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Technical Notes

Large Scale Deprotection of a *tert*-Butoxycarbonyl (Boc) Group Using Aqueous HCl and Acetone

D. Scott Coffey,*,† Mai Khanh N. Hawk,† Steven W. Pedersen,† Steven J. Ghera,† Paul G. Marler,† Paul N. Dodson,† and Michelle L. Lytle‡

Eli Lilly and Company, Chemical Product Research and Development, Indianapolis, Indiana 46285, U.S.A., and Eli Lilly and Company, Pharmaceutical Product Research and Development, Indianapolis, Indiana 46285, U.S.A.

Abstract:

A procedure for *tert*-butoxycarbonyl (Boc) group removal using concentrated HCl and acetone was developed and utilized on multi-kilogram scale in the synthesis of LY544344·HCl (1). The details surrounding this procedure and the advantages offered by it are described herein.

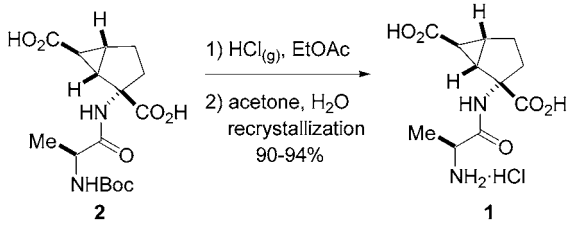
Introduction

LY544344·HCl (**1**) is a potent, orally active mGluR agonist that is currently being developed for the treatment of central nervous system disorders including generalized anxiety disorders. During the course of development, multi-kilogram quantities of **1** were required.[1] The final step in the synthetic process involved the removal of a *tert*-butoxycarbonyl (Boc) group from **2** to reveal **1**. This paper describes processing issues presented by this transformation and details the development of novel conditions for Boc group removal.

In the initial pilot plant scale-up (∼30 kg), **1** was prepared by treatment of **2** with a solution of $HCl_{(g)}$ in ethyl acetate (Scheme 1).[2] After recrystallization from acetone and water, **1** was isolated in a 90−94% overall yield with purities ranging from 97.8 to 99.5%.

While this process was high yielding, there were several processing issues that needed to be addressed prior to the next pilot plant campaign. In particular, since **2** was only partially soluble in ethyl acetate, conversion of **2** → **1** proceeded via a slurry-to-slurry transformation providing technical grade **1** as an amorphous solid.[3] As a result,

Scheme 1. **Boc removal in initial pilot plant scale-up**



filtration times were very long (>4 h on a 30 kg scale), and the rinse of the filter cake was not very efficient. Thus, it was difficult to remove the residual HCl from the filter cake. The residual HCl in the filter cake made it difficult to handle and also led to corrosion of a vacuum-dryer. Additionally, over the course of the reaction, partial hydrolysis of ethyl acetate occurred generating acetic acid and ethanol. This resulted in the generation of a monoethyl ester of **1** at levels up to 2%. While the subsequent recrystallization reduced these levels to 0.2−0.3%, we wanted to avoid generation of this impurity altogether. Thus, an alternative method was needed that would provide **1** as a crystalline solid in high yield with high purity.

While there are many methods in the literature for removal of a Boc group,[4] the physical properties of **1** were such that most of these methods could not be used. For example, **1** is insoluble in most organic solvents, but it is extremely water soluble (>650 mg/mL). Thus, appropriate solvent combinations that could be used to provide crystalline **1** were very limited.[5] We had already demonstrated that amorphous **1** was produced when ethyl acetate was used. Lower alcoholic solvents such as ethanol or methanol were not appropriate due to the propensity to form esters of **1**, and the high water solubility of **1** could present isolation issues if appreciable quantities of water were used.

The procedure used for the recrystallization of **1** in the initial pilot plant scale-up utilized an approximate 50:1 mixture of acetone−water. Since this solvent combination afforded crystalline **1**, we postulated that it could be used in

* To whom correspondence should be addressed: coffey_scott@lilly.com.
† Chemical Product Research and Development.
‡ Pharmaceutical Product Research and Development.

(1) (a) Coffey, D. S.; Dantzig, A. H.; Hillgren, K. M.; Massey, S. M.; Moher, E. D.; Monn, J. A.; Pedersen, S. W.; Sweetana, S. A.; Valli, M. J.; Bueno Melendo, A. B.; De Dios, A.; Dominguez-Fernadez, C.; Herin, M. G.; Martin-Cabrejas, L. M.; Martin, J. A.; Martinez-Grau, M. A.; Montero Salgado, C.; Pedregal-Tercero, C. Preparation of Prodrugs of Excitatory Amino Acids. WO 0255485. (b) Bueno Melendo, A. B.; Coffey, D. S.; Dantzig, A. H.; De Dios, A.; Dominguez-Fernadez, C.; Herin, M.; Hillgren, K. M.; Martin, J. A.; Martin-Cabrejas, L. M.; Martinez-Grau, M. A.; Massey, S. M.; Moher, E. D.; Monn, J. A.; Montero Salgado, C.; Pedersen, S. W.; Pedregal-Tercero, C.; Sweetana, S. A.; Valli, M. J. Preparation of Prodrugs of Excitatory Amino Acids. WO 0255481.
(2) Stahl, G. L.; Walter, R.; Smith, C. W. *J. Org. Chem.* **1978**, *43*, 2285.
(3) Compound **1** isolated from the deprotection reaction prior to recrystallization is referred to as technical grade **1**.
(4) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis;* Wiley: New York, 1999.
(5) Since this was the final step in the synthesis, only class 3 solvents as defined by ICH guidelines were considered. For more information, see: ICH Harmonised Tripartite Guideline, Impurities: Guidline for Residual Solvents, Q3C; July 1997.

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Table 1. **Boc deprotection of 2 using acetone and concentrated HCl at 50 °C**

entry	equiv. of HCl	reaction time (h)	yield tech grade (**1**) (%)
1	1.1	>24	*a*
2	1.5	16	98
3	1.6	8	97
4	1.7	6.5	98
5	1.8	5.5	97
6	2.0	3	99

[a] Reaction did not go to completion.

the deprotection step in combination with concentrated HCl to afford crystalline **1** directly. This approach would also eliminate the need for gaseous HCl. The combination of HCl and acetone, however, presented other issues. Specifically, the potential to produce mesityl oxide, diacetone alcohol, etc. by the self-condensation of acetone and the potential for the formation of imines between **1** and acetone were of major concern. Control of these processes would be vital to the success of this strategy.

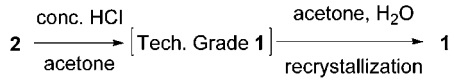
In the event, **2** was dissolved in a mixture of acetone (10 volumes based on **2**) and concentrated HCl (5 equiv based on **2**). Gratifyingly, **2**, while only partially soluble in acetone and insoluble in concentrated HCl, was completely soluble in this acetone−concentrated HCl mixture at rt. As the reaction progressed, **1** precipitated out of solution as a crystalline solid. After the reaction was complete (∼9 h), more acetone (10 volumes) was added to ensure complete recovery of **1**. Technical grade **1** was then isolated in 88% yield.

While these results were very encouraging, we wanted to avoid the use of a large excess of HCl. Furthermore, while the reaction times were normally ∼9 h, there were instances where the reaction would take up to 24 h. We felt that the process needed to be more consistent if it was going to be used on pilot plant scale. We, therefore, examined running the reaction at 50 °C. Initial results from these studies are detailed in Table 1. The most consistent results were obtained when 2.0 equiv. of concentrated HCl were used (entry 6). This set of conditions routinely afforded technical grade **1** in 97−98% yield, and the overall yield of **1** after recrystallization from acetone and water was 93−96% with purities >99%.

Following the successes described above, our efforts then focused on control of impurities produced in the reaction. The filtrates of the reaction mixtures were analyzed for mesityl oxide and diacetone alcohol.[6] By ^{1}H NMR spectroscopy, it was determined that <5% mesityl oxide was present in the filtrate. Further analysis by gas chromatography revealed that technical grade samples of **1** contained ∼200 ppm of mesityl oxide, and samples of **1** after recrystallization contained ≤10 ppm of mesityl oxide. For other reasons such as final form control, a recrystallization would likely be incorporated into the process. Thus, the recrystallization offered a control point for mesityl oxide making contamination of **1** with mesityl oxide a nonissue. Furthermore, after thorough examination of samples of **1** by LC-mass spectroscopy, we saw no evidence of imine formation. We also monitored the fate of the Boc group during the deprotection. From initial laboratory experiments, we knew that *tert*-butyl chloride and *tert*-butyl alcohol were produced in this reaction. Both were controlled at <0.1% in technical grade **1**, and *tert*-butyl chloride was controlled at <1 ppm in recrystallized **1**.

(6) Spiking studies confirmed that diacetone alcohol was converted to mesityl oxide under the reaction conditions.

Table 2. **Pilot plant scale up results**



batch	amount of **1** (kg)	yield (**1**) (%)	purity (%)
1	24.9	92	100.0
2	28.8	93	100.0
3	28.0	92	100.0
4	32.5	94	100.0
5	29.6	92	100.0
6	32.2	90	99.8
7	33.5	91	99.8
8	33.2	94	100.0

The procedure described above (2.0 equiv. concentrated HCl in acetone (10 volumes)) was implemented on pilot plant scale. As previously mentioned, technical grade **1** was recrystallized from acetone and water. To simplify the process, technical grade **1** was dried on the filter and taken directly into the recrystallization. The scale-up results are shown in Table 2. It should also be noted that mesityl oxide was not detected at levels >0.02% in any of the batches, and that *tert*-butyl chloride and *tert*-butyl alcohol were not detected at levels >0.1%.

Conclusion

We have shown that the Boc group of **2** can be deprotected with concentrated HCl in acetone on large scale to afford **1** in high yield and with high purity. The process is safe and cost-effective and utilizes a "process-friendly" solvent. This procedure could also find application to other systems, further details of which will be reported in due course.

Experimental Section.

General. All reagents were used without purification. Solvents were not distilled before use. ^{1}H NMR spectra were measured at 500 MHz on a Varian Inova spectrometer. Chemical shifts are reported in δ units with coupling constants reported in Hz. Spectra measured in DMSO-d_6 were referenced against residual solvent (δ 2.49 ppm). ^{13}C NMR spectra were recorded at 125 MHz. Chemical shifts are reported relative to the δ 39.4 ppm resonance of DMSO-d_6.

The method of analysis to determine the purity of **1** used an isocratic, reversed-phase ion-pairing HPLC, coupled with UV detection at 205 nm. The analytical column employed was a Zorbax SB-C8 (4.6 × 75 mm^2, 3.5 micron particle size). The mobile phase consisted of 17% acetontrile/83% 10mM 1-octanesulfonic acid, 0.1% (v/v) H_3PO_4 in water. A

flow rate of 2.0 mL/min, an injection volume of 20 μL, and a column temperature of 30 °C were utilized. Samples were dissolved in 10 mM 1-octanesulfonic acid, 0.1% (v/v) H_3PO_4 in water.

The quantity of mesityl oxide in **1** was determined using an Agilent 5973 Mass Selective Detector in conjunction with an Agilent 6890 Series GC system. Conditions: (scan range) SIM Mode with selected ions of 98 and 83 *m*/*z*; (column) J&W Scientific DB-1 MS, 30 M × 0.25 mm ID × 0.25 μm film; (oven temperature) 40 °C (0min) to 300 °C (5min), @15 °C/min; (injection size) 1 uL; (injection temperature) 250 °C; (split ratio) @25/1; (column helium flow) 1.2 mL/min; (mass transfer line) @300 °C; (sample preparation) 10 mg/mL concentration in MeOH; (standard preparation) two standards were prepared, one at 0.000 96 mg/mL and the second at 0.0096 mg/mL in MeOH.

Represented Laboratory Procedure of the Preparation of (1*S*,2*S*,5*R*,6*S*)-2-[(2′*S*)-(2′-Amino)-propionyl]amino-bicyclo[3.1.0]hexane-2,6-dicarboxylic Acid Hydrochloride (1). Concentrated hydrochloric acid (8.9 mL, 107 mmol) was added to a mixture of **2** (20.0 g, 53.4 mmol) and acetone (200 mL). The resulting solution was heated at 50 °C and stirred for 3 h. Acetone (200 mL) was then added over a period of 1 h while maintaining the temperature at 50 °C. The resulting slurry was filtered. The filtercake was dried and then dissolved in acetone (20.2 mL) and H_2O (10.1 mL). The resulting solution was heated to 50 °C. Acetone (305 mL) was then added over a period of 3 h while maintaining the temperature at 50 °C. Upon completion of the addition, the resulting slurry was stirred an additional 3 h at 50 °C. The slurry was filtered affording 14.8 g (95%) of **1** as a white crystalline solid: $[\alpha]^{25}_D = -7.80$ ($c = 1.0$, MeOH); ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.4 (br s, 2 H), 9.04 (s, 1 H), 8.21 (s, 2 H), 3.81 (br q, 1 H), 2.22 (dd, $J = 6.3$, 2.5 Hz, 1 H), 2.19 (dd, $J = 13.7$, 8.2 Hz, 1 H), 1.97−1.90 (m, 1 H), 1.85−1.80 (m, 2 H), 1.51 (t, $J = 3.0$ Hz, 1 H), 1.35 (d, $J = 6.6$ Hz, 3 H), 1.36−1.29 (overlapping m, 1 H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 173.53, 173.50, 169.6, 65.3, 47.8, 33.7, 31.4, 27.3, 25.9, 20.7, 17.2.

Represented Pilot Plant Procedure of the Preparation of (1*S*,2*S*,5*R*,6*S*)-2-[(2′*S*)-(2′-Amino)-propionyl]amino-bicyclo[3.1.0]hexane-2,6-dicarboxylic Acid Hydrochloride (1). Hydrochloric acid (16.2 L, 190 mmol, ∼11.7 M) was added to a mixture of **2** (35.5 kg, 94.8 mol) and acetone (356 L). The resulting solution was heated at 50 °C for ca. 5 h. Analysis of the reaction mixture by HPLC indicated that the reaction was complete. Over a period of 2 h, acetone (356 L) was added to the reaction mixture as it was cooling to room temperature. The mixture was then filtered. The filter cake was rinsed with acetone (71 L) and then blown dry with N_2 for a period of at least 4 h. The dried filter cake was then added to H_2O (17.4 L). Acetone (35 L) was added, and the mixture was heated to 50 °C and stirred until a clear solution resulted. The resulting solution was then polish filtered to remove any particulate matter. The solution was then seeded with **1**. While cooling to room temperature, acetone (512 L) was added over a period of 3 h. The resulting slurry was passed through an Urschel slurry mill and then filtered and rinsed with acetone (27 L). After drying on an agitated, vacuum filter dryer at 60 °C for ca. 24 h, 25.0 kg (92%) of **1** was obtained as a white crystalline solid. (528240).

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