



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

Takuya Yokosaka, Tetsuhiro Nemoto, Yasumasa Hamada *

Graduate School of Pharmaceutical Sciences, Chiba University, 1-8-1, Inohana, Chuo-ku, Chiba 260-8675, Japan

ARTICLE INFO

Article history:

Received 3 December 2012

Revised 7 January 2013

Accepted 9 January 2013

Available online 16 January 2013

Keywords:

Pyrrolidine

Piperidine

ipso-Friedel–Crafts reaction

Aza-Prins reaction

Skeletal rearrangement

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.

© 2013 Elsevier Ltd. All rights reserved.

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 hNK₁ 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 derivative⁷ to an allyl cation and subsequent rearomatization, entrapment of the iminium cation by an intramolecular aza-Prins reaction⁸ would produce functionalized 3-arylpyrrolidine derivatives ($n = 1$) or 4-arylpiperidine derivatives ($n = 2$) that are of potential interest as

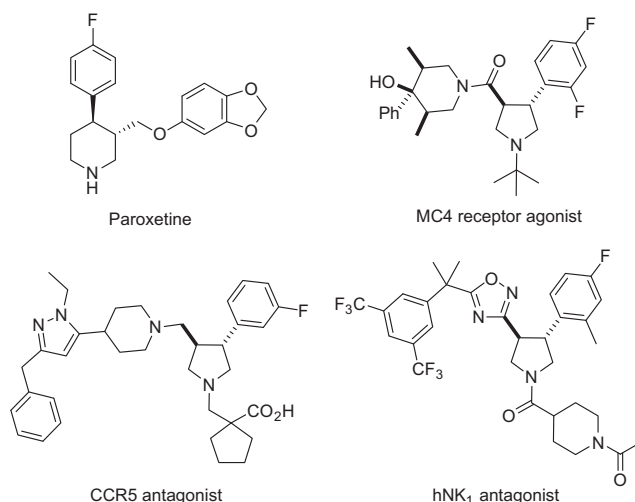


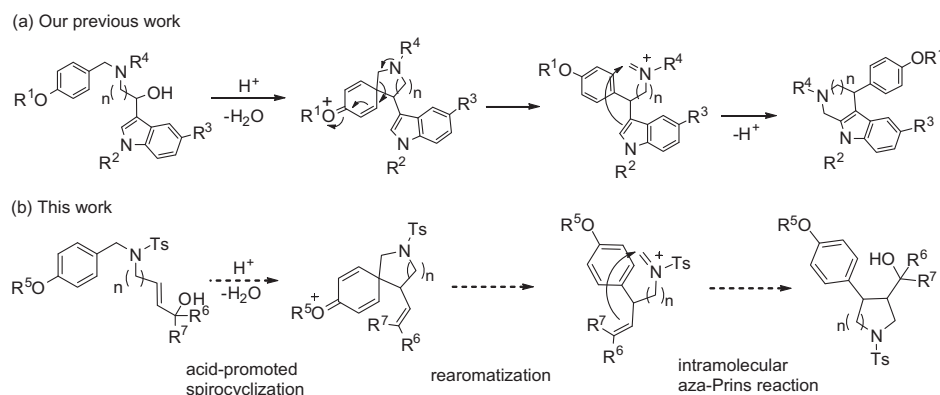
Figure 1. Examples of drugs and pharmaceutical leads containing 3-arylpyrrolidine or 4-arylpiperidine unit.

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.

Our studies began with model substrate **1a** (Table 1). Treatment of **1a** with trifluoroacetic acid (TFA) in CH₂Cl₂ at 0 °C led to the

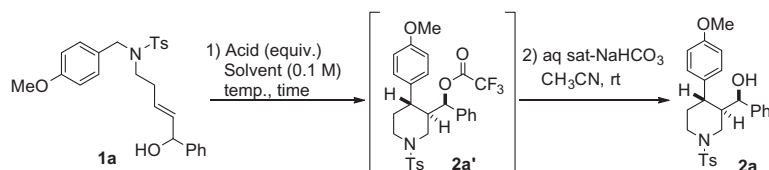
* Corresponding author. Tel./fax: +81 43 226 2920.

E-mail address: hamada@p.chiba-u.ac.jp (Y. Hamada).



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 ₂ Cl ₂	0 °C	24	0	—
2	TFA (2)	CH ₂ Cl ₂	0 °C	24	10	—
3	TFA (5)	CH ₂ Cl ₂	0 °C	24	55	14:1
4	TFA (10)	CH ₂ Cl ₂	0 °C	9	75	18:1
5	TFA (15)	CH ₂ Cl ₂	0 °C	1	82	18:1
6	TFA (20)	CH ₂ Cl ₂	0 °C	1	82	18:1
7	TFA (15)	CH ₃ CN	0 °C	3	14	13:1
8	TFA (15)	CH ₃ NO ₂	0 °C	1	78	17:1
9	TfOH (1)	CH ₂ Cl ₂	0 °C	0.2	Messy	—
10	Tf ₂ NH (1)	CH ₂ Cl ₂	0 °C	0.2	Messy	—
11	TsOH H ₂ O (1)	CH ₂ Cl ₂	0 °C	24	Trace	—
12	Sc(OTf) ₃ (0.2)	CH ₂ Cl ₂	rt	24	22	16:1
13	In(OTf) ₃ (0.2)	CH ₂ Cl 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-arylpi-peridine 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 CH₃CN or CH₃NO₂ instead of CH₂Cl₂ (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-arylpi-peridine 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 R³ 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** (R³ = R⁴ = Me), demonstrating that substrates applicable to this reaction are not limited to benzyl alcohol derivatives (entry 11). Furthermore, when substrate **1l**, bearing a CH₂ 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

Download English Version:

<https://daneshyari.com/en/article/5264542>

Download Persian Version:

<https://daneshyari.com/article/5264542>

[Daneshyari.com](https://daneshyari.com)