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Original article

Facile synthesis of suvorexant, an orexin receptor antagonist, *via* a chiral diazepane intermediate

Yin Chen [a,b,1], Yan Zhou [a,1], Jun-Hong Li [b], Jia-Quan Sun [b], Gui-Sen Zhang [a,b,*]

[a] *Systems Biology Theme, Department of Biomedical Engineering, College of Life Science and Technology, Huazhong University of Science and Technology, Wuhan 430074, China*
[b] *Jiangsu Nhwa Pharmaceutical Co., Ltd., Xuzhou 221116, China*

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ABSTRACT

A facile synthesis of suvorexant, an orexin receptor antagonist, is described. The key intermediate **6** was prepared from *R*-3-aminobutyric acid through protection, condensation, deprotection, cyclization, and hydrogenation steps. The title product was obtained with a total yield of 31% (>99% *ee*) after eight linear steps using commercially available raw materials.

1. Introduction

Insomnia is characterized by difficulties in initiating, maintaining, or obtaining good quality sleep and is a prevalent public health problem affecting large segments of the population on a situational, recurrent, or chronic basis. The estimated annual costs associated with insomnia number into the billions of dollars [1–4]. Over the past several years, the orexin system has gained major popularity as a novel mechanism for the control of sleep disorders due to its highly conserved nature and its ability to regulate arousal and wakefulness [5]. Orexin A (OX-A) and orexin B (OX-B) (the hypocretins), neuropeptides produced by neurons in the hypothalamus, are derived from the same precursor protein [6,7]. The relationship between reduced orexin levels and narcolepsy has been demonstrated in rodents, dogs, and humans [8]. These studies suggest the potential of an orexin receptor antagonist in the treatment of sleep disorders. Suvorexant (Fig. 1), a dual orexin receptor antagonist developed by Merck & Co. [9] completed phase III clinical trials for the treatment of primary insomnia.

In recent years, several protocols have been developed for the synthesis of suvorexant (Scheme 1). The original synthetic route was developed by Cox and coworkers in 2010 [9]. Central to this approach was the synthesis of the core diazepane R-**11**, which was afforded by a preparative chiral high-performance liquid chromatography (HPLC) separation of orthogonally protected racemic **11**. Removal of the Boc protecting group, coupling with acid **5**, and hydrogenolysis of the Cbz group yielded compound **9**. Finally, treatment of **9** with 2,5-dichloro-1,3-benzoxazole **8** in the presence of potassium carbonate completed the synthesis of **1**.

The large-scale synthesis of Suvorexant was reported in 2011 [10]. The key intermediate, R-isomer **12** could be achieved *via* the classical resolution, while the racemic **12** was prepared through the reductive amination of **13**, and **1** was accomplished followed by condensation with **5**. However, in addition to the desired product racemic **12** it was found that impurities **15** and **16** were generated [10] (Scheme 1).

Strotman et al. [11] offered the first asymmetric reductive amination of a dialkyl ketone with an alkyl amino. The desired diazepane ring R-**12** was produced in 97% yield and high enantiopurity (94.5% *ee*) by mediation with a novel Ru-based transfer hydrogenation catalyst.

More recently, Mangion et al. [12] reported yet another strategy for the synthesis of suvorexant. The transamination of compound **14** was conducted with a biological enzyme (*i.e.*, CDX-017), resulting in good conversion yields and high enantiopurity (>99% *ee*).

* Corresponding author at: Systems Biology Theme, Department of Biomedical Engineering, College of Life Science and Technology, Huazhong University of Science and Technology, Wuhan 430074, China.
E-mail address: gszhang@mail.hust.edu.cn (G.-S. Zhang).
[1] These authors contributed to this work equally.

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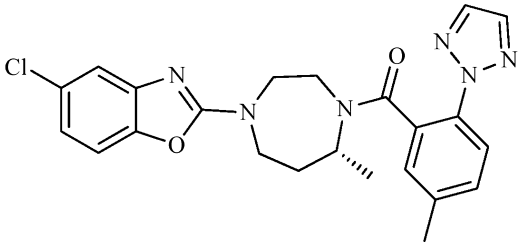


Fig. 1. Structure of suvorexant.

As a part of our continuing interest in developing practical and efficient processes for the synthesis of active pharmaceutical ingredients (APIs) and related intermediates, the current study describes recent efforts to develop a practical route to synthesizing suvorexant.

2. Experimental

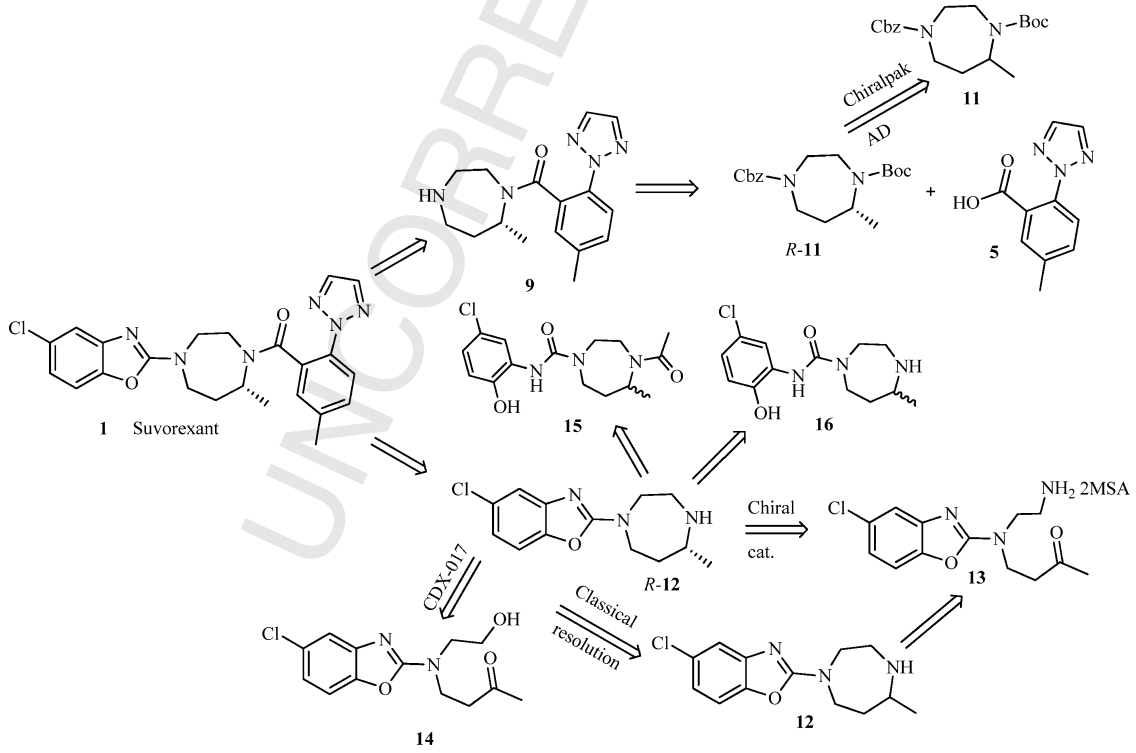
R-3-aminobutyric acid and compound **8** were purchased from commercial suppliers. Melting points were determined in open capillary tubes and are uncorrected. The reactions were monitored by thin-layer chromatography to detect the completion of the reaction. NMR spectra were recorded on a Bruker Ascend™ 600 spectrometer. Mass spectra were provided on Agilent 1100 LC-MS.

*2.1. Synthesis of (R)-methyl 2-(N-benzyl-3-((tert-butoxycarbonyl)amino)-butanamido)acetate (**3**)*

To a solution of methyl 2-(benzylamino)acetate (compound **10**, 50.14 g, 0.28 mol), (*R*)-3-((tert-butoxycarbonyl)amino)butanoic acid (50.75 g, 0.25 mol), 1-hydroxy-1*H*-benzotriazole (41.88 g, 0.31 mol), and dry triethylamine (37.95 g, 0.38 mol) in 320 mL of DMF was added EDC hydrochloride (57.51 g, 0.30 mol), and the reaction was stirred for 5 h at room temperature. The reaction was partitioned between EtOAc and 10% aqueous citric acid, the layers were separated and the organic was washed with 5% aqueous Na_2CO_3, then with brine, dried over $MgSO_4$ and concentrated by rotary evaporation. The residue was recrystallized from a mixture solvent (PE:EtOAc = 2:1) to provide compound **3** as a white solid, 83.01 g in 91% yield. Mp: 107 °C, $[\alpha]_D^{25}$ 22.0 (*c* 0.52, MeOH). ^{1}H NMR (600 MHz, DMSO-d_6): δ 7.38–7.23 (m, 5H), 6.73–6.72 (d, 1H, *J* = 6 Hz), 4.75–4.43 (m, 2H), 4.31–3.95 (m, 2H), 3.89–3.87 (t, 1H, *J* = 12 Hz), 3.64–3.62 (d, 3H, *J* = 12 Hz), 2.64–2.50 (m, 1H), 2.37–2.23 (m, 1H), 1.38–1.37 (d, 9H, *J* = 6 Hz), 1.08–1.06 (m, 3H); MS (ESI) *m*/*z*: 365.20 $[M+H]^+$. HR-MS(ESI): *m*/*z* [M+H] calcd. for $C_{19}H_{28}N_2O_5$: 365.2071; found: 365.2066.

*2.2. Synthesis of (R)-4-benzyl-7-methyl-1,4-diazepane-2,5-dione (**4**)*

A solution of compound **3** (15.93 g, 43.74 mmol) in 10 mL EtOAc was added 150 mL 45% HCl/EtOAc and the reaction was stirred for 4 h. The solvents were removed by rotary evaporation, and the residue was basified with saturated aqueous $NaHCO_3$, and extracted with CH_2Cl_2. The organic extracts were concentrated. The residue was dissolved in 150 mL of dehydrated MeOH, treated with CH_3ONa (2.84 g, 52.49 mmol), and stirred at room temperature overnight (N_2 protected, slightly exothermic). The reaction was cooled to room temperature and quenched with aqueous NH_4Cl. Most of the solvent was removed and the reaction was then dumped into a separatory funnel containing 5% aqueous Na_2CO_3 and extracted with CH_2Cl_2 three times. The organic layers were combined, dried over $MgSO_4$, and concentrated to provide compound **4** as a white solid 9.50 g in 94% yield. Analytical HPLC analysis carried out on Chiralpak AD column (4.6 mm × 250 mm) with 60% EtOH in hexanes (containing 0.1% diethylamine as a modifier), flow rate of 1 mL/min, indicated that intermediate (*R*)-**4** was of >99% *ee*. Mp: 122–123 °C. $[\alpha]_D^{25}$ 33.5 (*c* 0.56, MeOH). ^{1}H NMR (600 MHz, DMSO-d_6): δ 7.77–7.76 (bd, 1H, *J* = 6 Hz),



Scheme 1. Reported synthetic route of suvorexant.

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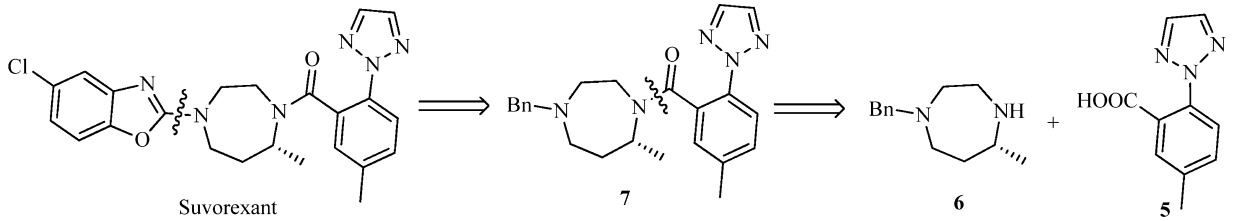
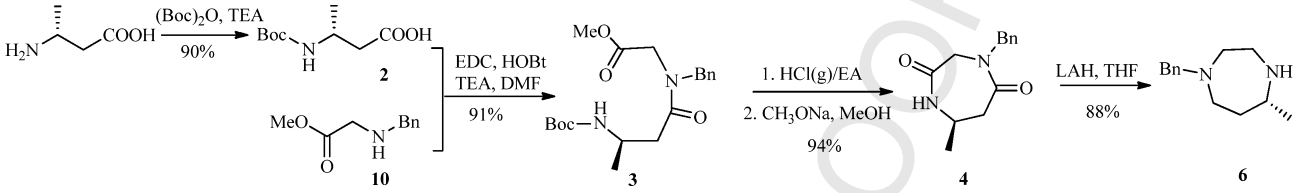


Scheme 2. Retro-synthesis of suvorexant.



Scheme 3. Synthesis of **6**.

7.33–7.25 (m, 5H), 4.59–4.53 (m, 2H), 4.10– 4.02 (m, 2H), 3.65–3.62 (m, 1H), 2.93–2.90 (m, 1H), 2.76–2.72 (m, 1H), 1.14–1.13 (d, 3H, J = 6 Hz); ^{13}C NMR (150 MHz, DMSO-d_6): δ 171.1, 168.4, 138.1, 128.9, 128.0, 127.7, 53.1, 50.6, 46.5, 40.5, 23.3. MS (ESI) m/z: 233.10 $[M+H]^+$. HR-MS(ESI): m/z [M+H] calcd. for $C_{13}H_{16}N_2O_2$: 233.1285; found: 233.1289.

2.3. Synthesis of (R)-1-benzyl-5-methyl-1,4-diazepane (6)

A solution of compound **4** (1.40 g, 6.0 mmol) in 60 mL THF at 0 °C was treated with $LiAlH_4$ (1.36 g, 36.0 mmol) in batches. The reaction was slowly warmed to room temperature and stirred for another 4 h. The reaction was then cooled to −10 °C and was carefully quenched with 1.5 mL water, then NaOH (1.5 mL, 15%) followed by an additional 4.5 mL of water. A portion of $MgSO_4$ was added and the mixture was stirred for 1 h before filtered. The filtrate was concentrated to provide light yellow oil 1.10 g in 88% yield. $[\alpha]_D^{25}$ −5.9 (c 1.00, $CHCl_3$), ee >99%, Analytical analysis was performed on Chrom Tech chiral-AGP column (150 mm × 4 mm) with 99% 1 mol/L ammonium dihydrogen phosphate and 1% acetonitrile, at flow rate of 0.5 mL/min with column temperature of 40 °C. ^{1}H NMR (600 MHz, DMSO-d_6): δ 7.32–7.20 (m, 5H), 3.57 (s, 2H), 3.48 (bs, 1H), 2.99–2.95 (m, 1H), 2.86–2.82 (m, 1H), 2.72–2.68 (m, 1H), 2.65–2.61 (m, 1H), 2.58–2.49 (m, 3H), 1.75–1.70 (m, 1H), 1.46–1.41 (m, 1H), 1.01–1.00 (d, 3H, J = 6 Hz); ^{13}C NMR (150 MHz, DMSO-d_6): δ 140.1, 128.9, 128.5, 127.1, 62.5, 58.8, 52.7, 52.6, 47.0, 37.5, 23.9. MS (ESI) m/z: 205.10 $[M+H]^+$. HR-MS(ESI): m/z [M+H] calcd. for $C_{13}H_{20}N_2$: 205.1699; found: 205.1692.

2.4. Synthesis of (R)-(4-benzyl-7-methyl-1,4-diazepan-1-yl)(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone (7)

To a solution of compound **6** (2.40 g, 11.76 mmol), compound **5** (2.86 g, 14.11 mmol), 1-hydroxy-1H-benzotriazole (1.90 g, 14.11 mmol), and dry triethylamine (3.56 g, 35.28 mmol) in 18 mL of dry DMF was added EDC hydrochloride (2.70 g, 14.11 mmol), and the reaction was stirred 2 h at room temperature. The reaction was partitioned between EtOAc and saturated aqueous $NaHCO_3$, the layers were separated and the organic was added to aqueous citric acid stirring for 1 h. Water was added and the mixture was partitioned. Combined the water layers and added saturated aqueous Na_2CO_3 to regulate pH > 9, then extracted with three portions of EtOAc. The organic layers were combined, dried over $MgSO_4$ and concentrated by rotary evaporation to provide compound **7** as a white power 4.30 g in 93% yield. Mp: 108–109 °C, $[\alpha]_D^{25}$ −58.4 (c 1.01, MeOH). ^{1}H NMR (600 MHz, DMSO-d_6): δ 8.00–7.76 (m, 3H), 7.37–7.17 (m, 7H), 4.40–4.09 (m, 1H), 3.63–3.48 (m, 2H), 3.44–3.02 (m, 3H), 2.82–2.75 (m, 1H), 2.63–2.47 (m, 1H), 2.63–2.14 (m, 5H), 2.02– 1.63 (m, 2H), 1.17–0.99 (m, 3H); MS (ESI) m/z: 390.30 $[M+H]^+$. HR-MS(ESI): m/z [M+H] calcd. for $C_{23}H_{27}N_5O$: 390.2288; found: 390.2281.

2.5. Synthesis of (R)-(7-methyl-1,4-diazepan-1-yl)(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone (9)

Compound **7** (5.86 g, 15.05 mmol) was dissolved in 58 mL MeOH. After a portion of 10% Pd/C was added, the reaction was stirred for 4 h under H_2 atmosphere at room temperature. The reaction was filtered through a pad of celite and the filtrate was concentrated to provide compound **9** as a white solid 4.01 g in 89% yield. Mp: 119–121 °C, $[\alpha]_D^{26}$ −14.4 (c 1.00, MeOH)). ^{1}H NMR (600 MHz, DMSO-d_6): δ 8.24–8.02 (m, 2H), 7.88–7.29 (m, 3H), 4.42–2.50 (m, 7H), 2.41 (s, 3H), 2.24–1.98 (m, 2H), 1.17–0.99 (m, 3H); ^{13}C NMR (150 MHz, DMSO-d_6): δ 168.6, 138.3, 136.9, 134.1, 131.1, 129.2, 128.3, 122.5, 52.6, 49.1, 44.4, 43.1, 37.8, 20.8, 20.6. MS (ESI) m/z: 300.20 $[M+H]^+$. HR-MS(ESI): m/z [M+H] calcd. for $C_{16}H_{21}N_5O$: 300.1819; found: 300.1812.

Table 1
Optimization of reaction temperature for the cyclization.[a]

Entry	T (°C)	Yield (%)[b]
1	r.t.	72.7
2	50	49.1
3	Reflux	35.5

[a] The amount of sodium methoxide: 1.5 equiv.
[b] Isolated yields.

Table 2
Optimization of the amount of sodium methoxide.[a]

Entry	MeONa (equiv.)	Yield (%)[b]
1	2	61.6
2	1.8	70.8
3	1.5	73.4
4	1.2	94.2
5	1	89.5

[a] Room temperature.
[b] Isolated yields.

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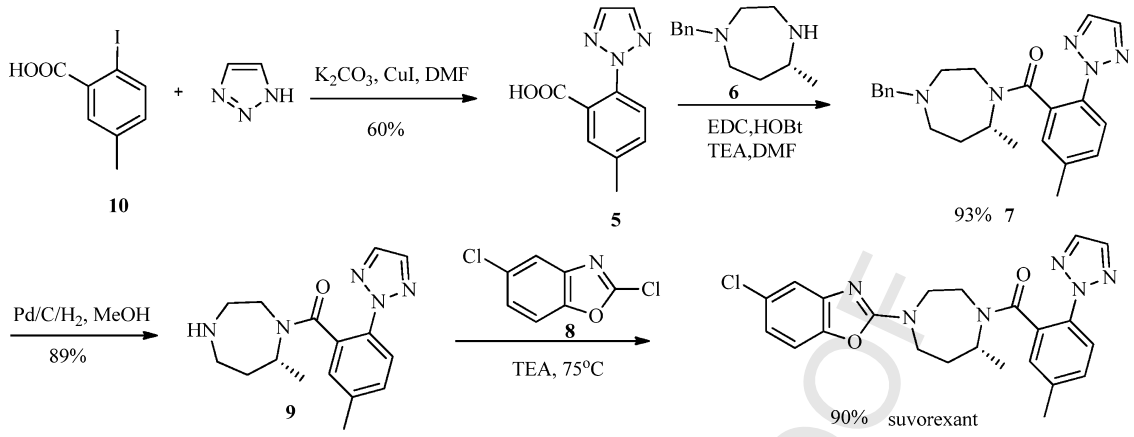

Scheme 4. Synthesis of suvorexant.

2.6. Synthesis of suvorexant

To compound **8** (0.56 g, 3 mmol) in 10 mL dry DMF was added TEA (0.91 g, 9 mmol) and compound **9** (0.89 g, 3 mmol), the mixture was stirred at 75 °C for 2 h. After cooling to room temperature, the reaction was diluted with EtOAc, washed with saturated aqueous $NaHCO_3$, water, brine and dried over $MgSO_4$. The residue was recrystallized from *i*-PrOH/EtOAc to provide a white solid 1.20 g in 90% yield. Mp: 149–150 °C, $[\alpha]_D^{25}$ −11.6 (*c* 1.00, MeOH). Analytical HPLC analysis carried out on a Chiralpak AD column (4.6 mm × 250 mm) with 60% EtOH in hexanes (containing 0.1% diethylamine as a modifier) at a flow rate of 1 mL/min, indicated that intermediate (*R*)-**4** was of >99% *ee*. Mp: 153 °C, $[\alpha]_D^{25}$ −11.7 (*c* 1.00, MeOH) [10], ^{1}H NMR (600 MHz, DMSO-d_6): δ 8.05–7.88 (m, 2H), 7.82–7.78 (m, 1H), 7.42–7.25 (m, 2H), 7.06–7.00 (m, 1H), 4.29–4.06 (m, 1H), 4.01–3.72 (m, 2H), 3.66–3.49 (m, 2H), 2.10 (s, 3H), 2.06–2.01 (m, 1H), 1.50 (m, 1H), 1.78–1.50 (m, 1H), 1.14–1.13 (d, 3H, J = 6 Hz); ^{13}C NMR (150 MHz, DMSO-d_6): δ 168.5, 163.4, 147.8, 145.2, 138.4, 136.6, 136.5, 134.1, 130.8, 129.8, 128.6, 122.8, 120.1, 115.6, 110.2, 52.3, 48.3, 45.1, 43.7, 35.6, 20.9, 17.2. MS (ESI) *m*/*z*: 451.20 $[M+H]^+$. HR-MS(ESI): *m*/*z* [M+H] calcd. for $C_{23}H_{23}ClN_6O_2$: 451.1644; found: 451.1639.

3. Results and discussion

The retrosynthetic procedure in Scheme 2 shows that the intermediate **6** can be converted to suvorexant *via* condensation, deprotection, and substitution. A benzyl moiety was selected as the protecting group, and the target molecule was achieved by the substitution of benzoxazole. Condensation of **6** and **5** resulted in amide **7**.

The synthesis begins with the protection of *R*-3-aminobutyric acid (Scheme 3). In accordance with a previously published procedure [13], triethylamine-assisted $(Boc)_2O$ protection was performed to furnish intermediate **2** in 90% yield. The Boc-amino acid (**2**) was then condensed with intermediate **10** under 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) and 1-hydroxybenzotriazole (HOBt) conditions to give compound **3** with 91% yield. The lactam ring **4** was then created with 94% yield by deprotection with gaseous hydrogen chloride (HCl) in ethyl acetate (EtOAc) followed by intramolecular cyclization with sodium methoxide (CH_3ONa). Reduction of the lactam (**4**) with lithium aluminum hydride at ambient temperature in anhydrous tetrahydrofuran (THF) gave the chiral diazepane (**6**) in good yield (88%) and high enantiopurity (>99% *ee*).

Preparation of the chiral diazepane ring is the key in the synthesis of diazepane **6**. This step was first conducted *via* Boc deprotection with gaseous HCl in EtOAc followed by intramolecular cyclization with 1.5 equiv. of CH_3ONa at 58 °C. However, the yield of this process was less than 50%. The reaction temperature and the amount of CH_3ONa were varied as shown in Tables 1 and 2, respectively, in order to improve cyclization yield. The results in Table 1 show that yields increased with decreasing reaction temperature. Thus, reactions were run at room temperature to optimize the amount of CH_3ONa added to the reaction mixture. The results in Table 2 show that increasing the amount of CH_3ONa decreased yields. The best results (94% yield, entry 4) were observed when the reaction was run at room temperature with 1.2 equiv. of CH_3ONa.

Condensation of diazepane **6** with triazole acid **5** which was synthesized from commercially available benzoic acid **10** to provide compound **7** with 93% yield. The benzyl protecting group was removed after catalytic hydrogenation at ambient pressure and room temperature on 10% Pd/C to produce a white solid **9** with 89% yield. There are no other impurities generated in the process of preparation of compound **9**. Finally, **9** was coupled with 2,5-dichloro-1,3-benzoxazole **8** to yield suvorexant (Scheme 4). After a typical workup, the crude product was recrystallized from *i*-PrOH/EtOAc, and suvorexant was isolated in 90% yield with 99% HPLC purity and >99% *ee*.

4. Conclusions

In summary, a practical procedure was devised for the synthesis of suvorexant from available raw materials. The chiral group was introduced *via* intramolecular cyclization of a chiral diazepane derivative prepared from *R*-3-aminobutyric acid. The synthetic improvements described herein led to the synthesis of suvorexant in an improved 31% overall yield with eight steps. The uses of biological enzyme, classical resolution and chiral HPLC separation have been avoided. Moreover, the target compounds at each step maintained a high level of enantiopurity. Thus, the high yields, high enantiopurity, and mild reaction conditions described herein provide a new method to synthesis of suvorexant.

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