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Generation of Isothiazole Analogues of *o*-Quinodimethane from Isothiazolo-3-sulfolenes

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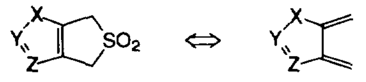
Abstract: The previously unknown isothiazole analogues of *o*-quinodimethane can be generated from the isoxazolo-3-sulfolenes and trapped with N-phenyl maleimide or dimethyl acetylenedicarboxylate. Copyright © 1996 Elsevier Science Ltd

Since Crew *et al.*[1] described that the highly reactive thiophene *o*-quinodimethane could be generated from thieno-3-sulfolene and efficiently intercepted by a number of dienophiles, increasing attention has been devoted to the synthesis of heterocycle-fused 3-sulfolenes. Although many of 5-membered heterocycle-fused sulfones **1a-g** have been prepared as synthetic equivalents to *o*-quinodimethanes **2a-g**,[2,3] the synthesis of isothiazolo-3-sulfolene **1h** (X = S, Y = N, Z =CR) and the generation of diene **2h** therefrom still remain unexplored.



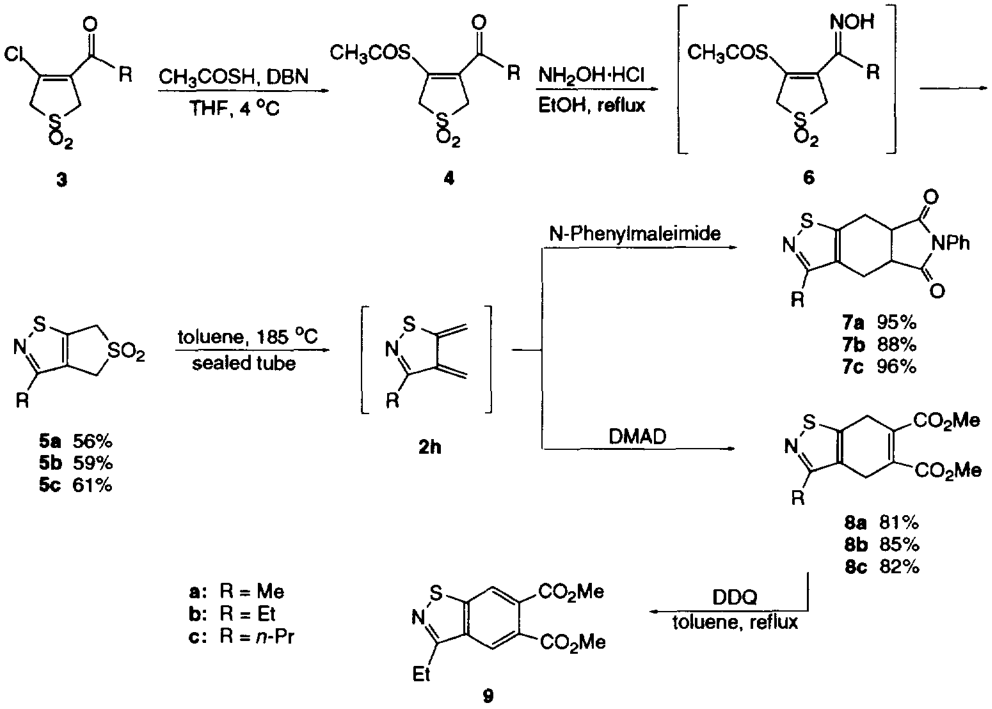
1 **2**

a X = O, Y = Z = CH, **b** X = NH, Y = Z = CH
c X = S, Y = Z = CH, **d** X = O, Y = N, Z = CH
e X = O, Y = CH, Z = N, **f** X = NH, Y = N, Z = CH
g X = O, Y = N, Z = CH, **h** X = S, Y = N, Z = CR

Our interest was focused on the unknown isothiazole *o*-quinodimethane **2h** as it might be readily trapped by dienophiles in [4 + 2] reaction to provide a new route to 1,2-benzisothiazole derivatives, a class of compounds with biological activity in the medical and agrochemical fields.[4]

Our approach to **2h** started with the β-chlorovinyl ketones **3**.[5] Treatment of compound **3b** (R = Et) with thiolacetic acid (1.8 equiv.) and 1,5-diazobicyclo[4.3.0]non-5-ene (DBN, 1 equiv.) in THF, for example, produced the 3-acetylthio-4-propionyl-3-sulfolene **4b** after standard work up. Reaction of the crude **4b**[6] with an excess amount of hydroxylamine hydrochloride (6 equiv.) in refluxing ethanol gave 59% overall yield of 3-ethyl-4,6-dihydrothieno[3,4-d]isothiazole 5,5-dioxide **5b** from **3b**, presumably via the oxime intermediate **6b**.[7] The structure of **5b**[8] was confirmed by NMR and mass spectra, the latter showing a highest mass peak at m/z 203 corresponding to the M^+. Heating a toluene solution of **5b** in the presence of N-phenylmaleimide or dimethyl acetylenedicarboxylate (DMAD) at 185 °C in sealed tube afforded the cycloadducts **7b** and **8b** in 88% and 85% yields, respectively. Subsequent oxidation of **8b** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ, 2.5 equiv.) in refluxing toluene afforded 60% yield of the 1,2-benzisothiazole **9**.

To be noteworthy is that, according to a similar reported synthesis of substituted isothiazoles,[9] attempts to prepare the fused sulfone **5b** by reaction of **3b** with ammonium thiocyanate in acetone failed (starting material **3b** was recovered quantitatively). The formation of **5a** (R = Me) and **5c** (R = *n*-Pr) in resonable yields demonstrated that compound **4** may serve as a useful building block for the synthesis of isothiazole-fused sulfone.[10]



References and Notes

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

2 For recent reviews, see (a) Chou, T. S. *Rev. Heteroatom. Chem.*, **1993**, *8*, 65; (b) Ando, K.; Takayama, H. *Heterocycles* **1994**, *37*, 1417.

3 Chou, T. S.; Chen, H. C.; Tsai, C. Y. *J. Org. Chem.*, **1994**, *59*, 2241.

4 De, A. *Prog. Med. Chem.*, **1981**, *18*, 117.

5 Tso, H. H.; Yang, N. C; Chang, Y. M. *J. Chem. Soc., Chem. Commun.*, **1995**, 1349.

6 Compound **4b** has been isolated in 50% yield by flash chromatography on silica gel. NMR spectral data ($CDCl_3$), δ: ^1H, 1.13 (t, 3 H, $J = 7.2$ Hz), 2.44 (s, 3 H), 2.62 (q, 2 H, $J = 7.2$ Hz), 4.13 (s, 2 H), 4.52 (s, 2 H); ^{13}C, 7.4, 31.0, 36.1, 56.0, 60.2, 133.6, 133.9, 191.7, 196.4. Treatment of **4b** with the hydroxylamine hydrochloride in refluxing ethanol afforded 49% yield of **5b**.

7 Dieter, R. K.; Chang, H. J. *J. Org. Chem.*, **1989**, *54*, 1088.

8 NMR spectral data ($CDCl_3$), δ: ^1H, 1.33 (t, 3 H, $J = 7.5$ Hz), 2.79 (q, 2 H, $J = 7.5$ Hz), 4.29 (s, 2 H), 4.52 (s, 2 H); ^{13}C, 11.8, 25.9, 54.9, 55.9, 128.8, 152.0, 167.4.

9 Schulze, B.; Dirsten, G.; Kirrbach, S.; Rahm, A.; Heimgartner, H. *Helv. Chim. Acta*, **1991**, *74*, 1059 and references cited therein.

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