Tetrahedron Letters,Vol.28,No.48,pp 6085-6088,1987	0040-4039/87 $3.00 + .00
Printed in Great Britain	Pergamon Journals Ltd.

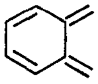
2,3-DIMETHYLENE-2,3-DIHYDROTHIOPHENE: THE THIOPHENE ANALOGUE OF ORTHO-XYLYLENE

Derek J. Chadwick* and Andrew Plant

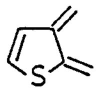
The Robert Robinson Laboratories, Department of Organic Chemistry,
Liverpool University, PO Box 147 Liverpool, L69 3BX, UK

Abstract: The hitherto unknown 2,3-dimethylene-2,3-dihydrothiophene (the thiophene analogue of ortho-xylylene) and a substituted derivative have been prepared in solution and trapped as Diels-Alder adducts in good to excellent yields.

ortho-Xylylene 1 has found wide application in organic chemistry, notably in the synthesis of natural products including steroids,[1] alkaloids,[2] and anthracyclinones.[3] We have now developed routes to the hitherto unreported[§] thiophene analogue of o-xylylene 2 (and to a substituted congener) based upon a directed metallation strategy for the construction of appropriate precursor molecules.



1

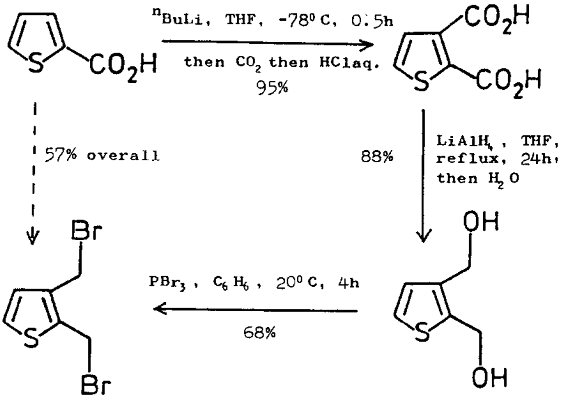


2

Our first approach utilizes the mono-anion of thiophene-2-carboxylic acid to direct lithiation into the β (3) position.[4] This permits the synthesis of 2,3-di(bromomethyl)thiophene 3 from thiophene-2-carboxylic acid in three, simple, steps (Scheme I). Treatment of the bis-bromide 3 with sodium iodide in dimethylformamide at 80°C in the presence of a dienophile[5] leads to the generation of 2,3-dimethylene-2,3-dihydrothiophene 2 which is trapped as its Diels-Alder adduct in good yield (Table I). Xylylene adducts 4 and 5

[§] Dr. Jan Skramstad, Department of Chemistry, University of Oslo, has advised us that he will shortly be reporting the synthesis and trapping of a phenyl-substituted derivative of this system.

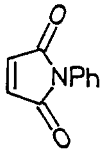
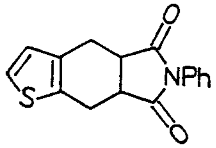
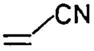
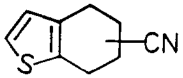
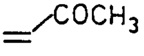
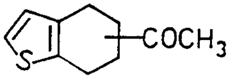
are obtained as mixtures of regioisomers. In the absence of dienophile, only polymeric material results.



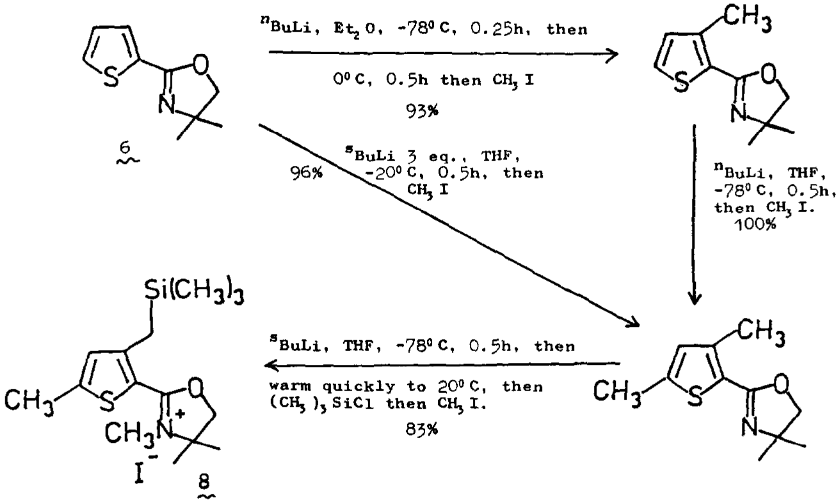
3

Scheme I

Table I Diels-Alder Trapping Experiments on o-Xylylene Analogue 2

Dienophile	Product	Yield (%)
		60
	 4	60
	 5	50

In a second approach to the thiophene o-xylylene system, oxazoline-directed metallation of 4,4-dimethyl-2-(2-thienyl)oxazoline[6] 6 provides access to the key, β-substituted, intermediates (Scheme II).



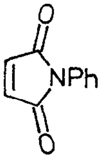
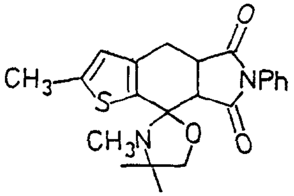
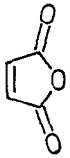
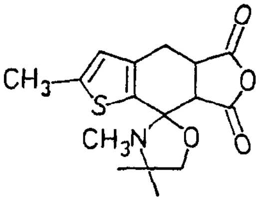
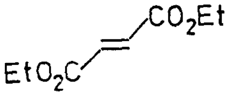
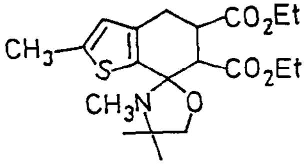
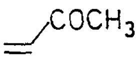
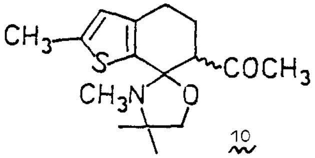
Scheme II

Lithiation of the 3,5-dimethyl-2-thienyloxazoline 7 occurs exclusively at the 3-methyl group. Reaction of the lithio-intermediate with chlorotrimethylsilane and methylation of the oxazoline nitrogen yields the required o-xylylene precursor 8. Treatment of this with caesium fluoride and acetonitrile in the presence of a dienophile[7] leads to the generation of a derivative of 2,3-dimethylene-2,3-dihydrothiophene bearing electron-donating substituents 9 which is trapped as its Diels-Alder adduct in high yield (Table II). Adduct 10 is obtained as a 1:1 mixture of diastereomers but is a single regioisomer.

We are currently applying these approaches to the preparation of other heterocyclic analogues of o-xylylene and investigating their synthetical utility.

Acknowledgment. A.P. is indebted to the SERC for the award of a studentship.

Table II Diels-Alder Trapping Experiments on o-Xylylene Analogue **9**

Dienophile	Product	Yield (%)
		74
		77
		85
	 **10**	87

References

(1) Funk, R.L. and Vollhardt, K.P.C. Chem.Soc.Rev. 1980, **9**, 41-61; Oppolzer, W. Synthesis 1978, 793-802; Kametani, T. and Nemoto, H. Tetrahedron 1981, **37**, 3-16; Djuric, S., Sarkar, T., and Magnus, P. J.Am.Chem.Soc. 1980, **102**, 6885-6.

(2) Oppolzer, W. and Keller, K. J.Am.Chem.Soc. 1971, **93**, 3836-7.

(3) Kerdesky, F.A.J., Ardecky, R.J., Lukshmikanthon, M.V., and Cava,M.P. J.Am.Chem.Soc. 1981, **103**, 1992-6.

(4) Carpenter, A.J. and Chadwick, D.J. Tetrahedron Lett. 1985, **26**, 1777-80.

(5) Saroja, B. and Srinivasan, P.C. Tetrahedron Lett. 1984, **25**, 5429-30.

(6) Carpenter, A.J. and Chadwick, D.J. J.Chem.Soc. Perkin Trans. I 1985, 173-181.

(7) Ito, Y., Amino, Y., Nakatsuka, M. and Saegusa, T. J.Am.Chem.Soc. 1983, **105**, 1586-90.

(Received in UK 7 October 1987)