HETEROCYCLES, Vol. 68, No. 6, 2006, pp. 1173 - 1183. © The Japan Institute of Heterocyclic Chemistry
Received, 2nd March, 2006, Accepted, 10th April, 2006, Published online, 11th April, 2006. COM-06-10717

CONCISE SYNTHESIS OF 3-ARYLPIPERIDINES

Meng-Yang Chang,*[a] Ru-Ting Hsu,[b] Hua-Ping Chen[a] and Pei-Jung Lin[a]

[a]Department of Applied Chemistry, National University of Kaohsiung, Kaohsiung 811, Taiwan. [b]Department of Nursing, Shu-Zen College of Medicine and Management, Kaohsiung 821, Taiwan. Email: mychang@nuk.edu.tw

Abstract – We present an easy and straightforward synthesis of 3-arylpiperidines by Grignard addition of piperidin-3-one with different arylmagnesium bromide reagents and acidic dehydroxylation of the resulting tertiary alcohol with the combination of triethylsilane and boron trifluoride etherate. This facile strategy was further used to synthesize preclamol. A highly regioselective dehydration of 3-arylpiperidin-3-ol with boron trifluoride etherate was investigated for preparing 3-aryl-1,4,5,6-tetrahydropyridine skeleton. A novel selenium dioxide mediated dihydroperoxidation of 3-aryl-1,4,5,6-tetrahydropyridine was also examined.

1. INTRODUCTION

3-Arylpiperidines have been investigated since the early 1980s in view of their therapeutic dopaminergic activities.[1-2] The most active of these compounds is 3-(3-hydroxyphenyl)-*N*-propylpiperidine (3-PPP, preclamol),[3-4] reported to be the first selective D_2-like dopamine autoreceptor agonist.[4] The *N*-propyl substituent has been suggested to be the most effective substitutions among several 3-arylpiperidines with different substituents on the aromatic ring.[5] These potent dopaminergic substances could be effective antipsychotic agents with therapeutic effect in the treatment of schizophrenia and Parkinson's disease. Due to its biological and pharmacological importance, there have been several reports on the synthesis of preclamol and the related analogs.[3]

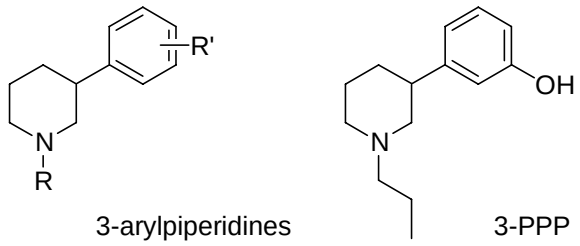
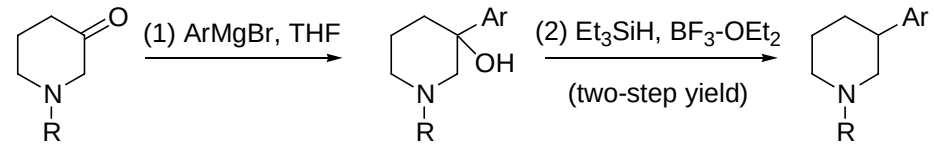


Figure 1. Structures of 3-arylpiperidines and 3-PPP

2. RESULTS AND DISCUSSION

2.1. Synthesis of 3-arylpiperidines

Very recently we reported the preparation of 4-aryl-1,2,5,6-tetrahydropyridines from 4-hydroxypiperidine and explored the related applications in the synthesis of racemic coerulescine, horsfiline, baclofen and fluoxetine.[6] To demonstrate the synthetic utility of the methodology and continue our investigation on the application of this approach, we describe an easy and straightforward synthesis of 3-arylpiperidines (**1**) from piperidin-3-ones *via* two simple steps as illustrated in Scheme 1.



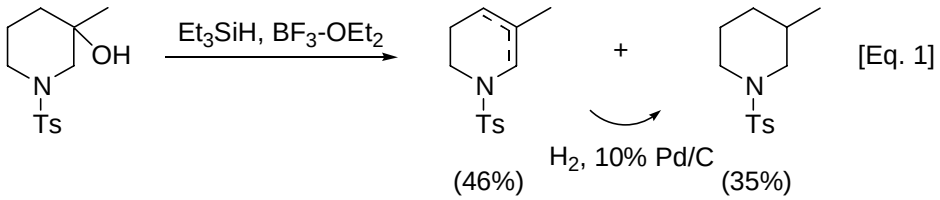
	R=Ms	R=Ts	
2A, R=Ms	**3Aa**, C_6H_5	**3Ba**, C_6H_5	**1Aa**, (90%); **1Ba**, (86%)
2B, R=Ts	**3Ab**, 3-$MeOC_6H_4$	**3Bb**, 3-$MeOC_6H_4$	**1Ab**, (88%); **1Bb**, (86%)
	3Ac, 4-$MeOC_6H_4$	**3Bc**, 4-$MeOC_6H_4$	**1Ac**, (85%); **1Bc**, (84%)
	3Ad, 3,4-$CH_2O_2C_6H_3$	**3Bd**, 3,4-$CH_2O_2C_6H_3$	**1Ad**, (82%); **1Bd**, (83%)

Scheme 1. Synthesis of 3-arylpiperidines (**1Aa**~**1Ad** and **1Ba**~**1Bd**)

For the preparation of different 3-arylpiperidines (**1**), the starting materials piperidin-3-ones (**2A** and **2B**) were respectively obtained by mesylation or tosylation of commercially available 3-hydroxypiperidine with mesyl chloride or tosyl chloride and triethylamine in dichloromethane and followed by Jones oxidation of the resulting sulfonyl alcohol in acetone. Next, there are two remarkable transformations were further examined. One is the rapid access to produce a wide variety of 3-arylpiperidin-3-ols (**3**) by Grignard addition of piperidin-3-ones (**2A**, R=Ms; **2B**, R=Ts) with different arylmagnesium bromide reagents (**a**, Ar=C_6H_5; **b**, Ar=3-$MeOC_6H_4$; **c**, Ar=4-$MeOC_6H_4$; **d**, Ar=3,4-$CH_2O_2C_6H_3$) in tetrahydrofuran at -78 ^oC. The other is the acidic dehydroxylation of 3-arylpiperidin-3-ols (**3**) with triethylsilane and boron trifluoride etherate at room temperature. The two-step synthesis of 3-arylpiperidines (**1**) was provided in 82~90% yields. Two synthetic procedures were monitored by TLC until the reaction was completed. The overall simple procedure was achieved within one working day.

2.2. Synthesis of 3-aryl-1,4,5,6-tetrahydropyridines

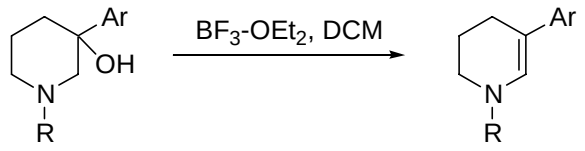
We had also tried to study the synthesis of 3-alkylpiperidine by the acidic dehydroxylation. The model substrate 3-methyl-1-tosylpiperidin-3-ol was treated with the combination of triethylsilane and boron trifluoride etherate, but the desired 3-methyl-1-tosylpiperidine was provided in only 35% yield. The unexpected major product was an inseparated olefinic mixture. By ^1H NMR spectral analysis, the 3-methyl-1,4,5,6-tetrahydropyridine was produced as the major product accompanied with a trace amount of 3-methyl-1,2,5,6-tetrahydropyridine in ca. 8:1 ratio (Eq. 1).



Equation 1. Reaction of 3-methyl-1-tosylpiperidin-3-ol with boron trifluoride etherate

With this result in hand, direct hydrogenation of the resulting olefinic mixture with hydrogen and a catalytic amount of 10% palladium on activated carbon was achieved to 3-methylpiperidine in nearly quantitative yield. Therefore the synthesis of 3-alkylpiperidine was accomplished from piperidin-3-one (**2**) *via* the Grignard addition, dehydration (and dehydroxylation), and hydrogenation. In comparison with the 3-substituted piperidin-3-ol between alkyl and aryl group, we believe the 3-aryl functional group is an important factor and provides a stable benzylic radical in the acidic dehydroxylation process. While poring over the related literature of the dehydration conditions,[7] we found that 3-substituted 1,2,5,6-tetrahydropyridine was usually provided as the major or sole product by various acidic reagents, such as *p*-toluenesulfonic acid, *p*-toluenesulfonic acid on silica gel, acetic acid/acetyl chloride, oxalic acid, trifluoroacetic acid, and thionyl chloride.[7] Among these acid-mediated dehydration reports, we only found that Sui's unique synthetic strategy was similar to our results.[8]

These interesting reports triggered our attention to further examine the dehydration of 3-aryl group of piperidin-3-ol skeleton (**3**). As shown in Scheme 2, 3-aryl-1,4,5,6-tetrahydropyridines (**4**) were yielded as the sole products by treatment of 3-arylpiperidin-3-ols with boron trifluoride etherate in dichloromethane at room temperature. The related mechanism and differences between 3-aryl and 3-alkyl group were not clear.[8] Here we developed a novel dehydration condition with the high regioselectivity by an appropriate Lewis acid for synthesizing 1,4,5,6-tetrahydropyridine skeleton. To our best knowledge, the Lewis acid-catalyzed regioselective dehydration reaction of 3-arylpiperidin-3-ol with high yield had not been reported in the literature. The formed structural framework (**4**) was useful building block for the preparation of natural products and pharmaceutical compounds with potential biological activities.[8,9] The present synthetic work is complementary to existing methodology.

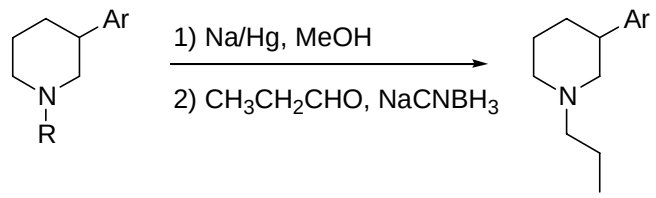


3Aa, R=Ms, Ar=C_6H_5 — **4Aa**, (91%)
3Ad, R=Ms, Ar=3,4-$CH_2O_2C_6H_3$ — **4Ad**, (82%)
3Ba, R=Ts, Ar=C_6H_5 — **4Ba**, (89%)
3Bc, R=Ts, Ar=4-$MeOC_6H_4$ — **4Bc**, (88%)

Scheme 2. Synthesis of 3-aryl-1,4,5,6-tetrahydropyridines (**4Aa**, **4Ad**, **4Ba**, and **4Bc**)

2.3. Synthesis of 3-aryl-1-propylpiperidines

Because of the importance of *N*-propyl substituent on the 3-arylpiperidine skeleton, we turn our attention to change the 1-substituent as the propyl group.[5] Unfortunately, the desired 1-propylpiperidin-3-one was afforded in very low yield by treatment of 1-propylpiperidin-3-ol with different oxidants. In order to achieve the synthesis of 3-aryl-1-propylpiperidines (**5**), we used *N*-sulfonyl group in place of *N*-propyl group as shown in Scheme 3. With the enough amounts of 3-arylpiperidines (**1**), the conversion was achieved though the desulfonation with sodium amalgam in methanol and followed by in situ propylation of the resultant desulfonated 3-arylpiperidine with propionaldehyde and sodium cyanoborohydride. The 3-(3-methoxyphenyl)-1-propylpiperidine (**5b**) was a key intermediate in the preparation of preclamol. Compound (**5b**) was treated with 48% hydrogen bromide to yield the preclamol.[3k] A new and facile strategy for the synthesis of preclamol from 3-hydroxypiperidine was provided.



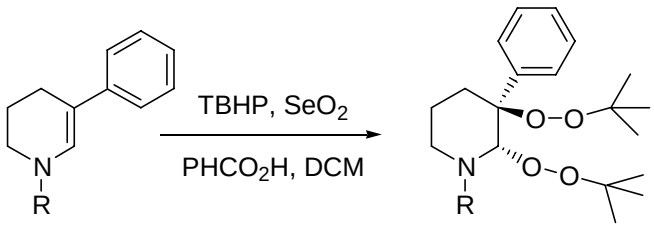
1Aa~**1Ac** and **1Ba**~**1Bc**

5a, Ar=C_6H_5 (66%);
5b, Ar=3-$MeOC_6H_4$ (62%);
5c, Ar=4-$MeOC_6H_4$ (58%)

Scheme 3. Synthesis of 3-aryl-1-*n*-propylpiperidines (**5a**, **5b** and **5c**)

2.4. Synthesis of 2,3-bis-*tert*-butylperoxy-3-phenylpiperidine

In order to investigate the other applications of the 3-aryl-1,4,5,6-tetrahydropyridine skeleton (**4**), allylic oxidation was next chosen to examine. When treatment of 3-phenyl-1,4,5,6-tetrahydropyridines[10] (**4Aa**, R=Ms; **4Ba**, R=Ts) with selenium dioxide and *tert*-butyl hydroperoxide (TBHP) in dichloromethane, the unexpected 2,3-bis-*tert*-butylperoxy-3-phenylpiperidines (**6A** and **6B**) were generated as the major products in only 16% and 24% yield (Scheme 4). We reported the novel selenium dioxide mediated dihydroperoxidation reaction of 3-phenyl-1,4,5,6-tetrahydropyridines (**4Aa** and **4Ba**). The structure of compound (**6B**) was determined by single-crystal X-Ray analysis as shown in diagram 1.



4Aa, R=Ms
4Ba, R=Ts

6A, (16%)
6B, (24%)

Scheme 4. Synthesis of 2,3-bis-*tert*-butylperoxy-3-phenylpiperidines (**6A** and **6B**)

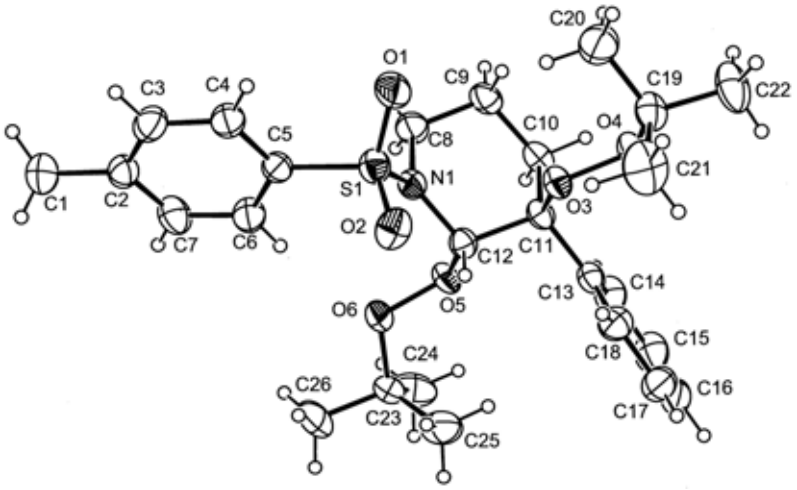
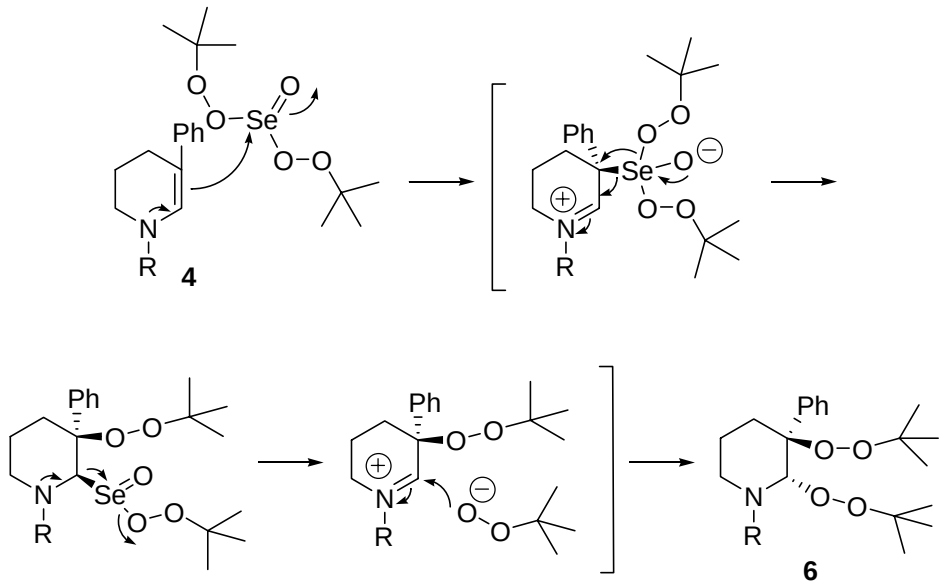


Diagram 1. X-Ray crystallography of compound (**6B**)

According to the X-Ray structural analysis, two *t*ert-butyl hydroperoxy groups were arranged as the *trans* configuration. We had also tried to study the other compounds (**4Ad** and **4Bd**) with the electron-donating group, but the predicted products were provided in trace yields (<5%) under the above reaction conditions. To improve the poor reaction condition, the model substrate 3-phenyl-1,4,5,6-tetrahydropyridine (**4Aa**) was treated with other commercial available reagents (e.g. *m*-chloroperoxybenzoic acid and dibenzoyl peroxide). The unsuccessful reaction was still obtained under the similar conditions. Although the synthetic application is decreased, the present work is novel and interesting methodology. How is the dihydroperoxidation reaction of compounds (**4Aa** and **4Ba**) initiated by selenium dioxide in dichloromethane? However, the initial event may be considered to be the formation of the intermediate (**I**) from selenium dioxide and excess *tert*-butyl hydroperoxide.[11] Mechanically it is not clear if the reaction follows the same pathway as shown in Scheme 5.



Scheme 5. The possible mechanism of dihydroperoxidation reaction by selenium dioxide

3. CONCLUSION

In summary, we developed a facile and straightforward methodology to synthesize two building blocks 3-arylpiperidines and 3-aryl-1,4,5,6-tetrahydropyridines. For the application and investigation of piperidin-3-one, a new synthetic study toward preclamol was also reported. We are currently studying the related application of the dihydroperoxidation reaction by selenium dioxide.

4. EXPERIMENTAL

4.1. General. Tetrahydrofuran (THF) was distilled prior to use from a deep-blue solution of sodium-benzophenone ketyl. All other reagents were obtained from commercial sources and used without further purification. Reaction was routinely carried out under an atmosphere of dry nitrogen with magnetic stirring. Extract was dried with anhydrous magnesium sulfate before concentration *in vacuo*. Crude product was purified using column chromatography on silica gel.

4.2. A representative procedure of compounds (1) is as follows: A solution of arylmagnesium bromide (3.3 mmol) in tetrahydrofuran (10 mL) was added to a stirred solution of 1-mesyl or 1-tosyl piperidin-3-one **(2A** and **2B)** (2.0 mmol) in tetrahydrofuran (20 mL) at -78 ^{o}C. The reaction mixture was stirred at room temperature for 2 h. Water (5 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 x 50 mL). The combined organic layers were washed with brine, dried, filtered and evaporated to afford crude product under reduced pressure. Without further purification, boron trifluoride etherate (1 mL) was added to a stirred solution of the crude product and triethylsilane (2 mL) in dichloromethane (2 mL) at rt. The reaction mixture was stirred at 0 ^{o}C for 4 h. Saturated sodium bicarbonate solution (5 mL) was added to the reaction mixture and the solvent was concentrated under reduced pressure. The residue was extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with brine, dried, filtered and evaporated to afford crude product. Purification on silica gel (hexane/ethyl acetate = 4/1~2/1) afforded compounds (**1Aa**~**1Ad** and **1Ba**~**1Bd**). Representative data for compound (**1Aa**): HRMS (ESI, M^{+}+1) calcd for $C_{12}H_{18}NO_2S$ 240.1058, found 240.1060; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39-7.22 (m, 5H), 3.95-3.81 (m, 2H), 2.96-2.82 (m, 1H), 2.80 (s, 3H), 2.67-2.60 (m, 2H), 2.11-1.48 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.68, 128.90 (2x), 127.37 (2x), 127.28, 52.69, 46.47, 42.50, 34.87, 30.95, 25.27. For compound (**1Ab**): HRMS (ESI, M^{+}+1) calcd for $C_{13}H_{20}NO_3S$ 270.1164, found 270.1168; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.82-6.76 (m, 4H), 3.89-3.78 (m, 2H), 3.79 (s, 3H), 2.90-2.76 (m, 1H), 2.79 (s, 3H), 2.71-2.60 (m, 2H), 2.07-1.53 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.01, 144.33, 129.88, 119.67, 113.43, 112.28, 55.46, 52.60, 46.46, 42.52, 34.85, 30.95, 25.45. For compound (**1Ac**): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18 (d, *J* = 8.1 Hz, 2H), 6.84 (d, *J* = 8.1 Hz, 2H),

3.89-3.79 (m, 2H), 3.80 (s, 3H), 2.84-2.78 (m, 1H), 2.80 (s, 3H), 2.72-2.53 (m, 2H), 2.09-1.58 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.75, 134.77, 128.30 (2x), 114.24 (2x), 55.51, 52.92, 46.44, 41.62, 34.83, 31.11, 25.52. For compound (**1Ad**): HRMS (ESI, M^++1) calcd for $C_{13}H_{18}NO_4S$ 284.0957, found 284.0960; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.67-6.62 (m, 3H), 5.91 (s, 2H), 3.83-3.78 (m, 2H), 2.88-2.56 (m, 3H), 2.78 (s, 3H), 2.03-1.44 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.98, 146.62, 136.60, 120.38, 108.60, 107.72, 101.23, 52.86, 46.40, 42.24, 34.86, 31.23, 25.47. For compound (**1Ba**): HRMS (ESI, M^++1) calcd for $C_{18}H_{22}NO_2S$ 316.1371, found 316.1375; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8.1 Hz, 2H), 7.36-7.18 (m, 7H), 3.91-3.81 (m, 2H), 2.95-2.82 (m, 1H), 2.44 (s, 3H), 2.37-2.17 (m, 2H), 1.98-1.72 (m, 3H), 1.50-1.35 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.78, 142.86, 133.38, 129.95 (2x), 128.85 (2x), 127.92 (2x), 127.44 (2x), 127.20, 52.94, 46.68, 42.38, 30.72, 25.27, 21.80. For compound (**1Bb**): HRMS (ESI, M^++1) calcd for $C_{19}H_{24}NO_3S$ 346.1477, found 346.1481; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 (d, *J* = 8.1 Hz, 2H), 7.37-7.20 (m, 3H), 6.80-6.65 (m, 3H), 3.92-3.81 (m, 2H), 3.78 (s, 3H), 2.90-2.78 (m, 1H), 2.43 (s, 3H), 2.36-2.20 (m, 2H), 1.97-1.73 (m, 3H), 1.51-1.36 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.94, 144.51, 143.80, 133.40, 129.95 (2x), 127.95 (2x), 127.89, 119.78, 113.54, 112.15, 55.46, 52.87, 46.68, 42.40, 30.69, 25.22, 21.78. For compound (**1Bc**): HRMS (ESI, M^++1) calcd for $C_{19}H_{24}NO_3S$ 346.1477, found 346.1479; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8.1 Hz, 2H), 7.26 (d, *J* = 8.1 Hz, 2H), 7.02 (d, *J* = 8.4 Hz, 2H), 6.78 (d, *J* = 8.4 Hz, 2H), 3.89-3.78 (m, 2H), 3.78 (s, 3H), 2.80-2.73 (m, 1H), 2.39 (s, 3H), 2.22-2.03 (m, 2H), 1.94-1.68 (m, 3H), 1.41-1.26 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.69, 143.64, 134.95, 133.43, 129.85 (2x), 128.33 (2x), 127.92 (2x), 114.16 (2x), 55.50, 53.17, 46.62, 41.48, 30.85, 25.29, 21.77. For compound (**1Bd**): HRMS (ESI, M^++1) calcd for $C_{19}H_{22}NO_4S$ 360.1270, found 360.1271; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 (d, *J* = 8.1 Hz, 2H), 7.25 (d, *J* = 8.1 Hz, 2H), 6.65-6.48 (m, 3H), 5.88 (s, 2H), 3.80-3.73 (m, 2H), 2.80-2.69 (m, 1H), 2.38 (s, 3H), 2.21-2.03 (m, 2H), 1.89-1.63 (m, 3H), 1.36-1.19 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.93, 146.57, 143.68, 136.79, 133.42, 129.88 (2x), 127.91 (2x), 120.47, 108.56, 107.72, 101.20, 53.11, 46.60, 42.10, 31.03, 25.24, 21.77.

4.3. A representative procedure of compounds (4) is as follows: A solution of boron trifluoride etherate (0.5 mL) in dichloromethane (2 mL) was added to a stirred solution of compounds (**3Aa**, **3Ad**, **3Ba** and **3Bc**) (1.0 mmol) in dichloromethane (10 mL) at 0 ^{o}C. The reaction mixture was stirred at 0 ^{o}C for 1 h. Saturated sodium bicarbonate solution (5 mL) was added to the reaction mixture and the solvent was concentrated under reduced pressure. The residue was extracted with ethyl acetate (3 x 30 mL). The combined organic layers were washed with brine, dried, filtered and evaporated to afford crude products under reduced pressure. Purification on silica gel (hexane/ethyl acetate = 5/1) afforded compounds (**4Aa**, **4Ad**, **4Ba** and **4Bc**). Representative data for compound (**4Aa**): HRMS (ESI, M^++1) calcd for $C_{12}H_{16}NO_2S$

238.0902, found 238.0905; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42-7.21 (m, 5H), 7.02 (s, 1H), 3.65-3.58 (m, 2H), 2.92 (s, 3H), 2.56-2.43 (m, 2H), 2.14-2.02 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.68, 128.79 (2x), 126.95, 124.73 (2x), 121.92, 119.35, 43.81, 37.83, 24.08, 21.86. For compound (**4Ad**): HRMS (ESI, M^++1) calcd for $C_{13}H_{16}NO_4S$ 282.0800, found 282.0802; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.92-6.75 (m, 4H), 5.94 (s, 2H), 3.59-3.52 (m, 2H), 2.89 (s, 3H), 2.43-2.37 (m, 2H), 2.08-1.96 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.14, 121.12 (2x), 119.29, 118.20 (2x), 108.46, 105.43, 101.29, 43.74, 37.76, 24.47, 21.86. For compound (**4Bc**): HRMS (ESI, M^++1) calcd for $C_{19}H_{22}NO_3S$ 344.1320, found 344.1323; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.1 Hz, 2H), 7.36 (d, *J* = 8.1 Hz, 2H), 7.30 (d, *J* = 8.4 Hz, 2H), 7.09 (s, 1H), 6.88 (d, *J* = 8.4 Hz, 2H), 3.80 (s, 3H), 3.43-3.38 (m, 2H), 2.41 (s, 3H), 2.38-2.30 (m, 2H), 1.85-1.76 (m, 2H).

4.4. A representative procedure of compounds (5) is as follows: 6% Sodium amalgam (Na/Hg, 1.0 g) and sodium phosphate (355 mg, 2.5 mmol) were added to a stirred solution of compounds (**1Aa**~**1Ac** and **1Ba**~**1Bc**) (1.0 mmol) in methanol (15 mL) at room temperature. The reaction mixture was vigorously stirred at rt for 2 h. The residue was filtered and washed with methanol (2 x 10 mL). The combined organic layers were washed with brine, dried, filtered and evaporated to afford crude product under reduced pressure. Without further purification, sodium cyanoborohydride (80 mg, 2.0 mmol) was added to a solution of the resulting amine and *n*-propylaldehyde (120 mg, 2.0 mmol) in the co-solvent of tetrahydrofuran and methanol (10 mL, v/v=1/1) at rt. The reaction mixture was stirred for 18 h at rt. Saturated sodium bicarbonate solution (1 mL) was added to the reaction mixture and the solvent was concentrated under reduced pressure. The residue was extracted with ethyl acetate (3 x 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 = 1/1) afforded compounds (**5a**~**5c**). Representative data for compound (**5a**): HRMS (ESI, M^++1) calcd for $C_{14}H_{22}N$ 204.1752, found 204.1753; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.26 (m, 2H), 7.23-7.17 (m, 3H), 3.06-2.99 (m, 2H), 2.85 (tt, *J* = 3.5, 11.7 Hz, 1H), 2.36-2.31 (m, 2H), 2.02-1.90 (m, 3H), 1.79-1.72 (m, 2H), 1.58-1.39 (m, 3H), 0.88 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.67, 128.37 (2x), 127.30 (2x), 126.35, 61.17, 61.07, 53.82, 42.73, 31.54, 25.62, 19.87, 12.00. For compound (**5b**): HRMS (ESI, M^++1) calcd for $C_{15}H_{24}N$ 234.1858, found 234.1861; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (t, *J* = 7.9 Hz, 1H), 6.82-6.72 (m, 3H), 3.78 (s, 3H), 3.07-3.01 (m, 2H), 2.88 (t, *J* = 11.6 Hz, 1H), 2.38-2.34 (m, 2H), 2.04-1.91 (m, 3H), 1.81-1.77 (m, 2H), 1.60-1.40 (m, 3H), 0.89 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.68, 146.68, 129.36, 119.60, 113.27, 111.50, 60.99, 60.93, 55.16, 53.81, 42.61, 31.43, 25.42, 19.73, 11.94. HRMS (ESI, M^++1) calcd for $C_{15}H_{24}N$ 234.1858, found 234.1861; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12 (d, *J* = 8.7 Hz, 2H), 6.82 (d, *J* = 8.7 Hz, 2H), 3.75 (s, 3H), 3.12-3.08 (m, 2H), 2.91 (tt, *J* = 3.3, 11.9 Hz, 1H),

2.45-2.39 (m, 2H), 2.09-1.99 (m, 2H), 1.93-1.77 (m, 3H), 1.61-1.53 (m, 2H), 1.48-1.38 (m, 1H), 0.88 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.25, 135.97, 128.06, 113.88 (3x), 60.68, 60.57, 53.43, 41.07, 31.26, 30.04, 24.94, 19.19, 11.86.

4.5. A representative procedure of compounds (6) is as follows: Selenium dioxide (60 mg, 0.54 mmol) and *tert*-butyl hydroperoxide (70% in water, 100 mg, 0.78 mmol) were added to a stirred solution of compounds (**4Aa** and **4Ba**) (0.32 mmol) and benzoic acid (100 mg, 0.82 mmol) in dichloromethane (10 mL) at room temperature. The reaction mixture was vigorously stirred at refluxed temperature for 10 h. Saturated sodium bicarbonate solution (5 mL) was added to the reaction mixture and the solvent was concentrated under reduced pressure. The residue was extracted with ethyl acetate (3 x 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) afforded compounds (**6A** and **6B**). Representative data for compound (**6B**): mp 149-151 ^{o}C (hexane/ethyl acetate); HRMS (ESI, M^{+}+1) calcd for $C_{26}H_{38}NO_6S$ 492.2420, found 492.2422; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.5 Hz, 2H), 7.54 (d, *J* = 7.5 Hz, 2H), 7.35 (t, *J* = 7.5 Hz, 2H), 7.28 (d, *J* = 7.5 Hz, 1H), 7.23 (d, *J* = 7.5 Hz, 2H), 5.73 (s, 1H), 3.46 (dd, *J* = 2.5, 13.0 Hz, 1H), 3.15 (td, *J* = 2.5, 13.0 Hz, 1H), 2.43-2.39 (m, 1H), 2.39 (s, 3H), 2.20-2.07 (m, 2H), 1.57-1.54 (m, 1H), 1.22 (s, 9H), 0.83 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.58, 141.82, 138.30, 129.07 (2x), 127.80 (2x), 127.48 (2x), 127.32, 126.91 (2x), 87.48, 81.10, 79.72, 79.49, 39.37, 26.62 (3x), 25.85 (3x), 24.98, 21.40, 20.42; Anal. Calcd for $C_{26}H_{37}NO_6S$ C, 63.52; H, 7.09; N, 2.85. Found C, 63.36; H, 7.13; N, 3.01. Single-crystal X-Ray diagram: crystal of compound (**6B**) was grown by slow diffusion of ethyl acetate into a solution of compound (**6B**) in dichloromethane to yield colorless prism. The compound crystallizes in the monoclinic crystal system, space group P21/c (No. 14), *a*=10.472(2) Å, *b*=29.329(6) Å, *c*=8.9052(18) Å, *V*=2719.9(9) Å^3, *Z*=4, d_{calcd}=1.201 g/cm^3, *F*(000)=1056, 2θ range 1.96~26.01^{o}, R indices (all data) R_1 = 0.1674, wR_2 = 0.1428.

ACKNOWLEDGEMENTS

The authors would like to thank the National Science Council (NSC 94-2113-M-390-001) of the Republic of China for financial support. We also thank Prof. Michael Y. Chiang (National Sun Yat-Sen University) for structural determination of compound (**6B**) by X-Ray diffraction analysis.

REFERENCES

1. U. Hacksell, L.-E. Arvidsson, U. Svensson, and J. L. G. Nilsson, *J. Med. Chem.*, 1981, **24**, 1475.
2. T. Hogberg, *Drugs Future*, 1991, **16**, 333.
3. (a) M. Macchia, L. Cervetto, G. C. Demontis, B. Longoni, F. Minutolo, E. Orlandini, G. Ortore, C.

Papi, A. Sbrana, and B. Macchia, *J. Med. Chem.*, 2003, **46**, 161. (b) M. Amat, M. Canto, N. Llor, C. Escolano, E. Molins, E. Espinosa, and J. Bosch, *J. Org. Chem.*, 2002, **67**, 5343. (c) M. Y. Chang, S. T. Chen, and N. C. Chang, *Tetrahedron*, 2002, **58**, 3623. (d) I. K. Buchner and P. Metz, *Tetrahedron Lett.*, 2001, **42**, 5381. (e) A. G. Chaudhary and J. P. McGrath, *J. Labelled Compd. Radiopharm.*, 2000, **43**, 683. (f) L. Cervetto, G. C. Demontis, G. Giannaccini, B. Longoni, B. Macchia, M. Macchia, A. Martinelli, and E. Orlandini, *J. Med. Chem.*, 1998, **41**, 4933. (g) Y.-S. Wong, Marazano, C. D. Gnecco, Y. Genisson, A. Chiaroni, and B. C. Das, *J. Org. Chem.*, 1997, **62**, 729. (h) C. Sonesson, N. Waters, K. Svensson, A. Carlsson, M. W. Smith, F. P. Montford, E. Meier, and H. Wikstrom, *J. Med. Chem.*, 1993, **36**, 3188. (i) N. A. Grayson, W. D. Brown, and K. C. Rice, *Heterocycles*, 1992, **34**, 2281. (j) K. Nilsson and A. Hallberg, *J. Org. Chem.*, 1992, **57**, 4015. (k) H. Law, G. A. Leclerc, and J. L. Neumeyer, *Tetrahedron: Asymmetry*, 1991, **2**, 989. (l) H. Tecle, S. C. Bergmeier, L. D. Wise, F. M. Hershenson, L. L. Coughenour, and T. G. Heffner, *J. Heterocycl. Chem*., 1989, **26**, 1125. (m) S.-O. Thorberg, S. Berg, J. Lundstroem, B. Pettersson, A. Wikstrom, D. Sanchez, P. Lindberg, and J. L. G. Nilsson, *J. Med. Chem.*, 1987, **30**, 2008. (n) H. Rollema, D. Mastebroek, H. Wikstrom, K. Svensson, A. Carlsson, and S. Sundell, *J. Med. Chem.*, 1986, **29**, 1889. (o) S.-O. Thorberg, L. Gawell, I. Csoregh, and J. L. G. Nilsson, *Tetrahedron*, 1985, **41**, 129. (p) H. Rollema, D. Mastebroek, H. Wikstrom, and A. S. Horn, *J. Pharm. Pharmacol.*, 1985, **37**, 314. (q) W. Arnold, J. J. Daly, R. Imhof, and E. Kyburz, *Tetrahedron Lett.*, 1983, **24**, 343. (r) H. J. J. Loozen and F. T. L. Brands, *J. R. Neth. Chem. Soc.*, 1981, **100**, 333.

4. (a) P. Astra, *Drugs Future*, 1987, **12**, 88. (b) H. Wikstrom, D. Sanchez, P. Lindberg, U. Hacksell, L.-E. Arvidsson, A. M. Johansson, S.-O. Thorberg, J. L. G. Nilsson, K. Svensson, S. Hjorth, D. Clark, and A. Carlsson, *J. Med. Chem*., 1984, **27**, 1030. (c) T. Liljefors and H. Wikstrom, *J. Med. Chem*., 1986, **29**, 1896.
5. (a) C. Sonesson, C.-H. Lin, L. Hansson, N. Waters, K. Svensson, A. Carlsson, M. W. Smith, and H. Wikstrom, *J. Med. Chem.*, 1994, **37**, 2735. (b) L. O. Hansson, N. Waters, S. Holm, and C. Sonesson, *J. Med. Chem*., 1995, **38**, 3121.
6. (a) M. Y. Chang, C. L. Pai, and Y. H. Kung, *Tetrahedron Lett.*, 2005, **46**, 8463. (b) M. Y. Chang, C. L. Pai, and Y. H. Kung, *Tetrahedron Lett.*, 2006, **47**, 855. (c) M. Y. Chang, C. Y. Lin, and C. L. Pai, *Tetrahedron Lett.*, 2006, **47**, 2565.
7. (a) R. B. Carlin and D. A. Constantine, *J. Am. Chem. Soc.*, 1947, **69**, 50. (b) C. M. Utermoehlen, M. Singh, and R. E. Lehr, *J. Org. Chem.*, 1987, **52**, 5574. (c) R. C. Hartley, S. Warren, and I. C. Richards, *J. Chem. Soc., Perkin Trans 1*, 1994, 507. (d) G. M. Taylor, S. J. Baker, A. Gedney, D. J. Pearson, and G. E. M. Sibley, *Tetrahedron Lett.*, 1996, **37**, 1297. (e) T. Kumagai, T. Okubo, H. Kataoka-Okubo, S. Chaki, S. Okuyama, and A. Nakazato, *Bioorg. Med. Chem.*, 2001, **9**, 1349. (f) J.

S. Ward, L. Merritt, V. J. Klimkowski, M. L. Lamb, C. H. Mitch, F. P. Bymaster, B. Sawyer, H. E. Shannon, P. H. Olesen, T. Honore, M. J. Sheardown, and P. Sauerberg, *J. Med. Chem.*, 1992, **35**, 4401.

8. Z. Sui, J. Dodd, and K. A. Ohemeng, *Synth. Commun.*, 1997, **27**, 175.
9. (a) G. R. Krow, J. Yuan, Q. Huang, M. D. Meyer, D. J. Anderson, J. E. Campbell, and P. J. Carroll, *Tetrahedron*, 2000, **56**, 9233. (b) P. A. Grieco and M. D. Kaufman, *J. Org. Chem.*, 1999, **64**, 6041. (c) T. Giard, M.-C. Lasne, and J.-C. Plaquevent, *Tetrahedron Lett.*, 1999, **40**, 5495. (d) P. Gharagozloo, M. Miyauchi, and N. J. M. Birdsall, *Tetrahedron*, 1996, **52**, 10185. (e) J.-C. Plaquevent and I. Chichaoui, *Bull. Soc. Chim. Fr.*, 1996, **133**, 369. (f) D. Hou, A. Oshida, and M. Matsuoka, *J. Heterocycl. Chem.*, 1993, **30**, 1571. (g) Y. Matsumura, J. Terauchi, T. Yamamoto, T. Konno, and T. Shono, *Tetrahedron*, 1993, **49**, 8503. (h) Q. Zheng, Y. Yang, and A. R. Martin, *Tetrahedron Lett.*, 1993, **34**, 2235. (i) C. Bigogno, B. Danieli, G. Lesma, and D. Passarella, *Heterocycles*, 1995, **41**, 973. (j) D. Berney, *Helv. Chim. Acta*, 1978, **61**, 1110. (k) R. V. Stevens and J. T. Shell, *J. Chem. Soc.*, *Chem. Commun.*, 1975, 682.
10. (a) J. R. Vyvyan, C. Loitz, R. E. Looper, C. S. Mattingly, E. A. Peterson, and S. T. Staben, *J. Org. Chem.*, 2004, **69**, 2461. (b) M. A. Umbreit and K. B. Sharpless, *J. Am. Chem. Soc.*, 1977, **99**, 5526.
11. H. Ichikawa, Y. Usami, and M. Arimoto, *Tetrahedron Lett.*, 2005, **46**, 8665 and cited references therein.