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Psychotropic Agents. VI.[1] An Improved Synthetic Method for 4′-Fluoro-4-[4-(2-thioxo-1-benzimidazolinyl)piperidino]butyrophenone

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The title compound (**8**) was prepared by two improved methods. Initially, the 4-aminopiperidine derivative (**11**) was prepared by treatment of 4-aminopyridine (**9**) with the aralkyl chloride (**5**), followed by $NaBH_4$ reduction of the resulting 4-aminopyridinium salt (**10**). Reaction of **11** with 2-chloronitrobenzene gave the intermediate (**6**).[2]

Subsequently, the key intermediate (**7**)[2] was similarly prepared starting from 4-chloropyridine (**12**) *via* the pyridinium salt (**14**). In this method the target compound (**8**) was prepared in good yield with the technical advantage that the four steps (**13**→**14**→**7**→**8**) could be conveniently carried out in a one-pot procedure.

Keywords——butyrophenone; 1-phenyl-1-butanone derivative; neuroleptics; 2-thioxobenzimidazoline derivative; pyridinium salt; one-pot reaction

A previous paper[2] from our laboratory reported the synthesis of 4′-fluoro-4-[4-(1-benzimidazolinyl)piperidino]butyrophenone derivatives. Among them, Timiperone, 4′-fluoro-4-[4-(2-thioxo-1-benzimidazolinyl)piperidino]butyrophenone (**8**), was found to have a potent neuroleptic activity in pharmacological evaluations.[2,3a–c] Further progress of clinical trials[4] of the agent prompted us to search for a practical synthetic method for **8**. We report here two procedures for the more convenient synthesis of **8**.

The compound (**8**)[2] was previously prepared in 12 steps starting from benzylamine (**1**) *via* the intermediates (**2**,[5] **3**,[6] **4**,[7] **6** and **7**), as shown in Chart 1. However, the procedure was not satisfactory for technical production of **8** because of the multiple steps and the low overall yield. With the aim of developing a more facile synthetic method for **8**, the following two alternative processes were investigated as shown in Chart 1.

It has been reported[8] that 4-amino-1-alkylpiperidine derivatives are obtained in excellent yields by alkylation of 4-aminopyridine, followed by sodium borohydride reduction of the resulting 1-alkyl-4-aminopyridinium salts. This method was thought to be applicable to the synthesis of the key intermediate, 1-[3-(4-fluorobenzoyl)propyl]-4-(2-nitroanilino)piperidine ethylene acetal (**6**). Alkylation of 4-aminopyridine (**9**) with 4-chloro-1-(4-fluorophenyl)-1-butanone ethylene acetal (**5**) gave the pyridinium salt (**10**) in good yield, and this was further hydrogenated with sodium borohydride in aqueous ethanol to give 4-amino-1-[3-(4′-fluorobenzoyl)propyl]piperidine ethylene acetal (**11**) (79.2%). The compound (**11**) was also prepared by catalytic hydrogenation of **10** in the presence of Raney Ni under 100 atmospheres pressure in 91.5% yield. Reaction of **11** with 2-chloronitrobenzene in the presence of Na_2CO_3 afforded the key intermediate (**6**) (61.8%), which was identical with the substance prepared by the method described previously.[2]

As an extension of the method described above, 4-(2-aminoanilino)pyridine (**13**)[9] was similarly converted to the piperidine derivative (**7**) by alkylation with **5**, followed by sodium borohydride reduction of the resulting pyridinium salt (**14**). As the isolations of the two intermediates (**14**, **7**) were troublesome and lowered the yields, the four reaction steps (**13**→**14**→**7**→**8**) were carried on in a one-pot procedure to give the desired butyrophenone (**8**), which was identified by mixed melting point test and comparison of its infrared (IR) spectrum with that of an authentic sample[2] prepared previously. The overall yield of **8** from **13** was 58.5%.

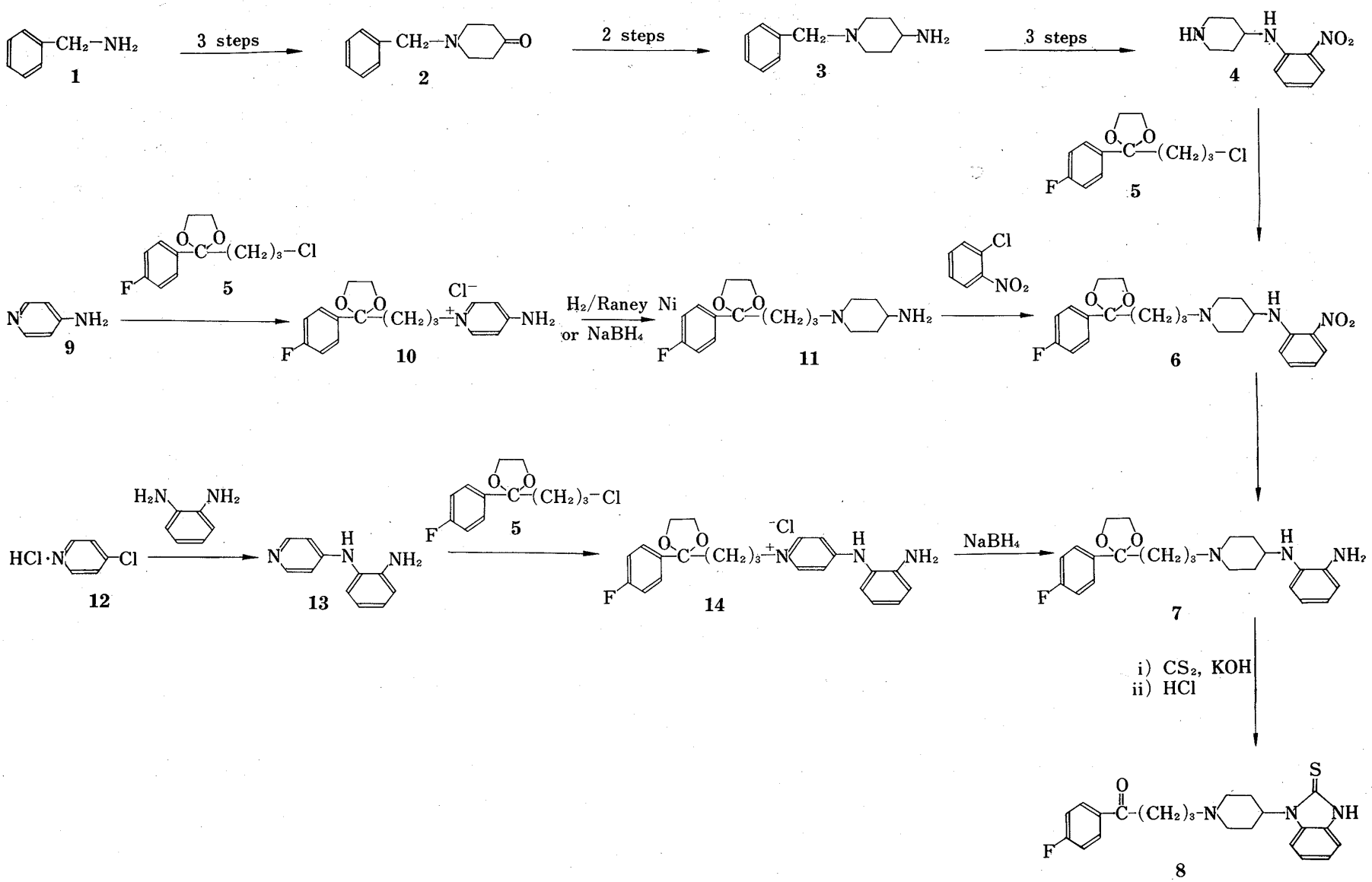

Chart 1

This new method not only provides a good overall yield but is also operationally more convenient than that reported previously.[2)]

Experimental

The following instruments were used. Infrared (IR) spectra, a Hitachi model 285 infrared spectrophotometer; nuclear magnetic resonance (NMR) (tetramethylsilane as an internal standard), a Hitachi R-20B spectrometer (60 MHz); melting points, a Yanagimoto melting point apparatus (Type MP-1). All melting points are uncorrected.

4-Amino-1-[3-(4-fluorobenzoyl)propyl]pyridinium Chloride Ethylene Acetal (10)——A mixture of 4-aminopyridine (**9**) (4.71 g, 0.05 mol), 4-chloro-1-(4-fluorophenyl)-1-butanone ethylene acetal (**5**) (12.24 g, 0.05 mol) and xylene (20 ml) was heated under reflux for 4 h with stirring, then cooled. The resulting precipitate was collected by filtration and washed with benzene to give pale brown crystals of **10**, which were used for the next step without further purification. Yield 14.72 g (86.9%); mp 207—210°C; IR ν_{max}^{KBr} cm^{-1}: 1640 (C=NH); NMR (δ in DMSO-d_6): 1.77 (4H, broad, $-C\underline{H}_2-C\underline{H}_2-CH_2-\overset{+}{N}$⟨○⟩), 3.6—4.05 (4H, m, ethylene acetal), 4.13 (2H, m, $-C\underline{H}_2-\overset{+}{N}$⟨○⟩), 6.93 (2H, d, J=8 Hz, $-\overset{+}{N}$⟨○⟩$-NH_2$), 7.1—7.55 (4H, m, $-$⟨○⟩$-F$), 8.21 (2H, d, J=8 Hz, $-\overset{+}{N}$⟨○⟩).

4-Amino-1-[3-(4-fluorobenzoyl)propyl]piperidine Ethylene Acetal (11)——(ex. 1): A mixture of the pyridinium salt (**10**) (3.39 g, 0.01 mol) and Raney Ni (10 ml) in EtOH (20 ml) was subjected to catalytic hydrogenation at an initial pressure of 100 atm at 100°C for 19 h. After cooling, the reaction mixture was filtered and the filtrate was concentrated. The residue was made alkaline with 10% NaOH and extracted with $CHCl_3$. The organic layer was washed with water, dried over Na_2SO_4 and concentrated to give **11** as a pale yellow oil (2.82 g, 91.5%). IR ν_{max}^{neat} cm^{-1}: 3350 (NH_2). NMR (δ in $CDCl_3$): 1.0—3.0 (17H, m, $-(CH_2)_3-\overset{+}{N}$⟨⟩$-NH_2$), 3.6—4.2 (4H, m, ethylene acetal), 6.98 (2H, t, J=9 Hz, $-$⟨○⟩$-F$), 7.4 (2H, q, J=9, 5.5 Hz, $-$⟨○⟩$-F$).

(ex. 2): $NaBH_4$ (757 mg, 0.02 mol) was added portionwise with stirring over 15 min to a solution of the pyridinium salt (**10**) (3.39 g, 0.01 mol) in EtOH (20 ml) and H_2O (10 ml), and the mixture was heated under reflux for 1 h, then cooled. Further $NaBH_4$ (757 mg, 0.02 mol) was added to the reaction mixture. The mixture was stirred for 30 min at room temperature, and heated under reflux for an additional 2 h, then concentrated to give a pasty residue. The residue was dissolved in $CHCl_3$ and H_2O, and the separated organic layer was washed with water, dried over Na_2SO_4 and concentrated to dryness. Et_2O was added to the residue and the insoluble precipitate was filtered off. The filtrate was concentrated to give **11** as a pale yellow oil (2.44 g, 79.2%), whose structure was confirmed by comparison of its IR spectrum with that of a sample prepared in ex. 1.

1-[3-(4-Fluorobenzoyl)propyl]-4-(2-nitroanilino)piperidine Ethylene Acetal (6)——A mixture of **11** (2.82 g, 9.15 mmol), 2-chloronitrobenzene (2.73 g, 17.3 mmol), Na_2CO_3 (498 mg, 4.7 mmol), KI (50 mg) and BuOH (2 ml) was heated under reflux for 31 h. The reaction mixture was dissolved in $CHCl_3$ (30 ml) and 5% NaOH (20 ml), and the separated aqueous layer was extracted with $CHCl_3$ (30 ml×2). The combined organic layers were washed with water, dried over Na_2SO_4 and concentrated to give a residue, which was chromatographed on silica gel (40 g) with benzene and $CHCl_3$. The $CHCl_3$ eluates were combined and concentrated to give yellow crystals, which were recrystallized from Et_2O–hexane to afford **6** as yellow crystals (2.43 g, 61.8%), mp 78—80°C. The structure of **6** was confirmed by comparison of its IR spectrum with that of an authentic sample prepared from **4** previously.[2)]

4-(2-Aminoanilino)-1-[3-(4-fluorobenzoyl)propyl]pyridinium Chloride Ethylene Acetal (14)——A mixture of 4-(2-aminoanilino)pyridine (**13**)[9)] (1.11 g, 6 mmol), 4-chloro-1-(4-fluorophenyl)-1-butanone ethylene acetal (1.35 g, 5.5 mmol) and xylene (2 ml) was heated under reflux for 13 h with stirring, then cooled. The solvent was removed by decantation, and benzene (5 ml) was added to the residue. The mixture was heated under reflux for 30 min and cooled. The solvent was removed by decantation, and the residue was dissolved in hot water (30 ml). The cooled solution was washed with AcOEt, and the aqueous layer was extracted with $CHCl_3$. The $CHCl_3$ layer was washed with water, dried over Na_2SO_4 and concentrated to give a pale yellow oil, which was triturated with Et_2O to afford **14** as a pale yellow powder (1.83 g, 77.4%). IR ν_{max}^{KBr} cm^{-1}:

3300, 3180 (NH_2), 1640 (C=N). NMR (δ in $CDCl_3$): 1.86 (4H, broad, $-(C\underline{H}_2)_2-CH_2-\overset{+}{N}\bigcirc-$), 3.6—4.1 (4H, m, ethylene acetal), 4.24 (2H, m, $-C\underline{H}_2-\overset{+}{N}\bigcirc-$), 6.46—7.6 (10H, m, aromatic ring protons), 8.11 (2H, d, $J=7$ Hz, α-protons of pyridine).

4′-Fluoro-4-[4-(2-thioxo-1-benzimidazolinyl)piperidino]butyrophenone (**8**)——A mixture of 4-(2-aminoanilino)pyridine (**13**)[9] (1.11 g, 6 mmol), 4-chloro-1-(4-fluorophenyl)-1-butanone ethylene acetal (**5**) (1.22 g, 5 mmol) and BuOH (2 ml) was heated under reflux for 2 h with stirring, then cooled. After addition of EtOH (8 ml) and H_2O (5 ml) to the reaction mixture, $NaBH_4$ (568 mg, 15 mmol) was added portionwise, and the whole was stirred for 30 min at room temperature and then heated under reflux for 1 h. Further $NaBH_4$ (568 mg, 15 mmol) was added to the cooled reaction mixture, and the whole was heated under reflux for an additional 1.5 h, and cooled. KOH (842 mg, 15 mmol), CS_2 (1.14 g, 15 mmol) and EtOH (3 ml) were added to the reation mixture and stirring was continued for 3 h under reflux. The reaction mixture was cooled in an ice-bath and acidified with concentrated HCl (6 ml). The mixture was heated again under reflux for 20 min. After cooling, the reaction mixture was made basic with 5% NaOH and extracted with $CHCl_3$. The organic layer was washed with 10% NaOH solution and water, dried over Na_2SO_4 and concentrated. The residue was chromatographed on silica gel with $CHCl_3$. Removal of the solvent gave a pale yellow solid, which was recrystallized from acetone to afford **8** (1.16 g, 58.5%), mp 201—203°C. The structure of **8** was confirmed by comparison (IR spectra and mixed melting point test) with an authentic sample synthesized previously.[2]

References and Notes

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