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A New and Simplified Process for Preparing *N*-[4-(3,4-Dichlorophenyl)-3,4-dihydro-1(2H)-naphthalenylidene]methanamine and a Telescoped Process for the Synthesis of (1*S*-*cis*)-4-(3,4-Dichlorophenol)-1,2,3,4-tetrahydro-*N*-methyl-1-naphthalenamine Mandelate: Key Intermediates in the Synthesis of Sertraline Hydrochloride

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Abstract:

***N*-[4-(3,4-Dichlorophenyl)-3,4-dihydro-1(2H)-naphthalenylidene]-methanamine, sertraline imine (3), is an intermediate for the synthesis of Zoloft, sertraline hydrochloride (1). A cleaner, simpler, and more efficient alternative to the Schiff base-mediated formation of sertraline imine has been developed and is presented in this paper. The condensation reaction between 4-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalone, sertraline tetralone (2), and monomethylamine was carried out in ethanol, without the need for classical dehydrating agent, such as $TiCl_4$, or more novel approaches, such as molecular sieves, both of which produce hazardous byproducts and solid wastes. The low solubility of the imine 3 in this type of solvent is exploited, such that the reaction equilibrium favorably enhances the imine formation. Furthermore, an improved and highly selective catalytic reduction of 3 with $Pd/CaCO_3$ catalyst in ethanol as the reaction solvent, followed by the resolution of the racemic cis isomer (6) with D-(−)-mandelic acid results in a more efficient telescoped commercial process to (1*S*-*cis*)-4-(3,4-dichlorophenol)-1,2,3,4-tetrahydro-*N*-methyl-1-naphthalenamine mandelate, sertraline mandelate (4). This new process has been implemented commercially and eliminates the use of hazardous material such as $TiCl_4$, significantly reduces undesirable byproducts, reduces the number of intermediate isolations, and improves the overall process yield and productivity on industrial scale.**

Introduction

Sertraline hydrochloride (**1**) (Figure 1) is an inhibitor of synaptosomal serotonin uptake, an important pharmaceutical agent for the treatment of depression as well as dependency- and other anxiety-related disorders.[1−3] There are a number of approaches reported for the synthesis of **1**, most of them involving D-(−)-mandelic acid as the resolving agent, forming sertraline mandelate (**4**) as the key intermediate.[2,4,5] The first commercial synthesis of **1** implemented at Pfizer involves a condensation reaction of the tetralone **2** with excess of monomethylamine, which is catalyzed by titanium tetrachloride (Scheme 1) to form the imine **3** (Figure 2). The availability of an efficient industrial synthesis for racemic **2**[9] (Scheme 2) makes it the most attractive building block for the synthesis of **1**. The reduction of **3** produces the racemic *syn*- and *anti*-diastereomers of the amine. The desired *syn*-amine is then selectively crystallized and resolved to produce **4** as the D-(−)-mandelic acid salt. This approach, as others reported in the literature,[2,4,5] although effective to complete the transformation from **2** to **4**, uses industrially undesirable reagents and/or produces hazardous byproducts. Control and safe handling of these reagents, including the removal of their byproducts, result in time-consuming operations that affect the efficiency of the commercial process. We herein present a uniquely simple and practicable approach that exploits solubility differences in alkanols to effect the transformation between **2** and **3**. Moreover, telescoping the transformation from **2** to **4**, in a single

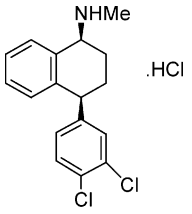

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Figure 1. **Sertraline hydrochloride.**

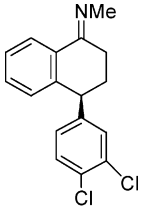

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Figure 2. **Sertraline imine.**

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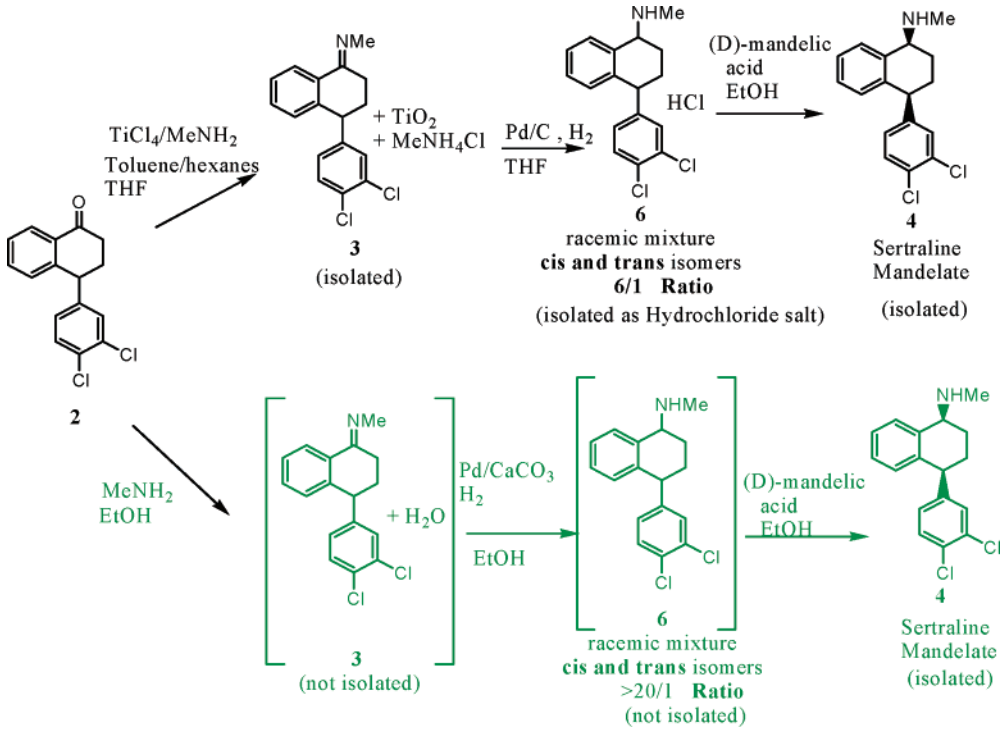
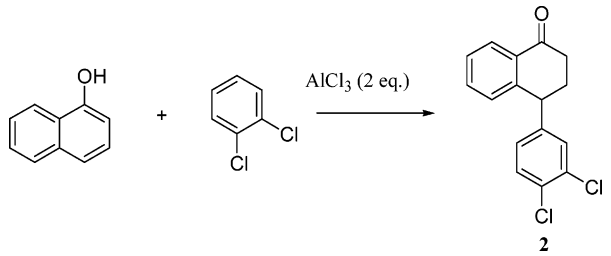
Scheme 1. **Route comparison between the old and new commercial synthesis of Zoloft**



Scheme 2. **Racemic sertraline tetralone synthesis**



common and benign solvent, allowed us to develop a comprehensive process for the synthesis of this key intermediate on the industrial synthesis of sertaline hydrochloride.

Results and Discussion

W. R. Welch et al. described the first synthesis of **1** in 1984.[2] Their process includes the titanium tetrachloride-mediated condensation of **2** with an excess of monomethylamine (5 equiv), producing **3** with titanium oxide and monomethylhydrochloride as insoluble byproducts. In this reaction, titanium tetrachloride is used to remove the water and drive the equilibrium from **2** to **3**. However, the safety concerns (due to extreme reactivity with water) and hazardous byproducts (titanium dioxide and monomethylamine hydrochloride) associated with the use of titanium tetrachloride have prompted evaluation of alternative dehydrating agents that would eliminate the formation of hazardous byproducts. The advantages associated with elimination of solid byproduct formation include not only improved safety but also improved productivity associated with elimination of the need for filtration of the byproduct from the reaction medium. The process of filtering titanium dioxide/monomethylamine hydrochloride on common commercially available isolation devices is very time-consuming due to the small particle size obtained for these two byproducts. An alternative variant was demonstrated by J. Spavins et al. using molecular sieves as the dehydrating agent to drive the equilibrium of **2** to **3**.[5] The appropriate type molecular sieves (specifically, those having a pore size of about 3 Å) are contacted in situ and stirred with the mixture of **2** and monomethylamine to adsorb the water formed from the condensation reaction. Once the desired condensation reaction is essentially complete, the water-saturated molecular sieves must be removed from the product-containing solution by filtration prior to the product isolation. Furthermore, used sieves must typically be regenerated by heating them if they are to be reused. In addition, excess of monomethylamine up to 17 equiv were needed to achieve reaction completion. Other approaches have been used for the synthesis of **3**, but all included the use of other Lewis acids and/or less benign solvents such as DMF.[7,10]

The reduction of **3** has been extensively studied with a variety of reducing conditions used to produce racemic sertraline. Welch et al.[2] used sodium borohydride in toluene as their reducing agent. The borohydride reduction gives a 1:1 diastereomeric mixture of cis and trans with their corresponding enantiomers. In other work, Quallich et al. increased the cis/trans ratio of this reduction to 7:3 by using molecular hydrogen in the presence of 10% Pd/C as the catalyst.[6]

Although the latter method increased the yield of the desired cis isomer, it also promoted aryl ring dechlorination (Figure 3), resulting in the formation of undesired byproducts such as mono- and dechlorinated recemic sertraline. The undesired trans isomer and the over-reduced product require lengthy and yield-consuming crystallizations using large

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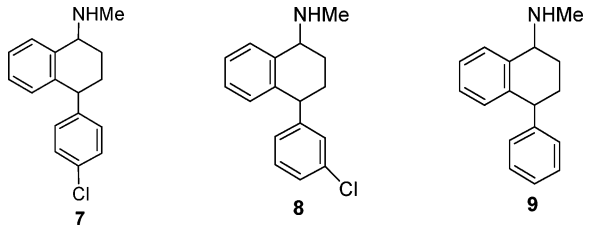

Figure 3. **Mono- and bis-dechlorination impurities.**

Table 1. **Sertraline imine (3) formation in different alcohols**

entry	solvent	temperature (°C)	hours	imine/ketone (%)
1	MeOH	60−65	12	97/3
2	IPO	60−65	10	93/7
3	EtOH	60−65	14	95/5
4	*n*-propanol	100−105	6	93/7

Table 2. **Sertraline imine (3) reduction performance between the old and new process**

entry	catalyst (5%)	cis/trans ratio	total % dechlorination byproducts	% reaction completion	in situ yield (%)
1	Pd/C	≤6/1	1.5	87−92	75−79
2	$Pd/CaCO_3$	>20/1	<1.0	>99	>94

volumes of solvent to effect their removal. Therefore, conditions to further improve this reaction's selectivity, without compromising the quality of the final product, were sought.

Our approach provides a simple method for the conversion of **2** to **3** that avoids the above-described disadvantages associated with the use of titanium tetrachloride. Moreover, the need for addition of a dehydration agent (e.g., titanium tetrachloride or molecular sieves or another such dehydration-promoting additive) is eliminated, as is the associated need for removal of byproducts or spent sieves from the completed reaction mixture. Our approach relies on the low-solubility characteristics of **3** in alkanol solvents to drive the reaction equilibrium to the final product (>95% of **3**, Table 1). More than 99% conversion of **2** to **6** is obtained when the equilibrium is driven further during the in situ reduction of **3** to **6**. To improve the selectivity on this reduction, we screened several catalysts and reaction conditions using a statistical design of experimentation approach (DOE). From this work, we found that using $Pd/CaCO_3$ (1% w/w to **2**) as the catalyst resulted in an improved cis/trans ratio of 20:1 (Table 2). This catalyst not only improved the cis/trans selectivity but also resulted in lower levels of the contaminating mono and deschloro impurities. Moreover, this catalyst was found to perform better in alkanol solvents, thus providing the framework for development of a telescoped process that uses the same solvent for the transformation of **2** to **4** in excellent yield and quality. As shown in Figure 4, the new process reduced the number of solvents from five to two and the total volumes to 24% of the original process.

The combined improvements of the imine formation and a more selective reduction allowed the use of this process to produce **4** on commercial scale with easier handling, greater efficiency, better purity, and lower cost.

With more than 100 metric tons of sertraline hydrochloride being manufactured every year, the improvements described translated to the elimination of 440 tons/year of TiO_2-$MeNH_2$·HCl wet-cake waste and over 40 tons of the unwanted trans isomer waste. In addition, worker safety was enhanced by the elimination of over 140 metric tons $TiCl_4$/year and the reduction of 90 metric tons of monomethylamine.[11]

Conclusions

We have developed an improved commercial process that is a highly efficient with dramatic environmental and worker safety improvements while still sustaining the highest-quality

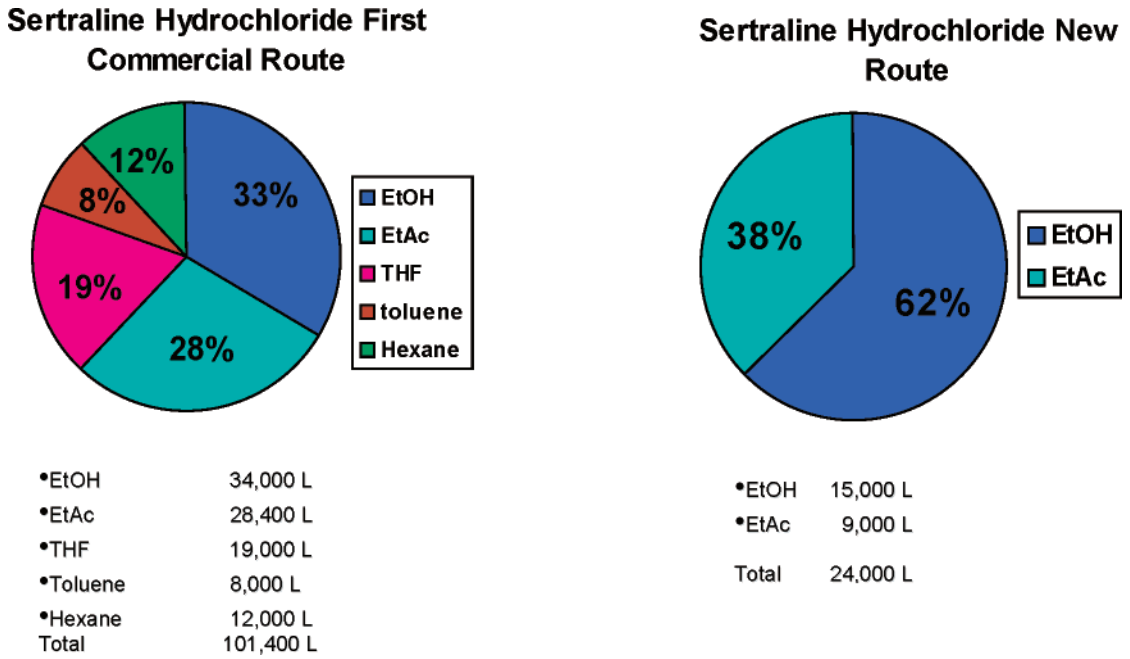

Figure 4. **Comparison of solvent utilization (solvents L/1000 kg of sertraline hydrochloride) between the first commercial route and the new route for Zoloft.**

product standards. The approach demonstrates that efficiency and simplicity are key drivers in enhancing the environmental performance of a large-scale process.[12]

Experimental Section

Solvents and reagents were obtained from commercial sources. NMR spectra were obtained on either a Brucker WM 300 (300 MHz) or a Varian Unity 400 (400 MHz) spectrometer in deuterio-chloroform. Infrared spectra were taken in KBr by diffuse reflectance infrared Fourier transform spectroscopy (DRIFTS).

(1*S*-*cis*)-4-(3,4-Dichlorophenol)-1,2,3,4-tetrahydro-*N*-methyl-1-naphthalenamine Mandelate (4) Formation in Ethanol. Sertraline tetralone (**2**) (63.6 g, 1 mol equiv) is combined with ethanol (anhydrous, 2B, 250 mL) in a suitable pressure-rated vessel equipped with agitation and hydrogen source. The mixture is cooled to 0 °C and monomethylamine (21.1 g, 3.1 mol equiv) added in a subsurface manner. The mixture is warmed to 50−55 °C and stirred under these conditions for approximately 16 h or until >95% conversion to imine has been shown to have occurred by suitable analysis. The mixture is then cooled to 20−22 °C, a palladium/calcium carbonate (Pd/$CaCO_3$) catalyst (1% w/w to tetralone) and decolorizing carbon (2−5% w/w to tetralone) are added, and the mixture is pressurized with hydrogen. The contents are warmed to between 25 and 40 °C to facilitate the rate of hydrogenation. The reaction is continued until hydrogen uptake ceases, or until the reaction mixture is shown to contain no greater than 3% total unreacted **2** and **3**. Upon completion, the mixture is cooled to less than 25 °C, and the carbon and catalyst are removed by filtration. Excess monomethylamine is then removed by vacuum distillation of ethanol, via displacement with fresh ethanol (2B, anhydrous). Once the level of residual monomethylamine is shown to be below 0.1% w/v, mandelic acid is added (30.0 g, 0.9 mol equiv) and the mixture heated to reflux. The desired (1*S*-*cis*)-4-(3,4-dichlorophenol)-1,2,3,4-tetrahydro-*N*-methyl-1-naphthalenamine mandelate is crystallized from the mixture by slow cooling to approximately 5 °C to control the selective crystallization. The product is isolated by filtration and washed with chilled ethanol. Typical yield from **2** to **4** is 40% with respect to input of racemic **2**.

(1*S*-*cis*)-4-(3,4-Dichlorophenol)-1,2,3,4-tetrahydro-*N*-methyl-1-naphthalenamine Mandelate (4) formation in Methanol. Sertraline tetralone **2** (63.6 g, 1 mol equiv) is combined with methanol (250 mL) in a suitable pressure-rated vessel equipped with agitation and hydrogen source. The mixture is cooled to 0 °C and monomethylamine (21.1 g, 3.1 mol equiv) added in a subsurface manner. The mixture is warmed to 50−55 °C and stirred under these conditions for approximately 16 hor until >95% conversion to imine has been shown to have occurred by suitable analysis. The mixture is then cooled to 0−20 °C, Pd/$CaCO_3$ catalyst (1%w/w to **2**) and decolorizing carbon (2−5% w/w to 2) are added, and the mixture is pressurized to approximately 50 psig with hydrogen. The contents are warmed to between 25 and 40 °C to facilitate the rate of hydrogenation. The reaction is continued until hydrogen uptake ceases or until the reaction mixture is shown to contain no greater than 3% total unreacted **2** and **3**. Upon completion, the mixture is cooled to less than 25 °C, and the carbon and catalyst are removed by filtration. Excess monomethylamine is then removed by vacuum displacement of methanol, through displacement with fresh methanol. Once the level of residual monomethylamine is shown to be below 0.1% w/v, mandelic acid is added (30.0 g, 0.9 mol equiv) and the mixture heated to reflux. The desired (1*S*-*cis*)-4-(3,4-dichlorophenol)-1,2,3,4-tetrahydro-*N*-methyl-1-naphthalenamine mandelate is crystallized from the mixture by slow cooling (to control the selective crystallization) to approximately −10 °C. The product is isolated by filtration and washed with chilled methanol. Typical yield from **2** to **4** with methanol as solvent is 36% with respect to input of racemic **2**.

***N*-[4-(3,4-Dichlorophenyl)-3,4-dihydro-1(2*H*)-naphthalenylidene]methanamine (3) in Isopropyl Alcohol.** Sertraline tetralone **2** (165 g, 1 mol equiv) is combined with isopropyl alcohol (700 mL) in a suitable pressure-rated vessel and the mixture cooled to −5 to −10°C. Monomethylamine (60.2 g, 3.4 mol equiv) is added and the mixture heated to 85−100°C for 16 h, whereupon 95% imine conversion is typically seen. The mixture is then cooled to −15°C for 24 h and the product isolated by filtration in approximately 92% yield and 95% purity.

***N*-[4-(3,4-Dichlorophenyl)-3,4-dihydro-1(2*H*)-naphthalenylidene]methanamine (3) in *n*-Propyl Alcohol.** Sertraline tetralone **2** (140 g, 1 mol equiv) is combined with *n*-propyl alcohol (700 mL) in a suitable pressure rated vessel. The mixture is cooled to −5 °C and monomethylamine (100 g, 6.7 mol equiv) added. The mixture is heated to 100 °C and stirred under these conditions for 12 h. After this time, the mixture is cooled to −15 °C and the product isolated by filtration in approximately 92% yield and 95% purity.

Acknowledgment

We dedicate this publication to Dr. Berkeley (Buzz) Cue, who retires as Vice President of Pharmaceutical Sciences, Pfizer Global Research and Development on April 6, 2004. Dr. Cue has been visionary in his support of both industry and academic education regarding the application of environmentally sound chemistry. His legacy to those pursuing the advancement of Green Chemistry is the sense of responsibility he has promoted in the belief that “industry’s commitment to improving health is not complete without a commitment to a healthy environment”. For his efforts in this pursuit, he is sincerely thanked. In addition, the contributions of colleagues in Pfizer Global Research and Development and Pfizer Global Manufacturing Division during the development of this process and all the scale-up activities are greatly appreciated.

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