Note

BF_3-OEt_2/Et_3SiH-mediated Rearrangement of 4-Aryl-5,5-diphenylazapan-4-ols

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Synthesis of 2-(2-arylethyl)-3,3-diphenylpyrrolidines has been established starting from different 4-aryl-5,5-diphenylazepan-4-ols via boron trifluoride etherate/triethylsilane-mediated rearrangement.

Keywords: Rearrangement; Boron trifluoride etherate; Triethylsilane; 2-(2-Arylethyl)-3,3-diphenylpyrrolidine; 3,3-Diphenylazepan-4-one.

INTRODUCTION

Recently, we explored some interesting rearrangement reactions toward different structural frameworks such as the regioselective Baeyer-Villiger reaction, ring-contractions and isomerization reactions via a convenient combination of *m*-chloroperoxybenzoic acid (MCPBA)/boron trifluoride etherate (BF_3-OEt_2) as shown in Fig. 1.[1-2] Continuing our investigation on the rearrangement,[1d] treatment of seven-membered 5,5-diphenylazepan-4-one[3] with Grignard reagent and followed by treatment of the resultant compound with this combination of boron trifluoride etherate (BF_3-OEt_2) and triethylsilane (Et_3SiH) were further investigated. Herein, an easy and straightforward methodology for synthesizing the framework of five-membered 2-(2-arylethyl)-3,3-diphenyl-1-tosyl-pyrrolidine is described from the seven-membered 5,5-diphenylazepan-4-one via the regiospecific ring-contraction with different Grignard reagents and the combination of BF_3-OEt_2 and Et_3SiH in good yields.

RESULTS AND DISCUSSION

For investigating the BF_3-OEt_2/Et_3SiH-mediated rearrangement, 4,4-diphenylmethylenepiperidine **1** was easily synthesized from 4-benzoyl-1-tosylpiperidine via Grignard addition with phenylmagnesium bromide in tetrahydrofuran and followed by dehydration with BF_3-OEt_2 in dichloromethane according to our preliminary experience.[1d] As shown in Scheme I, the sole seven-membered 5,5-diphenylazepan-4-one **2** was obtained in 30 mini-mole scale from the six-membered 4,4-diphenylmethylenepiperidine **1** via pinacol-type ring-expansion rearrangement.

Next, treatment of 5,5-diphenylazepan-4-one **2** with phenylmagnesium bromide and followed by dehydration

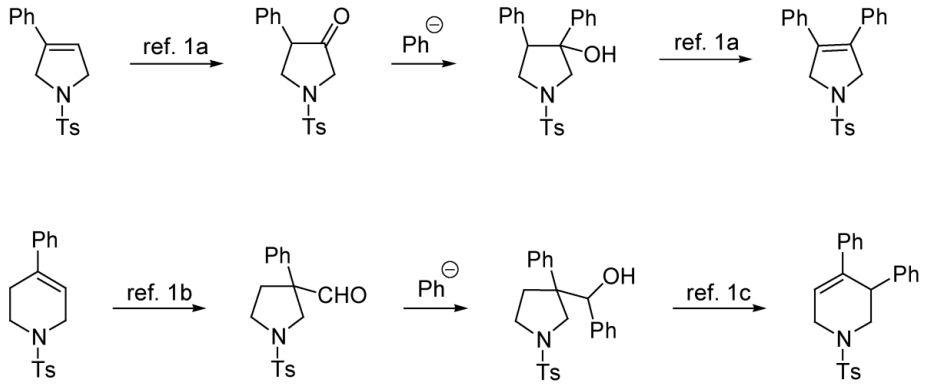
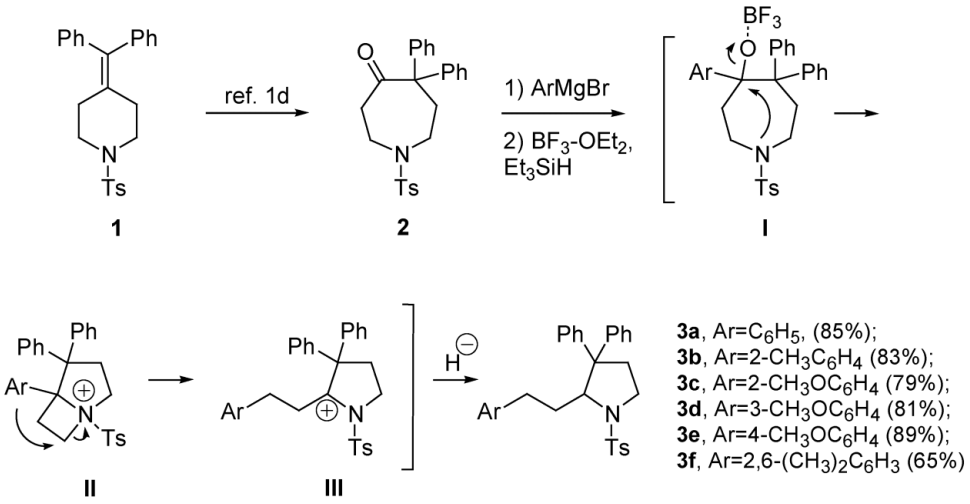


Fig. 1. Some interesting rearrangement reactions toward different structural frameworks.

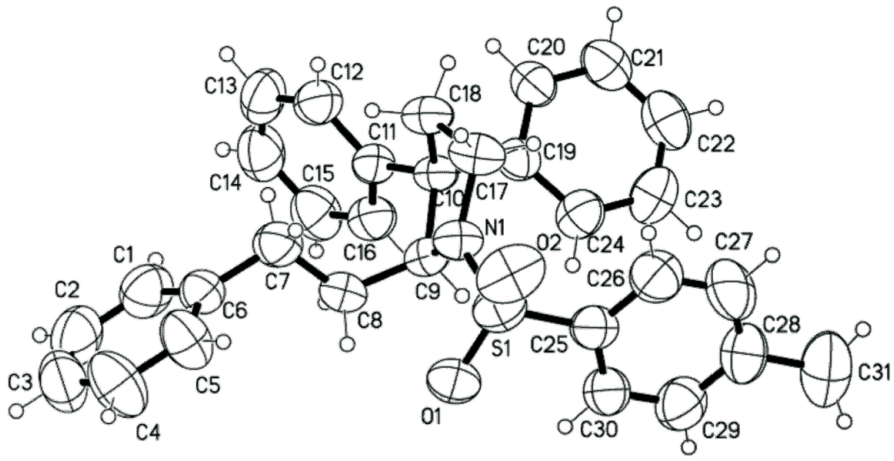
Scheme I Synthesis of 2-(2-arylethyl)-3,3-diphenyl-1-tosyl-pyrrolidines **3a**~**3f**



with BF_3-OEt_2 in Et_3SiH did not afford the predicted product of 4-phenyl-5,5-diphenyl-3-azepane with a seven-membered skeleton. Interestingly, the five-membered skeleton of 2-(2-phenylethyl)-3,3-diphenylpyrrolidine **3a** was generated in 85% yield during the rearrangement procedure. In order to demonstrate the regioselective ring-contraction reaction, compound **2** was further treated with five other arylmagnesium bromide reagents (b, 2-$CH_3C_6H_4$; c, 2-$CH_3OC_6H_4$; d, 3-$CH_3OC_6H_4$; e, 4-$CH_3OC_6H_4$; f, 2,6-$(CH_3)_2C_6H_3$) in tetrahydrofuran at -78 °C for 5 h and followed by BF_3-OEt_2/Et_3SiH-mediated rearrangement at 0 °C for 2 h to afford the sole 2-(2-arylethyl)-3,3-diphenylpyrrolidines **3b**~**3f** in 65~89% overall yields in two-steps. During the specific regioselective ring-contraction process, the other possible frameworks were not observed.

How is the ring-contraction of compound **3** initiated by the BF_3-OEt_2/Et_3SiH system? The explanation would be that BF_3-OEt_2/Et_3SiH-mediated dehydration of tertiary alcohol is controlled by involvement of the nitrogen lone pair on an azepane skeleton (see Scheme I). The initial event may be considered to be the formation of the intermediate **I**. Next, bicyclic intermediate **II** is formed by an intramolecular ring-closure of intermediate **I** and followed by the Ar group 1,3-shift of intermediate **II**. Finally, compounds **3a~3f** were yielded by a hydride reduction of intermediate **III**. The unique structural skeleton of 3,3-diphenylpyrrolidine **3a** with 2-phenylethyl side chain was determined by single-crystal X-ray analysis as shown in diagram 1.[4] It is worth noting that the geminal diphenyl groups at the pyrrolidine ring could be used as useful building blocks in

Diagram 1 X-ray crystallography of compound **3a**



search of various compounds with different applications.[5]

In summary, we developed an easy and straightforward methodology for synthesizing the framework of five-membered 2-(2-arylethyl)-3,3-diphenyl-1-tosyl-pyrrolidine **3** via regiospecific ring-contraction of 3,3-diphenyl-1-tosyl-azepan-4-one **2** with the combination of different Grignard reagents and the combination of BF_3-OEt_2 and Et_3SiH in good yields. Further application of this methodology for the formation of new carbon-carbon bonds is now underway.

EXPERIMENTAL

General

Tetrahydrofuran (THF) was distilled prior to use. All other reagents and solvents were obtained from commercial sources and used without further purification. Reactions were routinely carried out under an atmosphere of dry nitrogen with magnetic stirring. Products in organic solvents were dried with anhydrous magnesium sulfate before concentration *in vacuo*. All reported melting temperatures are uncorrected.

A representative procedure for compounds 3a~3f is as follows

A solution of different arylmagnesium bromide reagents (1.0 M in THF, 1 mL, 1.0 mmol) was added to a stirred solution of compound **2** (210 mg, 0.5 mmol) in THF (20 mL) at -78 °C. The reaction mixture was stirred at -78 °C for 5 h. H_2O (1 mL) was added to the reaction mixture and the mixture was filtered through a short plug of Celite. The filtrate was concentrated under reduced pressure. The residue was extracted with H_2O (10 mL) and EtOAc (3 × 20 mL). The combined organic layers were washed with brine, dried, filtered and evaporated to afford crude product. Without further purification, BF_3-OEt_2 (0.5 mL) was added to a stirred solution of the crude product in Et_3SiH (3 mL) at 0 °C for 2 h. Saturated $NaHCO_{3(aq)}$ solution (5 mL) was added to the reaction mixture and the solvent was concentrated under reduced pressure. The residue was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine, dried, filtered and evaporated to afford crude product. Purification on silica gel (hexane/EtOAc = 4/1 ~ 6/1) afforded compounds **3a~3f** in 65~89% overall yields.

1-Methylphenylsufonyl-3,3-diphenyl-2-(2-phenylethyl)-pyrrolidine (3a)[5]

Mp = 158-159 °C; IR ($CHCl_3$) 3447, 3025, 2917, 1731, 1598, 1495, 1338, 1161, 1094, 752, 700, 669 cm^{-1}; HRMS (ESI, $M^+ + 1$) calcd for $C_{31}H_{32}NO_2S$ 482.2154, found 482.2156; ^1H NMR (500 MHz, $CDCl_3$) δ 7.71 (d, J = 8.5 Hz, 2H), 7.29-7.02 (m, 15H), 6.73 (d, J = 7.0 Hz, 2H), 4.75 (t, J = 5.0 Hz, 1H), 3.55 (t, J = 8.0 Hz, 1H), 3.02-2.97 (m, 1H), 2.87 (dt, J = 8.5, 12.0 Hz, 1H), 2.45 (s, 3H), 2.44-2.38 (m, 2H), 2.20 (dt, J = 5.0, 12.0 Hz, 1H), 1.81-1.68 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.49, 143.35, 143.02, 141.90, 137.33, 129.60 (2x), 128.45 (2x), 128.32 (2x), 128.26 (2x), 128.21 (2x), 128.11 (2x), 127.12 (2x), 126.81 (2x), 126.71, 126.15, 125.60, 64.35, 58.32, 45.23, 36.62, 34.73, 32.75, 21.50; Anal. Calcd for $C_{31}H_{31}NO_2S$: C, 77.30; H, 6.49; N, 2.91. Found: C, 77.59; H, 6.88; N, 3.10. Single-crystal X-ray diagram: crystal of compound **3a** was grown by slow diffusion of ethyl acetate into a solution of compound **3a** in dichloromethane to yield a colorless prism. The compound crystallizes in the monoclinic crystal system. Space group P2(1)2(1)2(1), a = 7.1009(7) Å, b = 8.1070(8) Å, c = 45.591(4) Å, V = 2624.5(4) $Å^3$, Z = 4, d_{calcd} = 1.219 mg/m^3, absorption coefficient 0.151 mm^{-1}, F (000) = 1024, R indices (all data) R_1 = 0.1435, wR_2 = 0.1328, 2θ range (0.89~28.28°).

2-[2-(2-Methylphenyl)ethyl]-1-methylphenylsufonyl-3,3-diphenyl-pyrrolidine (3b)

Viscous oil; IR ($CHCl_3$) 3448, 2920, 1598, 1493, 1339, 1161, 1093, 749, 668 cm^{-1}; HRMS (ESI, $M^+ + 1$) calcd for $C_{32}H_{34}NO_2S$ 496.2310, found 496.2309; ^1H NMR (500 MHz, $CDCl_3$) δ 7.72 (d, J = 8.5 Hz, 2H), 7.28-6.97 (m, 15H), 6.40 (d, J = 7.5 Hz, 1H), 4.80 (t, J = 4.5 Hz, 1H), 3.58 (t, J = 8.0 Hz, 1H), 2.98 (ddd, J = 5.0, 8.0, 11.5 Hz, 1H), 2.87 (dt, J = 7.5, 11.5 Hz, 1H), 2.54-2.41 (m, 2H), 2.46 (s, 3H), 2.26 (dt, J = 5.0, 12.5 Hz, 1H), 1.90 (s, 3H), 1.80-1.66 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.49, 143.51, 143.02, 140.20, 137.30, 135.91, 129.94, 129.61 (2x), 128.96, 128.38 (4x), 128.20 (2x), 127.12 (2x), 126.71 (2x), 126.68, 126.12, 125.77, 125.72, 64.67, 58.33, 45.24, 35.31, 34.77, 30.36, 21.51, 18.74.

2-[2-(2-Methoxyphenyl)ethyl]-1-methylphenylsufonyl-3,3-diphenyl-pyrrolidine (3c)

Viscous oil; IR ($CHCl_3$) 3446, 3024, 2953, 1599, 1493, 1338, 1244, 1161, 1106, 1031, 755, 702 cm^{-1}; HRMS

(ESI, $M^+ + 1$) calcd for $C_{32}H_{34}NO_3S$ 512.2259, found 512.2263; ^1H NMR (500 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.0 Hz, 2H), 7.24 (d, *J* = 8.0 Hz, 2H), 7.19-7.07 (m, 10H), 6.79-6.71 (m, 4H), 4.85 (t, *J* = 4.5 Hz, 1H), 3.64 (s, 3H), 3.50 (t, *J* = 7.5 Hz, 1H), 3.03-2.98 (m, 1H), 2.89-2.83 (m, 1H), 2.56-2.49 (m, 1H), 2.47-2.41 (m, 1H), 2.43 (s, 3H), 2.32-2.26 (m, 1H), 1.78-1.68 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.35, 145.51, 143.60, 142.76, 137.54, 130.31, 129.89 (2x), 129.47 (2x), 128.39 (2x), 128.21 (2x), 128.16 (2x), 127.15 (2x), 126.89, 126.79 (2x), 126.38, 126.08, 120.13, 110.07, 64.79, 58.27, 54.96, 45.06, 34.61, 34.22, 27.50, 21.49.

2-[2-(3-Methoxyphenyl)ethyl]-1-methylphenylsufonyl-3,3-diphenyl-pyrrolidine (3d)

Mp = 138-140 °C; IR ($CHCl_3$) 3446, 2916, 2846, 1600, 1491, 1337, 1155, 752, 700, 592 cm^{-1}; HRMS (ESI, $M^+ + 1$) calcd for $C_{32}H_{34}NO_3S$ 512.2259, found 512.2262; ^1H NMR (500 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.0 Hz, 2H), 7.28-7.02 (m, 13H), 6.65 (dd, *J* = 2.5, 8.0 Hz, 1H), 6.34 (d, *J* = 7.5 Hz, 1H), 6.24 (s, 1H), 4.74 (t, *J* = 4.5 Hz, 1H), 3.72 (s, 3H), 3.55 (t, *J* = 8.0 Hz, 1H), 3.02-2.97 (m, 1H), 2.86 (dt, *J* = 8.0, 12.0 Hz, 1H), 2.45 (s, 3H), 2.43-2.37 (m, 2H), 2.18 (dt, *J* = 5.0, 12.0 Hz, 1H), 1.80-1.67 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.40, 145.48, 143.51, 143.35, 143.05, 137.32, 129.61 (2x), 129.05, 128.48 (2x), 128.25 (2x), 128.21 (2x), 127.10 (2x), 126.81 (2x), 126.70, 126.16, 120.70, 113.77, 111.23, 64.26, 58.33, 55.08, 45.24, 36.50, 34.73, 32.82, 21.49; Anal. Calcd for $C_{32}H_{33}NO_3S$: C, 75.11; H, 6.50; N, 2.74. Found: C, 75.32; H, 6.26; N, 2.86.

2-[2-(4-Methoxyphenyl)ethyl]-1-methylphenylsufonyl-3,3-diphenyl-pyrrolidine (3e)

Mp = 163-165 °C; IR ($CHCl_3$) 3445, 3025, 2926, 1598, 1513, 1447, 1337, 1245, 1161, 1033, 755 cm^{-1}; HRMS (ESI, $M^+ + 1$) calcd for $C_{32}H_{34}NO_3S$ 512.2259, found 512.2259; ^1H NMR (500 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.5 Hz, 2H), 7.28-7.19 (m, 5H), 7.13-7.02 (m, 7H), 6.70 (d, *J* = 8.5 Hz, 2H), 6.65 (d, *J* = 8.5 Hz, 2H), 4.73 (t, *J* = 4.5 Hz, 1H), 3.75 (s, 3H), 3.54 (t, *J* = 8.0 Hz, 1H), 3.02-2.96 (m, 1H), 2.86 (dt, *J* = 8.0, 12.0 Hz, 1H), 2.45 (s, 3H), 2.42-2.34 (m, 2H), 2.15 (dt, *J* = 5.5, 13.0 Hz, 1H), 1.76-1.67 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.58, 145.49, 143.39, 143.00, 137.34, 133.98, 129.59 (2x), 129.22 (2x), 128.45, 128.45 (2x), 128.23 (2x), 128.21 (2x), 127.12 (2x), 126.81, 126.68, 126.14, 113.53 (2x), 64.30, 58.32, 55.20, 45.22, 36.83, 34.71, 31.80, 21.51.

2-[2-(2,6-Dimethylphenyl)ethyl]-1-methylphenylsufonyl-3,3-diphenyl-pyrrolidine (3f)

Mp = 181-182 °C; HRMS (ESI, $M^+ + 1$) calcd for $C_{33}H_{36}NO_2S$ 510.2467, found 510.2465; ^1H NMR (500 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.0 Hz, 2H), 7.27-7.24 (m, 4H), 7.20-7.14 (m, 3H), 7.05-6.98 (m, 5H), 6.93-6.86 (m, 3H), 4.89 (t, *J* = 5.0 Hz, 1H), 3.63-3.58 (m, 1H), 2.95-2.86 (m, 2H), 2.64 (dt, *J* = 4.5, 13.0 Hz, 1H), 2.57-2.50 (m, 1H), 2.48-2.40 (m, 1H), 2.44 (s, 3H), 1.97 (s, 6H), 1.84-1.75 (m, 1H), 1.67-1.59 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.13, 143.70, 142.97, 138.82, 136.73, 136.24 (2x), 129.51 (2x), 128.56 (2x), 128.21 (2x), 128.18 (2x), 127.83 (2x), 127.23 (2x), 126.62, 126.40 (2x), 126.02, 125.48, 65.46, 58.29, 45.05, 34.44, 33.89, 27.03, 21.48, 19.38 (2x); Anal. Calcd for $C_{33}H_{35}NO_2S$: C, 77.76; H, 6.92; N, 2.75. Found: C, 77.96; H, 7.12; N, 3.03.

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4. CCDC 645143 (compound **5a**) 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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