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Optimization and Scale-Up of the Grandberg Synthesis of 2-Methyltryptamine

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Abstract:

An efficient, safe, and cost-effective synthesis of 2-methyltryptamine (2), a key starting material in the synthesis of the histone deacetylase inhibitor LBH589 (1) is described. The reaction of phenylhydrazine (7) with a stoichiometric amount of 5-chloro-2-pentanone (8) in aqueous ethanol at reflux furnished crude 2-methyltryptamine (2). The product 2 was obtained in 47% yield and >99% purity after crystallization from toluene.

Introduction

Histone deacetylase inhibitors (HDAIs) have been shown to inhibit the growth of tumor cells in vitro and activate genes regulating cell cycle arrest, apoptosis, and differentiation in a tumor cell-specific manner. *N*-Hydroxy-3-[4-[[[2-(2-methyl-1H-indol-3-yl)ethyl]amino]methyl]phenyl]-(2*E*)-2-propenamide (**1**, LBH589) (Figure 1) represents a new series of histone deacetylase inhibitors (HDAIs) based on the known HDAIs trichostatin A and trapoxin A.[1,2]

An important consideration for the synthesis of **1** is the availability of the key starting material 2-methyltryptamine (**2**). The medicinal chemistry routes to **2** are depicted in Schemes 1 and 2. In the initial synthesis, 2-methylindole (**3**) was acylated with one equivalent of oxalyl chloride in THF, and the resulting α-oxo acid chloride was allowed to react with an excess of aqueous ammonia to give the α-oxo amide **4** in good yield. This compound was reduced with lithium aluminum hydride in THF resulting in the formation of **2** (Scheme 1). Unfortunately, the purity of the 2-methyltryptamine (**2**) obtained by this method was low (60% by HPLC) with the major impurity being a dimer (**9**, Figure 2).

In the second medicinal chemistry synthesis, 2-methylindole-3-carboxaldehyde (**5**) was condensed with nitromethane to give the nitroolefin **6**. Reduction with lithium aluminum hydride afforded the desired product, this time in good yield and purity (Scheme 2).

Results and Discussion

The conditions used in both of the medicinal chemistry syntheses of **2** were deemed undesirable for scale-up in our pilot plant. The shortcomings included the low purity of the α-oxoamide **4** (development of a method of purification required), the need to use lithium aluminum hydride at reflux (additional safety studies needed), the cost of the 2-methylindole-3-carboxaldehyde (**5**), and the use of nitromethane (addressing the safety concerns would require significant

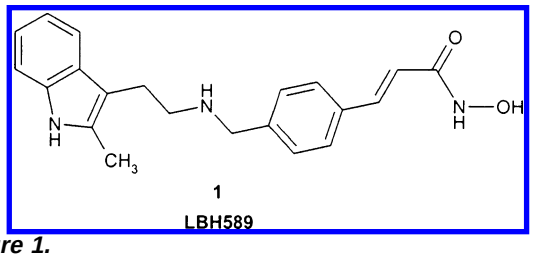
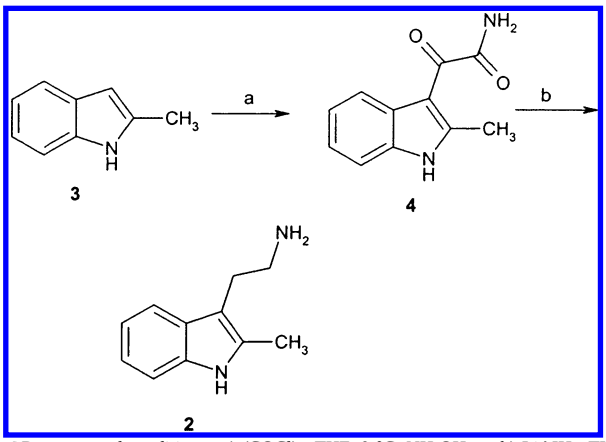


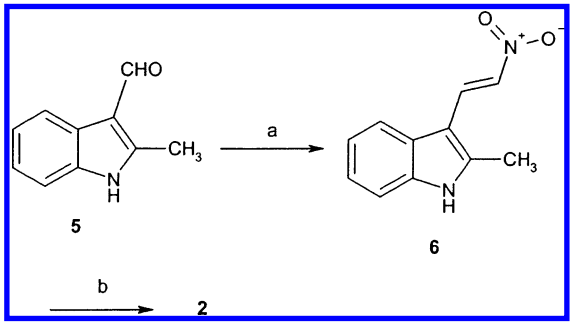
Figure 1.

Scheme 1[a]



[a] Reagents and conditions: a) $(COCl)_2$, THF, 0 °C; NH_4OH aq; b) $LiAlH_4$, THF reflux.

Scheme 2[a]



[a] Reagents and conditions: a) CH_3NO_2, NH_4OAc, HOAc; b) $LiAlH_4$, THF reflux.

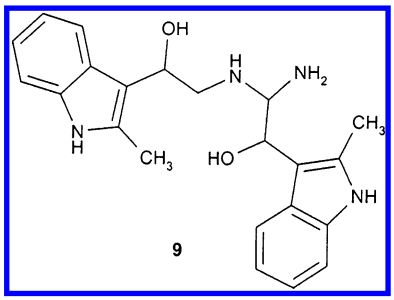


Figure 2.

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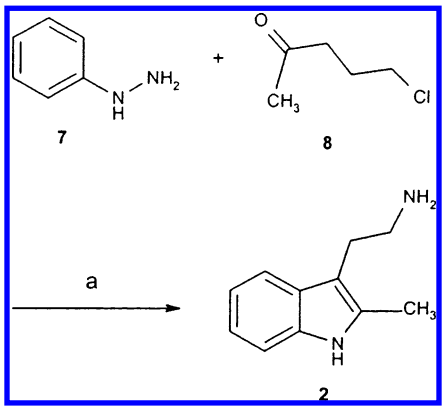
Scheme 3 [a]



[a] Reagents and conditions: a) Ethanol/water, heat.

additional research). Our goal was to eliminate the undesirable reagents and conditions and to develop a short and efficient route to **2** that would provide the compound in high purity at reasonable cost. After identifying significant problems with the medicinal chemistry routes to **2**, it was decided to pursue an alternative approach. Among the many routes developed for the synthesis of indoles,[3] the Grandberg approach[4] (Scheme 3), which is a variation of the Fischer indole synthesis,[3] appeared to be the most promising.[5]

Our preliminary work using the published reaction conditions indicated that this approach would indeed be feasible; however, there were scale-up problems associated with this transformation (mainly, uncontrolled exotherms which led to the formation of impurities which were difficult to remove) and with the workup and isolation. Specifically, we wished to develop a process which would be deemed safe for scale-up in the pilot plant and at the same time eliminate the need for chromatography. In addition, it was felt that optimization of the reaction conditions (stoichiometry and addition rate) would also be required prior to implementation of the chemistry in the pilot plant.

Based on the mechanistic assumptions associated with the Fischer indole synthesis,[3a] the hypothesis diagrammed in Scheme 4 has been put forward to explain tryptamine formation.[6]

Thus, initial formation of the hydrazone (**A**) is followed by a proton shift (**B**) and ring formation to afford **C**. Loss

Scheme 4

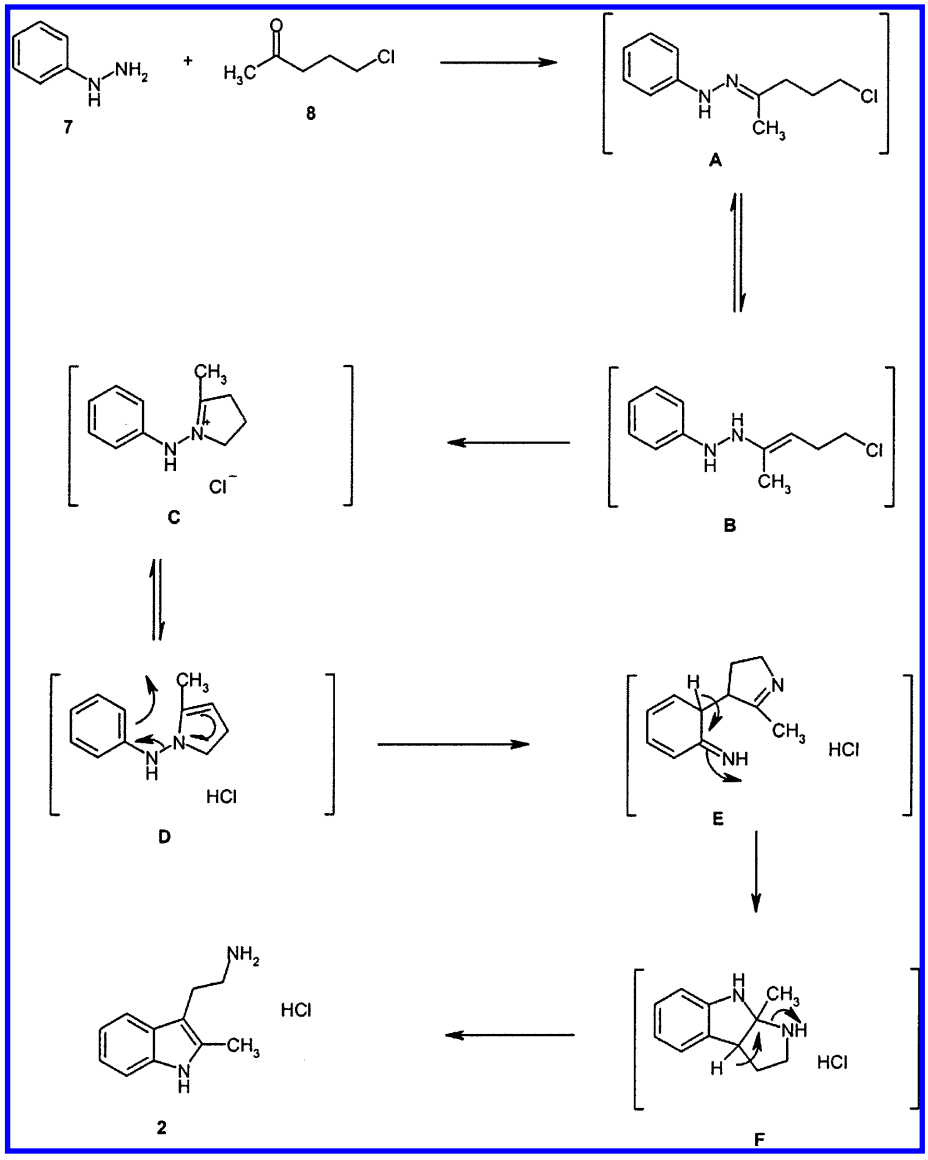


Table 1. **7 + 8 → 2: variation of stoichiometry**

expt[a]	ratio **7**:**8**	yield (%)	purity (%)[b]
1	1:1	47	>99.9
2	1:1.2	56	96.2
3	1.2:1	57	93.2
4	1:1.4	41	99.1
5	1.4:1	58	99.1
6	2:1	28	17.2
7	1:2	52	97.4

[a] Note: All reactions were carried out using the procedure described in the Experimental Section on one-fifth of the scale. [b] The products **2** were analyzed by HPLC (area normalization).

of a proton leads to rearrangement (**C** → **D** → **E** → **F**) and finally elimination of a proton to give **2**. Hydrazone **A** was not isolated but has been observed spectroscopically.[6]

By using excess pentanone (**8**) at low temperature (0−5 °C), we were able to isolate a solid which was identified by LC/MS as a mixture of hydrazone (**A**) [MH^+ 211/213] and product (**2**). Subjecting this mixture to the usual reaction conditions (see Experimental Section) resulted in complete conversion to 2-methyltryptamine (**2**).

The Grandberg synthesis of indoles involves mixing equimolar amounts of the hydrazine (**7**) and 5-chloro-2-pentanone (**8**) in an aqueous alcohol solvent system, followed by heating for a specified amount of time. A brief study was initiated in order to determine whether this was the optimum stoichiometry for the reaction. Table 1 summarizes the results obtained by varying the ratios of the phenylhydrazine and the 5-chloro-2-pentanone.

On the basis of the results shown in the table, the best combination of yield and purity was found when the stoichiometry was 1:1 (expt 1) and 1.4:1 (expt 5). For ease of product isolation, the former conditions were chosen for scale-up in the plant. Interestingly, the use of 2 equiv of **8** (expt 7) provided a good result on small scale. However, we felt that the presence of polar impurities in the isolated product could be problematic on scale-up. In all cases, the yields were based on the limiting reagent or **7**. It should also be noted that analysis of the reaction mixtures showed high conversions to product **2** and that the lower yields were due to losses during workup and crystallization (see below).

To understand better the energetics of the reaction, a calorimetric analysis (the reaction was carried out in the RC1 calorimeter) was performed. The procedure involved the addition of absolute ethanol to phenylhydrazine (**7**), heating to 35 °C, adding 5-chloro-2-pentanone (**8**) at this temperature, and heating to the reflux temperature after diluting with additional 95% ethanol. It was found that the addition of **8** was highly exothermic ($\Delta H \approx -85.8$ kJ/kg, $\Delta T_{adiabatic} \approx 44$ °C) but that the reaction was addition-controlled based on the fact that the calorimetric response ceased after the complete addition of two unequal portions of **8** using a dosing regimen (see Figure 3). On the basis of this information, we felt that the reaction could be scaled up safely by using a sufficiently slow rate of addition of **8**.

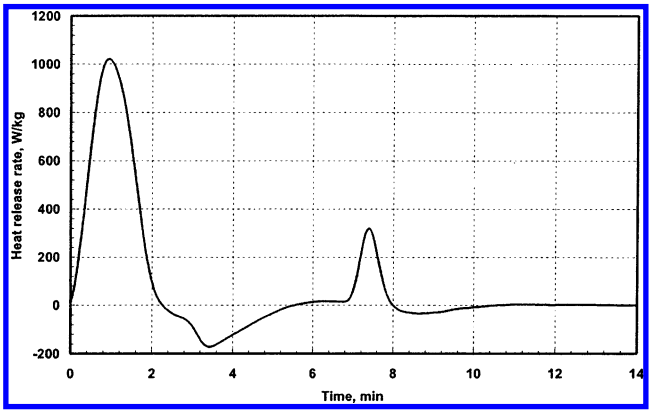


Figure 3. **Calorimetric response from the addition of two unequal portions of 8.**

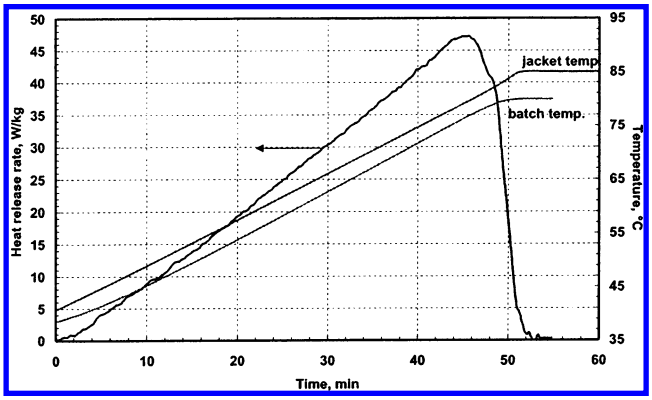


Figure 4. **Heat evolution profile**

The analysis also indicated that there was an exothermic response during the time that the reaction was being heated to the reflux temperature ($\Delta H \approx -73.5$ kJ/kg, $\Delta T_{adiabatic} =$ 38 °C) (see Figure 4). The reaction heat decreased sharply to zero upon attainment of reflux, with heat input from the jacket being used almost entirely for reflux and maintaining the batch temperature.

These results indicated that a slow rate of heating was desirable for scale-up to maintain the heat release at a safe level. This reaction was scaled up safely in the pilot plant as predicted by the calorimetric analysis.

With the reaction conditions defined, we next turned our attention to the workup and isolation. Specifically, a considerable amount of intractable material was generated during the reaction, which inhibited the crystallization of the product. In fact, according to the literature,[3,7] purification and isolation of **2** were usually accomplished by chromatography followed by distillation, or by crystallization of the amine as the oxalate. Due to the high boiling point of the 2-methyltryptamine (**2**) (190 °C/0.1 mm), the distillation method was not considered. Isolation of **2** as the oxalic acid salt directly

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(5) Subsequent to the completion of our work, a publication appeared in which the Grandberg modification of the Fischer indole synthesis was scaled up in the laboratory as part of the synthesis of PHA-565272-A. See: Fleck, T. J.; Chen, J. J.; Lu, C. V. *Org. Process Res. Dev.* **2006**, *10*, 334−38.
(6) Granberg, I. I.; Przheval'skii, I. M.; Vysotskii, V. I. *Khim. Geterotsikl. Soedin.* **1970**, *11*, 1499−1504.
(7) Grandberg, I. I.; Zuyanova, T. I. *Khim. Geterosikl. Soedin.* **1968**, *4*(5), 875−877.

from the reaction was successful (75% yield, high purity); however, neutralization of the salt for use in the following step was found to be problematic in terms of recovery due to the insolubility of the salt. Therefore, we turned our attention to developing a procedure which would allow for the isolation of **2** as a crystalline solid.

The workup procedure we followed involved solvent removal, basification to neutrality, and extraction. In our initial experiments using the above procedure, it proved difficult to separate the product from the polymeric materials formed in the reaction. Thus, **2** was isolated as a dark oil. If carried through the remainder of the synthesis, it was observed that the impurities present caused major purification problems. Therefore, we focused our efforts on developing a purification procedure for 2-methyltryptamine (**2**).

The use of ethanol/water (95/5) as the solvent system was important since the boiling point was high enough to allow for a rapid reaction. This was desirable since longer reaction times were found to give larger amounts of polymeric material. After removal of the ethanol and washing with toluene to remove any unreacted ketone as well as other unidentified neutral impurities, the aqueous phase was basified and the product extracted into toluene (note: ethyl acetate was also tried, but crystallization of the product from this solvent was more difficult).

For removing the polymeric impurities from **2**, several different types of solid adsorbents were investigated. These included: silica gel, alumina (basic and neutral), and activated carbon. We found that heating the toluene solution of **2** with activated carbon, followed by filtration through filter aid (Hyflo Supercel) was effective in removing the impurities to the extent that the product could be obtained in high purity upon crystallization. Initially, we chose to use an anti-solvent (*n*-heptane) and low temperature for the isolation of the **2** because these conditions afforded a higher yield (up to 65%). However, the problem of crusting of the solids on the walls of the flask made this unsuitable for the pilot plant. Therefore, the use of a higher crystallization temperature and elimination of the *n*-heptane anti-solvent provided a better pilot-plant fit in spite of the lower yield (46%).

One other problem which we addressed was the quality of **8**. All of our initial work had been carried out using the distilled ketone, since the commercial grade was only 85% pure and contained a large amount of black residue. Although the latter did not adversely affect the reaction, it was found that the impure material caused problems with the workup and isolation due to the presence of intractable impurities. Thus, we determined that the quality of the 5-chloro-2-pentanone (**8**) had a significant impact on the reaction in terms of the ease of purification of **2**. Fortunately, we were able to locate a supplier of **8** who provided us with material of sufficient quality to be used "as is".

Conclusions

In summary, an efficient, safe, and cost-effective synthesis of 2-methyltryptamine (**2**) was developed. The reaction of phenylhydrazine (**7**) with a stoichiometric amount of 5-chloro-2-pentanone (**8**) in aqueous ethanol at reflux furnished **2** in one operation from cheap and readily available starting materials. By carefully controlling the reaction conditions and using the appropriate workup protocol, the desired product was obtained as a crystalline solid without the need for extensive purification. The reaction scaled up well in our pilot plant. A total of 14.2 kg of **2** was prepared in 46% yield and high purity (the purity by HPLC and DSC was greater than 99.9%).

Experimental Section

The melting point reported is uncorrected. The ^{1}H NMR spectrum was recorded on a Bruker DPX300 instrument. The activated carbon (PICA P1400) was obtained from PICA U.S.A.

2-Methyltryptamine (2). An 800-L glass-lined steel reactor was charged with phenylhydrazine (**7**, 19.3 kg, 178.5 mol) and ethanol (200 proof, 82.8 kg). The solution was warmed to 35 °C and held at this temperature while 5-chloro-2-pentanone (**8**, 22.2 kg, 178.5 mol) was added via diaphragm pump at such a rate that the temperature was maintained between 35 and 40 °C. The total time of the addition was 40 min. The mixture was stirred an additional 30 min at 35−40 °C. Ethanol (190 proof, 165.7 kg) was added, and the reaction temperature was increased slowly over 35 min until reflux (batch T = 81 °C) was achieved. The reflux was maintained for 50 min at which time the reaction was cooled to an internal temperature of 20 °C over 1 h. A portion of the ethanol was removed under reduced pressure (jacket T = 45 °C, 45 mbar) until the final volume (approximately 105 L) was reached. To this solution was added deionized water (149 L), and the distillation was continued until the final volume was achieved (approximately 134 L). Once again, deionized water (120 L) was added to the distillation residue, followed by toluene (103 kg). The two-phase mixture was stirred for 10 min and allowed to settle for 35 min. The lower aqueous layer was separated and saved, and the upper toluene layer was discarded. The process was repeated using fresh toluene (103 kg). The aqueous solution was added back into the 800-L reactor, and sodium chloride solution (52.7 kg, prepared from 17.5 kg of sodium chloride and 52.5 L of deionized water) was introduced. After 15 min of agitation, toluene (258 kg) was added using isolated vacuum. The mixture was warmed to an internal temperature of 40−46 °C, which resulted in the formation of two phases. At this temperature, 50% aqueous sodium hydroxide (17.1 kg, 214 mol) was added over 5 min using a diaphragm pump. Vigorous stirring was maintained throughout the addition. After stirring for 15 min at 40−46 °C, agitation was stopped, and the mixture was held for 15 min. The layers were separated, and the lower aqueous layer was discarded. The temperature of the organic layer was maintained at 40−46 °C, and aqueous sodium chloride solution (70 kg, prepared from 17.5 kg of sodium chloride and 52.5 L of deionized water) was added over 10 min. After stirring for 15 min at 40−46 °C, agitation was stopped, and the mixture was held for 15 min. The layers were separated, and the lower aqueous layer was discarded. The toluene layer was concentrated under reduced pressure (110 mbar, batch T = 38−56 °C) to the desired volume (approximately 209

L). While holding the temperature at 65−70 °C, the toluene solution was added to an 800-L glass-lined steel reactor containing a suspension of carbon (PICA P1400, 3 kg) and Celite 545 (3 kg) in toluene (13 kg) at 65 °C. A toluene rinse (5 kg) was used. The suspension was stirred for 25 min at 65−70 °C and filtered using a 70-L glass-lined, steel Nutsche filter. Toluene (15 kg) was used to rinse the reactor and wash the filter cake. The filtrates were combined and cooled below 40 °C. With medium agitation, the mixture was seeded with a suspension of **2** in toluene (12 g in 100 mL). The temperature was lowered to 35 °C and held at this point for 1.5 h while the product crystallized. The resulting slurry was cooled to 21 °C over 1 h and held for an additional 2 h. The solids were collected by centrifugation and were washed with cold (0 °C) toluene (27.4 kg) containing Stadis 450 anti-static agent (1.6 g). The solids were dried under reduced pressure (20 mbar) at 45 °C until a constant weight was obtained to afford pure 2-methyltryptamine (**2**, 14.2 g, 46%): mp 90 °C. Lit.[8] mp 107 °C; DSC 86.77 °C; DSC purity 100.61 mol %; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.1 (bs, 2H), 2.30 (s, 3H), 2.77 (m, 2H), 2.92 (m, 2H), 7.01 (m, 2H), 7.17 (d, 91H), 7.42 (d, 1H), 7.97 (bs, 1H); MS (Positive-Ion DCI) 174.9 (MH^+); Anal. Calcd for $C_{11}H_{14}N_2$: C, 75.82; H, 8.10; N, 16.08. Found: C, 76.06; H, 8.23; N, 16.18.

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