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Editor's Choice

Ring Expansion Approach to Azaspiro[4.5]decane Skeletons via Electrophilic Activation of Benzocyclobutenols Bearing Pyridyl Group

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Facile construction of azaspiro[4.5]decane skeletons was enabled by the ring expansion of benzocyclobutenols substituted with a pyridyl group, triggered by electrophilic activation of the heteroaromatic moiety.

Spirobenzylisoquinoline alkaloids constitute an interesting class of natural products produced by plants of the Fumariaceae family (Figure 1).[1] The key structural feature shared by this class of compounds is an azaspiro[4.5]decane skeleton.

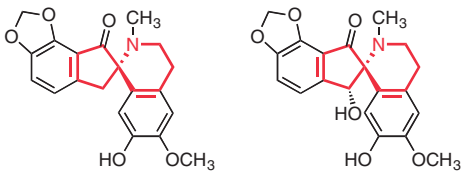
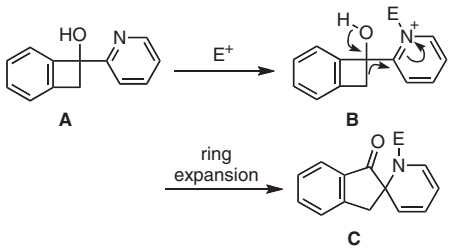


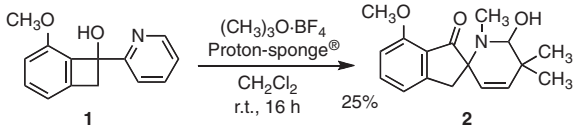
Figure 1.

We became interested in the possible construction of such azaspiro frameworks via the ring expansion of benzocyclobutenol **A** bearing a pyridyl group.[2,3] The electrophilic activation of the pyridine ring as in **B** would trigger ring expansion to produce the requisite azaspiro system **C** (eq 1).[4]



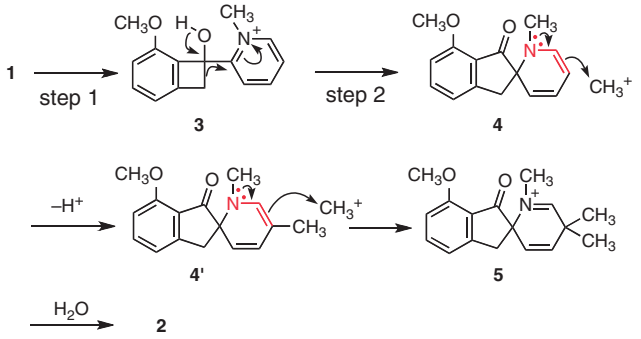
(1)

With this scenario in mind, a model substrate **1**[5] was prepared and subjected to activation of the pyridine moiety by *N*-methylation. When alcohol **1** was treated with the Meerwein salt[6] in the presence of Proton-sponge®, the starting material **1** was smoothly consumed, giving the spiro compound **2** in 25% yield (eq 2).



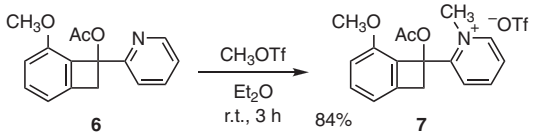
(2)

The formation of **2**, albeit in low yield, convinced us of the viability of the projected ring expansion, but at the same time revealed an issue in that the resulting product **4** could further undergo *C*-methylation (Scheme 1) leading to monomethylated product **4′** and further to bismethylated product **5**. The workup gave hemiaminal **2**.



Scheme 1.

In order to suppress this side reaction, we intended to separate the *N*-methylation (step 1) and the ring expansion (step 2). Indeed, acetate **6** underwent the *N*-methylation without further reaction, giving pyridinium salt **7** as a white powder (eq 3).[5]



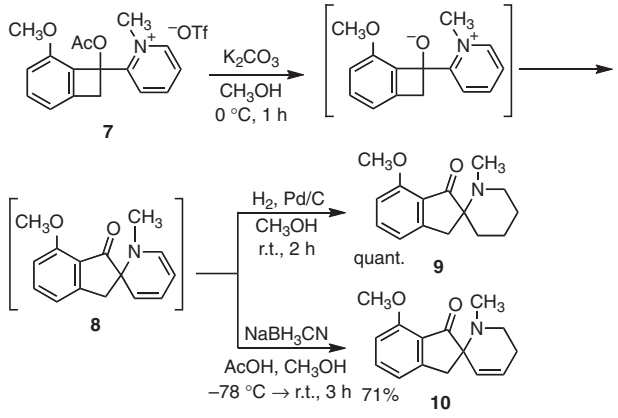
(3)

Hoping to trigger the ring expansion, acetate **7** was exposed to basic methanolytic conditions (K_2CO_3, MeOH), where the projected process indeed proceeded, giving the desired spiro compound **8**. However, we were again annoyed by the high lability of the product **8** (Scheme 2).

Assuming that the instability originates from the enamine moiety in **8**, we attempted to reduce it without purification. Pleasingly, two reductive protocols allowed us isolation of the desired spiro products in high yields: Hydrogenation gave piperidine **9** in quantitative yield from **7**, while the workup with $NaBH_3CN$[7] furnished tetrahydropyridine **10** in 71% yield.[5]

A typical procedure is described for the preparation of pyridinium salt 7, its ring expansion, and reductive workup: To a solution of acetate **6** (339 mg, 1.26 mmol) in Et_2O (12 mL) was added methyl trifluoromethanesulfonate (651 mg, 3.97 mmol) in Et_2O (2 mL) at room temperature. After stirring for 3 h, the resulting precipitates were collected by suction filtration, washed with Et_2O, and dried in vacuo to afford pyridinium salt **7** (461 mg, 84%) as a white solid, which was used for the next step.

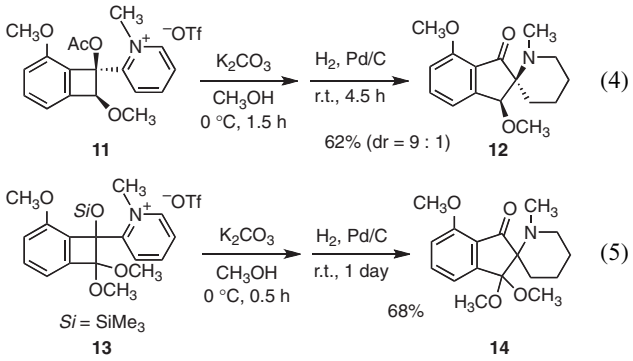
To a solution of pyridinium salt **7** (54.6 mg, 0.126 mmol) in MeOH (2 mL) was added K_2CO_3 (52.4 mg, 0.379 mmol) at 0 °C under an argon atmosphere. After stirring for 1 h, 5% Pd/C (28.7 mg) was added, and the reaction was further stirred under H_2 atmosphere (balloon) for 2 h. After filtration through a



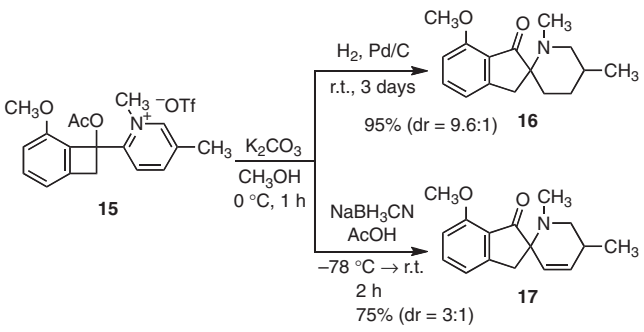
Scheme 2.

Celite® pad and washing with CH_2Cl_2, the filtrate was concentrated in vacuo. Purification on preparative TLC ($CHCl_3$/MeOH = 9/1) afforded piperidine **9** as a yellow oil.[5]

The protocols were applied to related substrates with different oxygenation patterns at the four-membered ring. Pyridinium salt **11** with an extra methoxy group on the four-membered ring[8] gave the spiro compound **12** in 9:1 diastereoselectivity (eq 4). Silyl-protected pyridinium salt **13** with two methoxy groups was also a viable substrate, giving spirocycle **14** in 68% yield (eq 5).

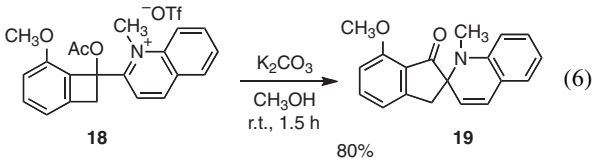


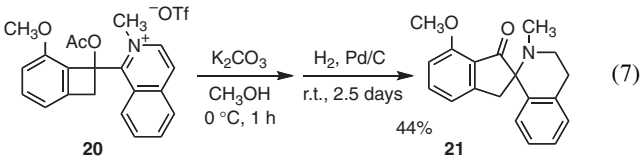
Scheme 3 shows the reactions of 3-picoline derivative **15**: the hydrogenolytic workup gave spiro-piperidine **16** (dr = 9.6:1),[9] while the workup with $NaBH_3CN$ led to spiro-tetrahydropyridine **17** (dr = 3:1).



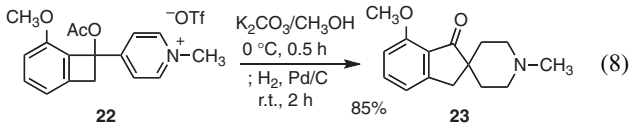
Scheme 3.

The ring expansion was also applicable to quinolinium salt **18** and isoquinolinium salt **20**,[10] giving the corresponding spirocycles **19** and **21**,[9] respectively (eqs 6 and 7). It is notable that the product **19** was amenable to clean isolation *without reductive workup*, as the enamine double bond is part of an aromatic ring.[5]





4-Pyridinium salt **22**[10] also underwent the ring expansion, and the workup by hydrogenation gave the product **23** with an all-carbon spirocenter (eq 8).[5]



In conclusion, we have described an approach to aza-spiro[4.5]decane skeletons, a structural feature shared by the spirobenzylisoquinoline alkaloids, via the electrophile-initiated ring expansion of benzocyclobutenols bearing a pyridyl group.

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References and Notes

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5 See the Supporting Information which is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.

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