Synthesis of Pyrroles from Benzyl Isocyanoacetate[1,2]

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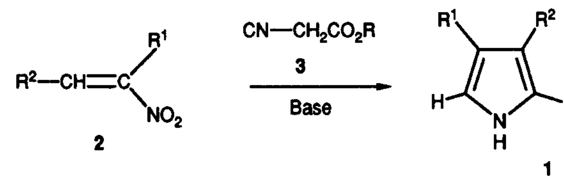
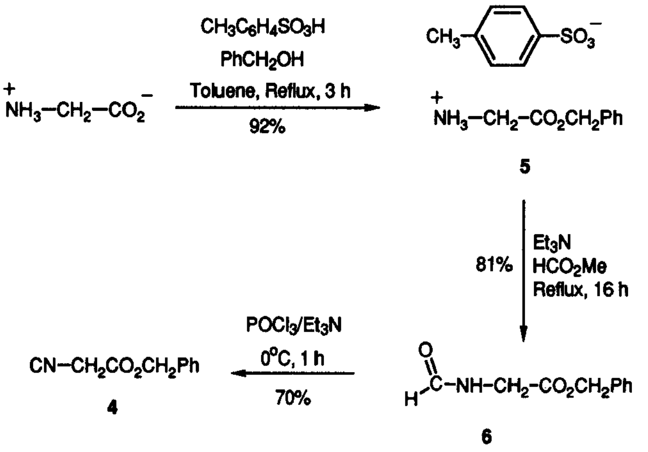
Benzyl esters of 5-unsubstituted pyrrole-2-carboxylic acids were prepared in excellent yields by the base-catalyzed condensation of benzyl isocyanoacetate with α-acetoxynitro compounds, or nitroalkenes, in refluxing tetrahydrofuran. These pyrrolic products are important intermediates in the synthesis of porphyrins and related compounds.

Esters of 5-unsubstituted pyrrole-2-carboxylic acids **1** are commonly used as intermediates in the synthesis of porphyrins,[3] expanded polypyrrolic macrocycles,[4] and open-chain tetrapyrroles.[3] Several methods[3,5,6] have been developed for the preparation of 5-unsubstituted pyrrole-2-carboxylates **1**, the most versatile of which was described relatively recently by Barton and Zard.[6] In this latter approach, the pyrrole nucleus is constructed by the condensation of nitroalkenes **2** with esters of isocyanoacetic acid **3** in the presence of a suitable non-nucleophilic base (Scheme 1). It is often convenient to generate the nitroalkenes in situ from the corresponding α-acetoxynitro compounds, and these reactants can be easily prepared in turn by base-catalyzed condensation of nitroalkanes with aldehydes (the Henry reaction), followed by reaction with acetic anhydride.[6] This methodology has been widely utilized in the preparation of methyl,[6,7] ethyl[6-10] and *tert*-butyl[6-8] pyrrole esters (**1**; R = Me, Et or *t*-Bu). Although the related benzyl esters (**1**; R = Bn) have not been prepared by this methodology, they are nonetheless particularly important intermediates in porphyrin synthesis[3] and we have made extensive use of these compounds in the preparation of naturally occurring sedimentary porphyrins.[11-13] In the present study, the Barton–Zard protocol has been extended to the synthesis of these valuable intermediates by using benzyl isocyanoacetate (**4**).



Scheme 1

Benzyl isocyanoacetate has previously been prepared by the dehydration of benzyl *N*-formylglycinate with phosgene or phosphorus oxychloride in triethylamine[14] and by the esterification of isocyanoacetic acid with benzyl bromide.[15] In this study, benzyl isocyanoacetate (**4**) was prepared in three steps from glycine (Scheme 2). Esterification of glycine with benzyl alcohol and a molar equivalent of *p*-toluenesulfonic acid gave the corresponding benzyl ester **5** as the *p*-toluenesulfonate salt. Reaction with methyl formate and triethylamine afforded benzyl *N*-formylglycinate (**6**) and subsequent dehydration with phosphorus oxychloride–triethylamine[16] then gave **4**. Excellent overall yields were obtained, as long as intermediates **5** and **6** were not rigorously purified.



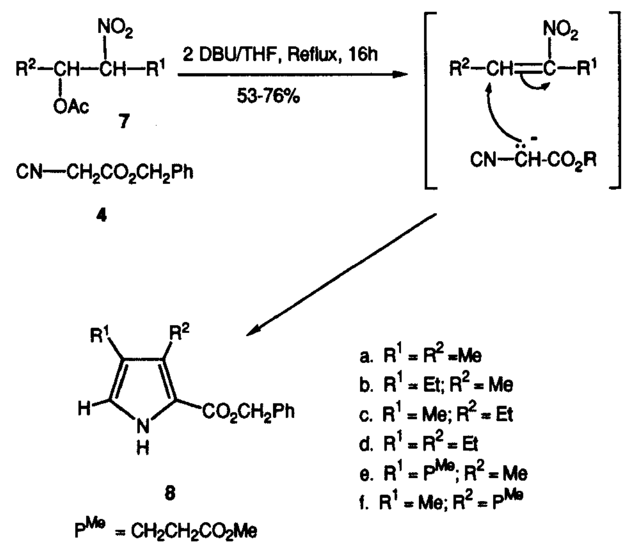
Scheme 2

Benzyl isocyanoacetate was condensed with α-acetoxynitro compounds **7**[6,9] in the presence of two equivalents of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in tetrahydrofuran to give the corresponding pyrrole esters **8a–f** (Scheme 3). In most cases, good yields of the α-unsubstituted pyrroles were obtained when the reaction was carried out at room temperature for 16 hour. However, superior and more reproducible results were obtained when the reaction was carried out under reflux, particularly in the case of **8f**. Benzyl isocyanoacetate was also found to condense with 1-nitrocyclohexene in the presence of one equivalent of DBU to give the tetrahydroisoindole **9** (Scheme 4), again in excellent yield. Pyrroles **8b**, **8c**, **8d** and **8e** were generally isolated as oils, although **8b** and **8c** could be induced to crystallize as low melting point solids (Table).

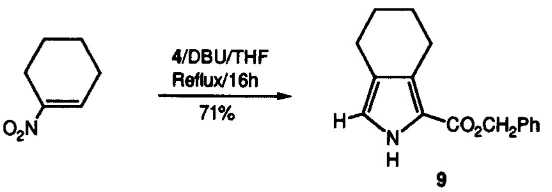
Table. Synthesis of Pyrroles from Benzyl Isocyanoacetate

	Yield[a] (%)	mp (°C)	Lit. mp (°C)
8a	72	74–76[b,c]	73–74[17a,b]; 73–75[17c]
8b	74	28–30[b,c,d]	31–32[18]
8c	76	35–36[b,c,d]	46.5–47[19a]; oil[19b]
8d[g]	74	oil[d]	–
8e	60[e]	oil[b]	41–42[20a]; 42.5–44.5[20b]; oil[13a]
8f	53	60.5–61[b,f]	57–58[21]
9	71	90–91[b,c]	88–90[7]; 91–92[10]

[a] Based on pure isolated material.
[b] Samples of synthetic pyrroles prepared by literature methods[7,17-21] were indistinguishable (IR, mp, NMR) from the compounds prepared in this study.
[c] Crystallized from hexane.
[d] Chromatographed on silica gel with 50% hexane–toluene.
[e] Reaction of **7e** (1.33 g) with benzyl isocyanoacetate (1.00 g) and 2 equivalents of DBU in 40% v/v *i*-PrOH/ THF (5 mL) at r.t. for 16 h gave **8e** (1.20 g) in 70% yield.
[f] Recrystallized from CH_2Cl_2–hexane.
[g] Satisfactory microanalysis obtained: C − 0.3, H − 0.22, N + 0.12.



Scheme 3



Scheme 4

This study provides a convenient route to benzyl esters of 5-unsubstituted pyrrole-2-carboxylates and should find wide application in the synthesis of porphyrins and related systems.

All reagents were purchased from Aldrich Chemical Co. and used without further purification. Silica gel (70–230 mesh, 60 A) for column chromatography was obtained from Aldrich Chemical Co., and columns were prepared by slurry packing. Melting points were determined on a Thomas Hoover capillary melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 1600 Series FT-IR Spectrometer and NMR spectra were obtained on a Varian Gemini-300 NMR spectrometer.

Benzyl Isocyanoacetate (4):

Benzyl glycinate p-toluenesulfonate (**5**):

In a 1 L three-necked round-bottom flask fitted with a mechanical stirrer, an addition funnel, and a reflux condenser was placed glycine (75.20 g), *p*-toluenesulfonic acid monohydrate (194.0 g), and benzyl alcohol (200 mL). The mixture was heated under gentle reflux, with the aid of an oil bath, for 1 hr. Toluene (200 mL) was placed in the addition funnel, and a Dean–Stark apparatus attached to the flask. Approximately 50 mL of toluene was added, and then the remaining toluene added over a period of 15 min. The resulting solution was refluxed for 2 hr, and approximately 35 mL of H_2O azeotropically removed. The mixture was poured into an 800 mL beaker and cooled in ice. The resulting precipitate was filtered, washed with anhyd. Et_2O, and dried under vacuum overnight to yield benzyl glycinate *p*-toluenesulfonate as white crystals; yield: 311.4 g (92 %); mp 116–125 °C (Lit.[22] mp 133–135 °C).

^{1}H NMR ($CDCl_3$): δ = 2.21 (3 H, s, CH_3), 3.69 (2 H, s, CH_2N), 4.96 (2 H, s, CH_2Ph), 6.96 (2 H, d, J = 8 Hz, 2 × tolyl *m*-H), 7.16–7.22 (5 H, m, Ph), 7.66 (2 H, d, J = 8 Hz, 2 × tolyl *o*-H), 8.08 (1 H, s, NH).

Benzyl N-formylglycinate (**6**):

In a 1000 mL three-necked round-bottom flask fitted with a pressure-equalizing addition funnel, and an efficient reflux condenser with a cold finger was placed benzyl glycinate *p*-toluenesulfonate (56.0 g) and methyl formate (84 mL). The suspension was stirred under reflux, while Et_3N (25 mL) was added over a period of 10 min and the resulting solution refluxed overnight. H_2O (600 mL) was added to the solution, and the mixture extracted with $CHCl_3$ (3 × 100 mL). The extracts were combined, and washed with 5 % aq $NaHCO_3$ solution (150 mL) and H_2O (150 mL). The organic layer was dried (Na_2SO_4) and the solvent evaporated under reduced pressure to yield benzyl *N*-formylglycinate as a yellow oil; yield: 26.03 g (81 %).

IR (neat): ν = 3035 (st, sh, NH), 1748, 1674 (st, sh, C=O) cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 4.07 (2 H, d, J = 5.6 Hz, $-C\underline{H}_2NH$), 5.16 (2 H, s, $-CH_2Ph$), 6.80 (1 H, br, NH), 7.34 (5 H, s, Ph), 8.18 (1 H, s, CHO).

In a 1 L three-necked round-bottom flask fitted with a pressure-equalizing addition funnel, a reflux condenser with a $CaCl_2$ drying tube, and a thermometer was placed benzyl *N*-formylglycinate (25.0 g), Et_3N (44 mL), and CH_2Cl_2 (200 mL). The resulting solution was cooled to 0 °C and $POCl_3$ (12.0 mL) was added, maintaining the temperature between 0–2 °C. Once the addition was complete, the solution was allowed to stir at 0 °C for 1 h. A solution of anhydr. Na_2CO_3 (26.0 g) in H_2O (120 mL) was added to the stirred mixture while maintaining the temperature below 30 °C. The biphasic mixture was stirred for 30 min at r.t., after which H_2O was added to bring the total aq volume to 400 mL. The aq layer was separated and extracted with CH_2Cl_2 (2 × 100 cm^{-1}). The CH_2Cl_2 solutions were combined, washed with H_2O (100 mL), and dried (K_2CO_3). The solution was filtered through Celite, the solvent evaporated under reduced pressure and the residue vacuum distilled to yield benzyl isocyanoacetate as a pale yellow oil; yield: 15.98 g (70 %); bp 110–120 °C at 0.075 Torr (Lit. bp[39] 110–120 °C at 0.05 Torr).

IR (neat): ν = 2163 (st, sh, C≡N), 1756 (st, sh, C=O) cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 4.21 (2 H, s, N-CH_2), 5.22 (2 H, s, CH_2Ph), 7.36 (5 H, s, Ph).

Benzyl 3,4-Dimethylpyrrole-2-carboxylate (8a); Typical Procedure: DBU (1.65 g) was added dropwise to a stirred solution of 2-acetoxy-3-nitrobutane (0.92 g) and benzyl isocyanoacetate (1.00 g) in THF (6 mL), maintaining the temperature of the reaction mixture between 20–30 °C throughout. The reaction flask was placed in an oil bath that had been preheated to 75 °C, keeping the liquid level in the flask slightly above the level of the oil, and the reaction mixture stirred under reflux for 16 h. The mixture was diluted with $CHCl_3$ (20 mL) and washed with 5 % HCl (25 mL). The aq phase was extracted with $CHCl_3$ (20 mL) and the combined organic phases evaporated under reduced pressure. The residue was chromatographed on silica gel eluting with toluene, and the product fractions crystallized from hexane to yield **8a** as white crystals; yield: 0.94 g (72 %); mp 74–76 °C (Lit. mp 73–74 °C;[17a,b] 73–75 °C[17c]).

IR (Nujol): ν = 3319 (st, sh, NH), 1670 (st, sh, C=O) cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 2.00 (3 H, s, 4-CH_3), 2.28 (3 H, s, 3-CH_3), 5.30 (2 H, s, $-CH_2Ph$), 6.65 (1 H, d, J = 2.3 Hz, 5-H), 7.25–7.4 (5 H, m, Ph), 8.75 (1 H, br, NH).

^{13}C NMR ($CDCl_3$): δ = 9.93, 10.38 (2 × pyrrole-CH_3), 65.62 (OCH_2), 118.93 (C-2), 120.45 (C-5), 120.72 (C-3), 127.17 (*o*- and *p*-Ph), 128.11 (*m*-Ph), 128.58 (C-4), 136.53 (Ph C_{att}), 161.40 (C=O).

Benzyl 4-Ethyl-3-methylpyrrole-2-carboxylate (**8b**):

IR (Nujol): ν = 3300 (st, sh, NH), 1687 (st, sh, C=O) cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.16 (3 H, t, J = 7.5 Hz, $CH_2C\underline{H}_3$), 2.30 (3 H, s, CH_3), 2.42 (2 H, q, J = 7.5 Hz, $C\underline{H}_2CH_3$), 5.30 (2 H, s, $-CH_2Ph$), 6.65 (1 H, d, J = 2.8 Hz, 5-H), 7.3–7.4 (5 H, m, Ph), 8.8 (1 H, br, NH).

^{13}C NMR ($CDCl_3$): δ = 10.30, 14.53, 18.21, 65.59 (OCH_2), 119.00, 119.37 (C-5), 126.39, 127.68, 128.08 (*o*- and *p*-Ph), 128.54 (*m*-Ph), 136.58 (Ph C_{att}), 161.44 (C=O).

Benzyl 3-Ethyl-4-methylpyrrole-2-carboxylate (**8c**):

IR (Nujol): ν = 3313 (st, sh, NH), 1678 (st, sh, C=O) cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.11 (3 H, t, J = 7.5 Hz, $CH_2C\underline{H}_3$), 2.02 (2 H, s, pyrrole-CH_3), 2.76 (2 H, q, J = 7.5 Hz, $C\underline{H}_2CH_3$), 5.29 (2 H, s, $-CH_2Ph$), 6.63 (1 H, d, J = 2.5 Hz, 5-H), 7.3–7.4 (5 H, m, Ph), 8.8 (1 H, br, NH).

^{13}C NMR (CDCl$_3$): δ = 9.77 (pyrrole-CH$_3$), 15.15 ($CH_2\underline{C}H_3$), 18.26 (pyrrole-CH$_2$), 65.69 (OCH$_2$), 118.29, 119.97, 120.72 (C-5), 128.13 (*o*- and *p*-Ph), 128.57 (*m*-Ph), 133.73 (C-4), 136.50 (Ph C$_{\text{att}}$), 161.26 (C=O).

Benzyl 3,4-Diethylpyrrole-2-carboxylate (**8d**):

IR (neat): ν = 3325 (st, NH), 1673 (st, sh, C=O) cm^{-1}.

^{1}H NMR (CDCl$_3$): δ = 1.12 (3 H, t, J = 7.5 Hz), 1.17 (3 H, t, J = 7.5 Hz) (2 × $CH_2C\underline{H}_3$), 2.44 (2 H, q, J = 7.5 Hz, 4-CH$_2$), 2.76 (2 H, q, 7.5 Hz, 3-CH$_2$), 5.30 (2 H, s, OCH$_2$), 6.64 (1 H, d, J = 2.8 Hz, 5-H), 7.3–7.4 (5 H, m, Ph), 8.9 (1 H, br, NH).

^{13}C NMR (CDCl$_3$): δ = 14.94, 15.58 (2 × $CH_2\underline{C}H_3$), 18.00, 18.22 (2 × $\underline{C}H_2CH_3$), 65.72 (OCH$_2$), 118.34, 119.68 (C-5), 127.02, 128.16 (*o*- and *p*-Ph), 133.09, 136.53 (Ph C$_{\text{att}}$), 161.33 (C=O).

Benzyl 4-(2-Methoxycarbonylethyl)-3-methylpyrrole-2-carboxylate (**8e**):

IR (neat): ν = 3328 (st, br, NH), 1736, 1688 (st, sh, C=O) cm^{-1}.

^{1}H NMR (CDCl$_3$): δ = 2.30 (3 H, s, pyrrole-CH$_3$), 2.52 (2 H, t, J = 7.5 Hz, pyrrole-CH$_2$), 2.73 (2 H, t, J = 7.5 Hz, CH$_2$CO), 3.65 (3 H, s, OCH$_3$), 5.29 (2 H, s, OCH$_2$), 6.66 (1 H, d, J = 2.8 Hz, 5-H), 7.3–7.5 (5 H, m, Ph), 9.0 (1 H, br, NH).

^{13}C NMR (CDCl$_3$): δ = 10.31 (pyrrole-CH$_3$), 20.47 (pyrrole-CH$_2$), 34.78 ($\underline{C}H_2CO$), 51.63 (OCH$_3$), 65.74 (OCH$_2$), 119.16, 120.31 (C-2 and C-5), 123.79 (C-4), 126.44 (C-3), 128.14 (*o*- and *p*-PH), 128.59 (*m*-Ph), 136.44 (Ph C$_{\text{att}}$), 161.51 (pyrrole C=O), 173.61 (methyl ester C=O).

Benzyl 4,5,6,7-Tetrahydro-2H-isoindole-1-carboxylate (**9**):

IR (Nujol): ν = 3316 (st, sh, N–H), 1664 (st, sh, C=O) cm^{-1}.

^{1}H NMR (CDCl$_3$): δ = 1.71 (4 H, m, 5,6-CH$_2$), 2.53 (2 H, t, 4-CH$_2$), 2.82 (2 H, t, 7-CH$_2$), 5.29 (2 H, s, –$C\underline{H}_2Ph$), 6.63 (1 H, d, J = 2.5 Hz, 5-H), 7.25–7.4 (5 H, m, Ph), 8.8 (1 H, br, NH).

^{13}C NMR (CDCl$_3$): δ = 21.91, 23.21, 23.34 (4 × CH$_2$), 65.52 (OCH$_2$), 117.42 (C-1), 119.01 (C-3), 122.32 (C-3a), 128.00 (C-7a, *o*- and *p*-Ph), 128.53 (*m*-Ph), 136.55 (Ph C$_{\text{att}}$), 161.25 (C=O).

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(1) Results taken, in part, from Bellettini, J. R. M. S. Thesis, Illinois State University, 1992.

(2) Results presented, in part, at the 25th Great Lakes Joint Regional American Chemical Society Meeting, Milwaukee, Wisconsin, June 1992. Bellettini, J. R., Lash, T. D. *Program and Abstracts*, 191A.

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