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Technical Notes

An Improved Synthetic Route for Preparative Process of Vardenafil

Yongjun Mao,[†] Guanghui Tian,[†] Zheng Liu,[‡] Jingkang Shen,[†] and Jingshan Shen*[,†,‡]

Shanghai Institute of Materia Medica, Chinese Academy of Sciences, 555 Zu Chong Zhi Road, Pudong, Shanghai 201203, China, and Topharman Shanghai Co., Ltd., 1088 Chuansha Road, Pudong, Shanghai 201209, China

Abstract:

A new, convergent synthetic route for the process optimization of vardenafil (Levitra), a potent and effective PDE5 inhibitor, is described. Key improved steps in the preparative process are that the chlorosulfonation reaction is at the beginning and the dehydration-cyclisation reaction is at a later stage so that the synthetic route has a better overall yield and simpler workup operations. The yield of vardenafil produced from this synthetic route is around 45% over seven steps with purity at 99.2% (HPLC).

Introduction

Vardenafil (**1**, Figure 1) is a selective inhibitor of phophodiesterase 5 (PDE5) for the treatment of male erectile dysfunction (MED).[1] Vardenafil (Levitra) has been approved as a new drug by the FDA and launched in late 2003. Further uses are being proposed and investigated, such as therapy for pulmonary hypertension.[2]

Several synthetic methods were reported for the preparation of vardenafil and related intermediates.[3] The commonly employed larger-scale synthetic route of **1** is shown in Scheme 1.[4] Commercially available 2-ethoxybenzamide (**5**) was used as the starting material and converted to the benzonitrile **6** at first. The benzamidine **8**, obtained from the benzamidoxime **7**, was converted to the benzamidrazone, **9**. The intermediate **9** was then condensed with **4**, afforded by Dakin−West reaction of the acylated alanine **3**, to give the cyclisation product **10**, which was transformed to the imidazolotriazinone **11** by dehydration−cyclisation reaction with acetyl chloride or $POCl_3$. The title compound **1** was produced from the intermediate **11** by sulfonation, chlorination, and sulfonamide formation with 1-ethylpiperazine in sequence.

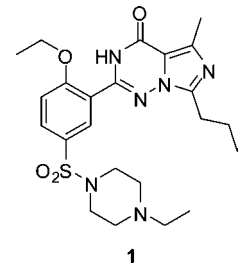

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Figure 1. **Chemical structure of vardenafil.**

This synthetic route had been used for preparing vardenafil on multikilogram scale, whereas the synthesis of imidazolotriazinone **11** gave a yield of around 50% over four steps.[4] Further, the sulfonation reaction of **11** was carried out with concentrated sulfuric acid (8−9 equiv), which afforded the sulfonic acid **12** in 80% yield. Then, **12** was converted to the sulfonyl chloride with thionyl chloride (10−11 equiv) while the intermediate was liable to hydrolysis whereby it was directly reacted with 1-ethylpiperazine to provide the title compound **1**.

Hence, we reviewed the earlier synthesis, modified the reaction conditions, and developed a new process for producing vardenafil.[5] This improved method, whose details are presented in this paper, is a potential process for scale-up preparation of vardenafil.

Results and Discussion

In the present synthetic route (Scheme 2), **5** is first converted to the sulfonyl chloride **13** by treating with chlorosulfonic acid (∼1.2 equiv) in dichloromethane at room temperature. The product **13** is relatively stable to ice−water and results in convenient operations with good yield. Then, **13** is treated with 1-ethylpiperazine at room temperature to provide **14**, which is dehydrated with $POCl_3$ at 80−90 °C to give the benzonitrile **15** in 70−75% yield (three steps). As reported by Dunn,[6] **15** could be also prepared from 2-ethoxybenzonitrile (**6**) only in 17.8% yield via column chromatography.

The benzamidine **16** is afforded by the reaction of **15** with lithium hexamethyldisilazane (∼1.2 equiv) in THF at room temperature in 80−85% yield. Then **16** is converted to the

* Author for correspondence. Telephone: +86 21 50805891. Fax: +86 21 64319573. E-mail: jsshen@mail.shcnc.ac.cn; jingshan.shen@topharman.com.
† Shanghai Institute of Materia Medica, Chinese Academy of Sciences.
‡ Topharman Shanghai Co., Ltd.

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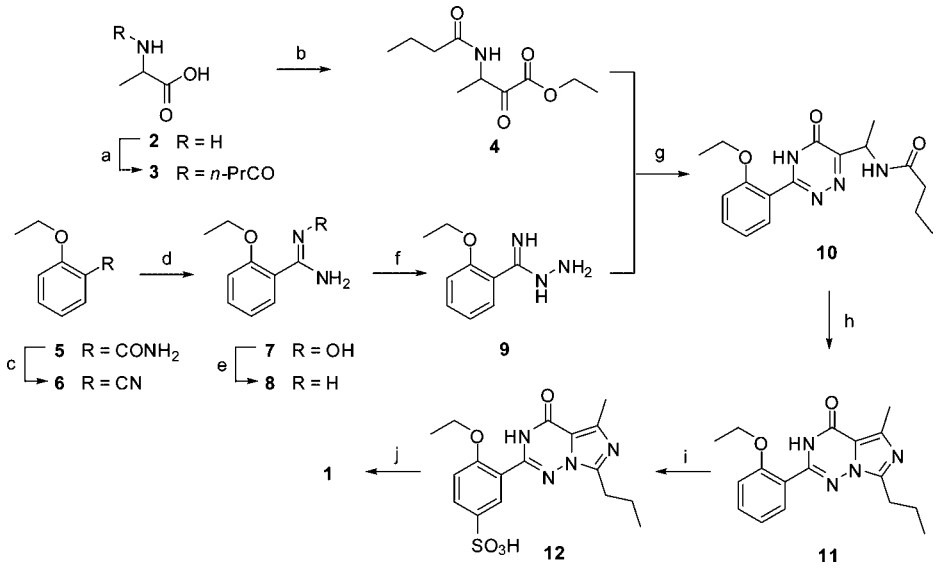
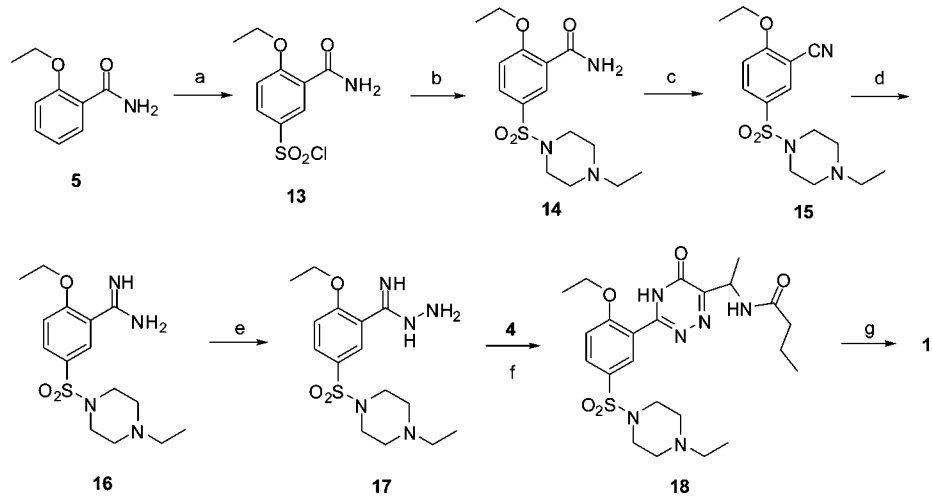
Scheme 1. **Reported large-scale synthesis of vardenafil**[a]



[a] Reagents and conditions: (a) *n*-PrCOCl, NaOH, 68%; (b) $ClCOCO_2Et$, DMAP, THF; (c) $SOCl_2$, toluene; (d) $NH_2OH \cdot HCl$, *i*-PrOH, 68.2%; (e) H_2, Pd−C, AcOH, 90.7%; (f) $N_2H_4 \cdot H_2O$, MeOH; (g) MeOH; (h) AcCl, HOAc, 54%; (i) H_2SO_4, 80.1%; (j) $SOCl_2$; 1-ethylpiperazine, 93.2%. (yield 24.8% from **5** to **1**).

Scheme 2. **Improved synthetic route of vardenafil**[a]



[a] Reagents and conditions: (a) $ClSO_3H$, CH_2Cl_2, < 20 °C; (b) 1-ethylpiperazine, rt, 86%; (c) $POCl_3$, 80−90 °C, 85%; (d) LHMDS, THF, rt, 83%; (e) $N_2H_4 \cdot H_2O$, EtOH, rt, 88%; (f) EtOH, reflux; (g) $POCl_3$, 70 °C, 84%. (yield 45% from 5 to 1).

benzamidrazone **17** by treating with hydrazine hydrate in ethanol. The intermediate **17** can be isolated as a crystalline compound which is probably purer than the benzamidrazone **9** (which does not crystallize and therefore has to be used in solution) of the original synthesis, which gives a better yielding coupling reaction with **4**. Compound **4** is prepared from (*R*,*S*)-alanine according to the method reported by Nowakowski.[4] Without isolation, **4** is reacted with **17** to afford the intermediate **18**, which is directly transformed into the title compound **1** by dehydration−cyclisation reaction (around 90% yield) with $POCl_3$ at 70−80 °C. The pure product **1** is produced by recrystallization from ethyl acetate−petroleum ether, resulting in 84% yield (over two steps).

This new synthetic route has several advantages. First, the chlorosulfonation reaction is now carried out, as a single step, at the beginning of the route, instead of two steps involving sulfonation and chlorination reactions, which gives purer product and simpler workup operations. Second, the key dehydration−cyclisation reaction to form the imidazo−triazinone ring of **1** is at a later stage of the route, which has a better yield (over 80%). Third, this new route is more convergent than the original synthesis, which leads to a higher yield. The overall yield of **1** obtained from this route is around 45% (from **5**, seven steps) with purity at 99.2% (HPLC).

Conclusions

In conclusion, we have developed a new, convergent synthetic route for preparative process of vardenafil. Key improved steps in the process are that the chlorosulfonation of **5** is introduced with chlorosulfonic acid at an early stage and the dehydration−cyclisation of **18** is carried out at a later stage of the route so that this synthetic route has a better overall yield and simpler workup operations, which makes it a potential preparative process of vardenafil.

Experimental Section

All commercially available materials and solvents were used as received products without further purification. ^{1}H NMR spectra were recorded with a Gemini-300 spectrometer using TMS as an internal standard. The mass spectra were obtained from a Finnigan MAT-95/711 spectrometer. Melting points were measured on a Büchi-510 melting point apparatus.

2-Ethoxy-5-[(4-ethyl-1-piperazinyl)sulfonyl]-benzamide (14). Chlorosulfonic acid (24 mL, 0.36 mol) was added dropwise to an ice-cooled solution of 2-ethoxybenzamide (50 g, 0.3 mol) in dichloromethane (400 mL), keeping the reaction temperature below 20 °C. The resulting mixture was stirred for 4−6 h at rt and then quenched with ice−water. The organic solution was washed with water and then cooled in an ice bath. 1-Ethylpiperazine (46 mL, 0.36 mol) was added to the mixture, which was further stirred at rt for 30 min. The organic layer was washed with water, dried, and concentrated to about 100 mL. Petroleum ether (200 mL) was added, and the resulting white solid was collected via suction filtration and dried to provide **14** (88.0 g, 86%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.01 (t, 3H, J = 6.9 Hz), 1.56 (t, 3H, J = 6.9 Hz), 2.38 (q, 2H, J = 6.9 Hz), 2.50 (t, 4H, J = 4.5 Hz), 3.03 (t, 4H, J = 4.5 Hz), 4.28 (q, 2H, J = 6.9 Hz), 6.14 (s, 1H), 7.06 (d, 1H, J = 8.9 Hz), 7.67 (s, 1H), 7.82 (dd, 1H, J = 8.9 Hz, 2.7 Hz), 8.58 (d, 1H, J = 2.7 Hz). EI-MS m/z 341 (M^+). Anal. Calcd for $C_{15}H_{23}N_3O_4S$: C, 52.77; H, 6.79; N, 12.31. Found: C, 52.61; H, 6.77; N, 12.02.

2-Ethoxy-5-[(4-ethyl-1-piperazinyl)sulfonyl]-benzonitrile (15). A mixture of the benzamide **14** (68.2 g, 0.2 mol) and $POCl_3$ (150 mL) was stirred at 80−90 °C for 1 h. The $POCl_3$ was then recovered, and the residue was added to ice slowly. The mixture was basified to pH ≈ 6 with 2 M NaOH, and the resulting solid was collected via suction filtration and dried. **15** was yielded as a white solid (55.0 g, 85%) via recrystallization from ethyl acetate−petroleum ether. Mp 84−87 °C (lit.[6] 86−88 °C). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.47 (t, 3H, J = 7.2 Hz), 1.54 (t, 3H, J = 7.2 Hz), 2.97 (q, 2H, J = 7.2 Hz), 3.10 (br, 4H), 3.55 (br, 4H), 4.26 (q, 2H, J = 7.2 Hz), 7.10 (d, 1H, J = 8.7 Hz), 7.85 (dd, 1H, J = 8.7 Hz, 2.4 Hz), 7.96 (d, 1H, J = 2.4 Hz). ESI-MS m/z 324.1 (M + 1).

2-Ethoxy-5-[(4-ethyl-1-piperazinyl)sulfonyl]-benzamidine (16). Lithium hexamethyldisilazane (180 mL of 1 M solution in THF, 0.18 mol) was slowly added to a solution of the benzonitrile **15** (48.5 g, 0.15 mol) in anhydrous THF (100 mL) at rt. The reaction mixture was stirred for 10 h and then acidified to pH∼3 with 1 M HCl. The solvent was removed and the solution was basified to pH∼12 with 2 M NaOH. The resulting solid was collected via suction filtration, dried to provide **16** (42.0 g, 83%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.02 (t, 3H, J = 6.9 Hz), 1.49 (t, 3H, J = 6.9 Hz), 2.40 (q, 2H, J = 6.9 Hz), 2.52 (t, 4H, J = 4.8 Hz), 3.03 (t, 4H, J = 4.8 Hz), 4.18 (q, 2H, J = 6.9 Hz), 7.02 (d, 1H, J = 8.7 Hz), 7.74 (dd, 1H, J = 8.7 Hz, 2.1 Hz), 7.94 (d, 1H, J = 2.1 Hz). ESI-MS m/z 341.2 (M + 1).

2-Ethoxy-5-[(4-ethyl-1-piperazinyl)sulfonyl]-benzamidrazone (17). Hydrazine hydrate (6.5 mL, 0.11 mol) was added slowly to a solution of the benzamidine **16** (34.0 g, 0.1 mol) in ethanol (200 mL). The mixture was stirred at rt for 1 h then concentrated to around 60 mL. The resulting solid was collected via suction filtration, washed with ethyl acetate and dried to yield a white solid **17** (31.2 g, 88%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.02 (t, 3H, J = 6.9 Hz), 1.49 (t, 3H, J = 6.9 Hz), 2.39 (q, 2H, J = 6.9 Hz), 2.51 (br, 4H), 3.05 (br, 4H), 4.18 (q, 2H, J = 6.9 Hz), 7.00 (d, 1H, J = 8.7 Hz), 7.69 (dd, 1H, J = 8.7 Hz, 2.1 Hz), 8.13 (d, 1H, J = 2.1 Hz). ESI-MS m/z 356.3 (M + 1). Anal. Calcd for $C_{15}H_{25}N_5O_3S$: C, 50.68; H, 7.09; N, 19.70. Found: C, 50.51; H, 7.17; N, 19.85.

***N*-[1-[3-[2-Ethoxy-5-[(4-ethyl-1-piperazinyl)sulfonyl]-phenyl]-2,5-dihydro-5-oxo-1,2,4-triazin-6-yl]ethyl]-butanamide (18).** As reported by Nowakowski,[4] compound **4** was prepared from (*R*,*S*)-alanine in 70−80% yield which was used in this step without isolation. A mixture of **4** (22.0 g, 0.1 mol) and the benzamidrazone **17** (14.5 g, 0.04 mol) in ethanol (100 mL) was heated to reflux for 2 h. The resulting solution was filtered, and the filtrate was concentrated to provide crude **18** (21.0 g) which was used directly in the next step. A small reference sample was obtained by chromatography on silica gel, ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.93 (t, 3H, J = 7.2 Hz), 1.02 (t, 3H, J = 7.2 Hz), 1.53 (d, 3H, J = 7.2 Hz), 1.63 (t, 3H, J = 7.2 Hz), 1.66 (m, 2H), 2.19 (t, 2H, J = 7.2 Hz), 2.44 (q, 2H, J = 7.2 Hz), 2.54 (br, 4H), 3.06 (br, 4H), 3.10 (m, 1H), 4.42 (q, 2H, J = 7.2 Hz), 6.85 (d, 1H, J = 9.0 Hz), 7.18 (d, 1H, J = 8.7 Hz), 7.90 (dd, 1H, J = 8.7 Hz, 2.4 Hz), 8.84 (d, 1H, J = 2.4 Hz), 12.32 (s, 1H). EI-MS m/z 506 (M^+). Anal. Calcd for $C_{23}H_{34}N_6O_5S$: C, 54.53; H, 6.76; N, 16.59. Found: C, 54.34; H, 6.90; N, 16.39.

2-[2-Ethoxy-5-[(4-ethyl-1-piperazinyl)sulfonyl]phenyl]-5-methyl-7-propyl- imidazo[5,1-*f*][1,2,4]triazin-4(1H)-one (1). A mixture of the amide **18** (21 g, 0.04 mol) and $POCl_3$ (60 mL) was stirred at 70−80 °C for 2 h. The $POCl_3$ was recovered, and the residue was added to ice slowly. The mixture was basified to pH ≈ 9 with 2 M NaOH. The resulting pale solid was then collected via suction filtration and dried. The target compound **1** was produced as a white solid (16.1 g, 84%) via recrystallization from ethyl acetate−petroleum ether, purity at 99.2% (HPLC). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.00 (t, 3H, J = 7.2 Hz), 1.08 (t, 3H, J = 7.2 Hz), 1.58 (t, 3H, J = 6.9 Hz), 1.86 (m, 2H), 2.49 (q, 2H, J = 7.2 Hz), 2.54 (br, 4H), 2.64 (s, 3H), 2.99 (t, 2H, J = 7.2 Hz), 3.15 (br, 4H), 4.32 (q, 2H, J = 6.9 Hz), 7.15 (d, 1H, J = 9.0 Hz), 7.88 (dd, 1H, J = 9.0 Hz, 2.1 Hz), 8.48 (d, 1H, J = 2.1 Hz), 9.52 (s, 1H). ESI-MS m/z 488.8 (M + 1), 511.4 (M + 23). **HPLC Conditions:** ZORBAX SB-C 18 4.6 mm × 150 mm × 5 μm; Detection: UV operated at 226 nm; Flow rate: 1.0 mL/min; Temperature: 25 °C; Injection load: 10 μL; Concentration: 0.5 mg/mL; Run time: 30 min; Mobile phase A: buffer (0.02 M KH_2PO_4 + 0.5% TEA, pH adjusted to 6.0 with dilute H_3PO_4); Mobile phase B: acetonitrile; Gradient program: time (min): 0 10 20 30; % of mobile phase A: 65, 65, 30, 30; % of mobile phase B: 35, 35, 70, 70; Retention time of **1**: 9.438 min.

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