Organic Process Research & Development **2006**, *10,* 1227–1230

Expeditious Process Improvement for the Synthesis of RWJ-333966

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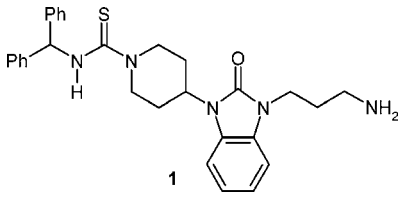
Abstract:

We improved chemical processes for synthesizing RWJ-333966 1 and obtained this compound over five steps in 40% overall yield.

Introduction

RWJ-333966 **1** is a selective vasopressin 1a receptor antagonist that presents utility in rodent models, predictive of clinical efficacy for the treatment of anxiety disorders. It is well tolerated after multiple daily administrations and does not adversely affect learning and memory.[1] Preclinical studies were initiated to support clinical proof-of-principle and clinical profile regarding sedation, motor impairment, and tolerance. Development was halted before first-in-human dose, after a proper GMP synthesis had been devised (Scheme 1).



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Results and Discussion

In the first step, **2** was protected with Boc-anhydride (1 equiv). Using more then 1 equiv led to the corresponding unwanted di-Boc derivative. Originally, the reaction was performed in THF, and compound **3** was obtained after a tedious workup. Therefore, three other solvents were screened: dichloromethane, toluene, and isopropanol. In the latter case, the product nicely precipitated, and we further optimized the process by reducing the amount of solvent and working at 0 °C. We obtained **3** with 82% yield (Table 1).

The second step (**3** to **5**) involves a nucleophilic substitution of protected amino alkyl bromide **4** on the benzimidazolone **3**. Results are presented in Table 2. The reaction was originally performed in DMF using Cs_2CO_3 as base. Because of the limited stability of DMF and because it contains dimethylamine in various quantities, we wanted to change it. We also wanted to use a cheaper base[2] and to obtain a crystalline compound. In a first series of trials (entries 1 and 2), we used *N*,*N*-dimethyl acetamide (DMA, 2 L/mol) instead of DMF and K_2CO_3 instead of Cs_2CO_3 and noticed no difference in reactivity. In a second series of trials, we used other solvents (acetone and MIK), but we observed lower conversion, longer reaction times, and/or formation of impurities as compared with DMA. In a third series of experiments (entries 5 and 6), we optimized reaction conditions using 1 L/mol DMA instead of 2 L/mol and 1 equiv of K_2CO_3 instead of 2 equiv. The reaction was carried out at 80 °C during 5−7 h.

Table 1

2 $\xrightarrow[\text{iPrOH}]{\text{Boc}_2\text{O}}$ **3**

^{i}PrOH (L/mol)	filtration (°C)	yield (%)
1	25	40
0.8	0	82

Addition of water generated an oily precipitate, and we therefore extracted the product with toluene (2 L/mol). Having noticed that the next step (BOC deprotection of **5** to **6**) worked well in dichloromethane with 5 equiv of trifluoroacetic acid, we tried the reaction directly on the toluene extract and successfully obtained the bis-trifluoroacetate of **6**[3] as a white crystalline compound with 82% yield. The fourth step (**6** to **8**) was originally performed by adding diphenyl isothiocyanate **7** to secondary amine **6**. Because of the limited commercial availability of **7**, it was decided to prepare this reagent in situ from diphenylamine and thiocarbonyldiimidazole (Scheme 2).

The reaction was performed in dichloromethane, and it was assumed that no additional base was required as far as released imidazole could neutralize the first equivalent of trifluoroacetic acid, the second equivalent being neutralized by the second imidazole formed in the reaction. The assumption was right: the reaction worked indeed well without adding a base. Surprisingly, the reaction proceeded well at 25 °C, whereas it is mentioned in literature that heating is often necessary for the second addition of amine.[4] After washing the reaction mixture with water, adding ethanol, and distilling off the dichloromethane, product **8** was crystallized with 84% yield.

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(1) Urbanski, M. J.; Gunnet, J. W.; Demarest, K. J. WO 02/0555 14, 2002.

(2) Comparison of commercial (Acros) prices indicates a huge difference: 665 EUR/kg for Cs_2CO_3 and 23 EUR/kg for K_2CO_3!

(3) The first equivalent of acid is obviously bound tightly to the NH of the secondary amine. On the contrary, the second equivalent of CF_3COOH (pKa ~0.5) is expected to bind only weakly with benzimidazolone (pKa = 0.76, simulated with ACD software). Anyway, titration results consistently indicate the presence of 2 equiv of acid.

(4) Grzyb, J. A.; Shen, M.; Yoshina-Ishii, Ch.; Chi, W.; Brown, R. S.; Batey, R. A. *Tetrahedron* **2005**, *61*, 7153.

10.1021/op0601565 CCC: $33.50
Published on Web 10/21/2006

Scheme 1

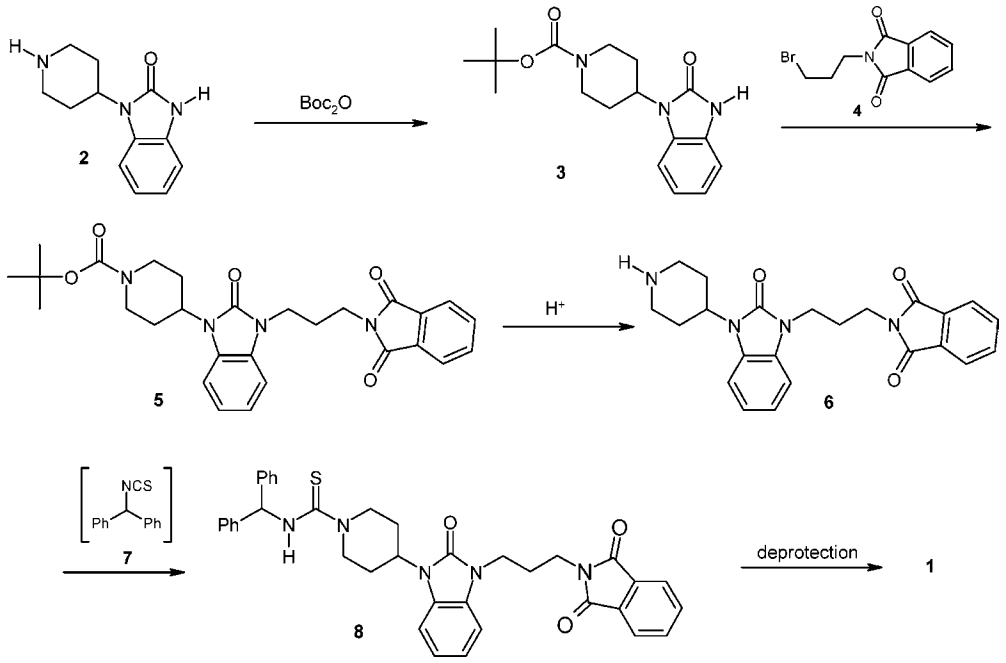
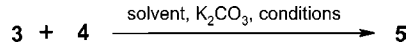
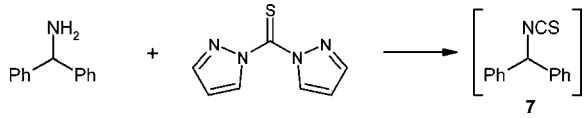


Table 2



entry	**3** (equiv)	**4** (equiv)	K_2CO_3 (equiv)	solvent, conditions	conversion
1	1	1	2	DMA, 2 L/mol, 80 °C, 2 h	>99%
2	1	1	2	DMA, 2 L/mol, 80 °C, 2 h	>99%
3	1	1	2	acetone, 2 L/mol, 56 °C (rfx.), 1 h	33%
4	1	1	2	MIK, 2 L/mol, 56 °C (rfx.), 16 h	>99% + impurities
5	1	1	1	DMA, 1 L/mol, 80 °C, 5 h	>99%
6	1	1	1	DMA, 1 L/mol, 80 °C, 7 h	>99%

Scheme 2



The last step (**8** → **1**) was by far the most difficult one (Scheme 3).[5]

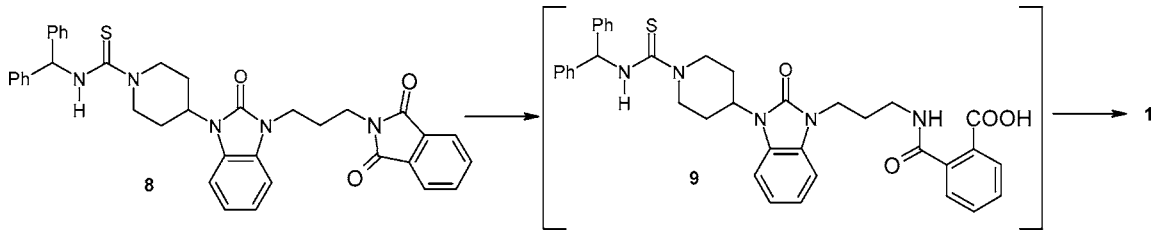
First, we tried the hydrolysis of the phthalimide moiety with HCl (in water and in water/EtOH). The SM disappeared, but a typical smell indicated that the thiourea had been hydrolyzed. Then, we tried ethylenediamine (2 equiv) in *s*-BuOH at 90 °C. After 30 min, some product was formed, but LC/MS analysis indicated a competition with aminolysis of thiourea. Then we used hydrazine (2 equiv) in EtOH. The conversion was not complete, and another 1 equiv was added. A precipitate was formed which contained the product but with insufficient purity, even after recrystallization from MeOH. With KOH (5 equiv) in EtOH the first imide carbonyl was cleaved to the amide after 30 min, but then, intermediate **9** was cleaved at the thiourea instead of the amide. Finally we performed the reaction with methylamine ($MeNH_2$). With 5 equiv in MeOH/H_2O, the reaction worked well, but still 11% (LC area%) of the amide remained after 1 h at 45 °C. At the same temperature, but with 10 equiv of $MeNH_2$, the product still contained 5% of the amide after 1.5 h. Having extracted the product, we evaporated the solvent and noticed the reclosure of the amide. To avoid this, we added HCl/H_2O after the reaction to precipitate the product. We obtained 90% active yield, but it contained unfortunately $MeNH_2$·HCl as well. We screened several acids to selectively isolate the product, but our attempts were unsuccessful. Therefore, compound **1** was chromatographed after base liberation. After the chromatography (RP, acetonitrile/water/NH_4OAc), we extracted the product with dichloromethane and evaporated the solvent. We noticed however some product degradation as outlined in Scheme 4.

Through the formation of the fumarate salt,[6] we were able to get rid of this limited amount of impurities (up to 3%). At lab scale, we synthesized about 70 g of DS in total. The project was discontinued before reaching the pilot plant scale.

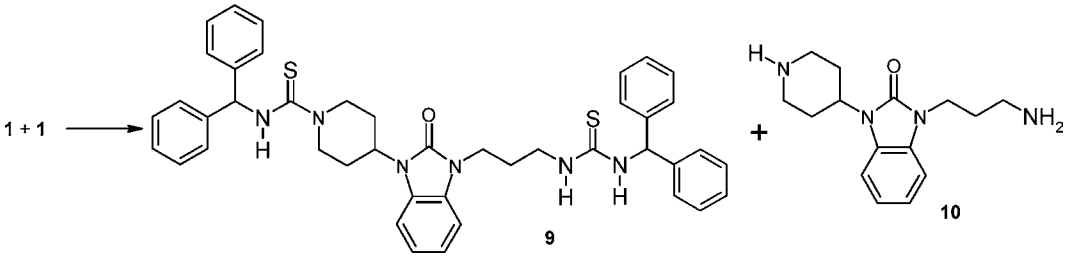
(5) For the deprotection of phtalimide derivatives, see references in: Greene, Th. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; Wiley: 1999; pp 564−566.

(6) The following acids were tried as well: succinic acid, maleic acid, mandelic acid, fumaric acid, citric acid, lactic acid, and diisopropylidene keto gulonic acid.

Scheme 3



Scheme 4



In conclusion, we developed an efficient and scalable method to synthesize compound **1** over five steps in 40% overall yield. Unfortunately, due to its amphiphilic nature (amine and thiourea on the same molecule), the product showed only limited stability and must be chromatographed before its salt is formed.

Experimental Section

General Procedures. Commercially available solvents and reagents were used without further purification. 1-Piperidin-4-yl-1,3-dihydrobenzoimidazol-2-one was obtained from a commercial source.

^{1}H NMR spectra were recorded on a Bruker Avance 400 MHz spectrometer, with TMS as internal standard in DMSO-d_6. MS spectra were determined with a Waters mass spectrometer with a UPLC technique. Elemental analysis were carried out on a Carlo Erba EA1110.

Trifluoroacetic and fumaric contents were measured by potentiometric acid titration on a Metrohm 716 DMS Titrino apparatus with a Ag/AgCl electrode.

Preparative HPLC was performed on a Merck system with UV detection at 260 nm through a Prochrom, KR100-10 RP 18 column. The separation was carried out by isocratic elution, using aqueous acetonitrile and ammonium acetate in the ratio 50:50. The flow rate was 500 mL/min.

4-(2-Oxo-2,3-dihydro-benzoimidazol-1-yl)-piperidine-1-carboxylic Acid *tert*-Butyl Ester (3). A suspension of 1-piperidin-4-yl-1,3-dihydrobenzoimidazol-2-one **2**[7] (217 g, 1 mol) in isopropanol (800 mL, 0.8 L/mol) was heated to 30 °C. Di-*tert*-butyl dicarbonate (218 g, 1 mol) was added, neat, keeping the temperature below 50 °C during addition. The reaction mixture was stirred at 40 °C during 1 h, cooled to 20 °C, and stirred 16 h at this temperature. The mixture was cooled to 0 °C and stirred for 1 h. The product was collected by filtration and dried in a vacuum oven at 50 °C. Yield: 260 g (82%).

(7) From our own production facility. This compound is also available in gram quantities from major fine chemical suppliers.

^{1}H NMR (DMSO-d_6, TMS, 400 MHz) δ (ppm): 1.44 (s,9H), 1.68 (dd, $J1 = 11.96$, $J2 = 1.89$ Hz, 2H), 2.20 (qd, $J1 = 12.55$, $J2 = 4.41$ Hz, 2H), 2.87 (m, 2H), 4.10 (d, $J = 11.83$ Hz, 2H), 4.29−4.38 (m, 1H), 6.94−7.00 (m, 3H), 7.15−7.21 (m, 1H), 10.83 (s,1H). MS (ESI) *m/z*: 318 (MH^+). Anal. Calcd for $C_{17}H_{23}N_3O_3$: C, 64.33; H, 7.30; N, 13.24. Found: C, 64.25; H, 7.36; N, 13.45.

2-[3-(2-Oxo-3-piperidin-4-yl-2,3-dihydrobenzoimidazol-1-yl)propyl]isoindole-1,3-dione Ditrifluoroacetate (6·2CF$_3$COOH). Bromopropylphtalimide **4** (13.4 g, 0.05 mol, 1 equiv) and potassium carbonate (6.9 g, 0.05 mol) were added to a solution of **3** (15.8 g, 0.05 mol) in 50 mL of DMA. The reaction mixture was heated to 80 °C and stirred for 6 h. Water was added (100 mL, 2 L/mol) followed by toluene (100 mL, 2 L/mol). The organic layer was separated and dried over Na_2SO_4 (50 g). One-third of the solvent was partially evaporated and cooled to 20 °C. Trifluoroacetic acid (28.5 g, 0.25 mol) was added to the residue, maintaining the temperature below 60 °C. The mixture was stirred at 60 °C during 4 h and cooled to 40 °C over 30 min. The mixture was seeded at 40 °C, cooled to 20 °C over 2 h, and then stirred for 16 h. The trifluoroacetic salt of **6** was filtered, washed with toluene, and dried in a vacuum at 40 °C during 4 h. Yield: 25.8 g (82%).

^{1}H NMR (DMSO-d_6, TMS, 400 MHz) δ (ppm): 1.88 (d, $J = 12.38$ Hz, 2H), 2.00−2.09 (q, $J = 7.2$ Hz, 2H), 2.49−2.61 (m, 2H), 3.07−3.17 (m, 2H), 3.45 (d, $J = 12.38$ Hz, 2H), 3.63 (t, $J = 7.08$ Hz, 2H), 3.91 (t, $J = 7.08$ Hz, 2H), 4.50−4.60 (m, 1H), 6.96−7.09 (m, 2H), 7.22−7.30 (m, 1H), 7.30−7.37 (m, 1H), 7.77−7.85 (m, 4H), 8.55 (m,1H), 8.79 (m, 1H). MS (ESI) *m/z*: 405 (MH^+). Acid titration for $C_{23}H_{24}N_4O_3 \cdot 2C_4H_2F_6O_4$: 100,7 w/w %. Anal. Calcd for $C_{23}H_{24}N_4O_3 \cdot 2C_4H_2F_6O_4$: C, 51.22; H, 4.11; N, 8.85. Found: C, 50.48; H, 4.09; N, 8.87.

4-{3-[3-(1,3-Dioxo-1,3-dihydroisoindol-2-yl)propyl]-2-oxo-2,3-dihydrobenzoimidazol-1-yl}piperidine-1-carbothioic Acid Benzhydrylamide (8). 1,1-Diphenylmethylamine (37.2 g, 0.22 mol) was added to a solution of thiocarbonyldiimidazole (39.2 g, 0.22 mol, 1.1 equiv) in

dichloromethane (200 mL, 1 L/mol)[8] maintaining the temperature below 35 °C. The reaction mixture was stirred at 20 °C for 1 h, and **6·2CF$_3$COOH** (126.4 g, 0.2 mol) was added portionwise keeping the temperature below 35 °C. The reaction mixture was stirred at 20 °C for 1 h, and water was added (400 mL, 2 L/mol). The organic layer was separated, and the solvent was two-thirds evaporated. Ethanol (1 L, 5 L/mol) was added to the residue. The mixture was further evaporated until a temperature of 80 °C was reached. The heterogeneous mixture was cooled to 20 °C, stirred for 4 h, cooled to 0 °C, and stirred for a 1 h. **8** was filtered and dried under a vacuum at 40 °C. Yield: 106 g (84%)

^{1}H NMR (DMSO-d_6, TMS, 400 MHz) δ (ppm): 1.77 (d, J = 9.73 Hz, 2H), 1.99−2.08 (q, J = 7.08 Hz, 2H), 2.20−2.32 (m, 2H), 3.16 (t, J = 12.38 Hz, 2H), 3.63 (t, J = 7.08 Hz, 2H), 3.89 (t, J = 7.08 Hz, 2H), 4.49−4.57 (m, 1H), 4.96 (d, J = 12.83 Hz, 2H), 7.02 (m, 2H), 7.12 (d, J = 7.08 Hz, 1H), 7.17 (d, J = 8.4 Hz, 1H), 7.23 (d, J = 7.52 Hz, 1H), 7.26−7.38 (m, 10H), 7.79−7.85 (m, 4H), 8.43 (d, J = 8.4 Hz, 1H). MS (ESI) *m/z*: 630 (MH^+). Anal. Calcd for $C_{37}H_{35}N_5O_3S$: C, 70.57; H, 5.60; N, 11.12. Found: C, 70.32; H, 5.50; N, 11.08.

4-[3-(3-Aminopropyl)]-2-oxo-2,3-dihydrobenzoimidazol-1-yl-piperidine-1-carbothioic Acid Benzhydrylamide (*E*)-2-Butenedioate (1·C$_4$H$_4$O$_4$). Phthalimide **8** (63 g, 0.1 mol) was dissolved in methanol (400 mL, 4 L/mol), and methylamine 40% in water (85 mL, 1 mol) was added. The reaction mixture was warmed to 45 °C and stirred for 1.5 h. After cooling to 10 °C with an ice bath, HCl conc. (85 mL) was added until pH ∼3. The heterogeneous mixture was stirred for awhile and filtered as **1·HCl**. Yield: 48 g (96%, 76% purity, this corresponds to an active yield of 72%)

Another quantity of **1·HCl** was obtained by adding another 50 mL of concentrated HCl and stirring overnight at room temperature. Yield: 21.2 g (43%, 41.5% purity, this corresponds to an active yield of 18%). Total active yield = 90%.

After base liberation **1** was purified by preparative chromatography. The resulting aqueous solution was extracted with dichloromethane, and the organic layer was carefully evaporated under a vacuum below 35 °C.

Salt formation: **1** (21.6 g, 0.043 mol) and fumaric acid (5.4 g, 1.1 equiv) were dissolved in ethanol (435 mL) at reflux, cooled to room temperature, and filtered. **1·C$_4$H$_4$O$_4$** was dried under a vacuum at 40 °C. Yield: 21.6 g (81%, 96.4% purity, this corresponds to an active yield of 78%).

^{1}H NMR (DMSO-d_6, TMS, 400 MHz) δ (ppm): 1.75 (d, J = 9.51 Hz, 2H), 1.91 (q, J = 7.2, 2H), 2.20−2.32 (m, 2H), 2.80 (t, J = 7.3 Hz, 2H), 3.14 (t, J = 12.44 Hz, 2H), 3.89 (t, J = 6.77 Hz, 2H), 4.49−4.6 (m, 1H), 4.93 (d, J = 12.81 Hz, 2H), 6.41 (s, 2H), 6.99−7.10 (m, 2H), 7.13 (d, J = 7.32 Hz, 2H), 7.24−7.37 (m, 11H), 8.47 (d, J = 8.78 Hz, 1H). MS (ESI) *m/z*: 500 (MH^+). Acid titration for $C_{29}H_{33}N_5OS\cdot C_4H_4O_4$: 99.1 w/w%. Anal. Calcd for $C_{29}H_{33}N_5OS\cdot C_4H_4O_4$: C, 64.37; H, 6.06; N, 11.37. Found: C, 64.16; H, 5.88; N, 10.85.

Received for review August 1, 2006.

OP0601565

(8) Based on compound **6·2CF$_3$COOH**.