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Synthesis of Pyrrole Derivatives Using Thioimidates

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Dimethyl acetylenedicarboxylate, ethyl propiolate, nitro olefins, or 2-nitroalkyl acetates react with thioimidate in the presence of organic bases to give the corresponding pyrroles in moderate-to-good yields.

A previous paper presented the synthesis of oxazoles and thiazoles by using imidothioates.$^{1)}$ As an extension of this work we intended to synthesize the pyrroles, starting from the stabilized imidothioate. Although many synthetic methods of pyrrole derivatives have been reported, due to their utility,$^{2)}$ the present method is a simple and effective procedure for the synthesis of pyrrole derivatives having a non-substituent in the 5-position or poly-substituents.

Imidothioates **1a** and **1b** were allowed to react with dimethyl acetylenedicarboxylate (DMAD) (**4a**) or ethyl propiolate (**4b**) in the presence of bases to afford the corresponding pyrrole derivatives in moderate yields (Scheme 1).

At a first experiment, some bases [*n*-BuLi, *t*-BuOK, EtONa, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), and potasium pivalate (*t*-BuCO$_2$K)] were examined for this reaction. The use of *t*-BuCO$_2$K as a sterically hindered base showed a successful result without the polymerization of **4a**. That is, **1a** was allowed to react with **4a** in the presence of *t*-BuCO$_2$K at 0—25 °C under stirring for 24 h to give a Michael addition product **2** in 34% yield together with a cyclized product **3** (7%). The main product **2** was then cyclized to **3** in 65% yield upon a treatment with DBU.

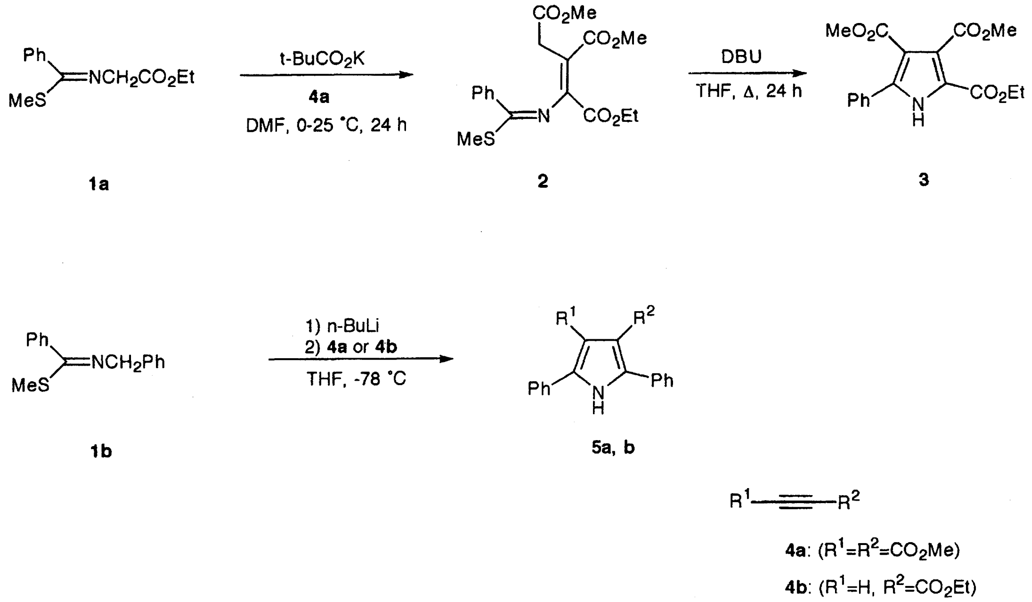
Imidothioate **1b** was successively treated with butyllithium and **4a** or **4b** to give the corresponding pyrroles, **5a** or **5b**, in the yields listed in Table 1.

Recently, Barton et al. have reported on a useful synthesis of pyrrole derivatives from the reaction of nitro olefins or 2-nitroalkyl acetates with 2-isocyano esters.$^{3a)}$

Table 1. Synthesis of Pyrroles **3**, **5a**, and **5b** Prepared

Imidothioates	4		Yield (**Product**)
	R^1	R^2	%
1a	CO$_2$Me	CO$_2$Me(**4a**)	29^a (**3**)
1b	CO$_2$Me	CO$_2$Me(**4a**)	45 (**5a**)
1b	H	CO$_2$Et(**4b**)	37 (**5b**)

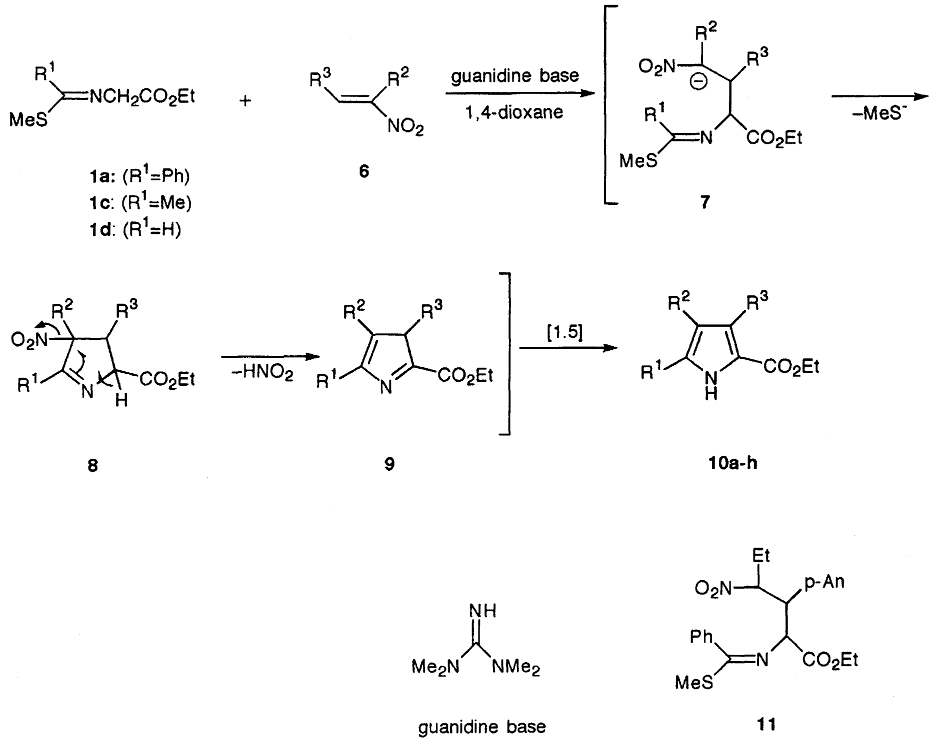
a) Overall yield was shown based on **1a**.



Scheme 1.

Table 2. Synthesis of Pyrroles **10a**—**h** Prepared

Imidothioates	Nitro olefins **6**		Conditions	Yield (**Product**)
R^1	R^2	R^3		%
Ph(**1a**)	p-MeOC$_6$H$_4$	Et	Δ, 4 h	84 (**10a**)
Me(**1c**)	p-MeOC$_6$H$_4$	Et	Δ, 3 d	52 (**10b**)
Me(**1c**)	Ph	Et	Δ, 3 d	47 (**10c**)
H (**1d**)	Ph	Et	Δ, 3 d	35 (**10d**)
Ph(**1a**)	Me	Et	R.t., 2 h then Δ, 4 h	52 (**10e**)
Me(**1c**)	Me	Et	R.t., 20 h then Δ, 48 h	12 (**10f**)
H (**1d**)	Me	Et	R.t., 20 h then Δ, 48 h	47 (**10g**)
Ph(**1a**)	Me	n-C$_5$H$_{11}$	R.t., 2 h then Δ, 4 h	69 (**10h**)



Scheme 2.

This reaction can give the pyrrole derivatives by using the imidothioate **1** in the place of the ill-smelling α-isocyanoesters, because *N*-(methylthio-methylene)glycine ethyl ester **1d** is synthetically equivalent to 2-isocyano esters.

Imidothioates **1a**, **1c**, and **1d** were allowed to react with 1-nitro-1-phenyl-1-butenes **6** in the presence of a guanidine base (1,1,3,3-tetramethylguanidine) under refluxing with 1,4-dioxane to afford the corresponding pyrrole derivatives, **10a**—**10h**, in 35—84% yields (Table 2).

In preparing **10a**, the reaction was performed at room temperature to give the corresponding intermediate **11** in 87% yield. The thus-obtained **11** was then treated with DBU to afford **10a** quantitatively. To obtain good yields of **10b**—**10h**, the reaction requires a long reaction time. For example, the yield of **10b** was 39% under refluxing for 1 d and 52% under refluxing for 3 d. It is known that 2-nitro-2-alkenes **6** are unstable to bases to give the polymers easily. Therefore, 2-nitro-2-alkenes **6** were generated in situ from the corresponding 1-(1-nitroethyl)alkyl acetates, and were used for preparing **10e**—**10h**.

The formation of **10** is considered as shown in Scheme 2: Carbanions generated from ethyl imidothioates (**1a**, **1c**, and **1d**) with a guanidine base react with **6** to give the adducts **7**, which can cyclize to **8** through an internal attack of the intermediate carbanion on the azomethine carbon. Then, **8** can change to **10** along with an elimination of nitrous acid, followed by aromatization via [1,5] sigmatropic shift of hydrogen.

The characterization of pyrroles prepared by the present method is summarized in Table 3.

The pyrroles produced here would be ideal building blocks for porphyrins and bile pigments,[3b)] because the use of **1d** gives 5-unsubstituted pyrroles, such as **10d** and **10g**, and the 2-position can be protected by an easily removable group, such as an ethoxycarbonyl. The substituents in the 3- and 4-positions originate from the readily variable nitro olefin components. In conclusion,

Table 3. Characterization of Pyrroles **3**, **5a**, **5b**, and **10a**—**h** Prepared

Compound	Mp °C	IR (KBr or neat) ν/cm^{-1}	^{1}H NMR (CDCl$_3$/TMS) δ	Molecular formula[a)]
3	114—115	3290, 2950, 1700	1.33 (3H, t, J=7.26 Hz), 3.96 (3H, s), 3.72 (3H, s), 4.28 (2H, q, J=7.26 Hz), 7.44—7.46 (3H, m), 7.54—7.58 (2H, m), 9.35 (1H, br).	$C_{16}H_{17}NO_6$ (331.3)
5a[4)]	146—147 (149—150)[4)]	3210, 2920, 1700	3.77 (6H, s), 7.36—7.45 (3H, m), 7.53—7.57 (2H, m), 8.58 (1H, br).	—[4)]
5b	158—158.5	3240, 1650, 1450 1240	1.28 (3H, t, J=7.25 Hz), 4.25 (2H, q, J=7.25 Hz), 7.02 (1H, d, J=2.97 Hz), 7.27—7.54 (6H, m), 7.64 (2H, d, J=1.32 Hz), 7.67 (2H, d, J=1.32 Hz), 8.55 (1H, br).	$C_{19}H_{17}NO_2$ (291.3)
10a	143.5—144.5	3250, 2920, 1650	0.92 (3H, t, J=7.58 Hz), 1.13 (3H, t, J=7.25 Hz), 2.55 (2H, q, J=7.58 Hz), 3.86 (3H, s), 4.15 (2H, q, J=7.25 Hz), 6.92—6.96 (2H, m), 7.26—7.55 (7H, m), 9.00 (1H, br).	$C_{22}H_{23}NO_3$ (349.4)
10b	127—128	3250, 2930, 1640	0.95 (3H, t, J=7.59 Hz), 1.13 (3H, t, J=7.25 Hz), 2.28 (3H, s), 2.34 (2H, q, J=7.59 Hz), 3.84 (3H, s), 4.13 (2H, q, J=7.25 Hz), 6.89—6.92 (2H, m), 7.21—7.25 (2H, m), 8.73 (1H, br).	$C_{17}H_{21}NO_3$ (287.4)
10c[5)]	153—154 (157.3—154)[5)]	3250, 2920, 1650	0.95 (3H, t, J=7.58 Hz), 1.09 (3H, t, J=7.25 Hz), 2.28 (3H, s), 2.33 (2H, q, J=7.58 Hz), 4.22 (2H, q, J=7.25 Hz), 7.29—7.35 (5H, m), 8.85 (1H, br).	—[5)]
10d	78.5—79	3250, 2920, 1650	1.08 (3H, t, J=7.58 Hz), 1.11 (3H, t, J=7.25 Hz), 2.40 (2H, q, J=7.58 Hz), 4.14 (2H, q, J=7.25 Hz), 6.79 (1H, d, J=2.96 Hz), 7.30—7.39 (5H, m), 9.02 (1H, br).	$C_{15}H_{17}NO_2$ (243.3)
10e	105—107	3220, 2950, 1640	1.37 (3H, t, J=7.14 Hz), 1.61 (3H, t, J=7.51 Hz), 2.36 (3H, s), 2.57 (2H, q, J=7.51 Hz), 4.33 (2H, q, J=7.14 Hz), 7.31—7.47 (5H, m), 8.79 (1H, br)	$C_{16}H_{19}NO_2$ (257.3)
10f[6)]	86.5—87 (89—90)[6)]	3250, 2920, 1650	1.04 (3H, t, J=7.58 Hz), 1.34 (3H, t, J=7.25 Hz), 2.20 (3H, s), 2.28 (3H, s), 2.38 (2H, q, J=7.58 Hz), 4.29 (2H, q, J=7.25 Hz), 8.55 (1H, br).	—[6)]
10g[7)]	Oil[7)]	3270, 2920, 1700	1.17 (3H, t, J=7.69 Hz), 1.35 (3H, t, J=7.26 Hz), 2.29 (3H, s), 2.43 (2H, q, J=7.69 Hz), 4.31 (2H, q, J=7.26 Hz), 6.67 (1H, d, J=2.99 Hz), 8.73 (1H, br).	—[7)]
10h	95.9—96	3200, 2900, 1640, 1430	0.84—1.63 (9H, m), 1.36 (3H, t, J=7.25 Hz), 2.35 (3H, s), 2.50—2.56 (2H, m), 4.32 (2H, q, J=7.25 Hz), 7.31—7.44 (5H, m), 8.78 (1H, br).	$C_{19}H_{25}NO_2$ (299.4)

a) Satisfactory microanalyses obtained: C, ± 0.14; H, ±0.16; N, ±0.10%.

the imidothioates are useful reagents for the pyrroles synthesis.

Experimental

The melting points were determined using a Yamato Melting Point Apparatus MP-21 and are uncorrected. ^{1}H NMR spectra were recorded on a JEOL JNM-FX-270 spectrometer. IR spectra were recorded on a Hitachi 215 spectrophotometer. Mass spectra were obtained on a JEOL JMS-HX 110A mass spectrometer. Wakogel B-5F and C-200 were used for preparative TLC (PTLC) and column chromatography, respectively.

Methyl *N*-[1-Ethoxycarbonyl-2,3-bis(methoxycarbonyl)-1-propenyl]benzimidothioate (2). Potassium pivalate (254 mg, 1.10 mmol) was added to a solution of thioimidate **1a**[1)] (237 mg, 1.00 mmol) in DMF (3mL). Then, DMAD (0.37 mL, 3.0 mmol) was added dropwise at 0 °C. The reaction mixture was first stirred at this temperature for 30 min, and then at room temperature overnight. The reaction mixture was diluted with benzene, and washed successively with water, aqueous $NaHCO_3$, and water. The benzene extract was dried over Na_2SO_4, concentrated under reduced pressure, and purified by column chromatography (EtOAc : hexane, 1 : 2) to give 130 mg of **2** (oil, 34%) together with 22.6 mg of **3** (7%). IR (neat) 2930, 1700, 1600 cm^{-1}. ^{1}H NMR δ=1.13 (3H, t, J=7.25 Hz), 2.48 (3H, s), 3.28 (2H, s), 3.59 (3H, s), 3.69 (3H, s), 3.99 (2H, q, J=7.25 Hz), 7.38—7.44 (3H, m), 7.60—7.63 (2H, m). MS (FAB): 380 (M+1)$^+$. Found: C, 56.93; H, 5.45; N, 3.63 %. Calcd for $C_{18}H_{21}NO_8S$: C, 56.98; H, 5.58; H, 3.69%.

2-Ethyl 3,4-Dimethyl 5-Phenylpyrrole-2,3,4-tricarboxylate (3). Compound **2** (176 mg, 0.46 mmol) was refluxed with DBU (0.21 mL, 1.4 mmol) in THF (1.5 mL) for 24 h. The reaction mixture was first washed with 1 M-HCl (1 M=1 mol dm^{-3}), and then with water, dried over Na_2SO_4, and concentrated to give crude **3**, which was then purified by PTLC (EtOAc : hexane, 1 : 2) to give **3** as a colorless solid (99.6 mg, 65%).

Dimethyl 2,5-Diphenylpyrrole-3,4-dicarboxylate (5a). Typical Procedure. To a solution of imidothioate **1b** (474 mg, 1.96 mmol) in THF (6 mL) was added 1.3 mL of butyllithium (1.63 M in hexane) at −78 °C. After stirring for 1 h, the mixture was slowly added with DMAD (0.72 mL, 5.88 mmol) and then stirred for 1 h. The resulting reaction mixture was washed with 1 M-HCl and extracted with diethyl ether. The ether extract was dried (Na_2SO_4), concentrated, and purified by column chromatography (EtOAc : hexane, 1 : 2) to give 294 mg of pyrrole derivative **5a** in 45% yield.

Ethyl 4-Ethyl-3-(4-methoxyphenyl)-5-phenylpyrrole-2-carboxylate (10a). Typical Procedure. Imidothioate **1a** (147 mg, 0.618 mmol), 1-(4-methoxyphenyl)-2-nitro-1-butene (141 mg, 0.680 mmol), and 1,1,3,3-tetramethylguanidine (guanidine base) (85.0 μL, 0.680 mmol) was first dissolved in 1 mL of 1,4-dioxane, and then refluxed for 4 h. After the resulting reaction mixture was filtered through a short column on silica gel (eluent; CH_2Cl_2), the filtrate was concentrated. Compound **10a** was obtained (101 mg, 84% yield) after purification by PTLC (EtOAc : hexane, 1 : 5). When this reaction was carried out at room temperature, methyl *N*-[1-ethoxycarbonyl-2-(4-methoxyphenyl)-3-nitropentyl]benzimidothioate **11** was obtained in 87% yield. This compound gave multiple ^{1}H NMR spectra as a mixture of diastereoisomers. IR (neat) 2930, 1720, 1600, 1540, 1360 cm^{-1}. MS (FAB) 353 (M+1)$^+$.

Ethyl 4-Ethyl-3-methyl-5-phenylpyrrole-2-carboxylate (10e). Typical Procedure. Imidothioate **1a** (237 mg, 1.00 mmol) and guanidine base (0.38 mL, 3.0 mmol) was dissolved in 1 mL of 1,4-dioxane. A solution of 1-methyl-2-nitrobutyl acetate[3b)] (263 mg, 1.50 mmol) in 1,4-dioxane (4 mL) was added dropwise over 45 min to the above-mentioned solution at room temperature. After stirring for 75 min, the reaction mixture was refluxed for 4 h. The resulting reaction mixture was worked up in the usual way, and then purified in the same manner as in the synthesis of **10a** to give **10e** (135 mg, 52% yield).

(*E*)-1-(4-Methoxyphenyl)-2-nitro-1-butene.[8)] Typical Procedure. A solution of *p*-anisaldehyde (1.25 mL, 10.0 mmol), 1-nitropropane (1.07 mL, 12.0 mmol), and ethylenediammonium diacetate (180 mg, 1.00 mmol) in methanol (3 mL) was refluxed for 24 h. The reaction mixture was concentrated and purified by column chromatography on silica gel ($CHCl_3$: hexane, 2 : 1). This compound was obtained as a yellow oil (1.06 g, 77%). IR (neat) 2920, 1630, 1580, cm^{-1}. ^{1}H NMR δ=1.29 (3H, t, J=7.43 Hz), 2.90 (2H, q, J=7.43 Hz), 3.87 (3H, s), 3.87 (3H, s), 6.98 (2H, m), 7.42 (2H, m), 8.02 (1H, s). This compound is considered to be the *E* isomer, because NOE was not observed between the olefinic proton and ethyl group.

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