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BF_3-Promoted Synthesis of Diarylhexahydrobenzo[*f*]isoquinoline

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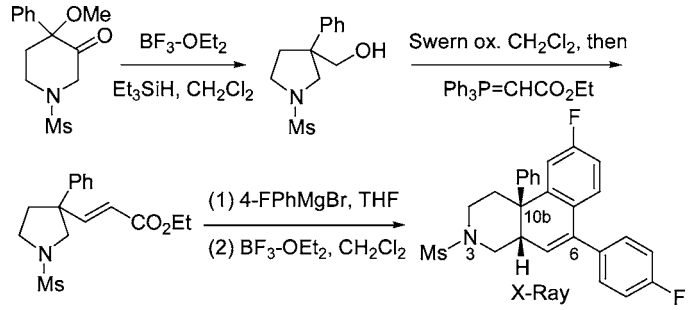
ABSTRACT



An easy and straightforward synthesis of 6,10b-diarylhexahydrobenzo[*f*]isoquinoline by the repeated treatment of boron trifluoride etherate (BF_3·OEt_2) is reported. The overall transformation from 4-arylpiperidin-3-one to benzo[*f*]isoquinoline proceeds via ring contraction, chain elongation, and intramolecular electrophilic cyclization in moderate yields. It presents a novel rearrangement reaction catalyzed by boron trifluoride etherate and broadens the scope of application.

Notably, boron trifluoride etherate (BF_3•OEt_2) has been reviewed for reactions involving carbon−carbon or carbon−heteroatom bond formations. Due to the numerous advantages associated with this ecofriendly compound, recent investigations have explored its applications as an effective reagent for various reactions. Some representative examples include cycloaddition, isomerization, unexpected rearrangement reactions, ring contraction, and ring expansion.[1] In previous studies, we investigated the interesting rearrangement reactions related to BF_3•OEt_2 in the context of synthesizing five-, six-, and seven-membered structural frameworks (pyrrolidine, piperidine, and azepane, etc).[2] To better understand the synthetic application of BF_3•OEt_2, a strategy for preparing diarylhexahydrobenzo[*f*]isoquinoline with a conformationally restricted 4,4-diarylpiperidine framework (3-azadecalin system) was developed.

The latter showed that BF_3•OEt_2 can act as a powerful reagent to promote an unusual Grob fragmentation of a piperidine ring and follow a tandem process, including the Mannich-type ring closure, Friedel−Crafts cyclization, and aromatization in the synthesis of the novel structural framework of a 3-azadecalin system. These unique structural features prompted various

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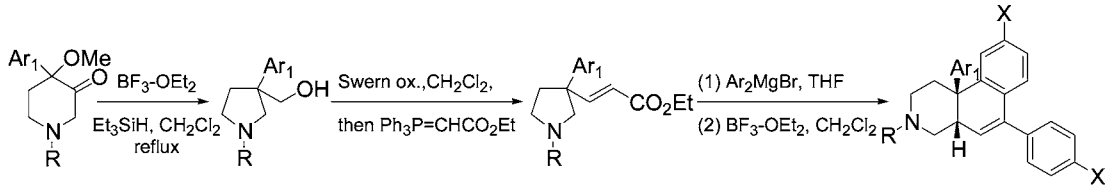
Scheme 1. Synthesis of Hexahydrobenzo[*f*]isoquinolines

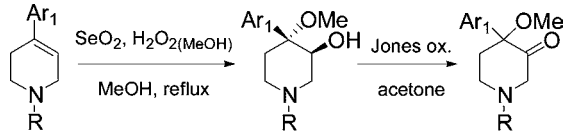


R = Ms	R = Ms	R = Ms	R = Ms
1a, Ar_1 = Ph	**2a**, Ar_1 = Ph (78%)	**3a**, Ar_1 = Ph (79%)	**4a**, Ar_1 = Ph, X = H (70%)
1b, Ar_1 = 3-CF_3Ph	**2b**, Ar_1 = 3-CF_3Ph (73%)	**3b**, Ar_1 = 3-CF_3Ph (72%)	**4b**, Ar_1 = Ph, X = F (58%)
1c, Ar_1 = 4-MeOPh	**2c**, Ar_1 = 4-MeOPh (80%)	**3c**, Ar_1 = 4-MeOPh (77%)	**4c**, Ar_1 = Ph, X = MeO (79%)
R = Bs	R = Bs	R = Bs	**4d**, Ar_1 = 3-CF_3Ph, X = H (69%)
1d, Ar_1 = Ph	**2d**, Ar_1 = Ph (80%)	**3d**, Ar_1 = Ph (78%)	**4e**, Ar_1 = 4-MeOPh, X = H (63%)
1e, Ar_1 = 3-CF_3Ph	**2e**, Ar_1 = 3-CF_3Ph (83%)	**3e**, Ar_1 = 3-CF_3Ph (70%)	R = Bs
1f, Ar_1 = 4-FPh	**2f**, Ar_1 = 4-FPh (70%)	**3f**, Ar_1 = 4-FPh (66%)	**4f**, Ar_1 = Ph, X = H (68%)
1g, Ar_1 = 2-MeOPh	**2g**, Ar_1 = 2-MeOPh (72%)	R = Ts	**4g**, Ar_1 = 3-CF_3Ph, X = H (72%)
1h, Ar_1 = 3-CF_3-4-ClPh	**2h**, Ar_1 = 3-CF_3-4-ClPh (68%)	**3g**, Ar_1 = Ph (76%)	**4h**, Ar_1 = 3-CF_3Ph, X = F (51%)
R = Ts	R = Ts		**4i**, Ar_1 = 4-FPh, X = H (65%)
1i, Ar_1 = Ph	**2i**, Ar_1 = Ph (76%)		R = Ts
			4j, Ar_1 = Ph, X = H (71%)

strategies from synthetic chemists.[3] Many researchers determined that some benzo[*f*]isoquinolines have a high affinity for the σ receptors as regard to psychotomimetic effects[4] or as potential calcium channel blockers.[5]

As shown in Scheme 1, a remarkable two-step transformation is described as follows: the rapid access to produce 3-arylpyrrolidines **2** by BF_3•OEt_2-mediated rearrangement reaction of 4-arylpiperidin-3-ones **1**; the other is the intramolecular electrophilic cyclization from the derived tertiary alcohols through Grignard addition of α,β-unsaturated esters **3** to benzo[*f*]isoquinolines **4**.

Scheme 2. Synthesis of 4-Arylpiperidin-3-ones **1**



5 **6** **1**

The starting materials **1** were prepared using the two-step protocol and are described as follows (Scheme 2): (i) the regioselective *trans*-methoxyhydroxylation of *N*-substituted 4-aryl-1,2,5,6-tetrahydropyridines **5** (R = Ms, Bs, Ts; Ar = Ph, 3-CF_3Ph, 4-MeOPh, 4-FPh, 2-MeOPh, 3-CF_3-4-ClPh) with selenium dioxide and hydrogen peroxide in MeOH at reflux temperature for 5 h; (ii) the oxidation of the resulting *trans*-1,2-methoxy alcohols **6** with excess Jones reagent in acetone at rt for 20 min.[6] Thus, nine compounds **1a**−**i** were provided in a 70−82% yield. Initially, we wanted to employ piperidinones **1a** and **1g** as the model substrates in the synthesis of the related paroxetine analogues[7] by the reductive demethoxylation reaction with the combination of triethylsilane and BF_3•OEt_2. Notably, a mixture of compounds **7** and **2** was isolated without the formation of the expected 4-arylpiperidin-3-one product. With the results in mind, treatment of ketone **1a** or **1g** with triethylsilane (2.0 equiv) and BF_3−OEt_2 (1.0 equiv) in CH_2Cl_2 (20 mL) in an ice bath for 10 h gave compounds **7a** or **7b** and **2a** or **2g**, respectively (Scheme 3). The ratios of products **7a**/**2a** and **7b**/**2g** are nearly 5/1 and 2/1. The structural framework of 1,2-methoxy alcohol **7a** and **7b** with *cis*-configuration was determined by single-crystal X-ray analysis.[8]

How are *cis*-1,2-methoxy alcohol **7** and primary alcohol **2** produced? The most likely explanation would be that regioselective reduction was effected by the chelation of boron complex[1b] between the 3-carbonyl and 4-methoxy group position of ketone **1**. With a less steric hindrance, hydride could attack the 3-carbonyl group to elicit the predicted intermediate **I**. We envisioned that the intermediate **I** could adopt the stable conformation (in situ generation from 1.0 equiv of BF_3•OEt_2) where the leaving group is antiperiplanar to the C2−C3 bond and the nitrogen electron pair

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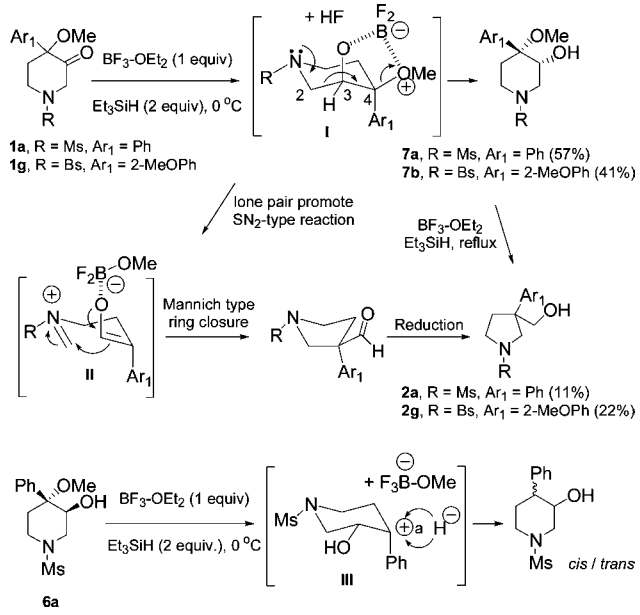
(8) 8CCDC 760205 (**7a**) and CCDC 720207 (**7b**) contain the supplementary crystallographic data for this paper. This data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: 44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk).

Scheme 3. BF_3•OEt_2/Et_3SiH-Mediated Reaction



is antiperiplanar to the C3−C4 bond. Through the involvement of the nitrogen electron pair and the chelation of the boron complex, the two driving forces could accelerate the regiospecific ring-opening of intermediate **I** to intermediate **II**.[9] After the S_N2-type displacement and an intramolecular Mannich-type ring closure, reduction of the resulting aldehyde yielded alcohol **2**. In this case, when the temperature was increased to reflux temperature, the ring contraction was generated from six-membered **7a** or **7b** to five-membered **2a** or **2g** in 91% or 83% yield, according to Baldwin's rules for the ring closure.[10] Therefore, we conclude that reaction temperature can play an important factor in controlling ring contraction. With the results in hand, a series of compounds **2a**−**i** was prepared through the treatment of compounds **1a**−**i** with triethylsilane and BF_3•OEt_2 at reflux temperature for 10 h in 68−83% yields.

Under similar reaction conditions, attempts at ring contraction of *trans*-1,2-methoxy alcohol **6a** were unsuccessful. Regarding intermediate **I**, a possible reason might be that the *trans*-isomer could not generate a boron-chelated conformation insofar as the chance of a regiospecific ring opening was decreased. For intermediate **III**, excess hydride might attack the resulting benzylic cation from an axial or equatorial position. A mixture of *cis*- and *trans*-4-phenylpiperidin-3-ols was isolated as major product (37%) among the complex products.[11] It seemed appropriate to examine the useful paroxetine analogs.[7a]

Next, we chose seven alcohols **2a**−**f**,**i** as the substrates for a one-pot reaction with Swern oxidation and Wittig olefination.[12] The products **3a**−**g** resulted in 66−79% yields. The esters **3** were converted into compounds **4** via Grignard addition with three arylmagnesium bromide reagents (Ar_2 = Ph, 4-FPh, 4-MeOPh) in THF in an ice bath for 5 h, followed by BF_3•OEt_2-mediated rearrangement in CH_2Cl_2 at rt for 30 min. Ten compounds **4a**−**j** were obtained in 51−79% overall yields.[13] Based on the results, we found that the isolated yields of compounds **4b** and **4g** with an electron-withdrawing group were poorer than compound **4c** with an electron-donating group. When Ar_2 is a phenyl group, the Ar_1 group is not an important substituent in the context of having a substantial effect on the distribution of the provided yields in the presence of an electron-withdrawing group or an electron-donating group.

The possible mechanism is described as follows (Scheme 4): (a) the initial event may be considered as the formation of the intermediate **A** with a stable benzylic cation, (b) double-bond migration of intermediate **A** is generated, (c) two intermediates, **B** and **C**, are formed at an equilibrium, (d) a regiospecific ring-opening, through involvement of nitrogen electron pairs, yields intermediates **D** and **E**, (e) the preferred intermediate **E** with *E*-orientation proceeds an intramolecular Mannich type ring closure, and (f) a stereoselective Friedel−Crafts ring cyclization is afforded from

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(13) A representative procedure of skeleton **4** is as follows: A solution of arylmagnesium bromide (5.0 mmol) in THF (10 mL) was added to a stirred solution of α,β-unsaturated esters **3** (2.0 mmol) in THF (20 mL) at ice bath temperature. The reaction mixture was stirred at rt for 5 h. Water (5 mL) was added to the reaction mixture, and the mixture was filtered through a short plug of Celite. The filtrate was concentrated under reduced pressure. The residue was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine, dried, filtered, and evaporated to afford crude product under reduced pressure. Without further purification, a solution of BF_3•OEt_2 (1 mL) in CH_2Cl_2 (5 mL) was added to a stirred solution of the crude product in CH_2Cl_2 (50 mL) at 0 °C. The reaction mixture was stirred at rt for 30 min. Saturated $NaHCO_3$(aq) solution (10 mL) was added to the reaction mixture, and the solvent was concentrated under reduced pressure. The residue was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine, dried, filtered, and evaporated to afford crude product under reduced pressure. Purification on silica gel (hexane/EtOAc = 8/1−4/1) afforded compounds **4**. Representative data for compound **4a**: mp = 183−184 °C; HRMS (ESI, M^+ + 1) calcd for $C_{26}H_{26}NO_2S$ 416.5561, found 416.5560; ^{1}H NMR (400 MHz) δ 7.41−7.11 (m, 14H), 5.85 (d, *J* = 6.4 Hz, 1H), 3.75−3.68 (m, 2H), 3.34 (ddd, *J* = 4.0, 6.4, 10.4 Hz, 1H), 3.06 (dt, *J* = 2.4, 12.0 Hz, 1H), 2.70 (s, 3H), 2.67 (dt, *J* = 2.4, 14.4 Hz, 1H), 2.59 (dd, *J* = 10.4, 12.0 Hz, 1H), 2.35 (ddd, *J* = 4.0, 12.0, 14.4 Hz, 1H); ^{13}C NMR (100 MHz) δ 145.62, 141.44, 139.78, 136.21, 135.21, 128.53 (2×), 128.22, 128.17 (2×), 128.06 (2×), 127.45, 127.43, 127.24, 127.04, 126.93 (2×), 126.54, 125.98, 45.55, 44.99, 42.93, 40.79, 34.85, 34.54. Anal. Calcd for $C_{26}H_{25}NO_2S$: C, 75.15; H, 6.06; N, 3.37. Found: C, 75.41; H, 6.23; N, 3.51. Compound **4b**: mp = 225−226 °C; HRMS (ESI, M^+ + 1) calcd for $C_{26}H_{24}F_2NO_2S$ 452.5370, found 452.5372; ^{1}H NMR (400 MHz) δ 7.28−6.92 (m, 12H), 5.80 (d, *J* = 6.0 Hz, 1H), 3.73−3.63 (m, 2H), 43.34 (ddd, *J* = 4.0, 6.0, 10.0 Hz, 1H), 3.07 (dt, *J* = 2.4, 11.2 Hz, 1H), 2.72 (s, 3H), 2.64−2.54 (m, 2H), 2.36 (ddd, *J* = 4.0, 11.2, 14.8 Hz, 1H); ^{13}C NMR (100 MHz) δ 163.89, 161.42, 144.63, 140.30, 139.55, 135.50, 131.26, 130.11, 128.96, 128.27 (2×), 126.86, 126.84, 125.47, 115.33, 115.12, 114.93, 114.70, 113.81, 113.60, 45.46, 45.19, 42.82, 40.60, 34.94, 34.37. Anal. Calcd for $C_{26}H_{23}F_2NO_2S$: C, 69.16; H, 5.13; N, 3.10. Found: C, 69.38; H, 5.29; N, 2.91.

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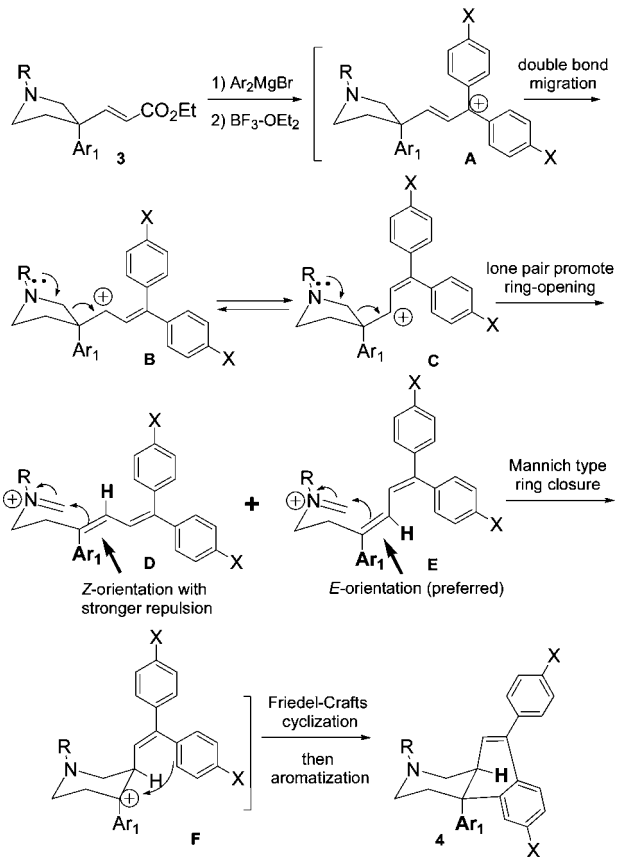
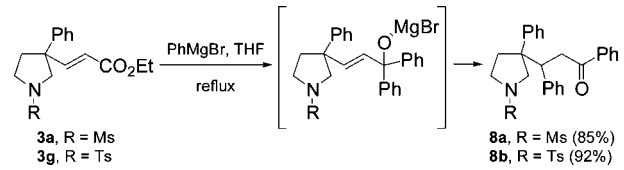
Scheme 4. BF_3•OEt_2-Mediated Rearrangement



an equatorial position of intermediate **F** and is followed by aromatization.[14] For intermediate **D**, the orientation of the Ar_1 group and the diarylethylenyl group on the central alkene is *trans* to one another (*Z*-orientation). It exhibited a stronger repulsion with steric hindrance than did intermediate **E**. As a result, the 3-azadecalin skeleton with *cis*-orientation was isolated as a sole isomer. The structural framework of compound **4b** was determined by single-crystal X-ray analysis.[15]

During the investigation of the Grignard addition of α,*β*-unsaturated esters **3a** or **3g** (1.0 equiv) with phenylmagnesium bromide (1.0 M, 6.0 equiv) at reflux temperature for 15 h, the sole product **8a** or **8b** was isolated in good yield, respectively (Scheme 5).[16] The structure of pyrrolidine **8b** was determined by single-crystal X-ray analysis.[17] We thought that the configuration was derived from the repulsion of two phenyl groups with steric hindrance during the base-induced 1,3-phenyl group migration; however, treatment of compound **3g** with 4-methoxyphenylmagnesium bromide at reflux temperature resulted in the rearrangement being unsuccessful. The 4-methoxyphenyl group with the electron-donating group may induce the reaction to produce a complex mixture. Although the synthetic application is decreased, this present work is complementary to existing methodology.

Scheme 5. PhMgBr-Mediated Rearrangement of α,*β*-Unsaturated Esters **3**



In summary, we have successfully presented a synthetic methodology for a novel series of 3-sulfonyl-6,10b-diaryl-hexahydrobenzo[*f*]isoquinolines **4** which involved BF_3•OEt_2-mediated intramolecular Grob rearrangement and followed a tandem electrophilic cyclization. The novel strategy showed that BF_3•OEt_2 is an excellent Lewis acid with which to promote the formation of a 3-azadecalin system. Further investigation is required regarding the synthesis of desulfonated compounds **4b** and **4h**, and their structure−activity in the context of psychotomimetic effects. Considering the utility of these heterocyclic aromatic compounds, the development of these general synthetic approaches is significant.

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Supporting Information Available: Experimental data and ^1H NMR ($CDCl_3$) spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) CCDC 760206 (**4b**) contains the supplementary crystallographic data for this paper. This data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: 44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk).

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(17) CCDC 655666 (**8b**) contains the supplementary crystallographic data for this paper. This data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: 44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk).