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Functionalised pyridine sulfolenes as precursors to pyridine *o*-quinodimethane derivatives and their [4+2] cycloadducts

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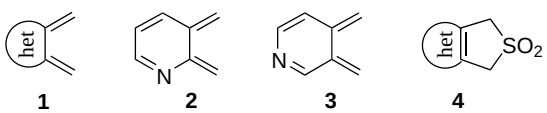
Abstract—An efficient route has been developed for the synthesis of polysubstituted 6,6-dioxo-6,7-dihydrothieno[3,4-*b*]pyridine **5**. This pyridine sulfolene compound serves as an excellent precursor for the corresponding pyridine *o*-quinodimethane. This reactive species is generated via thermal extrusion of sulfur dioxide and can be trapped in situ with both electron-rich and electron-deficient dienophiles. © 2001 Elsevier Science Ltd. All rights reserved.

The chemistry of heteroaromatic *o*-quinodimethanes (HAQDs) **1** (Fig. 1) has gained increasing interest in recent years.[1] However, only a few reports have appeared about the application of pyridine *o*-quinodimethanes **2** and **3**.[2] One general strategy applied is to generate the reactive HAQDs via thermolysis of heteroaromatic-fused 3-sulfolenes **4**.[3a–c] There are several advantages in the use of these sulfolene precursors. For one, extrusion of SO_2 usually occurs at moderately high temperatures under neutral conditions so that HAQDs can be trapped in situ in good yield. A further merit resides in the acid character of the protons α to the sulfone group, allowing the introduction of various substituents, e.g. dienophilic side chains. Until now three main routes leading to heteroaromatic-fused 3-sulfolenes have been reported: (1) the reverse addition of SO_2 to HAQDs,[3a] (2) transformation of bis(halomethyl) heterocyclic compounds,[3b] and (3) annulation of a heterocyclic core with a dihydrothiophene ring.[3c]



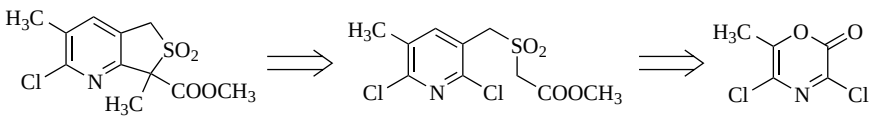
1 2 3 4

Figure 1.

We now disclose an efficient route for the preparation of the functionalised pyridine sulfolene **5**, and describe initial thermolysis experiments involving the generation of the corresponding pyridine HAQD and the in situ trapping of this reactive intermediate in Diels–Alder reactions with various dienophiles.

To generate the pyridine sulfolene **5**, base-induced cyclisation of the sulfone **6** was envisaged (Scheme 1). The polyfunctional pyridine ring system of **6** in turn could be constructed according to our general approach using cycloaddition of the oxazinone azadiene system **7** with alkynes.[4]

From the cycloaddition of oxazinone **7** and propargyl bromide, which proceeds with concomitant expulsion of carbon dioxide, pyridine **8** was produced as the only



5 6 7

Scheme 1.

Keywords: pyridines; sulfones; Diels–Alder reactions; quinonoid compounds.

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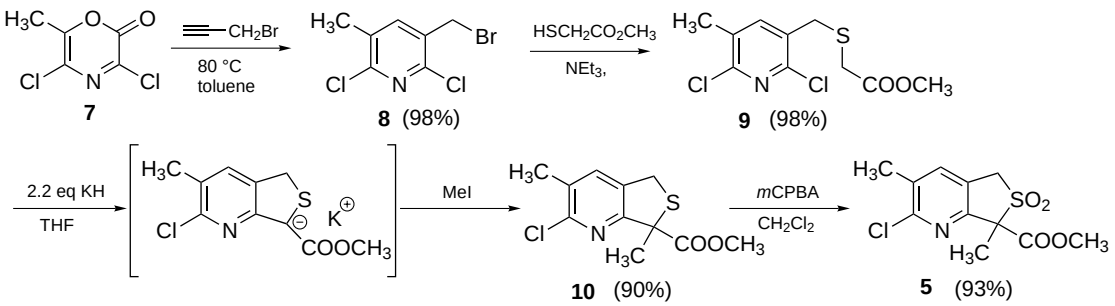
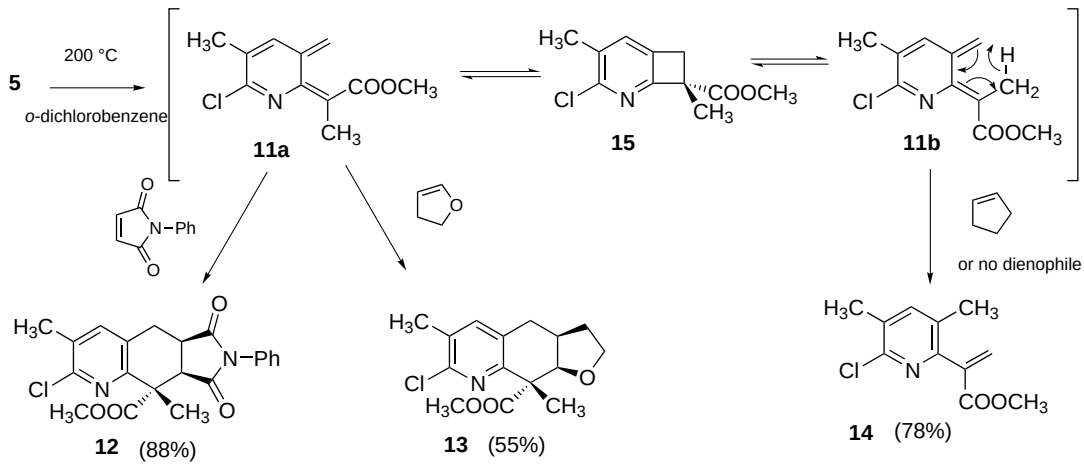
regioisomer in excellent yield (Scheme 2). Subsequent treatment of **8** with methyl thioglycolate afforded thioether **9** in 98% yield.

Oxidation of thioether **9** to the corresponding sulfone **6** was effected by using *m*CPBA in CH_2Cl_2 (85% yield). Several attempts to induce cyclisation of **6**, using various basic conditions, failed to produce the corresponding sulfolene pyridine. An explanation might be the weak nucleophilicity of the anion formed, due to its strong stabilisation by three electron-deficient groups. Therefore, a different route was followed, which involved cyclisation of the more reactive anion derived from thioether **9** by treatment with KH in THF. Due to the increased acidity of the α-proton remaining after cyclisation, an excess of KH was required to effect complete conversion of **9** to a cyclic anion intermediate. This can be converted to the free ester by careful neutralisation, or captured in situ by reaction with suitable electrophiles. Thus, addition of MeI afforded thienopyridine **10** (90%), which was oxidised with *m*CPBA to give the desired sulfolene **5** in 93% yield.

To demonstrate that compound **5** is indeed a valuable precursor for the pyridine *o*-quinodimethane system **11**, thermolysis of **5** was carried out at 200°C in the presence of an electron-poor, an electron-rich, and a neutral dienophile, i.e. *N*-phenylmaleimide, dihydrofuran, and cyclopentene (Scheme 3).[5] From the reaction with *N*-phenylmaleimide, cycloadduct **12** was isolated as a single stereoisomer (88%), and the stereostructure of **12** was established by X-ray diffraction (Fig. 2).[6] Since *N*-phenylmaleimide is known to



Scheme 2. Synthesis of sulfolene pyridine **5**.



Scheme 3. Generation of Diels–Alder adducts **12** and **13** and isomerisation product **14**.

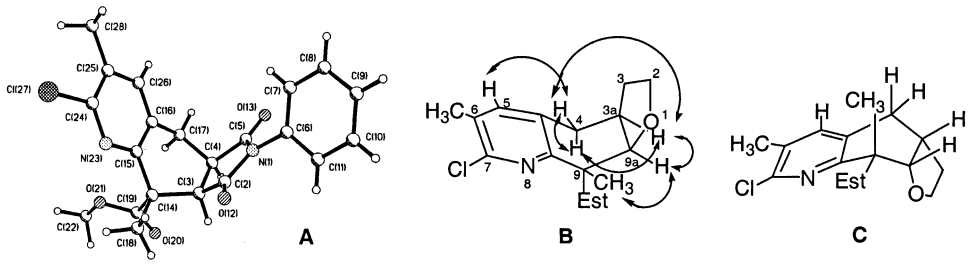


Figure 2. X-ray diffraction of adduct **12** (**A**) and structures of *endo*-adduct **13** (**B**) and alternative *exo*-adduct **C**.

add preferentially in the *endo* mode, due to the secondary orbital effect, cycloaddition apparently proceeds from an intermediate *o*-quinodimethane system that is primarily formed as the *E*-isomer **11a**. The preferential inward orientation of the ester group as compared to the outward one of the methyl group finds precedent in analogous trapping experiments involving similar substituted benzo-*o*-quinodimethane systems that are formed via thermal ring opening of benzocyclobutenes.[7] (Scheme 3).

The *cis*-fused dihydrofuran adduct **13** was produced as a single regio- and stereoisomer in 55% yield. The structure was derived from NOESY analysis, which revealed that the dihydrofuran adduct occurs as the (3a,9a)-ax,ax boat conformer **B**, corresponding to an *endo*-addition of dihydrofuran to *E*-isomer **11b** as observed with *N*-phenylmaleimide. The most important interactions are indicated in Fig. 2. The angular proton H-3a was shown to have an equatorial position since it gave a strong NOE with both the *cis*- and *trans*-disposed vicinal protons H-4 on the six-membered ring. Besides the expected *cis*-interaction with H-3a, the other angular proton H-9a also displayed a strong NOE with the 9-methyl group, consistent with a *trans*-eq,eq orientation of H-9a and 9-Me in form **B**. Admittedly, all of these interactions could also be accommodated by conformer **C**, corresponding to the alternative *exo*-addition of dihydrofuran to *E*-isomer **11b**. However, an axial 9-methyl group as shown in boat form **C**, seems to be precluded by the observation that 9-Me correlates with H-9a only, whereas one would expect an additional interaction with H-4ax. Model calculations using Hyperchem[8] confirmed that the boat conformers **B** and **C** are largely favoured over alternative half-chair forms in which the angular protons would have the H-3a,eq and H-9a,ax orientation.

Reaction with cyclopentene produced only the isomerisation product **14** (78%) instead of the Diels–Alder adduct. This can be accounted for if there is an equilibrium between the geometric isomers **11a** and **11b** proceeding via pyridocylobutene **15**. A similar reversible conversion of the *E*-and *Z*-isomers of analogous benzene *o*-quinodimethanes to the corresponding benzocyclobutenes has been reported.[7] Apparently, Diels–Alder reactions with neutral dienophiles such as cyclopentene proceed rather slowly, so that the *E*-isomer **11a** can be transformed to the *Z*-isomer **11b** via intermediate **15**, immediately followed by a non-reversible 1,5-H shift to give the acrylate **14**.[9] This was confirmed by thermolysis of pyridine sulfolene **5** in the absence of a dienophile, which also yielded the isomerisation product **14**.

In summary, a very efficient route for the preparation of pyridine sulfolene **5** has been developed. This compound is a good precursor for the corresponding pyridine *o*-quinodimethane, which can be trapped in situ with both electron-rich and electron-deficient dienophiles. Further applications of this and similar pyridine *o*-quinodimethane systems are being studied.

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5. All products were characterised by ^{1}H and ^{13}C NMR. Selected data for **5**: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.92 (s, 3H, CH_3), 2.42 (s, 3H, CH_3-pyr), 3.76 (s, 3H, CH_3O), 4.34 (d, 1H, $J=15.0$ Hz, H-5), 4.60 (d, 1H, $J=15.0$ Hz, H-5), 7.59 (s, 1H, H-pyr); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 13.8 (CH_3), 19.8 (CH_3-pyr), 52.9 (CH_3O), 54.6 (C-5), 72.9 (C-7), 128.1 (C-4a), 134.2 (C-3), 136.9 (C-4), 152 (C-7a), 152.9 (C-2), 166.5 (CO). Selected data for **12**: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.99 (s, 3H, CH_3), 2.33 (s, 3H, CH_3-pyr), 2.76 (dd, 1H, $J=7.9$, 15.8 Hz, H-5), 3.24 (dd, 1H, $J=2.8$, 15.8 Hz, H-5), 3.58 (ddd, 1H, $J=2.8$, 7.9, 8.9 Hz, H-5a), 3.68 (s, 3H, CH_3O), 4.11 (d, 1H, $J=8.9$ Hz, H-8a), 6.94 (dd, 2H, $J=1.4$, 6.4 Hz, H-*ortho*), 7.31 (s, 1H, H-pyr), 7.34 (m, 3H, H-*meta*, H-*para*); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 19.3 (CH_3-pyr), 19.6 (CH_3), 28.1 (C-5), 39.6 (C-5a), 46.6 (C-8a), 51.2 (C-9), 53.3 (CH_3O), 126.3 (C-*ortho*), 127.1 (C-3), 128.7 (C-*para*), 129.0 (C-*meta*), 131.5 (C-4a), 132.0 (C-*ipso*), 139.3 (C-4), 150.1 (C-2), 150.8 (C-9a), 174.9 (CO), 174.9 (C-8), 177.5 (C-6).

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