BF_3·OEt_2-Mediated Rearrangement of Cyclopropyl Carbinols: A Concise Route to Polycyclic Cyclobutanes

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Introduction

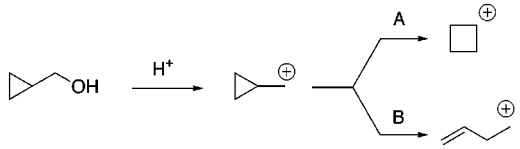
The acid-catalyzed rearrangement of cyclopropylcarbinols and of analogous systems is well documented.[1] The reaction proceeds through the initial formation of a cyclopropylcarbinyl cation[2] followed by either ring expansion (path A) or ring fission (path B) of the three-membered carbocycle (Scheme 1). This produces either a cyclobutyl or an allylcarbinyl cation.[3] These intermediates can be trapped by various nucleophiles.[4]

The driving forces for the cyclopropylcarbinyl−cyclobutyl interconversion could be the relief of ring strain and the formation of a more stable carbocationic intermediate. This transformation is closely related to the Wagner−Meerwein rearrangement.[5] Recently, Vonwiller et al. reported the intramolecular trapping of an arylfenchyl-derived carbocation by aniline or phenol nucleophiles.[6] With these results in mind, we examined the reaction of phenol-substituted cyclopropylcarbinol **1** under Lewis acid conditions and found that, upon treatment with 0.5 equiv of boron trifluoride etherate in CH_2Cl_2, **1** was smoothly converted to 1-phenyl-2-oxa-3,4-benzobicyclo-[3.2.0]heptane **2** in nearly quantitative yield within 15 min (Scheme 2).

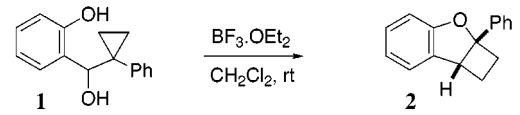
Results and Discussion

A possible reaction mechanism is depicted in Scheme 3. The first step involves the BF_3·OEt_2-induced formation of a cyclopropylcarbinyl cationic species **3**. This intermediate is in equilibrium with the more stable (presumably) cyclobutyl cation **4**, which is internally trapped by the adjacent hydroxyl group of the phenol. This tandem rearrangement−carbocation trapping provides concise access to polycyclic cyclobutane **2**.

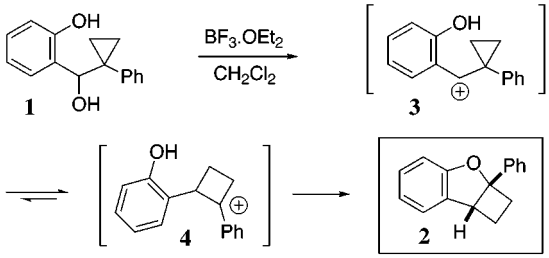
Scheme 1



Scheme 2



Scheme 3



To gauge the scope and limitations of this reaction, various substrates were prepared by metal−halogen exchange on the appropriate bromophenol,[7] followed by addition of the corresponding cyclopropanecarbaldehyde.[8] The resulting phenol-linked cyclopropylcarbinols were then subjected to reaction with BF_3·OEt_2 at room temperature. The overall yields were excellent and, in every case, greater than 90%. The reaction was successfully extended to 2-[1-hydroxy-1-(1-phenylcyclopropyl)methyl]-naphthol (Table 1, entry 2). The substitution of the cyclopropane ring was also studied and demonstrated that the process worked equally well on aryl or alkyl C1-substituted cyclopropanes (Table 1, entries 1, 3, and 4), as well as on tertiary carbinols (Table 1, entry 5). The effect of the stereochemistry of the starting cyclopropane was investigated: Both *cis*- (entry 6) and *trans*-cyclopropanes (entry 7) gave comparable yields but different ratios (95:5 and 65:35, respectively) of the two regioisomeric methylcyclobutanes. The main product resulted, in both examples, from the 1,2-migration of the carbon−carbon bond bearing the methyl group.[9] It should be noted that for each regioisomer a single diastereomer was obtained, albeit with unknown stereochemistry of the methyl group. Finally, a rearrangement attempt was conducted on substrate **5** (Table 1, entry 8). Unfortunately, under the aforementioned conditions, **5** afforded

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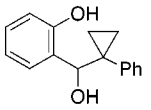
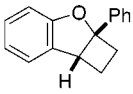
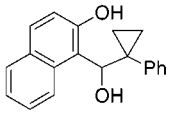
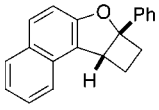
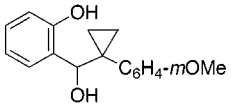
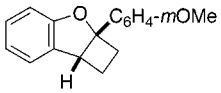
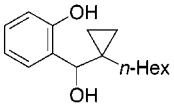
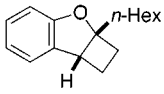
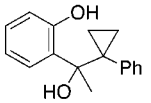
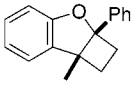
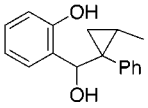
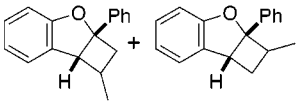
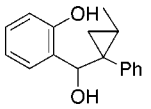
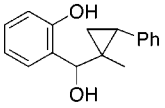
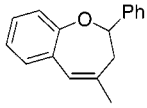
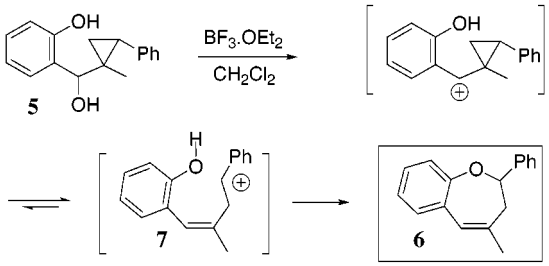
Table 1. Examples of BF_3·OEt_2-Mediated Rearrangement of Cyclopropyl Carbinols

entry	substrate	products[a]	yield[b]
1			97
2			91
3			97
4			90
5			91
6		(95:5) 	92[c]
7		(65:35)	94[c]
8			47

[a] Ratios in parentheses. [b] Isolated yields. [c] Combined yields.

Scheme 4



a moderate yield (47%) of 4-methyl-2-phenyl-2,3-dihydrobenzoxepin **6** (Scheme 4), together with many unidentified products. This result can be ascribed to the cation-stabilizing effect of the phenyl ring that directs the preferential intermediacy of the allylcarbinyl carbocation **7** over the "classical" cyclobutyl cation.

The utilization of substoichiometric amounts of BF_3·OEt_2 (0.5 equiv) in these reactions can be rationalized by the fact that HF is probably released during the rearrangement of the cyclopropylcarbinols. The acidic hydrogen fluoride then further catalyzes the formation of the transient cyclopropylcarbinyl carbocation.

In conclusion, we have shown that the boron trifluoride etherate-mediated rearrangement of phenol-substituted cyclopropylcarbinols provides a novel and direct access to polycyclic cyclobutane systems through a process analogous to the Wagner−Meerwein rearrangement.[10]

Experimental Section

General Methods. ^{1}H NMR and ^{13}C NMR spectra were recorded at 300 and 75 MHz using residual $CHCl_3$ (7.25 ppm) and $CDCl_3$ (77 ppm) as internal standard, respectively. Flash column chromatography was performed on Merck silica gel (60 Å, 230−400 mesh). All reactions were performed under Ar using anhydrous solvents. HRMS were recorded at the "Centre Régional de Mesures Physiques de l'Ouest". Reagents were purchased from Aldrich Chemical Co.

General Procedure for the Synthesis of Polycyclic Cyclobutanes for the Preparation of 1-Phenyl-2-oxa-3,4-benzobicyclo[3.2.0]heptane (2) (Table 1, Entry 1). At room temperature, to a stirred solution of BF_3·OEt_2 (12 μL, 0.5 equiv) in 2 mL of CH_2Cl_2 was added dropwise, over a period of 10 min, 2-[1-hydroxy-1-(1-phenylcyclopropyl)methyl]phenol **1** (0.040 g, 0.166 mmol, 1 equiv) in 3 mL of CH_2Cl_2. The reaction was further stirred for 5 min and quenched with 10% Na_2CO_3. The aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. After chromatography on silica (hexane/EtOAc, 9:1), 1-phenyl-2-oxa-3,4-benzobicyclo[3.2.0]heptane **2** was obtained as a colorless solid (mp 44 °C, 0.036 g, 97%): ^{1}H NMR δ 2.15 (m, 1H), 2.57 (m, 1H), 2.80−2.87 (m, 2H), 4.04 (m, 1H), 6.94 (m, 2H), 7.22 (m, 2H), 7.37 (m, 1H), 7.44 (m, 2H), 7.60 (d, J = 8.7 Hz, 2H); ^{13}C NMR δ 24.4, 34.6, 49.0, 91.5, 110.2, 120.7, 124.8, 127.6, 128.3, 128.4, 132.0, 141.7, 160.4; MS (CI/CH_4) 223 (M + 1, 100); IR (KBr) 1237 (C−O−C); HRMS calcd for $C_{16}H_{14}O_1$ $(M)^+$ 222.1044, found 222.1037.

1-Phenyl-2-oxa-3,4-naphthobicyclo[3.2.0]heptane (Table 1, Entry 2): oil; 91%; ^{1}H NMR δ 2.35 (m, 1H), 2.72 (m, 1H), 2.84−3.04 (m, 2H), 4.47 (m, 1H), 7.26−7.88 (m, 11H); ^{13}C NMR δ 23.7, 34.7, 48.4, 92.4, 112.8, 122.4, 122.9, 123.4, 125.0, 126.7, 127.7, 128.5, 128.8, 129.5, 130.6, 141.6, 157.7; MS (CI/NH_3) 307 (M + 35, 100); HRMS calcd for $C_{20}H_{16}O_1$ $(M)^+$ 272.1201, found 272.1195.

1-(3-Methoxyphenyl)-2-oxa-3,4-benzobicyclo[3.2.0]-heptane (Table 1, Entry 3): oil; 97%; ^{1}H NMR δ 2.10 (m, 1H), 2.57 (m, 1H), 2.76−2.88 (m, 2H), 3.84 (s, 3H), 4.02 (m, 1H), 6.85−6.95 (m, 3H), 7.11−7.25 (m, 4H), 7.34 (t, J = 7.9 Hz, 1H); ^{13}C NMR δ 24.5, 34.8, 49.1, 55.2, 91.4, 110.2, 110.8, 112.9, 117.1, 120.7, 124.9, 128.3, 129.5, 132.0, 143.4, 159.7, 160.3; MS (CI/NH_3) 270 (M + 18, 100); HRMS calcd for $C_{17}H_{16}O_2$ $(M)^+$ 252.1150, found 252.1140.

1-Hexyl-2-oxa-3,4-benzobicyclo[3.2.0]heptane (Table 1, Entry 4): oil; 90%; ^{1}H NMR δ 0.87 (t, J = 6.7 Hz, 3H), 1.29−1.43 (m, 8H), 1.81−1.94 (m, 3H), 2.16−2.43 (m, 3H), 3.61 (m, 1H), 6.83 (m, 2H), 7.14 (m, 2H); ^{13}C NMR δ 14.0, 22.5, 23.4, 23.9, 29.5, 31.7, 32.9, 36.3, 45.5, 91.9, 110.0, 120.3, 125.2, 128.1, 132.6, 160.6; MS (CI/NH_3) 230 (M^+, 100); HRMS calcd for $C_{16}H_{22}O_1$ $(M)^+$ 230.1670, found 230.1662.

5-Methyl-1-phenyl-2-oxa-3,4-benzobicyclo[3.2.0]-heptane (Table 1, Entry 5): oil; 91%; ^{1}H NMR δ 0.96 (s, 3H), 2.14 (m, 1H), 2.31 (m, 1H), 2.63 (m, 1H), 2.80 (m, 1H), 6.95 (m, 2H), 7.16−7.25 (m, 2H), 7.35 (m, 1H), 7.42 (m, 2H), 7.51 (m, 2H); ^{13}C NMR δ 22.1, 31.1, 32.1, 53.5, 94.2, 110.3, 120.9, 123.8, 125.6, 127.5, 128.2, 128.3, 138.7, 159.5; MS (CI/NH_3) 254 (M + 18, 100); HRMS calcd for $C_{17}H_{16}O_1$ $(M)^+$ 236.1201, found 236.1193.

6-Methyl-1-phenyl-2-oxa-3,4-benzobicyclo[3.2.0]-heptane and 7-Methyl-1-phenyl-2-oxa-3,4-benzobicyclo-[3.2.0]heptane (Table 1, Entries 6 and 7). These compounds were prepared starting from either *cis*- (entry 6) or *trans*-2-[1-hydroxy-1-(2-methyl-1-phenylcyclopropyl)methyl]phenol (entry 7). A mixture of 6-methyl- (compound **b**) and 7-methyl-1-phenyl-2-oxa-3,4-benzobicyclo[3.2.0]heptane (compound **a**) was obtained in both examples: entry 6 (ratio **b/a**: 95/5, oil, 92%), entry 7 (ratio **b/a**: 65/35, oil, 94%): ^{1}H NMR δ 0.74 (d, J = 7.1 Hz, 3Ha),

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1.31 (d, J = 6.7 Hz, 3Hb), 2.07 (m, 1Ha), 2.31 (m, 1Ha), 2.45−2.53 (m, 2Hb), 2.99 (m, 1Hb), 3.10 (m, 1Ha), 3.68 (brs, 1Hb), 4.18 (d, J = 8.4 Hz, 1Ha), 6.89 (m, 2Ha + 2Hb), 7.16 (m, 2Ha + 2Hb), 7.37−7.53 (m, 5Ha + 5Hb); ^{13}C NMR δ 16.6 (a), 21.3 (b), 33.1 (a), 34.0 (b), 41.1 (b), 41.6 (a), 44.6 (a), 55.4 (b), 90.3 (b), 95.3 (a), 109.9 (b), 110.3 (a), 120.6 (b), 124.2 (b), 125.1 (a), 125.3 (b), 125.8 (a), 127.4 (a), 127.7 (b), 128.1 (a), 128.2 (b), 128.4 (b), 131.6 (b), 132.1 (a), 138.3 (a), 142.5 (b), 159.8 (a), 160.7 (b); MS (CI/NH_3) 254 (M + 18, 100); HRMS calcd for $C_{17}H_{16}O_1$ $(M)^+$ 236.1201, found 236.1193.

4-Methyl-2-phenyl-2,3-dihydrobenzoxepin (6) (Table 1, Entry 8): colorless solid; mp 65 °C; 47%; ^{1}H NMR δ 1.97 (s, 3H), 2.60 (d, J = 18.5 Hz, 1H), 3.02 (dd, J = 10.5 Hz, 18.5 Hz), 4.99 (d, J = 10.5 Hz, 1H), 6.24 (s, 1H), 6.94−7.46 (m, 9H); ^{13}C NMR δ 26.5, 45.9, 80.7, 120.2, 122.6, 124.7, 125.9, 127.1, 127.5, 128.4, 128.7, 131.9, 137.7, 142.2, 158.7; MS (CI/NH_3) 254 (M + 18, 100); HRMS calcd for $C_{17}H_{16}O_1$ $(M)^+$ 236.1201, found 236.1193.

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Supporting Information Available: Reproductions of ^{1}H and ^{13}C NMR spectra of products described in Table 1. This material is available free of charge via the Internet at http://pubs.acs.org.

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