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An investigation of the synthesis of vilazodone

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Abstract

A novel synthetic route toward vilazodone is described by using 4-cyanoaniline and 5-bromo-2-hydroxybenzaldehyde as starting materials, with an overall yield of 24% and 99% purity. First, the intermediate (3-(4-chlorobutyl)-1*H*-indole-5-carbonitrile) is synthesized via diazotization of 4-cyanoaniline, followed by Fischer indole cyclization with 6-chlorohexanal. Subsequently, another intermediate, 5-(piperazin-1-yl)benzofuran-2-carboxamide, is generated via aromatic nucleophilic substitution of 5-bromobenzofuran-2-carboxamide with piperazine. Finally, vilazodone is obtained via nucleophilic substitution of the above two key intermediates by treatment with Et_3N/K_2CO_3. In comparison to the original process, this route avoids the use of expensive and toxic reagents and resolves issues such as safety, environmental concerns, and high costs.

Keywords

cyclization, diazotization, nucleophilic substitution, synthetic route, vilazodone

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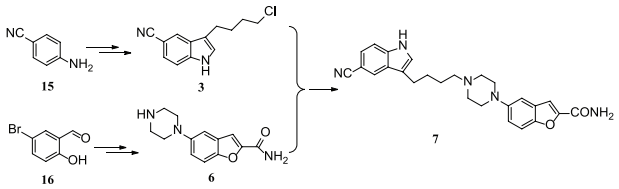

Introduction

Vilazodone (**7**), a new type of antidepressant drug, is widely used for the treatment of major depression in adults. To date, several efficient methods for synthesis of vilazodone have been reported. For example, in 2004, Timo Heinrich's group described a synthetic route for the preparation of vilazodone by using 5-cyanoindole and 5-nitrobenzofuran-2-carboxamide as starting materials, with an overall yield of 10%–20% being obtained.[1,2] First, 5-cyanoindole (**1**) was reacted with 4-chlorobutanoyl chloride under catalysis by isobutyl-$AlCl_2$ to afford the chloride **2**, which was then reduced to 3-(4-chlorobutyl)-1*H*-indole-5-carbonitrile (**3**) by treatment with 2-(methoxyethoxy)aluminum hydride. Subsequently, 5-nitrobenzofuran-2-carboxamide (**4**) was reduced to compound **5** via hydrogenation with Pd/C and, then, further transformed into 5-(piperazin-1-yl)benzofuran-2-carboxamide (**6**) by reaction with bis(2-chloroethyl)amine. Vilazodone (**7**) was finally obtained by through nucleophilic substitution of compounds **3** and **6** with K_2CO_3/DMF (Scheme 1). This synthetic route employed many expensive and toxic reagents, leading to environmental and high cost issues. Subsequently, Xu's group provided another synthetic route toward compound **3** (Scheme 2). 5-Cyanoindole (**1**) was protected using TsCl to give compound **8**, which was then reacted with 4-chlorobutanoyl chloride under catalysis of $AlCl_3$ to afford compound **9** in 90% yield. Compound **9** was reduced to compound **10** by treatment with $NaBH_4$/CF_3COOH in 95% yield.[3] Finally, 3-(4-chlorobutyl)-1*H*-indole-5-carbonitrile (**3**) was obtained via hydrolysis of compound **10**. Vilazodone (**7**) was obtained via nucleophilic substitution reaction of compounds **3** and **6**, using the same method as Tim Heinrich's group.[1–3]

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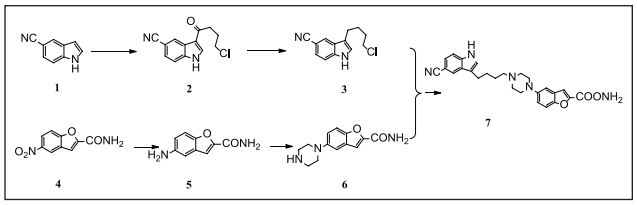
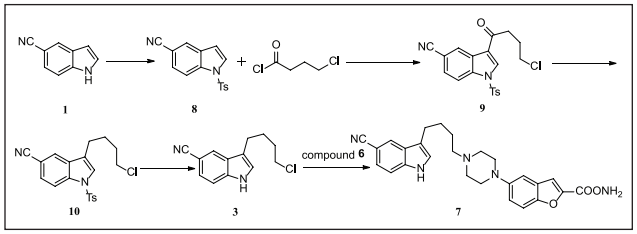


Scheme 1. Current synthesis of vilazodone (**7**).



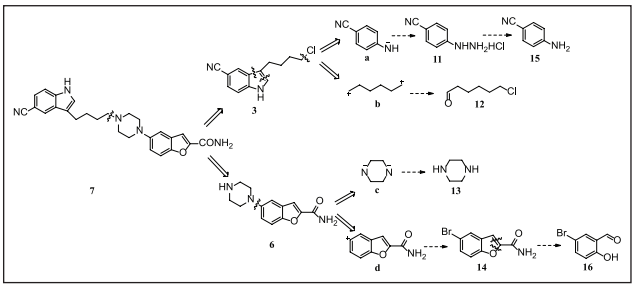
Scheme 2. Current optimal synthesis of 3-(4-chlorobutyl)-1*H*-indole-5-carbonitrile (**3**).

The two above-mentioned synthetic routes both involve environmentally unfriendly reagents,[4,5] such as bis(2-chloroethyl)amine and $NaBH_4$. In addition, 5-cyanoindole (**1**) and 5-nitrobenzofuran-2-carboxamide (**4**) were also demonstrated to be expensive and difficult to synthesize. Herein, we describe a novel synthetic route toward vilazodone (**7**) that is more suitable for industrial production. This route is advantageous due to its low cost and high yield.

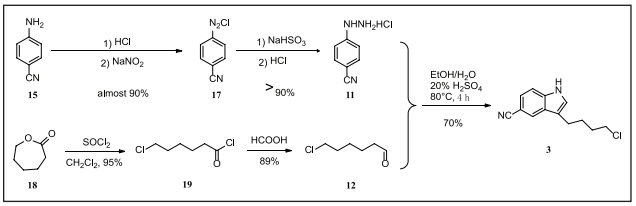
Results and discussion

A retrosynthesis of the new synthetic route is shown in Scheme 3. Vilazodone (**7**) can be disconnected into intermediates **3** and **6**. These intermediates **3** and **6** would give four fragments **a**, **b**, **c**, and **d**, and these fragments can be disconnected into compounds **11**, **12**, **13**, and **14**. Compound **11** can be synthesized through diazotization and reduction of amine **15**, and compound **14** can be synthesized via cyclization of aromatic aldehyde **16** with $BrCH_2COOCH_2CH_3$.

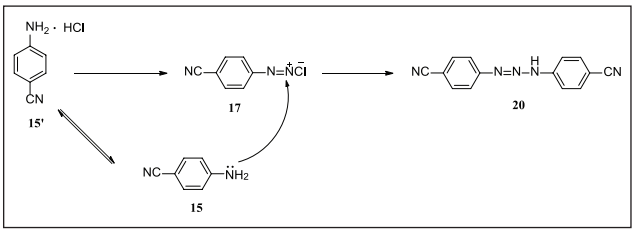
There have been several routes reported for synthesis of compound **3**.[6–8] One of the most suitable routes, which was developed by Xu's group,[3] employed 1*H*-indole-5-carbonitrile (**1**) as the starting material. We have developed an efficient synthetic route to prepare compound **3** (Scheme 4), which is inexpensive and uses commercially available reagents. First, because of the strong electron-withdrawing substituent, it proved difficult to convert 4-aminobenzonitrile (**15**) into the corresponding salt with HCl. In order to increase the yield of 4-cyanobenzenediazonium hydrochloride (**17**), 3 equiv. of HCl and 1.1 equiv. of $NaNO_2$ were required, and the extent of conversion of 4-aminobenzonitrile (**15**) was almost 90%. However, the by-product **20** (Scheme 5) was also observed during this process.[9] To decrease the formation of **20**, the effect of the reaction temperature on this reaction was investigated. Fortunately, it was observed that increasing the reaction temperature reduced the quantity of by-product **20**, and a temperature of 2°C proved to be the best choice (Figure 1). Subsequently, 4-cyanophenylhydrazine hydrochloride (**11**) was easily



Scheme 3. The retrosynthesis of vilazodone (**7**).



Scheme 4. The efficient synthesis of the key intermediate **3**.



Scheme 5. The formation of by-product **20**.

obtained in 90% yield via reduction of 4-cyanoaniline diazonium salt **17** with $NaHSO_3$ at 85°C for 2 h (Scheme 4). However, there existed a problem in which a large quantity of HCl (36.5%, triple the volume of the reaction solution) was needed to salt out compound **11**, which resulted in a lot of waste acid. In order to solve this problem, the HCl was recycled at least four times. The results indicated that the yield of compound **11** using recycled HCl four times was almost 80% and was reduced markedly after more than five times (Figure 2).

Further, 6-chlorohexanal (**12**) could be obtained quite conveniently from compound **18** in two steps by employing $SOCl_2$ and HCOOH and was isolated in a total yield of 85%. Compound **3** could be obtained via a Fischer reaction between compound **11** and aldehyde **12**. For the purpose of increasing the yield of compound **3**, a variety of parameters such as the solvent, catalyst, temperature, and reaction time were screened to determine the optimum reaction condition, and the results are summarized in Table 1. The experimental results indicate that raising the reaction temperature to 170°C led to a decrease in the yield, accompanied with the formation of additional by-product, as detected by thin-layer chromatography (TLC). Following this screening, it was concluded that EtOH/H_2O and 20% H_2SO_4 was a better system to accomplish this Fischer transformation because of the better yield (70%) and lower cost.[9–12]

With compound **3** in hand, we next attempted to explore an efficient route to synthesize carboxamide **6** by using

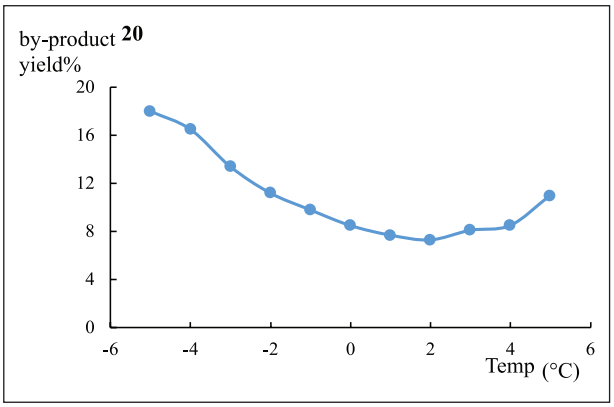


Figure 1. Change in the yield of by-product **20** based on the reaction temperature during diazotization. Reaction conditions: 1 equiv. of 4-aminobenzonitrile, 3 equiv. of HCl, 1.1 equiv. of $NaNO_2$, 1 h.

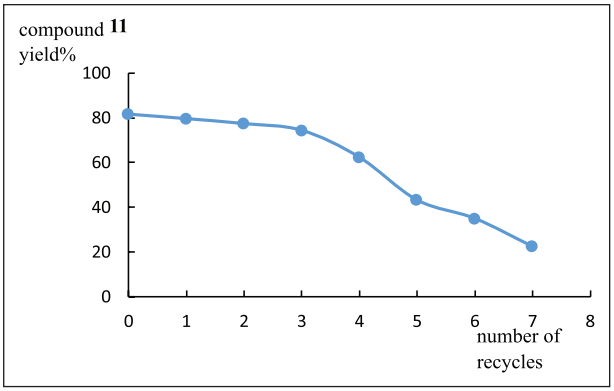


Figure 2. Change in the yield of compound **11** with recycled times of HCl during salting out. Recycled HCl was used directly without any purification.

5-bromo-2-hydroxybenzaldehyde (**16**) as the starting material (Scheme 6). Initially, acid **21** was easily prepared via condensation between compound **16** and ethyl 2-bromoacetate and was isolated in an excellent yield (90%).[13,14] The piperazine moiety can be easily introduced through a C–N cross-coupling reaction under basic conditions to give the intermediate **22**. Although the yield of **22** was not satisfactory, we found that any unconverted compound **21** could be easily recycled. After the reaction, HCl was added to the reaction solution, and the unreacted compound **21** was salted out, while the intermediate **22** stayed in the reaction solution. Finally, intermediate **22** was transformed into carboxamide **6** in 80% yield by treatment with $SOCl_2$ and NH_3 (two steps without isolation).[15,16]

Subsequently, vilazodone (**7**) was prepared via nucleophilic substitution between chloride **3** and carboxamide **6** (Scheme 7). The experimental results indicated that the Et_3N/K_2CO_3 system was very effective for this transformation, and the desired product vilazodone (**7**) was obtained in 65% yield.[1]

Conclusion

In conclusion, we have developed an efficient and potentially commercial process for the synthesis of vilazodone (**7**) by employing 4-aminobenzonitrile and 5-bromo-2-hydroxybenzaldehyde as starting materials. This novel synthetic route involves diazotization, a Fischer reaction, cyclization, and substitution to afford vilazodone in an overall yield of 24% and with 99% purity. It is noteworthy that the reagents and materials used in this synthetic route are inexpensive, and the process should be suitable for industrial production.

Experimental

Melting points were determined using a Buchi digital melting point apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Varian spectrometer at working frequencies of 400 and 100 MHz, respectively, in DMSO-d_6 using tetramethylsilane (TMS) as an internal standard. All chemical shifts are reported as δ values (ppm) relative to TMS and observed coupling constants (*J*) are given in Hertz (Hz). MS data were obtained on an instrument of Agilent 6545 Q-TOF. All reagents were purchased from commercial sources and used without prior purification. Column chromatography was performed on silica gel (200–300 mesh) eluting with *n*-hexane/ethyl acetate.

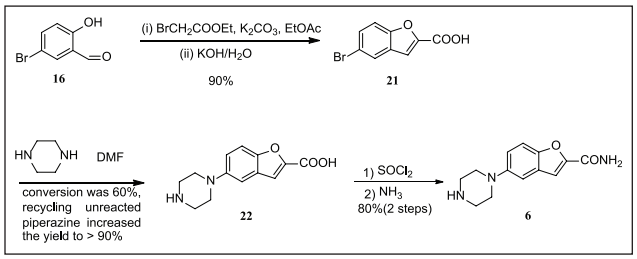
4-Hydrazinylbenzonitrile hydrochloride (**11**): 4-Aminobenzonitrile (118 g, 1.0 mol) was dissolved in hydrochloric acid (36.5%, 300 g, 3.0 mol in 500 mL of H_2O). $NaNO_2$ (79.5 g, 1.1 mol) and H_2O (200 mL) were added into the solution slowly for 1 h at 2°C. Then, reaction mixture was filtered, and the residue was dried for 12 h and identified as by-product **20** (12.3 g). The filtrate was transferred to a new vessel and $NaHSO_3$ (520 g, 5.0 mol) was added, and the mixture was stirred at 85°C for 2 h. After filtering, the filtrate was distilled to remove one-third of the solvent, and then, 36.5% HCl (1 L) was added to the residue solution. After stirring at 50°C for 30 min, the mixture was filtered, and the product was obtained as a white solid. Yield 137 g (81%). High-performance liquid chromatography (HPLC) purity 94.2%. m.p. 238.8–240.5°C. (Lit[17] 240°C). ^1H NMR (400 MHz, D_2O): δ 7.54–7.32 (m, 2H), 6.93–6.83 (m, 2H), 4.67 (s, 1H), 3.33 (s, 2H). ^{13}C NMR (100 MHz, D_2O): δ 158.7, 134.6, 134.6, 122.3, 114.5, 114.5, 103.3. HRMS (ESI): m/z $[M+H]^+$ calculated for $C_7H_8ClN_3$: 170.0480, found: 170.0477.

3-(4-Chlorobutyl)-1H-indole-5-carbonitrile (**3**): Compound **11** (169 g, 1 mol) was dissolved in EtOH/H_2O (1:1, 100 mL), and then, 20% H_2SO_4 (20 mL) and 6-chlorohexanal **12** (134 g, 1.0 mol) were added. The mixture was stirred at 80°C for 4 h. After the reaction was complete, the aqueous was extracted with CH_2Cl_2. The combined CH_2Cl_2 fractions were evaporated to afford product **3** as a milky-white solid. Yield 162 g (70%), 97% purity. m.p. 97.6–99.5°C. (Lit[1] 99–99.5°C) ^1H NMR (400 MHz, DMSO-d_6): δ 11.38 (s, 1H), 8.08 (s, 1H), 7.55–7.25 (m, 3H), 3.67 (t, J=6.1 Hz, 2H), 2.75 (t, J=6.7 Hz, 2H), 1.77 (dd, J=6.3, 3.1 Hz, 4H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 137.8, 127.2, 124.8, 124.5, 123.2, 120.7, 117.1, 111.9, 102.2, 44.9, 32.4, 27.3, 24.2. HRMS (ESI): m/z $[M+Na]^+$ calculated for $C_{13}H_{13}ClN_2$: 255.0659, found: 255.0657.

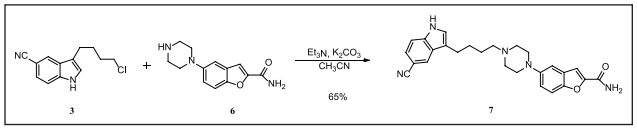
5-Bromobenzofuran-2-carboxylic acid (**21**): 5-Bromo-2-hydroxybenzaldehyde (**16**) (201 g, 1.0 mol) was dissolved in

Table 1. Optimization of the Fischer indole reaction in the synthesis of compound **3**.

Entry	Solvent	Catalyst	Temperature (°C)	Time (h)	Yield (%)
1	EtOH/H_2O	20% CH_3COOH	80	4	–
2	EtOH/H_2O	36.5% HCl	80	4	35
3	EtOH/H_2O	20% H_2SO_4	80	4	70
4	EtOH/H_2O	10% TFA	80	4	68
5	*n*-butanol/H_2O	20% CH_3COOH	110	4	–
6	*n*-butanol/H_2O	36.5% HCl	110	4	34
7	*n*-butanol/H_2O	20% H_2SO_4	110	4	65
8	*n*-butanol/H_2O	10% TFA	110	4	68
9	Ethylene glycol/H_2O	20% CH_3COOH	170	2	–
10	Ethylene glycol/H_2O	36.5% HCl	170	2	23
11	Ethylene glycol/H_2O	20% H_2SO_4	170	2	47
12	Ethylene glycol/H_2O	10% TFA	170	2	51



Scheme 6. The efficient synthesis of key intermediate **6.**



Scheme 7. Synthesis of vilazodone (**7**).

ethyl acetate (1 L), and then, $BrCH_2COOCH_2CH_3$ (334 g, 2 mol) and K_2CO_3 (410 g, 3 mol) were added. The mixture was stirred and refluxed for 6 h. After the reaction was complete, the liquid was filtered and the filtrate was concentrated under vacuum. KOH (84 g, 1.5 mol) and H_2O (500 mL) were added to the residue, and the resulting mixture was stirred at 80°C for 3 h. Subsequently, HCl (3 mol L^{-1}) was added to adjust the pH to 2. After filtration, the product **21** was obtained as a white solid. Yield 217 g (90%) with 94% purity. m.p. 255.5–256.8°C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.64 (s, 1H), 7.95 (d, J = 1.9 Hz, 1H), 7.77–7.46 (m, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 159.4, 153.0, 146.9, 129.9, 128.8, 125.1, 115.8, 114.0, 112.5. HRMS (ESI): m/z $[M + H]^+$ calculated for $C_9H_5BrO_3$: 240.9495, found: 240.9490.

5-(Piperazin-1-yl)benzofuran-2-carboxylic acid (**22**): Compound **21** (241 g, 1.0 mol) and piperazine (430 g, 5 mol) were dissolved in dimethylformamide (DMF), and the mixture was stirred at 140°C for 6 h. After the reaction was complete, HCl (10 mol L^{-1}, 500 mL) was added. After filtration, KOH/H_2O was added into the filtrate until pH 6–7. The solution was extracted with CH_2Cl_2, and then, the organic phase was concentrated under vacuum to obtain product **22** as a faint yellow solid. Yield 221 g (90%) with 95% purity. m.p. 275–278.2°C. (Lit[18] 274–276°C). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.58 (s, 1H), 8.19–7.28 (m, 4H), 3.02 (d, J = 4.2 Hz, 4H), 2.86 (s, 4H), 2.51 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 159.6, 149.6, 148.2, 126.8, 117.9, 110.9, 109.6, 107.7, 107.3, 52.3(2), 45.5(2). HRMS (ESI): m/z $[M + H]^+$ calculated for $C_{13}H_{14}N_2O_3$: 247.1077, found: 247.1080.

5-(Piperazin-1-yl)benzofuran-2-carboxamide (**6**): Compound **22** (246 g, 1.0 mol) was dissolved in $ClCH_2CH_2Cl$, and $SOCl_2$ (119 g, 1 mol) was added slowly to the solution and the resulting mixture was stirred at 60°C for 4 h. After filtration, the solid was dissolved in tetrahydrofuran (THF) (1 L), and then, NH_3 gas (0.3 MPa in high-pressure reactor) was poured into the solution. The resulting mixture was stirred at 25°C for 30 min. After the reaction was complete, the mixture was concentrated under vacuum to provide the product **6**. Yield 196 g (80%) with 97% purity. m.p. 251.3–254.3°C. (Lit[19] 253–255°C). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.19–7.28 (m, 4H), 7.15 (d, J = 6.6 Hz, 2H), 3.02 (d, J = 4.2 Hz, 4H), 2.86 (s, 4H), 2.51 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 159.9, 149.2, 148.6, 127.5, 117.9, 111.4, 109.6, 107.3, 107.2, 51.0(2), 45.71, 45.7. HRMS (ESI): m/z $[M + H]^+$ calculated for $C_{13}H_{15}N_3O_2$: 246.1237, found: 246.1245.

Vilazodone (**7**): Compound **3** (233 g, 1.0 mol) and **6** (245 g, 1.0 mol) were dissolved in acetonitrile (3 L), and then, triethylamine (101 g, 1.0 mol) and K_2CO_3 (138 g, 1.0 mol) were added to the solution. The mixture was heated at reflux for 12 h. Subsequently, the reaction mixture was poured into cold water (3 L). After filtration, the solid was dissolved in EtOAc, and then, HCl-EtOAc saturated solution was added to enable crystallization. Product **7** was obtained as a white solid. Yield 287 g (65%) with 99% HPLC purity after the mixture was filtered. m.p. 276.5–279.2°C (Lit[1] 277–279°C). ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.35 (s, 1H), 8.04 (d, J = 18.3 Hz, 2H), 7.74–6.88 (m, 8H), 3.69–3.15 (m, 8H), 2.74 (t, J = 7.2 Hz, 2H), 2.37 (t, J = 7.2 Hz, 2H), 1.80–1.61 (m, 2H), 1.54 (d, J = 6.8 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 159.9, 148.8, 147.9, 138.6, 137.7, 127.8, 126.9, 124.7, 124.0, 123.3, 120.9, 117.8, 115.7, 112.4, 111.6, 109.5, 107.3, 100.0, 57.5, 52.8(2), 49.8(2), 27.7, 26.1, 24.1. HRMS (ESI): m/z $[M + H]^+$ calculated for $C_{26}H_{27}N_5O_2$: 442.2238, found: 442.2240.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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