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

Wen-Sheng Chung* and Jing-Horng Liu

Department of Applied Chemistry, National Chiao Tung University, Hsinchu, Taiwan 30050, R.O.C.

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.

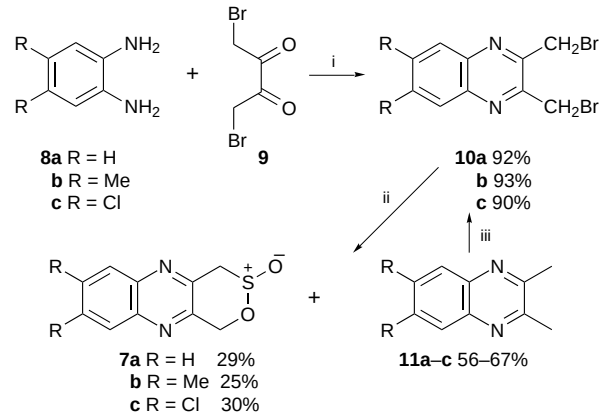
The chemistry of heterocyclic *o*-quinodimethanes **1** has attracted a great deal of attention recently.[1] Various methods for generating these highly reactive dienes have been developed.[2] Among them, cheletropic elimination of SO_2 from heteroaromatic-fused 3-sulfolenes **2** has drawn the most 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.

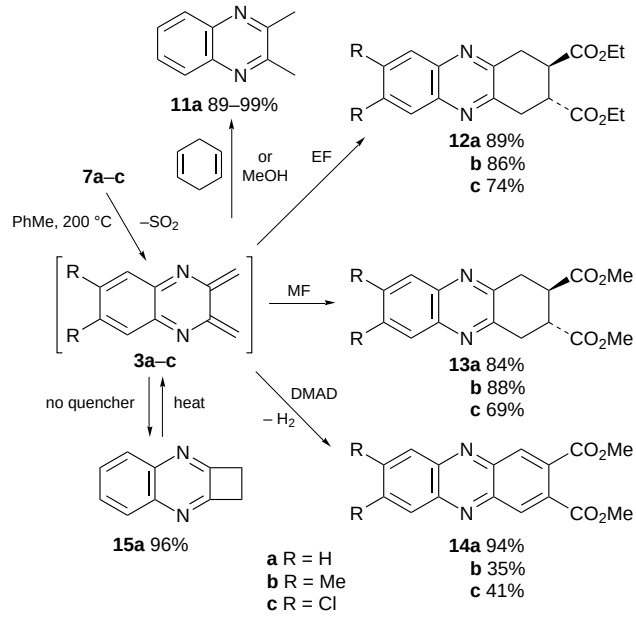
Previously unknown sultines **7a**–**c** were synthesized in two steps with good yields as shown in Scheme 1. Reaction of the appropriate *o*-diamino-substituted benzene **8** with 1,4-dibromobutane-2,3-dione **9** gave the known 2,3-bis(bromomethyl)quinoxaline **10a**,[9a] 6,7-dimethylquinoxaline **10b**,[4,9b] 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.

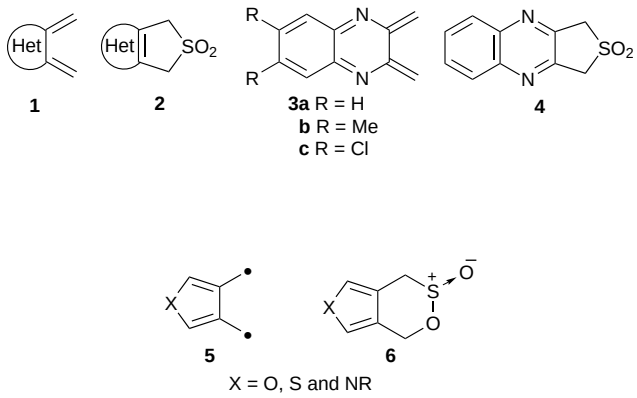
In the absence of a dienophile, sultine **7a** underwent thermal extrusion of SO_2 and formed the cyclobuta[1,2-*b*]quinoxaline **15a** almost quantitatively. In contrast, **15a** was reported[5] to be isolated only in low yield (10%) when the corresponding sulfolene **4** was flash pyrolysed at 500 °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

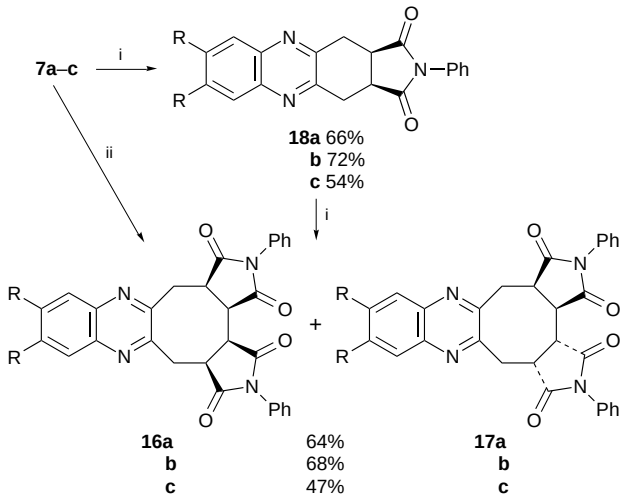


estingly, Diels–Alder adducts (such as **12**–**14a**) were also formed in excellent yield when the cyclobutene **15a** was heated in the presence of dienophiles at 200 °C, indicating that cyclobutene **15a** is also a good precursor of *o*-quinodimethane **3a**.

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.

We thank the National Science Council of the Republic of China for its financial support (Grant No. NSC 85-2113-M-009-002).



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.

Received, 2nd October 1996; Com. 6/06764F