99018-05-0; (3-propyl-2,4-hexanedionato)difluoroborane, 99018-06-1; (3-propyl-2,4-pentanedionato)difluoroborane, 99018-07-2; (2,4-hexanedionato)difluoroborane, 15130-15-1; benzyl 4-[((benzyloxy)carbonyl)methyl]-3,5-dimethylpyrrole-2-carboxylate, 99018-00-5; benzyl 4-[(methoxycarbonyl)methyl]-3,5-dimethylpyrrole-2-carboxylate, 31837-62-4; diethyl oximinomalonate, 6829-41-0; bis(3,5-heptanedionato)copper, 15716-70-8.

Bridgehead Hydrazines. 2.[1] Preparation and Photolysis of 2-Phenyl-*s*-triazolo[1,2-*a*]pyridazine-1,3-dione and of Pyridazino[1,2-*b*]phthalazine-6,11-dione

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Received June 26, 1985

The two title compounds **6** and **10** were prepared by Diels–Alder reactions of the appropriate cyclic azo compounds with butadiene followed by bromination and bisdehydrobromination. Photolysis of **6** in methanol resulted in 1,2- and 1,4-additions of the solvent to the dienic system and in (2 + 2) dimerization. Photolysis in dichloromethane resulted in rearrangement to a pyrrolo[1,2-*a*]triazine and in (2 + 2) dimerization. Photolysis of **10** was solvent independent and gave only (4 + 2) dimer. Mechanistic aspects of the photoreactions are discussed.

Previous work on the photolysis of 1,2-dihydropyridazines revealed two main pathways, internal (2 + 2) cycloaddition[2] (path a) and electrocyclic opening[2,3] (path b).

0022-3263/85/1950-5604$01.50/0