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Synthesis of T2288: From Bench Synthesis to Pilot Production

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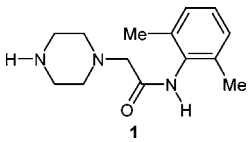
Abstract:

A practical process to make *N*-(2,6-dimethylphenyl)-2-piperazin-1-yl-acetamide 1 is described, starting from piperazine 2 and *N*-chloroacetyl-2,6-xylidine 3. The unwanted *N*,*N*′-bis-alkylated product 4 can be removed by simple filtration of the reaction mixture, while the excess of piperazine remains in the aqueous phase after extracting the filtrate with toluene at 70 °C. The product precipitates from the organic phase with 68% active yield.

Introduction

The production of *N*-(2,6-dimethyl-phenyl)-2-piperazin-1-yl-acetamide **1** at pilot scale (10−100 kg) was necessary as part of a drug development program.[1]



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A survey of the literature indicated that an efficient process for the synthesis of **1** had never been investigated: the product previously had been made via a three-step synthesis,[2] starting from piperazine, which was first mono-protected to obtain *N*-benzylcarbamoyl-piperazine;[3] after condensation with *N*-chloroacetyl-2,6-xylidine, **3**, and deprotection, HCl was added, and compound **1** was obtained as a dihydrochloride adduct with an overall yield of 2.1%. (Scheme 1)

Results and Discussion

From the outset, we performed the straightforward coupling of piperazine **2** with the corresponding α-chloroacetamide **3**, as outlined in Scheme 2.

Despite the simplicity of the reaction, several drawbacks had to be overcome to obtain a suitable process. The results are summarized in Table 1.

First we tried to minimize the formation of *N*,*N*′-bis-alkylated product **4**. We performed the reaction in 2-propanol (^{i}PrOH) at reflux (80 °C), using 1 equiv of **3** combined with reasonable amounts of piperazine **2** (up to 3 equiv, entries 1−3). Even with 3 equiv (entry 3), still 28% (HPLC area %) of *N*,*N*′-bis-alkylated product **4** was formed. Therefore, we used increasing quantities of aqueous HCl to moderate the reactivity of piperazine through *N*-protonation (entries 4−7). Using 3 equiv of piperazine and 3 equiv of aqueous HCl in ^{i}PrOH limited the formation of *N*,*N*′-bis-alkylated product to 7% (entry 7).

Having limited but not suppressed its formation, we still had to remove **4**. Having noticed it was virtually insoluble, it was easily eliminated by filtering the suspension over Celite.

The acidic filtrate still contained the excess of piperazine in water/^{i}PrOH, together with compound **1**. After alkalinisation of the clear solution with aqueous NaOH, several solvents were screened for the extraction: tetrahydrofuran, *tert*-butyl methyl ether, 2-propanone, *n*-butanol, *sec*-butanol, toluene, and ethyl acetate. At 25 °C, toluene and EtOAc gave the best results, and after evaporation, we obtained compound **1** as a solid residue which was in turn subjected to recrystallization experiments with the following solvents: methanol, 2-propanol, *n*-butanol, *sec*-butanol, ethyl acetate, and toluene. Toluene gave the best recrystallization, and therefore we used it for both extraction and crystallization purposes. The reaction was performed in ^{i}PrOH (1 L/mol) with 3 equiv of piperazine and 3 equiv of HCl/H_2O (entry 7) at reflux (80 °C). After elimination of the *N*,*N*′-bis-alkylated product **4** by filtration and alkalinization of the filtrate, toluene (2 L/mol) was added, ^{i}PrOH was removed azeotropically, and the reaction mixture was cooled to room temperature; the filtrate was filtered off and dried to give **1** with 70% yield.

To further improve the reaction, we performed it in acidic water (no ^{i}PrOH, entry 8). With 3 equiv of piperazine and 3 equiv of HCl, it was complete after 2 h at 80 °C with a comparable selectivity as with ^{i}PrOH/H_2O. Facile filtration of undesired compound **4** and alkalinization of the filtrate were followed by extraction with toluene (2.4 L/mol, 25 °C). We noticed that the extraction yield was about 40% under these conditions, the main part of the product remaining in the water layer.[4] At 70 °C, the extraction was complete. The layers were separated at that temperature, about 2/3 of the toluene was distilled off, and the mixture was cooled as described above. The yield (70%) was similar to that obtained in the presence of ^{i}PrOH.

In conclusion, we found a convenient way to synthesize compound **1** (68% active yield, compared to 2.1% in the literature) by coupling piperazine **2** with α-chloroacetamide

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(1) Patent application pending.

(2) (a) Foye, W. O.; Levine, H. B.; Mc Kenzie, W. L. *J. Med. Chem.* **1966**, *9*, 61. (b) Rampa, A.; Valenti, P.; Da Re, P.; Carrara, M.; Zampiron, S.; Cima, L.; Giusti, P. *Arch. Pharmacol. (Weinheim)* **1989**, *322*, 359.

(3) Foye, W. O.; Fedor, L. R. *J. Am. Pharm. Assoc*. **1959**, *48*, 412.

(4) We performed the extraction with EtOAc and noticed a quantitative extraction in the same conditions.

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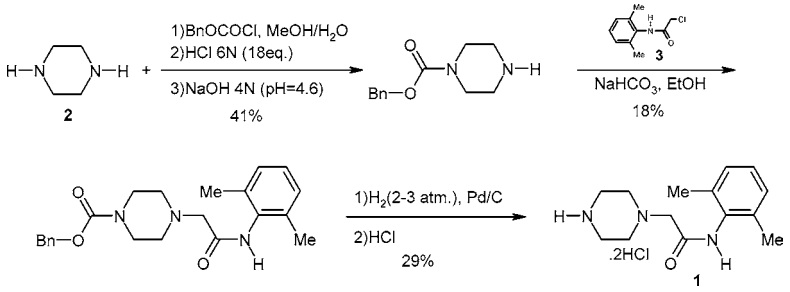
Scheme 1



Scheme 2

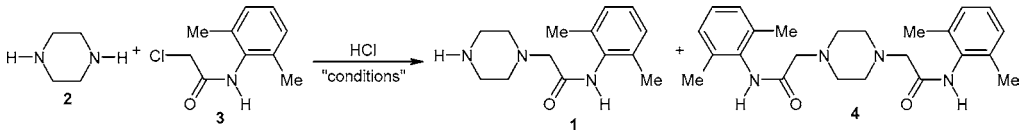


Table 1

entry	**3** (equiv)	**2** (equiv)	HCl (equiv)	solvent	time (h)	selectivity [**1**]:[**4**] (LC area%)
1	1	1	0	^{i}PrOH (1 L/mol)	21	38:62
2	1	2	0	^{i}PrOH (1 L/mol)	2	72:28
3	1	3	0	^{i}PrOH (1 L/mol)	2	72:28
4	1	2	2	^{i}PrOH (0.66 L/mol)/H_2O (0.09 L/mol)	4	83:17
5	1	2	2.25	^{i}PrOH (0.66L/mol)/H_2O (0.09 L/mol)		83:17
6	1	2	2.5	^{i}PrOH (0.66L/mol)/H_2O (0.09 L/mol)	3	83:17
7	1	3	3	^{i}PrOH (1 L/mol)/H_2O (0.135 L/mol)	3	93:7
8	1	3	3	H_2O (0.4 L/mol)	2	93:7

3 in acidic water. The undesired impurity **4** could easily be removed as a precipitate, after which the product was extracted at 70 °C with toluene and crystallized from the same solvent. The process has been successfully scaled-up (up to 30 mol) in the pilot plant.

Experimental Section

General Procedures. All materials were purchased from commercial suppliers and used without further purification. All reactions were conducted under an atmosphere of nitrogen. In the lab, only glass vessels are used; in the pilot plant, either steel or glass-lined vessels are used. For each reaction, a sample of the reaction mixture was collected and analyzed by means of HPLC.

***N*-(2,6-Dimethyl-phenyl)-2-piperazin-1-yl-acetamide 1 (T2288).** *1. Lab Procedure.* In a 250-mL, four-necked flask equipped with a stirrer, piperazine **2** (12.9 g, 0.15 mol, 3 equiv) was suspended in water (20 mL, 0.4 L/mol **3**). The mixture was stirred vigorously, and HCl_{cp} (12 N, 12.5 mL, 0.15 mol, 3 equiv) was added cautiously (**Exothermic**!). The temperature rose to 45 °C, and the mixture became homogeneous. After cooling to 20−25 °C, α-chloro-*N*-(2,6-dimethylphenyl)acetamide **3** (9.9 g, 0.05 mol, 1 equiv) was added, and the mixture was heated to 80 °C and stirred for 2 h. The reaction mixture was then cooled to 60 °C and filtered at that temperature over Celite, to remove the precipitate of *N*,*N*′-bis-alkylated product **4**. The filtrate was treated at 60 °C with NaOH 50% in water (8.5 mL, 0.16 mol, 3.2 equiv, pH > 10), and toluene (120 mL, 2.4 L/mol) was added. The mixture was then heated to 70 °C and stirred 15 min, and the layers were separated at that temperature. After discarding the water layer, about two-thirds of the organic phase was distilled off, and the mixture was slowly cooled to 22 °C over 3 h. Seeding was performed at 60 °C. The mixture was further cooled to 0−5 °C and stirred at that temperature during 1 h. The precipitate was filtered off, washed with toluene (10 mL, 0.2 L/mol), and dried during 16 h at 40 °C under vacuum. **1** was obtained as a white precipitate: mp 118 °C. Yield: 8.6 g (70%, 68% active yield). HPLC:[5] Retention time = 2.6 min. Purity: 100% w/w abs. Base titration:[6] 97.5%. ^{1}H NMR ($CDCl_3$, 360 MHz) δ: 1.62 (bs, 1H, NH), 2.22 (s, 6H), 2.63 (m, 4H), 2.93 (m, 4H), 3.15 (s, 2H), 7.02−7.13 (m, 3H), 8.71 (bs, 1H, CONH). Anal. Calcd for $C_{14}H_{21}N_30$: C, 67.98; H, 8.56; N, 16.99. Found: C, 68.21; H, 8.38; N, 17.22.

2. Pilot-Plant Procedure. In a 100-L reactor, piperazine **2** (7.74 kg, 90 mol, 3 equiv) and water (12 L, 0.4 L/mol) were introduced under nitrogen. The mixture was cooled to 10 °C with ice/water. Aqueous HCl (12 N, 8.2 L, 3 equiv) was added over 30 min, so that the temperature remained under 30 °C. Then, α-chloro-*N*-(2,6-dimethylphenyl)acetamide **3** (5.94 kg, 30 mol, 1 equiv) was added, the mixture was heated to 80 °C and stirred at that temperature during 2 h. After centrifugation at 60−70 °C, the filtrate was

(5) HPLC method: Hypersil BDS 50 mm × 4.6 mm, 3 mm; flow: 2 mL/min; eluent A: NH_4OAc; B: CH_3CN; Gradient: 0 min: 100% A, 0% B; 4.5 min: 0% A, 100% B; 5.5 min: 0% A, 100% B; 5.6 min: 100% A, 0% B; 8.0 min: 100% A, 0% B. UV detection at 254 nm.

(6) Titration method: combined glass Ag/Ag^+ electrode; titrating solution: 0.1 N $HClO_4$; solvent: 2-propanone/acetic acid 7:1.

reintroduced in the reactor. Toluene (72 L, 2.4 L/mol) was added. The mixture was neutralized with 50% aqueous sodium hydroxide (4.8 L, 90 mol, 3 equiv). The content of the reactor was heated to 70 °C and stirred at that temperature during 1 h. The layers were separated, and a second extraction of the water layer was performed with toluene (10 L, 0.33 L/mol) at 70 °C. The organic layers were mixed together, and 52 L solvent (about 2/3) was distilled off. The reaction mixture was cooled to 20−25 °C, stirred 1 h at that temperature, and then cooled further to 0−5 °C and stirred 2 h at that temperature; the precipitate was centrifuged and washed with 2 L of toluene. It was dried under vacuum (50 °C, 16 h); 5.12 kg **1** was obtained. HPLC: 99.8% w/w. Base titration: 98.8%.

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