An Efficient Synthesis of Risperidone via Stille Reaction: Antipsychotic, 5-HT₂, and Dopamine-D₂-Antagonist

Dong-myung Kim¹², Min-Seok Kang¹, Jeong Sook Kim¹, and Jin-Hyun Jeong¹²
¹PDT Bio Co. Ltd. and ²College of Pharmacy, Kyung Hee University, Seoul 130-701, Korea

(Received June 20, 2005)

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-HT₂, Dopamine-D₂-antagonist

INTRODUCTION

Schizophrenia is a complex disorder affecting approximately 1% of the population (Reynolds 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 'atypical' 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-HT₂A 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 weak point as difficult to remove solvent. The most important step in this process is the alpha-halogenation and stille reaction. This reaction uses Br₂ and the tributyl (vinyl) stannane and Pd (PPh₃)₄ via a stille reaction at room temperature.

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-difluorobenzyl)piperidin-1-yl)ethanone (6).

MATERIALS AND METHODS

All the reactions were carried out under an inert
atmosphere (N₂) 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 F₂₅₄ Merck plates). The infrared spectra (IR) were measured on a Jasco FT-IR instrument. The ¹H-NMR, ¹³C-NMR were determined in CDCl₃ and D₂O 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-4H-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.NaHCO₃ solution. The organic layer was dried over MgSO₄, concentrated at reduced pressure to give crystal product 2 (6.5 g, 95%). m.p. 150-151°C; ¹H-NMR (200 MHz, CDCl₃): 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⁺).

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