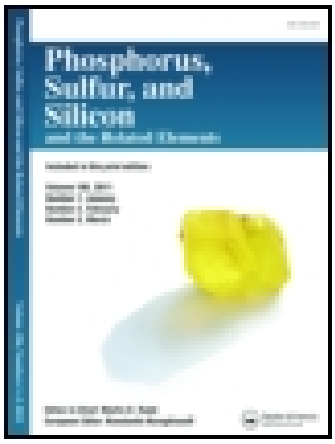

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Pyrophosphoryl Chloride: A Green, Reductive Chlorination Reagent Utilized in the One-Pot Synthesis of Quetiapine

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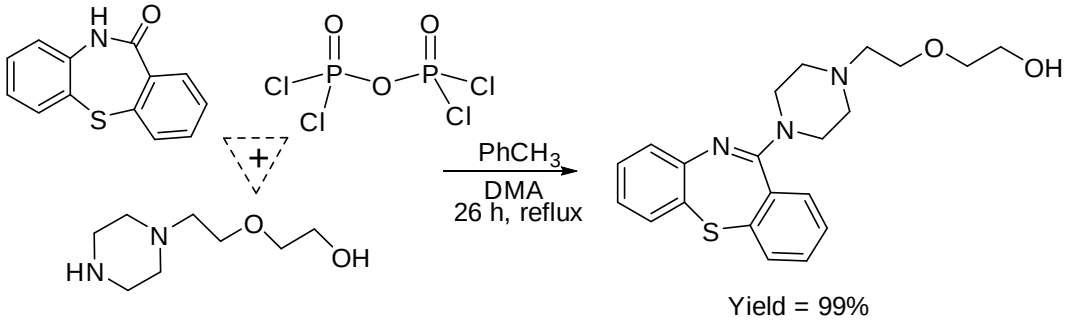
Abstract *A one-pot synthesis of quetiapine from dibenzo[b,f][1,4]thiazepin-11(10H)-one and 4-hydroxyethoxy ethyl piperazine (HEEP) in toluene using N,N-dimethylaniline (DMA) and pyrophosphoryl chloride ($P_2O_3Cl_4$) as a green reductive chlorination agent is described . A significant shortening of reaction times, a nearly quantitative yield, and high atom economy in the product were observed. The simplicity of the reaction, ease of execution, simple workup, and good yields, together with the use of easily accessible starting materials and an environmentally friendly procedure, are hallmarks of this process.*



Keywords One-pot synthesis; Quetiapine, Pyrophosphoryl chloride; Antipsychotic; 4-Hydroxyethoxy ethyl piperazine (HEEP)

INTRODUCTION

Quetiapinefumarate, a 2:1 salt of 2-[2-(4-dibenzo[b,f][1,4]thiazepin-11-yl-1-piperazinyl)ethoxy]ethanol with fumaric acid is one of the most widely used antipsychotic drugs. The salt is a white crystalline powder that is moderately soluble in water. Quetiapine in tablet form contains either 50,100, 200, or 300 mg of the active substance.

Quetiapine acts as an antagonist for multiple neurotransmitter receptor sites, including serotonin ($5HT_{1A}$; $5HT_{2A}$), dopamine (D_1; D_2), histamine (H_1), and adrenaline (Alpha1; Alpha2) in the brain, as an antipsychotic agent and as an antischizophrenic. Quetiapine has a lower affinity for D_2 receptors than dopamine, leading to an alternating D_2 blockade, and could contribute to the impressive tolerability profile of the substance. Quetiapine may act on depression through its antagonism of 5-HT_{2A} receptors, and on mania through its antagonism of D_2 receptors. The compound was also found to be useful in the treatment of acute bipolar mania, either as a monotherapy or in combination with other mood stabilizers, and was useful as a monotherapy in acute bipolar depression.[1-14]The initial synthesis of quetiapine was disclosed by Warawa and Migler in a patent issued to ICI (now AstraZeneca) in 1987.[15]

Several other synthetic routes to quetiapine have been reported. Recently a company in Budapest reported an alternative synthesis of quetiapine designed to provide a more economical process.[15-17] As part of our studies towards the development of new routes to the synthesis of medicinal compounds [18–25], we wish to report a facile and efficient route for the one-pot synthesis of quetiapine.

RESULTS AND DISCUSSION

As far as we can tell, the one-pot synthesis of quetiapine in the presence of *N*,*N*-dimethylaniline (DMA) **3** and pyrophosphoryl chloride ($P_2O_3Cl_4$) **4** as a reductive chlorination reagent has not been reported.[26] Pyrophosphoryl chloride **4** previously was used in Vilsmeier formylation and glycolation reactions of nucleophilic aromatic compounds. According to Figure 2, one equivalent of pyrophosphorylchloride **4** can convert two equivalents of **2** in to two equivalents of the chlorinated compound **5** via the in-situ formed active chlorinating agent **6.** Thus, in comparison to the use of other commercially available chlorinating reagents (e.g. $POCl_3$), the reduced amounts of **4** needed will result in a smaller volume of HCl gas being generated.[27] The reaction of phosphoric oxide with phosphorus pentachloride, the latter formed *in situ* from phosphorus and chlorine, provides an excellent route to pyrophosphoryl chloride.

Initially, we examined different bases and solvents to optimize the reaction conditions for preparation of **1** (Figure 3). The results are listed in Table 1. The reaction required more time in the absence of catalyst, generating a low yield of product. Without a catalyst the reaction was incomplete even after 48h (Table 1, entry 1).

In comparison to other bases such as pyridine, piperidine and triethylamine (TEA), *N*,*N*-dimethylaniline (DMA) gave a good yield of product (Table 1, entry 5). Generally, the reaction was incomplete in the presence of inorganic bases such as NaOH, K_2CO_3 and *t*-BuOK. After optimization, intermediate **5** could be prepared in 72% yield from commercially available

starting materials **2** and **4** by refluxing in toluene for 4.5 h in the presence of DMA . The same reaction run in xylene required 7 h reaction time and gave a lower yield (68%) of **5**.

Optimizing this reaction played a keyrole in the design of a one-pot synthesis of quetiapine **1** via a multicomponent reaction of compounds **2**, **3** and **4** in toluene in the presence of DMA (Fig. 2 & Fig. 3) which proceeds in 99% yield. Other attempts to prepare **1** using the isolated intermediate **3** in a two-step process gave only a72% yield of **1**. Thus the one-pot conversion gave a 27% improvement in the yield of **1** when compared to the two-step process.

A nearly quantitative yield, a one-step process with a simple workup, ease of execution (e.g., no isolation of unstable iminochloride **5**), together with the use of the environmentally friendly reagent pyrophosphoryl chloride ($P_2O_3Cl_4$) **4**, are hallmarks of this process.

Previously a two-step synthesis of **1** using NaOH and $POCl_3$ in xylene has been reported to give a 68% yield.[15] The one-pot process described in this work could be easily scaled up for the synthesis of 16.6 g (43.3 mmol) of **1**: **2** (10 g, 44 mmol, 1 equivalent), **4** (7 g, 4.1 mL, 27 mmol, 0.63 equivalent), and DMA (6g, 49 mmol, 1.11 equivalent) were combined in toluene (60 mL), and the mixture was allowed to reflux for 4.5 h at 110 ^{o}C. To the resulting solution containing intermediate **5** was added **3** (29.2 mL, 31 g, 178 mmol, 4 equivalent), and the mixture was allowed to reflux for an additional 21 h at 105 ^{o}C. Conversion to **1** resulted via the nucleophilic aromatic iminochloride substitution reaction of **3** and **5** in the presence of DMA, as shown in Fig. 2 & Fig. 3. The resulting quetiapine free base was isolated and reacted with fumaric acid in a mixture of MeOH and water (pH of 4.5 to 5) to form the corresponding hemifumarate salt. IR,

^{1}H NMR, ^{13}C NMR and mass spectroscopy confirmed the proposed structure for the synthesized quetiapine salt.

EXPERIMENTAL

Products were characterized by comparison of their physical data with those of standard samples. IR spectra were obtained using a Shimadzo 8400-s instrument. NMR data were recorded in DMSO and $CDCl_3$ with a Bruker DRX500 spectrometer. ^{1}H and ^{13}C chemical shifts are reported in ppm (δ) using TMS as an internal reference. Mass spectra were recorded using an ESI method with a Termo-LCQ Deca mass spectrometer. Sample ^{1}H and ^{13}C NMR spectra for quetiapine base and quetiapine hemifumarate are presented in the Supplemental Materials (Figures S 1 – S 4)

Preparation of 11-chloro-dibenzo[b,f][1,4]thiazepine(5)

To a 500 mL three-neck round-bottom flask equipped with a reflux condenser were added dibenzo[b,f][1,4]thiazepin-11(10*H*)-one **2** (10 g, 44 mmol), dry toluene 60 mL, pyrophosphoryl chloride **4 (**4.1 mL, 7g, 27 mmol) and *N*,*N*-dimethylaniline (6g, 49 mmol, 1.11 eq). The resulting white suspension was mixed at 20-25°C for 30 minutes. The reaction mixture was then refluxed at 110-112°C for 4.5 h. At that point the reaction was complete and all starting material had been consumed (yield 72%). The flask temperature was reduced to 25°C slowly.

Preparation of 2-[2-(4-dibenzo[b,f][1,4]thiazepin-11-yl-1-piperazinyl)ethoxy]ethanol (1)

To the same flask containing the iminochloride intermediate **5** was added 4-hydroxyethoxy ethyl piperazine **3** (29.2 mL,31 g, 178 mmol, 4 equivalent) at 25°C. The reaction mixture was refluxed for 21 hours at 105-107 °C. After completion of the reaction the mixture was allowed to cool to room temperature. 100 mL of 5% NaOH solution was added to the reaction mixture over 15

minutes. After 30 min stirring, the organic and aqueous phases were separated. The organic phase was washed with 200 mL of water, the layers separated, and 70 mL of water was added to the organic phase. The product was converted to its water-soluble HCl salt by adding 32% HCl until the pH was between 2 and 3. The aqueous phase was separated and stirred, 80 mL of CH_2Cl_2 added, followed by 25% aqueous NaOH solution until the pH was adjusted to 10-11. The CH_2Cl_2 phase was separated, dried with 5 g of Na_2SO_4, and the CH_2Cl_2 distilled at atmospheric pressure. Quetiapine free base was obtained (16.6 g, 43 mmol, 99% yield).

Preparation of Quetiapine hemifumarate salt

To a 250 mL round-bottom flask containing quetiapine free base (16.6 g, 43 mmol) were added MeOH (70 mL) and activated carbon (1g) for decolorization. The resulting suspension was heated at reflux for 30 min, then was filtered and allowed to cool to 40°C. Once at this temperature solid fumaric acid was added slowly to the solution until the pH was adjusted to 4-5. Quetiapine hemifumarate precipitated after cooling the reaction mixture to 0-5°C. The resulting solid was filtered and dried to yield (16.5 g, 98%) of quetiapine hemifumarat eas a white powder, mp = 173^{o}C.

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Table 1 Optimization of the catalyst

Entry	Catalyst	Time (h)	Yield (%)[b]
1	None	48	21
2	Pyridine	36	54
3	Piperidine	28	70
4	TEA	36	65
5	DMA	25.5	99
6	Inorganic base[a]	48	Incomplete

a) NaOH, K_2CO_3 or *t*-BuOK; b) isolated yield

Figure 1: Structure formula proposed for quetiapinehemifumarate

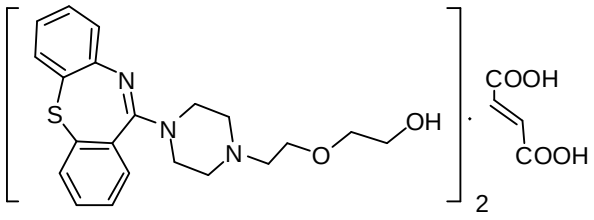

Figure 2 Synthesis of advanced intermediate **5**

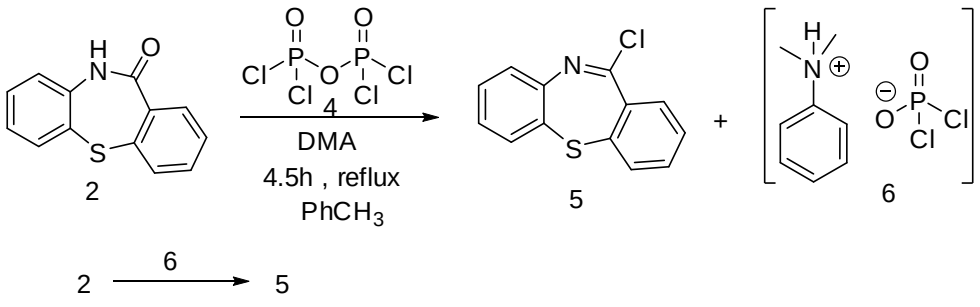

Figure 3 One-Pot Synthesis of Quetiapine **1**