Pergamon

Tetrahedron Letters, Vol. 38, No. 20, pp. 3639-3642, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)00689-8

Synthesis and Cycloaddition Reactions of Pyrrole-Fused 3-Sulfolenes: a New Versatile Route to Tetrabenzoporphyrins

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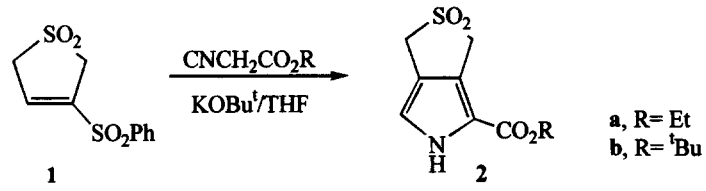
Abstract: Pyrrole-fused 3-sulfolenes **2a,b** were prepared from the corresponding α,β-unsaturated sulfone **1**. These pyrroles undergo thermal extrusion of sulfur dioxide to produce highly reactive *o*-quinodimethanes which can be trapped in Diels-Alder reactions. The resulting pyrroles are important starting reagents in porphyrin synthesis. © 1997 Elsevier Science Ltd.

Substituted pyrroles are key building blocks in the total synthesis of natural and synthetic porphyrins. A new method for preparing esters of pyrrole-2-carboxylic acids from nitroalkenes and alkyl isocyanoacetates, known as the Barton-Zard pyrrole condensation,[1] has been extensively used in porphyrin synthesis.[2] This convenient one-step method has been extended to the synthesis of 5-unsubstituted pyrrole-2-carboxylates from readily available α,β-unsaturated sulfones.[3] The phenylsulfonyl group is conveniently introduced *via* addition of phenylsulfenyl chloride[4] to olefins, followed by elimination of HCl and oxidation of the α,β-unsaturated sulfide to the corresponding α,β-unsaturated sulfone.

Extrusion of sulfur dioxide from aromatic fused 3-sulfolenes produces highly reactive *o*-quinodimethanes which can be trapped in Diels-Alder reactions.[5] Cycloaddition reactions involving heterocyclic *o*-quinodimethanes and dienophiles are an attractive route to heteropolycyclic compounds.[6] We report here the preparation of pyrrole-fused 3-sulfolenes **2**, from the α,β-unsaturated sulfone **1**, which are valuable precursors for the synthesis of tetrabenzoporphyrins. This class of porphyrins with extended π-systems have very interesting physical properties[7] and, in particular, show red shift absorptions with extinction coefficients two to three times larger than the corresponding porphyrins. Recently, benzoporphyrin derivatives have been used as photosensitizers for photodynamic therapy of cancer tissues in *in vivo* studies.[8] However, the already available synthetic methods give very low yields of tetrabenzoporphyrins together with non-desirable contaminants, that are usually difficult to separate.[9] We report here a new method for the synthesis of tetrabenzoporphyrin **8** that can also be used for the preparation of functionalized tetrabenzoporphyrins.

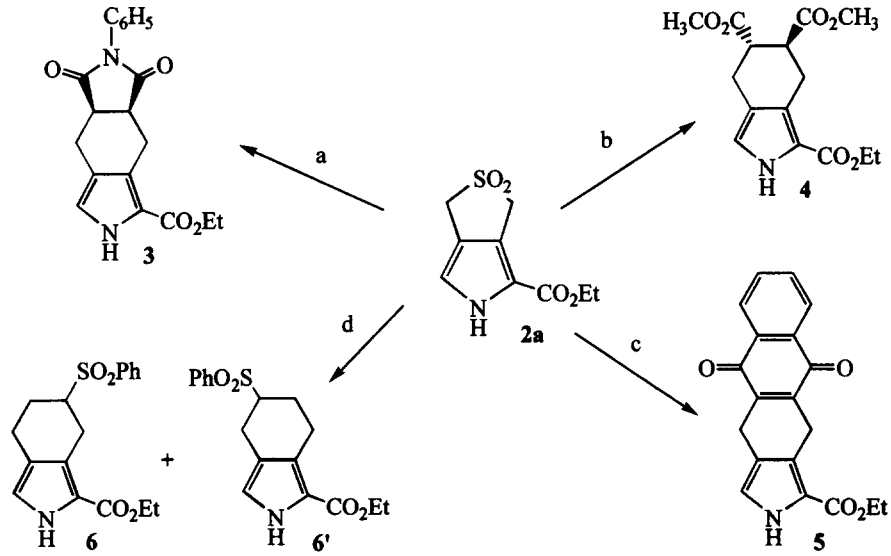
Pyrrole-fused 3-sulfolene **2a** was prepared in 40-50% yield from the reaction of the readily available α,β-unsaturated sulfone **1**[4,10] with ethyl isocyanoacetate (Scheme 1). The corresponding *tert*-butyl ester **2b** was also prepared in similar yields using *tert*-butyl isocyanoacetate. Pyrrole **2a** was fully characterized by ^{1}H- and ^{13}C-NMR, MS and elemental analysis.[11]



1 2

Scheme 1

Cycloaddition reactions with N-substituted pyrrole-fused 3-sulfolenes[12] and with pyrrole-fused sultines[13] have already been reported but it was believed that the protection of the nitrogen was necessary for cycloaddition reaction.[14] We found that Diels-Alder adducts **3-6** can be obtained in good yields (43-96%) by heating pyrrole **2a**, in refluxing 1,2,4-trichlorobenzene, in the presence of the corresponding dienophiles (Scheme 2).[15] Adducts **3** and **4** were obtained as racemic mixtures (one enantiomer shown). Their NMR and MS spectra[16] are in agreement with the proposed structures; pyrrole **4** was recently prepared from another α,β-unsaturated sulfone.[3b] As expected, compound **5** was the only isolated product from the reaction of pyrrole **2a** with an excess of 1,4-naphthoquinone (3 equiv.); the Diels-Alder adduct was dehydrogenated to the more stable quinone **5**. The MS spectrum of compound **5** shows an intense peak corresponding to M^+ (*m/z*= 321) and in the ^{1}H-NMR spectra the two methylene groups appear as triplets (*J*= 5.5 Hz) as a result of the long-range coupling between them through the double bond. This was confirmed by spin decoupling experiments: irradiation of a CH_2 resonance resulted in the elimination of the coupling on the other one. When phenylvinylsulfone was used as the dienophile, a mixture of the two possible regioisomers (in a 3:2 ratio, by NMR) was obtained. This mixture was used as such in the synthesis of porphyrins **7** (*vide infra*).

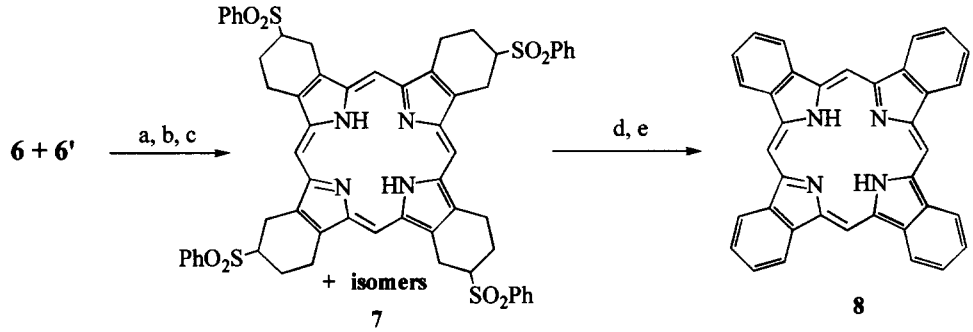


a) N-phenylmaleimide, 95%; b) dimethyl fumarate, 96%; c) 1,4-naphthoquinone, 43%; d) phenylvinylsulfone, 62%

Scheme 2

Attempted tetramerization of pyrrole **2a** (by reduction of the ethyl ester function with $LiAlH_4$, followed by reaction in acetic acid and oxidation of the resulting porphyrinogen to produce the corresponding tetrasulfone-porphyrin) produced only a very insoluble, difficult to handle and to characterize product. However, pyrroles **6** were tetramerized by the same procedure to produce a mixture of porphyrins **7** in 60% yield (Scheme 3). Porphyrins **7** showed a maximum absorption in the UV-visible spectrum at 621 nm and a parent ion at *m/z*= 1087 in the MS spectrum (FAB^+). Peaks corresponding to the loss of one (*m/z*= 945, 30%), two (*m/z*= 803, 5%), three (*m/z*= 661, 4%) and four (*m/z*= 519, 100%) phenylsulfonyl groups were also observed in the MS spectrum of **7**. Treatment of porphyrins **7** with KOH/CH_3OH, in refluxing toluene, resulted in the elimination of the four phenylsulfonyl groups in quantitative yield. The mixture of porphyrins obtained show a parent ion at *m/z*= 519 in the MS spectrum (FAB^+). Treatment of this mixture with DDQ in refluxing toluene gave tetrabenzoporphyrin **8** in 55% overall yield. The UV/Vis spectrum of **8** showed a 40 nm red shift of λ_{max} relatively to **7**, as expected from literature.[9]

The utilisation of pyrrole-fused 3-sulfolenes **2** as the main building block for the synthesis on new functionalized tetrabenzoporphyrins is underway in our laboratory.



a) $LiAlH_4$; b) CH_3CO_2H; c) DDQ; d) KOH/CH_3OH, Toluene, 110°C; e) DDQ
Scheme 3

Acknowledgements: JNICT financial support to Project n° PBIC/C/QUI/2156/95 and Research Unit 62/94 is gratefully acknowledged. One of us (A. W.) thanks PDT Euronet (contract # CHRX-CT930178) for a grant. Thanks are also due to Dr. A. Silva (Univ. Aveiro) for the NMR decoupling studies.

RERERENCES AND NOTES:

† On leave from Prof. F.-P. Montforts' research group, Institute für Organische Chemie, Universität Bremen, Germany, under the Human Capital and Mobility Programme (PDT Euronet).

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11. Pyrrole **2a**: ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.36 (t, 3H, CH_2CH_3), 4.17 and 4.34 (d, 2H each, CH_2, J= 0.7 Hz), 4.33 (q, 2H, CH_2CH_3), 6.89 (d, 1H, CH, J= 2.5 Hz), 9.39 (s, 1H, NH); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 14.4 (CH_2CH_3), 53.2 and 54.2 (2 CH_2), 60.9 (CH_2CH_3), 116.1, 117.6, 118.4 and 120.8 (pyrrolic-C), 160.0 (CO); MS (EI) m/z = 229 (M^+); Anal. Calcd. for $C_9H_{11}O_4SN$: C, 47.15; H, 4.84; N, 6.11 %; Found: C, 47.37; H, 4.68; N, 6.10 %.
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14. Similar observation was made for pyrazole-fused 3-sulfolenes; see ref. 6b and references cited therein.
15. Typical procedure: Pyrrole **2a** (50 mg; 0.22 mmol) and N-phenylmaleimide (76 mg; 2 equiv.) were heated in 1,2,4-trichlorobenzene (5 ml) at reflux, under nitrogen atmosphere, for 3 hours. After cooling to room temperature, the mixture was applied to the top of a column of silica; the trichlorobenzene and the excess of N-phenylmaleimide were eluted with petroleum ether: dichloromethane (7:3) and the adduct **3** (70 mg; 95 % yield) was then eluted with chloroform.
16. Selected spectroscopic data: adduct **3**: ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.36 (t, 3H, CH_2CH_3), 2.79 (dd, 1H, J= 5.9 and 14.8 Hz), 2.92 (dd, 1H, J= 6.5 and 15.4 Hz), 3.21 (dd, 1H, J= 2.2 and 14.9 Hz), 3.43 (m, 2H), 3.80 (dd, 1H, J= 2.2 and 14.8 Hz), 4.30 (q, 2H, CH_2CH_3), 6.72 (d, 1H, J= 2.6 Hz), 7.01-7.04 (m, 2H), 7.28-7.40 (m, 3H), 9.30 (s, 1H, NH); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 14.4, 22.0, 22.3, 40.1, 40.4, 60.3, 118.3, 118.4, 119.2, 124.3, 126.3, 128.4, 129.0, 131.8, 161.5, 178.8, 179.1; MS (EI) m/z = 338 (M^+, 85%); adduct **4**: ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.34 (t, 3H, CH_2CH_3), 2.63-2.86 (m, 2H), 2.95-3.08 (m, 3H), 3.39 (dd, 1H, J= 4.7 and 16.8 Hz), 3.73 (s, 3H, CO_2CH_3), 3.74 (s, 3H, CO_2CH_3), 4.30 (q, 2H, CH_2CH_3), 6.69 (d, 1H, J= 2.8 Hz), 9.30 (s, 1H, NH); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 14.5, 24.7, 25.9, 42.5, 45.1, 52.0, 60.1, 118.3, 117.7, 118.6, 118.9, 124.5, 161.3, 175.2, 175.3; MS (EI) m/z = 309 (M^+, 60%); adduct **5**: ^{1}H-NMR (300 MHz, $CDCl_3$ + Acetone-d_6): δ 1.33 (t, 3H, CH_2CH_3), 3.72 (t, 2H, J= 5.5 Hz), 3.96 (t, 2H, J= 5.5 Hz), 4.28 (q, 2H, CH_2CH_3), 6.86 (d, 1H, J= 2.4 Hz), 7.68 (m, 2H), 8.05 (m, 2H), 10.21 (s, 1H, NH); MS (EI) m/z = 321 (M^+, 47%); adducts **6+6'**: ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.28 (2 overlapping t, 6H), 1.69-1.83 (m, 2H), 2.40-2.96 (m, 8H), 3.15-3.35 (m, 4H), 4.26 (2 overlapping q, 4H), 6.66 (2 overlapping d, 2H), 7.56-7.71 (m, 6H), 7.92-7.96 (m, 4H), 9.44 (broad s, 2H, NH); MS (EI) m/z = 333 (M^+).

(*Received in UK* 25 *March* 1997; *accepted* 10 *April* 1997)