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Amidation and N-Boc Deprotection Process Improvement for the Preparation of 5-(1-Piperazinyl)benzofuran-2-carboxamide, a Key Intermediate of Vilazodone

Prasenjit Das, Bindu Srivastava, Sony Joseph, Hashim Nizar,* and Mohan Prasad

Chemical Research Division, Ranbaxy Research Laboratories, Gurgaon, Haryana 122001, India

ABSTRACT: An improved process for the preparation of 5-(1-piperazinyl)benzofuran-2-carboxamide, a key intermediate used in the synthesis of antidepressant drug vilazodone is reported.

INTRODUCTION

Vilazodone (**1**; Figure 1) is an antidepressant approved by the US FDA for the treatment of major depressive disorder (MDD).[1,2] Vilazodone has dual activity as a selective serotonin reuptake inhibitor (SSRI) and a partial agonist of the serotonin 5-HT_{1A} receptor.[3]

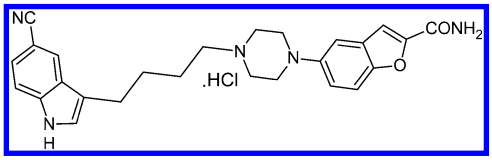

Figure 1. Vilazodone (**1**).

Several synthetic methods are reported[3,4] for the preparation of vilazodone which mainly involves the coupling of 3-(4-chlorobutyl)-1H-indole-5-carbonitrile (**2**) with 5-(piperazin-1-yl)benzofuran derivatives (**3**) (Scheme 1). The intermediate ethyl-5-(1-piperazinyl)benzofuran-2-carboxylate (**3a**) on condensation with **2**, gives vilazodone ethyl ester **4.** It is converted to vilazodone by amidation of **4** with 1-methyl-2-chloropyridinium iodide (Mukaiyama Reagent)[4] or carbonyldiimidazole (CDI) and ammonia.[5] The strategy to perform amidation in the last step of API synthesis is not favorable from the scale up point of view. The preparation of vilazodone using 5-(1-piperazinyl)benzofuran-2-carboxamide (**3b**) is a better commercial approach as it eliminates the use of expensive and hazardous reagents at final step of API manufacture. Herein we report an efficient and scalable synthesis of key intermediate **3b**.

RESULTS AND DISCUSSION

As per literature[6] **3b** is prepared from *tert*-butyl 4-[2-(ethoxycarbonyl)-1-benzofuran-5-yl]piperazine-1-carboxylate (**5**) in two steps (Scheme 2). Step-1 is the amidation reaction using formamide (3.0 equiv) and sodium methoxide (7.0 equiv) in *N*-methyl pyrrolidone (NMP) to yield *tert*-butyl 4-(2-carbamoyl-1-benzofuran-5-yl)piperazine-1-carboxylate (**6**). The mechanistic pathway as per literature[7] for amidation involves (a) formamide deprotonation by sodium methoxide (b) acyl transfer from ester to form sodium N-acylformamide (c) formyl transfer to yield desired amide (Scheme 3). Step-2 is the boc-deprotection of **6** using methanolic HCl to give **3b**. The side reaction associated with the amidation reaction is the formation of ester hydrolyzed impurity **7** which led to poor yield. The amidation of **5** using NMP (8 vol) led to the formation of impurity benzofuran-2-carboxylic acid **7** in 12.17% and 83.41% product formation by HPLC monitoring (entry 4, Table 1). The residual carboxylic acid impurity reacts with **2** in the final step gives vilazodone carboxylic acid as an impurity in API. Thus, it is necessary to control this impurity at intermediate stage. Further amidation reaction is reported in 33 vol of NMP which required excess quantity of water during the isolation of the product owing to high solubility of **6** in NMP. In Step-2, BOC-deprotection using methanolic HCl led to no product formation. These challenges prompted us to search for improved reaction condition for the synthesis of **3b**. Moreover, the development of a reproducible synthetic process and control in the cost of commercial production was highly desirable. Thus, adopting the same synthetic strategy for **3b,** optimization studies were carried out to improve the reaction condition and overall yield. The results are tabulated in Table 1.

The experiments were performed using NMP (8 vol) as solvent. The amidation of **5** using formamide (2.0 equiv) and sodium methoxide (2.0 equiv) resulted in poor conversion (75.4% product formation) with formation of impurity **7** in 21.03%. The product formation was improved using 2.5 equiv each of formamide and sodium methoxide to 83.9%. The reaction using 3.5 equiv of formamide and 3.65 equiv of sodium methoxide resulted in 84.4% product formation with the carboxylic acid impurity **7** reduced to 9.9%. Further experiment was performed with increased quantity of formamide (8.3 equiv) and sodium methoxide (3.65 equiv) which led to product formation 88.90% with reduction in ester hydrolysis impurity **7** to 6.6%. The above trend indicated that increasing the quantity of formamide, resulted in a better conversion. These findings prompted us to evaluate formamide as a solvent for amidation reaction replacing NMP. The experiments were carried out with formamide (3 vol and 5 vol) and the results are tabulated in Table 2.

In both the experiments formation of carboxylic acid impurity **7** was drastically reduced to 1.25% and 0.92%. Furthermore, optimal product formation increased significantly

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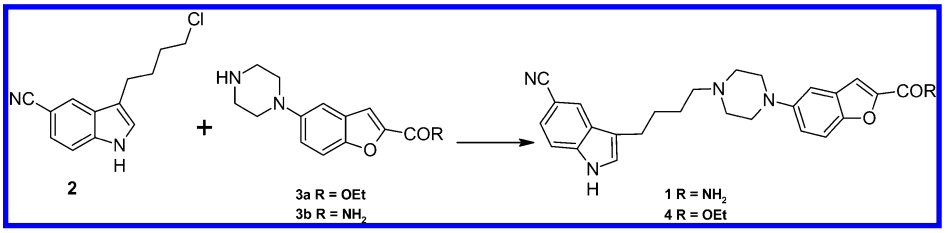
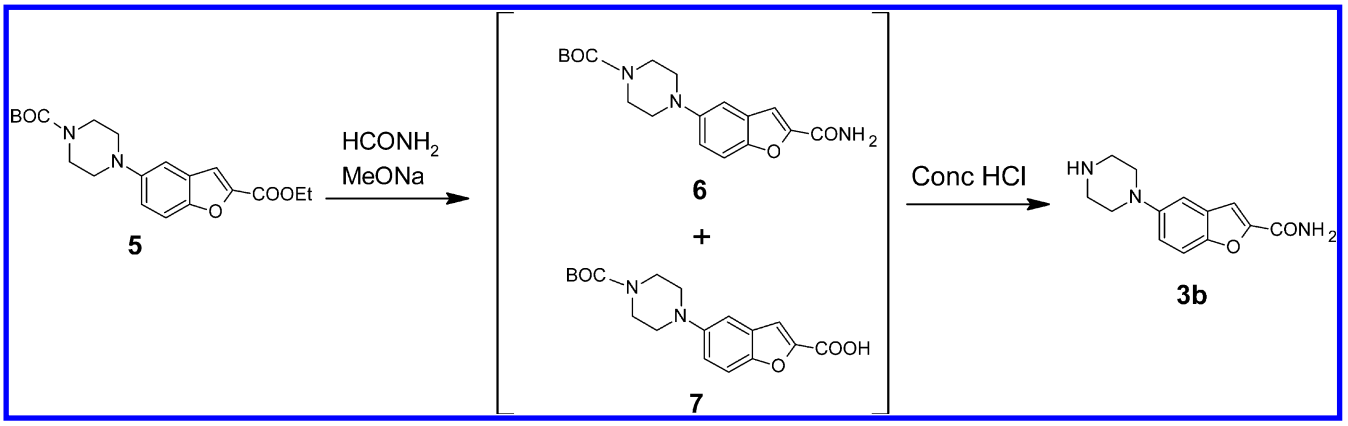
Scheme 1. Synthesis of Vilazodone



Scheme 2. Synthesis of 3b



Scheme 3

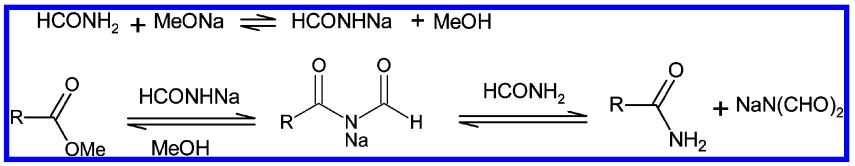


Table 1. Amidation of 5

entry	formamide (equiv)	sodium methoxide (equiv)	equiv ratio	product **6** formation (HPLC area %)	impurity **7** formation (HPLC area %)
1	1.5	1.5	1:1	75.57	21.69
2	2.0	2.0	1:1	75.4	21.03
3	2.5	2.5	1:1	83.9	14.28
4	3.5	7.0	1:2	83.41	12.17
5	3.5	3.65	1:1.04	84.4	9.9
6	8.3	3.65	1:0.43	88.90	6.57

Table 2. Amidation of 5 in Formamide

entry	formamide (vol)	sodium methoxide (equiv)	product **6** formation (% HPLC)	impurity **7** formation (% HPLC)
1	3	2.5	96	1.25
2	5	2.0	95.2	0.92

to 96%. Since the reaction mixture is heterogeneous, using formamide (3 vol) resulted in thick slurry with improper agitation. This may have implications during scale up operations. Thus, the quantity of formamide was optimized to 5 vol for better mixing. Quenching of formamide reaction requires only 10 vol of water as antisolvent for product isolation, whereas the reaction using NMP requires 30 vol of water for the complete isolation of product. This provided an additional advantage of capacity enhancement on commercial scale.

Further **3b** was prepared by deprotection of **6**. The conventional deprotection of **6** using dil HCl or methanolic HCl did not give the desired product and reaction was found to be feasible only when concentrated HCl was used at 45−50 °C. The optimization for quantity of concentrated HCl using 1 and 2.5 vol of concentrated HCl was performed. Results are tabulated in Table 3.

The reaction slurry was very thick when 1 vol of concentrated HCl was used, resulting in incomplete conversion

Table 3. Deprotection of 5

entry	conc HCl (vol)	reaction temp (°C)	remark
1	1	45	[a]thick slurry, incomplete reaction
2	2.5	RT	[a]incomplete reaction
3	2.5	45	product formation 94.79% (HPLC)

[a]Reaction is monitored by TLC.

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whereas, with 2.5 vol concentrated HCl, complete conversion was achieved with 94.79% product formation at 45 °C. Under these conditions **3b** was obtained in 78% overall yield in formamide reaction against 54−55% in NMP.

In a typical experiment **5** was suspended in formamide (5 vol) and a solution of sodium methoxide in methanol was slowly added at room temperature (rt). After stirring for 1 h at rt, the reaction mixture was quenched with water (10 vol) and filtered to give **6**. The wet compound thus obtained was directly deprotected with concentrated HCl (2.5 vol) at 45−50 °C to give **3b** in 78% overall yield with chromatographic purity 99.5%. Thus, after considerable efforts, the optimized process proved robust and reliable and was successfully scaled to provide kilograms of intermediate **3b**. Besides, the present process had the advantage of replacing NMP with the use of amidating reagent formamide as the solvent and simplified the work up procedure.

CONCLUSION

An improved scalable process for the preparation of 5-(1-piperazinyl)benzofuran-2-carboxamide (**3b**) has been developed. A process impurity formed during the reaction was controlled by optimizing the reaction conditions, resulting in better yield and quality of product.

EXPERIMENTAL SECTION

General. Reagents were used as such without purification. Water content of NMP and formamide was determined by Karl Fischer titration and was controlled below 0.15%. ^{1}H NMR spectra was recorded using a Bruker 400 MHz spectrometer. The chemical shift data are reported as δ (ppm) using tetramethyl silane as internal standard. Mass spectra were recorded using an API 2000 (MPS SCIEX) instrument. Infrared spectra were recorded using PerkinElmer FTIR (Spectrum One) instrument. HPLC analysis was performed on a Waters/Agilent instrument with a UV detector (235 nm) using a Kromosil C18 (250 mm × 4.6 mm, 3 μm) column and mobile phase [0.174% (w/v) dipotassium hydrogen orthophosphate solution (adjust pH to 5. 0 ± 0.05 with 0.1% v/v orthophosphoric acid): acetonitrile, gradient 90:10 (0−5 min), 50:50 (5−30 min), 30:70 (30−55 min), 90:10 (55−57 min) and 90:10 (57−65 min)] with flow rate 1 mL/min. (Column oven temperature 30 °C) Retention times: **3b**, 5 min; **5**, 48 min; **7**, 23.6 min.

Preparation of 5-(1-Piperazinyl)benzofuran-2-carboxamide (3b). *Step 1: Preparation of **6**.* To a suspension of **5** (1.0 kg, 2.67 mol) in formamide (5 L), methanolic solution (30% w/w) of sodium methoxide (0.963 kg, 5.34 mol) in 20−30 min at 20−30 °C. The reaction mixture was stirred at RT for 1 h and monitored by HPLC. Then cooled the reaction mixture to 0−5 °C, added water (10 L) at 5−25 °C (addition is slightly exothermic) and stirred at rt for 1 h. The precipitate was filtered and washed with water (2 L). The wet solid of **6** (∼1.0 kg) is used as such for next step.

*Step 2: Preparation of **3b**.* The above wet solid of **6** was added portion wise to concentrated HCl (2.50 L) at 35−45 °C and stirring continued for 1 h at 45−50 °C. The reaction mixture was then cooled to 10 °C, water (7 L) added and adjusted pH to 4−4.5 with 10% (w/v) aqueous sodium hydroxide solution and added activated carbon (100 g). The resulting mixture was stirred for 15 min, filtered and adjusted pH to 9.5−10 using sodium hydroxide solution (10% w/v). The precipitated solid was filtered, washed with water (2 L) and dried at 55−60 °C under vacuum to furnish the titled product **3b** (510 g, 77.86%). HPLC analysis: 99.5% ; IR(KBr) cm^{-1} 3200,2820, 1654, 1572: . MS (m/z): 246.2 [M + H]$^+$; ^{1}H NMR (DMSO-d_6) δ: 2.84−2.86 (m, 4H), 3.00−3.02 (m, 4H), 7.14−7.16 (dd, J = 2.3 Hz, 1H), 7.40−7.41 (s, 1H), 7.45-7.47 (dd, J = 9.9 Hz, 2H), 7.58 (bs, 1H), 8.01 (bs, 1H).

AUTHOR INFORMATION

Corresponding Author

*E-mail: hashim.nizar@ranbaxy.com; Telephone: 91-124-4011832.

Notes

The authors declare no competing financial interest.

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