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PRACTICAL PREPARATION OF 3-CHLORO-4-METHOXYBENZYLAMINE HYDROCHLORIDE

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ABSTRACT: The title compound was prepared in a practical manner by chlorinating 4-methoxybenzylamine with sulfuryl chloride in acetic acid in 79-82 % yields with little side reaction.

3-Chloro-4-methoxybenzylamine has been used as an important building block for pharmaceutically active compounds in several therapeutic areas, in particular, cardiovascular.[1] In addition, many companies are now working on compounds directed at treating male erectile dysfunction (MED). Public attention at the launch of Viagra®[2] is an indication of interest in this area. Many of the compounds under investigation for treatment of MED use 3-chloro-4-methoxybenzylamine as a starting material.[3] Despite this, no simple, productive preparation of this compound has been reported.

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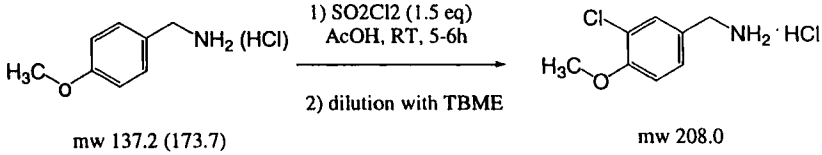
Chlorination of commercially available 4-methoxybenzylamine is short and appears at first sight to be an easy process. However, a reported literature procedure[4] that uses chlorine gas gives not only a low yield (34 %) but also requires a tedious work up, namely concentration of acetic acid, extraction of free base and distillation. A major drawback of the reaction is that chlorine gas is not selective and gives polychlorinated byproducts.

Recently, a Japanese company disclosed a synthesis from 2-chloroanisole in relation to their MED compounds which requires three steps.[3]



mw 137.2 (173.7) mw 208.0

Herein is reported an easy, practical preparation of the title compound by chlorinating 4-methoxybenzylamine with sulfuryl chloride in acetic acid. Sulfuryl chloride is selctive and gives very little polychlorinated byproducts. This process involves no extraction nor distillation. The quality product simply precipitates out as hydrochloride salt in good yield upon dilution with t-butylmethyl ether. Since the free base is unstable in air and solidifies with time, isolating as the hydrochloride salt (which is a stable solid) is also advantageous. The chlorination can be done on either free base or hydrochloride salt of 4-methoxybenzylamine in the same manner, giving 78-82 % yields. In the process, 1.5 equivalent of

sulfuryl chloride is added into a mixture of 4-methoxybenzylamine (or HCl salt) and acetic acid with ice cooling to maintain the temperature at 20-25°C. After stirring at room temperature for 5-6h, the product is precipitated out by adding 2 parts of t-butylmethyl ether. The isolated product is very clean, containing less than 0.5 % of bischlorinated product and requires no further purification.

EXPERIMENTAL

In a 1L 3-necked flask equipped with mechanical stirrer, thermometer, dropping funnel and argon inlet was placed 4-methoxybenzylamine (25.0g, 98 %). Acetic acid (250 mL) was added with ice cooling, keeping the temperature around 20°C. Sulfuryl chloride (22.0 mL) was dropwise added over 20 min maintaining the temperature below 25°C with ice cooling. The cooling bath was removed and the resulting mixture (slurry) was stirred at room temperature for 5h.[5] The reaction mixture was diluted with t-butylmethyl ether (500 mL) and stirred at room temperature for 1h. The white crystalline solid was collected by filtration, washed with t-butylmethyl ether (100 mL), and dried in a vacuum oven (40°C) for 18h to constant weight. Yield 29.8g (78.7%). NMR spectrum was identical to that of reported.[3, 4] HPLC purity: 98.0 area %, starting material 1.8 area %, bischlorinated benzylamine 0.2 area %.

REFERENCES AND NOTES

1. Nemeth, E.F. et al., US patent 292827;940819 (1994); Malamas, M.S. and Nelson, J.A., US patent 148603;931108 (1993); Ozaki, F. et al., JP patent 299110;941109 (1994).

2. Tarrett, N.K., Bell, A.K., Brown, D., Ellis, P. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1819

3. Watanabe, N., Kabasawa, Y., Takase, Y., Matsukura, M., Miyazaki, K., Ishihara, H., Kodama, K., and Adachi, H. *J. Med. Chem.* **1998**, *41*, 3367.

4. Charifson, P.S., Wyrick, S.D., Hoffman, A.J., Ademe Simmons, R.M., Phillip Bowen, J., McDougald, D.L., and Mailman, R.B. *J. Med. Chem.* **1988**, *31*, 1941.

5. The reaction may be monitored by HPLC: column: YMC ODS S5 4.6 x 150 mm; solvent A: 10% MeOH/H2O/0.2% H3PO4; solvent B: 90% MeOH / H2O /0.2% H3PO4; start with 0% B, linear gradient to 100% B over 20 min; injection volume: 5μL; flow rate: 1 mL/min; detection: 220nm.

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