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A novel method for synthesizing 3-arylpyrrolidine and 4-arylpiperidine derivatives through an acid-promoted skeletal rearrangement

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ABSTRACT

A novel method for synthesizing 3-arylpyrrolidine and 4-arylpiperidine derivatives through an acid-promoted skeletal rearrangement is described. Using trifluoroacetic acid as the acid promoter, an intramolecular *ipso*-Friedel–Crafts-type addition of phenols to allyl cations, formation of iminium cations through rearomatization of the spirocyclohexadienone units, and an intramolecular aza-Prins reaction, proceeded sequentially to afford 3-arylpyrrolidine and 4-arylpiperidine derivatives in good yield with high diastereoselectivity.

Pyrrolidine and piperidine rings are ubiquitous structures in a wide variety of alkaloids. Alkaloids bearing these heterocyclic frameworks often exhibit diverse biological activities and are attractive synthetic targets in medicinal chemistry.[1] Therefore, considerable efforts have been directed toward the development of an efficient synthetic method for functionalized pyrrolidine and piperidine derivatives.[2] Among them, 3-arylpyrrolidines and 4-arylpiperidines are the most important classes of compounds. These structural motifs are found in various pharmaceuticals and drug candidates, such as Paroxetine,[3,4] MC4 receptor agonists, [5a] CCR5 antagonists,[5b] and hNK_1 antagonists[5c] (Fig. 1).

As part of our ongoing studies aimed at developing efficient synthetic methods for functionalized heterocycles, we recently reported a novel synthetic method for tricyclic indole derivatives through an acid-promoted skeletal rearrangement (Scheme 1a).[6] The method is based on a three-step reaction sequence: (1) intramolecular *ipso*-Friedel–Crafts-type addition of phenol derivatives to 3-alkylidene indolenium cations, (2) formation of iminium cations through rearomatization of spirocyclohexadienone units, and (3) an intramolecular Pictet–Spengler reaction. We hypothesized that, after the generation of an iminium cation via the intramolecular *ipso*-Friedel–Crafts-type addition of a phenol derivative[7] to an allyl cation and subsequent rearomatization, entrapment of the iminium cation by an intramolecular aza-Prins reaction[8] would produce functionalized 3-arylpyrrolidine derivatives ($n = 1$) or 4-arylpiperidine derivatives ($n = 2$) that are of potential interest as drug design scaffolds (Scheme 1b). Herein, we report a novel method for synthesizing 3-arylpyrrolidine and 4-arylpiperidine derivatives possessing three contiguous chiral centers through an acid-promoted skeletal rearrangement.

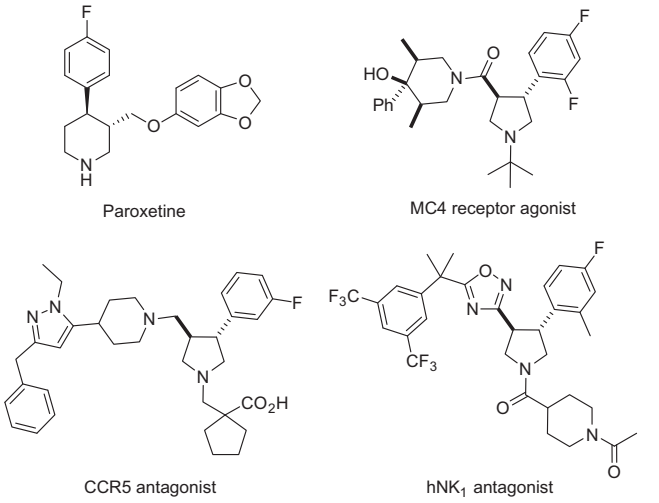

Figure 1. Examples of drugs and pharmaceutical leads containing 3-arylpyrrolidine or 4-arylpiperidine unit.

Our studies began with model substrate **1a** (Table 1). Treatment of **1a** with trifluoroacetic acid (TFA) in CH_2Cl_2 at 0 °C led to the

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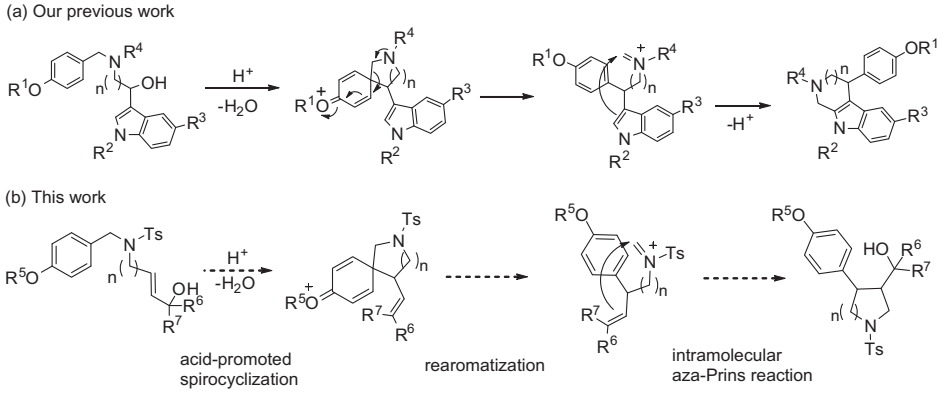
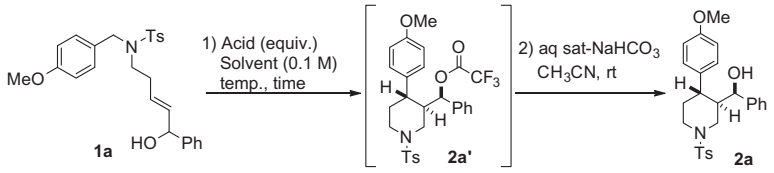


Scheme 1. Backgrounds and plan of this work.

Table 1
Optimization of the reaction conditions



Entry	Acid (equiv)	Solvent	Temp.	Time (h)	Yield[a] (%)	dr[b]
1	TFA (1)	CH_2Cl_2	0 °C	24	0	–
2	TFA (2)	CH_2Cl_2	0 °C	24	10	–
3	TFA (5)	CH_2Cl_2	0 °C	24	55	14:1
4	TFA (10)	CH_2Cl_2	0 °C	9	75	18:1
5	TFA (15)	CH_2Cl_2	0 °C	1	82	18:1
6	TFA (20)	CH_2Cl_2	0 °C	1	82	18:1
7	TFA (15)	CH_3CN	0 °C	3	14	13:1
8	TFA (15)	CH_3NO_2	0 °C	1	78	17:1
9	TfOH (1)	CH_2Cl_2	0 °C	0.2	Messy	–
10	Tf_2NH (1)	CH_2Cl_2	0 °C	0.2	Messy	–
11	TsOH H_2O (1)	CH_2Cl_2	0 °C	24	Trace	–
12	$Sc(OTf)_3$ (0.2)	CH_2Cl_2	rt	24	22	16:1
13	$In(OTf)_3$ (0.2)	CH_2Cl_2	rt	24	39	17:1

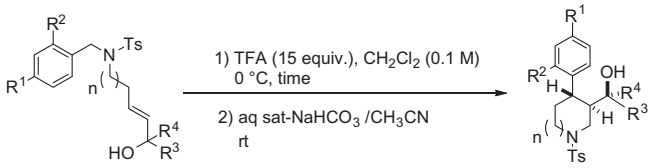
[a] Isolated yield.
[b] Determined by ^1H NMR analysis.

gradual consumption of **1a** and the formation of trifluoroacetate adduct **2a**′ as the initial adduct. Due to susceptibility of **2a**′ to hydrolysis during silica gel column chromatography, the reaction was purified after converting **2a**′ into **2a** by aqueous basic treatment of the concentrated reaction mixture. Reactivity was gradually improved by increasing the amount of TFA (entries 1–6). When the reaction was performed using 15 equiv of TFA, 4-arylpiperidine derivative **2a** was obtained in 82% yield with high diastereoselectivity (diastereomeric ratio = 18:1) (entry 5).[9] The yield decreased when the reaction was performed in CH_3CN or CH_3NO_2 instead of CH_2Cl_2 (entries 7 and 8). The use of more acidic promoters resulted in a messy reaction (entries 9–11). The same reaction was also examined using several Lewis acid catalysts. With 20 mol % of $Sc(OTf)_3$ or $In(OTf)_3$ as an acid promoter, the reaction proceeded slowly at room temperature to provide **2a** in 22% and 39% yields, respectively, (entries 12 and 13). Thus, we selected the reaction conditions in entry 5 as optimum for this process.

We next examined the scope and limitations of different substrates under the optimized reaction conditions (Table 2). In addition to *para*-substituted *O*-methyl ether derivative **1a** (entry 1), phenol derivative **1b**, *O*-benzyl ether derivative **1c**, and *O*-*t*-butyldimethylsilyl (TBS) ether derivative **1d** were applicable to this reaction, and the corresponding 4-arylpiperidine derivatives **2b**, **2c**, and **2d** were obtained in 68%, 91% and 95% yields, respectively (entries 2–4). Substrates **1e**–**i**, bearing a tolyl group or a naphthyl group on the R^3 position, also reacted smoothly to give the corresponding products **2e**–**i** in excellent yield with high diastereoselectivity (entries 5–9). Moreover, *ortho*-substituted *O*-TBS ether derivative **1j** was suitable substrates for this reaction, affording the corresponding product **2j** in good yield (entry 10). This reaction system was also effective for *tert*-allyl alcohol derivatives with dialkyl substituents **1k** ($R^3 = R^4 = Me$), demonstrating that substrates applicable to this reaction are not limited to benzyl alcohol derivatives (entry 11). Furthermore, when substrate **1l**, bearing a CH_2 unit-shorter tether than **1a**, was treated with 15 equiv of TFA under diluted conditions, the reaction proceeded smoothly to give 3-arylpyrrolidine derivative **2l** in 88% yield (entry 12).

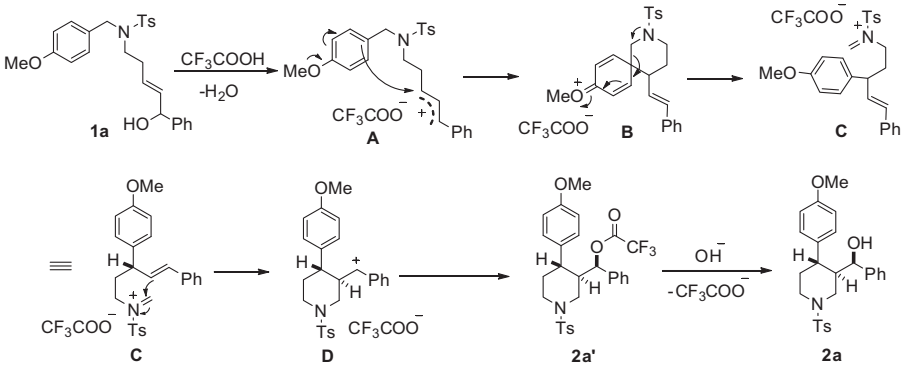
A plausible reaction pathway is shown in Scheme 2. Initially, allyl cation **A** is formed by the acid-promoted dehydration of **1a**. Subsequently, an intramolecular *ipso*-Friedel–Crafts-type addition of the phenol derivative to the allyl cation proceeds to give dearomatized cationic species **B**. Sequential rearomatization of the spirocyclohexadienone moiety accompanying the C–C bond cleavage results in the formation of iminium cation **C**. An intramolecular aza-Prins reaction of intermediate **C** occurs subsequently in a diastereoselective manner, resulting in the formation of piperidine derivative **D**, bearing a carbocation on the exocyclic benzylic position. Finally, this benzylic cation is captured by a trifluoroacetate

Table 2
Substrate scope



Entry	Substrate[a]	R^1	R^2	R^3	R^4	*n*	Product	Time (h)	Yield[b] (%)	dr[c]
1	**1a**	OMe	H	Ph	H	1	**2a**	1	82	18:1
2	**1b**	OH	H	Ph	H	1	**2b**	22	68	13:1
3	**1c**	OBn	H	Ph	H	1	**2c**	2	91	>20:1
4[d]	**1d**	OTBS	H	Ph	H	1	**2d**	3	95	>20:1
5	**1e**	OMe	H	4-Tolyl	H	1	**2e**	2	99	>20:1
6	**1f**	OMe	H	3-Tolyl	H	1	**2f**	2	92	>20:1
7	**1g**	OMe	H	2-Tolyl	H	1	**2g**	2	98	>20:1
8	**1h**	OMe	H	1-Naphthyl	H	1	**2h**	2	91	>20:1
9	**1i**	OMe	H	2-Naphthyl	H	1	**2i**	2	95	>20:1
10 [d]	**1j**	H	OTBS	Ph	H	1	**2j**	1	83	>20:1
11	**1k**	OMe	H	Me	Me	1	**2k**	4	55	>20:1
12[d]	**1l**	OMe	H	Ph	H	0	**2l**	7	88	>20:1

[a] Pure *E* isomers were used as substrates.
[b] Isolated yield.
[c] Determined by ^{1}H NMR analysis.
[d] The reaction was performed in CH_2Cl_2 (0.025 M).



Scheme 2. Proposed reaction pathway.

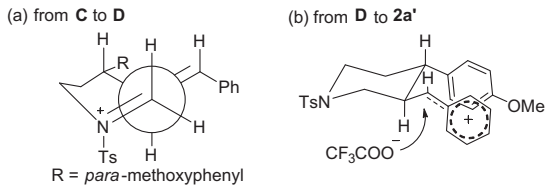


Figure 2. Rationale for the high diastereoselectivity.

anion to give **2a′**, which is converted into **2a** by base-promoted hydrolysis.

The high diastereoselectivity observed in the 4-arylpiperidine synthesis can be explained by the transition state models shown in Figure 2. From **C** to **D**: Intramolecular C–C bond formation proceeds through a transition state with minimum allylic strain (Fig. 2a). The 3,4-*trans* configuration is constructed during this process. From **D** to **2a′**: Allylic strain should also play an important role in determining the conformational preference of the transition state structure, because the C–C bond between the phenyl group and the cationic benzylic carbon bond has partial double bond characters. As shown in Figure 2b, the *para*-methoxylphenyl group effectively shields the one face of the benzylic cation from the nucleophile. A trifluoroacetate anion selectively attacks from another accessible face and the product with three contiguous chiral centers is obtained with high diastereoselectivity.[10]

In conclusion, we developed an innovative method for synthesizing 3-arylpyrrolidine and 4-arylpiperidine derivatives through an acid-promoted skeletal rearrangement. Structurally diverse pyrrolidine and piperidine derivatives were obtained in good yield with high diastereoselectivity under mild and simple reaction conditions. Further studies are in progress to investigate the pharmacological activity of these derivatives.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.01.034.

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9. Among the four possible diastereomers, only two isomers were observed in ^{1}H NMR analysis of the crude reaction mixture. Diastereomeric ratio represents the ratio of these isomers. For determination of the relative configuration of the reaction adducts, see the Supplementary data.
10. A π–electron interaction between the phenol derivative moiety (electron-rich aromatic ring) and the benzylic cation moiety (electron-deficient aromatic ring) might be participated in the stabilization of the transition state.