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Synthesis of *cis*-3,4-diarylpiperidines and *cis*-3,4-diaryltetrahydropyrans

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Abstract—Substituted *cis*-3,4-diarylpiperidines and *cis*-3,4-diaryltetrahydropyrans are synthesized in modest overall yields starting from 4-aryl-1,2,5,6-tetrahydropyridines and 4-aryl-1,2,5,6-tetrahydropyrans via the following sequence: (1) pinacol-type ring contraction having the combination of *m*-chloroperoxybenzoic acid and boron trifluoride etherate, (2) Grignard addition with arylmagnesium bromide reagents and followed by boron trifluoride etherate-mediated intramolecular ring-expanded rearrangement, and (3) hydrogenation with hydrogen on 10% palladium-activated carbon. A facile synthesis of 3,4-diarylpyridines was also described by base-induced aromatization.
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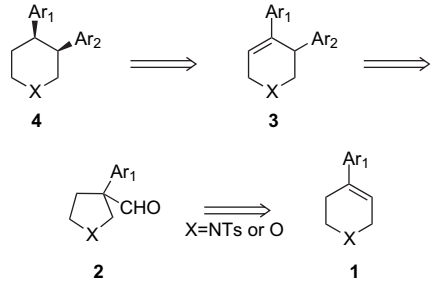
1. Introduction

Depending on the substitution pattern and functionalization, different derived substitutents in the structural skeleton of piperidines[1] and tetrahydropyrans[2] with six-membered heterocyclic ring have been shown to be effective biologically active compounds. While a great number of piperidines, tetrahydropyrans, and their derivatives with this specific substitution pattern are of particular interest, more significant efforts toward the development of new methods for synthesizing different substituted piperidines[3] and tetrahydropyrans[4] are needed. In order to address this issue and continue our preliminary investigation,[5] we want to utilize this useful combination of *m*-chloroperoxybenzoic acid (MCPBA) and boron trifluoride etherate (BF_3-OEt_2) toward the frameworks of *cis*-3,4-diarylpiperidines and *cis*-3,4-diaryltetrahydropyrans.

As shown in Scheme 1, an easy synthetic approach of *cis*-3,4-diarylpiperidines and *cis*-3,4-diaryltetrahydropyrans starting from 4-aryl-1,2,5,6-tetrahydropyridine and 4-aryl-1,2,5,6-tetrahydropyran was described as the following sequence: (1) regioselective pinacol-type ring contraction with the combination of *m*-chloroperoxybenzoic acid and boron trifluoride etherate, (2) Grignard addition with different arylmagnesium bromide reagents, (3) boron trifluoride etherate-mediated regioselective rearrangement, and (4) hydrogenation with hydrogen in the presence of a catalytic amount of 10% palladium on activated carbon.



Scheme 1. Synthetic approach toward *cis*-3,4-diarylpiperidines and *cis*-3,4-diaryltetrahydropyrans.

2. Results and discussion

2.1. Synthesis of *cis*-3,4-diarylpiperidines and *cis*-3,4-diaryltetrahydropyrans

For the preparation of *cis*-3,4-diarylpiperidines **4Aa**–**4Ae** and **4Ba**–**4Be** and *cis*-3,4-diaryltetrahydropyrans **4Ca**–**4Ce**, three starting materials 4-aryl-1,2,5,6-tetrahydropyridines **1A** (Ar_1=C_6H_5) and **1B** (Ar_1=4-FC_6H_4) and 4-phenyl-1,2,5,6-tetrahydropyran **1C** were easily prepared from 1-tosylpiperidin-4-one and tetrahydro-4*H*-pyran-4-one via Grignard addition followed by dehydration. By our preliminary synthetic experiences,[5a–c] aldehydes **2A**–**2C** were first prepared by epoxidation of olefin **1A**–**1C** with

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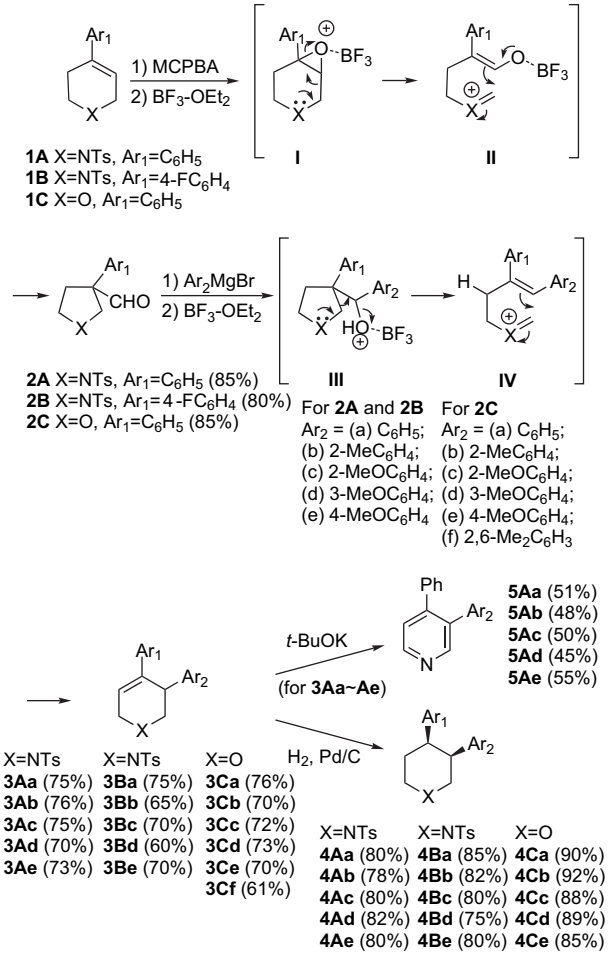
m-chloroperoxybenzoic acid at rt for 3 h followed by regioselective ring contraction of the resulting epoxides with boron trifluoride etherate at 0 °C for 15 min.

Next, Grignard addition of aldehydes **2A**–**2C** with different arylmagnesium bromide reagents (a, C_6H_5; b, 2-MeC_6H_4; c, 2-$MeOC_6H_4$; d, 3-$MeOC_6H_4$; e, 4-$MeOC_6H_4$; f, 2,6-$Me_2C_6H_3$) in tetrahydrofuran at −78 °C for 2 h yielded a pair of secondary alcohols in nearly 1:1 ratios (monitored by TLC plate) as shown in Scheme 2. Without purification, boron trifluoride etherate-mediated rearrangement of the resulting secondary alcohols afforded 4,5-diaryl-1,2,5,6-tetrahydropyridines **3Aa**–**3Ae** and **3Ba**–**3Be**, and 4,5-diaryl-1,2,5,6-tetrahydropyrans **3Ca**–**3Cf** at 0 °C for 2 h.



Scheme 2. Synthesis of *cis*-3,4-diarylpiperidines **4Aa**–**4Ae** and **4Ba**–**4Be**, *cis*-3,4-diaryltetrahydropyrans **4Ca**–**4Ce**, and 3,4-diarylpyridines **5Aa**–**5Ae**.

How is the regioselective rearrangement of ring contraction and ring expansion initiated by boron trifluoride etherate? During the ring-reconstructed structural migration of intermediate **I** with six-membered piperidine or tetrahydropyran ring and intermediate **III** with five-membered pyrrolidine or tetrahydrofuran ring, the most likely explanation would be that it is controlled by involvement of the heteroatom (nitrogen or oxygen) lone pair. We believed that heteroatom lone pair plays the important role to promote the occurrence of rearrangement reaction.[6] The resulting aldehydes **2A**–**2C** and olefins **3Aa**–**3Ae**, **3Ba**–**3Be**, and **3Ca**–**3Cf** were immediately formed as the sole products by the intramolecular rearrangement of intermediates **II** and **IV**. During two regioselective approaches, other rearranged frameworks were not observed under the boron trifluoride etherate-mediated condition.

Compounds **4Aa**–**4Ae**, **4Ba**–**4Be**, and **4Ca**–**4Ce** were easily obtained by the hydrogenation with hydrogen on 10% palladium-activated carbon at rt for 10 h (Scheme 2). The relative configuration of the structure of compound **4Cb** with two contiguous stereocenters is based on a single-crystal X-ray analysis as shown in Figure 1.[7] With the result in hand, the assignment of two diaryl functional groups on the other framework of 3,4-diarylpiperidines **4Aa**–**4Ae** and **4Ba**–**4Be**, and 3,4-diaryltetrahydropyrans **4Ca**–**4Ce** could be also arranged as the *cis* configuration.

To deserve to be mentioned, compounds **4Ad** and **4Bd** were the 4-arylpreclamol analogs. Preclamol was reported to be the first selective D_2-like dopamine autoreceptor agonist.[8] If the –CH_2O– motif was introduced into compounds **4Ba**–**Be** between 3-aryl group and piperidine skeleton during the structural modification, it would exhibit the structural characteristics of paroxetine. Paroxetine (Paxil/Seroxat) is a selective serotonin reuptake inhibitor used as an antidepressant and anti-Parkinson agent.[9]

With compounds **3Aa**–**3Ae** in hand, a facile synthesis of 3,4-diarylpyridines **5Aa**–**5Ae** via potassium *tert*-butoxide-mediated aromatization was also examined. Treatment of compounds **3Aa**–**3Ae** with potassium *tert*-butoxide in tetrahydrofuran at rt for 10 min afforded 3,4-diarylpyridines **5Aa**–**5Ae** in 45–55% yields.[10] In view of the experimental simplicity, the preparation of 3,4-diarylpiperidine **5Aa** was also conducted in a multigram scale (20 mmol) with 31% overall yield in three steps from aldehyde **2A**.

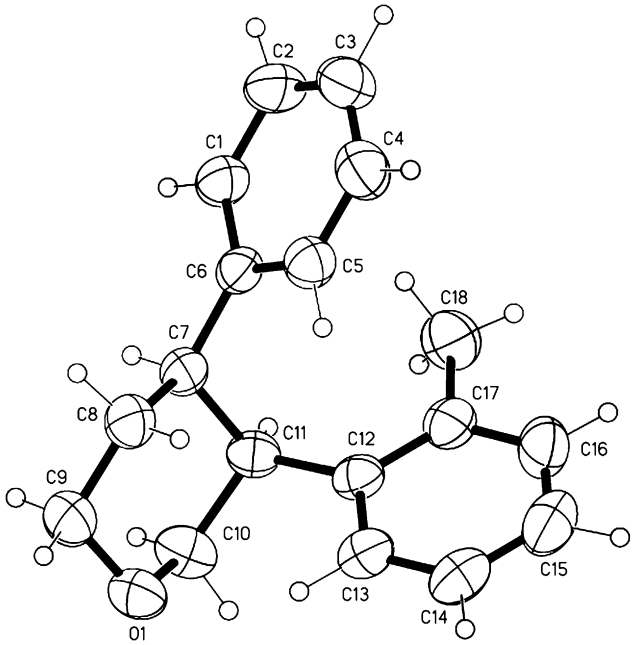


Figure 1. X-ray crystallography of compound **4Cb**.

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