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Improved Process for the Preparation of 6-Chloro-5-(2-chloroethyl)oxindole

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Abstract:

The current process for ziprasidone involves preparation and isolation of the key intermediate 6-chloro-5-(2-chloroethyl)oxindole. An improved process for the synthesis of this intermediate is reported here. The new process involves use of a novel Lewis acid-mediated selective deoxygenation of the precursor ketone with tetramethyldisiloxane. The new method affords the desired compound in a one-pot process obviating the need for isolation of the potentially hazardous precursor ketone. This process was successfully scaled up to multikilo scale.

Introduction

Ziprasidone hydrochloride is a selective serotonin and dopamine antagonist that is marketed as Geodon by Pfizer.[1] It is an atypical antipsychotic that has good efficacy and safety profile. Ziprasidone hydrochloride is well tolerated and is not associated with any clinically significant weight gain or adverse effects on glycemic control.[2]

The existing process for the preparation of ziprasidone involves preparation of a key intermediate **2**.[3] Here we report an improved process for the preparation of this intermediate.

Results and Discussion

The existing process for the preparation of ziprasidone hydrochloride is shown in Scheme 1. This process involves the preparation of a key intermediate **2** which is then coupled to 3-benzisothiazolylpiperazine, resulting in the formation of ziprasidone free base. The intermediate **2** is prepared from 6-chlorooxindole by a two-step process involving Friedel−Crafts acylation reaction followed by reductive deoxygenation of the chloroketone **1**. In this process the precursor α-chloroketone **1** is first isolated, dried, and then carried forward to the next reduction step.

This chloroketone is known to be a strong skin sensitizer. The manufacture and handling of this intermediate on large scale is potentially hazardous. Due to the hazardous nature of the intermediate and reagents that are used in the process, the manufacture of the first two steps of the process can only be performed in the commercial-scale manufacturing facility with high level of containment. In order to provide operational flexibility and enhance safety it is desirable to avoid either formation of the chloroketone intermediate or to have a process that would not involve isolation of this intermediate. Several attempts have been made to design synthetic routes that did not require formation of the hazardous intermediate **1**;[4] however, the route reported below is the first commercially viable process.

Development of the New Process. In order to avoid isolation of hazardous **1**, we decided to evaluate $AlCl_3$-mediated in situ reduction of this ketone with silane. Although several methods exist for the deoxygenation of carbonyl oxygen to methylene, all of them have some limitations.[5] Lewis acid-mediated reductive deoxygenation of carbonyl compounds with silanes has previously been reported.[6] Depending on the substrate, these reductions are often accompanied by minor side products of the corresponding alcohols and ethers. After Friedel−Crafts acylation (step 1) was complete, triethyl silane (TES) (2 equiv) was added slowly to the reaction mixture at 0−5 °C. After ∼2 h a mixture of products was obtained containing primarily desired **2** and starting material **1** along with a minor amount of intermediate alcohol **6** (Scheme 2). Addition of excess (4 equiv) triethyl silane resulted in the complete reduction of chloroketone side chain, affording mainly **5** as the major product. We found it difficult to minimize formation of this side product to an acceptable level under a variety of reaction conditions.

Aluminum chloride-catalyzed reduction of activated and unactivated alkyl halides with triethyl silane occurs under mild conditions.[7] Under similar conditions polymeric siloxane (PMHS) was reported to be unreactive for this transformation. There are very few literature reports of Lewis acid catalyzed reductive deoxygenation of carbonyl compounds with siloxanes.[6c−e] In order to improve chemoselectivity of our transformation we decided to attempt this reduction with tetramethyl disiloxane (TMDS). In our experience the silyl byproducts originating from this reagent after aqueous workup are easier to purge in organic solvents compared to byproduct from the longer-chain siloxanes

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(1) Howard, H. R.; Prakash, C.; Seeger, T. F. *Drugs Future* **1994**, *19* (6), 560.
(2) Greenberg, W. M.; Citrome, L. *CNS Drug Rev.* **2007**, *13* (2), 137.
(3) (a) Lowe, J. A., III; Nagel, A. A. U.S. Patent 4,831,031, 1989; *Chem. Abstr.* **1989**, *111*:153842. (b) Bowles, P. U.S. Patent. 5,206,366, 1993; *Chem. Abstr.* **1993**, *119*:203320. (c) Allen, D. J. M.; Busch, F. R.; DiRoma, S. A.; Dennis, M. G. European patent EP 586191, 1994; *Chem. Abstr.* **1994**, *120*:226951.
(4) (a) Urban, F. J.; Breitenbach, R.; Gonyaw, D. *Synth. Commun.* **1996**, *26* (8), 1629. (b) Gurjar, M. K.; Murugaiah, A. M. S.; Reddy, D. S.; Chorghade, M. S. *Org. Process Res. Dev.* **2003**, *7*, 309. (c) Zanon, J.; Martini, O.; Ciardella, F.; Gregori, L.; Sbrogio, F.; Castellin, A. European patent EP 1787990A2, 2007; *Chem. Abstr.* **2007**, *146*:521828.
(5) March, J. *Advanced Organic Chemistry* 5th ed.; Wiley: New York, 2001; Chapter 19, p 1547 and references therein.
(6) (a) Doyle, M. P.; West, C. T.; Donnelly, S. J.; McOsker, C. C. *J. Organomet. Chem.* **1976**, *117*, 129. (b) Fry, J. L.; Orfanopoulos, M.; Adlington, M. G., Jr.; Silverman, S. B. *J. Org. Chem.* **1978**, *43* (2), 374. (c) Imuta, M.; Kobayashi, M.; Lizuka, T. European patent EP 0604150A1, 1994; *Chem. Abstr.* **1994**:157508. (d) Jaxa-Chamiec, A.; Shah, V. P.; Kruse, L. I. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1705. (e) Chandrasekhar, S.; Reddy, C. R.; Babu, B. N. *J. Org. Chem.* **2002**, *67*, 9080.
(7) Doyle, M. P.; McOsker, C. C.; West, C. T. *J. Org. Chem.* **1976**, *41* (8), 1393.

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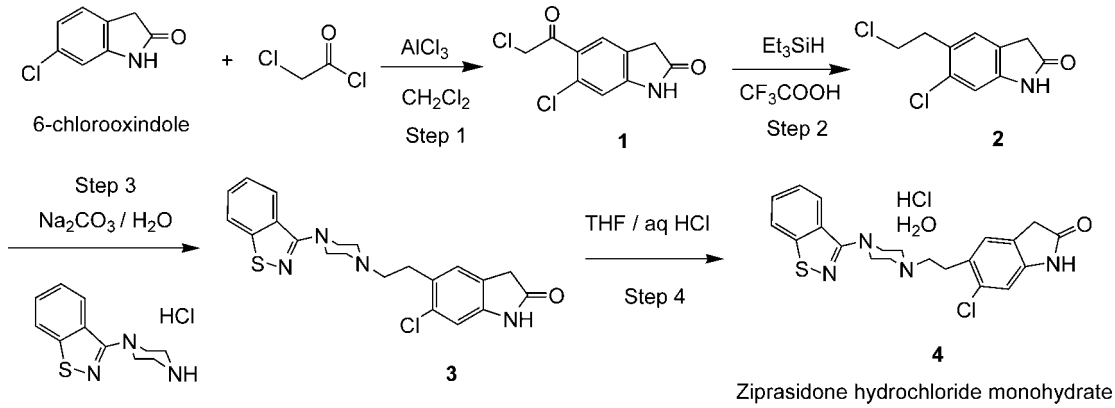
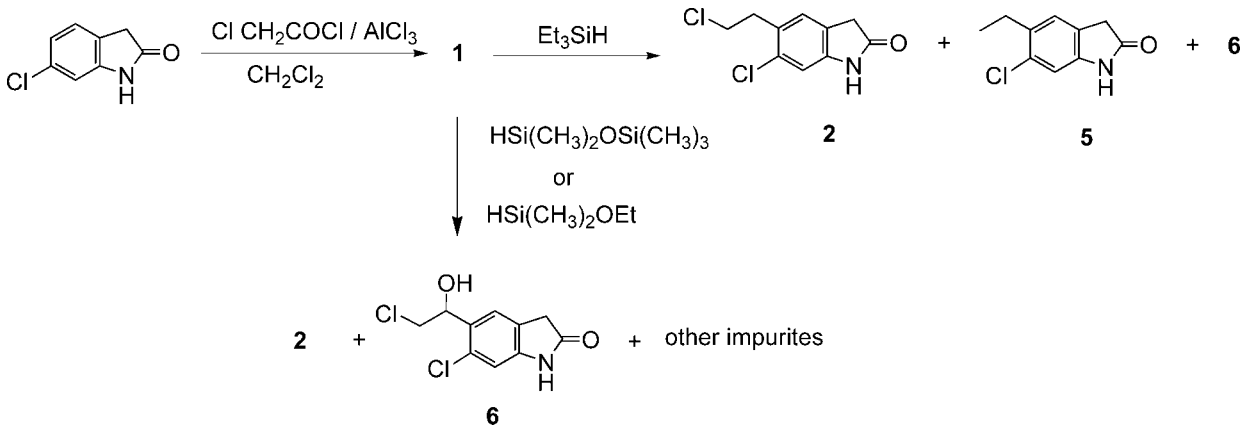
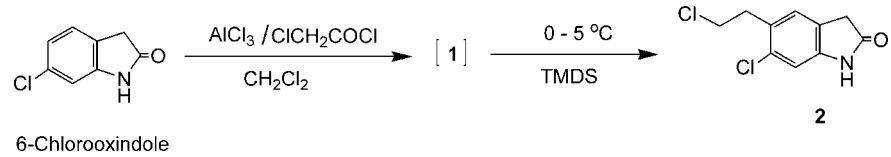
Scheme 1. **Current process for the preparation of ziprasidone hydrochloride**



Scheme 2. **Reduction of 1 with silyl hydride reducing agents**



Scheme 3. **Improved process for the preparation of 2**



such as polymethylhydrosiloxane (PMHS). Addition of TMDS (2 equiv) to the reaction mixture after the step 1 reaction at 0−5 °C resulted in clean and complete conversion of the precursor ketone **1** to the desired product **2** in 4−5 h. Only minor amounts (<1% HPLC area) of the dehalogenated impurity **5** was present in the reaction mixture. The in situ yield of the product was estimated to be ∼88% over two steps on the basis of an external reference standard of **2**. Interestingly, other reducing agents such as pentamethylhydrosiloxane and dimethylethoxy silane were less selective for this transformation. Combination of these reagents with $AlCl_3$ resulted in incomplete reaction, affording a mixture of products.

Due to the change in the process chemistry for the step 2 process, it was necessary to develop new workup and product isolation procedures. The reaction mixture was quenched in water to effect hydrolysis of aluminum chloride-related intermediates. After evaporation of methylene chloride from the reaction mixture, THF was added to the product slurry to extract the product. The THF layer was separated and then concentrated under reduced pressure, resulting in the precipitation of product from the solution. The product was isolated from the mixture after filtration and drying. By utilizing this procedure initially we were able to obtain the desired product in ∼75% yield over two steps. However, a significant amount of product was lost in the mother liquor even at low (0−5 °C) crystallization temperatures. In order to minimize these losses, a small amount of isopropanol was added to the product slurry during crystallization as an antisolvent. This improved the recovery of the desired product by ∼8 −10%. After some experimentation, the crystallization conditions were optimized to consistently afford good quality product in 82−85% isolated yield over two steps. The new process chemistry is depicted in Scheme 3.

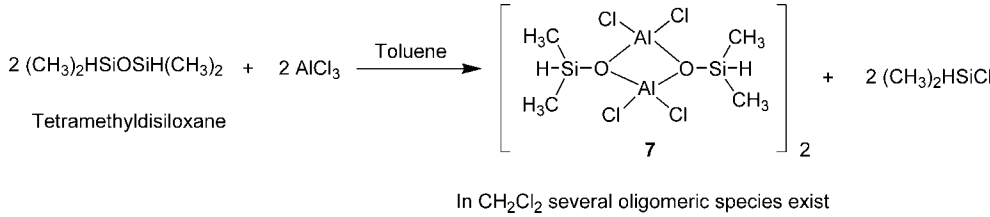
The new process was successfully evaluated on multikilo scale (see Experimental Section). No significant process related issues were encountered during the scale-up campaign. Addition of TMDS to the step 1 reaction mixture was very exothermic, but was controlled by a slow addition of TMDS at −20−0 °C. All the siloxane containing byproducts were purged from the crystallized product during the subsequent filtration followed by washing with isopropanol. Product **2** was obtained in high yield and met all specifications.

Effect of Process Parameters on Product Yields. An experimental design approach was used to gain further understanding of the effect of process parameters on in situ reaction

Table 1. **Experimental design for the reduction step**

entry	step 1 product concn (mL of CH_2Cl_2/g of 6-chlorooxindole)	temp (°C)	TMDS (equiv/equiv of 6-chlorooxindole)	in situ product yield (%)
1	10	0	2	94
2	3	0	2	100
3	10	0	4	50.2
4	3	25	2	93
5	10	25	2	98.2
6	6.5	12.5	3	96.5
7	10	25	4	73.2
8	3	0	4	71.4
9	3	25	4	78.8

Scheme 4. **Reaction of aluminum chloride with tetramethyldisiloxane**



yields. Since the chloroketone **1** was not isolated, we decided to keep parameters involved in the step 1 Friedel−Crafts acylation reaction constant. Three factors were selected for evaluation of the reduction step: temperature, substrate concentration, and equivalents of TMDS. Fully resolved three-factor 2-level factorial design with one center point was chosen for this evaluation. The experimental design details and results are shown in Table 1.

Analysis of results indicated that the TMDS charge was the major factor affecting product yield. The highest yield was achieved when the TMDS charge was between 2 to 3 equiv in the present reaction model. The other two factors, temperature and substrate concentration, did not have a significant effect on product conversion. In cases where lower in situ product yield was observed, the reaction remained incomplete even after longer reaction times. The remainder of the material in those cases contained a mixture of reaction intermediates such as unchanged **1** and chloroalcohol **6**. In earlier experiments we had observed poor in situ product yields with 1.5 equiv of TMDS. Therefore, we chose 2 equiv as the lower limit for the TMDS charge for this design of experiments (DOE) evaluation. Unexpectedly, we observed poor in situ product yield also at higher amounts (4 equiv) of TMDS.

In order to shed light on these observations we performed the following experiments,

1. A preformed mixture of $AlCl_3$/TMDS in equimolar ratio (4 equiv each) was added to the isolated chloroketone **1** (1 equiv) at 0−5 °C in CH_2Cl_2. At the end of the reaction the HPLC assay showed complete conversion of ketone to the desired product **2**.

2. The same experiment (as in 1) was repeated but with 2 equiv of reagents. In this case the reaction remained incomplete even after longer reaction time. Addition of an extra 1 equiv of $AlCl_3$ to the same reaction mixture at 0−5 °C resulted in a complete product conversion.

Our results from DOE indicated that the ratio of $AlCl_3$/TMDS was important for good product yields. It appears that, in this reductive deoxygenation reaction, lower yields were observed if the TMDS charge was higher than the stoichiometric charge of $AlCl_3$. Under the optimized operating conditions of our reduction reaction we had limited flexibility in significantly altering the charge of $AlCl_3$. This charge was determined by the Friedel−Crafts acylation reaction conditions in step 1.

The reaction of $AlCl_3$ with TMDS in toluene solution has been reported to produce the dimer **7** along with chlorodimethylsilane (Scheme 4).[8] In halogenated solvents such as methylene chloride and chloroform, the spectroscopic evidence suggested the presence of several oligomeric species. In order to investigate the reducing ability of chlorodimethylsilane, a solution of chloroketone **1** in methylene chloride was treated with 2 equiv of chlorodimethylsilane under the same reaction conditions that were used for the standard reaction with TMDS. This reaction remained incomplete, resulting in the formation of a significant amount of completely reduced product **5** along with the desired product **2**. Under similar conditions the reaction with TMDS was highly chemoselective, affording **2** as the major product in high yield. The reducing mixture produced by the combination of $AlCl_3$ and TMDS under the reaction conditions employed here was perhaps less reactive compared to the triethylsilane and $AlCl_3$ combination towards the dehalogenation of even reactive α-chloroketones such as **1**.

Conclusions

A new one-pot process for preparation of the key intermediate **2** was developed. This process does not require isolation of the hazardous intermediate chloroketone **1**. The new process was scaled up on multikilo scale to afford desired product **2** in high yield and good quality.

Experimental Section

All solvents and reagents were purchased from commercial sources and used without further purification. Starting material 6-chlorooxindole was purchased from Aldrich and other commercial suppliers. Proton NMR spectra were recorded at 400 MHz with solvent as an internal standard.

(8) Bissinger, P.; Mikulcik, P.; Riede, J.; Schier, A.; Schmidbaur, H. *J. Organomet. Chem.* **1993**, *446*, 37.

New Process for the Preparation of 6-Chloro-5-(2-chloroethyl)-1,3-dihydro-2H-indol-2-one (2). A dry 50 L reactor was charged with methylene chloride (10 L) and anhydrous aluminum chloride (6.56 kg, 49.2 mol, 3.3 equiv) under nitrogen. The contents were cooled to 10−15 °C and stirred for 15 min. Chloroacetyl chloride (2.70 kg, 23.9 mol, 1.6 equiv) was added over 2 h. To this reaction mixture was added 6-chlorooxindole (2.50 kg, 14.9 mol, 1 equiv) as a solid. The reaction mixture was stirred and heated at 30−40 °C under nitrogen atmosphere until an in-process control sample indicated completion of reaction by HPLC assay. At the end of the reaction period, the mixture was cooled to 0−5 °C. To the reaction mixture was slowly added 1,1,3,3-tetramethyldisiloxane (4.01 kg, 29.8 mol, 2.0 equiv). The reaction mixture was stirred at this temperature for 4−6 h. After completion of the reaction as judged by the HPLC assay, the reaction mixture was quenched with addition of water (30−40 L) over 3 h. The HCl gas that evolved during this quench was scrubbed by a caustic scrubber. The reaction mixture was distilled at atmospheric pressure until the temperature reached 50 °C to remove most of the methylene chloride. The reaction mixture was cooled to 25 °C. Tetrahydrofuran (65.7 L) was charged, and the reaction mixture was agitated and heated to dissolve all solids. The reaction mixture was allowed to settle. The lower aqueous phase was separated and discarded. The organic layer was concentrated to a volume of 10−15 L by distillation under reduced pressure. The resulting product slurry was cooled to 25 °C, and isopropanol (5 L) was added to the slurry. The reactor contents were cooled to 0−5 °C and stirred for 2 h. The product slurry was filtered through a large (I.D. 457 mm) Büchner filter funnel. The product was washed with isopropanol (1 L). The isolated material was dried in a tray drier at 40−50 °C for 12 h to yield 2.98 kg (86.8% yield) of the desired product **2**.

^{1}H NMR (DMSO): δ 3.06 (t, 2H, J = 7.3 Hz), 3.44 (s, 2H), 3.75 (t, 2H, J = 7.3 Hz), 6.80 (s, 1H), 7.23 (s, 1H), 10.43 (s, 1H).

^{13}C NMR (DMSO): δ 35.99, 36.18, 44.48, 110.28, 125.87, 127.76, 128.20, 132.27, 144.56, 176.91.

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Supporting Information Available

Experimental procedures for the preparation of **5** and for reduction of **1** with other silane-reducing agents; ^{1}H and ^{13}C NMR for compounds **1**, **5**, and **6**; general procedure for the design of experiments. This material is available free of charge via the Internet at http://pubs.acs.org.

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