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Bridged Synthons from Tetrabromocyclopropene: Studies on the Rearrangement of the Primary Diels−Alder Adduct with 2,5-Dimethylfuran

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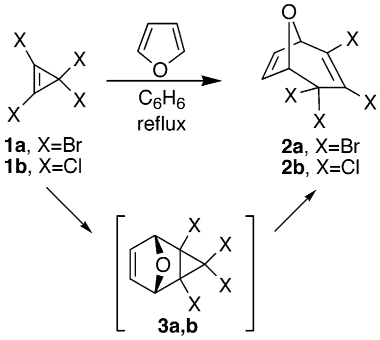
Abstract: The reaction of tetrabromocyclopropene and furan leads directly to 8-oxabicyclo[3.2.1]octadiene derivatives. It has been proposed that this involves an initial Diels−Alder reaction followed by rearrangement of the primary adduct. We have, for the first time, isolated a primary adduct and established through X-ray crystallographic analysis that the adduct is the product of an exo-selective addition. Kinetic studies suggest the intermediacy of charged intermediates during the rearrangement.

The 8-oxabicyclo[3.2.1]octane nucleus has found wide application for the synthesis of natural products and other important compounds.[1] These types of intermediates are traditionally accessed through a [4 + 3] cycloaddition of a furan and an oxyallyl cation equivalent.[2] We have been interested[3] in exploiting a complementary yet unique approach to these types of derivatives through a process first reported by Tobey and Law in 1968 (Scheme 1).[4]

They observed that furan would readily participate in a reaction with both tetrachloro- and tetrabromocyclopropene to produce novel halogenated oxabicyclo[3.2.1]-octadienes **2a**,**b** directly and in high yields. They proposed that the reaction occurred through an initial Diels−Alder reaction between the cyclic diene and the cyclopropene to produce 8-oxatricyclo[3.2.1.0^{2,4}]oct-6-ene derivatives **3a**,**b**.

These highly strained intermediates suffer a spontaneous rearrangement that formally involves a 1,2-migration of a halogen atom with concomitant opening of the internal bond of the cyclopropane. It was originally proposed, by analogy to other cyclopropene cycloadditions,[5] that the primary adducts were formed as the endo isomers, although the spontaneous conversion of these compounds to dienes **2a**,**b** prevented a more rigorous determination of their structure. Subsequent indirect studies[6] with fluorine-substituted adducts, which do not rearrange, led to a revision of the structures of **3a**,**b** to the exo orientation. However, all studies have been conducted on adducts that could not undergo the rearrangement, and hence, a direct investigation of the parent system has been lacking.

SCHEME 1. Cycloaddition of Perhalocyclopropenes



During our investigation of these compounds as synthons for various natural products, we have been able to conduct a detailed investigation into the structure of a primary adduct[7] and its conversion to the oxabicyclo-[3.2.1]octadiene system. While preparing a novel substituted adduct from 2,5-dimethylfuran (**4**), it was observed that reaction under the usual conditions in refluxing benzene led to violent decomposition of the starting materials (Scheme 2).

Because of the apparently exothermic nature of the reaction, the cycloaddition was conducted at low temperature, which resulted in a smooth conversion to a new cycloadduct. The proton and carbon NMR revealed the presence of a highly symmetrical compound that was assigned as the primary adduct **5** and not the rearranged product **6**. Apparently, at the lower temperatures used for this reaction, the primary Diels−Alder adduct survives and can be easily isolated. Heating the primary adduct in benzene led to a clean conversion to the expected oxabicyclo[3.2.1]octadiene **6** in quantitative yield. The rearrangement would also occur spontaneously over several weeks at room temperature but the adduct appeared to be stable for long periods of time at low temperature. With easy access to a relatively stable primary adduct and conditions for effecting the subsequent rearrangement established, we were in a position to conduct a more detailed investigation into this unusual rearrangement process.

The first issue that was addressed was the stereochemistry of the initial cycloadduct. Because there are

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[1] Harmata, M.; Rashatasakhon, P. *Tetrahedron* **2003**, *59*, 2371.

[2] (a) Takaya, H.; Makimo, S.; Hayakawa, Y.; Noyori, R. *J. Am. Chem. Soc.*, **1978**, *100*, 1756. (b) Noyori, R.; Hayakawa, Y. *Tetrahedron* **1985**, *41*, 5879.

[3] Orugunty, R. S.; Wright, D. L.; Battiste, M. A.; Abboud, K. A. *Org. Lett.* **2002**, *4*, 1997.

[4] (a) Law, D. C. F.; Tobey, S. W. *J. Am. Chem. Soc.* **1968**, *90*, 2376. (b) Tobey, S. W.; Law, D. C. F. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 649.

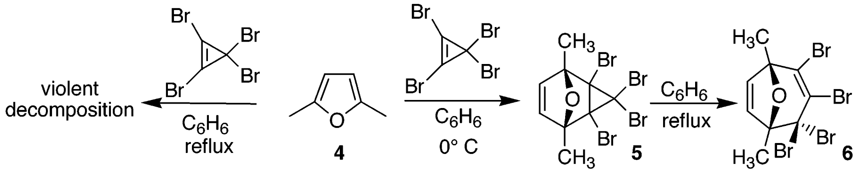
[5] (a) Wiberg, K. B.; Bartley, W. J. *J. Am. Chem. Soc.* **1960**, 6375. (b) Battiste, M. A. *Tetrahedron Lett.* **1964**, *5*, 3795. (c) Closs, G. L.; Closs, L. E.; Boll, W. A. *J. Am. Chem. Soc.* **1963**, *85*, 3796. (d) Deem, M. L. *Synthesis* **1972**, 675.

[6] (a) Battiste, M. A.; Posey, R. G. *J. Fluorine Chem.* **2000**, *102*, 285 and references therein. (b) Dolbier Jr., W. R.; Battiste, M. A. *Chem. Rev.* **2003**, *103*, 1071.

[7] The isolation of the primary adduct of furan and tetrachlorocyclopropene has been claimed and was assigned as the exo-adduct based on X-ray analysis. However, the actual crystal structure has not been disclosed. Apeloig, Y.; Arad, D.; Kapon, M.; Wallerstein, M. *Tetrahedron Lett.* **1987**, *28*, 5917.

10.1021/jo0352631 CCC: $27.50

SCHEME 2. Isolation and Rearrangement of the Primary Adduct



SCHEME 3. Synthesis of a Triazole Derivative of the Primary Adduct

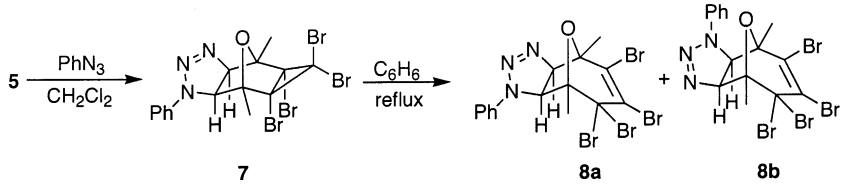


TABLE 1. Activation Parameters for the Rearrangement of Adducts 5 and 7

compd	solvent	ΔH (kcal/mol)	ΔS (cal/mol/K)	ΔG (kcal/mol)
5	toluene-d_8	24.59	−7.88	27.06
5	DMF-d_7	21.23	−9.59	24.04
7	toluene-d_8	24.79	−8.04	27.32
7	DMF-d_7	21.81	−7.31	23.95

TABLE 2. First-Order Rate Constants for the Rearrangment of 5 and 7

compd	T (°C) (PhCH$_3$)	k (PhCH$_3$)	T (°C) (DMF)	k (DMF)
5			19.2	6.6975×10^{-6}
	40.7	9.3065×10^{-7}	40.3	7.9800×10^{-5}
	62.6	1.2555×10^{-5}	62.2	8.0100×10^{-4}
	84.4	1.3175×10^{-4}	83.4	5.8520×10^{-3}
7			19.6	8.0514×10^{-6}
	41.2	6.4245×10^{-7}	41.7	1.1001×10^{-4}
	62.7	9.1356×10^{-6}	62.8	1.1568×10^{-3}
	84.7	9.1097×10^{-5}		

relatively few protons present on the ring system, NMR was incapable of determining the relative stereochemistry of the adduct. Attempts to grow crystals of **5** were unsuccessful. However, it was found that the adduct was stable enough to undergo a subsequent reaction with phenyl azide[8] to give a highly crystalline derivative **7** (Scheme 3).

Dipolar cycloaddition of phenyl azide to the primary adduct **5** led to the fused triazole **7** without rearrangement of the cyclopropane. The adduct could be forced to undergo the ring expansion upon heating in benzene to give a 1:1 mixture of the two regioisomeric triazoles **8a** and **8b**. An X-ray structure determination of adduct **7** showed that the initial Diels−Alder reaction had occurred through an exo mode of addition. Furthermore, the cycloaddition of the azide had proceeded from the exo-face of the bridged intermediate.

The relatively slow conversion of cyclopropane **5** to the bridged diene **6** allowed the process to be easily monitored by NMR spectroscopy. Through the use of variable-temperature NMR, the conversion of **5** to **2a** and **7** to **8a/b** could be studied in detail. The reactions could be studied at various temperatures in order to construct an Eyring plot which yielded the activation parameters and first-order rate constants for the rearrangement process (Tables 1 and 2).

Cyclopropanes **5** and **7** display basically the same activation parameters and first-order rate constants for the rearrangement, indicating that the distal double bond in these tricyclo[3.2.1.0^{2,4}] compounds exert little effect on the rearrangement. This is opposed to the effects observed by Creary[9] in the rearrangement of *endo*- and *exo*-tricyclo[3.2.1.0^{2,4}]octanyl triflates. In fact, the k for **5** is only about 1.5 times that of **7**. The 1:1 ratio of **8a** and **8b** formed during the course of rearrangement also suggests that the triazole does not have a significant effect on the reaction. The first-order rate constants that were observed for **5** in toluene at 40 and 60 °C are 9.3×10^{-7} and 1.25×10^{-5}, respectively. These values are very close to the rate constants observed by De Selms[10] for the thermal rearrangement of 3,3-dichloro-*exo*-tricyclo-[3.2.1.0^{2,4}]oct-6-ene to the corresponding bicyclo[3.2.1]oct-2-ene system. In addition, the $k_{\mathrm{DMF}}/k_{\mathrm{toluene}}$ for **5** is 85 while the $k_{\mathrm{DMF}}/k_{\mathrm{toluene}}$ for **7** is 173. This suggests a significant development of charge at the transition state, thus a diradical mechanism for this rearrangement can be ruled out.[11] The $\Delta\Delta S$ for this reaction upon changing from toluene to DMF is about 1.7 eu. The small value implies that the reaction does not involve an extensive rearrangement of the solvent sphere around the reacting molecule in its transition state.

Although the exact nature of the developing cation cannot be established, generation of an intimate ion pair, assisted by the stereoelectronically controlled[12] breaking of the intercyclic σ-bond can be considered a reasonable mechanism, consistent with previous observations.[12] A key finding from this study was the rate acceleration observed upon changing the solvent from toluene to DMF.[13] This suggests the presence of charged intermediates that are stabilized by the solvent with a higher dielectric constant such as cationic intermediate **9** rather than a direct migration of a bromine atom (Scheme 4).

The data are therefore consistent with the expected mechanism[14] that involves an initial ionization of bromide assisted by opening of the internal bond of the fused

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[8] (a) Peeran, M.; Wilt, J. W.; Subramanian, R.; Crumrine, D. S. *J. Org. Chem.* **1993**, *58*, 202. (b) Heller, C.; Martin, H. *Tetrahedron Lett.* **1976**, *17*, 4329.

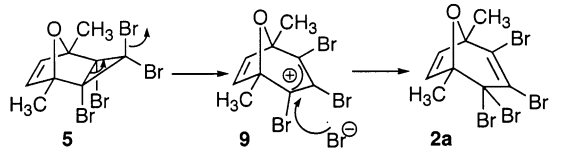
[9] Creary, X. *J. Org. Chem.* **1975**, *40*, 3326.

[10] De Selms, R. C.; Combs, C. M. *J. Org. Chem.* **1963**, *28*, 2206.

[11] Gassman, P. G.; Sangdon, H.; Chyall, L. J. *Tetrahedron Lett.* **1998**, *39*, 5459.

[12] Woodward, R. B.; Hoffmann, R. *J. Am. Chem. Soc.* **1965**, *87*, 395.

SCHEME 4. Proposed Mechanism for Cyclopropane Rearrangement



cyclopropane to produce allylic cation **9**. This cation is assumed to be short-lived and may be regarded as an intimate ion pair since the magnitude of the rate acceleration in DMF is not large enough to suggest extensive solvation of the cation. The flattening of the halogenated bridge that occurs upon ionization appears to introduce a steric interaction with the bridgehead substituent which may explain the greater thermal stability of the dimethyl adduct **5** relative to its unsubstituted counterpart. Addition of bromide to the terminus of the tribromoallyl cation produces the rearranged product **2a**. The intermediacy of the cation **9** is also supported by the observation that it can be generated irreversibly from adducts analogous to **2a** upon treatment with silver ion[3] and then trapped with good nucleophiles such as activated aromatics.

Experimental Section

General Methods. All solvents used in the reactions were distilled prior to use. 2,5-Dimethylfuran was obtained from Aldrich and distilled prior to use. Tetrabromocyclopropene was synthesized according to the literature procedure[15] and was distilled twice before the cycloaddition reaction. Subsequent reactions resulted in compounds that were pure for kinetic studies. Melting points are reported uncorrected. IR spectra were recorded on a FT-IR spectrometer. NMR spectra were recorded at 300 MHz for ^{1}H and at 75 MHz for ^{13}C. Chemical shifts are reported in ppm relative to tetramethylsilane (TMS).

2,3,3,4-Tetrabromo-1,5-dimethyl-8-oxatricyclo[3.2.1.0^{2,4}]-oct-6-ene (5). 2,5-Dimethylfuran (0.46 g, 4.8 mmol) was added to tetrabromocyclopropene (1.4 g, 3.9 mmol) in a sealed tube and cooled in an ice bath. The resulting mixture was kept in the ice bath and stirred with the help of a magnetic stir bar. The solution gradually turns into a pale brown semisolid and is complete after 24 h. The reaction mixture was subjected to column chromatography on silica gel, and the product was eluted using 10% methylene chloride in hexane. The solvent was removed under reduced pressure at room temperature (higher temperatures lead to significant rearrangement of the product) to give a colorless solid (1.5 g, 84%): mp 110−112 °C; ^{1}H NMR (300 MHz, CDCl$_3$) δ 6.55 (s, 2H), 1.82(s, 6H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 144.6, 91.4, 60.8, 45.6, 14.6; IR (NaCl) cm^{-1} 2984, 1563, 1381, 1125, 960, 906, 718; MS(EI) m/z 452 (M$^+$, 5), 437 (21), 371 (50), 292 (94), 211 (96), 89 (100). Anal. Calcd for $C_9H_8Br_4O$: C, 23.93; H, 1.78. Found: C, 24.18; H, 1.75.

2,3,3,4-Tetrabromo-1,5-dimethyl-8-oxabicyclo[3.2.1]oct-6-ene (6). Compound **5** (0.1 g, 0.02 mmol) was dissolved in 5 mL of dry benzene and refluxed for 3 h. The benzene was removed under reduced pressure to afford 100 mg of **6** as a white solid: mp 30−32 °C; ^{1}H NMR (300 MHz, CDCl$_3$) δ 6.50 (d, J = 5.5 Hz, 1H), 6.25 (d, J = 5.5 Hz, 1H), 1.93 (s, 3H), 1.68 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 141.1, 135.5, 133.1, 128.5, 93.2, 89.5, 71.1, 23.9, 22.1; IR (NaCl) cm^{-1} 2985, 2935, 1564, 1444, 1377, 1306, 1159, 1090, 942, 869, 758, 726, 714; MS (EI) 452 (M$^+$, 11), 371 (92), 292 (100), 213 (82), 89 (71). An analytically pure sample was obtained by sublimation. Anal. Calcd for $C_9H_8Br_4O$: C, 23.93; H, 1.78. Found: C, 24.25; H, 1.75.

Synthesis of Triazole Adduct 7. Compound **5** (0.407 g, 0.9 mmol) was dissolved in 1 mL of dichloromethane. Phenyl azide (0.119 g, 1 mmol) was added to the above solution and stirred at room temperature for 2 days. The methylene chloride was allowed to evaporate slowly at room temperature when colorless crystals of the product were obtained. The crystals were washed with 20% ether in pentane to remove excess phenyl azide and recrystallized from 20% ether in pentane. The first crop of crystals weighed 240 mg. The mother liquors were evaporated and the residue was subjected to recrystallization to afford an additional 220 mg of **7** (89% overall): mp 129−130 °C (with violent decomposition); ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.20−6.80-(m, 5H), 4.92 (d, J = 8.8 Hz), 4.02 (d, J = 8.8 Hz), 1.70 (s, 3H), 1.30 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 141.1, 129.7, 123.4, 114.8, 91.8, 90.53, 90.51, 63.5, 55.4, 54.9, 34.6, 13.5; IR (NaCl) cm^{-1} 1599, 1494, 1380, 1355, 965, 750, 690; MS(EI) 541 (M− 28, 81), 344 (55), 97 (100). An analytically pure sample was obtained by recrystallizing the compound from 20% ether in pentane. Anal. Calcd for $C_{15}H_{13}Br_4N_3O$: C, 31.56; H, 2.30. Found: C, 31.62; H, 2.29.

Synthesis of Triazoles 8a/8b. Compound **7** (0.01 g, 0.018 mmol) was dissolved in 1 mL of benzene and refluxed for 2 h. The solvent was removed to afford a 1:1 mixture of triazoles **8a** and **8b** as a pale brown amorphous solid. The mixture was inseparable by TLC or column chromatography. The spectral data provided are for the mixture: ^{1}H NMR (300 MHz, CDCl3) δ 7.10−6.40 (m 10H), 4.98 (d, J = 8.79 Hz, 1H), 3.98 (d, J = 8.85, 1H) 3.89 (d, J = 8.85, 1H), 3.05 (d, J = 8.79, 1H), 1.63 (s, 3H), 1.29 (s, 3H), 0.82 (s, 3H); ^{13}C (75 MHz, CDCl3) δ 141.3,141.2 133.4, 132, 129.5, 127.6, 127.4, 125.2, 123.2, 122.8, 115.1, 114.8, 93.8, 92.8, 92.1, 89.9, 88.3, 88.2, 73, 72.6, 65, 61.3, 21.9, 21.4, 20.6, 20.3; IR (NaCl) cm^{-1} 1602, 1492, 1380, 1358, 965, 750; MS-(EI) 543 (M − 28, 55), 345 (62), 266 (100), 77 (90). Anal. Calcd for $C_{15}H_{13}Br_4N_3O$: C, 31.56; H, 2.30. Found: C, 31.49; H, 2.32.

Kinetic Studies. The reaction was monitored by ^{1}H NMR at 500 MHz on a spectrometer equipped with a 5 mm indirect detection probe. Ca. 5 mg of pure sample was dissolved in 0.75 mL of solvent, and the tubes were sealed to prevent evaporation. The reactions in toluene-d_8 were run at 40, 60, and 80 °C; the reactions in DMF-d_7 were run at 20, 40, 60, and 80 °C. During the reaction, the temperature was regulated within 0.1 °C by the variable-temperature unit of the spectrometer. At the end of the reaction, a standard sample of ethylene glycol was allowed to reach the temperature for 1 h and then the temperature was monitored every minute for 20 min, allowing a measurement of an average temperature within 0.02 °C. During the reaction typically 100 spectra were collected, at time intervals of 30 min at 20 and 40 °C, 12 min at 60 °C, and 6 min at 80 °C. Each spectrum was collected with the maximum number of 6 s scans. The integrals of the signals of the starting material (SM) were normalized against the integrals of the residual signals of the solvent. The plots ln([SM$_{\text{initial}}$]/[SM]) vs time afforded the rates (k), with a typical R^2 of 0.9996. The plots ln(k) vs 1/T fitted a line with a typical R^2 of 0.9999. The enthalpy and entropy of activation were calculated from the slope (a) and intercept (b) of this line as DH = $-a$(8.31/4184) (kcal/mol) and DS = (b − 23.76)(8.31/4.184) (cal/mol/K).

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Supporting Information Available: X-ray data for **7** and representative kinetic data for the rearrangement studies of **5** and **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) The dielectric constants for toluene and carbon tetrachloride are 2.4 and 2.22 D; therefore, comparison of rates is meaningful. A similar argument can be made for comparison of rates in acetonitrile (36.2 D) vs DMF (37.0 D). Kosower, E. M. *An Introduction to Physical Organic Chemistry*; John Wiley & Sons: New York, 1968.

(14) These types of cationic intermediates were originally proposed by Tobey and Law; see ref 4a.

(15) Tobey, S. W.; West, R. *J. Am. Chem. Soc.* **1966**, *88*, 2481.