Tetrahedron Letters, Vol.32, No.51, pp 7609-7612, 1991
Printed in Great Britain

0040 4039/91 $3.00 + .00
Pergamon Press plc

A New Route to Heterocyclic Fused 2,5-Dihydrothiophene S,S-Dioxides: Formation of Pyrazole Analogues of *o*-Xylylenes

Lynne M. Chaloner, Andrew P.A. Crew, Richard C. Storr*

School of Chemistry, Liverpool University, P.O. Box 147, Liverpool L69 3BX

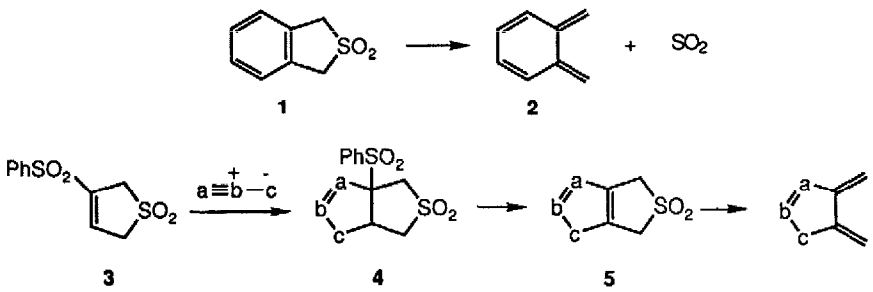
Michael Yelland

ICI Fine Chemicals Manufacturing Organisation, Hexagon House, Blackley, Manchester M9 3DA

Key Words: 2,5-Dihydrothiophene S,S-dioxides; Diazomethane addition; Heterocyclic xylylenes; Dihydro-bis-methylenepyrazoles

Abstract: Addition of diazomethane to 3-phenylsulphonyl-2,5-dihydrothiophene S,S-dioxide **3**, followed by base induced aromatisation gives the sulphone **7**, a precursor to pyrazole analogues of *o*-xylylene (*o*-quinodimethane).

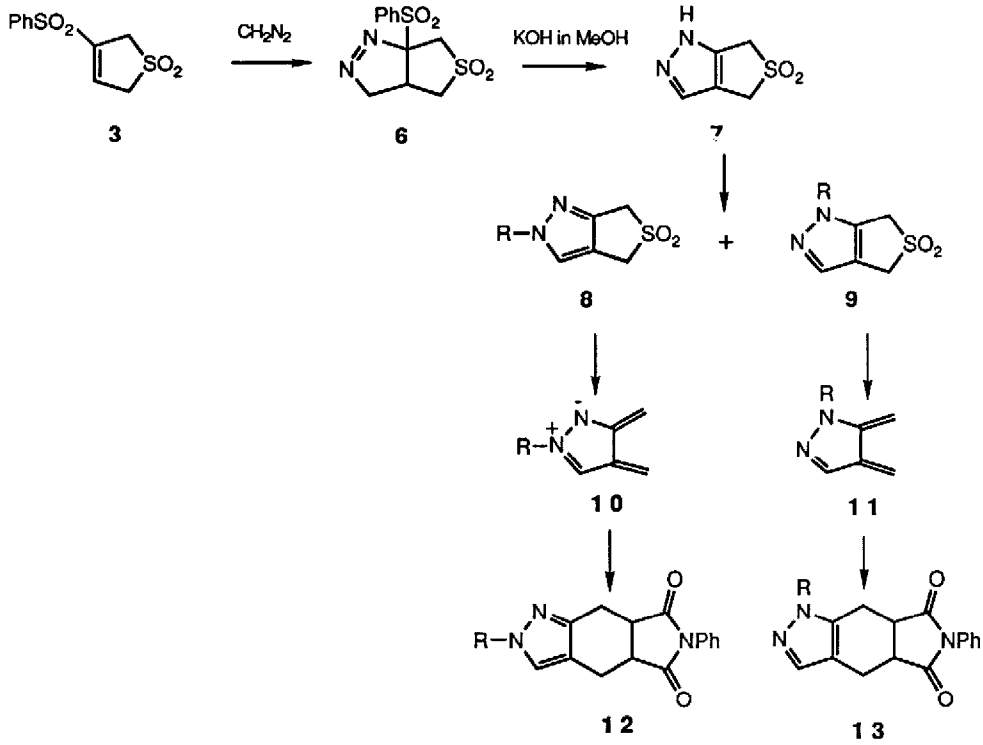
Thermal extrusion of sulphur dioxide from 1,3-dihydrobenzo[c]thiophene 2,2-dioxides **1** has proved to be a useful route to *o*-xylylenes **2** [1] and we have recently shown that this method can be extended to the generation of heterocyclic analogues.[2] Existing routes to such fused sulphones involve interaction of the xylylene with sulphur dioxide or construction of the sulphone ring on to an aromatic precursor. An attractive alternative approach would be to start with a simple 1,3-dihydrothiophene dioxide and to build on the fused aromatic ring.[3]



3-Phenylsulphonyl-2,5-dihydrothiophene dioxide **3** is readily available[4] and has the requirements of a versatile intermediate for synthesis of a range of heterocyclic fused sulphones by 1,3-dipolar cycloaddition. The phenylsulphonyl substituent should activate the 3,4-double bond towards cycloaddition and is an ideal leaving group to permit aromatisation of the initial cycloadducts **4** to the desired heterocycles **5**. Since there is precedent for formation of pyrazoles from sulphonyl alkenes and diazocompounds by such an addition-elimination sequence[5] we chose to evaluate this approach by attempts to form pyrazole fused sulphones and the corresponding xylylenes.

The sulpholene **3** gradually dissolved in ether containing an excess of diazomethane and the insoluble pyrazoline **6**[6] separated out and after 12h was isolated pure by filtration (85-90%). The regioselectivity of the cycloaddition was confirmed by ^{13}C NMR spectroscopy[7] and is as expected from frontier orbital considerations

for addition of a diazo compound to an electron deficient dipolarophile.[8] Treatment of **6** with potassium hydroxide in methanol gave the pyrazole fused sulphone **7** (95%)[9].

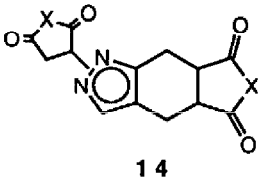


The pyrazole **7** was converted into N-substituted derivatives by standard procedures. Methylation using dimethyl sulphate and sodium methoxide in methanol gave a mixture of the methylpyrazoles **8** and **9**, (R=Me) in a ratio of 3:1 (75%)[10]. These isomers could not be separated by chromatography and the structural assignment was based on an alternative route to **9**, (R=Me) (see later). Benzoylation with benzoyl chloride in pyridine at room temperature gave a 1:1 mixture of two benzoyl derivatives (65%).[11] In one of these isomers the ^1H chemical shifts of the two methylene groups were very similar whereas in the other isomer they were markedly different and hence they were assigned as **8** and **9**, (R=COPh) respectively. The two compounds were not separable but on heating in solution **9** was converted into **8**; this rearrangement was complete within 1h. at 150°C.

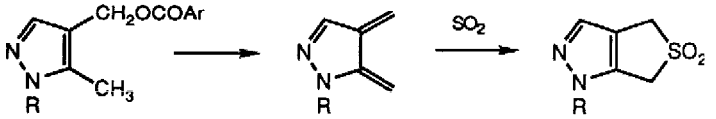
On heating at 200°C in 1,2,4-trichlorobenzene for 1h. in the presence of N-phenylmaleimide, the mixed methylpyrazole sulphones **8** and **9**, (R=Me) (3:1) gave two methylpyrazole xylylene adducts in the ratio 3:1 (total yield 56%) which were, therefore, assigned structures **12** and **13** respectively[12]. Bond fusion might be expected to render xylylene **11** more stable than **10**[13] and indeed sulphone **9**, (R=Me) undergoes extrusion of SO_2 at a significantly lower temperature (180°C) than the isomer **8** (200°C). The benzoyl sulphone **8**,

(R=COPh) with N-phenylmaleimide in refluxing trichlorobenzene gave two xylylene Diels-Alder adducts **12** and **13** (R=COPh)[14] (45%) in the ratio 10:1. These adducts were separated by chromatography and the pure isomers were shown to equilibrate to a 10:1 mixture of **12:13** under the reaction conditions. This is consistent with loss of SO_2 from the sulphone **8**, (R=COPh) (the predominant isomer at 200°C) to give the pyrazole xylylene **10** which is intercepted by the N-phenylmaleimide, the final mixture of adducts resulting from isomerisation of **12** to **13**. However, in view of the ready thermal migration of benzoyl groups in pyrazoles and the more facile extrusion of SO_2 from **9**, (R=Me) than **8**, (R=Me), it is possible that an appreciable proportion of the products arise via **9**, (R=COPh) and the xylylene **11** even though **9** can only be present in low standing concentration during the thermolysis. There is no evidence for addition of the dienophile/dipolarophile across the azomethine imine function of the xylylenes **10**, (R=COPh or Me).

Attempts to trap the unsubstituted pyrazole xylylene **10/11**, (R=H) by heating the sulphone **7** in trichlorobenzene or sulpholane containing maleic anhydride, N-phenylmaleimide or 1,4-benzoquinone were disappointing. Mixed 2:1 adducts of the type **14**, identified by ^1H nmr spectroscopy and mass spectrometry, were isolated in low yields from the complex reaction mixtures.



14



15

Successful generation of a pyrazole xylylene by dehalogenation of 1-benzoyl-3-phenyl-4,5-bisbromomethylpyrazole has been described previously.[15] We have also reported an unsuccessful attempt to generate a pyrazole xylylene by flash pyrolysis of 1-phenyl-5-methylpyrazol-4-ylmethyl 4-chlorobenzoate **15**, (R=Ph).[16] However, the corresponding 1-methyl derivative **15**, (R=Me), on flash pyrolysis and co-condensation with thiophenol gives adducts characteristic of a pyrazole xylylene. Trapping with SO_2 gave a product which is identical with the minor isomer **9** formed by methylation of **7** and so confirms the structural assignment of these isomers.

Acknowledgements: We thank ICI and SERC for support and D. Walton and P.M. O'Neill (Nuffield Undergraduate Research Bursar) for experimental assistance.

REFERENCES AND NOTES

1. Cava, M.P.; Deana A.A. *J. Am. Chem. Soc.* **1959**, *81*, 4266.

2. Crew, A.P.A.; Jenkins, G; Storr, R.C.; Yelland, M. *Tetrahedron Lett.* **1990**, *31*, 1491.

3 Note added in proof: A route to 4,6-dihydrothieno[3,4-b]thiophene 5,5-dioxide which makes use of this alternative stratagy has just been reported. Chou, T.; Tsai, C-Y. *J Chem Soc. Chem. Comm.* **1991**, 1287.

4. Chou, S-S P.; Sun, C-M. *Tetrahedron Lett.* **1990**, *31*, 1035.

5. Parham, W.E.; Blake, F.D.; Theissen, D.R. *J. Org. Chem.* **1962**, *27*, 2415.

6. Compound 6: m.p. 158-159°C; δ ($CDCl_3$) 7.98 (d, 2H), 7.82 (t, 1H), 7.68 (t, 2H), 5.13 (dd, 1H, J=19, 10 Hz), 4.94 (dd, 1H, J=19, 4 Hz), 3.83 (d, 1H, J=14 Hz), 3.64-3.47 (m, 2H), 3.4 (dd, 1H, J=14, 2 Hz) and 3.11 (dd, 1H, J=13, 2 Hz).

7. Signals at δ 115.5 (s) and 34.9 (d) in the ^{13}C NMR spectrum correspond to the ring junction carbons and confirm the regiochemistry of the cycloaddition leading to compound 6.

8. Houk, K.N.; Yamaguchi, K. Theory of 1,3-Dipolar Cycloadditions. In *1,3-Dipolar Cycloaddition Chemistry Vol. 2*; Padwa, A. Ed.; Wiley-Interscience, 1984; p 407.

9. Compound 7: m.p. 156-157°C; ν_{max} 3360 (NH) and 1140 cm^{-1} (SO_2); δ (d_6DMSO) 7.80 (s, 1H), 6.07 (br. s, 1H, NH), 4.36 (s, 2H) and 4.30 (s, 2H).

10. Major isomer 8, R=Me: δ ($CDCl_3$) 7.34 (s, 1H), 4.26 (s, 2H), 4.24 (s, 2H) and 3.95 (s, 3H). Minor isomer 9, R=Me: 7.46 (s, 1H), 4.29 (s, 2H), 4.25 (s, 2H) and 3.87 (s, 3H).

11. Compound 8, R=COPh: δ ($CDCl_3$) 8.44 (s, 1H), 8.09 (d, 2H), 7.66 (t, 1H), 7.53 (t, 2H), 4.34 (s, 2H) and 4.33 (s, 2H). Compound 9, R=COPh: 8.16 (d, 2H), 7.79 (s, 1H), 7.67 (t, 1H), 7.54 (t, 2H), 4.71 (s, 2H) and 4.27 (s, 2H).

12. Two inseparable adducts formed in a ratio of 3:1 (56%). Major isomer 12, R=Me: δ ($CDCl_3$) 7.10-7.50 (m, 5H), 3.83 (s, 3H), 3.57-3.42 (m, 2H), 3.38 (dd, 1H, J=16, 3 Hz), 3.27 (dd, 1H, J=15, 3 Hz), 2.97 (dd, 1H, J=16, 8 Hz) and 2.85 (dd, 1H, J=15, 7 Hz). Minor isomer (not fully resolved): 7.1-7.5 (m, 5H), 3.80 (s, 3H), 3.57-3.36 (m, 3H), 3.25 (dd, 1H, J=16, 3Hz), 2.90 (dd, 1H, J=16, 7 Hz) and 2.86 (dd, 1H).

13. Furan and thiophene-3,4-xylylenes are more reactive than the corresponding 2,3-analogues: Stone, K.J.; Greenberg, M.M.; Goodman, J.L.; Peters, K.S.; Berson, J.A. *J. Amer. Chem. Soc.* **1986**, *108*, 8088.

14. Major isomer 12, R=COPh: δ ($CDCl_3$) 8.24 (s, 1H), 8.10 (d, 2H), 7.67 (t, 1H), 7.54 (t, 2H), 3.62-3.35 (m, 4H), 3.07 (dd, 1H, J=15, 8 Hz) and 2.97 (ddd, 1H, J=16, 7, 2 Hz). Minor isomer 13: 8.00 (d, 2H), 7.65-7.44 (m, 7H), 7.22 (d, 2H), 4.09 (dd, 1H, J=17, 2.6Hz), 3.66-3.41 (m, 3H), 3.23 (dd, 1H, J=16, 3Hz) and 2.99 (dd, 1H, J=16, 8Hz). This structure assignment is consistent with deshielding of the proximate methylene hydrogens in 13 by the 1-benzoyl substituent. Steric hindrance in 13 is more severe than in 12 and this is also consistent with the predominance of 12 at equilibrium.

15. Mitkidou, S.; Stephanidou-Stephanatou, J. *Tetrahedron Lett.* **1990**, *31*, 5197.

16. Chauhan, P.M.S.; Crew, A.P.A.; Jenkins, G.; Storr, R.C.; Walker, S.M.; Yelland, M. *Tetrahedron Lett.* **1990**, *31*, 1487.

(Received in UK 10 October 1991)