# Quinoxalino-fused sultines and their application in Diels–Alder reactions

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**The synthesis of 7,8-disubstituted quinoxalino[2,3-*d*]-[1,2λ⁴]oxathiine 2-oxides 7a–c, precursors for quinoxalino-*o*-quinodimethanes 3a–c, and their application in the Diels–Alder reactions are reported.**

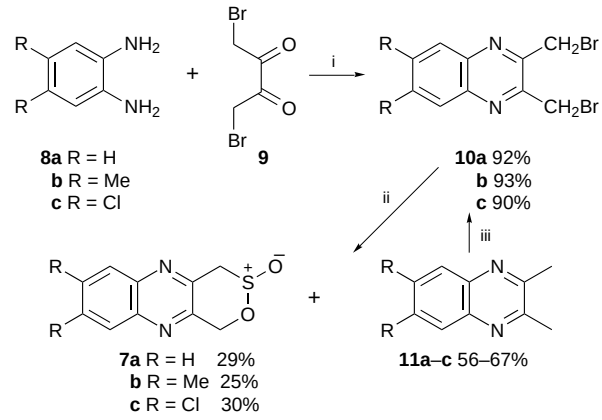
The chemistry of heterocyclic *o*-quinodimethanes **1** has attracted a great deal of attention recently.[1] Various methods for generating these highly reactive dienes have been developed.[2] Among them, cheletropic elimination of $SO_2$ from heteroaromatic-fused 3-sulfolenes **2** has drawn the most attention.[1–3] Quinoxalines are important naturally occurring heterocycles and are usually found to have biological and pharmaceutical activity.[4] Finding an easy, high-yield method for generating quinoxalino-*o*-quinodimethanes **3** is thus of particular interest.

Although Chou *et al*. reported[5] generating quinoxalino-*o*-quinodimethanes **3a** using $SO_2$ extrusion of the quinoxalino-fused sulfolene **4**, all their attempts to isolate the Diels–Alder adducts failed. Recently we described[6] the generation of nonclassical heteroaromatic *o*-quinodimethanes **5** by thermal extrusion of $SO_2$ from corresponding sultines **6**. A significant advantage of using sultines is that their thermolysis occurs at a much lower temperature than that of corresponding sulfolenes.[6–8] We report here our work on the synthesis of quinoxalino-fused sultines **7a–c** and their applications in Diels–Alder reactions with alkenes and alkynes.

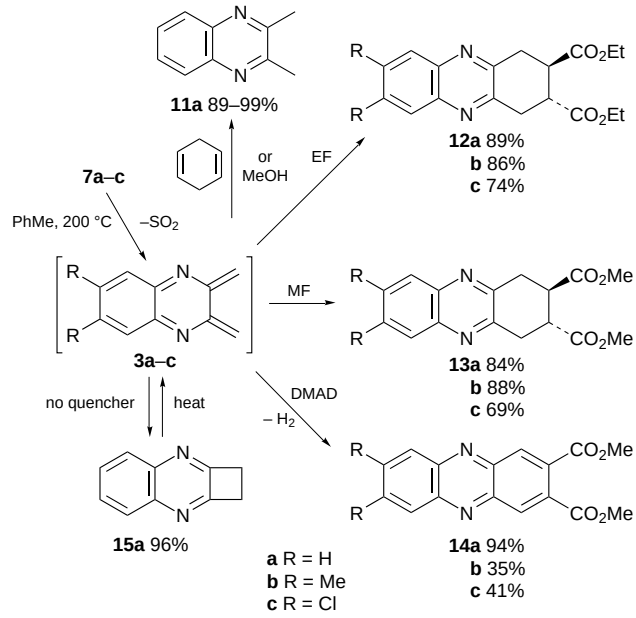
Previously unknown sultines **7a–c** were synthesized in two steps with good yields as shown in Scheme 1. Reaction of the appropriate *o*-diamino-substituted benzene **8** with 1,4-dibromobutane-2,3-dione **9** gave the known 2,3-bis(bromomethyl)quinoxaline **10a**,[9a] 6,7-dimethylquinoxaline **10b**,[4,9b] and 6,7-dichloroquinoxaline **10c**.[4] The desired quinoxalino-fused sultines **7a–c**† and by-products **11** were obtained by the use of Rongalite[8] (sodium formaldehyde sulfoxylate) with the corresponding dibromides **10a–c**. Although the yields of sultines **7a–c** were only *ca*. 30%, fortunately the by-product **11** can be converted back to dibromide **10** *via* *N*-bromosuccinimide bromination,[4b] which makes the syntheses of the sultines more efficient.

The Diels–Alder reactions of quinoxalino-fused sultines **7a–c** with several dienophiles are presented in Scheme 2. When heated in toluene (200 °C, sealed tube) in the presence of 3 equiv. of diethyl fumarate (EF) or dimethyl fumarate (MF), the sultines **7a–c** all underwent extrusion of $SO_2$ and the resulting quinoxalino-*o*-quinodimethanes **3a–c** were intercepted as the 1 : 1 adducts (**12** and **13**) in 69–89% yield. The reactions with dimethyl acetylenedicarboxylate (DMAD) went similarly to 1 : 1 adducts and after loss of $H_2$ gave **14a–c** in 35–94% yield.

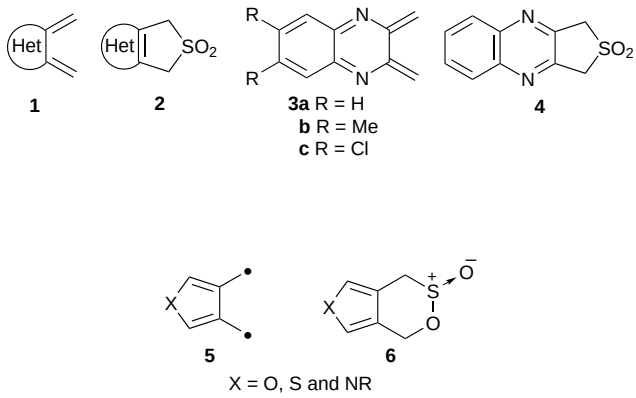
In the absence of a dienophile, sultine **7a** underwent thermal extrusion of $SO_2$ and formed the cyclobuta[1,2-*b*]quinoxaline **15a** almost quantitatively. In contrast, **15a** was reported[5] to be isolated only in low yield (10%) when the corresponding sulfolene **4** was flash pyrolysed at 500 °C followed by addition of excess *N*-phenylmaleimide (NPM). Thermolysis of **7a** in the presence of methanol or cyclohexa-1,4-diene, on the other hand, gave 2,3-dimethylquinoxaline **11a** in 89–99% yield. Inter-




**Scheme 1** *Reagents and conditions*: i, benzene, reflux, 1 h; ii, Rongalite, DMF, 0 °C, 7 h; iii, NBS




**Scheme 2**



estingly, Diels–Alder adducts (such as **12**–**14a**) were also formed in excellent yield when the cyclobutene **15a** was heated in the presence of dienophiles at 200 °C, indicating that cyclobutene **15a** is also a good precursor of *o*-quinodimethane **3a**.

The reaction of **7a**–**c** with excess NPM at 200 °C gave a pair of new adducts **16** and **17** in 47–68% yields (Scheme 3). These 2 : 1 adducts showed similar spectral characteristics, consistent with the *cis* and *trans* cyclooctaquinoxalines **16** and **17**.‡ When only 1 equiv. of NPM was used, the yield of 1 : 1 adduct **18b** was optimized to 72% and the 2 : 1 adducts (**16** and **17**) were present in only trace amounts. Similar observation of these 2 : 1 adducts in the trapping of pyrimidine *o*-quinodimethanes by NPM has been reported recently by Tomé *et al.*[3a,c] We were, however, surprised to see that different adducts were reported[10] when **10a** was heated with sodium iodide in the presence of NPM, even though this method is generally assumed to give a synthetic equivalent of *o*-quinodimethane **3a**. The real reason for this difference may be just as the authors described:[10] the reaction of **10a** and sodium iodide probably did not involve dehalogenation to give a true *o*-quinodimethane **3a**, but rather the adducts might have been formed by a mechanism involving displacement of a halogen atom by the dienophile.

Thus our results, obtained by pyrolysing 7,8-disubstituted quinoxalino-fused sultines **7a**–**c**, strongly support the formation of quinoxalino-*o*-quinodimethanes **3a**–**c**, which differ from the products formed when sulfolene **4** is pyrolysed, or when **10a** and sodium iodide react.[10] The easily synthesized sultines **7a**–**c** reacted under milder conditions (200 °C) than the corresponding sulfolene **4** (⩾290 °C is required) and their reaction products were different in many cases. When generated in the presence of a dienophile, sultines **7a**–**c** provided elegant synthons for the formation of [4 + 2] cycloadducts. If no trapping agents were used, the sultines gave cyclobuta[1,2-*b*]quinoxaline **15** almost quantitatively, which again is a good precursor of *o*-quinodimethanes **3**. Further work to study the mechanism by laser flash photolysis is in progress.

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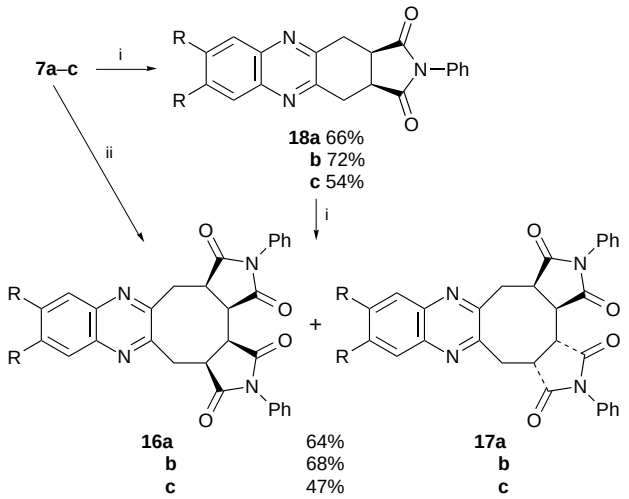


**Scheme 3** *Reagents and conditions*: i, NPM (1 equiv.), toluene, 200 °C; ii, NPM (3 equiv.), toluene, 200 °C

## Footnotes

† Cyclobuta[1,2-*b*]quinoxaline **15** has been reported in the literature (ref. 5) and our samples correspond in all aspects with the reported properties. Satisfactory spectral data were obtained for all products. *Selected data* for **7a**: white solid, mp 137–138 °C; $^1$H NMR (300 MHz, $CDCl_3$) δ 8.08–8.03 (2 H, m), 7.82–7.77 (2 H, m), 5.63 (1 H, AB, *J* 16.1 Hz), 5.32 (1 H, AB, *J* 15.6 Hz), 4.59 (1 H, A′B′, *J* 16.1 Hz) and 4.14 (1 H, A′B′, *J* 16.1 Hz); $^{13}$C NMR (75.4 MHz, $CDCl_3$), δ 147.11 ($C_q$), 142.51 ($C_q$), 142.10 ($C_q$), 141.45 ($C_q$), 130.68 (CH), 130.39 (CH), 128.82 (CH), 128.77 (CH), 62.56 ($CH_2$) and 57.92 ($CH_2$); *m/z* 220 ($M^+$, 23%), 156 ($M^+ - SO_2$, 100), 129 (16), 102 (15). For **7b**: white solid, mp 158–159 °C; $^1$H NMR δ 7.79 (2 H, s), 5.61 (1 H, AB, *J* 15.6 Hz), 5.28 (1 H, AB, *J* 15.6 Hz), 4.57 (1 H, A′B′, *J* 16.6 Hz), 4.08 (1 H, A′B′, *J* 16.6 Hz) and 2.50 (6 H, s); $^{13}$C NMR, 145.98 ($C_q$), 141.55 ($C_q$), 141.43 ($C_q$), 141.12 ($C_q$), 140.83 ($C_q$), 140.43 ($C_q$), 127.68 (CH), 127.65 (CH), 62.64 ($CH_2$), 57.93 ($CH_2$), 20.39 (Me) and 20.36 (Me); *m/z* 248 ($M^+$, 21), 184 ($M^+ - SO_2$, 100), 169 (38), 103 (9). For **7c**: orange solid, mp 205–206 °C, $^1$H NMR δ 8.17 (2 H, s), 5.59 (1 H, AB, *J* 16.1 Hz), 5.30 (1 H, AB, *J* 16.1 Hz), 4.54 (1 H, A′B′, *J* 16.5 Hz) and 4.13 (1 H, A′B′, *J* 16.4 Hz); $^{13}$C NMR, 148.40 ($C_q$), 143.53 ($C_q$), 141.15 ($C_q$), 140.16 ($C_q$), 135.46 ($C_q$), 135.20 ($C_q$), 129.48 (CH), 129.43 (CH), 62.32 ($CH_2$) and 57.76 ($CH_2$); *m/z* 288 ($M^+$, 8), 224 (100), 226 (63), 189 (40), 154 (2).

‡ *Selected data* for a 1 : 1 mixture of **16a** and **17a**: $^{13}$C NMR δ 178.93 ($C_q$), 177.22 ($C_q$), 176.13 ($C_q$), 175.90 ($C_q$), 151.80 ($C_q$), 151.12 ($C_q$), 141.51 ($C_q$), 140.69 ($C_q$), 132.23 ($C_q$), 131.35 ($C_q$), 130.26 (CH), 130.06 (CH), 129.17 (CH), 129.80 (CH), 128.96 (CH), 128.89 (CH), 128.82 (CH), 128.39 (CH), 126.47 (CH), 126.37 (CH), 42.42 (CH), 41.19 (CH), 39.64 (CH), 38.08 (CH), 34.27 ($CH_2$), 32.48 ($CH_2$); *m/z* 502 ($M^+$, 36), 381 (54), 329 ($M^+$ − NPM, 52), 181 (100) (Found: $M^+$, 502.1652. $C_{30}H_{22}N_4O_4$ requires *M*, 502.1641). Currently, stereochemistry cannot be assigned unambiguously.

## References

1 For recent review, see R. A. Aitken, I. Gosney and J. I. G. Cadogan, *Prog. Heterocycl. Chem.*, 1992, **4**, 1; 1993, **5**, 1; T.-S. Chou, *Rev. Heteroatom Chem.*, 1993, **8**, 65; K. Ando and H. Takayama, *Heterocycles*, 1994, **37**, 1417; K. Ando, M. Kankake, T. Suzuki and H. Takayama, *Tetrahedron*, 1995, **51**, 129.

2 J. L. Charlton and M. M. Alauddin, *Tetrahedron*, 1987, **43**, 2873; R. L. Funk and K. P. C. Vollhardt, *Chem. Soc. Rev.*, 1980, **9**, 41; W. Oppolzer, *Synthesis*, 1978, 793; K. C. Nicolaou, W. E. Barnette and P. Ma, *J. Org. Chem.*, 1980, **45**, 1463.

3 (*a*) A. C. Tomé, J. A. S. Cavaleiro and R. C. Storr, *Tetrahedron*, 1996, **52**, 1735; 1723; (*b*) L. A. White, P. M. O'Neill, B. K. Park and R. C. Storr, *Tetrahedron Lett.*, 1995, **36**, 5983; (*c*) A. C. Tomé, J. A. S. Cavaleiro and R. C. Storr, *Tetrahedron Lett.*, 1993, **34**, 6639; (*d*) P. M. S. Chauhan, A. P. A. Crew, G. Jenkins, R. C. Storr, S. M. Walker and M. Yelland, *Tetrahedron Lett.*, 1990, **31**, 1487; 1491.

4 (*a*) D. Villemin and B. Martin, *Synth. Commun.*, 1995, **25**, 2319; (*b*) R. B. Baudy, L. P. Greenblatt, I. L. Jirkovsky, M. Conklin, R. J. Russo, D. H. Bramlett, T. A. Emrey, J. T. Simmonds, D. M. Kowal, R. P. Stein and R. P. Tasse, *J. Med. Chem.*, 1993, **36**, 331.

5 T.-S. Chou and C.-W. Ko, *Tetrahedron*, 1994, **50**, 10 721.

6 W.-S. Chung, W.-J. Lin, W.-D. Liu and L. G. Chen, *J. Chem. Soc., Chem. Commun.*, 1995, 2537.

7 For a review of sultines, see D. C. Dittmer and M. D. Hoey, *The Chemistry of Sulphinic Acids, Esters and Their Derivatives*, Wiley, Chichester, 1990, pp. 239–273.

8 M. D. Hoey, D. C. Dittmer, *J. Org. Chem.*, 1991, **56**, 1947; W. F. Jarvis, M. D. Hoey, A. L. Finocchio and D. C. Dittmer, *J. Org. Chem.*, 1988, **53**, 5750; G. Attardo, W. Wang, J.-L. Kraus and B. Belleau, *Tetrahedron Lett.*, 1994, **35**, 4743.

9 (*a*) M. M. Roland and R. C. Anderson, *J. Heterocycl. Chem.*, 1977, **14**, 541; (*b*) J. Pohmer, M. V. Lakshimikantham and M. P. Cava, *J. Org. Chem.*, 1995, **60**, 8283.

10 N. E. Alexandrou, G. E. Mertzanos, J. Stephanidou-Stephanatou, C. A. Tsoleridis and P. Zachariou, *Tetrahedron Lett.*, 1995, **36**, 6777.

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