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CONVENIENT AND SCALABLE PROCESS FOR THE PREPARATION OF BUPROPION HYDROCHLORIDE VIA EFFICIENT BROMINATION OF *m*-CHLOROPROPIOPHENONE WITH *N*-BROMOSUCCINIMIDE

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A convenient, scalable, and commercially viable process for the production of the antidepressant drug bupropion hydrochloride (1) is reported. The process relies upon an improved, large-scale synthesis of the key intermediate, m-chloro-α-bromopropiophenone (4). During process development, bromine was replaced with N-bromosuccinimide (NBS) in the presence of para-toluene sulfonic acid (p-TSA), for the bromination of m-chloropropiophenone (3), in either a very low volume of acetonitrile or under solvent-free conditions, to furnish 4. Intermediate 4 was further reacted with t-butylamine in N-methyl-2-pyrrolidinone (NMP) to afford bupropion free base (5), followed by treatment with a saturated solution of hydrochloric acid in isopropyl alcohol (IPA-HCl) to afford bupropion hydrochloride (1). This improved process provides pure bupropion hydrochloride (1) in good yields and at considerably lower cost than existing processes, and it does not involve the use of hazardous reagents.

Keywords: α-Bromination; bupropion hydrochloride; *N*-bromosuccinimide; solvent-free

INTRODUCTION

The hydrochloride salt of bupropion (**1**, Fig. 1) has valuable pharmacological properties. Bupropion was first marketed in 1985 by Burroughs-Wellcome (now GlaxoSmithKline) as an antidepressant under the trade name Wellbutrin. After further evaluation, the drug was found to be effective in the treatment of nicotine dependence and was subsequently marketed as a smoking cessation agent in 1997 with a new trade name, Zyban.[1–4]

The aim of process research and development work in the pharmaceutical industry is to produce a scalable and noninfringing process for the manufacture of a key intermediate or an active pharmaceutical ingredient (API) at low cost and with high purity. In general, the cost of the active pharmaceutical ingredient is dependent

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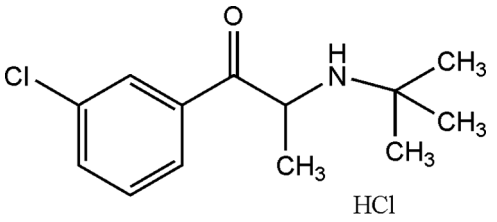
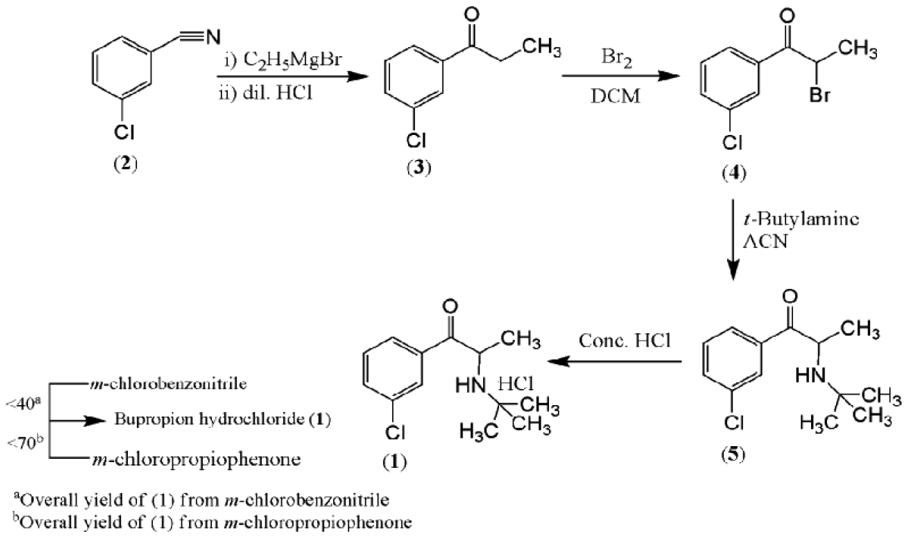


Figure 1. Bupropion hydrochloride (**1**).

on the time of its introduction into the market and decreases gradually as the drug transitions to generic status. Hence, process chemistry plays a key role in efforts to gain a competitive market advantage. In addition, in the generic pharmaceutical industry, the development of noninfringing processes for active pharmaceutical ingredients (APIs) and commercially useful drug intermediates to avoid patent litigations is very difficult and challenging. In this respect, exploring new synthetic methodologies, or exploring existing synthetic procedures to enhance the yield and quality of a drug substance, constitute significant challenges for the process chemist engaged in the process development of APIs. In this report, we describe our efforts to meet these challenges for bupropion hydrochloride (**1**) by providing a low-cost process for the preparation of this drug, which precludes the use of the hazardous reagent, bromine.

The first reported synthetic method for the preparation of bupropion was described by Mehta,[5] who used a convergent approach to **1**, which required more than 24 h to complete, and afforded an overall yield of less than 40%. This process involved the reaction of *m*-chlorobenzonitrile (**2**) with ethylmagnesium bromide to give *m*-chloropropiophenone (**3**), which on bromination with bromine in



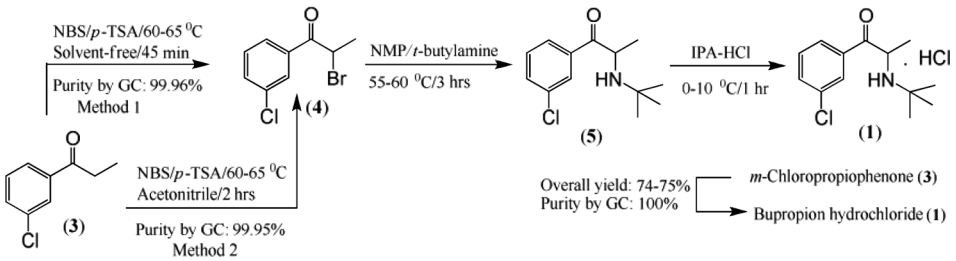
Scheme 1. Synthesis of bupropion hydrochloride (**1**) after Mehta et al.[5]

dichloromethane afforded the key intermediate, *m*-chloro-α-bromopropiophenone (**4**). This was followed by the reaction of **4** with *t*-butylamine in acetonitrile to give bupropion free base (**5**). Bupropion free base was then converted to the hydrochloride salt by treatment with 35% (w/v) hydrochloric acid in isopropyl alcohol (Scheme 1). This process suffers from several disadvantages: (i) the use of the hazardous reagent bromine in the bromination of **3** (bromine is caustic to both the skin and the lungs), (ii) the use of dichloromethane as process solvent in the bromination step (dichloromethane is highly volatile and its hazardous vapors are toxic to the liver and possibly carcinogenic), (iii) the generation of hydrobromic acid gas during bromination of **3** (this gas is toxic and hazardous and requires a special trap or acid-scavenger apparatus), and (iv) the purification of bupropion hydrochloride by recrystallization from a mixture of isopropyl alcohol and absolute ethanol (this choice of solvent affords a poor yield of the final product).

RESULTS AND DISCUSSION

In all syntheses of bupropion reported thus far,[6–8] bromine is still used as the brominating agent for the preparation of the key intermediate, **4**, and up until this current study, no process-development methodologies have ever utilized *N*-bromosuccinimide (NBS) as a brominating agent for the preparation of **4**. In addition, these previous processes are either lengthy, lead to the formation of several process-related impurities, use unacceptable process solvents, or contain operations that are not optimal for safety when adopted for large-scale production.[6–8]

We now report a convenient, scalable, and commercially viable process for the preparation of the key intermediate **4**, starting from commercially available **3**. In this process, NBS is utilized as an efficient brominating agent in the presence of *p*-toluenesulfonic acid (*p*-TSA) as a catalyst in a very low volume of acetonitrile or under solvent-free conditions at 60–65 °C. Intermediate **4** is then reacted with *t*-butylamine in a mixture of *N*-methyl-2-pyrrolidinone (NMP) and toluene at 55–60 °C to furnish bupropion free base (**5**). Treatment of **5** with a saturated solution of hydrochloric acid in isopropyl alcohol (IPA-HCl) affords bupropion hydrochloride (**1**) in 75% overall yield and 100% purity (as determined by gas chromatographic, GC, analysis). This process is devoid of the aforementioned disadvantages of current methodologies and avoids the use of high volumes of hazardous solvents (Scheme 2).



Scheme 2. Final optimized synthesis of bupropion hydrochloride (**1**) utilizing NBS/*p*-TSA as brominating agent.

Table 1. Effect of a variety of solvents on the conversion of *m*-chloropropiophenone (**3**) to *m*-chloro-α-bromopropiophenone (**4**) via bromination with NBS/*p*-TSA

Entry	Solvent[a–c]	Time	Percentage of unreacted *m*-chloro propiophenone (**3**)[d]	Percentage of *m*-chloro-α,α[1]-dibromopropiophenone[d]	Percentage of *m*-chloro-α-bromopropiophenone (**4**)[d]
1	Acetonitrile	2 h	0.05	—	99.95
2	Chloroform	2 h	35.29	1.63	63.03
3	Toluene	2 h	33.46	1.59	64.91
4	THF	2 h	22.56	0.08	77.35
5	DMF	2 h	11.38	0.12	88.50
6	Water	2 h	32.90	0.05	67.00
7	No solvent	45 min	0.04	—	99.96

[a]1.0 mol **3**, 1.1 mol NBS, 0.1 mol *p*-TSA.
[b]50% w/v of **3** in the appropriate solvent.
[c]Reactions were run at 60–65 °C.
[d]Area percentage by GC analysis.

Our main focus during process development was on process optimization for the manufacture of the key intermediate **4** from **3**, utilizing NBS/*p*-TSA as an alternative brominating agent to liquid bromine. Initially, bromination of **3** with NBS in the presence of *p*-TSA at 60–65 °C in acetonitrile was examined as a model reaction (Table 1). When a mixture containing 1.0 mol of **3**, 1.1 mol of NBS, 0.1 mol of *p*-TSA, and a 50% w/v solution of **3** in acetonitrile was run, the reaction was complete within 2 h and furnished 99.95% of **4** (entry 1). The effect of different solvents on the amount of **4** formed was also examined. The amount of **4** formed in the reaction decreased to <90% in nonpolar solvents ($CHCl_3$ or toluene), as well as in polar solvents [tetrahydrofuran (THF), dimethylformamide (DMF), and water] (entries 2–6). Importantly, it was also observed that the reaction proceeded smoothly and was completed within 45 min at 60–65 °C under solvent-free conditions to afford 99.96% of **4** (entry 7).

The effect of varying the percent w/v of **3** in acetonitrile on the NBS/*p*-TSA bromination reaction was also examined (Table 2). When 50% w/v of **3** in acetonitrile was utilized, 99.95% of **4** was formed (entry 1). The amount of **4** formed

Table 2. Effect of varying percentage w/v of *m*-chloropropiophenone (**3**) in acetonitrile on the amount of *m*-chloro-α-bromopropiophenone (**4**) formed from the bromination of **3** with NBS/*p*-TSA

Entry	Percent w/v of **3** in acetonitrile[a,b]	Percentage of unreacted *m*-choro propiophenone (**3**)[c]	Percentage of *m*-chloro-α,α[1]-dibromo-propiophenone[c]	Percentage of *m*-chloro-α-bromo-propiophenone (**4**)[c]
1	50% (1:1)	0.05	—	99.95
2	33% (1:2)	6.7	17.52	75.72
3	25% (1:3)	2.3	28.59	69.06

[a]1.0 mol **3**, 1.1 mol NBS, 0.1 mol *p*-TSA.
[b]Reactions were run at 60–65 °C.
[c]Area percentage by GC analysis.

Table 3. Effect of a variety of acid catalysts on the amount of *m*-chloro-α-bromopropiophenone (**4**) formed from the bromination of *m*-chloropropiophenone **3** with NBS

Entry	Acid catalyst[a–c]	Percentage of unreacted *m*-chloro propiophenone (**3**)[d]	Percentage of *m*-chloro-α,α[1]-dibromo-propiophenone[d]	Percentage of *m*-chloro-α-bromo-propiophenone (**4**)[d]
1	*p*-TSA	0.05	—	99.95
2	H_2SO_4	46.24	1.12	52.35
3	NH_2SO_3H	27.0	0.29	72.60
4	CH_3SO_3H	39.43	1.09	59.22

[a]1.0 mol **3**, 1.1 mol NBS, 0.1 mol acid catalyst.
[b]50% w/v of **3** in acetonitrile.
[c]Reactions were run at 60–65 °C.
[d]Area percentage by GC analysis.

in the reaction was reduced to <80% when 33% w/v and 25% w/v of **3** in acetonitrile were utilized because of an increase in the formation of the impurity *m*-chloro-α,α[1]-dibromopropiophenone (i.e., 17.52% and 28.59%, respectively) (entries 2 and 3).

The effect of different acid catalysts on the NBS/*p*-TSA bromination reaction was also examined (Table 3). The amount of **4** formed was decreased to <80% when either sulfuric acid, sulfamic acid, or methanesulfonic acid was utilized (entries 2–4) in place of *p*-TSA (entry 1).

The effect of temperature on the reaction of **3** with NBS/*p*-TSA was also examined (Table 4). It was observed that bromination of **3** with NBS proceeded smoothly at 60–65 °C, and 99.95% of **4** was formed within 2 h (entry 1). Interestingly, 1.35% of **4** was formed at 20–25 °C, 27.34% at 40–45 °C, and 74.62% at 50–55 °C (entries 2–4).

The key intermediate **4**, was synthesized utilizing the two most promising conditions (entries 1 and 7, Table 1), and each of the two products obtained was treated with *t*-butylamine in *N*-methyl-2-pyrrolidinone (NMP)/toluene (1:5 v/v) at 55–60 °C to furnish bupropion free base (**5**). This was followed by treatment of each of the free bases formed these two procedures with IPA-HCl to afford bupropion hydrochloride (**1**) in 74–75% overall isolated yield (each procedure afforded 100% of **1** by GC analysis) (Table 5).

Table 4. Effect of reaction temperature on the percentage of *m*-chloro-α-bromopropiophenone (**4**) formed from the bromination of *m*-chloropropiophenone (**3**) with NBS/*p*-TSA

Entry	Temperature (°C)[a,b]	Percentage of unreacted *m*-chloro propiophenone (**3**)[c]	Percentage of *m*-chloro-α,α[1]-dibromopropiophenone[c]	Percentage of *m*-chloro-α-promopro-piophenone (**4**)[c]
1	60–65	0.05	—	99.95
2	20–25	99.65	—	1.35
3	40–45	72.66	—	27.34
4	50–55	25.38	—	74.62

[a]1.0 mol **3**, 1.1 mol NBS, 0.1 mol *p*-TSA.
[b]50% w/v of **3** in acetonitrile.
[c]Area percentage by GC analysis.

Table 5. Preparation of bupropion hydrochloride (**1**) from *m*-chloropropiophenone (**3**) *via* efficient bromination of **3** with NBS/*p*-TSA either under solvent-free conditions (method 1) or in acetonitrile (method 2)

	Bromination of *m*-chloropropiophenone (**3**)[a–c] with NBS/*p*-TSA			GC analysis and yield of bupropion hydrochloride (**1**) from methods 1 and 2	
Method	Solvent	Time	Percentage of *m*-chloro-α-bromo-propiophenone (**4**)[d]	Percentage of **1**[d]	Overall yield of **1** (%)[e]
1	No solvent	45 min	99.96	100	75
2	Acetonitrile[b]	2 h	99.95	100	74

[a]1.0 mol of (**3**), 1.1 mol of NBS, 0.1 mol of *p*-TSA.
[b]Reactions were run at 60–65 °C.
[c]50% w/v of **3** in acetonitrile.
[d]Area percentage by GC analysis.
[e]Based on overall isolated yield of the bupropion hydrochloride (**1**) from *m*-chloropropiophenone (**3**).

EXPERIMENTAL

Method 1

Preparation of bupropion hydrochloride (**1**) via efficient bromination of *m*-chloropropiophenone (**3**) with NBS under solvent-free conditions (method 1): NBS (116 g) was added to a solid mixture of *m*-chloropropiophenone (100 g) and *p*-toluenesulfonic acid monohydrate (11.2 g) at −20–25 °C. The solid reaction mixture was stirred with a mechanical stirrer for 15 min, then slowly heated to 60 °C to give a syrupy liquid. Stirring was continued at 60–65 °C for a further 45 min. The progress of the reaction was monitored by silica-gel thin-layer chromatography (TLC). After completion of the reaction, the reaction mixture was cooled to 20–25 °C using an ice-water bath. Water (500 ml) and toluene (500 ml) were added, and the resulting mixture was stirred for 15 min. The separated organic layer was then washed with water (500 ml × 2) and brine (500 ml). The organic layer (containing *m*-chloro-α-bromopropiophenone; 99.96% by GC analysis) was added to a mixture of NMP (100 ml) and *t*-butylamine (108.3 g) at 20–25 °C. The temperature of the reaction mixture was slowly raised to 55 °C, and the mixture was stirred at 55–60 °C for 3 h. The progress of the reaction was monitored by silica-gel TLC. After completion of the reaction, the reaction mixture was cooled to 20–25 °C in an ice-water bath, water (500 ml) was added, and the mixture was stirred for 15 min. The separated organic layer was washed with water (500 ml × 2) and then brine (500 ml). The organic layers were combined and cooled to 0–5 °C in an ice-water bath, and a saturated solution of IPA-HCl was added slowly over a period of 10 min until complete precipitation of the product had occurred. The resulting suspension was then stirred for 1 h at 0–10 °C. The solid that separated was filtered, washed with toluene (100 ml), suction-dried at the pump, and then dried overnight in a vacuum oven at 60–65 °C to afford pure (100% by GC analysis) bupropion hydrochloride (123 g, 75%), mp 233–234 °C (lit.[5] mp 233–234 °C). ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.75 (d, $J = 12.3$ Hz, 1H), 8.63 (br s, 1H), 8.27 (s, 1H),

8.17 (d, $J = 7.8$ Hz, 1H), 7.85 (d, $J = 7.8$ Hz, 1H), 7.69 (t, 1H), 5.32 (q, $J = 7.2$ Hz, 1H), 1.53 (m, $J = 7.2$ Hz, 3H), 1.32 (s, 9H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ 203.60, 136.56, 133.83, 132.94, 130.70, 127.87, 126.98, 52.10, 50.31, 29.39, 22.18 ppm.

Method 2: Preparation of Bupropion Hydrochloride via Efficient Bromination of *m*-Chloropropiophenone with NBS in Acetonitrile

NBS (116 g) was added to a mixture of *m*-chloropropiophenone (100 g) and *p*-toluenesulfonic acid monohydrate (11.2 g) in acetonitrile (100 ml) at 20–25 °C. The suspension was stirred with a mechanical stirrer for 15 min at ambient temperature, heated with stirring to 60 °C over 5 to 10 min, and then stirred at 60–65 °C for a further 2 h. The progress of the reaction was monitored by silica-gel TLC. After completion of the reaction, the reaction mixture was cooled to 20–25 °C in an ice-water bath, water (500 ml) and toluene (500 ml) were added, and the resulting mixture was stirred for 15 min. The separated organic layer was then washed with water (500 ml × 2) and brine (500 ml). The organic layer (containing 99.95% *m*-chloro-α-bromopropiophenone by GC analysis) was processed in similarly to that described in method 1 to afford bupropion hydrochloride (121.5 g, 74%; 100% by GC analysis), mp 233–234 °C (lit.[5] mp 233–234 °C). ^{1}H and ^{13}C NMR were identical to those obtained for the product from method 1.

CONCLUSION

In conclusion, we have developed an improved, scalable, and commercially viable manufacturing process for the preparation of bupropion hydrochloride via a new and efficient synthesis of the key intermediate, *m*-chloro-α-bromopropiophenone (**4**). Bromination of the starting material, *m*-chloroprophenone, utilizing NBS/*p*-TSA in a low volume of acetonitrile or under solvent-free conditions, afforded **4** in good yields, at a considerably lower cost than existing processes, and did not involve the use of the hazardous reagent bromine. There was not much difference in the yield and quality of the products from method 1 (Table 5, solvent-free bromination) and method 2 (Table 5, bromination in acetonitrile), and these two methods were both found to be suitable for the laboratory-scale (up to 100-g scale) synthesis of bupropion hydrochloride. However, in method 2, the use of acetonitrile as solvent increases the miscibility of the reactants to afford a homogeneous reaction mixture, which facilitates the effective bromination of *m*-chloropropiophenone with the NBS/*p*-TSA reagent (i.e., a reaction time of 45 min for the solvent-free reaction, compared to 2 h for the bromination reaction in acetonitrile (Table 1). Hence, method 2 is likely to be the preferred procedure for the plant-scale (1–100 kg) production of bupropion hydrochloride.

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