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New synthesis of SKF 89976A

Meng-Yang Chang,[a,*] Si-Yun Wang[a] and Chun-Li Pai[b]

[a]Department of Applied Chemistry, National University of Kaohsiung, Kaohsiung 811, Taiwan
[b]Department of Chemistry, National Sun Yat-Sen University, Kaohsiung 804, Taiwan

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Abstract—Substituted 4,4-diaryl-3-butenyl-1-amines are synthesized in nearly 34–47% overall yields starting from 3-hydroxypiperidine by the regioselective Baeyer–Villiger lactonization, Grignard addition and elimination sequence. This facile strategy was also used to synthesize racemic SKF 89976A.

1. Introduction

These substituted and functionalized 4,4-diaryl-3-butenyl-1-amines and their analogs are often used as key intermediates for the synthesis of GABA-uptake inhibitors with potential biological activities of different classes.[1] The compounds with different N-substituted diarylbutenyl group display anti-convulsant activities such as compound SKF 89976A, SKF 100300A, SKF 100561 and tiagabine.[1,2] Development of a general procedure for 4,4-diaryl-3-butenyl-1-amine provides an expedient entry point.[2]

Basically, the adopted strategies can be summarized in Lewis acid-catalyzed,[3,4] for example, tin(II) triflate, ytterbium(III) triflate, boron trifluoride etherate, hydrogen bromide and palladium(II)-promoted[5] cyclopropane rearrangement and organolithium addition of *N*-(2-chloroethyl)benzamide with 1,1-diarylmethanone[6] (Fig. 1).

Herein, we want to develop an easy and straightforward strategy to substituted 4,4-diaryl-3-butenyl-1-tosylamines **1a**–**f** via key regioselective Baeyer–Villiger lactonization of 1-tosylpiperidin-3-one with *m*-chloroperoxybenzoic acid.

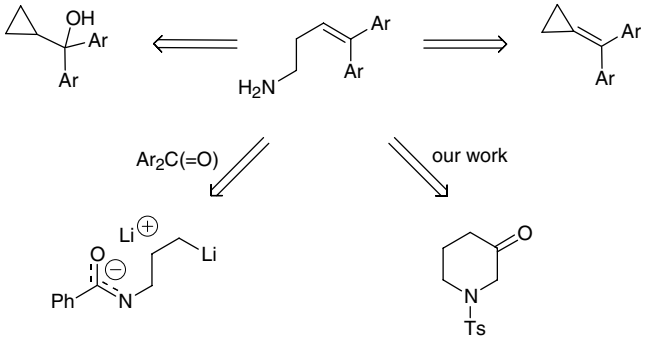

Figure 1.

2. Results and discussion

For synthesizing compounds **1a**–**f**, 3-hydroxypiperidine (**2**) was chosen as the starting material as shown in Scheme 1.[7] Compounds **1a**–**f** were prepared by the five-step protocol and described as follows: (i) *N*-tosylation of compound **2** with *p*-toluenesulfonyl chloride and triethylamine at 0 °C for 1 h, (ii) oxidation of the resulting 1-tosylpiperidin-3-ol with Jones reagent at 0 °C for 15 min, (iii) specific regioselective Baeyer–Villiger lactonization[8] of 1-tosylpiperidin-3-one (**3**) at rt for 10 h, (iv) Grignard addition of 3-tosyl[1,3]oxazepan-7-one (**4**) with different arylmagnesium bromide reagents (a, Ar = C_6H_5; b, Ar = 2-$CH_3C_6H_4$; c, Ar = 2-$CH_3OC_6H_4$; d, Ar = 3-$CH_3OC_6H_4$; e, Ar = 4-$CH_3OC_6H_4$; f, Ar = 3,4-$CH_2O_2C_6H_3$) at −78 °C for 2 h, (v) dehydration of the resulting tertiary alcohols with boron trifluoride etherate at 0 °C for 15 min.[9]

Keywords: 3-Hydroxypiperidine; Baeyer–Villiger lactonization; 3-Tosyl-[1,3]oxazepan-7-one; 4,4-Diaryl-3-butenyl-1-amines.
* Corresponding author. Tel.: +886 7 5919464; fax: +886 7 5919348; e-mail: mychang@nuk.edu.tw

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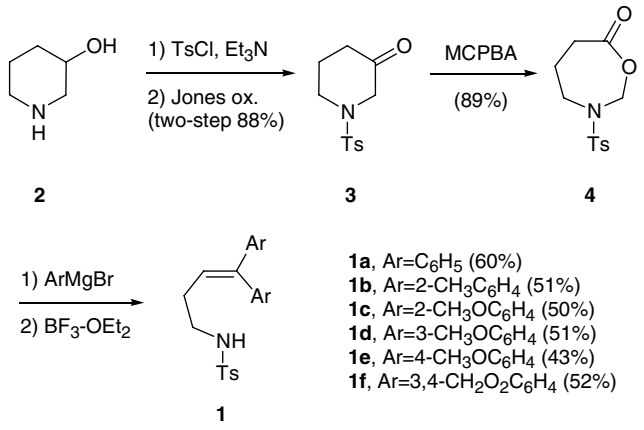


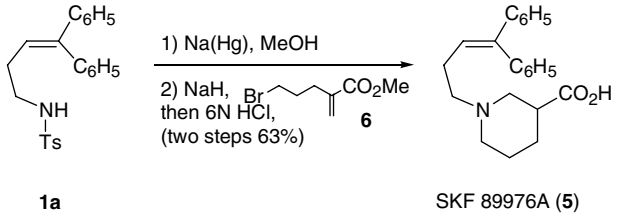
Scheme 1.

While poring over the related literature of regioselective Baeyer–Villiger ring expansion reaction, we found that Young and co-workers had developed copper(II) acetate-mediated ring expansion of 4-ketoprolines with *m*-chloroperoxybenzoic acid in modest yield.[10] The unique synthetic methodology was similar to our results. How is the regioselective Beayer–Villiger lactonization initiated? According to literature reports, the most likely explanation would be that it is controlled by involvement of the nitrogen lone pair on substituted pyrrolidin-4-one.[10]

We also found that reaction of 1-tosylpiperidin-4-one with *m*-chloroperoxybenzoic acid under the similar conditions was unsuccessful. The starting material was recycled and the ring-expanded product was not obtained. In comparison with the regioselectivity of Beayer–Villiger process of 1-tosylpiperidin-4-one, we believe the amino group can play an important factor to initiate the ring expansion. During the process, the 4-tosyl[1,4]oxazepan-2-one framework was not observed.

For the two-step transformation of Grignard addition and dehydration, substituted compounds **1a**–**f** were obtained in 43–60% yield from compound **4**. For the introduction of different 4,4-diaryl group of compounds **1a**–**f**, the present strategy exhibited a facile methodology in comparison with the reported literature.[3] The total synthetic procedure could be monitored by TLC until the reaction was complete within a working day. During separation of compound **1e**, 2,2-bis(4-methoxyphenyl)-1-tosylpyrrolidine (ca. 10%) was the yield.[11] Silica gel-mediated intramolecular cyclization of compound **1e** by the 4-methoxy group was provided. The compounds with other electron donating groups did not show the similar phenomena. For the 4,4-dialkyl group, some complex and inseparated products having different cis and trans three substituted olefinic isomers were afforded in the synthesis of 4,4-diethylbutenyl-1-amine.

In view of the experimental simplicity, the preparation of compound **1a** was also conducted in a multigram scale (10 mmol) with 55% overall yield of two steps. With these results in hand, the next focus was to examine the synthesis of racemic SKF 89976A (**5**). Desulfonation of the compound **1a** with sodium amalgam yielded



Scheme 2.

the primary amine. SKF 89976A (**5**) was afforded by the alkylation of the resulting amine with compound **6**[12] and subsequently followed by hydrolysis (Scheme 2).

3. Conclusion

In summary, we present an easy and straightforward synthesis of compounds **1a**–**f** by the regioselective Baeyer–Villiger lactonization, Grignard addition and elimination sequence. This facile strategy was also used to synthesize SKF 89976A (**5**).

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.06.156.

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8. Synthesis of compound **4** is as follows: A solution of *m*-chloroperoxybenzoic acid (11.5 g, 75%, 50.0 mmol) in dichloromethane (10 mL) was added to a solution of compound **3** (10.12 g, 40.0 mmol) and sodium carbonate (6.36 g, 60.0 mmol) in dichloromethane (200 mL) at 0 °C. The reaction mixture was stirred at rt for 6 h. Saturated sodium carbonate solution (40 mL) was added to the reaction mixture and the solvent was concentrated under reduced pressure. The residue was extracted with ethyl acetate (3 × 100 mL). The combined organic layers were washed with brine, dried, filtered and evaporated to afford crude product under reduced pressure. Purification on silica gel (hexane/ethyl acetate = 4/1–2/1) afforded compound **4** (9.58 g, 89%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (d, $J = 8.1$ Hz, 2H), 7.31 (d, $J = 8.1$ Hz, 2H), 5.45 (s, 2H), 3.63 (t, $J = 5.4$ Hz, 2H), 2.66–2.62 (m, 2H), 2.42 (s, 3H), 1.44–1.36 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.29, 144.69, 137.14, 130.28 (2×), 127.76 (2×), 76.04, 49.51, 33.86, 22.28, 21.84; HRMS (ESI) *m*/*z* calcd for $C_{12}H_{16}NO_4S$ (M^++1) 270.0800, found 270.0802.
9. A representative procedure of compounds **1a**–**f** is as follows: A solution of arylmagnesium bromide (3.0 mL, 1.0 M in tetrahydrofuran, 3.0 mmol) was added to a stirred solution of compound **4** (270 mg, 1.0 mmol) in tetrahydrofuran (10 mL) at −78 °C. The reaction mixture was stirred at rt for 6 h. Water (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 ethyl acetate (3 × 30 mL). The combined organic layers were washed with brine, dried, filtered and evaporated to afford crude product under reduced pressure. Without further purification, a solution of boron trifluoride etherate (1 mL) was added to a stirred solution of the crude product in dichloromethane (20 mL) at 0 °C. The reaction mixture was stirred at rt for 15 min. Saturated sodium bicarbonate solution (10 mL) was added to the reaction mixture and the solvent was concentrated under reduced pressure. The residue was extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with brine, dried, filtered and evaporated to afford crude product under reduced pressure. Purification on silica gel (hexane/ethyl acetate = 4/1–2/1) afforded compounds **1a**–**f**. For compound **1a**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (d, $J = 8.5$ Hz, 2H), 7.38–7.23 (m, 8H), 7.16–7.10 (m, 4H), 5.91 (t, $J = 7.5$ Hz, 1H), 4.36 (t, $J = 6.0$ Hz, 1H), 3.05 (q, $J = 7.0$ Hz, 2H), 2.42 (s, 3H), 2.28 (q, $J = 7.0$ Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.81, 143.35, 141.88, 139.38, 136.84, 129.68 (2×), 129.64 (2×), 128.36 (2×), 128.12 (2×), 127.33, 127.26, 127.19 (2×), 127.06 (2×), 124.41, 43.02, 29.81, 21.52; HRMS (ESI) *m*/*z* calcd for $C_{23}H_{24}NO_2S$ (M^++1) 378.1528, found 378.1529. For compound **1b**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, $J = 8.5$ Hz, 2H), 7.27–7.03 (m, 10H), 5.63 (t, $J = 7.5$ Hz, 1H), 4.30 (t, $J = 6.0$ Hz, 1H), 3.03 (q, $J = 7.0$ Hz, 2H), 2.42 (s, 3H), 2.22 (s, 3H), 2.19 (q, $J = 7.0$ Hz, 2H), 2.07 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.93, 143.35, 141.76, 139.23, 136.81, 136.10, 135.30, 130.81, 130.43, 130.28, 129.74, 129.66 (2×), 128.48, 127.26, 127.02 (2×), 126.93, 125.52, 125.46, 42.85, 29.71, 21.50, 20.99, 19.96; HRMS (ESI) *m*/*z* calcd for $C_{25}H_{28}NO_2S$ (M^++1) 406.1841, found 406.1844. For compound **1c**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (d, $J = 8.0$ Hz, 2H), 7.30–7.20 (m, 2H), 7.12 (d, $J = 8.0$ Hz, 2H), 7.05 (td, $J = 2.0$, 8.0 Hz, 2H), 6.96–6.91 (m, 2H), 6.86 (d, $J = 7.5$ Hz, 2H), 5.57 (t, $J = 7.5$ Hz, 1H), 5.33 (t, $J = 5.0$ Hz, 1H), 3.88 (s, 3H), 3.71 (s, 3H), 3.00 (q, $J = 5.5$ Hz, 2H), 2.36 (s, 3H), 2.12 (q, $J = 7.0$ Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.82, 155.94, 142.84, 138.20, 136.70, 131.85, 130.85, 130.26, 129.37 (2×), 129.32, 129.10, 128.37, 128.13, 127.11 (2×), 120.58, 120.29, 111.35, 110.96, 55.69, 55.54, 41.96, 29.07, 21.40; HRMS (ESI) *m*/*z* calcd for $C_{25}H_{28}NO_4S$ (M^++1) 438.1739, found 438.1738. For compound **1d**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (d, $J = 8.0$ Hz, 2H), 7.28–7.24 (m, 3H), 7.17 (t, $J = 8.0$ Hz, 1H), 6.86 (ddd, $J = 1.0$, 2.5, 8.0 Hz, 1H), 6.79–6.76 (m, 2H), 6.73 (dd, $J = 2.0$, 2.0 Hz, 1H), 6.69 (d, $J = 8.0$ Hz, 1H), 6.65 (dd, $J = 1.0$, 2.0 Hz, 1H), 5.92 (t, $J = 7.5$ Hz, 1H), 4.57 (t, $J = 6.0$ Hz, 1H), 3.78 (s, 3H), 3.76 (s, 3H), 3.04 (q, $J = 7.0$ Hz, 2H), 2.41 (s, 3H), 2.26 (q, $J = 7.0$ Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.54, 159.41, 144.38, 143.35, 143.13, 140.68, 136.84, 129.69 (2×), 129.38, 129.05, 127.04 (2×), 124.71, 122.03, 119.73, 115.00, 113.13, 112.90, 112.47, 55.21, 55.20, 42.99, 29.83, 21.49; HRMS (ESI) *m*/*z* calcd for $C_{25}H_{28}NO_4S$ (M^++1) 438.1739, found 438.1740. For compound **1e**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (d, $J = 8.0$ Hz, 2H), 7.26 (d, $J = 8.0$ Hz, 2H), 7.08 (d, $J = 9.0$ Hz, 2H), 7.02 (d, $J = 8.5$ Hz, 2H), 6.89 (d, $J = 8.5$ Hz, 2H), 6.79 (d, $J = 9.0$ Hz, 2H), 5.75 (t, $J = 7.5$ Hz, 1H), 4.34 (t, $J = 6.0$ Hz, 1H), 3.84 (s, 3H), 3.79 (s, 3H), 3.04 (q, $J = 7.0$ Hz, 2H), 2.42 (s, 3H), 2.27 (q, $J = 7.0$ Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.99, 158.71, 143.92, 143.32, 136.56, 134.98, 131.84, 130.82 (2×), 129.66 (2×), 128.39 (2×), 127.06 (2×), 122.36, 113.68 (2×), 113.44 (2×), 55.27, 55.23, 43.15, 29.75, 21.51; HRMS (ESI) *m*/*z* calcd for $C_{25}H_{28}NO_4S$ (M^++1) 438.1739, found 438.1740. For 2,2-Bis(4-methoxyphenyl)-1-(4-methylsulfonylphenyl)pyrrolidine: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25–7.22 (m, 4H), 7.00 (d, $J = 8.5$ Hz, 2H), 6.93 (d, $J = 8.5$ Hz, 2H), 6.78–6.75 (m, 4H), 3.83 (s, 6H),3.81 (t, $J = 7.0$ Hz, 2H), 2.52 (t, $J = 7.0$ Hz, 2H), 2.35 (s, 3H), 1.84–1.79 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.48 (2×), 141.89, 138.47, 134.87 (2×), 130.48 (4×), 128.64 (2×), 128.54 (2×), 112.62 (4×), 75.12, 55.28 (2×), 50.40, 45.51, 22.35, 21.40; HRMS (ESI) *m*/*z* calcd for $C_{25}H_{28}NO_4S$ (M^++1) 438.1739, found 438.1742. For compound **1f**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (d, $J = 8.5$ Hz, 2H), 7.28 (d, $J = 8.5$ Hz, 2H), 6.79 (d, $J = 8.0$ Hz, 1H), 6.69 (d, $J = 8.0$ Hz, 1H), 6.65 (d, $J = 1.5$ Hz, 1H), 6.61 (dd, $J = 1.5$, 8.0 Hz, 1H), 6.55 (d, $J = 8.0$ Hz, 1H), 6.54 (s, 1H), 5.98 (s, 2H), 5.93 (s, 2H),

5.72 (t, $J = 7.5$ Hz, 1H), 4.41 (t, $J = 6.0$ Hz, 1H), 3.02 (q, $J = 6.5$ Hz, 2H), 2.42 (s, 3H), 2.26 (q, $J = 7.0$ Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.57, 147.52, 146.96, 146.74, 143.88, 143.39, 136.84, 136.47, 133.17, 129.68 (2×), 127.05 (2×), 123.23, 123.03, 121.11, 110.05, 108.17, 107.81, 107.55, 101.04 (2×), 43.05, 29.82, 21.49; HRMS (ESI) *m*/*z* calcd for $C_{25}H_{24}NO_6S$ (M^++1) 466.1324, found 466.1326.

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