Pergamon

Tetrahedron Letters 43 (2002) 799–802

TETRAHEDRON LETTERS

Sulfolene pyridinones as precursors for pyridinone *ortho*-quinodimethanes and their Diels–Alder adducts

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Received 2 October 2001; accepted 29 November 2001

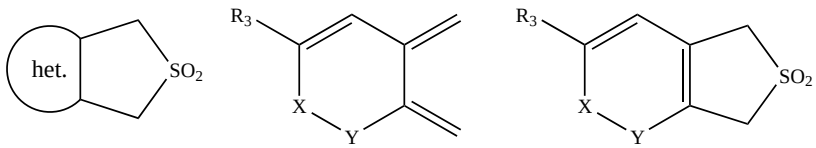
Abstract—2(1*H*)-Pyrazinones were converted into [3,4-*b*] and [3,4-*c*] sulfolene pyridinones **4** and **5**, serving as precursors for the corresponding 3,4- and 5,6-dimethylene 2(1*H*)-pyridinone *ortho*-quinodimethanes. These were trapped by in situ reaction with dienophiles. Tethering of **4** also enabled intramolecular cycloaddition.

Over the last decade the chemistry of heteroaromatic *o*-quinodimethanes (*o*-QDM) has been explored extensively.[1] The unstable and reactive *o*-QDM are commonly generated in situ from a suitable precursor. Various methods have been reported for generation of these *o*-QDM intermediates, e.g. electrocyclic ring opening of cyclobutaheterocycles,[2] 1,4-elimination of bis(halomethyl)heterocycles,[3] and cheletropic extrusion of SO_2 from heteroaromatic sulfolenes **1**.[4] Among these, the sulfolene approach seems to be the most suitable since these precursors are easily accessible and extrusion of SO_2 proceeds at moderately low temperatures so that the resulting *o*-QDM can be conveniently trapped in situ to afford the adducts in good yield.

As the pyridinone ring is incorporated in a number of natural products and various compounds of pharmacological interest,[5] we embarked on a study aiming at the generation of the pyridinone *o*-QDM systems **2**, **3** (Fig. 1) and their cycloaddition with various dienophiles to produce polycyclic pyridinones. A further advantage of the sulfolene precursor type is that it can be used also for tethering of a dienophilic side chain, enabling an introductory study of the intramolecular cycloaddition presented in this communication.

The required sulfolene pyridinone systems **4** and **5** were derived from 2(1*H*)-pyrazinones **6** and **7**,[6] via intramolecular cycloaddition to a sulfur containing dienophilic side chain attached to position 3 or 6 (Scheme 1). Thermolysis of thioethers **10** and **11** derived from thioesters **8** and **9** should result in cycloaddition of the alkyne side chain to the azadiene system with concomitant expulsion of cyanogen chloride, in preference to loss of benzyl isocyanate, to provide dihydrothienopyridinones **12** and **13**.

According to this synthetic plan, pyrazinone **6** was subjected to Stille coupling using $Sn(CH_3)_4$ to introduce a methyl group at the reactive 3-position.[7] Subsequent



1

2 X = N-Bn, Y = CO
R_3= H
3 X = CO, Y = N-Bn
R_3= OMe

4 X = N-Bn, Y = CO
R_3= H
5 X = CO, Y = N-Bn
R_3= OMe

Figure 1.

Keywords: *ortho*-quinodimethane; pyridinone; Diels–Alder reaction.

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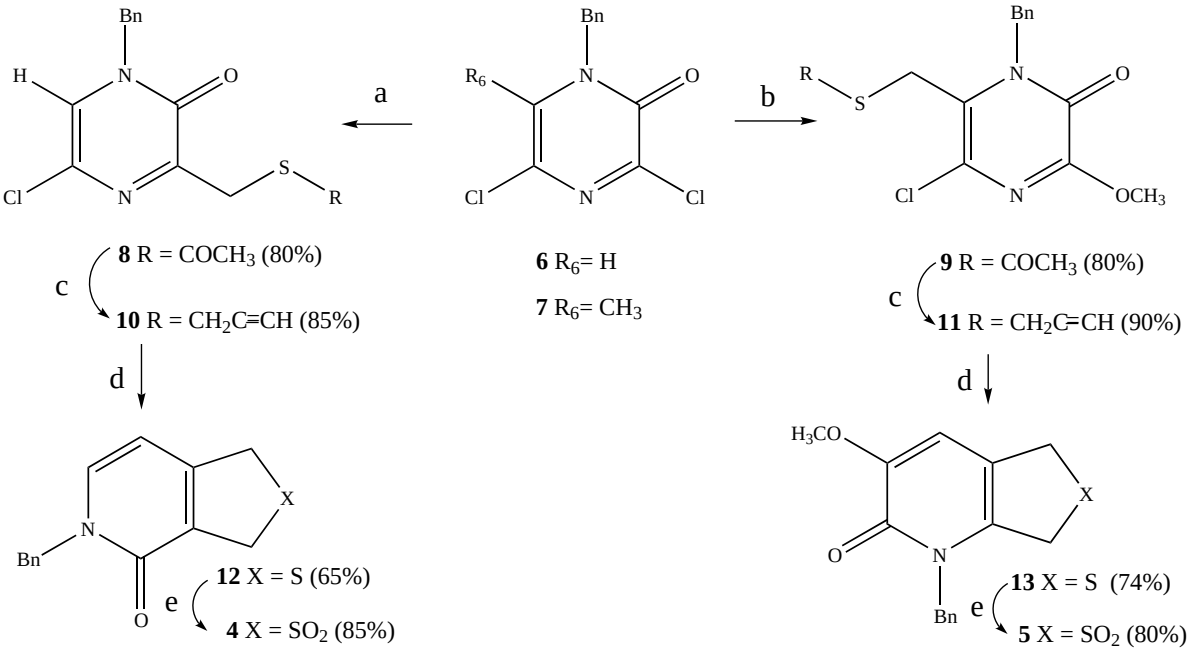
0040-4039/02/$ - see front matter
PII: S0040-4039(01)02275-4



Scheme 1. Synthesis of the sulfolene pyridinones **4** and **5**. *Reagents and conditions*: (a) (i) 1.2 equiv. $SnMe_4$, 0.01 equiv. $Pd(P(Ph)_3)_4$, toluene, 110°C, 48 h, (ii) 1.2 equiv. NBS, CCl_4, benzoyl peroxide, reflux, 3 h, (iii) 1.1 equiv. thiolacetic acid, 3 equiv. NEt_3, THF, rt, 2 h; (b) (i) 1.3 equiv. NaOMe, MeOH, rt, (ii) 1.2 equiv. NBS, CCl_4, benzoyl peroxide, reflux, 3 h, (iii) 1.1 equiv. thiolacetic acid, 3 equiv. NEt_3, THF, rt, 2 h; (c) (i) 1.3 equiv. NaOMe, MeOH, rt, (ii) 3 equiv. propargyl bromide; (d) toluene, reflux, 6–12 h; (e) 3 equiv. *m*-CPBA, CH_2Cl_2, rt.

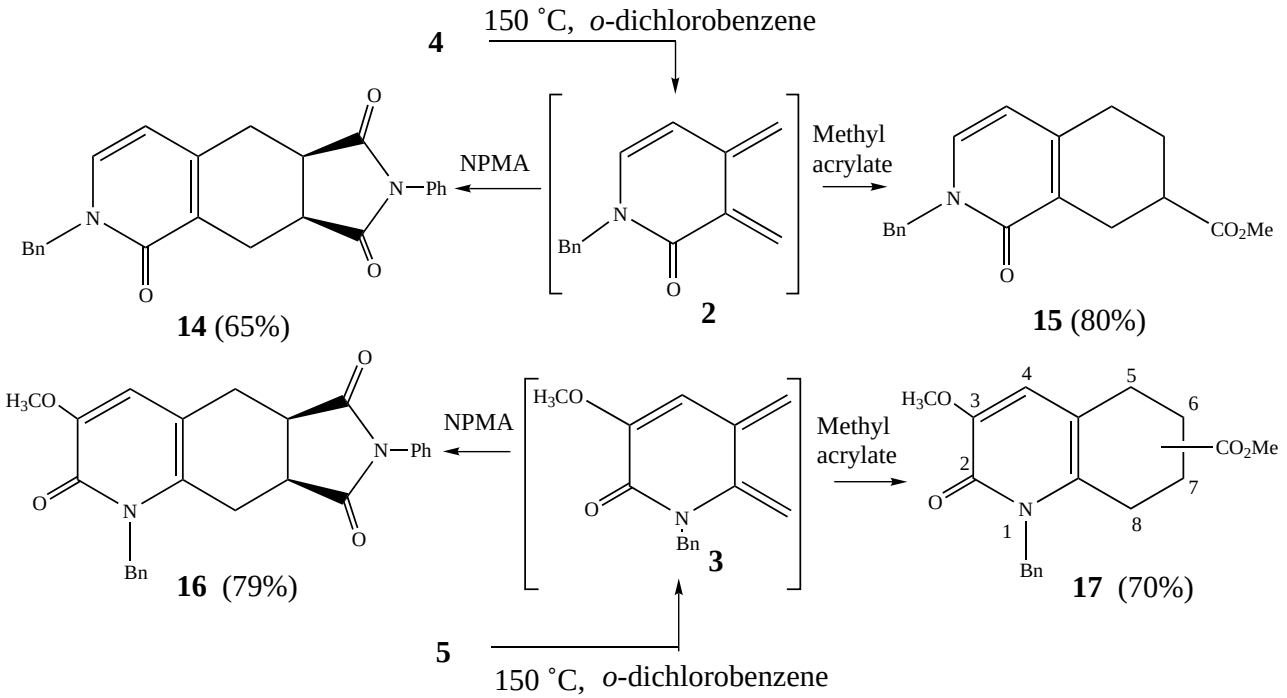
bromination of this methyl group and substitution of the bromide with thiolacetic acid furnished thioester **8**. An analogous sequence was used to transform 6-methylpyrazinone **7** into thioester **9**, i.e. conversion of the reactive imidoyl chloride into the 3-methoxy derivative, bromination of the 6-methyl group,[8] and final substitution with thiolacetate. The intermediate thiolate anions generated by treatment of thioesters **8** and **9** with sodium methoxide in methanol were alkylated in situ with propargyl bromide to produce **10** and **11**, respectively. As expected, thermolysis of these thioethers exclusively yielded pyridinones **12** and **13**, resulting from expulsion of cyanogen chloride. Final oxidation of the sulfur atom with *m*-CPBA afforded the [3,4-*c*] and [3,4-*b*] sulfolene pyridinones **4** and **5** (Scheme 1).

Upon thermolysis the sulfones **4**, **5** underwent fairly rapid loss of sulfur dioxide, i.e. at 150°C as compared to 200–220°C for the sulfolene pyridines.[4i–j] The resulting *o*-QDM intermediates **2**, **3** could be intercepted in good yields by in situ reaction with dienophiles (Scheme 2).

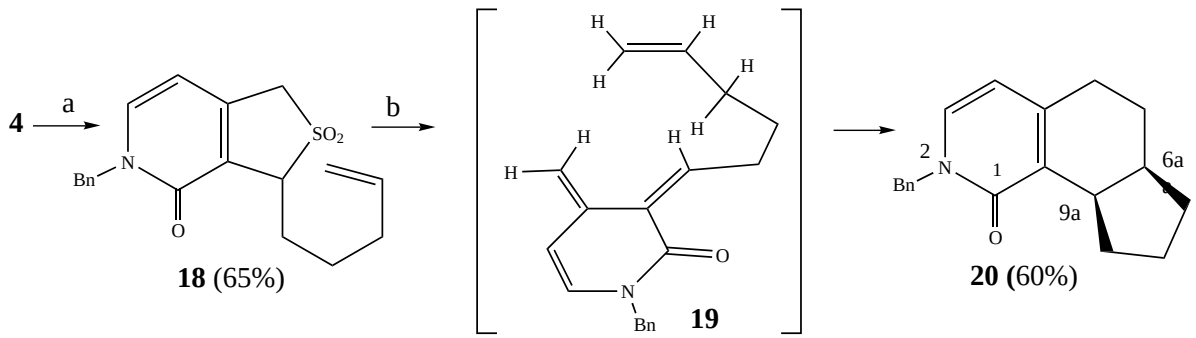
Thus, adduct **14** was produced by heating a solution of **4** with 3 equiv. of *N*-phenylmaleimide in *o*-dichlorobenzene at 150°C for 12 h.[9] Regioselective addition of methyl acrylate to form adduct **15** was accomplished by heating **4** with 5 equiv. of the volatile dienophile in a sealed tube for 12 h. The structure of adduct **15** was assigned on the basis of ASIS (aromatic solvent induced shift) ^{1}H NMR data.[10] In the $CDCl_3$ spectrum the aliphatic protons H-5 and H-8 were found to coincide at values between 2 and 3 ppm, but in C_6D_6 the protons H-8 in *peri*-position of the pyridinone carbonyl moiety were shifted downfield. The coupling pattern of these protons (H-8ax: 3.17 ppm, dd, $^2J_{8ax-8eq}$ = 18 Hz, $^3J_{8a-7}$ = 10 Hz; H-8eq: 2.83 ppm, dd, $^2J_{8ax-8eq}$ = 18 Hz, $^3J_{8eq-7}$ = 5.5 Hz) reveals the 7-equatorial position of the ester substituent. The protons H-5 were detected at higher field (H-5_{ax}: 2.00 ppm, m; H-5_{eq}: 2.17 ppm, dt, $^2J_{5ax-5eq}$ = 18.0 Hz, ^3J = 5 Hz).

Thermolysis of the isomeric sulfolene pyridinone **5** proceeded in a comparable way to give the NMPA adduct **16** in good yield.[9] However, with methyl acrylate a non-regioselective addition was observed, affording an unseparable mixture (ca. 1:1) of isomeric adducts **17**. The ASIS technique, complemented with NOE experiments, was again utilised to differentiate the various aliphatic protons H-5 and H-8. In the C_6D_6 spectrum two dd signals at 2.32 ppm (1H, ^2J = 16.0 Hz, ^3J = 5.4 Hz, H-5eq) and 2.54 ppm (1H, ^2J = 16.0 Hz, ^3J = 9.8 Hz, H-5ax) were identified as the geminal protons H-5eq and H-5ax of the 6-substituted isomer, as demonstrated by a NOE interaction between H-5eq and the adjacent *peri*-proton H-4. In a similar way the geminal protons H-8 of the 7-substituted isomer were identified as two dd signals observed at 2.42 ppm (1H, ^2J = 17.2 Hz, ^3J = 6.0 Hz) and 2.58 ppm (1H, ^2J = 17.2 Hz, ^3J = 8.8 Hz), showing no NOE correlation with H-4.

The precursor **4** could be regioselectively functionalised via sequential addition of 2.1 equiv. BuLi and 1.1 equiv. 5-bromopentene, to provide the 3-(4-pentenyl)



Scheme 2. Generation and cycloaddition of pyridinone *ortho*-quinodimethane systems **2** and **3**.



Scheme 3. Substitution of the sulfolene precursor and intramolecular Diels–Alder reaction. *Reagents and conditions*: (a) (i) 2.1 equiv. BuLi, THF, −78°C, (ii) 1.1 equiv. 5-bromopentene; (b) *o*-DCB, 150°C, 5 h, inert atm.

sulfolene pyridinone **18** via selective substitution at the more reactive position of the dianion intermediate.

Thermolysis of the functionalised precursor **18** afforded the tricyclic pyridinone compound **20** (Scheme 3). Extrusion of SO_2 probably leads to the thermodynamically more stable (*Z*)-intermediate **19**, whereupon *endo*-cycloaddition yields the *cis*-fused adduct **20**. The complexity of the ^{1}H NMR spectrum was initially thought to be due to a mixture of *cis*- and *trans*-fused isomers. However, the $^3J_{6a,9a}$ values (6.0 and 7.2 Hz) determined for both forms were lower than expected for a *trans*-diaxial relationship of the angular protons H-6a and H-9a, suggesting the existence of a slow equilibrium between two *cis*-fused conformers. This was confirmed by a NOE-diff experiment: presaturation of H-9a (2.23 ppm) did not result in any NOE-enhancement of adjacent protons, but instead in the observation of a negative signal at 3.04 ppm, apparently due to saturation transfer of H-9a from one conformer to the other.

In summary, a route leading to [3,4-*b*] and [3,4-*c*] sulfolene pyridinones has been developed. These compounds are good precursors for pyridinone *ortho*-quinodimethanes, which react in situ with dienophiles. Further applications of these intermediates in cycloaddition reactions as well as further functionalisation of the precursor compounds are being studied.

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9. Selected data for adduct **14**: ^{1}H NMR ($CDCl_3$) δ (ppm) 2.76 (dd, 1H, 6.8 Hz, 16.6 Hz, H-4), 2.82 (dd, 1H, 6.4 Hz, 14.9 Hz, H-9), 2.99 (dd, 1H, 3.2 Hz, 14.9 Hz, H-9), 3.33–3.42 (m, 2H, H-9a+H-3a), 3.49 (dd, 1H, 2.8 Hz, 15.6 Hz, H-4), 5.08 (d, 1H, 14.5 Hz, H-benzyl), 5.14 (d, 1H, 14.5 Hz, H-benzyl), 6.05 (d, 1H, 6.8 Hz, H-8), 7.06–7.08 (m, 2H, H-Ph), 7.16 (d, 1H, 6.8 Hz, H-7), 7.23–7.38 (m, 8H, H-Ph); for adduct **16**: ^{1}H NMR ($CDCl_3$) δ (ppm) 2.51 (dd, 1H, $^2J=15.6$ Hz, $^3J_{ax-eq}=5.0$ Hz, H-5_{ax}), 2.71 (dd, 1H, $^2J=14.0$ Hz, $^3J_{ax-eq}=4.5$ Hz, H-9_{ax}), 3.06 (dd, 1H, $^2J=14.0$ Hz, $^3J_{eq-eq}=2.0$ Hz, H-9_{eq}), 3.34–3.36 (m, 2H, H-5a+H-8a), 3.42 (dd, 1H, $^2J=15.6$ Hz, $^3J_{eq-eq}=2.2$ Hz, H-5_{eq}), 5.06 (d, 1H, $^2J=16.0$ Hz, H-Bn), 5.86 (d, 1H, $^2J=16.0$ Hz, H-Bn), 6.51 (s, 1H, H-4), 6.98 (dd, 2H, $J_o=8.0$ Hz, $J_m=1.0$ Hz, H-Ph), 7.17 (d, 2H, $J_o=7.3$ Hz, H-Ph), 7.25–7.42 (m, 6H, H-Ph).
10. Selected data for adduct **15**: ^{1}H NMR (C_6D_6) δ (ppm) 1.51–1.61 (m, 1H, H-6), 1.75–1.79 (m, 1H, H-6), 2.00–2.07 (m, 1H, H-5_{ax}), 2.17 (dt, 1H, 18 Hz, 5 Hz, H-5_{eq}), 2.31–2.35 (m, 1H, H-7), 2.85 (dd, 1H, 5.5 Hz, 18.0 Hz, H-8_{eq}), 3.17 (dd, 1H, 10.0 Hz, 18.0 Hz, H-8_{ax}), 3.32 (s, 3H, CH_3), 4.77 (d, 1H, 14.2 Hz, CH_2), 4.87 (d, 1H, 14.2 Hz, CH_2), 5.37 (d, 1H, 7.0 Hz, H-4), 6.51 (d, 1H, 7.0 Hz, H-3), 7.00–7.15 (m, 3H, H-Ph), 7.17–7.19 (m, 2H, H-Ph).