Pergamon

Tetrahedron 58 (2002) 3623–3628

TETRAHEDRON

New synthesis of 3-aryl-*N*-*n*-propyl-piperidines

Meng-Yang Chang,[a] Shui-Tein Chen[a,*] and Nein-Chen Chang[b,*]

[a]*Institute of Biological Chemistry, Academia Sinica, Nankang, Taipei 115, Taiwan, ROC*
[b]*Department of Chemistry, National Sun Yat-Sen University, Kaohsiung 804, Taiwan, ROC*

Received 29 January 2002; accepted 4 March 2002

Abstract—The synthesis of 3-aryl-*N*-*n*-propyl-piperidines is described in six steps starting from α-sulfonyl acetamide via the formal [3+3] cycloaddition reaction of the latter into glutarimide. The pathway involves an efficient cycloaddition and regioselective reduction, and yields useful building blocks for heterocyclic chemistry.

1. Introduction

3-Arylpiperidines have been investigated since the early 1980s in view of their therapeutic dopaminergic activities.[1,2] The most therapeutically active of these compounds is 3-(3-hydroxyphenyl)-*N*-(*n*-propyl)-piperidine (3-PPP, preclamol),[3,4] reported to be the first selective D_2-like dopamine autoreceptor agonist.[4] The *N*-*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.

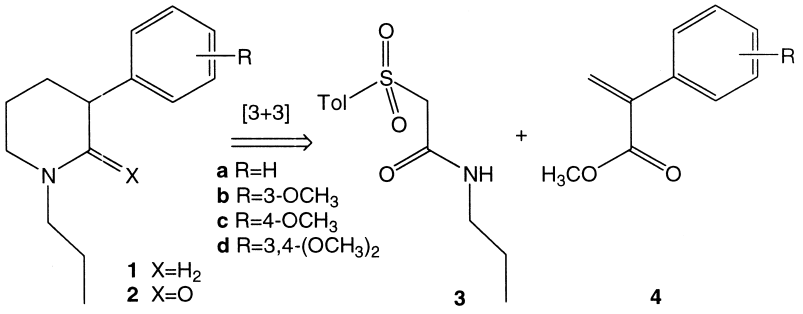
2. Results and discussion

2.1. Retrosynthetic analysis of 3-aryl *N*-*n*-propyl-piperidines

We describe the stepwise reduction leading to 3-aryl-*N*-*n*-propyl-piperidines as illustrated in Scheme 1. There are two remarkable steps for the synthesis of **1**. One is the rapid access to produce a wide variety of 3-aryl-piperidin-2,6-diones by formal [3+3] cycloaddition reaction.[6a] The other is the regioselective transformation from α-sulfonyl piperidin-2,6-diones to vinyl sulfonyl pyridinones using reduction followed by acidic dehydration.

2.2. Synthesis of 3-aryl-*N*-*n*-propyl-piperidines

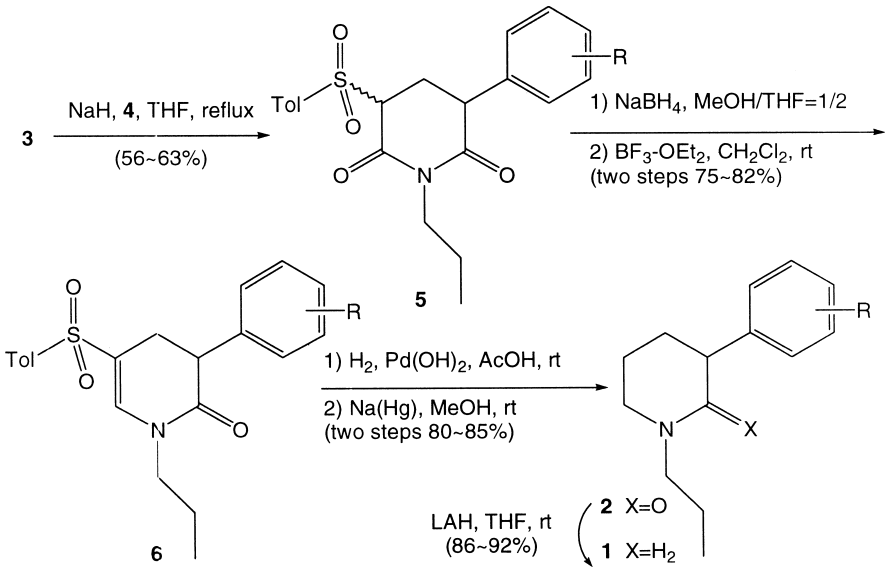
The synthesis began from the glutarimides **5a**–**d** (**5a** R=H; **5b** R=3-OMe; **5c** R=4-OMe; **5d** 3,4-OMe_2) which were the cycloadducts of formal [3+3] cycloaddition reactions[6] as shown in Scheme 2. *N*-*n*-Propylamine was treated with chloroacetyl chloride and triethylamine to produce α-chloride acetamide. Chloride compound was treated with *p*-toluenesulfonic acid sodium salt to give *N*-*n*-propyl α-sulfonyl acetamide **3** as the starting material of formal [3+3] cycloaddition reaction in the synthesis of 3-aryl-*N*-*n*-propyl-piperidines (85% two steps).



Scheme 1. Retrosynthetic analysis of 3-aryl-*N*-*n*-propyl-piperidines.

Keywords: formal [3+3] cycloaddition reaction; α-sulfonyl acetamide; 3-aryl-*N*-*n*-propyl-piperidines; preclamol.
* Corresponding authors. Tel.: +886-7-5292000x3913; fax: +886-7-5253913; e-mail: ncchang@mail.nsysu.edu.tw

0040–4020/02/$ - see front matter
PII: S0040-4020(02)00282-X



Scheme 2. Synthesis of 3-aryl-*N*-*n*-propyl-piperidines.

Compound **3** was deprotonated with sodium hydride to produce the dianion intermediate. The dianion of **3** was reacted with α,β-unsaturated esters **4** to yield the glutarimides **5** in an efficient procedure. The key step in our preparation of 3-aryl-*N*-*n*-propyl-piperidines **1** was a formal [3+3] cycloaddition reaction. We initially used glutarimide **5a** as a model substrate to synthesize target **1a** in two steps (desulfonation [Na/Hg] then reduction [LAH]), but desulfonation of glutarimide **5a** with sodium amalgam produced complex results. The six-membered ring of glutarimide **5a** might open, producing other compounds as monitored by TLC in the basic desulfonation. The desired desulfonyl glutarimide was obtained in less than 5% yield. The desulfonyl compound was treated with lithium aluminum hydride to obtain 3-phenyl-*N*-*n*-propyl-piperidine in 62% yield. This synthesis of 3-phenyl-*N*-*n*-propyl-piperidine resulted in very low total yield in three steps.

In order to prevent ring-opening of α-sulfonyl piperidin-2,6-diones thus to increase the total yield of 3-aryl-*N*-*n*-propyl-piperidines, we regioselectively reduced the piperidin-2,6-diones into 6-hydroxy piperidinones. The glutarimides **5a**–**d** treated with sodium borohydride followed by dehydration with boron trifluoride etherate yielded the vinyl olefinic sulfones **6a**–**d**. According to a related reported,[7] regioselective reduction with sodium borohydride was effected by the α-substituted group at glutarimide ring. In our case, chelation between 5-sufonyl and 6-carbonyl group position of glutarimides **5a**–**d** was induced by sodium borohydride to produce the regioselective 6-hydroxy piperidinones at 4–7°C. When the temperature was increased to 20–25°C, the glutarimide ring was still opening as determined by TLC. The 6-hydroxy piperidinones was dehydrated with boron trifluoride etherate to give olefins **6a**–**d**. The two steps from **5a**–**d** to **6a**–**d** gave 75–82% overall yield.

After hydrogenation of olefins **6a**–**d** by palladium hydroxide under standard conditions, the resulting 2-aryl-*N*-*n*-piperidinones **2a**–**d** was smoothly obtained by treatment of the sulfones with an excess of sodium amalgam in 80–85% yield. Finally, the reduction of piperidinones **2a**–**d** by treatment with lithium aluminum hydride gave the 2-aryl-*N*-*n*-piperidines **1a**–**d** in 86–92% yield.

3. Conclusion

In summary, the synthesis of target **1** demonstrates the utility of the formal [3+3] cycloaddition reaction of α-sulfonyl acetamide and yields the skeleton of piperidine ring. Formal synthesis of 3-PPP is also described by the above method.[8]

4. Experimental

4.1. General

Methylene chloride and tetrahydrofuran were 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 were uncorrected.

4.2. Synthesis of *N*-propyl-2-(4-methylphenyl)sulfonyl acetamide (3)

A solution of chloroacetyl chloride (5.99 g, 53.0 mmol) in tetrahydrofuran (40 mL) was added to a stirred solution of *N*-*n*-propylamine (2.95 g, 50.0 mmol) and triethylamine (5.57 g, 55.0 mmol) in tetrahydrofuran (100 mL) in an ice bath for 1 h. The reaction mixture was stirred at room temperature for 4 h and concentrated under reduced pressure. The residue was diluted with water (30 mL) and extracted with ethyl acetate (3×100 mL). The combined organic layers were washed with brine (2×50 mL), dried

over anhydrous magnesium sulfate, filtered and evaporated. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.70 (br s, 1H), 4.03 (s, 2H), 3.26 (q, J=6.9 Hz, 2H), 1.60–1.52 (m, 2H), 0.93 (t, J=7.4 Hz, 3H). Without further purification, the crude product was refluxed with *p*-toluenesulfonic acid sodium salt ($TolSO_2Na$–$2H_2O$, 16.05 g, 75.0 mmol) in dioxane (150 mL) and water (150 mL) for 10 h. Then the mixture was concentrated under reduced pressure. The residue was extracted with ethyl acetate (3×150 mL). The combined organic layers were washed with brine (2×50 mL), dried over anhydrous magnesium sulfate, filtered and evaporated. Recrystallization on hexane (60 mL) and ethyl acetate (30 mL) produced 10.83 g (85%) of **3** as a solid: mp=114–117°C; IR ($CHCl_3$) 3293, 2970, 1662, 1568, 1321, 1159, 1088, 820 cm^{-1}; ESI-MS: $C_{12}H_{18}NO_3S$ *m/z* (%)=256 (M^++1, 100); HRMS (ESI, M^++1) calcd for $C_{12}H_{18}NO_3S$ 256.1007, found 256.1014; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, J=8.3 Hz, 2H), 7.34 (d, J=8.3 Hz, 2H), 6.75 (br s, 1H), 3.96 (s, 2H), 3.20 (q, J=6.9 Hz, 2H), 2.42 (s, 3H), 1.57–1.47 (m, 2H), 0.91 (t, J=7.4 Hz, 3H); Anal. calcd for $C_{12}H_{17}NO_3S$ C, 56.45; H, 6.71. Found C, 56.06; H, 6.67.

4.3. Synthesis of α,β-unsaturated esters (4)

A three-necked flask with a dropping funnel, stirrer, and reflux condenser, magnesium turnings (10.0 mmol) was filled with dry tetrahydrofuran (20 mL) and treated with about 1/20 of a total of arylbromide (5.0 mmol) in tetrahydrofuran (20 mL) while stirring. After the reaction had started, the remaining arylbromide was added dropwise with further stirring in such a way that the ether boils gently. When the Grignard reagent was prepared, the reagent was added dropwise via a syringe to a solution of methyl pyruvate (5.0 mmol). After the addition was complete, the mixture is heated in a water bath (60°C) with stirring for 30 min, then cooled, then hydrolyzed by the addition of water (1 mL), and subsequently treated with 1N hydrogen chloride (2×20 mL) to dissolve the precipitate that had been formed. The mixture was filtered and extracted with ethyl acetate (3×50 mL). The combined organic layers were washed with brine (2×20 mL), dried by magnesium sulfate, filtered and evaporated. Without purification, the resulting alcohol was added to a stirred solution of *p*-toluenesulfonic acid (100 mg) in benzene (50 mL) and the reaction mixture was stirred at refluxed temperature under a Dean–Stark trap for 4 h. The cooled reaction mixture was diluted with ether (30 mL) and washed successively with sodium bicarbonate solution (10 mL). The combined organic layers were washed with brine (2×20 mL), dried with magnesium sulfate, filtered and evaporated. Purification on silica gel (hexane/ethyl acetate=10/1–8/1) produced α,β-unsaturated esters **4** in 36–45% yield.

4.4. Procedure of formal [3+3] cycloaddition reaction

A solution of acetamide **3** (1.28 g, 5.0 mmol) in tetrahydrofuran (30 mL) was added to a rapidly stirred suspension of sodium hydride (420 mg, 10.5 mmol, 60%) in tetrahydrofuran (40 mL). After the reaction mixture was stirred at room temperature for 15 min, a solution of α,β-unsaturated esters **4** (5.0 mmol) in tetrahydrofuran (10 mL) was added. The resulting mixture was refluxed for 30 min, quenched with saturated ammonium chloride solution (2 mL) in an ice bath, and concentrated under reduced pressure. The residue was diluted with water (10 mL) and extracted with ethyl acetate (3×20 mL). The combined organic layers were washed with brine (2×20 mL), dried over anhydrous magnesium sulfate, filtered and evaporated. Purification on silica gel (hexane/ethyl acetate=4/1–2/1) produced **5a–d** in 56–63% yield.

4.4.1. *N*-1-Propyl-3-phenyl-5-[(4-methylphenyl)sulfonyl]-piperidin-2,6-dione (5a). Yield 60%; mp=190–192°C; IR ($CHCl_3$) 2965, 2360, 1727, 1677, 1320, 1149 cm^{-1}; ESI-MS: $C_{21}H_{24}NO_4S$ *m/z* (%)=137 (48), 154 (58), 202 (25), 386 (M^++1, 100); HRMS (ESI, M^++1) calcd for $C_{21}H_{24}NO_4S$ 386.1427, found 386.1422; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, J=8.3 Hz, 1/2H), 7.76 (d, J=8.3 Hz, 3/2H), 7.39–7.29 (m, 5H), 7.20–7.17 (m, 2H), 4.45 (dd, J=5.6, 11.8 Hz, 3/4H), 4.31 (dd, J=5.6, 13.0 Hz, 1/4H), 4.14 (dd, J=3.9, 5.8 Hz, 3/4H), 3.87–3.76 (m, 3/2H), 3.72–3.66 (m, 3/4H), 3.00 (ddd, J=3.9, 5.7, 14.9 Hz, 3/4H), 2.83 (dt, J=5.1, 13.5 Hz, 1/4H), 2.68–2.53 (m, 1H), 2.46 (s, 3H), 1.60–1.48 (m, 2H), 0.90 (t, J=7.5 Hz, 9/4H), 0.83 (t, J=7.5 Hz, 3/4H); Anal. calcd for $C_{21}H_{23}NO_4S$ C, 65.43; H, 6.01. Found C, 65.62; H, 6.06.

4.4.2. *N*-1-Propyl-3-(3-methoxyphenyl)-5-[(4-methylphenyl)sulfonyl]-piperidin-2,6-dione (5b). Yield 63%; mp=130–132°C; IR ($CHCl_3$) 2964, 2360, 1729, 1678, 1149 cm^{-1}; ESI-MS: $C_{22}H_{26}NO_5S$ *m/z* (%)=136 (25), 154 (30), 204 (33), 232 (72), 416 (M^++1, 100); HRMS (ESI, M^++1) calcd for $C_{22}H_{26}NO_5S$ 416.1533, found 416.1528; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, J=8.3 Hz, 4/7H), 7.76 (d, J=8.3 Hz, 10/7H), 7.37 (d, J=8.3 Hz, 2H), 7.30–7.25 (m, 1H), 6.87–6.83 (m, 1H), 6.76–6.70 (m, 2H), 4.40 (dd, J=5.6, 11.5 Hz, 5/7H), 4.31 (dd, J=5.4, 13.2 Hz, 2/7H), 4.14 (dd, J=4.1, 5.6 Hz, 5/7H), 3.83–3.76 (m, 10/7H), 3.79 (s, 3H), 3.73–3.67 (m, 4/7H), 3.66–3.60 (m, 2/7H), 3.00–2.95 (m, 5/7H), 2.83–2.78 (m, 2/7H), 2.65–2.52 (m, 1H), 2.45 (s, 3H), 1.63–1.45 (m, 2H), 0.90 (t, J=7.4 Hz, 15/7H), 0.82 (t, J=7.4 Hz, 6/7H); Anal. calcd for $C_{22}H_{25}NO_5S$ C, 63.59; H, 6.06. Found C, 63.73; H, 6.20.

4.4.3. *N*-1-Propyl-3-(4-methoxyphenyl)-5-[(4-methylphenyl)sulfonyl]-piperidin-2,6-dione (5c). Yield 56%; mp=208–210°C; IR ($CHCl_3$) 2964, 2360, 1728, 1678, 1516, 1149 cm^{-1}; ESI-MS: $C_{22}H_{26}NO_5S$ *m/z* (%)=136 (30), 154 (42), 204 (46), 232 (80), 416 (M^++1, 100); HRMS (ESI, M^++1) calcd for $C_{22}H_{26}NO_5S$ 416.1533, found 416.1531; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, J=8.3 Hz, 1/2H), 7.76 (d, J=8.3 Hz, 3/2H), 7.37 (d, J=8.1 Hz, 2H), 7.12–7.08 (m, 2H), 6.91–6.87 (m, 2H), 4.39 (dd, J=5.5, 11.7 Hz, 3/4H), 4.30 (dd, J=5.5, 13.1 Hz, 1/4H), 4.13 (dd, J=4.0, 5.8 Hz, 3/4H), 3.80–3.75 (m, 3/2H), 3.79 (s, 3H), 3.68 (t, J=7.5 Hz, 1/2H), 3.63 (dd, J=4.7, 13.7 Hz, 1/4H), 2.97 (ddd, J=4.0, 5.5, 14.8 Hz, 3/4H), 2.80 (d, t, J=5.1, 13.4 Hz, 1/4H), 2.64–2.49 (m, 1H), 2.46 (s, 3H), 1.59–1.46 (m, 2H), 0.89 (t, J=7.4 Hz, 9/4H), 0.82 (t, J=7.4 Hz, 3/4H); Anal. calcd for $C_{22}H_{25}NO_5S$ C, 63.59; H, 6.06. Found C, 63.67; H, 6.26.

4.4.4. *N*-1-Propyl-3-(3,4-dimethoxyphenyl)-5-[(4-methylphenyl)sulfonyl]-piperidin-2,6-dione (5d). Yield 63%; mp=171–173°C; IR ($CHCl_3$) 2964, 2360, 1727, 1677,

1518, 1148 cm^{-1}; ESI-MS: $C_{23}H_{28}NO_6S$ *m/z* (%)=136 (38), 154 (50), 262 (61), 445 (100), 446 (M^++1, 100); HRMS (ESI, M^++1) calcd for $C_{23}H_{28}NO_6S$ 446.1638, found 446.1636; ^1H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, *J*=8.2 Hz, 1/4H), 7.76 (d, *J*=8.2 Hz, 7/4H), 7.37 (d, *J*=8.2 Hz, 2H), 6.87–6.83 (m, 1H), 6.74–6.67 (m, 2H), 4.38 (dd, *J*=5.5, 11.7 Hz, 7/8H), 4.30 (dd, *J*=5.5, 13.0 Hz, 1/8H), 4.14 (dd, *J*=4.0, 5.8 Hz, 7/8H), 3.86 (s, 6H), 3.78 (t, *J*=7.5 Hz, 7/4H), 3.70 (t, *J*=7.5 Hz, 1/4H), 3.62 (dd, *J*=4.7, 13.8 Hz, 1/8H), 3.00 (ddd, *J*=4.1, 5.4, 14.8 Hz, 7/8H), 2.85–2.78 (m, 1/8H), 2.56 (ddd, *J*=5.9, 11.7, 14.8 Hz, 1H), 2.46 (s, 3H), 1.60–1.53 (m, 2H), 0.90 (t, *J*=7.4 Hz, 21/8H), 0.83 (t, *J*=7.4 Hz, 3/8H); Anal. calcd for $C_{23}H_{27}NO_6S$ C, 62.00; H, 6.11. Found C, 61.93; H, 6.20.

4.5. Procedure of regioselective reduction [$NaBH_4$] and acidic dehydration [BF_3-OEt_2]

A solution of compound **5** (2.0 mmol) in a co-solvent of tetrahydrofuran (10 mL) and HPLC-grade methanol (5 mL) was stirred at 4–7°C. Sodium borohydride (150 mg, 4.0 mmol) was added at 4–7°C. The mixture was stirred for 2 h at that temperature. Saturated sodium bicarbonate solution (1 mL) was added to the mixture and concentrated under reduced pressure. The residue was diluted with water (5 mL) and extracted with dichloromethane (3×10 mL). The combined organic layers were washed with brine (2×10 mL), dried over anhydrous magnesium sulfate, filtered and evaporated. Without further purification, the crude hydroxy-lactam was dissolved in dichloromethane (10 mL), and a catalytic amount of boron trifluoride etherate (0.1 mL) and magnesium sulfate (0.5 g) were added. The mixture was stirred for 5 h at room temperature. Saturated sodium bicarbonate solution (5 mL) was added to the resulting mixture and concentrated under reduced pressure. The residue was diluted with water (5 mL) and extracted with dichloromethane (3×10 mL). The combined organic layers were washed with brine (2×10 mL), dried over anhydrous magnesium sulfate, filtered and evaporated. Purification on silica gel (hexane/ethyl acetate=4/1–2/1) produced **6a**–**d** in 75–82% yield.

4.5.1. *N*-1-Propyl-3-phenyl-5-[(4-methylphenyl)sulfonyl]-1,2,3,4-tetrahydro-2-pyridinone (6a). Yield 80%; gum; IR ($CHCl_3$) 2963, 2360, 1693, 1651, 1383, 1138 cm^{-1}; ESI-MS: $C_{21}H_{24}NO_3S$ *m/z* (%)=167 (20), 279 (8), 289 (10), 307 (16), 370 (M^++1, 100); HRMS (ESI, M^++1) calcd for $C_{21}H_{24}NO_3S$ 370.1478, found 370.1481; ^1H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, *J*=8.2 Hz, 2H), 7.33 (s, 1H), 7.26 (d, *J*=8.2 Hz, 2H), 7.21–7.18 (m, 3H), 7.05–7.02 (m, 2H), 3.76 (t, *J*=7.9 Hz, 1H), 3.55 (t, *J*=7.2 Hz, 2H), 2.85 (dd, *J*=7.3, 17.0 Hz, 1H), 2.68 (dd, *J*=8.3, 17.0 Hz, 1H), 2.41 (s, 3H), 1.66–1.54 (m, 2H), 0.88 (t, *J*=7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.09, 144.17, 138.37, 137.28, 136.78, 129.92, 128.65 (2×), 127.64 (3×), 127.55 (2×), 127.48, 116.19, 49.53, 45.77, 27.02, 22.15, 21.58, 11.00; Anal. calcd for $C_{21}H_{23}NO_3S$ C, 68.27; H, 6.27. Found C, 68.46; H, 6.16.

4.5.2. *N*-1-Propyl-3-(3-methoxyphenyl)-5-[(4-methylphenyl)sulfonyl]-1,2,3,4-tetrahydro-2-pyridinone (6b). Yield 75%; gum; IR ($CHCl_3$) 2962, 2360, 1691, 1651, 1381, 1138 cm^{-1}; ESI-MS: $C_{22}H_{26}NO_4S$ *m/z* (%)=136 (46), 154 (70), 307 (20), 400 (M^++1, 100); HRMS (ESI, M^++1) calcd for $C_{22}H_{26}NO_4S$ 400.1584, found 400.1583; ^1H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, *J*=8.3 Hz, 2H), 7.32 (s, 1H), 7.24 (d, *J*=8.3 Hz, 2H), 7.11–7.07 (m, 1H), 6.74–6.72 (m, 1H), 6.62–6.60 (m, 2H), 3.74 (t, *J*=4.2 Hz, 1H), 3.72 (s, 3H), 3.55 (t, *J*=7.4 Hz, 2H), 2.84 (ddd, *J*=0.8, 7.4, 17.0 Hz, 1H), 2.67 (dd, *J*=8.0, 17.0 Hz, 1H), 2.40 (s, 3H), 1.66–1.57 (m, 2H), 0.88 (t, *J*=7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.95, 159.75, 144.13, 138.75, 138.34, 136.73, 129.89, 129.61, 127.58 (3×), 119.73, 116.16, 113.35, 113.03, 55.18, 49.51, 45.75, 27.01, 22.15, 21.56, 11.00; Anal. calcd for $C_{22}H_{25}NO_4S$ C, 66.14; H, 6.31. Found C, 66.26; H, 6.33.

4.5.3. *N*-1-Propyl-3-(4-methoxyphenyl)-5-[(4-methylphenyl)sulfonyl]-1,2,3,4-tetrahydro-2-pyridinone (6c). Yield 79%; gum; IR ($CHCl_3$) 2963, 2360, 1691, 1649, 1513, 1138 cm^{-1}; ESI-MS: $C_{22}H_{26}NO_4S$ *m/z* (%)=136 (35), 154 (62), 307 (31), 400 (M^++1, 100), 400 (M^++1, 100); HRMS (ESI, M^++1) calcd for $C_{22}H_{26}NO_4S$ 400.1584, found 400.1591; ^1H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, *J*=8.2 Hz, 2H), 7.31 (s, 1H), 7.25 (d, *J*=8.2 Hz, 2H), 6.95 (dd, *J*=3.0, 8.7 Hz, 2H), 6.71 (dd, *J*=3.0, 8.7 Hz, 2H), 3.74 (s, 3H), 3.71 (t, *J*=7.7 Hz, 1H), 3.53 (t, *J*=7.4 Hz, 2H), 2.82 (ddd, *J*=0.9, 7.3, 16.8 Hz, 1H), 2.65 (dd, *J*=7.9, 16.8 Hz, 1H), 2.41 (s, 3H), 1.65–1.56 (m, 2H), 0.87 (t, *J*=7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.38, 158.93, 144.14, 138.36, 136.83, 129.90, 129.23, 128.54 (2×), 127.65 (4×), 116.11, 114.05, 55.22, 49.50, 44.94, 27.00, 22.15, 21.57, 11.00; Anal. calcd for $C_{22}H_{25}NO_4S$ 66.14; H, 6.31. Found C, 66.02; H, 6.12.

4.5.4. *N*-1-Propyl-3-(3,4-dimethoxyphenyl)-5-[(4-methylphenyl)sulfonyl]-1,2,3,4-tetrahydro-2-pyridinone (6d). Yield 82%; mp=150–152°C; IR ($CHCl_3$) 2963, 2360, 1690, 1651, 1517, 1138 cm^{-1}; ESI-MS: $C_{23}H_{28}NO_5S$ *m/z* (%)=136 (15), 154 (18), 178 (56), 429 (91), 430 (M^++1, 100); HRMS (ESI, M^++1) calcd for $C_{23}H_{28}NO_5S$ 430.1689, found 430.1684; ^1H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, *J*=8.2 Hz, 2H), 7.30 (s, 1H), 7.25 (d, *J*=7.4 Hz, 2H), 6.69–6.58 (m, 3H), 3.81 (s, 3H), 3.79 (s, 3H), 3.72 (t, *J*=7.2 Hz, 1H), 3.53 (td, *J*=2.4, 7.0 Hz, 2H), 2.76 (qd, *J*=7.2, 16.8 Hz, 2H), 2.40 (s, 3H), 1.63–1.55 (m, 2H), 0.86 (t, *J*=7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.32, 149.04, 148.51, 144.22, 138.26, 136.82, 129.87 (2×), 129.52, 127.60 (2×), 119.42, 116.06, 111.13, 110.89, 55.87 (2×), 49.48, 45.13, 26.70, 22.13, 21.56, 10.66; Anal. calcd for $C_{23}H_{27}NO_5S$ C, 64.31; H, 6.34. Found C, 64.48; H, 6.62.

4.6. Procedure of hydrogenation [H_2/$Pd(OH)_2$] and desulfonation [Na/Hg]

Palladium hydroxide (100 mg) on activated carbon as catalyst was added to a solution of olefinic sulfone (1.0 mmol) in acetic acid (10 mL). Hydrogen was bubbled into the mixture for 10 min, and the mixture stirred at room temperature for 3 h. Filtration through a short plug of Celite and washing with ethyl acetate (3×10 mL) resulted in the crude sulfone. Without further purification, 6% sodium amalgam (Na/Hg, 1.5 g) and sodium phosphate (355 mg, 2.5 mmol) were added to a stirred solution of crude sulfone (ca. 1.0 mmol) in HPLC-grade methanol (15 mL), and vigorously stirred

for 2 h at room temperature. The residue was filtered and washed with methanol (2×10 mL). The combined organic layers were concentrated to obtain the crude desulfonyl compound. Purification on silica gel (hexane/ethyl acetate=1/1–1/2) produced **2a–d** in 80–85% yield.

4.6.1. *N*-1-Propyl-3-phenyl-piperidin-2-one (2a). Yield 80%; oil; IR ($CHCl_3$) 2933, 2360, 1634, 1248 cm^{-1}; ESI-MS: $C_{14}H_{20}NO$ *m/z* (%)=218 (M^++1, 100); HRMS (ESI, M^++1) calcd for $C_{14}H_{20}NO$ 218.1546, found 218.1547; ^1H NMR (400 MHz, $CDCl_3$) δ 7.30–7.24 (m, 2H), 7.21–7.15 (m, 3H), 3.66 (t, *J*=6.9 Hz, 1H), 3.53–3.36 (m, 2H), 3.36–3.24 (m, 2H), 2.18–2.10 (m, 1H), 1.97–85 (m, 2H), 1.82–1.75 (m, 1H), 1.67–1.58 (m, 2H), 0.92 (t, *J*=7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.36, 141.98, 128.42 (4×), 126.47, 49.20, 48.58, 48.21, 30.54, 20.98, 20.39, 11.39.

4.6.2. *N*-1-Propyl-3-(3-methoxyphenyl)-piperidin-2-one (2b).[3i] Yield 85%; oil; IR ($CHCl_3$) 2935, 2360, 1637, 1261 cm^{-1}; ESI-MS: $C_{15}H_{22}NO_2$ *m/z* (%)=136 (16), 154 (23), 247 (25), 248 (M^++1, 100); HRMS (ESI, M^++1) calcd for $C_{15}H_{22}NO_2$ 248.1652, found 248.1651; ^1H NMR (400 MHz, $CDCl_3$) δ 7.20 (t, *J*=7.8 Hz, 1H), 6.77–6.72 (m, 3H), 3.76 (s, 3H), 3.63 (t, *J*=6.8 Hz, 1H), 3.56–3.49 (m, 1H), 3.44–3.38 (m, 1H), 3.35–3.20 (m, 2H), 2.15–2.11 (m, 1H), 1.95–1.87 (m, 2H), 1.81–1.75 (m, 1H), 1.67–1.57 (m, 2H), 0.92 (t, *J*=7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.19, 159.60, 143.51, 129.36, 120.65, 113.67, 111.79, 55.15, 49.18, 48.56, 48.19, 30.42, 20.95, 20.38, 11.39.

4.6.3. *N*-1-Propyl-3-(4-methoxyphenyl)-piperidin-2-one (2c). Yield 85%; oil; IR ($CHCl_3$) 2934, 2360, 1638, 1245 cm^{-1}; ESI-MS: $C_{15}H_{22}NO_2$ *m/z* (%)=136 (12), 154 (20), 247 (20), 248 (M^++1, 100); HRMS (ESI, M^++1) calcd for $C_{15}H_{22}NO_2$ 248.1651, found 248.1662; ^1H NMR (400 MHz, $CDCl_3$) δ 7.10–7.06 (m, 2H), 6.84–6.81 (m, 2H), 3.75 (s, 3H), 3.59 (t, *J*=7.4 Hz, 1H), 3.52–3.37 (m, 2H), 3.34–3.21 (m, 2H), 2.15–2.07 (m, 1H), 1.94–1.83 (m, 2H), 1.81–1.70 (m, 1H), 1.65–1.56 (m, 2H), 0.89 (t, *J*=7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.61, 158.66, 134.07, 129.16, 114.11 (3×), 55.24, 49.16, 48.19, 47.73, 30.50, 21.02, 20.38, 11.38.

4.6.4. *N*-1-Propyl-3-(3,4-dimethoxyphenyl)-piperidin-2-one (2d). Yield 83%; oil; IR ($CHCl_3$) 2935, 2359, 1633, 1240 cm^{-1}; ESI-MS: $C_{16}H_{24}NO_3$ *m/z* (%)=58 (100), 91 (18), 154 (20), 278 (M^++1, 70); HRMS (ESI, M^++1) calcd for $C_{16}H_{24}NO_3$ 278.1757, found 278.1750; ^1H NMR (400 MHz, $CDCl_3$) δ 6.80–6.78 (m, 1H), 6.72–6.69 (m, 2H), 3.84 (s, 3H), 3.83 (s, 3H), 3.61–3.51 (m, 2H), 3.42 (ddd, *J*=5.2, 7.6, 12.3 Hz, 1H), 3.35–3.29 (m, 1H), 3.25–3.17 (m, 1H), 2.15–2.09 (m, 1H), 1.97–1.85 (m, 2H), 1.82–1.72 (m, 1H), 1.61 (sext, *J*=7.4 Hz, 2H), 0.92 (t, *J*=7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.52, 148.83, 147.73, 136.10, 120.11, 111.95, 111.32, 55.94, 55.88, 49.15, 48.19, 48.06, 30.36, 21.04, 20.38, 11.38.

4.7. Reduction [LAH] of 3-arylpiperidinones

A solution of piperidinone **2** (0.7 mmol) in tetrahydrofuran (10 mL) was added to a solution of lithium aluminum hydride (53 mg, 1.45 mmol) in tetrahydrofuran (20 mL) via syringe at 0°C. The mixture was refluxed for 2 h, quenched with saturated aqueous ammonium chloride solution (2 mL) under cooling, and concentrated. The residue was diluted with water (15 mL) and extracted with ethyl acetate (3×30 mL). The organic layer was washed with brine and water, dried ($MgSO_4$), filtered and concentrated to produce crude compound **1**. Purification on silica gel (ethyl acetate/methanol=4/1–2/1) produced **1a–d** in 86–92% yield.

4.7.1. *N*-1-Propyl-3-phenyl-piperidine (1a).[1,5a,b] Yield 89%; oil; IR ($CHCl_3$) 2932, 2360, 1453, 1089, 698 cm^{-1}; ESI-MS: $C_{14}H_{22}N$ *m/z* (%)=174 (21), 202 (25), 204 (M^++1, 100); HRMS (ESI, M^++1) calcd for $C_{14}H_{22}N$ 204.1754, found 204.1745; ^1H 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 (2×), 127.30 (2×), 126.35, 61.17, 61.07, 53.82, 42.73, 31.54, 25.62, 19.87, 12.00; Anal. calcd for $C_{14}H_{21}N$ C, 82.70; H, 10.41. Found C, 82.61; H, 10.55.

4.7.2. *N*-1-Propyl-3-(3-methoxyphenyl)-piperidine (1b).[1,3] Yield 86%; oil; IR ($CHCl_3$) 2932, 2360, 1602, 1584, 1262, 1050 cm^{-1}; ESI-MS: $C_{15}H_{24}NO$ *m/z* (%)=204 (55), 232 (87), 234 (M^++1, 100); HRMS (ESI, M^++1) calcd for $C_{15}H_{24}NO$ 234.1859, found 234.1860; ^1H 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; Anal. calcd for $C_{15}H_{23}NO$ C, 77.21; H, 9.93. Found C, 77.44; H, 10.06.

4.7.3. *N*-1-Propyl-3-(4-methoxyphenyl)-piperidine (1c).[1] Yield 90%; oil; IR ($CHCl_3$) 2933, 2360, 1514, 1247, 1038 cm^{-1}; ESI-MS: $C_{15}H_{24}NO$ *m/z* (%)=204 (58), 232 (95), 234 (M^++1, 100); HRMS (ESI, M^++1) calcd for $C_{15}H_{24}NO$ 234.1859, found 234.1865; ^1H 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 (3×), 60.68, 60.57, 53.43, 41.07, 31.26, 30.04, 24.94, 19.19, 11.86.

4.7.4. *N*-1-Propyl-3-(3,4-dimethoxyphenyl)-piperidine (1d).[1k] Yield 92%; oil; IR ($CHCl_3$) 2933, 2360, 1517, 1263, 1030 cm^{-1}; ESI-MS: $C_{16}H_{26}NO_2$ *m/z* (%)=234 (57), 262 (80), 264 (M^++1, 100); HRMS (ESI, M^++1) calcd for $C_{16}H_{26}NO_2$ 264.1965, found 264.1967; ^1H NMR (400 MHz, $CDCl_3$) δ 6.80–6.73 (m, 3H), 3.85 (s, 3H), 3.83 (s, 3H), 3.11–3.07 (m, 2H), 2.85 (dd, *J*=3.5, 11.8 Hz, 1H), 2.45–2.34 (m, 2H), 2.05–1.98 (m, 2H), 1.94–1.88 (m, 2H), 1.82–1.76 (m, 2H), 1.60–1.47 (m, 1H), 1.46–1.37 (m, 1H), 0.88 (t, *J*=7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.88, 147.65, 136.94, 118.85, 111.29, 110.83, 60.81, 60.61, 55.92, 55.89, 53.45, 41.77, 31.43, 25.11, 19.36, 11.91.

Acknowledgements

The authors would like to thank the National Science Council of the Republic of China for financial support.

References

1. Hacksell, U.; Arvidsson, L.-E.; Svensson, U.; Nilsson, J. L. G. *J. Med. Chem.* **1981**, *24*, 1475–1482.
2. Hogberg, T. *Drugs Future* **1991**, *16*, 333–357.
3. (a) Buchner, I. K.; Metz, P. *Tetrahedron Lett.* **2001**, *42*, 5381–5383. (b) Chaudhary, A. G.; McGrath, J. P. *J. Labelled Compd Radiopharm.* **2000**, *43*, 683–692. (c) Cervetto, L.; Demontis, G. C.; Giannaccini, G.; Longoni, B.; Macchia, B.; Macchia, M.; Martinelli, A.; Orlandini, E. *J. Med. Chem.* **1998**, *41*, 4933–4938. (d) Wong, Y.-S.; Marazano, C.; Gnecco, D.; Genisson, Y.; Chiaroni, A.; Das, B. C. *J. Org. Chem.* **1997**, *62*, 729–733. (e) Sonesson, C.; Waters, N.; Svensson, K.; Carlsson, A.; Smith, M. W.; Montford, F. P.; Meier, E.; Wikstrom, H. *J. Med. Chem.* **1993**, *36*, 3188–3196. (f) Grayson, N. A.; Brown, W. D.; Rice, K. C. *Heterocycles* **1992**, *34*, 2281–2292. (g) Nilsson, K.; Hallberg, A. *J. Org. Chem.* **1992**, *57*, 4015–4017. (h) Law, H.; Leclerc, G. A.; Neumeyer, J. L. *Tetrahedron: Asymmetry* **1991**, *2*, 989–992. (i) Tecle, H.; Bergmeier, S. C.; Wise, L. D.; Hershenson, F. M.; Coughenour, L. L.; Heffner, T. G. *J. Heterocycl. Chem.* **1989**, *26*, 1125–1128. (j) Thorberg, S.-O.; Berg, S.; Lundstroem, J.; Pettersson, B.; Wikstrom, A.; Sanchez, D.; Lindberg, P.; Nilsson, J. L. G. *J. Med. Chem.* **1987**, *30*, 2008–2012. (k) Rollema, H.; Mastebroek, D.; Wikstrom, H.; Svensson, K.; Carlsson, A.; Sundell, S. *J. Med. Chem.* **1986**, *29*, 1889–1896. (l) Thorberg, S.-O.; Gawell, L.; Csoregh, I.; Nilsson, J. L. G. *Tetrahedron* **1985**, *41*, 129–139. (m) Rollema, H.; Mastebroek, D.; Wikstrom, H.; Horn, A. S. *J. Pharm. Pharmacol.* **1985**, *37*, 314–319. (n) Arnold, W.; Daly, J. J.; Imhof, R.; Kyburz, E. *Tetrahedron Lett.* **1983**, *24*, 343–346. (o) Loozen, H. J. J.; Brands, F. T. L. *J. R. Neth. Chem. Soc.* **1981**, *100*, 333–336.
4. (a) Astra, P. Preclamol 3-PPP. *Drugs Future* **1987**, *12*, 88–89. (b) Wikstrom, H.; Sanchez, D.; Lindberg, P.; Hacksell, U.; Arvidsson, L.-E.; Johansson, A. M.; Thorberg, S.-O.; Nilsson, J. L. G.; Svensson, K.; Hjorth, S.; Clark, D.; Carlsson, A. *J. Med. Chem.* **1984**, *27*, 1030–1036. (c) Liljefors, T.; Wikstrom, H. *J. Med. Chem.* **1986**, *29*, 1896–1904.
5. (a) Sonesson, C.; Lin, C.-H.; Hansson, L.; Waters, N.; Svensson, K.; Carlsson, A.; Smith, M. W.; Wikstrom, H. *J. Med. Chem.* **1994**, *37*, 2735–2753. (b) Hansson, L. O.; Waters, N.; Holm, S.; Sonesson, C. *J. Med. Chem.* **1995**, *38*, 3121–3131.
6. (a) Chang, M. Y.; Chang, B. R.; Tai, H. M.; Chang, N. C. *Tetrahedron Lett.* **2000**, *41*, 10273–10276. (b) Chang, M. Y.; Chang, C. H.; Chen, S. T.; Chang, N. C. *J. Chin. Chem. Soc.* **2002**, *49* in press.
7. (a) Estiarte, M. A.; de Souza, M. V. N.; del Rio, X.; Dodd, R. H.; Rubiralta, M.; Diez, A. *Tetrahedron* **1999**, *55*, 10173–10186. (b) Ducrot, P.; Thal, C. *Tetrahedron Lett.* **1999**, *40*, 9037–9040. (c) Heaney, H.; Taha, M. O. *Tetrahedron Lett.* **2000**, *41*, 1993–1996.
8. Compound **1b** was treated with 48% hydrogen bromide to yield the 3-PPP. The procedure was shown in Ref. 3h.