Regioselective Synthesis of 5-Unsubstituted Benzyl Pyrrole-2-carboxylates from Benzyl Isocyanoacetate

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A general synthesis of 5-unsubstituted benzyl pyrrole-2-carboxylates was developed based on the reaction of β-nitroacetates with benzyl isocyanoacetate. The advantage of this route over other pyrrole syntheses was the regiochemical control of the substitution pattern on the pyrrole ring.

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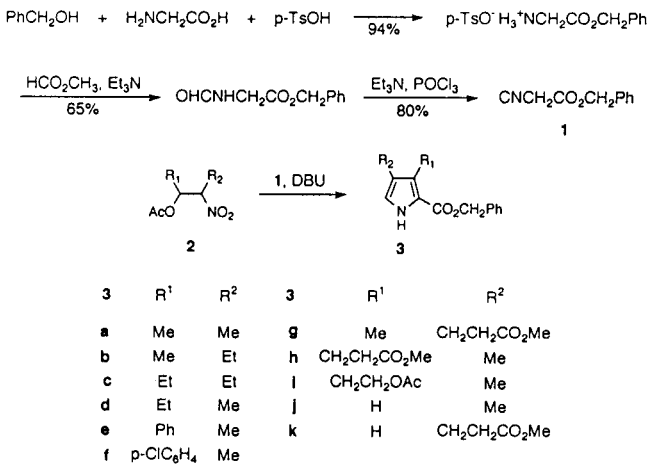
The synthesis of pyrroles gains its importance since they are the dominant subunits in the pigments of life. In particular, 5-unsubstituted benzyl pyrrole-2-carboxylates **3** are ideal building blocks for synthesis of such pigments since they are unsubstituted in the 5-position and the benzyl ester may be deprotected under mild conditions by hydrogenolysis [1]. However, the synthesis of **3** can rarely be carried out directly by conventional methods. They have traditionally been synthesized by rather lengthy schemes which involve th Knorr reaction, base-catalyzed transesterification and demethylation at the 5-position. Demethylation is generally carrried out by trichlorination with sulfuryl chloride, hydrolysis, and decarboxylation (standard degradation of Knorr's pyrrole) [2]. Although this method is effective for the preparation of **3** with simple alkyl substituents, it is difficult to prepare pyrroles with functional substituents and also difficult to control the regiochemistry of the 3,4 positions by this standard method. Recently, a new method for preparing 5-unsubstituted pyrrole esters, using ethyl (or *t*-butyl) isocyanoacetate and nitroalkenes, has been developed [3]. Hence, the reaction of nitroalkenes with benzyl isocyanoacetate **1** could be expected to be the simplest method to form **3**. Isonitrile **1** could also be expected to be a very useful reagent for the synthesis of amino acids and various heterocyclic compounds [4]. However, there have been reported only a few methods to prepare **1** and it has not been widely used in organic synthesis. In the literature methods, **1** was prepared by the reaction of isocyanoacetic acid with benzyl bromide [5] or dehydration of *N*-formylglycine benzyl ester [6]. These methods are not suitable to prepare a large quantity of **1**, for relatively expensive isocyanooacetic acid or benzyl bromide are required for these methods. We report here a modified procedure for the preparation of **1** and the regioselective synthesis of **3** using **1** and β-nitroacetates **2**.

N-Formylglycine benzyl ester was prepared by formylation of glycine benzyl ester with methyl formate and triethylamine. Glycine benzyl ester was readily prepared by the reaction of glycine with benzyl alcohol in the presence of *p*-toluenesulfonic acid [7]. Glycine benzyl ester can also be prepared by the use of anhydrous hydrochloride instead of *p*-toluenesulfonic acid, but *p*-toluenesulfonic acid is more easily handled in a laboratory than anhydrous hydrochloric acid. Benzyl isocyanoacetate was readily prepared in 80% yield by dehydration of *N*-formylglycine benzyl ester with phosphorus oxychloride [4]. Phosgene, diphosgene and triphogene may also be used for this conversion [8]. Benzyl pyrrole-2-carboxylates **3** were readily prepared by the reaction of **1** with β-nitroacetates **2** in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). When R^1 and R^2 were not H, the yields of **3** were in the range of 70-80%, but the yields of **3** were reduced to 40-50% when R^1 was H. The results are summarized in Table 1. As the requisite β-nitroacetates **2** are available from aldehydes (R^1CHO) and nitroalkanes ($R^2CH_2NO_2$), various substituents (R^1 and R^2) can be readily introduced regioselectively at the 3 and 4 positions of **3** by this method.

Scheme I



3	R^1	R^2	3	R^1	R^2
a	Me	Me	g	Me	$CH_2CH_2CO_2Me$
b	Me	Et	h	$CH_2CH_2CO_2Me$	Me
c	Et	Et	i	CH_2CH_2OAc	Me
d	Et	Me	j	H	Me
e	Ph	Me	k	H	$CH_2CH_2CO_2Me$
f	p-ClC_6H_4	Me			

The pyrroles prepared by this method are useful intermediates for the synthesis of porphyrins or related substances. Although some pyrroles in Table 1 can be prepared by conventional methods involving a multistep procedure [9-15], the present method has several merits over the conventional ones. The most important merit lies in its flexibility of the introduction of R^1 and R^2. As pyrroles

Table I

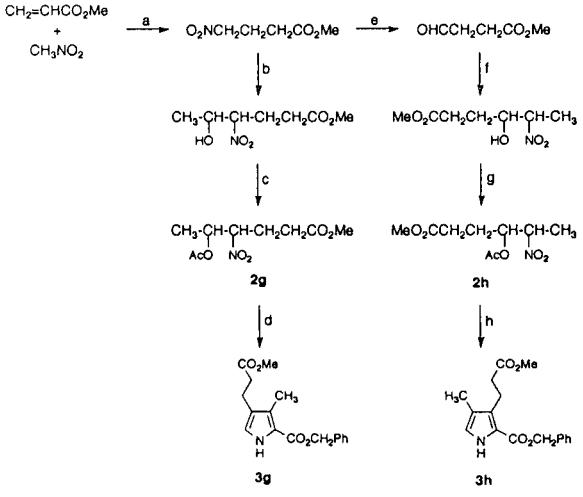
Benzyl Pyrrole-2-carboxylates 3 Prepared

Entry 3	Yield[a] (%)	Mp (°C) (Lit Mp)	IR ν (cm^{-1}) C=O	EIMS (22.5 eV) m/z (%)	^{1}H-NMR (CDCl^3) δ, J (Hz)	Molecular Formula	Calcd/Found C	H	N
a	71	78-80 (73-74) [9]	1650	229 (M^+, 33), 122 (16), 91 (100)	1.95 (s, 3H), 2.25 (s, 3H), 5.20 (s, 2H), 6.55 (d, 1H, J = 2), 7.32 (m, 5H) 9.12 (1H, NH)	$C_{14}H_{15}NO_2$	73.33 72.99	6.60 6.68	6.11 6.11
b	70	oil (31-32) [10]	1650	243 (M^+, 100), 228 (30), 152 (42), 91 (100)	1.15 (t, 3H, J = 7.5) 2.29 (s, 3H), 2.41 (q, 2H, J = 7.5), 5.29 (s, 2H), 6.04 (d, 1H, J = 3), 7.31 (m, 5H), 8.90 (1H, NH)	$C_{15}H_{17}NO_2$	74.04 73.99	7.05 7.09	5.76 5.66
c	71	oil	1640	257 (M^+, 21), 166 (33), 146 (10), 91 (100)	1.10 (t, 3H, J = 7), 1.13 (t, 3H, J = 7), 2.21-2.95 (m, 4H), 5.26 (s, 2H), 6.65 (d, 1H, J = 3), 7.32 (m, 5H), 9.19 (1H, NH)	$C_{16}H_{19}NO_2$	74.68 74.33	7.44 7.30	5.44 5.40
d	74	oil (oil) [11]	1660	243 (M^+, 66), 152 (100), 134 (50), 91 (100)	1.11(t, 3H, J = 7), 2.0 (s, 3H), 2.76 (q, 2H, J = 7), 5.30 (s, 2H), 6.61 (d, 1H, J = 3), 7.38(m, 5H), 9.04 (1H, NH	$C_{15}H_{17}NO_2$	74.04 73.85	7.05 7.02	5.76 5.60
e	74	78-81	1650	291 (M^+, 100), 184 (28), 91 (100)	1.97 (s, 3H), 5 15 (m, 2H) 675 (d, 1H, J = 3), 7.25-7.35 (m, 10H) 9.14 (1H NH)	$C_{19}H_{17}NO_2$	78.32 78.00	5.89 5.74	4.81 4.52
f	74	152-153	1670	325 (M^+, 100), 218 (24), 154 (30), 91 (100)	1.96 (s, 3H), 5.15 (s, 2H), 6.78 (d, 1H, J = 3), 7.21-7.31 (m, 9H), 8.99 (1H, NH)	$C_{19}H_{16}NO_2Cl$	70.05 69.79	4.95 5.01	4.30 4.30
g	73	42.5-43 (42.5-44.5) [12] (41-42) [13]	1680	301 (M^+, 100), 228 (100), 194 (43), 91 (100)	2.25 (s, 3H), 2.54-2.72 (m, 4H), 3.64 (s, 3H), 5.26 (s, 2H), 6.69 (d, 1H, J = 3), 7.36 (m, 5H), 8.92 (1H, NH)	$C_{17}H_{19}NO_4$	67.76 67.46	6.35 6.21	4.65 4.62
h	69	56-57 (57-58) [14]	1670	301 (M^+, 24), 210 (36), 178 (100), 91 (100)	2.03 (s, 3H), 2.50 (t, 2H, J = 7), 3.09 (t, 2H, J = 7), 3.62 (s, 3H), 5.28 (s, 2H), 6.63 (d, 1H, J = 3), 7.38 (m, 5H), 9.06 (1H, NH)	$C_{17}H_{I9}NO_4$	67.76 67.48	6.35 6.29	4.65 4.56
i	82	oil	1665	301 (M^+, 4), 242 (9), 241 (41), 91 (100)	2.01 (s, 3H), 2.31 (s, 3H), 2.72 (t, 2H, J = 7), 5.30 (s, 2H), 6 69 (d, 1H, J = 3), 7.36 (m, 5H), 9.24 (1H, NH)	$C_{17}H_{19}NO_4$	67.76 67.48	6.35 6.40	4.65 4.65
j	41	50-51 (44.5-45.5) [15]	1710	215 (M^+, 100), 108 (48), 91 (100)	2.09 (s, 3H), 5.28 (s, 2H), 6.68 (m, 1H), 6.77 (m, 1H), 7.27-7.42 (m, 5H), 9.24 (1H, NH)	$C_{13}H_{13}NO_2$	72.54 72.32	6.09 6.05	6.51 6.26
k	48	oil	1680	287 (M^+, 100), 214 (63), 180 (44), 91 (100)	2.5-2.9 (m, 4H), 3.67 (s, 3H), 5.28 (s, 2H), 6.75 (s, 1H), 6 89 (d, 1H), 7.35 (m, 5H), 9.50 (1H, NH)	$C_{16}H_{17}NO_4$	66.94 66.78	5.96 5.88	4.88 4.96

[a] Yield of pure isolated products.

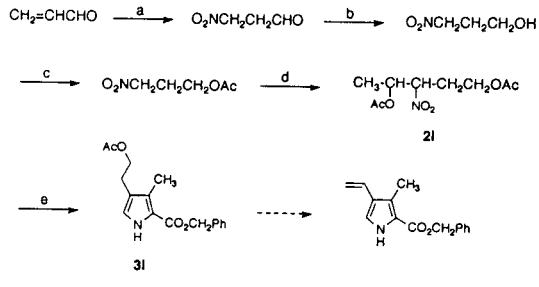
substituted with a propionic acid or a vinyl group are involved in various naturally occurring linear- and macrocyclic tetrapyrroles, the preparation of **3g, 3h,** and **3i** is important in porphyrin chemistry. The preparation of these pyrroles by the traditional methods and required an extensive multistep procedure beginning with benzyl acetoacetate [9]. The present method can simplify the procedure for the preparation of such pyrroles as shown in Schemes II and III. For example, pyrroles **3g** and **3h** were directly prepared in about 70% yield by the reaction of **2g** and **2h** with **1**, respectively. The requisite **2g** and **2h** were readily prepared by a simple method starting from the Michael addition product of nitromethane to methyl acrylate [16]. Pyrrole **3i**, a precursor of 4-vinylpyrrole, was also readily prepared in 82% yield by the reaction of **2i** and **1** as shown in Scheme III. The requisite **2i** was prepared from 3-nitropropanol *via* acetylation followed by nitro-aldo condensation with acetaldehyde. 3-Nitropropanol was prepared according to the literature method starting from acrolein [17]. Thus, the synthetic method based on the reaction of benzyl isocyanoacetate with β-nitroacetate provides a very convenient route to benzyl pyrrole-2-carboxylates substitued with various functional groups. The flexibility of the synthetic route to β-nitroacetates enhances the utility of this method, which may be widely used in porphyrin synthesis.

Scheme II



a) DBU, b) CH_3CHO, DBU, 84%, c) Ac_2O, catalytic H_2SO_4, >99%, d) 1,DBU, e) $KMnO_4$, $MgSO_4$, 0°C, f) $C_2H_5NO_2$, DBU, 85%, g) Ac_2O, catalytic H_2SO_4, 94%, h) 1, DBU

Scheme III



a) $NaNO_2$, AcOH, b) $(CH_3)_2SBH_3$, Et_2O, c) Ac_2O, catalytic H_2SO_4, d) 1) CH_3CHO, DBU, 82%, 2) Ac_2O, catalytic H_2SO_4, >99%, e) 1, DBU

EXPERIMENTAL

The ^1H nmr spectra were measured on a JEOL JNM-JSX 270 spectrometer (270 MHz) in deuteriochloroform. Chemical shifts of the protons are reported in δ ppm relative to tetramethylsilane as an internal standard. The ir spectra were recorded on a Hitachi 270-30 spectrometer. Mass spectra were measured on a Hitachi M-80B instrument operating at 20 eV. Microanalyses were performed on a Perkin-Elmer 240C elementary analyzer. These analyses were all performed at the Advanced Instrumentation Center for Chemical Analysis, Ehime University.

Benzyl Isocyanoacetate (**1**).

p-Toluenesulfonic acid salt of glycine benzyl ester was prepared by modification of a literature procedure [7]. A mixture of glycine (15.1 g, 0.2 mole), *p*-toluenesulfonic acid monohydrate (45.6 g, 0.24 mole) and benzyl alcohol (140 ml) was heated at 110-120° for 5 hours. The resulting solution was cooled to 0-5° and 800 ml of dry diethyl ether was added. The precipitated white solid was filtered to afford *p*-toluenesulfonic acid benzyl ester (63.2 g, 94% yield), which was used for the next step without further purification. To a stirred suspension of *p*-toluenesulfonic acid salt of glycine benzyl ester (67.5 g, 0.2 mole) in methyl formate (150 ml) was added triethylamine (22.3 g, 0.2 mole). The resulting mixture was stirred and heated under reflux for 20 hours, cooled to room temperature, and filtered. The filtrate was concentrated on a rotary evaporator to give the clear oil, which was purified by short silica gel column chromatography eluted by dichloromethane, yielding 25.1 g (65% yield) of *N*-formylglycine benzyl ester. A solution of *N*-formylglycine benzyl ester (19.3 g, 0.1 mole) and triethylamine (25.0 g, 0.25 mole) in 200 ml of dichloromethane was cooled at 0° with an ice-salt bath under a nitrogen atmosphere. To the resulting solution was added phosphorus oxychloride (15.3 g, 0.1 mole) dropwise over 15-20 minutes with stirring under a nitrogen atmosphere while the temperature was kept at 0°. The mixture was stirred at 0° for an additional 1 hour. To the stirred mixture, a solution of anhydrous sodium carbonate (20 g) in 90 ml of water was added dropwise at a rate such that the temperature of the mixture was maintained at 25-30°. The mixture was stirred for another 30 minutes, after which 130 ml of water was added. The aqueous layer was separated and extracted with dichloromethane. The dichloromethane solutions are combined, washed with saturated sodium chloride solution, and dried over anhydrous potassium carbonate. Evaporation of the solvent and distillation of the residue gave 14 g (80% yield) of benzyl isocyanoacetate, bp 120° (0.5 mm Hg), lit 130° (0.9 mm Hg) [5]; ^1H nmr: δ 4.25 (s, 2H), 5.20 (s, 2H), 7.40 (m, 5H).

General Procedure for the Synthesis of Nitroalcohols and β-Nitroacetate (**2**).

To a stirred solution of nitro compounds (10 mmoles) and aldehydes (10 mmoles) in 5 ml of tetrahydrofuran was added DBU (0.1 g) at 10-20°. The resulting mixture was stirred at room temperature for 5-10 hours depending on the substrates. The mixture was then diluted with ether and water. The organic layer was washed with saturated aqueous sodium hydrogencarbonate and brine. The aqueous layers were back-extracted with diethyl ether, dried with magnesium sulfate, filtered, and concentrated *in vacuo* to afford oils. The crude nitroalcohols were taken up in dichloromethane and treated with acetic anhydride and sulfonic acid (0.1 g). After being stirred for 1-3 hours at room temperature, the reaction mixture was poured into water. The organic layer was washed with aqueous sodium hydrogencarbonate and then concentrated. Purification by short column chromatography (silica gel, hexane-ethyl acetate) gave **2** in 80-90% yield, which was used directly in the next step. Most of the compounds **2** are known except for **2i**.

Compound **2i** had ir (sodium chloride): 1720, 1540, 1360, 1220, 1030 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.33 (d, 3 H, J = 7.1 Hz), 2.05 (s, 3 H), 2.06 (s, 3 H), 2.03-2.26 and 2.29-2.54 (m, 2 H), 4.01-4.13 and 4.15-4.26 (m, 2 H), 4.67-4.79 (m, 1 H), 5.22-5.35 (m, 1 H).

Benzyl 3,4-Dimethylpyrrole-2-carboxylate (**3a**). Typical Procedure for 5-Unsubstituted Pyrroles.

To a solution of β-nitroacetate **2a** (2.42 g, 15 mmoles) and **1** (2.66 g, 15.2 mmoles) in 10 ml of tetrahydrofuran was added DBU (4.55 ml, 30.4 mmoles). The resulting mixture was stirred at room temperature for 10 hours, poured into water, and extracted with dichloromethane. The organic layer was dried over sodium sulfate and then concentrated. Purification by column chromatography (silica gel, hexane-ethyl acetate) gave **3a** (2.42 g) in 71%

yield, mp 78-80°; ir (potassium bromide): 3290, 1650, 1450, 1400, 1360, 1345, 1265, 1150, 1095, 765, 725, 690 cm^{-1}; ^1H nmr: δ 1.95 (s, 3 H), 2.25 (s, 3 H), 5.20 (s, 2 H), 6.55 (d, 1 H, J = 2 Hz), 7.32 (m, 5 H), 9.12 (broad 1 H, NH); ms: m/z 229 (M^+, 33), 122 (16), 91 (100).

Anal. Calcd. for $C_{14}H_{15}NO_2$: C, 73.33; H, 6.60; N, 6.11. Found: C, 72.99; H, 6.68; N, 6.11.

The pyrroles, **3b, 3c, 3d, 3e, 3f, 3g, 3h** and **3i** were prepared by the procedure described above.

Benzyl 4-Methylpyrrole-2-carboxylate (**3j**). Typical Procedure for 3,5-Unsubstituted Pyrroles.

A solution of 1-acetoxy-2-nitropropane **2j** (228 mg, 1.55 mmoles) in 5 ml of tetrahydrofuran was added in small portions over 30 minutes to a solution of isocyanide **1** (2.63 mg, 1.5 mmoles) and DBU (0.46 ml) in 3 ml of tetrahydrofuran. The resulting mixture was stirred at room temperature for 3 hours then worked up in the same way as in the preparation of **3a**, mp 50-51°; ir (potassium bromide): 3260, 1665, 1560, 1470, 1390, 1090, 965, 690 cm^{-1}; ^1H nmr: δ 2.09 (s, 3 H), 5.28 (s, 2 H), 6.68 (m, 1 H), 6.77 (m, 1 H), 7.27-7.42 (m, 5 H), 9.24 (broad, 1 H, NH); ms: m/z 215 (M^+, 100), 108 (48), 91 (100).

Anal. Calcd. for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.32; H, 6.05; N, 6.26.

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