Chinese Chemical Letters Vol. 14, No. 4, pp 365 – 367, 2003
http://www.imm.ac.cn/journal/ccl.html

An Efficient Process for Preparing 4-Methyl-2-phenyl Piperazine Hydrochloride and its Derivatives

Bai Shu GUO, Yu She YANG*, Ru Yun JI

Institute of Materia Medica, Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences,Shanghai 200031

Abstract: An improved method for preparation of 4-methyl-2-phenyl piperazine and its derivatives with higher yield and inexpensive reagents was developed, the products were characterized by ^{1}H-NMR and MS.

Keyword: 4-Methyl-2-phenyl piperazine, mirtazapine, intermediate.

4-Methyl-2-phenyl piperazine **1** and its derivatives are the important intermediates for preparing the tetracyclic compounds like mirtazapine, which is an efficient potent antipressant[1]. To date there have been some known synthetic methods reported for preparation of 4-methyl-2-phenyl piperazine **1** and its derivatives. The method described by Roderick[2, 3] starting from 2-phenyl piperazine which was methylated with methyl iodide (**Scheme 1**, a-b-c'-d'), this step afforded low yields because it was not avoidable to produce the biproduct dimethyl phenyl piperazine. Another route was published by Dolitzky[4], where the piperazine ring was obtained by reaction between beta-chloro-N-methyl-N-chloroethyl and p-toluenesulfonamide, then deprotected the p-toluenesulfonamide to give the product **1**. The overall yield of the two-step was 40% or so, but it is difficult to prepare the starting materials. In this communication, we would like to report our method for preparation of 4-methyl-2-phenyl piperazine and its derivatives as shown in **Scheme 1** (a-b-c-d-e-f). In the process, the key step is protecting the amino group of 3-phenyl-2-piperazone, followed by reduction of **5** with $LiAlH_4$ to give **6**, which was methylated or alkylated, then deproteceted to give the product **1** and its derivatives. The overall yield of **1** from **4** was about 80%. In comparison, compound **1** was obtained in an overall yield of 45% from **4** in rout **1**. It does not need to isolate the intermediate **6**. Moreover, the methylation reagent I not so expensive.

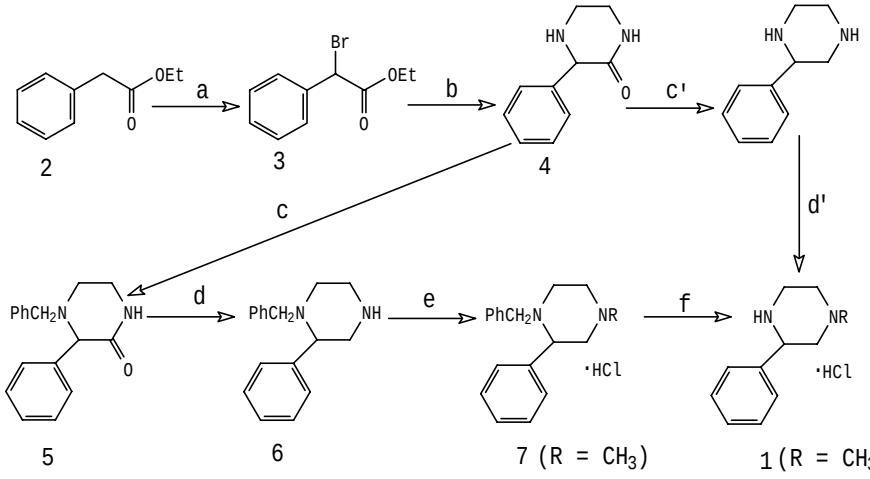
Experimental

*Preparation of 4-benzyl-3-phenyl-piperazone **5***

The mixture of 3-phenyl-2-piperazone **4** (62 g, 0.35 mol) obtained by the reported

*E-mail: ysyang@mail.shcnc.ac.cn

Scheme 1



a: CCl_4, NBS, reflux; b: C_2H_5ONa, C_2H_5OH, acetone, Et_2N, reflux; c: $PhCH_2Br$, toluent, reflux; d: $LiAlH_4$, THF, reflux; e: HCHO/ HCOOH, reflux, HCl; f: Pd/C, CH_3OH, H_2. C': $LiAlH_4$, THF, reflux; d': CH_3I, THF.

methods [lit.[2, 5] mp138-140°C] benzyl bromide (66 g, 0.39 mol), triethylamine (150 mL) and toluene (600 mL) were refluxed for 6 h, and then cooled and filtrated. The solid was collected and suspended in water (200 mL) stirred for 1hr, filtrated and the solid was washed with water, dried under 50°C, yielding 80g (85.4%) of compound **5** as white solid. mp>210°C . ^{1}HNMR($CDCl_3$, δ ppm): 2.53 (m, 1H), 3.01 (m, 1H), 3.23 (m, 2H), 3.54 (m, 1H), 3.76 (m, 1H), 4.09 (m, 1H), 7.19-7.31 (m, 5H), 7.37-7.40 (m, 3H), 7.55 (d, 2H, J=7.33 Hz).

*Preparation of 1-benzyl-2-phenyl piperazine **6***

4-Benzyl-3-phenyl-2-piperazone **5** (80 g, 0.3 mol) was added to the suspension of $LiAlH_4$ (28.5 g, o.75 mol) in anhyrous THF (600 mL) cooled with ice-water bath in portions carefully. The mixture was stirred for 1 h at r.t and refluxed for 20 h. The excess $LiAlH_4$ was destroyed at 0°C with water (28.5 mL) and 20% NaOH (117 mL). After filtration, the filtrate was evaporated to dryness to yield crude 2-phenyl-1-benzyl piperazine **6**, which can be used for the next step without purification.

*Preparation of 1-benzyl-2-phenyl-4-methyl piperazine hydrochloride **7***

Formaldehyde (63.4 mL) and formic acid (88.8 mL) were added to the crude **6** cooled with ice-water bath, the mixture was refluxed for 12 h until no gas ceased. Cooled the mixture to r.t. and 37% HCl was added dropwise to the mixture with stirring for 1hr. the excess formaldehyde and formic acid were evaporated and the residue was recrystallized from ethanol/ethyl acetate (1:1, v/v) yielding **7** 89.2 g as white crystals. The overall

yield of the two steps was 98.4%. mp>200°C. ^{1}HNMR ($CDCl_3$, δppm): 2.17 (t, 1H, J=10.8 Hz), 2.28 (s, 3H), 2.30 (m, 1H), 2.80 (m, 1H), 2.84-2.90 (m, 4H), 3.46 (dd, 1H, J=2.93,10.52 Hz), 3.81 (d, 1H, J=13.55 Hz), 7.20 (m, 1H), 7.22-7.30 (m, 5H), 7.35 (t, 2H J=6.96 Hz), 7.50 (d, 2H, J=6.59 Hz).

*Preparation of 1-mehyl-3-phenyl piperazine hydrochloride **1***

The mixture of **7** (89.2 g, 0.3 mol), 10% Pd/C (4.0 g) and methanol (500 mL) was hydrogenated with H_2 at r.t under normal pressure with stirring for 5 h, filtrated and the filtrate was evaporated to dryness. The residue was recrystallized from ethanol-ethylacetate (1:1, v/v) to yield 1-methyl-3-phenyl piperazine hydrochloride **1** 59.7 g (95.3%) as white crystals. mp>200°C. ^{1}HNMR ($CDCl_3$, δppm): 2.38 (s, 3H), 2.52 (m, 2H), 2.93 (m, 2H), 3.08 (m, 2H), 4.07 (dd, 1H, J=10.71,2.74 Hz), 7.26-7.34 (m, 3H), 7.47 (m, 2H). MS: 176 (M-HCl).

References

1. H. Koch, *Drugs of future*，**1989**, 14, 1211.
2. W. R. Roderrick, H. J. Plattle, G.B. Pollard *et al.*, *J. Med. Chem.*, **1966**, *9*, 181-185.
3. J. S. Richard, R. M. James, *et al*. *Heterocycles*, **1989,** *29*, 359-363.
4. B. Z. Dolitzky, *WO* 0063185 (**2000**), **1999** (C A.133: P321902e)
5. J. W. Epstein, H. J. Brabander, W.J. Fanshawe, *et al*., *J. Med. Chem.*, **1981**, *24*, 481-490.

Received 4 June, 2002