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An Efficient Synthesis of Risperidone *via* Stille Reaction: Antipsychotic, 5-HT_2, and Dopamine-D_2-Antagonist

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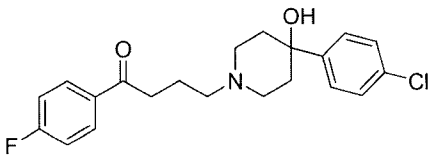
Risperidone has been reported to have neuroleptic activity. In this study, risperidone was synthesized using a new method involving a stille reaction, in which 2-methyl-3-vinyl-6,7,8,9-tetrahydropyrido[1,2-a]pyrimidin-4-one was synthesized (**5**). The chemical synthesis process was found to be simple and produced risperidone in a high yield. In addition, can be easily scaled up for large scale synthesis.

Key words: Risperidone, Stille reaction, Synthesis, Antipsychotic, 5-HT_2, Dopamine-D_2-antagonist

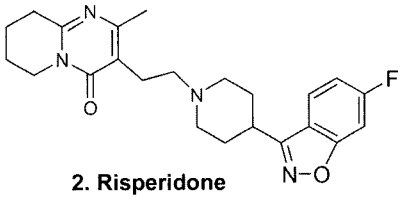
INTRODUCTION

Schizophrenia is a complex disorder affecting approximately 1% of the population (Reynold *et al.*, 1992). Classical neuroleptics used in its treatment, such as haloperidol 1, are largely ineffective against its negative symptoms. Furthermore, these classical antipsychotics have severe side effects, notably acute extrapyramidal symptoms(EPS), which appear to be an unavoidable consequence of their mechanism of action. Risperidone 2 (Niemegeers *et al.*, 1988) is a member of a new group of 'atypacal' or non-classical antipsychotics that cause no EPS and are effective against the negative symptoms of schizophrenia (Filton *et al.*, 1990). Since risperidone blocks not only the dopamine receptors (Sanders *et al.*, 1996) but also the subtype 5-HT_2A serotonin receptors, it is believed that its atypical activity profile may be due to its effect on an interaction between the serotonin and dopamine system (Enrique *et al.*, 2001). Their representative chemical structures are shown in Fig. 1.

The original method for synthesizing risperidone produced a low yield, and uses DMF as a solvent, which is difficult to remove and harmful to the human body. Our synthetic method improves this week point as difficult to remove solvent. The most important step in this process is the alpha-halogenation and stille reaction. This reaction uses Br_2 and the tributyl (vinyl), stannane and Pd $(PPh_3)_4$

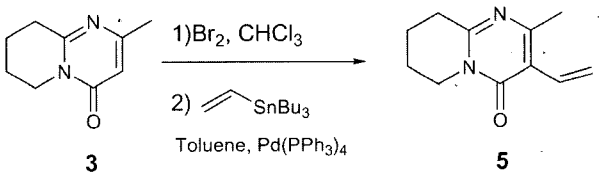


1. Haloperidol



2. Risperidone

Fig. 1. Structure of classical and non-classical neuroleptics



3 **5**

Scheme 1. Risperidone synthesis using the stille reaction

via a stille reaction at room temperature.

This paper describes the synthesis of Risperidone, beginning from readily available pyridin-2-amine (**1**) and 1-(4-(2,4-difluorobenzoyl)piperidin-1-yl)ethanone (**6**).

MATERIALS AND METHODS

All the reactions were carried out under an inert

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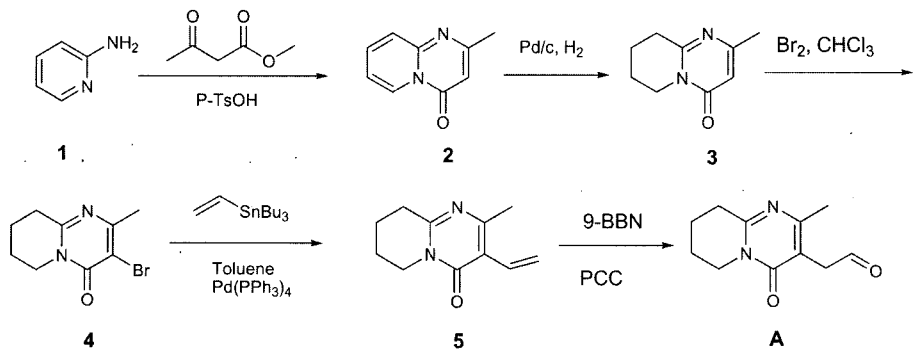
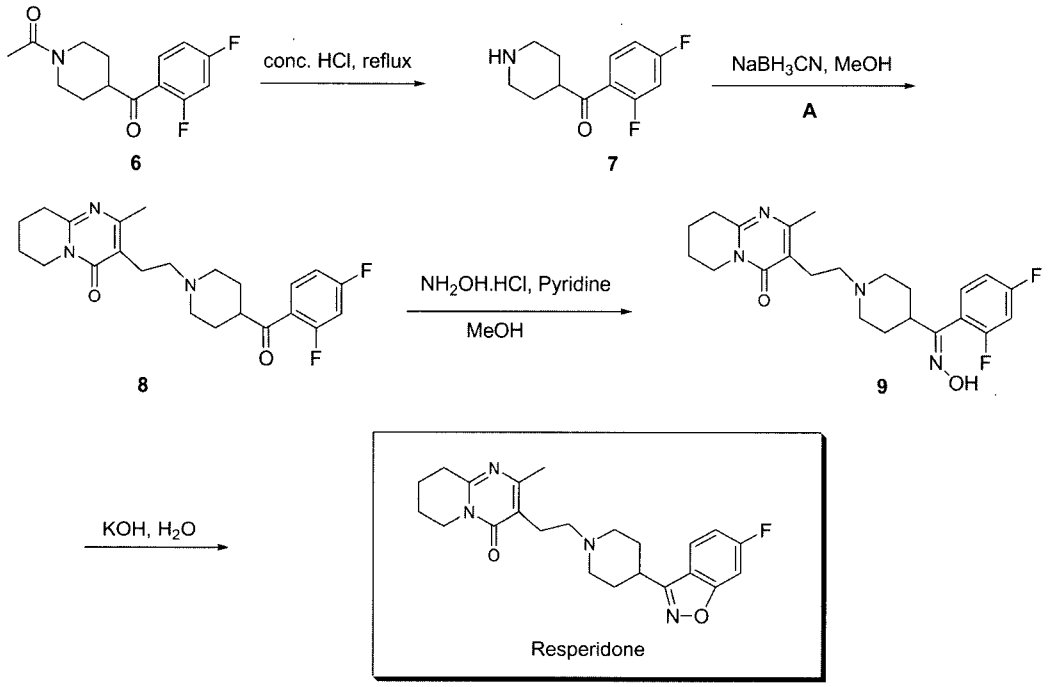


Scheme 2. Synthesis of compound A



Scheme 3. Synthesis of risperidone

atmosphere (N_2) and at room temperature unless stated otherwise. The solvents and reagents were obtained commercially and were used without further purification. All the reported yields are of the isolated products and were not optimized. The reactions were routinely monitored by thin-layer chromatography (TLC) on silica gel (pre-coated F_{254} Merck plates). The infrared spectra (IR) were measured on a Jasco FT-IR instrument. The ^{1}H-NMR, ^{13}C-NMR were determined in $CDCl_3$ and D_2O solutions using a Varian Gemini 200 spectrometer. The peaks positions are given in parts per million (δ) downfield from tetramethylsilane as the internal standard, with multiplicities reported in the usual manner and J values given in hertz. Flash chromatography was performed using Merck 60-200 mesh silica gel. Mass spectrometry was performed at the KOREA Univ. Mass Spectroscopy center.

2-Methyl-4*H*-pyrido[1,2-a]pyrimidin-4-one (2)

2-Amino pyridine (4.0 g) was added to a well stirred solution of methyl acetoacetate (5.4 g) and *p*-TsOH (0.2 g) in toluene (100 mL). The reaction mixture was distilled at 104-105°C/12 h, cooled to room temperature and washed with a sat.$NaHCO_3$ solution. The organic layer was dried over $MgSO_4$, concentrated at reduced pressure to give crystal product **2** (6.5 g, 95%). m.p. 150-151°C; ^{1}H-NMR (200 MHz, $CDCl_3$), δ (ppm): 9.05 (d, 1H), 7.75 (d, 1H), 7.62 (m, 1H), 7.15 (m, 1H), 2.48 (s, 3H); MS (FAB); 160.06 (M^++H^+).

2-Methyl-6,7,8,9-tetrahydropyrido[1,2-a]pyrimidin-4-one (3)

A stirring mixture of compound **2** (30 g) and Pd/C (2 g) in 6N HCl (20 mL) was hydrogenated under a 125 psi

pressure at room temperature for 18 h. The resulting mixture was filtered through celite and the organic solution was concentrated at a reduced pressure to give compound **3** (18 g, 74%). m.p. 148-150°C; ^{1}H-NMR (200 MHz, $CDCl_3$), δ (ppm): 6.17 (s, 1H), 3.93 (t, 2H, *J*=5.82 Hz), 2.92 (t, 2H, *J*=6.6 Hz), 2.24 (s, 3H), 1.98~1.88 (m, 4H); MS (FAB); 164.08 (M^++H^+).

3-Bromo-2-methyl-6,7,8,9tetrahydropyrido[1,2a]-pyrimidin-4-one (4)

Compound **3** (30 g) was dissolved in CH_3Cl (100 mL) at 0°C. Br_2 (31.6 g) was added to this solution dropwise over a 1h period and stirred at room temperature for 3 h. The resulting reaction mixture filtered and solution washed with 20% Sodium thiosulfate. The organic layer was concentrated at reduced pressure to give compound **4** (32.5 g, 73%). m.p. 219-221°C; ^{1}H-NMR (200 MHz, $CDCl_3$), δ (ppm): 3.99 (t, 2H, *J*=12.36 Hz), 2.87 (t, 2H, *J*=13.24 Hz), 2.44 (s, 3H, *J*=9.01 Hz), 1.98~1.88 (m, 4H); MS (FAB); 242.01 (M^++H^+).

2-Methyl-3-vinyl-6,7,8,9-tetrahydropyrido[1,2-a]-pyrimidin-4-one (5)

The obtained compound **3** was dissolved in THF (20 mL). tributyl(vinyl)stannane (1.3 g) and $Pd(PPh_3)_4$ (0.08 g) in toluene (20 mL) was added to this solution. The reaction mixture was heated 100-105°C for 15 h, cooled to room temperature and filtered through celite. The solvent removed and evaporated. The residue was chromatographed on a silica gel column to give compound **5** (0.78 g, 83%). m.p. 180-183°C; ^{1}H-NMR (200 MHz, $CDCl_3$), δ (ppm): 6.63 (t, 1H, *J*=13.38 Hz), 6.25 (d, 1H, *J*=17.95 Hz), 5.49 (d, 1H, *J*=12.94 Hz), 3.96 (t, 2H, *J*=5.97 Hz), 2.88 (t, 2H, *J*=6.56 Hz), 2.36 (s, 3H), 1.95~1.8 8(m, 4H); MS (FAB); 190.1 (M^++H^+).

2-(2-Methyl-4-oxo-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]-pyrimidin-3-yl)acetaldehyde (A)

Compound **5** (1.3 g) was dissolved in 20 mL THF and a solution (6.2 mL) of 9-BBN in THF (0.5M) was added with constant stirring at 60°C for 3 h. The reaction mixture cooled to room temperature, added to PCC (5.0 g) in CH_2Cl_2 (50 mL) and stirred at 90-98°C for 3 h. The resulting was cooled to room temperature and concentrated under reduced pressure to the give crude product. The crude product was purified using chromatography on silica gel column to give the product **A** (0.74 g, 53%). m.p. 224-226 °C, ^{1}H-NMR (200 MHz, $CDCl_3$), δ(ppm): 9.58 (s, 1H), 7.15 (m, 1H), 3.81 (t, 2H), 3.53 (s, 2H), 2.78 (t, 2H), 2.10 (s, 3H), 1.90~1.88 (m, 4H); MS (FAB); 206.2 (M^++H^+).

3-(2-(4-(2,4-Difluorobenzoyl)piperidin-1-yl)ethyl)-2-methyl-6,7,8,9-tetrahydropyrido[1,2-a]pyrimidin-4-one (8)

$NaBH_3CN$ (1.1 g) and AcOH (0.1 mL) was added to a stirred solution of compound **7** (2.5 g) in MeOH (10 mL). Compound A (1.2 g) was added to this solution over a 5min period and the resulting slurry was stirred at room temperature for 6 h. The reaction was quenched with water (1.0 mL), and the solvent was removed and evaporated. The residue was chromatography on silica gel column to give product **8** (2.3 g, 88%). m.p. 466-467 °C ^{1}H-NMR (200 MHz; D_2O), δ (ppm): 7.85~8.0 (m, 1H), 7.05~7.20 (m, 2H), 4.0 (t, 2H), 3.85 (m, 2H), 3.65 (m, 1H), 3.20~3.35 (m, 4H), 3.20 (t, 2H), 2.90~3.10 (m, 2H), 2.45 (s, 3H), 2.20~2.40 (m, 2H), 1.80~2.10 (m, 6H); MS (FAB); 414 (M^++H^+).

(*Z*)-3-(2-(4-((2,4-Difluorophenyl)(hydroxyimino)methyl)-piperidin-1-yl)ethyl)-2-methyl-6,7,8,9-tetrahydropyrido [1,2-a]pyrimidin-4-one (9)

Compound **8** was added to a well stirred solution of $NH_2OH.HCl$ (1.6 g) and pyridine (20 mL) in MeOH. The reaction mixture was heated at 100~110°C for 8 h, cooled to room temperature and solvent was evaporated. After removing the solvent, the residue was redissolved in CH_2Cl_2 (100 mL), washed with sat. NaCl (20 mL), dried over $MgSO_4$ and evaporated *in vaccuo* to dryness. The residue was purified by chromatography to give crystal form compound **9** (1.4 g, 64%). ^{1} H-NMR (200 MHz, $CDCl_3$), δ (ppm): 10.80 (s, 1H), 7.20 (m, 1H), 6.90 (m, 2H), 3.90 (t, 2H), 3.10 (m, 2H), 3.65 (m, 1H), 2.80 (t, 2H), 2.70 (m, 2H), 2.20 (m, 3H), 1.70~2.10 (m, 10H); MS (FAB); 431.23 (M^++H^+).

3-(2-(4-(6-Fluorobenzo[d]isoxazol-3-yl)piperidin-1-yl)-ethyl)-2-methyl-6,7,8,9-tetrahydropyrido[1,2-a]pyrimidin-4-one (Risperidone)

Compound **9** was dissolved in 30% KOH and stirred at 120°C for 5 h, cooled to room temperature and then the solution was extracted with several portion of CH_2Cl_2 and the combined organic phase was washed with water, dried over $MgSO_4$ and evaporated *in vaccuo* to dryness. The crude product was purified by flash column chromatography as an eluent to obtain the pure final product. (1.4 g, 64%); m.p. 547-548°C ^{1}H-NMR (200 MHz, $CDCl_3$), δ (ppm): 7.65~7.61 (m, 1H), 7.18~7.14 (m, 1H), 7.00~6.94 (m, 1H), 3.87~3.83(m, 2H), 3.42~3.07 (m, 2H), 2.97~3.02 (m, 1H), 2.81~2.76(m, 2H), 2.71~2.66 (m, 2H), 2.48~2.43 (m, 1H), 2.23 (s, 3H), 2.34~2.19 (m, 2H), 2.05~2.01 (m, 4H), 1.87~1.79 (m, 4H); MS (FAB); 410.2163 (M^++H^+).

RESULTS AND DISCUSSION

An efficient synthetic pathway was developed for synthesizing risperidone. In particular, it was possible to obtain an 88% yield with reductive reaction of compound A and **7** using a methanol solvent. At this time the reducing reagents, $NaBH_4$, $NaBH_3CN$, $Pd/C/H_2$, and $LiAlH_4$, were used but the result was found to be most efficient using $NaBH_3CN$ in MeOH, EtOH, water and ether. The olefin compound **5** could undergo hydroboration and oxidation to compound A in the 9-BBN and PCC condition. The best condition for hydroboration was to use 9-BBN in a THF solution. The next oxidation step to obtain the target product A from the hydroboration compound was accomplished using PCC at *in situ*. The hydroboration of terminal alkenes, followed by PCC oxidation, is a direct convenient method for the transformation of alkenes into the corresponding aldehydes (Archana *et al.*, 1994; Herbert *et al.*,1986). The synthesis of the final compound was accomplished using the intramolecular displacement of halogen by the oxime (Joseph *et al.*, 1985). This could be achieved by refluxing the ketone, compound **8**, with potassium hydroxide, hydroxylamine hydrochloride and water to yield the desired heterocyclic compound.

The high yield, reaction conditions and easy workup procedure make this a highly convenient method for risperidone synthesis synthesizing risperidone.

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