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Direct Stereoselective Diels–Alder Synthesis of Benzocantharidin

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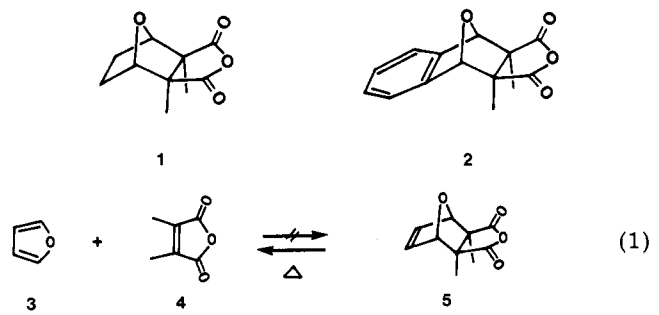
Isobenzofuran (7) and dimethylmaleic anhydride (4) undergo cycloaddition in refluxing xylene to give benzocantharidin (2) in 95% yield, together with 5% of the endo stereoisomer, isobenzocantharidin (8). This Diels–Alder reaction was shown to be reversible, which apparently accounts for the high stereoselectivity in favor of the exo isomer. The successful use of 4 to form the 7-oxabicyclo[2.2.1]heptenyl system by the Diels–Alder cycloaddition, which is in contrast to the previously reported complete failure of the reaction when furan itself was the diene partner, provides a practical approach to synthesis of cantharidin analogues for physiological studies.

The total synthesis of cantharidin (1) long has been an intriguing pursuit, owing to its enchantingly simple structure as well as its physiological properties. The Diels–Alder reaction of furan (3) and dimethylmaleic anhydride (4), followed by hydrogenation, might provide cantharidin readily, as was surmized by von Bruchhausen and Bersch[1a] as well as Diels and Alder.[1b] Although both groups reported the smooth cycloaddition of furan and maleic anhydride,[1] the Diels–Alder reaction of 3 and 4 has not been accomplished; on the contrary, the retro-Diels–Alder reaction of 5 to give 3 and 4 has been observed (eq 1).[1a]



1 2

3 + 4 ⇌ 5 (1)

Reports of the failure of the simple Diels–Alder approach to cantharidin stimulated attempts to use such a strategy in a modified manner, giving rise to more complicated approaches and to syntheses of "cantharidin-like"[2] compounds: the methylene-bridged analogue was prepared from the reaction of cyclopentadiene and 4;[3,4] use of butadiene in this reaction afforded deoxycantharidin;[5,6] the latter Diels–Alder reaction initiated two circuitous routes to cantharidin itself;[6] and imaginative, sequential use of two Diels–Alder reactions was employed to accomplish the first stereospecific cantharidin total synthesis, which, however, required considerable manipulation in the later stages.[7]

Recently, efforts to utilize very high pressure to coerce furan and various dienophiles into cycloaddition led to the report that 3 and an ingeniously chosen cyclic sulfide derivative of 4 undergo quantitative cycloaddition at ca. 22000 psi, the products being formed in a favorable 85:15 exo/endo ratio.[8b] The work demonstrated for the first time that a single Diels–Alder reaction can result in generation of the vicinally tetrasubstituted 7-oxabicyclo[2.2.1]heptenyl system, in this case by modification of the dimethylmaleic anhydride partner.

We now report that appropriate modification of furan can permit use of unaltered 4, in spite of its electronic and/or steric deficiencies,[8] to form the intact cantharidin skeleton by use of a Diels–Alder reaction. Isobenzofuran (7), which has become readily available,[9–11] possesses excellent Diels–Alder reactivity owing to favorable changes

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(2) Woodward, R. B.; Baer, H. *J. Am. Chem. Soc.* **1948**, *70*, 1161.
(3) Schenck, G. O.; Kuhls, J.; Krauch, C. H. *Justus Liebigs Ann. Chem.* **1966**, *693*, 20.
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(10) Rynard, C. M.; Thankachan, C.; Tidwell, T. T. *J. Am. Chem. Soc.* **1979**, *101*, 1196.
(11) After the completion of this work, the Aldrich Chemical Co. published a review on isobenzofuran chemistry that mentioned unpublished work on the reaction of 7 and 4 to give benzocantharidin. No information regarding stereochemistry or the isomerization of stereoisomers was given: Wiersum, U. E. *Aldrichimica Acta* **1981**, *14*, 53.

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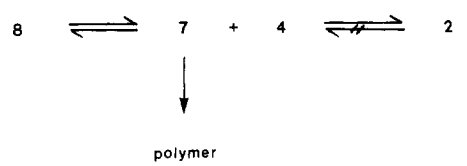
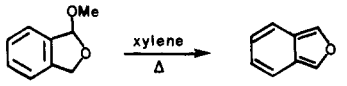
Scheme I



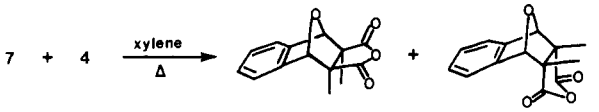
in aromatic stabilization during the course of the cycloaddition. Thus, its use in place of furan may have minimal effect on the steric factors in the transition state of the cycloaddition but replaces aromatic disruption with incipient aromatic stabilization.

Isobenzofuran is quantitatively formed by elimination of methanol from 1,3-dihydro-1-methoxyisobenzofuran (6) upon heating (eq 2), making the latter a convenient in situ



(2)

6 7



(3)

2 8

source of 7.[9] Reflux in xylene of an excess of 4 together with 6 for 15 h resulted in quantitative formation of cycloadducts, based on 6, as determined by ^{1}H NMR (eq 3).[11] This spectrum further showed (by analysis of methyl absorption intensities) the exo/endo stereoselectivity to be ca. 95:5 in favor of the desired exo isomer, a selectivity that parallels that observed for the high-pressure experiments.[8b] The excess dimethylmaleic anhydride was separated from the crude reaction mixture by sublimation, after which recrystallization readily provided pure benzocantharidin (2). Isobenzocantharidin (8) was obtained from the mother liquor by chromatography on silica gel followed by recrystallization. The stereochemical assignments were made initially on the basis of an upfield shift of the endo methyl protons in the ^{1}H NMR spectrum of 2, as well as upfield shifts of the endo carbon atoms in the ^{13}C NMR spectra of 2 and 8. This assignment was confirmed by a single-crystal X-ray diffraction study of the exo isomer[12]

The preferential formation of the exo isomer 2 may result in part from the relative thermodynamic stabilities of the isomers and the reversible nature of the cycloaddition, as evidenced by additional experiments carried out in toluene. Thus, when the reaction described above was performed in refluxing toluene for 4 h, a 55% yield of cycloadducts (90:10, exo/endo ratio) was obtained, while a 15-h reaction time afforded a 93:7 isomer ratio in an 86% yield. When the pure endo isomer was refluxed for 15 h in toluene in the presence of 10 molar equiv of 4, analysis of the quantitatively recovered cycloadducts showed the exo/endo ratio to be 2:3. Reflux of the pure endo isomer in the absence of 4 led to partial destruction of the cycloadduct, apparently owing to polymerization of 7 formed by the retro-Diels-Alder reaction (Scheme I). All of the recovered cycloadduct retained the endo stereochemistry. These results provide evidence that isomerization leads preferentially to the exo isomer by an intermolecular process that can compete effectively with polymerization of 7 only when a substantial excess of the dieneophile 4 is present. Such facile thermal isomerization and retro-Diels–Alder reactions of furan adducts in general[13] and of the furan–maleic anhydride adduct in particular[2,14] are well-known.

In contrast, reflux of the exo isomer in toluene for 7 h revealed it to be stable toward isomerization under these conditions. This isomer did, however, undergo the retro-Diels–Alder reaction at a higher temperature: ^{1}H NMR analysis of the material obtained by heating benzocantharidin (mp 180–181 °C) in an NMR tube at 200 °C for 1 h indicated that 94% of 2 was decomposed to dimethylmaleic anhydride and unidentified material, presumably polymer derived from isobenzofuran.

The mechanistic implications of this successful use of dimethylmaleic anhydride as a Diels–Alder partner with a furan derivative, in contrast to the previous thermal and high-pressure results with furan itself,[8] remain a subject for conjecture. However, it is evident that failure of the latter reaction cannot be ascribed entirely to 4 and that appropriate modification of the furan partner may provide a practical approach to cantharidin synthesis.

Experimental Section

1,3-Dihydro-1-methoxyisobenzofuran (6) was prepared as described in the literature.[9] For column chromatography, Merck PF_{254} silica gel 60 was used. Elemental analyses were performed by Galbraith Laboratories.

The instruments used are as follows: ^{1}H NMR, Varian (360L) at 60 MHz; ^{13}C NMR, JEOL at 15.04 MHz; IR, Beckman IR10; MS, Du Pont 21-490 (EI); melting point, Thomas-Hoover capillary apparatus (uncorrected).

Benzocantharidin (2). A mixture of 500 mg (3.33 mmol) of 1,3-dihydro-1-methoxyisobenzofuran (6), 1.04 g (8.25 mmol) of dimethylmaleic anhydride (4), and 40 mL of xylene was refluxed for 15 h, followed by evaporation of the solvent to provide a crystalline reaction mixture. Examination of this mixture by ^{1}H NMR indicated quantitative conversion of 6 into 2 and 8, with the ratio of 2 (methyl groups at 0.88 ppm) to 8 (methyl groups at 1.63 ppm) of 95:5. Sublimation in vacuo (0.07 torr) at 70 °C for 2.5 h provided a white sublimate (4, 678 mg) and a residual solid, which was recrystallized from diethyl ether to give 580 mg (2.38 mmol, 71%) of 2 as colorless crystals: R_f 0.22 (silica gel, benzene); mp 180–181 °C; IR ($CHCl_3$) 1850, 1780 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.88 (6, s), 5.47 (2, s), 7.2–7.5 (4, m); ^{13}C NMR ($CDCl_3$) δ 14.1, 55.8, 87.1, 122.2, 128.0, 141.2, 174.2; MS, m/z (relative intensity) 129 (5), 128 (7), 119 (10), 118 (100), 90 (7), 89 (6). Anal. Calcd for $C_{14}H_{12}O_4$: C, 68.85; H, 4.95. Found: C, 68.75; H, 5.04.

As an alternative method of purification, unreacted 4 could be removed from the reaction mixture by chromatography on silica gel (eluted with benzene/hexane, 1:1), to permit higher isolated yields of 2. However, the sublimation procedure is simpler, off-setting the small loss of product that results from retro-Diels–Alder reaction during sublimation.

Isobenzocantharidin (8). Isobenzocantharidin was obtained from the crude reaction mixture described above by column chromatography (silica gel, eluted with benzene/hexane, 1:1) followed by recrystallization from diethyl ether to give 8 as colorless leaflets: R_f 0.17 (silica gel, benzene); mp 152.5–153.0 °C; IR ($CHCl_3$) 1850, 1780 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.63 (6, s), 5.22 (2, s), 7.2–7.4 (4, m); ^{13}C NMR ($CDCl_3$) δ 16.8, 57.9, 88.3, 121.2, 128.7, 140.5, 171.6; MS, m/z (relative intensity) 129 (4), 128 (5), 119 (10), 118 (100), 90 (5), 89 (5). Anal. Calcd for $C_{14}H_{12}O_4$: C, 68.85; H, 4.95. Found: C, 68.65; H, 4.89.

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Registry No. 2, 82799-13-1; 4, 766-39-2; 6, 67536-29-2; 8, 82838-30-0.

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