Tetrahedron Letters,Vol.27,No.39,pp 4689-4692,1986 0040-4039/86 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

THE SYNTHESIS OF 1-ALKYLTHIOPYRROLES

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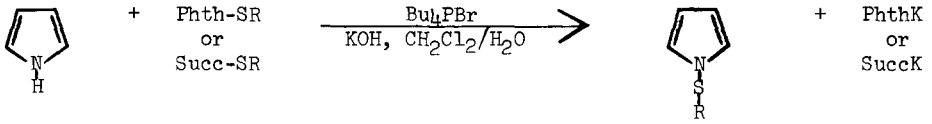
Abstract: Reaction of various S-substituted thiophthalimides or thiosuccinimides and pyrrole, under phase transfer conditions, provides an efficient way to prepare 1-alkylthiopyrroles in high yield.

In an attempt to synthesize some new sulfur containing heterocyclic systems it was necessary to prepare some new 1-substituted thiopyrroles. It has been reported that polyhaloalkylsulfenyl chlorides react with pyrazole and indazole to yield the corresponding 1-(polyhaloalkylthio)pyrazoles[1] and indazoles.[2] 1-(Polyhaloalkylthio)pyrroles cannot be synthesized by this method.[3] The reaction of aryl sulfenyl halides and pyrrole or potassium pyrrole results only in 2- and 2,5-substitution.[4] Because of the utility of S-substituted thiophthalimides as reagents for sulfenylations[5], their reaction with potassium pyrrole was investigated and found to form 1-alkylthiopyrroles in low yield. However, treatment of various S-substituted thiophthalimides[6] or thiosuccinimides[7] and pyrrole with concentrated aqueous potassium hydroxide, under phase transfer conditions, gave the desired 1-alkylthiopyrroles; previously unreported.



Phth = N-phthalimide R = CH_3, C_2H_5, CH_2Ph, Ph
Succ = N-succinimide

In a typical reaction 20 mmol of the substituted thiophthalimide in 150 ml methylene chloride is added in 10-15 min to a vigorous mechanically stirred mixture of 10 mmol pyrrole, 1 mmol tetrabutylphosphonium bromide, 10 ml 50% aqueous potassium hydroxide,

and 25 ml methylene chloride at room temperature. After one-half of the thiophthalimide was added, an additional 1 mmol of tetrabutylphosphonium bromide was added to the reaction mixture. The reaction mixture was washed three times with 100 ml water. The last washing was acidified with acetic acid to destroy any excess base, the solvent dried over anhydrous sodium sulfate and evaporated. The product can be isolated by distillation of the residue at reduced pressure or the residue can be extracted three times with warm hexane. Evaporation of the hexane left a residue from which the product can be isolated by preparative gas chromatography. Results are in Table I.

Table I. PRODUCTS FROM THE SULFENYLATION OF PYRROLE AND INDOLE.

Heterocycle	Thiolating Agent	Product[a]	Number	Yield,%		bp
				gc	isolated	
Pyrrole	Phth-SCH_3	1-methylthiopyrrole	1	95	85	38-42°/17 mm
Pyrrole	$CH_3SSO_2CH_3$	1-methylthiopyrrole	1	75		
Pyrrole	Phth-SC_2H_5	1-ethylthiopyrrole	2	89	85	60-64°/17 mm
Pyrrole	Succ-SCH_2Ph	1-benzylthiopyrrole	3	96	84	102-103°/1 mm
Pyrrole	Succ-SPh	1-phenylthiopyrrole	4	90	84	85-87°/0.5 mm
Indole	Phth-SCH_3	1-methylthioindole	5	85	52	b

[a] Satisfactory C, H and N analyses were obtained for compounds 1 - 5.

[b] Isolated by preparative gc.

The phase transfer reaction must be carried out rapidly and with vigorous mechanical stirring. If the basic reaction mixture is allowed to stand for longer periods of time the yield will be decreased considerably. Phase transfer agents such as tetrabutylammonium hydrogen sulfate or 18-crown-6 ether can also be used with only slightly lower yields. It was also observed that 1-methylthioindole (5) can be prepared similarly to 1-methylthiopyrrole (1). However, more acidic azoles such as imidazole, pyrazole, and 1,2,4-triazole do not give good yields of the corresponding 1-alkylthioazoles under these phase transfer conditions. The synthesis of these 1-alkylthioazoles is presently under investigation.

Methyl, ethyl, benzyl and phenyl thioimides have been used successfully in this

phase transfer reaction. Substituents which are sensitive to base, such as those with ester or aromatic nitro groups, cannot be used. S-Methyl thiomethanesulfonate can also be used as a methylthiolating agent forming 1 in high yield.

Spectroscopic evidence for the structure of the 1-alkylthiopyrroles includes the ^1H NMR spectrum which has a two proton absorption near 6.5 ppm for the 2- and 5-hydrogens and a two proton absorption near 6.0 ppm for the 3- and 4-hydrogens characteristic of 1-substituted pyrroles.[8] The mass spectra include the molecular ion, M + 1 and M + 2 ions consistent with structures 1 - 5.[8] A new strong IR absorption band appears at 1190 cm^{-1} for all of the 1-alkylthiopyrroles (1 - 4). This band is apparently due to the N-S stretch which absorbs at a somewhat lower wave number than the N-C stretch of 1-alkylpyrroles which absorb at 1284 ± 4 cm^{-1}.[9]

1-Methylthiopyrrole (1) can be oxidized to 1-methylsulfoxylpyrrole with m-chloro peroxybenzoic acid in high yield (79%) under mild conditions. Addition of an excess of m-chloroperoxybenzoic acid forms a low yield (5%) of the known 1-methylsulfonylpyrrole[10], providing further evidence for the structure of 1. Apparently excess oxidizing agent attacks the pyrrole ring preferentially and hence cannot be used as a synthetic method for the preparation of 1-alkylsulfonylpyrroles.

1-Alkylthiopyrroles can be stored in a refrigerator for days but become colored when exposed to air with extensive decomposition. They are sensitive to base and readily form the corresponding disulfide and pyrrole. For example, 1-phenylthiopyrrole (4) was completely decomposed in two hours at 55° in the presence of 2% ethanolic potassium hydroxide. A 73% yield of diphenyldisulfide was isolated.

A methylene chloride solution of an 1-alkylthiopyrrole is stable to an equal molar amount of acetic acid but is rapidly decomposed with an equal molar amount of trifluoroacetic acid. Pyrrole 1 is completely decomposed to pyrrole (85%), 2-methylthiopyrrole[11] (15%) and highly colored products in thirty minutes at room temperature. When this rearrangement is carried out with an excess of 1-methylpyrrole a high yield of 1-methyl-2-methylthiopyrrole (92%) and only a small amount of 2-methylthiopyrrole (8%) is formed, suggesting that pyrrole 1 acts as a good methylthiolating agent. Similar results are obtained with pyrrole 4 except that a mixture of 1-methyl-2-phenylthiopyrrole and 1-methyl-3-phenylthiopyrrole (10:1 ratio) was obtained [12], suggesting that the intermolecular mechanism is preferred.

Work is continuing on the chemistry of 1-alkylthiopyrroles and the conversion of these pyrroles to some new sulfur containing heterocyclic systems.

Acknowledgment: I gratefully acknowledge a generous grant from Rhodes College in support of this work.

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8. ^{1}H NMR spectra were taken on a Varian 360A instrument in $CDCl_3$, ppm, TMS. Mass spectra were taken on a Hewlett-Packard 5970A mass spectrometer and a 5880A gas chromatograph, m/e (relative abundance).

   1: ^{1}H NMR: 2.57 (3H, s), 6.00 (2H, t), 6.57 (2H, t); MS: M^+ 113 (100), M^{+1} 114 (7), M^{+2} 115 (5).

   2: ^{1}H NMR: 1.20 (3H, t) 2.78 (2H, q), 5.97 (2H, t), 6.53 (2H, t); MS: M^+ 127 (88), M^{+1} 128 (7), M^{+2} 129 (4).

   3: ^{1}H NMR: 3.87 (2H, s), 5.89 (2H, t), 6.30 (2H, t), 7.25-6.60 (5H, m); MS: M^+ 189 (13), M^{+1} 190 (2), M^{+2} 191 (1).

   4: ^{1}H NMR: 6.10 (2H, t), 6.61 (2H, t), 6.8-7.1 (5H, m); MS: M^+ 175 (100), M^{+1} 176 (15), M^{+2} 177 (5).

   5: ^{1}H NMR: 2.42 (3H, s), 6.30 (1H, d), 6.75-7.50 (5H, m); MS: M^+ 163 (64), M^{+1} 164 (8), M^{+2} 165 (3).

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(Received in USA 28 May 1986)