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Pyrazino-*O*-Quinodimethanes from Pyrazine-Fused 3-Sulfolenes

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Abstract

We have developed a simple one-pot reaction to synthesize pyrazino-3-sulfolenes **7a-c**. The synthesis was accomplished by treating a mixture of an α-dicarbonyl **14a-c** and 3,4-diazido-2-sulfolene **13** in the presence of PPh_3. The corresponding *o*-quinodimethanes were generated by thermolysis of **7a-c** and trapped with dienophiles.

Keywords: Pyrazino-3-sulfolenes, pyrazine-fused 3-sulfolenes, thermolysis, *o*-quinodimethanes

It is now well established that heteroaromatic-fused 3-sulfolenes **1** serve as good precursors for the corresponding heteroaromatic *o*-quinodimethanes **2** which are highly reactive and structurally interesting [1]. The existence of **2** is most frequently demonstrated by the formation of Diels-Alder cycloadducts **3** when generated in the presence of proper dienophiles [2], and less frequently detected spectroscopically at low temperatures [3]. With only a few exceptions [4], compounds **1** usually lose SO_2 upon thermolysis at about 160–180 °C.

We recently reported an efficient synthesis of quinoxalino-3-sulfolenes **4** [5] and have discovered that the removal of SO_2 from this molecules require a high temperature (>290 °C). Interestingly, Diels-Alder cycloadducts were not produced when the *o*-quinodimethane **5** was generated from **4**. A fused cyclobutene **6** was formed, instead. Stephanidou-Stephanatou et al. [6] reported later the generation of **5** from a different precursor by reductive 1,4-elimination at a lower temperature and they were successful in trapping **5** with dimethyl acetylenedicarboxylate. A possible factor for the unusual difficulty in the extrusion of SO_2 from **4** is the low bond order between C_3 and C_4 of the 3-sulfolene moiety [5, 7]. In order to understand whether the C_3-C_4 bond order is a general factor governing the SO_2 extrusion temperature from various fused 3-sulfolenes, we carried out the study of a related system, the so far unknown pyrazino-3-sulfolene **7**, where the C_3-C_4 bond order is different from that in **4**.

The first route that we tried in the synthesis of **7** was based on the same strategy as we used for the preparation of **4** [5] which involves the reaction of *o*-phenylenediamine with either 3,4-dibromosulfolane **8** [8] or 4-bromo-3-sulfolanone **9** [9] and subsequent oxidative aromatization. Unfortunately, the reactions of ethylenediamine **10** or diaminomaleonitrile **11** with either **8** or **9** produced only complex mixtures containing no desired products. (Scheme 2)

An alternative route would be to use 3,4-diaminosulfolane **12** [10] condensed with an α-dicarbonyl compound. However, compound **12** is known to dimerize read-

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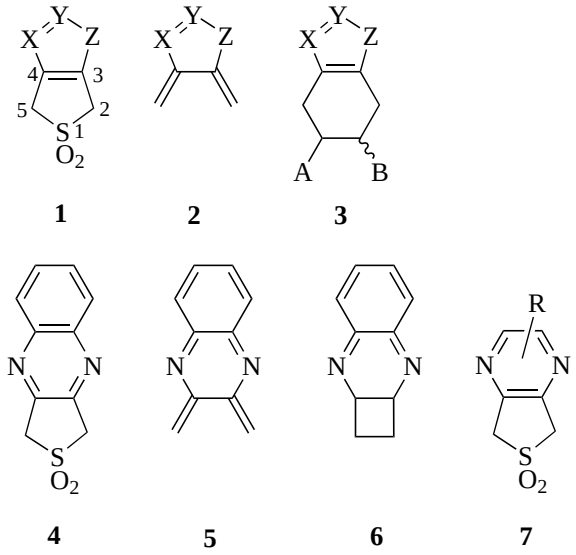


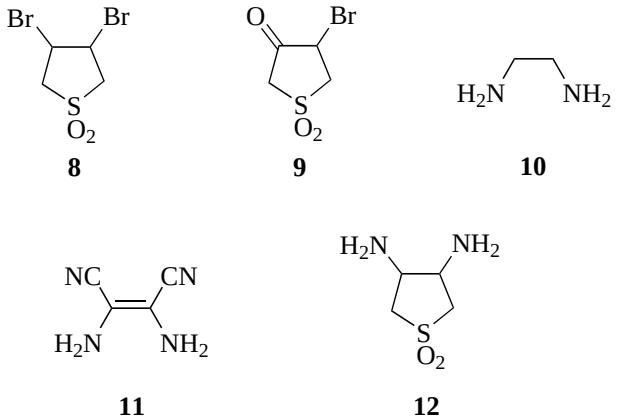
1 **2** **3**

4 **5** **6** **7**

X, Y= CR or N
Z= NR, O, S, C=N

Scheme 1

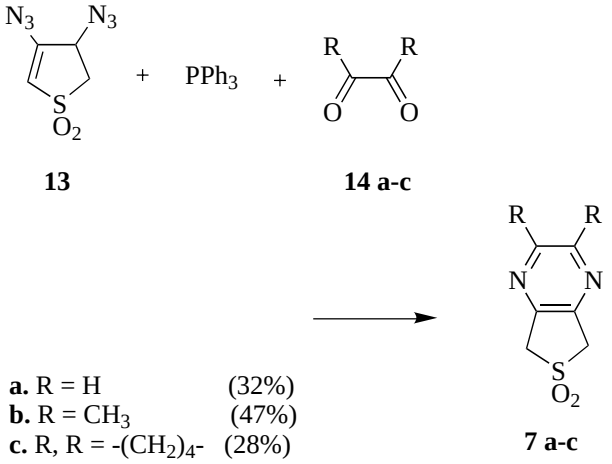
ily. Moreover, the condensation product from **12** and an α-dicarbonyl would have a lower degree of unsaturation than the desired aromatic pyrazino-3-sulfolene **7**. For these reasons, diazido-2-sulfolene **13** [11] was used as our starting material. When a mixture of **13** and glyoxal **14a** in THF was heated in the presence of PPh_3, the 3-sulfolene **7a** was produced in 32% yield (Scheme 3). Although the exact steps in the progress of the reaction have not been clarified, intermediate phosphine imines and sequential inter- and intramolecular aza-Wittig reactions [12] must have been involved. Under similar conditions, compounds **7b** and **7c** were prepared from 2,3-butanedione **14b** and 1,2-cyclohexanedione **14c**, respectively.



8 **9** **10**

11 **12**

Scheme 2



13 **14 a-c**

a. R = H (32%)
b. R = CH_3 (47%)
c. R, R = -$(CH_2)_4$- (28%)

7 a-c

Scheme 3

It was found that compounds **7a-c** lose SO_2 only at temperatures above 290 °C indicating the thermolysis of **7** to be more difficult than that of benzo-3-sulfolenes **15** which requires 240 °C or higher [13]. The preferred temperature for efficient thermolysis of **7** is 300 °C. In the presence of dienophiles, the pyrazino-*o*-quinodimethane intermediates **16a-c** can be trapped as Diels-Alder cycloadducts (Scheme 4) and the results are summarized in Table 1.

The reactions of dimethyl fumarate **17** or fumaronitrile **18** with all of these *o*-quinodimethanes **16a-c** proceeded smoothly (entries 1, 2, 3, 4, 8 and 9). The trapping of **16b** with *N*-phenylmaleimide **19** was unsuccessful (entry 5). Neither starting material **7b** nor the desired cycloadduct was detected in the complex product mixture when **7b** was heated with **19** at 300 °C for 6 h. The reason for this failure is the decomposition of **19** at elevated temperatures. We found that within 1 h compound **19** completely disappeared when it was heated as a solution in toluene at 300 °C.

The desired cycloadduct **24** was not obtained in the reaction of **7b** with the vinyl sulfone **20** (entry 6), the obtained product was dimethylquinoxaline **25** which should be the secondary product from **24** via elimination of $PhSO_2H$ and subsequent oxidative aromatization.

The reaction of **7b** with dimethyl maleate **21** (10 equiv) produced a mixture of the expected cycloadduct **26** (29%) and its *trans* isomer **22b** (46%) (entry 7). Since it is unlikely that the cycloaddition reaction proceeds via a stepwise non-stereoselective pathway, the formation of **22b** serves as an indication of the existence of dimethyl fumarate **17** in the reaction medium. One possibile source of **17** is contamination in the starting material, the reagent grade dimethyl maleate. When we examined the starting material **21** by NMR, we found that it did indeed contain less than 2% of the fumarate **17**. However, this contamination could not account for more than 20% of the cycloadduct

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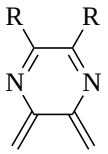
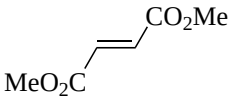
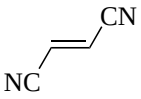


16 a-c



17

a. R = H
b. R = CH_3
c. R, R = -$(CH_2)_4$-



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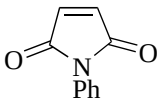

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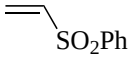

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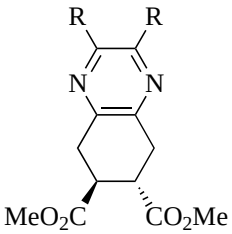
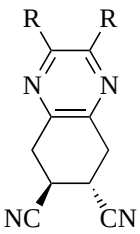
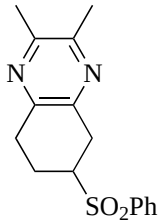


22 a-c



23 a-c



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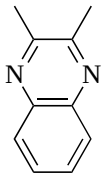

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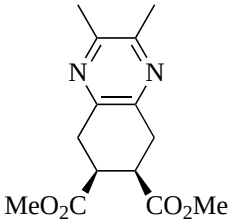

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Scheme 4

22b, considering that ten equivalents of dienophile was used and that fumarate is a far better dienophile than maleate. We then heated a toluene solution of **21** at 300 °C for 1 h and discovered that it turned into a 1:1 mixture of **17** and **21**. Therefore, the major reason for the formation of **22b** in this reaction should be the thermal isomerization of **21** to **17**.

The SO_2 extrusion temperature of **7a-c** (290–300 °C) is similar to that of quinoxalino-3-sulfolene **4** [5]. Since the C_3-C_4 bond order in **7a-c** is similar to that in **15** and significantly higher than that in **4**, the difficulty in SO_2 extrusion from **7a-c** cannot be explained satisfactorily by bond-order arguments. A more likely factor is the disturbance of the stabilization energy of the aromatic ring upon the extrusion SO_2 from 3-sulfolenes. When a benzo-3-sulfolene **15** is thermolyzed to generate the corresponding *o*-quinodimethane, the aromatic stabilization of the benzene ring is disturbed so that a high activation barrier needs to be overcome, whereas no such aromatic stabilization is involved in the thermolysis of simple 3-sulfolene to the corresponding 1,3-diene. Therefore, a higher SO_2 extrusion temperature is observed for a benzo-3-sulfolene than a non-fused 3-sulfolene. The order of the temperature required for the thermolysis of **7** (290–300 °C), **15** (210 °C) and other heteroaromatic-fused 3-sulfolenes (usually 160–180 °C) is consistent with the order of their aromatic stabilizing energies [14]. This argument can serve as an alternative explanation for the unusually high SO_2 extrusion temperature of compound **4** and naphthaleno-3-sulfolene [15].

In summary, we have prepared three pyrazino-3-sulfolenes **7a-c** and demonstrated that they are good precursors for the so far unknown pyrazino-*o*-quinodimethanes **16a-c**. The transit intermediacy of these *o*-quinodimethanes is demonstrated by trapping reactions with dienophiles. The unusually high temperature required for the thermolysis of **7a-c** can be rationalized by the high aromatic stabilization of the pyrazine ring.

Experimental Part

^{1}H-NMR spectra were determined on a Bruker AC-300 NMR spectrometer as solutions in $CDCl_3$. IR spectra were determined on a Perkin-Elmer Paragon 1000 IR spectrophotometer. Mass spectra and high resolution mass spectra were determined on a VG 70–250S mass spectrometer.

Table 1. *Diels-Alder reactions of pyrazino-o-quinodimethanes **16a-c** with dienophiles [a].*

entry	3-sulfolene	intermediate	dienophile	reaction time	cycloadduct and yield
1	**7a**	**16a**	**17**	1h	**22a** (75%)
2	**7a**	**16a**	**18**	1h	**23a** (76%)
3	**7b**	**16b**	**17**	1h	**22b** (78%)
4	**7b**	**16b**	**18**	1h	**23b** (80%)
5	**7b**	**16b**	**19**	6h	no cycloadduct
6	**7b**	**16b**	**20**	1h	**25** (64%) [b}
7	**7b**	**16b**	**21**	1h	**22b** (46%) + **26** (29%)
8	**7c**	**16c**	**17**	1h	**22c** (68%)
9	**7c**	**16c**	**18**	1h	**23c** (68%)

*[a]The reactions were performed by mixing the pyrazino-3-sulfolene **7a-c** (0.1 mmol) with a dienophile (1.0 mmol) in freshly distilled toluene (20 ml) in a sealed tube heated at 300 °C under N_2.*
*[b]See Ref. 5 for spectral data of compound **25**.*

Elemental analyses were performed on a Perkin-Elmer 240C analyzer. Dichloromethane, THF and toluene were freshly distilled from CaH_2, K and Na ,respectively, before used.

*General Procedure for the Synthesis of Pyrazino-3-sulfolene **7a-c***

To a mixture of 3,4-diazido-2-sulfolene 13 [11] (0.5 mmol) and an a-dicarbonyl **14a-c** (0.55 mmol) in anhydrous THF (5 ml), a solution of Ph_3P (1.0 mmol) in THF (5 ml) was added dropwise. The mixture was stirred at room temperature for 2.5 h and then heated under reflux for 15 h. After the solvent was removed under reduced pressure, the crude oil was purified by column chromatography (silica gel, hexane/EtOAc, 2:1) to give the pure product **7a-c**.

*2,4-Dihydrothieno[3, 4-b]pyrazine 3,3-Dioxide (**7a**)*

Obtained from the reaction of **13** with glyoxal **14a** in 32% yield as a white solid: mp 188–189 °C; IR (KBr) 2902, 1382, 1316, 1222, 1131 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 4.60 (s, 4H), 8.58 (s, 2H). MS *m/z* 170 (M^+), 106 (100%), 79. HRMS calcd. for $C_6H_6N_2O_2S$ 170.0150, found 170.0151.

*2,3-Dimethyl-5,7-dihydrothieno[3, 4-b]pyrazine 6,6-Dioxide (**7b**)*

Obtained from the reaction of **13** with 2,3-butanedione **14b** in 47% yield as a white solid: mp 142–143 °C; IR (KBr) 2984, 2930, 1367, 1310, 1168, 1113, 978, 883, 688 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 2.57 (s, 6H), 4.50 (s, 4H); MS *m/z* 198 (M^+), 134 (100%), 119, 93, 66. Anal. Calcd. for $C_8H_{10}N_2O_2S$: C, 48.47; H, 5.08; N, 14.13. Found: C, 48.41; H, 4.81; N, 13.75.

*7,9-Dihydrothieno[3, 4-b]-2,3,4,5-tetrahydroquinoxaline 2,2-Dioxide (**7c**)*

Obtained from the reaction of **13** with 1,2-cyclohexanedione **14c** in 28% yield as a white solid: mp 195–197 °C; IR (KBr) 2978, 2951, 1379, 1302, 1225, 1120, 942, 885, 823 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.93–1.97 (m, 4H), 2.95–3.10 (m, 4H), 4.50 (s, 4H); MS *m/z* 224 (M^+), 160 (100%), 132, 79. Anal. Calcd. for $C_{10}H_{12}N_2O_2S$: C, 53.55; H, 5.39; N, 12.49. Found: C, 53.60; H, 5.18; N, 12.09.

*General Procedure for the Thermolysis of **7a-c** in the Presence of a Dienophile*

A mixture of a pyrazino-3-sulfolene **7a-c** (0.1 mmol) and a dienophile **17**–**21** (1.0 mmol) in anhydrous toluene (20 ml) was heated in a sealed tube at 300 °C for 1 h. After the solvent was removed under reduced pressure, the crude oil was purified by column chromatography (silica gel, hexane/EtOAc, 4:1) to give the pure cycloadduct. The yields are summarized in Table 1.

*trans-6,7-Dimethoxycarbonyl-5,6,7,8-tetrahydroquinoxaline (**22a**)*

A white solid: mp 164–165 °C; IR (KBr) 2953, 1735, 1435, 1406, 1314, 1199, 1159, 1005 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 3.14–3.34 (m, 6H), 3.76 (s, 6H), 8.38 (s, 2H); MS *m/z* 250 (M^+), 219, 191, 131 (100%), 104, 77. HRMS calcd. for $C_{12}H_{14}N_2O_4$ 250.0966, found 250.0954.

*2,3-Dimethyl-trans-6,7-dimethoxycarbonyl-5,6,7,8-tetrahydroquinoxaline (**22b**)*

A white solid: mp 109–111 °C; IR (KBr) 2951, 1716, 1399, 1354, 1219, 1170, 987, 916, 776 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 2.49 (s, 6H), 3.02–3.13 (m, 2H), 3.19–3.26 (m, 4H), 3.74 (s, 6H); MS *m/z* 278 (M^+), 247, 219 (100%), 159, 118, 91, 77. HRMS calcd. for $C_{14}H_{18}N_2O_4$ 278.1266, found 278.1255.

*trans-2,3-Dimethoxycarbonyl-1,2,3,4,6,7,8,9-octahydrophenazine (**22c**)*

A white solid: mp 138–140 °C; IR (KBr)2935, 2362, 1731, 1174, 1149, 1003 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.88–1.95 (m, 4H), 2.85–2.96 (m, 4H), 3.00–3.13 (m, 2H), 3.19–3.25 (m, 4H), 3.74 (s, 6H); MS *m/z* 304 (M^+), 273, 245 (100%), 185, 149, 134, 111, 97, 83, 71, 57. HRMS calcd. for $C_{16}H_{20}N_2O_4$ 304.1423, found 304.1428.

*trans-6,7-Dicyano-5,6,7,8-tetrahydroquinoxaline (**23a**)*

A white solid: mp 170–172 °C; IR (KBr)2936, 2254, 1436, 1146, 917 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 3.36–3.43 (m, 2H), 3.53–3.64 (m, 4H), 8.50 (s, 2H); MS *m/z* 184 (M^+) (100%), 157, 144, 130, 119, 106, 79. HRMS calcd. for $C_{10}H_8N_4$ 184.0749, found 184.0755.

*2,3-Dimethyl-trans-6,7-dicyano-5,6,7,8-tetrahydroquinoxaline (**23b**)*

A white solid: mp 204–206 °C; IR (KBr)2929, 2896, 2266, 1712, 1445, 1402, 1220, 1170, 987 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 2.53 (s, 6H), 3.23–3.33 (m, 2H), 3.45–3.60 (m, 4H); MS *m/z* 212 (M^+) (100%), 170, 149, 134, 103, 93, 76. Anal. Calcd. for $C_{12}H_{12}N_4$: C, 67.91; H, 5.70; N, 26.40. Found: C, 67.58; H, 5.54; N, 25.97.

*trans-2,3-Dicyano-1,2,3,4,6,7,8,9-octahydrophenazine (**23c**)*

A white solid: mp 225–227 °C; IR (KBr)2930, 2246, 1424, 1397, 1186, 1145 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.90–1.99 (m, 4H), 2.93–2.98 (m, 4H), 3.22–3.36 (m, 2H), 3.44–3.60 (m, 4H). MS *m/z* 238 (M^+), 167, 149, 111, 97, 79 (100%). HRMS calcd. for $C_{14}H_{14}N_4$ 238.1218, found 238.1217.

*2,3-Dimethyl-cis-6,7-dimethoxycarbonyl-5,6,7,8-tetrahydroquinoxaline (**26**)*

A white solid: mp 113–114 °C; IR (KBr) 2972, 1728, 1439, 1406, 1269, 1207, 997 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 2.48 (s, 6H), 3.12–3.23 (m, 2H), 3.31–3.41 (m, 4H), 3.71 (s, 6H); MS *m/z* 278 (M^+), 247, 219, 159 (100%), 118, 91, 77. HRMS calcd. for $C_{14}H_{18}N_2O_4$ 278.1266, found 278.1274.

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