

## HETEROCYCLIC O-XYLYLENES: THIAZOLE, OXAZOLE AND IMIDAZOLE ANALOGUES

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**SUMMARY:** Oxazole, thiazole and imidazole analogues of *o*-xylylene have been generated flash pyrolytically and trapped with thiophenol and sulphur dioxide and in the case of the oxazole derivative with methyl acrylate.

The wide use of derivatives of *o*-xylylene (1) in organic synthesis renders their heterocyclic analogues of considerable interest. Indole-2,3-xylylenes have been extensively applied in the alkaloid field,<sup>1</sup> otherwise studies of the 5-membered heterocyclic analogues have been limited largely to the furan (2),<sup>2</sup> thiophene (3)<sup>3</sup> and their benzo derivatives. We now report the flash-pyrolytic formation of several new heterocyclic xylylenes and identify some of the structural features which determine their stability.

The furan xylylene (2) has been generated flash pyrolytically by elimination of benzoic acid from the ester (4).<sup>2a</sup> It is remarkably stable, can be isolated at low temperature and treatment of the cold pyrolysate with dienophiles in solution gives Diels-Alder adducts. The thiophene derivative (3), when generated similarly, is much more reactive; it polymerises and cannot be intercepted in Diels-Alder reactions even when the pyrolysate is co-condensed with dienophiles<sup>4</sup>. However, it can be trapped with HCl and with thiophenol<sup>3a</sup> and in the accompanying paper<sup>5</sup> we report that cheletropic addition of SO<sub>2</sub> is also very efficient.

The thiazole-4,5-xylylene (9; R = H, X = S) and its 2-phenyl derivative (9; R = Ph, X = S) were generated by flash pyrolysis (700°C/10<sup>-2</sup> Torr) of the *p*-chlorobenzoate esters (8; X = S, R = H and Ph) which were readily obtained as indicated in the Scheme. The flash pyrolysates from esters (8; X = S, R = H and Ph) gave insoluble polymers when condensed at -80°C or -196°C; no dimers were detected. Co-condensation of the pyrolysate from (8; X = S, R = Ph) with thiophenol gave a 4:5 mixture of thioethers (10) and (11), (40%), identified by GC/MS and <sup>1</sup>Hmr spectroscopy.<sup>6</sup> Co-condensation with SO<sub>2</sub> also gave an adduct (25%) for which singlet methylene absorptions at  $\delta$  3.78 and  $\delta$  3.64 support the cyclic sulphone (12; R = Ph, X = S) rather than sulphinate ester structure. The thiophene xylylene (3) also gives a cyclic sulphone with SO<sub>2</sub> and in that case the sulphone structure was confirmed by an alternative, unambiguous synthesis.<sup>5</sup> All attempts to intercept the thiazole xylylene in Diels-Alder reactions by co-condensation with a range of dienophiles failed.

Oxazole-4,5-xylylene (9; R = H, X = O) was generated similarly by flash pyrolysis (700°C/10<sup>-2</sup> Torr) of the *p*-chlorobenzoate ester (8; R = H, X = O), prepared as indicated in the Scheme. This again led to a regioisomeric mixture of adducts (10 and 11; R = H, X = O) (39%, ratio 3:5) and a cyclic sulphone (12; R = H, X = O) (25%) when the flash pyrolysate was co-condensed with thiophenol and SO<sub>2</sub> respectively.<sup>7</sup> However, in contrast to the thiophene (3) and thiazole (9; X =

S) xylylenes, co-condensation with methyl acrylate gave a Diels-Alder adduct (13; R = H, X = O, Z = CO<sub>2</sub>Me).<sup>8</sup> On warming to room temperature in the absence of trapping agents the pyrolysate from (8; R = H, X = O) yielded polymer and the head to head dimer (14).<sup>9</sup>

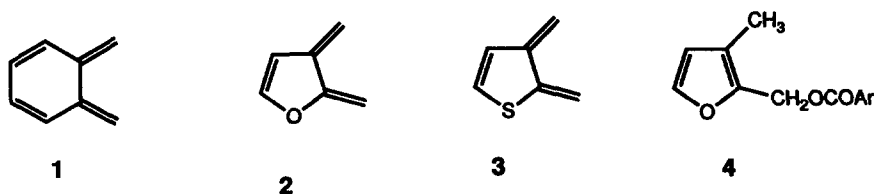
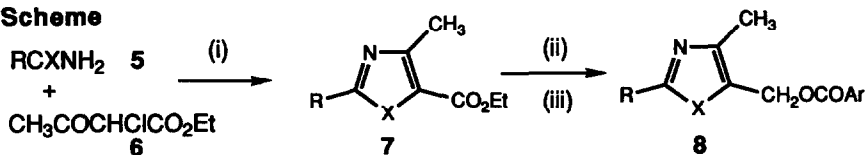
1-Methylimidazole-4,5-xylylene (9; R = H, X = NMe) was also obtained by flash pyrolysis of the regioisomeric esters (15) and (16). These esters were produced by methylation of ethyl 4(5)-methylimidazole-5(4)-carboxylate<sup>10</sup> and separation of the two isomers followed by their reduction with lithium aluminium hydride and esterification with *p*-chlorobenzoyl chloride. Pyrolysis of either ester at 650°C/10<sup>-4</sup> Torr<sup>11</sup> gave an identical mixture of adducts (10 and 11; R = H, X = NMe) (65%, ratio 4:5) when the pyrolysate was co-condensed with thiophenol<sup>12</sup> and a cyclic sulphone (12; R = H, X = NMe) (70%) when condensed with SO<sub>2</sub>.<sup>13</sup> All attempts to intercept the imidazole xylylene with dienophiles have so far failed.

The ester (17), readily available from the pyrazole (18),<sup>14</sup> was considered as a precursor to the corresponding 1-phenylpyrazole-4,5-xylylene. However, although (17) gave *p*-chlorobenzoic acid quantitatively on flash pyrolysis (700°C/10<sup>-4</sup> Torr) there is no clear evidence for formation of the xylylene. After collection at -80°C the pyrolysate gives a dark coloured, uncharacterisable material and co-condensation with thiophenol, HCl or SO<sub>2</sub> gave no trace of xylylene adducts.

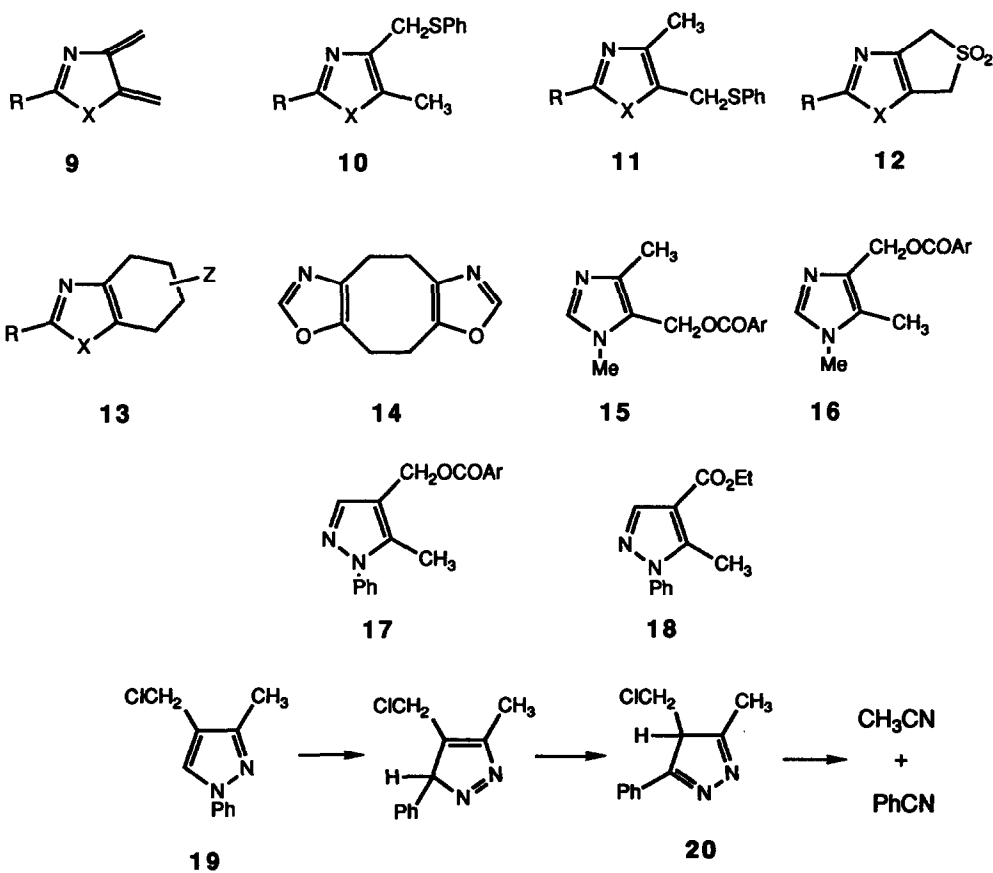
Attempts to make the isomeric pyrazole-3,4-xylylene by flash pyrolysis of the chloride (19) also failed. In this case the only products identified were PhCN and MeCN. These products can be rationalised by 1,5-sigmatropic migrations in the pyrazole ring which lead to the non aromatic pyrazole (20) and hence the observed fragments.

The experiments described above clearly demonstrate that thiazole, oxazole and imidazole analogues of *o*-xylylene can be generated flash pyrolytically from simple, readily available precursors. Comparison of their properties with those of the previously described furan and thiophene derivatives indicates that the oxazole and furan analogues are similar in their stability as indicated by their survival to undergo Diels-Alder reactions rather than polymerisation. The thiazole and imidazole derivatives resemble the thiophene xylylene, being more reactive and undergoing preferential polymerisation even in the presence of dienophiles. Thus, the stability of the xylylene appears to parallel the degree of aromaticity of the parent heterocycle; the greater the aromatic character of the heterocycle, the higher the reactivity of the derived xylylene. Although the failure of intermolecular Diels-Alder reactions of the flash pyrolytically generated thiazole and imidazole xylylenes is disappointing it may well be possible to achieve this if these species can be produced in solution at low standing concentration by alternative routes as has already been demonstrated for the thiophene system.<sup>3b</sup> Also, trapping of the flash pyrolytically generated thiazole and imidazole xylylenes with SO<sub>2</sub> may be particularly significant in view of the ready regeneration of the thiophene xylylene in solution from its SO<sub>2</sub> adduct under conditions where it undergoes Diels-Alder reactions.<sup>5</sup>

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**Scheme**

(i)  $\text{HCl/EtOH}$  (ii)  $\text{LiAlH}_4/\text{Et}_2\text{O}$  then  $\text{H}_2\text{O}$  (iii)  $p\text{-ClC}_6\text{H}_4\text{COCl}$



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1. K. Cardwell, B. Hewitt, M. Ladlow and P. Magnus, *J. Am. Chem. Soc.*, 1988, **110**, 2242 and references therein.
2. (a) W.S. Trahanovsky, T.J. Cassady and T.L. Woods, *J. Am. Chem. Soc.*, 1981, **103**, 6691; C-H. Chou and W.S. Trahanovsky, *ibid.*, 1986, **108**, 4138; C-H. Chou and W.S. Trahanovsky, *J. Org. Chem.*, 1986, **51**, 4208. (b) J. Jullien, M. Pechine, F. Perez and J.J. Piade, *Tetrahedron Lett.*, 1979, **19**, 3079. (c) A. Schweig and N. Munzel, *Angew. Chem. Int. Ed. Engl.*, 1987, **26**, 474. (d) K.J. Stone M.M. Greenberg, S.C. Blackstock and J.A. Berson, *J. Am. Chem. Soc.*, 1989, **111**, 3659; 3671. (e) P.J. Garratt and S. B. Neoh, *J. Org. Chem.*, 1979, **44**, 2667.
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4. When generated in low standing concentration in solution the thiophene xylylene can be intercepted in Diels-Alder reactions (reference 3b).
5. A.P.A. Crew, G. Jenkins, R.C. Storr and M. Yelland, following paper.
6. Adduct (10):  $\delta$ CDCl<sub>3</sub> 3.80(s, 2H) and 2.52(s, 3H). Adduct (11):  $\delta$ CDCl<sub>3</sub> 3.91(s, 2H) and 2.60(s, 3H).
7. Adduct (10):  $\delta$ CDCl<sub>3</sub> 3.62(s, 2H) and 2.32(s, 3H). Adduct (11):  $\delta$ CDCl<sub>3</sub> 3.68(s, 2H) and 2.26(s, 3H). Adduct (12): m.p. 133-135°,  $\delta$ CDCl<sub>3</sub> 8.92(s, 1H), 4.04(s, 2H) and 3.88(s, 2H).
8. GC/MS indicates that the adduct consists of a pair of regioisomers. However, these were not separable by preparative TLC or resolvable by <sup>1</sup>Hmr spectroscopy.  $\delta$ CDCl<sub>3</sub> 8.64 (s, 1H), 3.59 (s, 3H) and 2.91-1.49(m, 7H).
9. Two methylene groups are observed at  $\delta$  2.96 and 2.74. An analogous dimer is formed by the furan xylylene (2) (reference 2a)
10. H.A. Staab and G.A. Schwalbach, *Liebigs Ann. Chem.*, 1968, **715**, 128.
11. Ester (15) also gave small amounts of methyl *p*-chlorobenzoate but no associated imidazole moiety was identified. At pyrolysis temperatures above 650°C the pyrolysates from both esters were complex and the xylylene was no longer formed as judged by the absence of adducts with thiophenol and SO<sub>2</sub>.
12. Adduct 10:  $\delta$ CDCl<sub>3</sub> 7.42(m, 5H, Ph), 4.08(s, 2H, CH<sub>2</sub>), 3.47(s, 3H, NMe) and 2.02(s, 3H, Me). Adduct 11:  $\delta$ CDCl<sub>3</sub> 7.33-7.27 (m, 5H, Ph), 3.98(s, 2H, CH<sub>2</sub>), 3.58(s, 3H, NMe) and 1.86(s, 3H, Me). An authentic sample of (10) was obtained by reaction of thiophenol with 4-chloromethyl-1,5-dimethylimidazole which was prepared from (7; R = H, X = NMe) by reduction with LiAlH<sub>4</sub> and treatment with SOCl<sub>2</sub>. 5-Chloromethyl-1,4-dimethylimidazole (reference 10) with thiophenol gave (11).
13.  $\delta$ CDCl<sub>3</sub> 7.55(s, 1H), 4.33(s, 2H) 4.27(s, 2H) and 3.67(s, 3H).
14. G. Menozzi, L. Mosti and P. Schenone, *J. Het. Chem.*, 1987, **24**, 1669.