Thermal decomposition of 1,1-bis(methylthio)ethene, pyran-2-one Diels-Alder adducts: an unusual [1,5]-sulfenyl rearrangement

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This article is dedicated to Professor James M. Coxon in honour of his 65th birthday

Abstract

The thermal decomposition of two Diels-Alder adducts derived from pyran-2-ones and bis(methylthio)ethene has been studied. A product obtained from the thermal decomposition of one of these Diels-Alder adducts (**1**), derives from a [1,5]-sulfenyl shift, the first well-documented report of such a process occurring under non-polar conditions. The rearrangement in this case probably occurs via a radical pathway. No such rearrangement was observed on decarboxylation of a Diels-Alder adduct (**7**) derived from a benzopyranone. This latter thermolysis required more vigorous conditions as required for the application of this class of compounds as potential anti-cancer prodrugs.

Keywords: [1,5]-Sulfenyl rearrangement, retro-Diels-Alder, anti-cancer, prodrug

Introduction

Appropriately functionalised polycyclic aromatic compounds have anti-tumour activity by virtue of their ability to intercalate between adjacent heterocyclic bases of DNA. By contrast non-planar precursors to such molecules are likely to exhibit low affinity for DNA. Hence some bridged Diels-Alder adducts can be considered as low cytotoxicity precursors, 'prodrugs', of intercalating agents. The activation of such adducts selectively at a tumour site might form the basis of anti-cancer chemotherapies with reduced side effects.[1] Since thiol groups can be selectively released from appropriately substituted precursors at tumours[2] we targeted pyran-2-one-derived Diels-Alder adducts with thioether substituents as potential anti-tumour prodrugs where cleavage of a thioether linkage can lead to aromatisation of ring system (Figure 1). Generation of a thione via C-S bond cleavage allows the possibility of tautomerism to form an

enethiol. The presence of an extra double bond in the ring system dramatically affects the adduct stability; such species generally decarboxylate at below room temperature.[3]

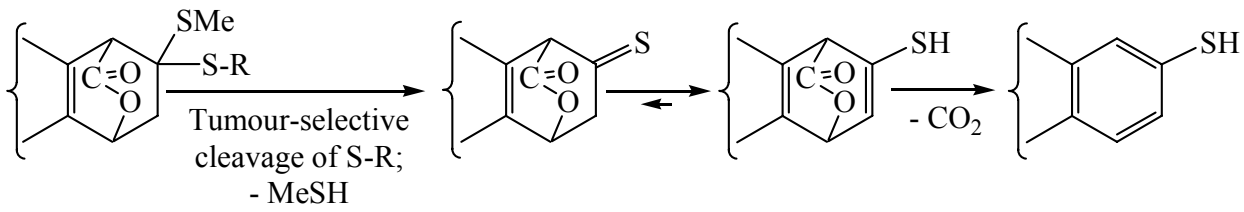
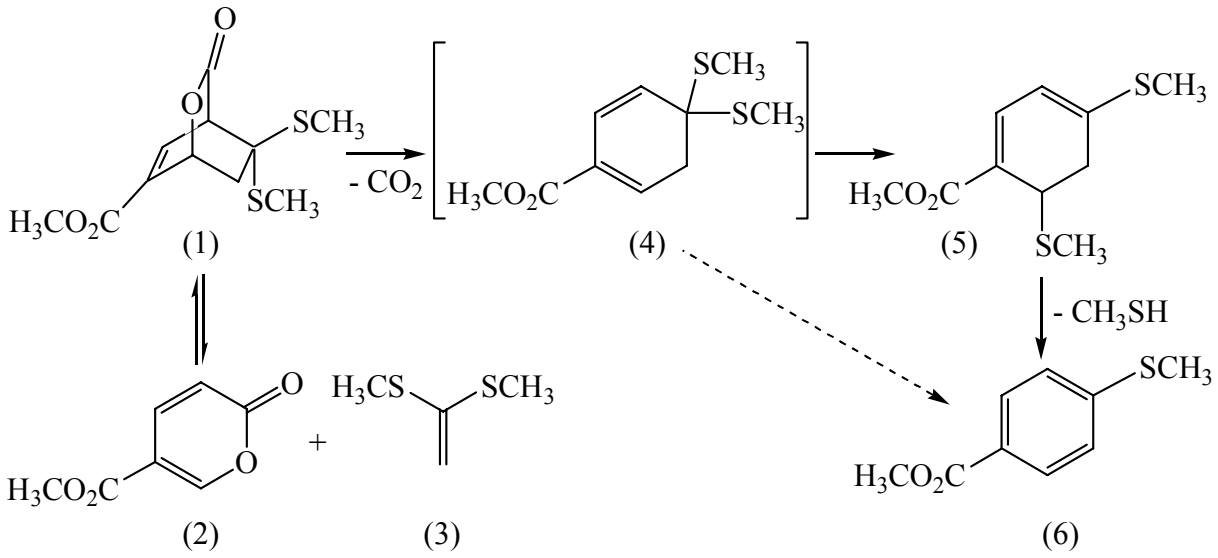


Figure 1

We have demonstrated that dithioketene acetals undergo Diels-Alder reactions with pyran-2-ones to generate bridged adducts.[4] This chemistry provides a general route for the synthesis of sulfur-substituted pyran-2-one Diels-Alder adducts. The utilisation of adducts of this type as anti-cancer prodrugs requires that they be stable with respect to decarboxylation at ambient temperatures but that they decarboxylate readily on modification of the thioketal group. We here report the thermal decarboxylation chemistry of two of these adducts.

Results and Discussion

The bridged Diels-Alder adduct 1 can be prepared by reaction of methyl coumalate **2** with 1,1-bis(methylthio)ethene **3**, in refluxing toluene.[4] This adduct was heated neat at 145 °C and the decomposition chemistry monitored by proton NMR. A thermally-induced decomposition took place to give a clean mixture of three products which were isolated. One product was methyl coumalate **2**; resulting from a reversal of the cycloaddition reaction used to prepare the adduct; it is surprising that this *retro*-Diels-Alder reaction can successfully compete with decarboxylation. The expected substituted benzene compound **6** was also present. This is formed when the initial adduct loses carbon dioxide and methanethiol. The other product isolated was an unexpected cyclohexadiene **5**. This is presumably due to decarboxylation of 1 followed by rearrangement. Diene **4**, was not observed. The driving force of this rearrangement is likely to be the greater extent of conjugation in **5** relative to diene **4**. The conjugated diene **5** was also formed if the Diels-Alder reaction of **2** with **3** was carried out over an extended period.



The cyclohexadiene **5** was sufficiently stable to be isolated and examined by standard spectroscopic methods. However it eliminated methanethiol within a few days to give **6**. Cyclohexadiene **5** absorbed strongly at 1700 cm^{-1}, characteristic of a conjugated carbonyl group and at 342 nm, consistent with a conjugated diene, carbonyl system. Unsuccessful attempts were made to trap cyclohexadiene **5** as a Diels-Alder adduct with maleic anhydride.

Figure 2 shows the progress for one particular decomposition. The absolute rate of decomposition was not reproducible under the conditions used, but the general reaction profile was similar in each case. This variability in rates appears to be the artifact of a radical-based process, with variable initiation efficiencies. The initial adduct **3** can undergo two possible *retro*-Diels-Alder reactions. The first is the reverse of the reaction that formed the adduct originally. This results in the formation of methyl coumalate **2** and 1,1-bis(methylthio)ethene **3**. The gradual build up of the pyranone can be seen in Figure 2. The volatility of **1** precludes its accumulation. The second possible *retro*-Diels-Alder reaction is the extrusion of carbon dioxide to form the diene **4**. As this compound was not observed, it must rapidly lose methanethiol to give the substituted benzene **6**; or rearrange by way of a [1,5]-sulfenyl migration to give **5**. The greater build up of **5** and **6** compared to **2** suggests that the latter is the more favourable reaction. As both dienophiles from these two *retro*-Diels-Alder reactions appear to be lost from the system, the reverse reaction to form **3** again cannot occur. Under these conditions it is an irreversible reaction. The cyclohexadiene derivative **5** builds up to become the major component of the mixture (Figure 2), suggesting that for **4**, the [1,5]-sulfenyl migration is more facile than the elimination of methanethiol. It is only after this point that the aromatic compound **6** is formed at an appreciable rate. This suggests that **6** is formed principally via the [1,5]-sulfenyl migration pathway rather than directly from **4**.

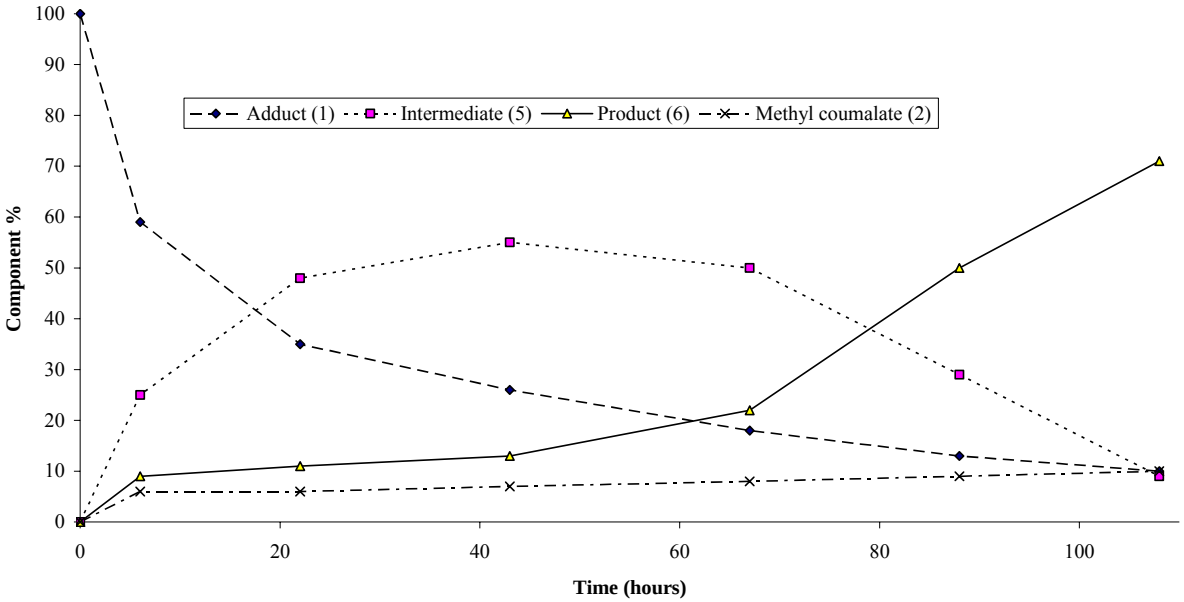


Figure 2. The thermal decomposition of Diels-Alder adduct (**1**). The proportion of each compound present is plotted as a function of time. The formation of the decomposition products was monitored by proton NMR. The measurements were made by comparing the integration of the methyl ester peak corresponding to each compound.

Reports of [1,5]-sulfenyl migrations are comparatively rare. Although such a process has been invoked to explain a thermally induced rearrangement observed by Vishwakarma *et al.*[5], the only well-documented examples have been reported under polar conditions. There has been a single example of a base-induced [1,5]-sulfenyl rearrangement occurring via an intermolecular pathway.[6] Recently the first example of an acid-catalysed rearrangement of this type[7] has been reported. This reaction was also shown to be intermolecular in nature; a cationic intermediate was invoked.

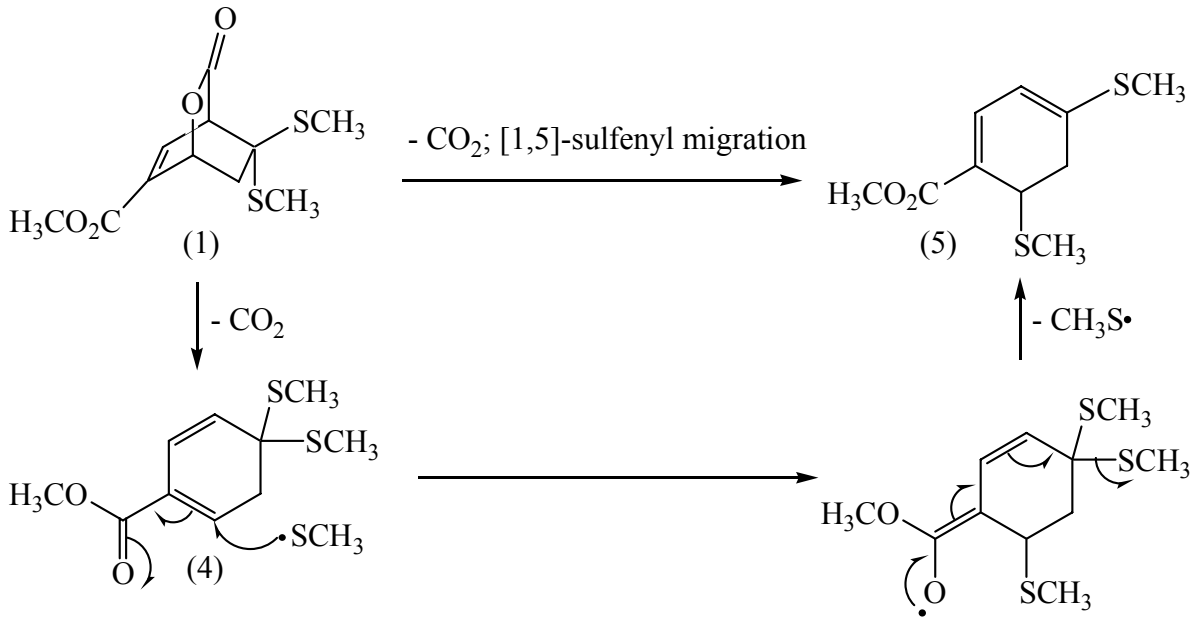
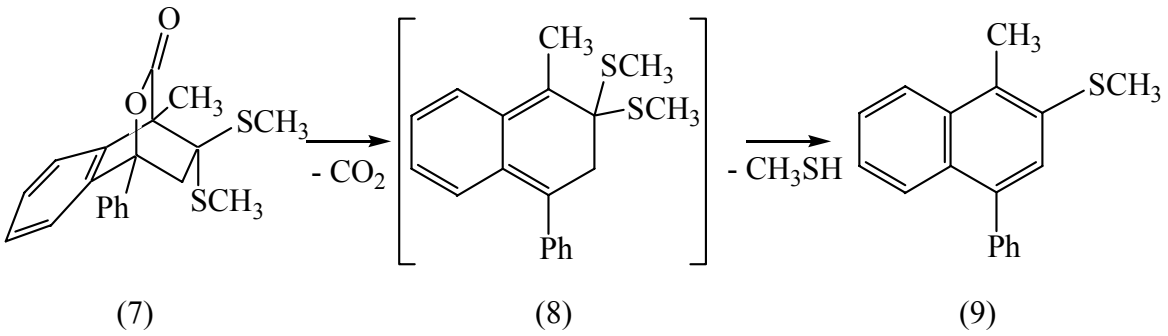


Figure 3. Suggested radical mechanism for the sulfenyl migration on thermolysis of (1).

The fact that the rearrangement reported here occurs under neutral conditions suggests that the mechanism is not ionic in nature. The most likely mechanism is an intermolecular radical process. It is known that thermolysis of dithioacetals generates radicals.[8] Furthermore, [1,3] sulfenyl rearrangements of allyl thioethers have been shown to proceed via a thiyl-radical mechanism.[9] This example, in keeping with both previous reports of [1,5] sulfenyl rearrangements, has the opportunity to react via a conjugated diene-carbonyl system. This allows delocalisation of both radical and ionic intermediates. The nature of the stabilisation is shown for the radical case in Figure 3.

The thermal decomposition of the adduct **7** resulting from the Diels-Alder reaction of 4-methyl-1-phenyl-3*H*-2-benzopyran-3-one with 1,1-bis(methylthio)ethene,[4] was then examined. The decomposition chemistry was much simpler for this adduct, with only one product being isolated; the substituted naphthalene **9** (Figure 4). No intermediates resulting from just decarboxylation (**8**) or subsequent sulfenyl migration were observed. It was expected that **7** would be more stable than **1** due to the initial loss of benzenoid aromaticity upon decarboxylation.[2] This was found to be the case: 97% of **7** remained after 25 hours of heating neat at 145 °C, compared with 35% of **1**. The increased thermal stability of the benzofused adduct is exactly as required for the employment of such species as potential prodrug precursors to polycyclic aromatic compounds.



(7) (8) (9)

Figure 4. Thermal decomposition of Diels-Alder adduct (7).

Conclusions

A [1,5]-sulfenyl rearrangement was observed during the thermal decomposition of the methyl coumalate, 1,1-bis(methylthio)ethene Diels-Alder adduct **1**. This is the first well-documented example of such a rearrangement occurring under non-polar conditions. It appears that the presence of a conjugated carbonyl-like moiety may be crucial for the observance of a [1,5]-sulfenyl rearrangements The benzopyranone, 1,1-bis(methylthio)ethene adduct **7** was observed to have greater thermal stability than **1**, presumably due to the initial loss of aromaticity upon decarboxylation. The latter property is important for the development of anti-cancer prodrugs based on this class of Diels-Alder adducts.

Experimental Section

General Procedures. Radial chromatography was performed using a 1 mm silica plate with an elution gradient from 100% petroleum ether to 100% ethyl acetate. The plate was washed and reactivated using methanol. Melting points (m.p.) were determined on a Reichert Hotstage microscope and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 1600-FTIR spectrophotometer. The sample was presented as a $CDCl_3$ solution in a 0.1 or 1.0 mm NaCl solution cell. Selected absorptions (ν_{max}) are recorded in wavenumbers (cm^{-1}) and relative intensities denoted as weak (w), medium (m) or strong (s). Ultraviolet spectra were scanned on a Hewlett Packard 8452A diode array spectrometer and the wavelengths (nm) of maximum absorptions (λ_{max}) recorded. The intensities of the maxima are expressed as molar absorptivities (ε). Proton (^{1}H NMR) and carbon-13 (^{13}C NMR) nuclear magnetic resonance spectra were performed on a Varian Unity 300 MHz Fourier transform spectrophotometer. Peaks are quoted in ppm relative to TMS (δ) and the $CHCl_3$ signal referenced to 7.24 ppm (^{1}H NMR) and 77.0 ppm (^{13}C NMR). Coupling constants (*J*) are quoted in Hertz (Hz). Electron characteri mass spectra

(m/z) were performed on a Kratos MS80RFA operating at 4 KV and electron impact at 70 eV. The high resolution mass of the parent ion is compared with the expected calculated value.

Compound characterization

Methyl 4,6-bis(methylthio)-1,3-cyclohexadienoate (5) and methyl 4-(methylthio)benzoate (6). 7,7-Bis(methylthio)-3-carbomethoxy-5-oxabicyclo[2.2.2]oct-2-en-6-one[3] (**1**) (10 mg, 0.04 mmol) was heated neat under nitrogen at 145 °C for 17 hours. The resulting mixture was purified using radial silica chromatography. Eluting with 90% petroleum ether/10% ethyl acetate gave (**6**) (1 mg, 15%) as a white crystalline solid m.p. 78-80 °C. (Found $M^{+\cdot}$ 182.0402, Calc. for $C_9H_{10}O_2S$ $M^{+\cdot}$ 182.0402). ^{1}H NMR δ ($CDCl_3$) 2.52, s, 3H; 3.90, s, 3H; 7.25, dd, *J* 6.8, 1.9 Hz, 2H; 7.94, dd, *J* 6.8, 1.9 Hz, 2H. ^{13}C NMR δ ($CDCl_3$) 14.82, 52.02, 124.90, 126.25, 129.87, 145.40, 166.86. ν_{max} 1717 (s), 1596 (w), 1560 (w), 1437 (w), 1289 (m) cm^{-1}. Mass spectrum *m/z* 182 (M, 100%), 152 (M-OCH_2), 123 (M-CO_2CH_3), 108 (M-CO_2CH_3, -CH_3).

Further elution with 80% petroleum ether/20% ethyl acetate gave (5) (2 mg, 24%) as a yellow oil. (Found $M^{+\cdot}$ 230.0438, Calc. for $C_{10}H_{14}O_2S_2$ $M^{+\cdot}$ 230.0435). ^{1}H NMR δ ($CDCl_3$) 2.08, s, 3H; 2.36, s, 3H; 2.62, dd, *J* 17.6, 1.5 Hz, 1H; 2.98, ddd, *J* 17.6, 7.3, 2.4 Hz, 1H; 3.79, s, 3H; 4.01, dd, *J* 7.3, 1.5 Hz, 1H; 5.72, dd, *J* 6.4, 2.4 Hz, 1H; 7.16, d, *J* 6.4 Hz, 1H. ^{13}C NMR δ ($CDCl_3$) 13.72, 14.31, 36.06, 38.23, 51.76, 112.24, 122.42, 133.64, 145.39, 166.87. ν_{max} 1700 (s), 1540 (s), 1437 (w), 1282 (m), 1243 (m), 1090 (m) cm^{-1}. λ_{max} (cyclohexane) 342 (ε = 9610) nm. Mass spectrum *m/z* 230 (M), 182 (M-CH_3SH, 100%), 152 (M-SCH_3-OCH_3), 124 (M-SCH_3-CO_2CH_3).

1-Methyl-2-methylthio-4-phenylnaphthalene (9). 11,11-Bis(methylthio)-1-methyl-9-oxa-8-phenyltricyclo[6.2.2.$0^{2,7}$]dodec-2,4,6-trien-10-one[3] (**7**) (10 mg, 0.03 mmol) was heated neat under nitrogen at 145 °C for 20 days. The resulting mixture was purified using radial chromatography, eluting with 90% petroleum ether/10% ethyl acetateto give (**9**) (5 mg, 61%) as a colourless oil. (Found $M^{+\cdot}$ 264.0975, Calc. for $C_{10}H_{14}O_2S_2$ $M^{+\cdot}$ 264.0973). ^{1}H NMR δ ($CDCl_3$) 2.54, s, SCH_3; 2.81, s, Ar-CH_3; 7.35-7.56, m, 8H; 7.83, d, *J* 7.8 Hz, 1H; 8.07, d, *J* 7.3 Hz, 1H. ^{13}C NMR δ ($CDCl_3$) 15.64, 16.86, 124.04, 125.03, 125.74, 126.30, 126.67, 127.30, 128.26, 129.89, 130.13, 131.47, 132.96, 133.67, 138.92, 140.57. ν_{max} 3676 (m), 3064 (w), 2926 (w), 1718 (m), 1602 (m), 1560 (m) cm^{-1}. Mass spectrum *m/z* 264 (M, 100%), 249 (M-CH_3), 234 (M-CH_3-CH_3), 217 (M-SCH_3), 215, 202 (M-SCH_3-CH_3).

Acknowledgements

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