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Synthesis of diarylazepan-4-ones

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Abstract—Synthesis of several 3,3-diarylazepan-4-ones and 5,5-diarylazepan-4-ones has been established starting from two tetrasubstituted olefins, which is derived from commercially available piperidine-3-carboxylic acid ethyl ester and piperidine-4-carboxylic acid ethyl ester. The single isomer with the structural skeleton of 3,3-diarylazepan-4-one and 5,5-diarylazepan-4-one is constructed in two functional group transformations of Grignard addition/dehydration and epoxidation/pinacol rearrangement.

1. Introduction

Recently, we have introduced an easy and straightforward approach for synthesizing 3-arylpyrroline and 3-aryl-2,5-dihydrofuran,[1a,b] unsymmetrical *cis*-3,4-diarylpyrrolidine,[1c] and 4-aryl-3-hydroxyprolinol skeletons[1d] with potential biological activities via the unique reaction using the combination of *m*-chloroperoxybenzoic acid and boron trifluoride etherate.[1]

To demonstrate the synthetic application of our methodology, a facile strategy for preparing various 3,3-diarylazepan-4-ones and 5,5-diarylazepan-4-ones was investigated. Basically, some synthetic methods of the substituted azepan-4-one and its related analogs can be summarized in nickel-promoted cyclization of a nitrogen atom onto a diene moiety,[2] ring enlargement with diazo compound,[3] ring-closing metathesis,[4] and intramolecular cyclization[5] as shown in Figure 1.

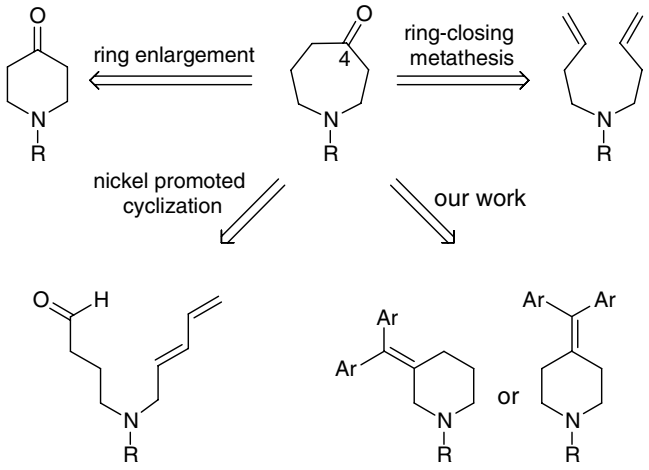

Figure 1. Synthetic studies of substituted azepan-4-ones.

Our interest in synthesizing substituted azepan-4-ones was piqued on the different biological properties and because it is an important intermediate for preparing the substituted azepanes.[6] A series of azepanone-based inhibitors of the osteoclast specific cysteine protease cathepsin have been reported from the literature.[6] Azepanone derivatives (e.g., SB 468430) was shown to be a potent inhibitor of cathepsin L in vitro as well as an inhibitor of bone resorption in cell-based assays.[6d] Other analogs have also been shown to be a potent inhibitor of calcium ion release in the TPTX rat and to inhibit bone turnover in the ovariectomized monkey.[6a,g]

The regiocontrolled ring enlargement of piperidin-4-one framework has been established as a reliable method,[3,6c] difficulties are often encountered in this process due to lack of regiochemistry and harshness of reaction conditions. During the course of our investigation, it became apparent that many of the substituted azepan-4-ones required by us could not be obtained in satisfactory yields following reported methods. Here, an easy and straightforward methodology for synthesizing 3,3-diaryl-azepan-4-ones **1Aa**–**Af** and 5,5-diaryl-4-azepanones

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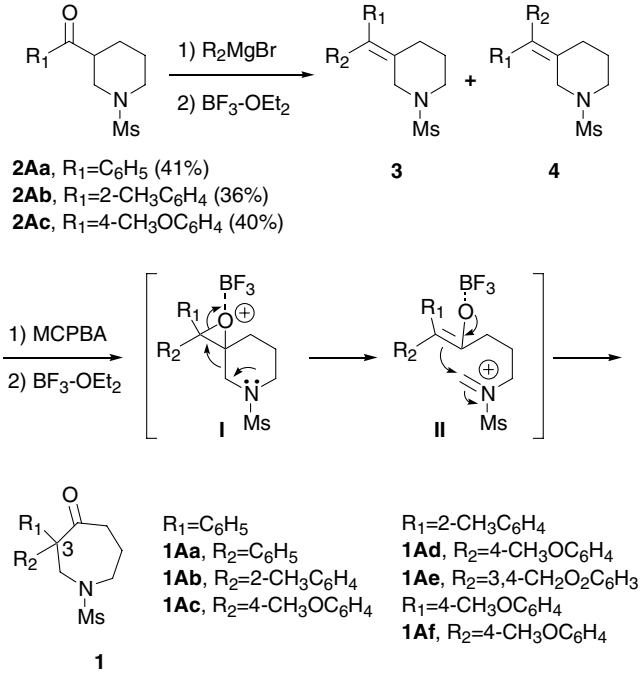
1Ba–**Bg** with all-carbon quaternary center neighboring α-carbonyl group was reported by the treatment of tetrasubstituted olefins with the combination of *m*-chloroperoxybenzoic acid and boron trifluoride etherate in good yields.[7]

2. Results and discussion

2.1. Regioselective synthesis of 3,3-diarylazepan-4-ones 1Aa–Af

Regioselective synthesis of 3,3-diarylazepan-4-ones **1Aa**–**Af** via the ring-expanded reaction is shown in Scheme 1. Three 3-(arylcarbonyl)piperidines **2Aa**–**Ac** were synthesized from commercially available piperidine-3-carboxylic acid ethyl ester in 36–41% overall yields and the simple five-step standard reaction sequence was described as follows: (i) mesylation with triethylamine and methanesulfonyl chloride in dichloromethane at 0 °C for 4 h, (ii) reduction with lithium aluminum hydride in tetrahydrofuran at 0 °C for 5 h, (iii) oxidation with pyridinium chlorochromate and Celite in dichloromethane at rt for 5 h, (iv) Grignard addition with three arylmagnesium bromide reagents (a, $R_1 = C_6H_5$; b, $R_1 = 2\text{-}CH_3C_6H_4$; c, $R_1 = 4\text{-}CH_3OC_6H_4$) in tetrahydrofuran at −78 °C for 5 h, and (v) oxidation with pyridinium chlorochromate and Celite in dichloromethane at rt for 5 h.

Further, ketones **2a**–**c** were converted into tetrasubstituted olefinic mixture **3** and **4** via Grignard addition with four arylmagnesium bromide reagents (a, $R_2 = C_6H_5$; b, $R_2 = 2\text{-}CH_3C_6H_4$; c, $R_2 = 4\text{-}CH_3OC_6H_4$; d, $R_2 = 3,4\text{-}CH_2O_2C_6H_3$) in tetrahydrofuran at −78 °C for 5 h and followed by subsequent boron trifluoride etherate-mediated dehydration in dichloromethane at 0 °C for 15 min.



Scheme 1. Synthesis of 3,3-diarylazepan-4-ones **1Aa**–**1Af**.

Table 1. The yields of 3,3-diaryl-4-azepanones **1Aa**–**Af**[a,b]

Entry	R_1	R_2	**1**, yield (%)
1	C_6H_5	C_6H_5	**1Aa**, 47
2	C_6H_5	$2\text{-}CH_3C_6H_4$	**1Ab**, 43
3	C_6H_5	$4\text{-}CH_3OC_6H_4$	**1Ac**, 40
4	$2\text{-}CH_3C_6H_4$	$4\text{-}CH_3OC_6H_4$	**1Ad**, 36
5	$2\text{-}CH_3C_6H_4$	$3,4\text{-}CH_2O_2C_6H_3$	**1Ae**, 39
6	$4\text{-}CH_3OC_6H_4$	$4\text{-}CH_3OC_6H_4$	**1Af**, 38

[a] The yields of ketones **1Aa**–**Af** were adjusted based on isolated products.
[b] All yields were based on ketones **2Aa**–**Ac** confirmed.

Treatment of olefinic mixture **3** and **4** with the combination of *m*-chloroperoxybenzoic acid and boron trifluoride etherate provided 3,3-diarylazepan-4-ones **1Aa**–**Af** as the single isomer in 36–47% overall yields.[8,9] These experimental results are summarized in Table 1.

During the specific regioselective ring-expanded process, the other possible 4,4-diarylazepan-3-one framework and two six-membered aryl-(4-arylpiperidin-4-yl)methanone analogs were not observed. This combination could provide an easy and straightforward operation protocol with better yields for the introduction of different 4,4-diaryl group of compounds **1Aa**–**Af** in comparison with the reported literature. The structure of ketone **1Aa** with germinal diaryl group was determined by single-crystal X-ray analysis as shown in Diagram 1.[10]

How is the pinacol-type rearrangement of olefins **3** and **4** initiated by the combination of *m*-chloroperoxybenzoic acid and boron trifluoride etherate? Mechanically it is not clear if the reaction follow the same pathway (Scheme 1).[8] The most likely explanation would be that boron trifluoride etherate-mediated regiospecific ring-opening of epoxide is controlled by the involvement of the nitrogen lone pair on piperidin-3-one skeleton. The initial event may be considered to be the formation of intermediate **I**. By the involvement of nitrogen lone pair, intermediate **II** can be generated via a regiospecific ring-expanded rearrangement of intermediate **I**. Therefore,

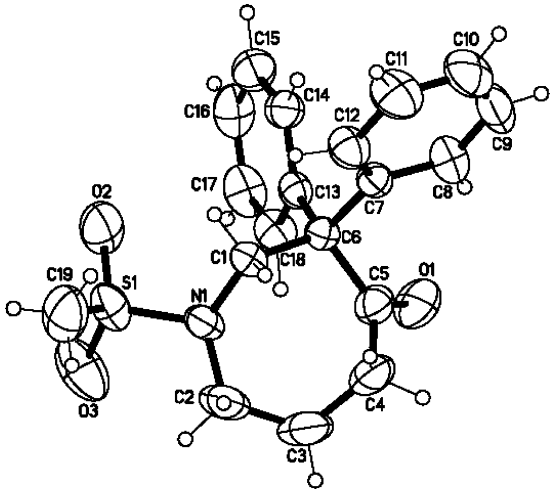


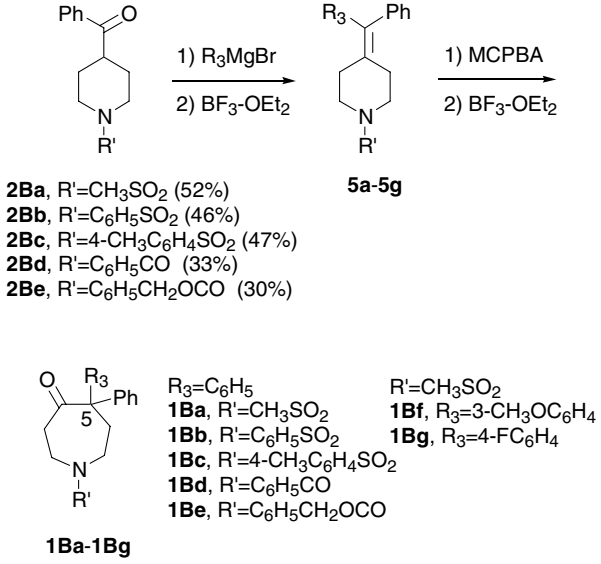
Diagram 1. X-ray crystallography of 3,3-diphenylazepan-4-one **1Aa**.

we believe the amino group can play an important factor to initiate the ring expansion.

When treatment of ketone **2Aa** with methylmagnesium bromide and followed by dehydration with boron trifluoride etherate, 3-(1-phenylvinyl)piperidine was isolated in 82% yield instead of the tetrasubstituted olefins **3** and **4**. Based on the results, the diaryl group is an important substituent for providing a stable benzylic cation in the dehydration process. The reaction of ketone **2Ab** with 2-methylphenylmagnesium bromide was unsuccessful under a variety of conditions (addition of cerium trichloride, prolonged reaction time, elevated temperature, different solvents). We envisioned that the reason was derived from the repulsion of two 2-methylphenyl groups with steric hindrance. In the other hand, dehydration of the formed tertiary alcohol from the Grignard addition of ketone **2Ac** with 3,4-methylenedioxyphenylmagnesium bromide was treated with different Lewis acids (e.g., aluminum trichloride, silver triflate, and boron trifluoride etherate) to produce complex mixture. The reason was not further investigated. Although the related application is decreased, the present work is complementary to existing methodology.

2.2. Synthesis of 5,5-diarylazepan-4-ones 1Ba–Bg

According to the five-step preparation of ketones **2Aa**–**Ac**, 1-substituted 4-benzoylpiperidines **2Ba**–**Be** (a, $R' = CH_3SO_2$; b, $R' = C_6H_5SO_2$; c, $R' = 4\text{-}CH_3C_6H_4SO_2$; d, $R' = C_6H_5CO$; e, $R' = C_6H_5CH_2OCO$) were also synthesized from commercially available piperidine-4-carboxylic acid ethyl ester in 30–52% overall yields. Seven 1-substituted 4,4-diarylmethylenepiperidines **5a**–**g** were yielded via the Grignard addition of ketones **2Ba**–**Be** with three arylmagnesium bromide reagents (a, $R_3 = C_6H_5$; b, $R_3 = 3\text{-}CH_3OC_6H_4$; c, $R_3 = 4\text{-}FC_6H_4$) in tetrahydrofuran at −78 °C and dehydration with boron trifluoride etherate in dichloromethane at 0 °C. As shown in Scheme 2, 5,5-diarylazepan-4-ones **1Ba**–**Bg** were obtained as the single isomer via the ring-expanded rearrangement reaction with the combination of *m*-chloroperoxybenzoic acid and boron trifluoride etherate in 70–83% yields (Table 2).



Scheme 2. Synthesis of 5,5-diaryl-4-azepanones **1Ba**–**Bg**.

Table 2. The yields of compounds **5a**–**g** and **1Ba**–**Bf**[a,b]

Entry	(R′; R_3)	**5**, yield (%)	**1**, yield (%)
1	CH_3SO_2; C_6H_5	**5a**, 90	**1Ba**, 78
2	$C_6H_5SO_2$; C_6H_5	**5b**, 91	**1Bb**, 82
3	4-$CH_3C_6H_4SO_2$; C_6H_5	**5c**, 94	**1Bc**, 83
4	C_6H_5CO; C_6H_5	**5d**, 73	**1Bd**, 75
5	$C_6H_5CH_2OCO$; C_6H_5	**5e**, 70	**1Be**, 70
6	CH_3SO_2; 3-$CH_3OC_6H_5$	**5f**, 92	**1Bf**, 82
7	CH_3SO_2; 4-$FC_6H_4C_6H_5$	**5g**, 92	**1Bg**, 80

[a] The yields of olefins **5a**–**g** and ketones **1Ba**–**Bg** were adjusted based on isolated products.

[b] All yields were based on phenyl-4-(piperidin-4-yl)methanone and olefins **5a**–**g** confirmed.

Based on the results, 5,5-diaryl-4-azepanones **1Bf**–**Bg** with donating group or withdrawing group were provided in a good selectivity during the pinacol rearrangement process. In view of the experimental simplicity, the overall yields of compound **1Ba** (6.5 g, 64%) was also provided in a multigram scale from ketone **2Ba** (8.0 g, 30 mmol).

3. Conclusion

In summary, we developed an easy and straightforward ring-expanded reaction of six-membered tetrasubstituted olefins to synthesize seven-membered 3,3- or 5,5-diarylazepan-4-ones via the useful combination of *m*-chloroperoxybenzoic acid and boron trifluoride etherate in modest overall yields. A new methodology for establishing all-carbon quaternary center neighboring α-carbonyl group was further investigated. It is worthy of note that product **1Aa** and **1Ba** is a cyclic analog of methadone[11] and could be applied in the preparation of cyclic γ-aminocarbonyl skeleton.[12]

Acknowledgment

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10. CCDC 623605 (compound **1Aa**) contains 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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