

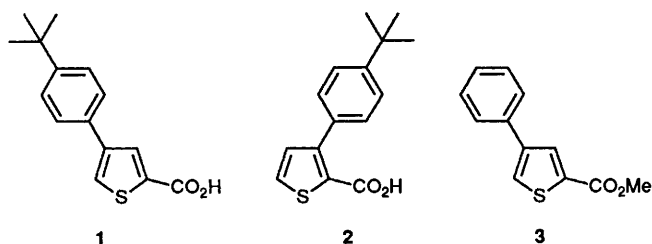
## A Regiospecific Synthesis of 3-Arylpyrroles

Peter T. Gallagher,\* Jane L. Palmer and Sarah E. Morgan  
*Lilly Research Centre, Eli Lilly & Co., Windlesham, Surrey, GU20 6PH, UK*

3-Arylpyrroles were synthesised by cyclisation of appropriate 2-aryl-3-(dimethylamino)-allylidene(dimethyl)ammonium perchlorates.

Whilst synthesising a series of arylthiophene carboxylic acids we wanted to synthesise the 2,4-disubstituted thiophene **1**. However, the method of synthesis available (lithiation of the 3-arylthiophene, followed by quenching with carbon dioxide) produced a mixture of 2,4-disubstituted thiophene **1** and the 2,3-disubstituted thiophene **2**. Chromatographic separation was necessary to produce pure **1**.

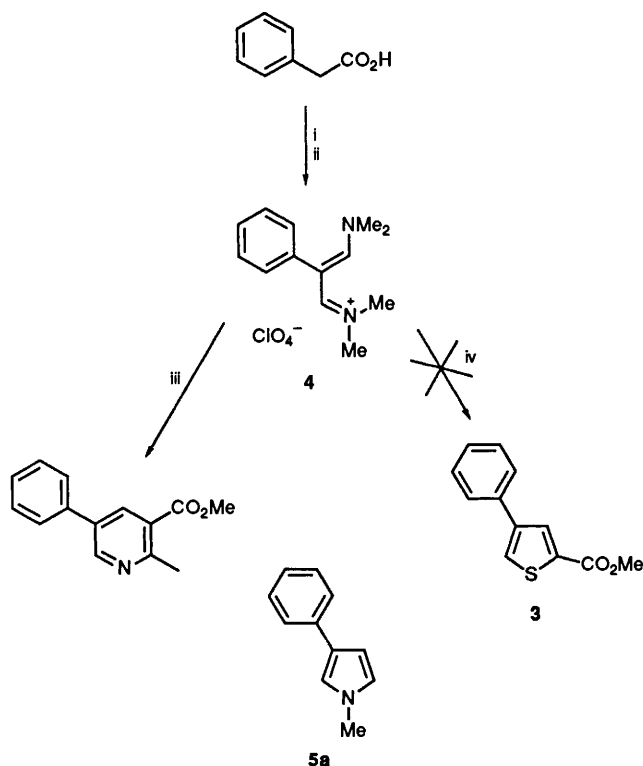
In an attempt to produce **3** to demonstrate the feasibility of the synthesis of compounds of type **1**, perchlorate **4**, available<sup>1</sup>



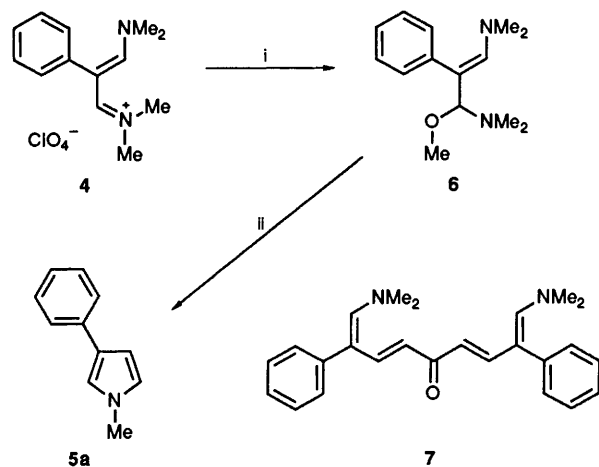
from phenylacetic acid in one step by the use of phosphorus oxychloride and dimethyl formamide (DMF), was subjected to reaction with methyl mercaptoacetate under basic conditions. These conditions are analogous to those used in the synthesis of pyridines<sup>2</sup> from methyl 3-aminobut-2-enoate and perchlorates (Scheme 1). Reaction with methyl mercaptoacetate failed to produce any arylthiophene; however, a small quantity of 1-methyl-3-phenylpyrrole **5a** was isolated.

Examination of the literature<sup>3</sup> revealed a similar observation. When perchlorate **4** was treated with potassium methoxide in methanol, enamine **6** was produced. Heating **6** with acetone at 70–80 °C produced bisdienone **7** and 1-methyl-3-phenylpyrrole **5a** in 70 and 11% respectively (Scheme 2).

The synthesis of 3-substituted pyrroles is complicated by the tendency of pyrroles to undergo electrophilic substitution in the 2-position,<sup>4</sup> although strategies involving *N*-protection with the phenylsulphonyl group, subsequent electrophilic substitution in the 3-position and then removal of the protecting group have been developed.<sup>5,6</sup> Known cyclisation reactions involve the



**Scheme 1.** Reagents: i,  $\text{POCl}_3/\text{DMF}$ ; ii,  $\text{NaClO}_4$ ; iii,  $\text{NH}_2\text{C}(\text{Me})=\text{CCO}_2\text{Me}$ , pyridine/ $\text{NaOMe}/\text{MeOH}$ ; iv,  $\text{HSCH}_2\text{CO}_2\text{Me}$ , pyridine/ $\text{NaOMe}/\text{MeOH}$ .

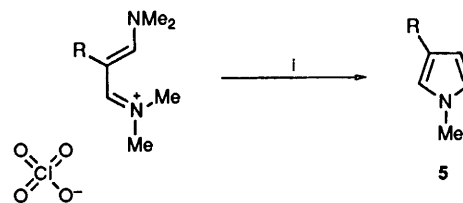


**Scheme 2.** Reagents and conditions: i,  $\text{KOMe}/\text{MeOH}$ ; ii, acetone, 70–80 °C.

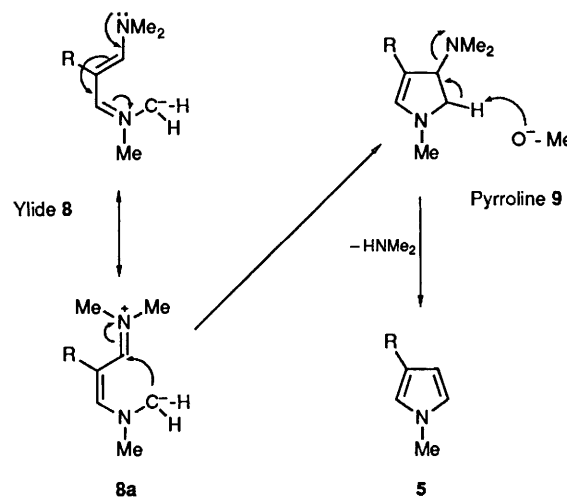
production of pyrroles with pendant groups other than in the 3-position, e.g. the Knorr pyrrole synthesis,<sup>7</sup> or alternatively cyclisation produces a 2,4-disubstituted pyrrole which subsequently has to be modified.<sup>8</sup> We therefore investigated the possibility of improving the yield of arylpyrrole from the attempted thiophene synthesis.

Omitting the methyl mercaptoacetate from the reaction mixture but otherwise maintaining the reaction conditions as before gave a 60% yield of 1-methyl-3-phenylpyrrole **5a** (Scheme 3). The synthesis has been extended to the analogues shown in Table 1. Limitations of the synthesis include the low yield of the nitro analogue **5f**, and the availability of perchlorates.

A possible explanation for the course of the reaction is initial ylide **8** formation followed by tautomerisation to **8a** then a 5-



**Scheme 3.** Reagents: i,  $\text{NaOMe}/\text{MeOH}$ , pyridine.



**Scheme 4.**

**Table 1.** Yields and melting points of the arylpyrroles **5**.

R	Yield (%)	M.p. (lit., <sup>8</sup> )/°C
<b>5a</b> Ph	60	46–47 (47–48)
<b>5b</b> 4- $\text{ClC}_6\text{H}_4$	41	117.5–119.5 (116)
<b>5c</b> 4- $\text{MeOC}_6\text{H}_4$	39	126–128 (124)
<b>5d</b> 2- $\text{ClC}_6\text{H}_4$	47	b.p., 200 °C/0.65 mmHg <sup>a</sup>
<b>5e</b> 3- $\text{FC}_6\text{H}_4$	21	94–96 <sup>b</sup>
<b>5f</b> 4- $\text{NO}_2\text{C}_6\text{H}_4$	5	191–194 (195)
<b>5g</b> 4- $\text{BrC}_6\text{H}_4$	43	132 (132–133)
<b>5h</b> 1-naphthyl	55	b.p., 245 °C/0.8 mmHg <sup>c</sup>

<sup>a</sup>  $\text{M}^+$ , 191.050 53. <sup>b</sup> Found: C, 75.4; H, 5.75; N, 8.0.  $\text{C}_{11}\text{H}_{10}\text{N}$  requires C, 75.3; H, 5.6; N, 8.1%. <sup>c</sup>  $\text{M}^+$ , 207.105 53.

*exo*-trig cyclisation to give a pyrroline **9** intermediate which then loses dimethylamine to give the substituted pyrrole **5** (Scheme 4).

In conclusion, this regiospecific pyrrole synthesis provides monosubstituted 3-arylpyrroles from readily available arylacetic acids in two steps.

## Experimental

**General procedure:** 3-(4-Bromophenyl)-1-methylpyrrole **5g**.—Sodium (0.75 g, 32.65 mg atom) in methanol (11  $\text{cm}^3$ ) was added dropwise with magnetic stirring under nitrogen to 2-(4-bromophenyl)-3-(dimethylamino)allylidene(dimethyl)ammonium perchlorate<sup>1</sup> (5.66 g, 14.8 mmol) in pyridine (60  $\text{cm}^3$ , dried over 4 Å sieves) and heated under reflux for 24 h, cooled, the solvent removed *in vacuo* and the residue partitioned between ethyl acetate (100  $\text{cm}^3$ ) and hydrochloric acid (2 mol  $\text{dm}^{-3}$ , 100  $\text{cm}^3$ ). The ethyl acetate layer was washed with more hydrochloric acid (2 mol  $\text{dm}^{-3}$ , 3 × 100  $\text{cm}^3$ ), aqueous sodium hydrogen carbonate (2 × 100  $\text{cm}^3$ ), dried ( $\text{MgSO}_4$ ), and the solvent removed *in vacuo* to give **5g** (1.505 g, 43%), m.p. 132 °C (petroleum ether b.p. 60–80 °C), (lit.,<sup>8</sup> 132–133 °C).

**References**

- 1 C. Jutz, R. Kirchlechner and H-J. Seidel, *Chem. Ber.*, 1969, **102**, 2301.
- 2 C. Jutz, H-G. Löbering and K. H. Trinkl, *Synthesis*, 1977, 326.
- 3 Zh. A. Krasnaya and V. F. Kucherov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1980, 1064.
- 4 A. Jones, in *Comprehensive Heterocyclic Chemistry*, eds. A. R. Katritzky and C. W. Rees, OUP, 1984, vol. 4, p. 205.
- 5 R. X. Xu, H. J. Anderson, N. J. Gogan, C. E. Loader and R. McDonald, *Tetrahedron Lett.*, 1981, **22**, 4899.
- 6 J. Rokach, P. Hamel and M. Kakushima, *Tetrahedron Lett.*, 1981, **22**, 4901.
- 7 J. Sundberg, in *Comprehensive Heterocyclic Chemistry*, eds. A. R. Katritzky and C. W. Rees, OUP, 1984, vol. 14, p. 331.
- 8 S. Hauptmann and J. Weisflog, *J. Prakt. Chem.*, 1972, **314**, 353.

Paper 0/03334K

Received 23rd July 1990

Accepted 20th August 1990