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BF_3-promoted synthesis of spiroindenyl heterocycles

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ABSTRACT

An easy and straightforward synthesis of spiroindenyl heterocycles by the repeated treatment of boron trifluoride etherate (BF_3-OEt_2) is reported. The overall transformation from ketones **1** to spiro-fused indenes **3** proceeds via Wittig olefination, deconjugation, Grignard addition, and intramolecular electrophilic cyclization in moderate yields. It presents a novel rearrangement reaction catalyzed by boron trifluoride etherate and broadens the scope of application.

1. Introduction

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 eco-friendly 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, azepane, and benzoisoquinoline).[2] To further investigate the synthetic application of boron trifluoride etherate, a simple strategy for preparing spiroindenyl heterocycles was developed. The unique spiro-fused structural features prompted various strategies from synthetic chemists.[3] Most of them are indane, indoline, or dihydrobenzofuran derivatives and were obtained through a number of different chemical routes related to carbanionic reactions,[3a,b] free radical cyclization,[3c] Heck reaction,[3d] and Fischer reaction.[3e]

Indeed, the molecular framework of spiropiperidine has been used as a core template to design ligands binding to various molecular targets (Fig. 1).[4] Efange et al. had identified some spiropiperidinyl heterocycles with the conformationally restricted spiro-fused 4-phenylpiperidine framework which have greater selectivity for the vesamicol receptor.[4a] Chambers et al. had found that some spiroindenyl piperidines have high affinity for σ receptors in the psychotomimetic effects.[3a] Herein, an easy and novel methodology for synthesizing spiroindenyl heterocycles with aryl group at C-3 indene framework is described via a BF_3-mediated cascade intramolecular electrophilic rearrangement of tertiary diaryl alcohol as the key step in good yields.

2. Results and discussion

As shown in Table 1 and Eq. 1, synthesis of spiroindenyl heterocycles is described as follows. β,γ-Unsaturated esters **2a–f** were prepared by the two-step protocol: (i) Wittig olefination of cyclic ketones **1a–f** (a, benzenesulfonylpiperidin-4-one; b,

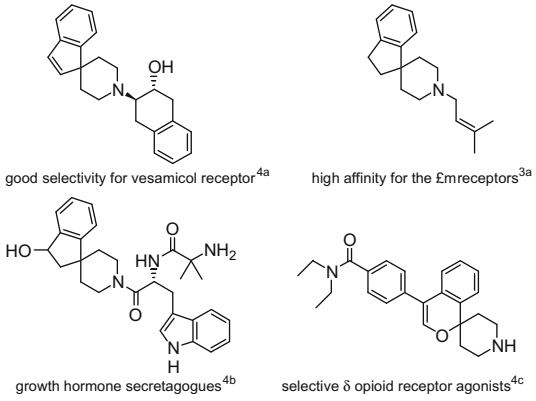

Figure 1. Biologically active spiropiperidines.

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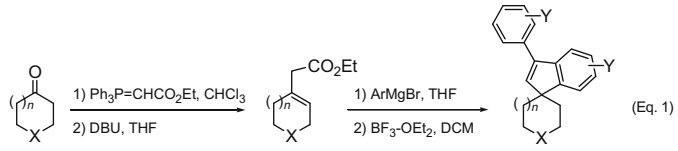
Table 1
Synthesis of spiroindenyl heterocycles **3**[a,b]



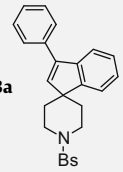
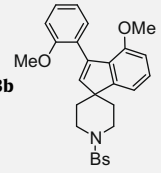
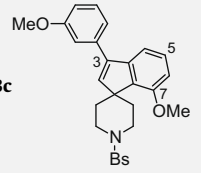
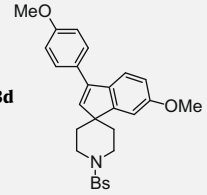
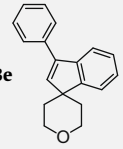
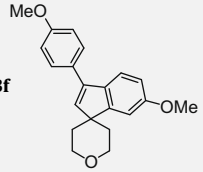
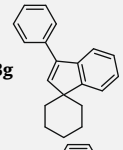
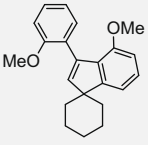
n = 1
1a, X = NBs
1b, X = O
1c, X = CH_2

X = CH_2
1d, *n* = 0
1e, *n* = 2
1f, *n* = 3

n = 1
2a, X = NBs (70%)
2b, X = O (62%)
2c, X = CH_2 (52%)

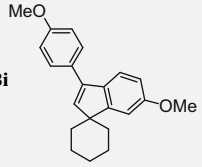
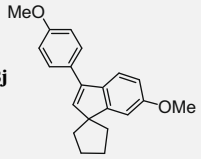
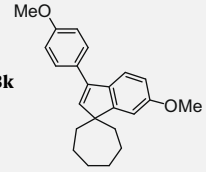
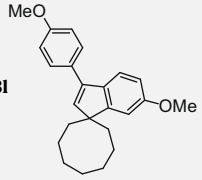
X = CH_2
2d, *n* = 0 (40%)
2e, *n* = 2 (48%)
2f, *n* = 3 (52%)

3a-3l

Entry	Reactant	Grignard reagent	Yield (%)/product
1	**2a**	PhMgBr	81/**3a** 
2	**2a**	2-MeOPhMgBr	87/**3b** 
3	**2a**	3-MeOPhMgBr	85/**3c** 
4	**2a**	4-MeOPhMgBr	91/**3d** 
5	**2b**	PhMgBr	75/**3e** 
6	**2b**	4-MeOPhMgBr	89/**3f** 
7	**2c**	PhMgBr	63/**3g** 
8	**2c**	2-MeOPhMgBr	63/**3h** 

(*continued on next page*)

Table 1 (*continued*)

Entry	Reactant	Grignard reagent	Yield (%)/product
9	**2c**	4-MeOPhMgBr	82/**3i** 
10	**2d**	4-MeOPhMgBr	52/**3j** 
11	**2e**	4-MeOPhMgBr	43/**3k** 
12	**2f**	4-MeOPhMgBr	40/**3l** 

[a] The yields of isolated products **3a–l** based on the β,γ-unsaturated esters **2a–f**.
[b] Each product showed satisfactory NMR and HRMS data.

tetrahydropyran-4-one; c, cyclohexanone; d, cyclopentanone; e, cycloheptanone; f, cyclooctanone) with ethyl triphenylphosphoranylidene acetate ($Ph_3P{=}CHCO_2Et$) in chloroform at reflux temperature for 10 h, (ii) deconjugation of the resulting α,β-unsaturated esters with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in tetrahydrofuran at reflux temperature for 10 h.[5] After careful repeated purification, six compounds **2a–f** were isolated from the crude products with a mixture of nonconjugated and conjugated isomer in 40–70% yields. For both compounds **2a** and **2b**, the ratios of nonconjugated to conjugated isomer were nearly 3/1. For four compounds **2c–f** with a cycloalkane ring, the relative ratios of nonconjugated to conjugated isomer were from 2/1 to 1/1. Under various reaction conditions, attempts at a complete deconjugation of α,β-unsaturated esters **2** were unsuccessful.[5a]

Initially, we employed compound **2a** as the model substrate to examine the reaction via Grignard addition with arylmagnesium bromide reagents (Ar = Ph, 2-MeOPh, 3-MeOPh, 4-MeOPh) in tetrahydrofuran in ice bath for 5 h and followed by subsequent BF_3-mediated reaction in dichloromethane at rt for 45 min.[6] Notably, four spiroindenyl piperidines **3a–d** were isolated in good yields by a two-step method (entries 1–4) without the formation of the expected 4-diarylethylenyl-1,2,3,6-tetrahydropyridine. The characteristic structural framework of compounds **3b** and **3d** was determined by single-crystal X-ray analysis.[7] The X-ray structure of compound **3d** is shown in Figure 2.

How is skeleton **3** produced? The possible mechanism is described as follows (Scheme 1): (a) the initial event may be considered as the formation of the intermediate **A** with a stable benzylic cation, (b) carbocation migration from the resonance form of structure **A** and **B** is generated, (c) a 5-*endo*-*trig* cyclization, according to Baldwin's rules[8] for the ring closure, yields intermediates **C**, (d) skeleton **3** is afforded from intermediate **D** via an intramolecular 1,3-proton shift[9] of intermediate **C**, and followed by aromatization. Based on the results, we found that the sole compound **3c** with 7-methoxy isomer was obtained in 85% yield and another 5-methoxy isomer was not isolated (entry 3). Regarding intermediate **C**, a possible reason might be that 7-methoxy group could chelate secondary carbocation to generate a five-membered stable conformation insofar as the chance of a regiospecific ring closure was increased. In view of the experimental simplicity, the preparation of compound **3a** was also conducted in a multigram scale (10 mmol) with 72% overall yield in two steps. With the result in hand, treatment of compounds **2b–f** with the two-step protocol was also afforded under the rearrangement process (entries 5–12). Twelve spiro-fused

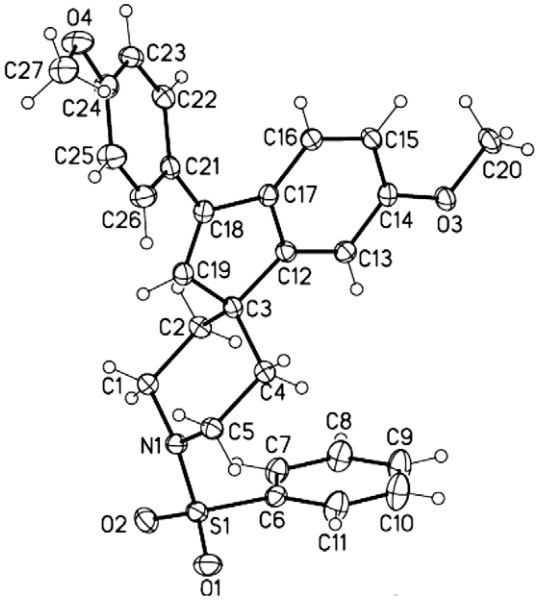
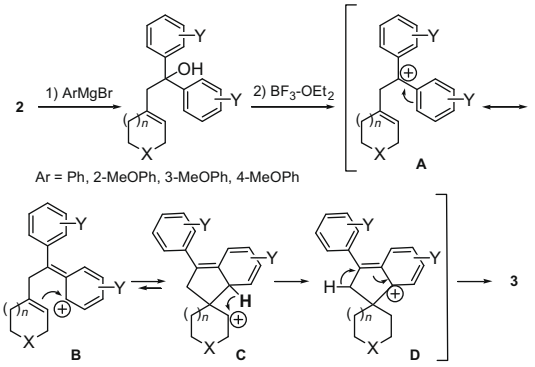


Figure 2. X-ray structure of compound **3d**. The unit cell contains solvent (EtOAc), which is omitted.

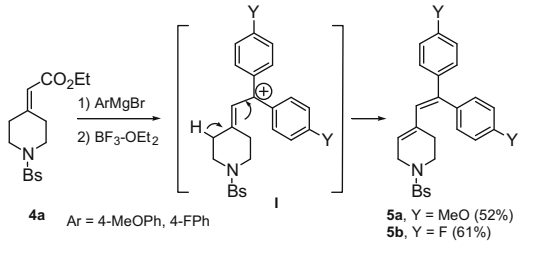


Scheme 1. The possible rearrangement mechanism.

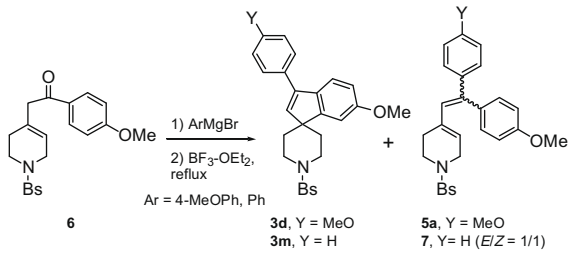
spiroindenyl products **3a**–**l** were provided after separation in 40–91% yield from compounds **2a**–**f**.

Under similar reaction conditions, attempts at two-step cyclization reaction of α,β-unsaturated ester **4a** were unsuccessful and the structure of 4-diarylethylenyl-1,2,3,6-tetrahydropyridine was generated. This is an interesting result. Treatment of compound **4a** with electron-donating group (Ar = 4-MeOPh) or electron-withdrawing group (Ar = 4-FPh) and then followed by subsequent boron trifluoride etherate yielded diene **5a** or **5b** in 52% or 61% yield, respectively. The possible mechanism is described in Scheme 2. The initial event may be considered to be the formation of the intermediate **I**. After double bond migration and proton abstraction, diene **5** is generated. It is worth noting that skeleton **2** was more appropriate for this role in preference to spiro skeleton **3** than skeleton **4** due to its *endo* olefin group, which would ultimately facilitate the possibility of intramolecular cyclization under the reaction condition.

During the further investigation, the temperature of BF_3-promoted reaction was examined (Scheme 3). Under reflux temperature, reaction of the tertiary alcohol (from Grignard reaction of ketone **6**) with boron trifluoride etherate produced the rearranged and dehydrated products. When Ar was a 4-methoxyphenyl group, products **3d** and **5a** were isolated in 85% yield as the inseparated mixture. When Ar was a phenyl group, a mixture of a sole



Scheme 2. The possible dehydration mechanism.



Scheme 3. BF_3-promoted rearrangement/dehydration reaction.

compound **3m** and dienyl compound **7** with *E*- and *Z*-isomers (1:1) were yielded. The ratio was determined by ^{1}H NMR analysis. We thought that the 4-methoxyphenyl group may induce the regioselective cyclization in the formation of spiro compound **3m**. Although the synthetic application is decreased, this present work is complementary to existing methodology.

3. Conclusion

In summary, we have successfully presented a synthetic methodology for a novel series of spiroindenyl heterocycles **3** which involved BF_3-promoted intramolecular electrophilic cyclization. The novel strategy showed that boron trifluoride etherate is an excellent Lewis acid to promote the formation of a spiroindene system with.

Acknowledgments

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6. A representative procedure of skeleton **3** is as follows: A solution of arylmagnesium bromide (3.0 mmol) in tetrahydrofuran (10 mL) was added to a stirred solution of β,γ-unsaturated esters **2a**–**f** (1.0 mmol) in tetrahydrofuran (20 mL) in an ice bath. 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 ethyl acetate (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 boron trifluoride etherate (1 mL) in dichloromethane (5 mL) was added to a stirred solution of the crude product in dichloromethane (50 mL) at 0 °C. The reaction mixture was stirred at rt for 45 min. Saturated sodium bicarbonate solution (10 mL) was added to the reaction mixture and the solvent was concentrated under reduced pressure. The residue was extracted with ethyl acetate (3 × 30 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/ethyl acetate = 8/1:4/1) afforded compounds **3a**–**l**. Representative data for compound **3a**: mp = 190–191 °C; HRMS (ESI, M^++1) calcd for $C_{25}H_{24}NO_2S$ 402.5295, found 402.5298; ^{1}H NMR (400 MHz): δ 7.87–7.84 (m, 2H), 7.69–7.57 (m, 3H), 7.51–7.47 (m, 3H), 7.43–7.27 (m, 6H), 6.52 (s, 1H), 3.97 (dt, J = 2.8, 12.4 Hz, 2H), 2.72 (dt, J = 2.8, 12.4 Hz, 2H), 2.30 (dt, J = 4.4, 14.0 Hz, 2H), 1.51 (d, J = 14.0 Hz, 2H); ^{13}C NMR (100 MHz): δ 152.00, 143.83, 141.74, 136.36, 135.58, 135.31, 132.85, 129.15 (2×), 128.56 (2×), 127.95, 127.64 (2×), 127.57 (2×), 127.20, 125.95, 121.96, 120.97, 49.82, 44.98 (2×), 33.33 (2×); Anal. Calcd for $C_{25}H_{23}NO_2S$: C, 74.78; H, 5.77; N, 3.49. Found: C, 74.94; H, 5.89; N, 3.61.

7. CCDC 772318 (**3b**) and 762275 (**3d**) 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).
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