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# Synthesis of T2288: From Bench Synthesis to Pilot Production

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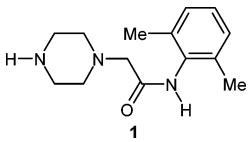
**Abstract:**

**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]




**1**

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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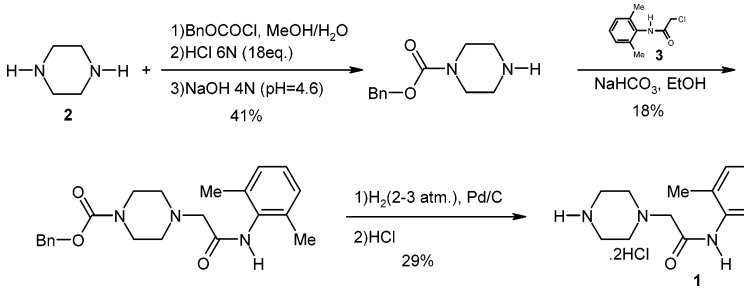
**Scheme 1**




**Scheme 2**

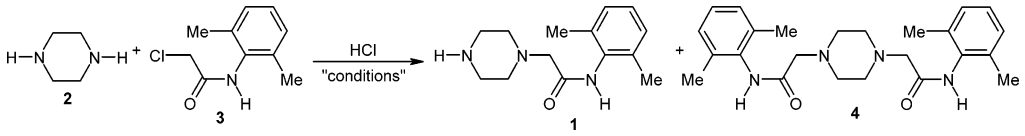



**Table 1**

| 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) $\delta$: 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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