PREPARATION AND REACTIONS OF SOME PYRRYLTHIOL ESTERS

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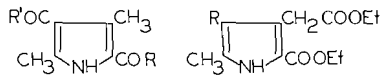
ABSTRACT

Two syntheses and some reactions of pyrrylthiol esters are described. The value of the thiol ester residue as a protecting group in the synthesis of complex pyrroles and their derivatives is considered. A simplified synthesis of a pyrrole related to the uroporphyrins is reported.

The synthesis of complex pyrromethanes and porphyrins requires the use of protecting groups. The literature contains numerous examples, but among the most favored groups are the carboxylic esters of ethyl (e.g. ref. 1), benzyl (e.g. ref. 2), and *t*-butyl (e.g. ref. 3) alcohols. One disadvantage of the ester grouping is that it is frequently necessary to remove it by de-esterification and decarboxylation, to free the specific pyrrole ring position for further synthetic operations.

When considering methods of simplifying classical syntheses of pyrroles and pyrromethanes, we investigated the properties of pyrrylthiol esters. The thiol ester group is potentially valuable since it is easily converted into formyl by treatment with an appropriate grade of Raney nickel.

Pyrrylthiol esters can readily be prepared by ring synthesis, and ethyl acetothiolacetate can be used in Knorr-type syntheses wherever the oxygen analogue has been employed. To test the scope of the synthesis, the three possible thiol ester variants on the Knorr pyrrole (I*a*–I*c*) were prepared. It might be expected that the use of zinc dust in the condensation step would lead to some desulfurization and reduced yields. However, a



Ia R = SEt; R' = OEt
Ib R = OEt; R' = SEt
Ic R = R' = SEt

IIa R = CH_2CH_2COOEt
IIb R = COSEt
IIc R = CHO
IId R = CH=CHCOOEt

comparison between a modified Knorr method (2) and the variant with sodium dithionite as reducing agent (4) showed that the former gave superior yields, which were comparable with those obtained in the synthesis of the analogous oxygen compound.

A second successful synthesis of pyrrylthiol esters involves the use of preformed pyrrole rings. Phenyl isothiocyanate reacts with alkylated pyrroles in α- or β-positions to give very high yields of thiocarbanilides (5). By analogy with the thiobenzanilides, the pyrrylthiocarbanilides were readily S-alkylated by dimethyl sulfate (with or without added base), or by alkyl halides and base. Hydrolysis of the S-alkylthioanilides with very dilute mineral acid gave good yields of the corresponding thiol esters. The products isolated by this method were difficult to purify for analysis (possibly as a result of partial hydrolysis), but behaved as expected in subsequent reactions.

Conversions of the thiol ester group into hydroxymethyl (6) or into aldehyde (7) have been reported. By use of the appropriate grade of Raney nickel we have converted

pyrrylthiol esters into the corresponding formyl derivatives. To obtain simple products it is necessary to prepare the nickel strictly according to the published method (8).

As an example of the use of a thiol ester in synthesis we have prepared a pyrrole (II*a* (9)) related to the uroporphyrins. A Knorr-type condensation of ethyl acetothiolacetate with nitrosated diethyl acetonedicarboxylate (10) gave the thiol ester II*b*. The product was desulfurized with W-2 Raney nickel by a novel technique to give the aldehyde II*c* in about 80% yield. Condensation of II*c* with ethyl hydrogen malonate in pyridine (11) gave a good yield of the acrylic ester II*d*, and this was reduced almost quantitatively to II*a* by hydrogen over Adams' catalyst.

Pyrrylthiol esters behave very much like their oxygen analogues. They are generally colorless and can be purified by crystallization or sublimation. Ethyl 2,4-dimethylpyrrole-5-thiolcarboxylate was compared closely with the corresponding ester, and in some of the common reactions of pyrrole synthesis (e.g. acylation, formylation, and Houben–Hoesch reaction) gives yields and products analogous to those obtained from the oxygen compound.

EXPERIMENTAL

Infrared spectra were recorded on a Perkin–Elmer 237B instrument, ultraviolet spectra on a Beckmann DK-2A, and nuclear magnetic resonance (n.m.r.) spectra on a Varian A-60. Melting points were taken in capillaries and are uncorrected. Analyses are by A. Bernhardt (Mülheim, Germany). Ultraviolet spectra were recorded for solutions in 95% ethanol. Petroleum ether refers to the fraction boiling at 60–80 °C.

Ethyl Acetothiolacetate

Two methods of preparation were used. Claisen condensation (12) of ethyl thiolacetate (13) gave a reasonable yield, but a preparation from diketene is simpler.

(*a*) Ethanethiol (100 g) and anhydrous sodium acetate (0.5 g) were mixed in ligroin (300 ml, b.p. 80–90°); diketene (135 g; T. Schuchardt GMBH, Munich) was added dropwise over 4 h. The reagents were protected against moisture and allowed to stand overnight at room temperature. The solvent was removed by distillation under reduced pressure, and the ester isolated by fractional distillation. The fraction distilling at 92–94° and 12 mm weighed 89 g (38%). This reaction is accompanied by the formation of a large amount of dehydracetic acid.

(*b*) Ethanethiol (15 g) and triethylamine (3 drops) were dissolved in ligroin (100 ml) and treated dropwise with diketene (21 g), with stirring, under gentle reflux. After the solution had been allowed to stand at room temperature overnight, it was poured into ice water. The layers were separated and the aqueous layer was washed twice with ether. The combined organic phases were washed with warm (30–35°) sodium bicarbonate solution and then with water, and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure and the thiol ester (19.5 g, 55%) was distilled at 92–94° and 12 mm.

Ethyl 2,4-Dimethyl-3-ethylthiolcarbonylpyrrole-5-carboxylate (Ib)

(*a*) To ethyl acetoacetate (1.3 g) in acetic acid (1.2 ml) was added sodium nitrite (0.7 g, in the minimum volume of water) dropwise, with stirring. The stirring was continued for another 4 h at room temperature, after which the solution was neutralized (Universal indicator paper) with 20% sodium hydroxide solution. Ethyl acetothiolacetate (1.4 g) was added, followed by sodium dithionite (2.6 g (4)), the mixture being kept neutral (by adding 20% caustic soda) and the temperature of the solution being maintained at about 40 °C. After addition of the dithionite the mixture was stirred for another hour at 40 °C and then made alkaline to phenolphthalein. After the solution had stood for 12 h, crystals separated out. The mixture was diluted with water and extracted with ether (3 × 25 ml). The ether extract was washed and dried (Na_2SO_4), and evaporation of the solvent gave a gummy solid which slowly crystallized. Recrystallization from ethanol–water gave colorless needles (0.85 g, 40%), m.p. 112–113 °C, identical with the material described in method *b* below.

(*b*) Sodium nitrite (0.22 g) in water (0.3 ml) was added dropwise to a solution of ethyl acetoacetate (0.4 g) in acetic acid (0.9 ml) at 5 °C, with stirring. The solution was left to stand for 1 h, and then added dropwise to a stirred mixture of ethyl acetothiolacetate (0.41 g), acetic acid (1.4 ml), and zinc dust (0.6 g) at 60°. The temperature of the mixture rose to 100°; this temperature was maintained (steam bath) for 1½ h, and the mixture left to stand overnight at room temperature. The product was isolated as in method *a* above and yielded colorless needles (0.45 g, 57%), m.p. 112–113 °C after crystallization from chloroform – petroleum ether. The product was sublimed (100° at 15 mm) for analysis. Ultraviolet absorption, maxima at 231, 247, and 285.5 mμ ($\log_{10} \epsilon_{max}$ 4.28, 4.16, and 4.14, respectively). The infrared spectrum (KCl disk) showed maxima (*inter alia*) at 1 634 and 1 669 cm^{-1}.

Anal. Calcd. for $C_{12}H_{17}NO_3S$: C, 56.44; H, 6.71; N, 5.49; S, 12.59. Found: C, 56.14; H, 6.65; N, 5.37; S, 12.34.

Ethyl 2,4-Dimethyl-3-ethoxycarbonylpyrrole-5-thiolcarboxylate (Ia)

This compound was prepared by method *b* above, on the same scale. In this case the ethyl acetothiolacetate was nitrosated and added to ethyl acetoacetate in the reducing mixture. The product formed very pale yellow needles when crystallized from chloroform – petroleum ether, m.p. 143–144 °C (0.51 g, 60%). Ultraviolet absorption, maxima at 232 and 302 mμ ($\log_{10} \epsilon_{max}$ 4.27 and 4.35, respectively). The infrared spectrum (KCl disk) included peaks at 1 675 and 1 619 cm^{-1}.

Anal. Calcd. for $C_{12}H_{17}NO_3S$: C, 56.44; H, 6.71; N, 5.49; S, 12.59. Found: C, 56.26; H, 6.53; N, 5.60; S, 12.45.

Diethyl 2,4-Dimethylpyrrole-3,5-dithiolcarboxylate (Ic)

The dithiol ester was prepared by method *b* above, except that in this case both halves of the potential pyrrole ring were derived from ethyl acetothiolacetate. The product formed colorless needles, m.p. 107–108 °C (0.59 g, 66%) when crystallized from chloroform – petroleum ether. Ultraviolet absorption, maxima at 237 and 308 mμ ($\log_{10} \epsilon_{max}$ 4.26 and 4.38, respectively). The infrared spectrum (KCl disk) included maxima at 1 650 and 1 594 cm^{-1}.

Anal. Calcd. for $C_{12}H_{17}NO_2S_2$: C, 53.10; H, 6.32; N, 5.16. Found: C, 53.05; H, 6.23; N, 5.30.

Methyl 2-Methylpyrrole-5-thiolcarboxylate

2-Methylpyrrole-5-thiocarbanilide (12 g (5)) was rapidly stirred with caustic soda (3 *N*, 24 ml) and dimethyl sulfate (7 ml) on a steam bath. The two-phase mixture was cooled and treated with ammonium hydroxide (6 *N*, 30 ml) to decompose excess dimethyl sulfate. The mixture was extracted with ether (3 × 50 ml), and the combined extracts were washed with water and dried (Na_2SO_4). Removal of the ether gave a yellowish oil which was crude 2-methylpyrrole-5-(S-methyl)-thiocarbanilide (12 g). This material was used without purification.

The oily product (above) was suspended in hydrochloric acid (1 *N*, 240 ml) and stirred at 100° for 2 h. Crystalline material was deposited and removed (after the mixture had been cooled in ice) by filtration. The filtrate was again heated until no more crystalline material accumulated. The combined precipitates (6.5 g, 75% based on the thioanilide) were recrystallized from chloroform – petroleum ether to give colorless needles, m.p. 126–127°. A sample was sublimed for analysis. Ultraviolet absorption, maxima at 283 and 311.5 mμ ($\log_{10} \epsilon_{max}$ 4.34 and 3.67, respectively). Infrared absorptions (Nujol mull) included a band at 1 620 cm^{-1}. The n.m.r. spectrum (CH_2Cl_2) showed peaks at τ 3.02 and 4.15 (pseudo triplets, ring proton absorptions), 7.58 (S-methyl), and 7.67 (ring methyl).

Anal. Calcd. for C_7H_9NOS: C, 54.17; H, 5.81; N, 9.02; S, 20.66. Found: C, 54.19; H, 5.90; N, 9.20; S, 20.57.

Ethyl 2-Methylpyrrole-5-thiolcarboxylate

This compound was prepared in a manner similar to the above, except for the formation of the S-ethyl-thiocarbanilide. 2-Methylpyrrole-5-thiocarbanilide (6 g (5)) was added to a stirred mixture of sodium hydroxide solution (3 *N*, 24 ml) and ethyl bromide (4 ml). The mixture was boiled under reflux for 4 h, cooled, and extracted with ether (3 × 30 ml). The ether extract was worked up as above to give an almost quantitative yield of the crude S-ethylthioanilide. This compound could be crystallized from aqueous ethanol or chloroform – petroleum ether to give yellow plates, m.p. 49.5–51°, but this was unnecessary for a successful preparation of the ester. The S-ethyl thioanilide (3 g) was hydrolyzed in the same way as the S-methyl compound to give the ethyl thiol ester as colorless needles (1.8 g, 84%), m.p. 88–90 °C. The infrared spectrum showed a maximum at 1 616 cm^{-1} (thiol ester carbonyl).

By analogous reactions, 2,4-dimethylpyrrole-5-(S-ethyl)-thiocarbanilide, m.p. 69.5–70.5°, and ethyl 2,4-dimethylpyrrole-5-thiolcarboxylate, m.p. 111.5–113°, were prepared.

Methyl 2-Methyl-3-formylpyrrole-5-thiolcarboxylate

Methyl 2-methylpyrrole-5-thiolcarboxylate (2.8 g) was added to a cooled mixture of dimethylformamide (6 g) and phosphorus oxychloride (2 ml) while the temperature was maintained below 0°. The red solution was warmed on an oil bath at 35° for 30 min (aldimine hydrochloride begins to crystallize at this point), cooled, and poured into an ice-cold solution of sodium hydroxide (4 g) in water (8 ml). After 10 min the solution was brought to pH 6 with cold 3 *N* hydrochloric acid, and after 10 min more the pinkish precipitate was filtered off. Crystallization of the aldehyde from aqueous ethanol gave off-white needles (2.78 g, 85%), m.p. 179–181°. Ultraviolet spectrum, maxima at 229, 272.5, and 307 mμ ($\log_{10} \epsilon_{max}$ 4.30, 4.04, and 4.26, respectively).

Anal. Calcd. for $C_8H_9NO_2S$: C, 52.50; H, 4.96. Found: C, 52.25; H, 4.98.

Methyl 2,4-dimethyl-3-formylpyrrole-5-thiolcarboxylate, m.p. 145–146°, was prepared in an analogous manner.

Methyl 2-methyl-3-(ethylglyoxalyl)pyrrole-5-thiolcarboxylate, m.p. 167.5–169°, was prepared by a Houben–Hoesch reaction (14) between ethyl cyanoformate and methyl 2-methylpyrrole-5-thiolcarboxylate.

Ethyl 2,4-Dimethyl-3-acetylpyrrole-5-thiolcarboxylate

(*a*) Ethyl 2,4-dimethylpyrrole-5-thiolcarboxylate (0.25 g) in a mixture of acetic acid (2 ml) and acetic anhydride (1 ml) was treated with 70% perchloric acid (5 drops). After 15 min the reddish solution was

poured into ice-cold water. The solid precipitate was collected and crystallized from aqueous ethanol to give colorless crystals, m.p. 123–124°, in an almost quantitative yield. Infrared bands (Nujol mull) at 1 666 and 1 594 cm^{-1} (*inter alia*).

Anal. Calcd. for $C_{11}H_{15}NO_2S$: C, 58.64; H, 6.48; N, 6.22; S, 14.23. Found: C, 58.54; H, 6.75; N, 6.41; S, 14.14.

(*b*) A Knorr-type, ring synthesis reaction between nitrosated ethyl acetothiolacetate (see above) and acetylacetone gave a product identical (melting point, mixed melting point, and spectra) with that prepared by method *a* above.

Desulfurization Experiments

W-2 Raney nickel (8) was used as the standard desulfurization material. It was deactivated with boiling acetone for various periods of time, depending on the activity required. In a typical batchwise desulfurization, Raney nickel (2.8 g) was deactivated by refluxing it with acetone (6 ml) for 1 h. Methyl 2-methylpyrrole-5-thiolcarboxylate (0.25 g) was added, followed by acetone (2 ml) and water (2 ml). The mixture was boiled under reflux for another hour, cooled, and filtered through diatomite. Removal of the solvent *in vacuo* yielded an oily product which rapidly crystallized when treated with a drop of methanol. The crystalline product, 2-methyl-5-formylpyrrole, after sublimation, had m.p. 68.5–69.5° (lit. (15) m.p. 68°) and formed an oxime, m.p. 151–152° (lit. (15) m.p. 153°). The n.m.r. spectrum (CCl_4) showed absorptions at τ 0.69 (singlet, formyl), 3.13 and 3.98 (pseudo triplets, ring protons), and 7.57 (singlet, methyl).

Diethyl Acetonedicarboxylate

The commercial acid (Eastern Chemical Corp., Pequannock, New Jersey) was esterified (10) in very high (81.5%) yield, b.p. 119–124° at 6 mm.

Ethyl 5-Carbethoxy-4-carbethoxymethyl-2-methylpyrrole-3-thiolcarboxylate (IIb)

Freshly distilled amyl nitrite (57 g) was added during 1 h at 20° to a stirred, cooled mixture of ethyl acetonedicarboxylate (97 g) and concentrated hydrochloric acid (0.8 ml). The mixture was allowed to warm up to room temperature spontaneously, and then was heated at 40° for 2 h. The mixture was treated with sodium acetate (1.0 g) and then added (over 30 min) to a vigorously stirred mixture of ammonium acetate (75 g), acetic acid (500 ml), ethyl acetothiolacetate (70 g), and zinc dust (25 g) which was cooled in ice water. During the addition of the nitroso compound, zinc dust (50 g) was added in small portions. After the initial temperature rise had ceased, the reaction mixture was slowly heated to 90°, with continued stirring, during 2 h. The hot solution was decanted from excess zinc into stirred ice water (6 l). The zinc was washed with a little hot 50% acetic acid, and the washings were added to the aqueous mixture. After 2 h the precipitate was collected, washed with 50% aqueous ethanol (200 ml), and crystallized from absolute ethanol to yield colorless, flat prisms (75 g, 48%), m.p. 102–103°. The n.m.r. spectrum (CCl_4) showed absorptions at τ −0.27 (broad, NH), 5.73 and 5.88 (O—CH_2, quartets), 5.81 (—CH_2—CO), 7.02 (S—CH_2, quartet), 7.69 (CH_3), and 8.63, 8.69, and 8.76 (ester CH_3, triplets).

Anal. Calcd. for $C_{15}H_{21}O_5NS$: C, 55.04; H, 6.47; N, 4.29; S, 9.80. Found: C, 55.10; H, 6.47; N, 4.40; S, 9.68.

Ethyl 2-Methyl-3-formyl-4-carbethoxymethylpyrrole-5-carboxylate (IIc)

(*a*) W-2 Raney nickel (50 g) was added to acetone (150 ml) and heated under reflux for 2 h with magnetic stirring. A solution of the above thiol ester (IIb, 3.72 g) in acetone (100 ml) and methanol (50 ml) was added, and the mixture was refluxed for another 2 h. The catalyst was removed and the filtrate evaporated to dryness *in vacuo*. The residue was recrystallized from methanol to give white needles (2.16 g, 71%), m.p. 153–154.5° (lit. (9) m.p. 154°).

(*b*) When the foregoing reaction was repeated with the thiol ester (IIb, 0.75 g) and Urushibara nickel-B (10 g (16)), the aldehyde IIc was again isolated (0.52 g, 85%), m.p. 153–154.5°.

(*c*) W-2 Raney nickel (65 g) and silica gel (100 g) were mixed well and packed into a chromatographic column (25 × 500 mm). Acetone (100 ml) was allowed to percolate through the column at about 2–3 ml/min. The exterior of the column was warmed with a water jacket at 50°, and a solution of the thiol ester (IIb, 4.95 g) in methanol (180 ml) and acetone (20 ml) was run through the column at about 2 ml/min. Fractions were collected and the amount of aldehyde present in each was estimated from the n.m.r. spectrum. When the emerging solution showed gross contamination with starting material and a by-product, the earlier fractions were combined and yielded almost pure aldehyde (3.1 g, 77%) as white needles, m.p. 153–154.5°.

Ethyl 3-Carbethoxymethyl-4-(2'-carbethoxyvinyl)-5-methylpyrrole-2-carboxylate (IId)

A mixture of the foregoing aldehyde (IIc, 3.0 g), ethyl hydrogen malonate (1.8 g), pyridine (10 ml), and piperidine (8 drops) was heated at 90° for 6 h, and then refluxed for another 3 h. The mixture was poured into ice water and neutralized with dilute hydrochloric acid. After 3 h the precipitate was collected, washed with water, and recrystallized from aqueous methanol and then hexane to give colorless prisms, m.p. 88–89° (2.3 g). The filtrate and mother liquors were combined and extracted with ether to yield a further crop of the vinyl ester (0.5 g, total yield 74%).

Anal. Calcd. for $C_{17}H_{23}O_6N$: C, 60.51; H, 6.88; N, 4.16. Found: C, 60.45; H, 6.85; N, 4.14.

The n.m.r. spectrum (CCl_4) showed absorptions at τ −0.25 (broad, NH), 2.40 and 4.10 (olefinic CH, AB quartet, J = 16.5 c.p.s.), 5.77 (quartet, O—CH_2), 6.01 (singlet, —CH_2—CO), 7.71 (CH_3), and 8.68 (triplet,

ester CH_3). The ester signals were not resolved in the spectrum of this compound and the signals for the $O—CH_2—CH_3$ groups are broad. Integrated areas for all the peaks are in accord with structure II*d*.

Ethyl 3-Carbethoxymethyl-4-(2'-carbethoxyethyl)-5-methylpyrrole-2-carboxylate (IIa)

A solution of the vinyl ester (II*d*, 2.0 g) in 95% ethanol (50 ml) was shaken for 1 h with Adams' catalyst (50 mg) under hydrogen (at 50 lb/sq. in.) at room temperature. The platinum was removed and the solvent distilled off *in vacuo*. The residue was crystallized from cyclohexane to give white needles (1.91 g, 95%), m.p. 63–64° (lit. (9) m.p. 63.5°).

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