

Demethylation of 4-Methoxyphenylbutyric Acid Using Molten Pyridinium Hydrochloride on Multikilogram Scale

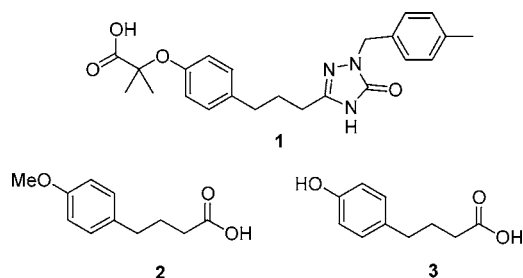
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Abstract:

4-Methoxyphenylbutyric acid (**2**) is smoothly demethylated in 3 h at 180 °C when melted with pyridinium hydrochloride (Pyr·HCl), affording 4-hydroxyphenylbutyric acid (**3**), a key starting material for the preclinical candidate LY518674 (**1**). The adaptation of this chemistry to 22-L and pilot-plant scale is described, including findings to facilitate product isolation, selection of a compatible extraction solvent, and observation of an unusual relationship between the number of solvent extractions and the Pyr·HCl stoichiometry. To the best of our knowledge, this represents the first literature report of the use of this classic demethylation chemistry on multikilogram scale.

The selection of LY518674 (**1**) for preclinical evaluation required the development of a synthesis capable of delivering kilogram quantities of the compound. One particular need was ready access to 4-hydroxyphenylbutyric acid (**3**), a key feedstock for the synthesis.¹ This compound had been



previously obtained from commercially available 4-methoxyphenylbutyric acid (**2**) via demethylation using hydrogen bromide in refluxing acetic acid as the only reported method for its synthesis.² When this approach failed to perform acceptably in our hands, we extended the scope of our research to include the broad range of alternative chemistry available for demethylation of methyl aryl ethers.³ Herein we report our findings that pyridinium hydrochloride melt-based demethylation serves as an efficient and scaleable synthetic methodology to accomplish this transformation. We further detail our adaptation of this approach to 22-L and pilot-plant scale equipment as evidence that it can be readily employed on multikilogram scale.

During the synthesis development for LY518674, it became apparent that conventional methods of demethylation of **2**, i.e., BBr_3 ,⁴ $\text{BBr}_3/\text{Me}_2\text{S}$,⁵ BCl_3 ,⁶ NaSR ,⁷ $\text{AlX}_3/\text{thiol}$, or dialkylsulfide,⁸ as well as the existing literature method,² all exhibited undesirable features of one sort or another, prompting us to examine other alternatives. We turned to the classic pyridinium hydrochloride (Pyr·HCl) melt demethylation, used frequently throughout the literature⁹ but having limitations that might preclude its use on scale. The reaction typically required high temperature (usually 200–220 °C) and extended reaction times, with this high melting point ionic liquid usually employed in large excess as solvent. Furthermore, since Pyr·HCl solidified at fairly high temperature, product isolation was potentially problematic. Finally, the reaction would have to demonstrate a thermal hazard profile consistent with safe operation on scale.

Nevertheless, on gram scale, the demethylation of **2** using Pyr·HCl proceeded smoothly to completion within 3 h at the lower temperature of 180–190 °C, affording **3** as the only observable product by HPLC and NMR. The simplicity and efficiency of the transformation led us to pursue the development of a product isolation procedure that would make this methodology adaptable to kilogram and multikilogram scale.

Critical to the successful use of this chemistry on scale was the need to keep the reaction mixture and subsequent extractions and phase splits in the liquid state, that is, to prevent solidification of the Pyr·HCl. We observed that the mixture, upon completion of reaction, would solidify in the 75–80 °C range, preventing agitation. In practice, it was found that adding a molar equivalent of 5 N HCl¹⁰ to the stirring liquid at or about 90 °C, followed by further dilution with water, produced a homogeneous solution that remained as a nonviscous liquid at room temperature, permitting extraction of 4-hydroxyphenylbutyric acid with an organic

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 (10) Addition of 1 equiv of acid is required by reaction stoichiometry to neutralize the pyridinium carboxylate of **3**.

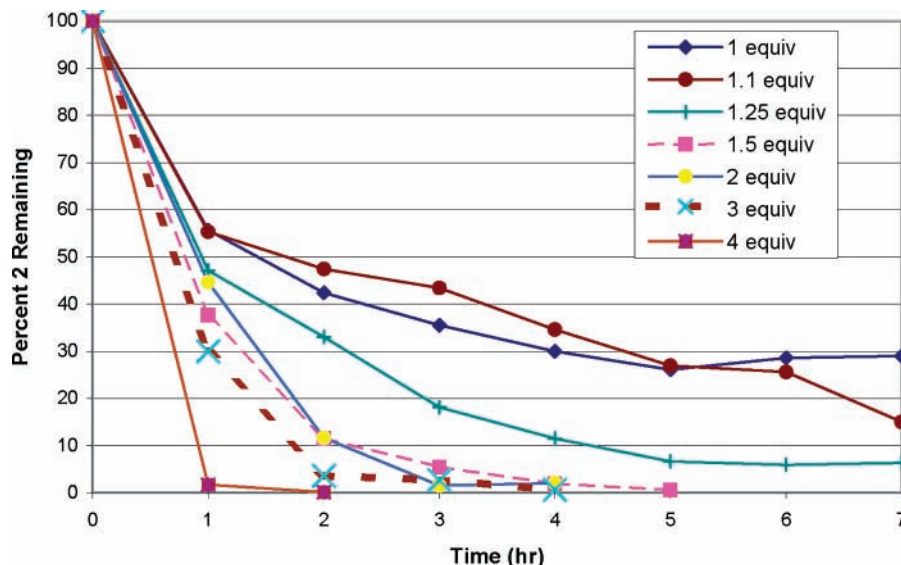
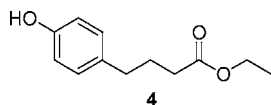


Figure 1. Percent of 2 remaining (190 °C) vs time for various equivalents of Pyr·HCl.

solvent. The direct addition of the aqueous quenches into the molten liquid phase also alleviated concerns of possible freezing during transfer of the molten mixture to a separate quench vessel. Safety evaluation of the reaction mixture using accelerated rate calorimetry gave no indication of any thermal hazards.

Of the solvents examined for the extraction, we initially employed ethyl acetate but observed a low level impurity that grew to become more significant on further scale-up. This proved to be 4-hydroxyphenylbutyric acid ethyl ester (**4**), produced via transesterification of ethyl acetate with the desired product upon extended contact with the aqueous HCl/Pyr·HCl layer. While there is literature precedent for the use



of Pyr·HCl to effect esterification of carboxylic acids,^{9,11} we were nevertheless surprised to observe this behavior, particularly during an aqueous organic extraction. As a result, we opted to extract product **3** with *tert*-butyl methyl ether (MTBE). Several extractions, followed by washing with 5 N HCl and drying with sodium sulfate, afforded a solution of **3** in MTBE that could be conveniently concentrated to a solid at 22-L scale on a rotary evaporator in excellent yield and purity. Phase splits obtained from extractions and washings were rapid and clean, with no significant interphase layer problems. Despite the acidic nature of the aqueous phase, we did not observe any decomposition of the MTBE. Overall yields ranged from 87 to 97% of 99% potency material using this procedure, which was employed to deliver some 5.77 kg of the desired compound, the reactions being run in 12- and 22-L glass vessels.

The success of this chemistry in 22-L equipment led us to consider whether it could be adapted to run on pilot-plant scale. Our review of the literature failed to disclose any examples of the use of this methodology beyond multigram

scale.¹² On multikilogram scale, the key to successful implementation came in combining the two primary needs of the process, high-temperature operation and low volume stir capability, in a single equipment set. After some evaluation, a 190-L reactor with these two key features was selected and the reaction volumes sized so the aqueous quench could be added directly to the reactor following reaction completion and cooling.

Implementation of this chemistry on 190-L scale allowed for more thorough optimization of reaction stoichiometry and temperature. The reaction was found to require at least 1.5 equiv of Pyr·HCl to go to completion (Figure 1) when run at 190 °C. Using this stoichiometry, the reaction temperature was varied, giving the data shown in Figure 2. Based on these findings, a set point reactor temperature of 200–212 °C was chosen. Optimization of the workup revealed an interesting phenomenon, a relationship between equivalents of Pyr·HCl used and number of organic extractions required following dilution with aqueous HCl. With 2.5 equiv of Pyr·HCl, three or more MTBE extractions were required to fully remove the desired **3**, whereas the compound was completely removed with two MTBE extractions when 1.5 equiv of Pyr·HCl was used. These observations led to the design of a smoothly operating process on pilot plant scale. Substrate **2**, a low melting (mp 47 °C) solid, was charged first to the reactor and liquefied at about 60 °C. The Pyr·HCl was then added, the molten substrate assisting in dissolution of the Pyr·HCl upon addition, so that a stirable, partially liquefied slurry was obtained. After heating to a 210 °C setpoint for 2 h, the reaction was cooled to below 90 °C, 2 N HCl was added, and the mixture cooled to rt. Two extractions with 4 volumes each of MTBE were sufficient to completely remove product **3** from the aqueous layer. The combined organic layers were washed with 2 volumes of 2 N HCl. The product was solvent exchanged into toluene and seeded to effect crystallization, which was followed by cooling and filtration.

(12) A single reference details the use of pyridinium hydrochloride in the demethylation of metaclopramide on 500-g scale. See: Wynberg, H.; Van Echten, E.; Ten Hoeve, W. EP 431561 A2 19910612.

(11) For example, see: Hertler, W. R. WO 9115453 A1 19911017.

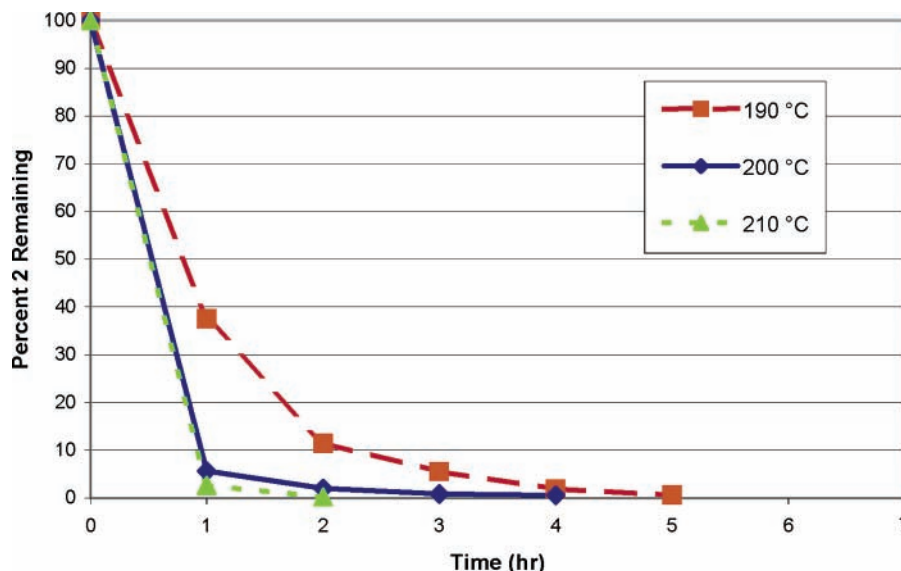


Figure 2. Percent of **2** remaining (1.5 equiv of Pyr·HCl) vs time for various reaction temperatures.

Yields for the two runs in 190-L equipment (~32 kg each) were 94% and 96% of 99.0% or higher potency material. Treatment of the waste stream consisted of neutralization to pH 7.

In preparing for scale-up, several operational issues were also addressed. First, the product had a tendency to sublime onto the cooler head and condenser of the laboratory glassware. The problem was overcome at scale through the appropriate placement of the system purge, condenser temperature setpoint, and additional insulation for the reactor head. A modified vacuum sampling system was employed to prevent sublimation if the temperature was to drop too low. An unusual third issue involved the handling of Pyr·HCl. During laboratory work, handling Pyr·HCl with a metal spatula would result in discolored product that could not be distinguished from “typical” product analytically. While it was not clear why the very short contact time had such a drastic effect, the use of plastic scoops remedied the issue.

The Pyr·HCl melt demethylation of 4-methoxyphenylbutyric acid **2** was found to be readily adaptable to pilot-plant scale, affording product 4-hydroxyphenylbutyric acid **3** in high yield and purity. Key to the success of this reaction on scale were the findings that the reaction proceeded rapidly at pilot-plant attainable temperatures of 180–210 °C and that addition of aqueous HCl to the still molten Pyr·HCl phase provided a consistent aqueous liquid phase from which product could be extracted. With reasonable modifications, the chemistry was scaled successfully to pilot plant equipment possessing both high temperature and low-stir volume capabilities. An interesting relationship was uncovered between Pyr·HCl stoichiometry and the number of MTBE extractions required to remove product 4-hydroxyphenylbutyric acid. We believe this to be the first literature disclosure of the use of a Pyr·HCl melt demethylation on kilogram or multikilogram scale. The successful demonstration of a Pyr·HCl melt demethylation in 22-L and 190-L equipment permits this methodology to be added to the process chemist’s list of transformations known to be viable on scale.

Experimental Section

4-(4-Hydroxyphenyl)butyric Acid (3), 22-L Scale. To a 22-L four-necked round-bottom flask equipped with a condenser, nitrogen inlet, and thermometer lead, and overhead stirring apparatus was charged 4-(4-methoxyphenyl)butyric acid (2250 g, 11.58 mol) followed by pyridinium hydrochloride (5360 g, 46.34 mol, 4 equiv). The resulting mixture of the two solids was heated under nitrogen to 185–195 °C, with stirring commencing by 50 °C. The flask contents were held at 185–195 °C, and reaction progress was monitored by TLC (50/50 v/v hexanes/ethyl acetate + 1% v/v acetic acid, *p*-anisaldehyde stain for visualization). After 2 h, TLC analysis indicated complete consumption of starting material. The heat source was removed, and the mixture was allowed to cool to 90 °C, after which 5 N HCl (2900 mL, 14.5 mol, 1.25 equiv) and H₂O (2700 mL) were added sequentially. Stirring was continued until the pot temperature reached 35 °C. The mixture was transferred to a 22-L bottom-outlet flask and diluted with MTBE (6000 mL). The layers were separated, and the aqueous portion was re-extracted with MTBE (3 × 4000 mL). The organic portions were combined and back-washed with 5 N HCl (750 mL). After drying (Na₂SO₄) and filtration, the solution was concentrated in vacuo to afford the title compound as a white solid (2020 g, 96.8%). ¹H NMR (500 MHz, DMSO-*d*₆) δ 1.70 (m, 2 H), 2.15 (t, 2 H), 2.45 (t, 2 H), 3.33 (s, 1 H), 6.65 (d, 2 H), 6.95 (d, 2 H). ¹³C NMR (125 MHz, DMSO-*d*₆) δ 26.5, 32.5, 33.5, 114.6, 129.0, 131.2, 155.3, 174.2.

4-(4-Hydroxyphenyl)butyric Acid (3), Pilot Plant Scale. To a well-insulated 190-L reactor was charged 4-(4-methoxyphenyl)butyric acid (32.0 kg, 164.75 mol). The reactor was heated to 55–65 °C to achieve complete melt of the solid with stirring commencing as melting initiated. Pyridinium hydrochloride (28.6 kg, 247.5 mol, 1.5 equiv) was added, and the resulting mixture was further heated under nitrogen to 200–212 °C. The reactor contents were held at 200–212 °C, and reaction progress was monitored by HPLC (40/60 v/v acetonitrile/0.1% trifluoroacetic acid, Zorbax SB-

C18 4.6 × 250 mm² ambient column, 1 mL/min, 220 nm). After 2 h, HPLC analysis indicated >99.5% consumption of starting material. The mixture was cooled to 80–90 °C, and 2 N HCl (128 L, 256 mol, ~1.5 equiv) was added. Stirring was continued until the pot temperature reached <50 °C. The mixture was transferred to a 380-L reactor and diluted with MTBE (128 L). The layers were separated, and the aqueous portion was re-extracted with MTBE (128 L). The organic portions were combined and washed with 2 N HCl (64 L). The organic phase was then concentrated to 120–130 L via atmospheric distillation. The solution was cooled, and toluene (128 L) was added. Distillation resumed

with toluene being added at the same rate as distillate was collected, maintaining the reactor volume at ~250–260 L. Solvent exchange was considered complete when the distillate temperature exceeded 110 °C (final distillate temperature 110.9 °C, 256 L toluene used). The solution was cooled to 80 °C and seeded to induce crystallization. The mixture was slowly cooled to 0–5 °C, filtered, and rinsed with cold toluene (64 L). Drying in vacuo afforded the title compound as a white solid (28.655 kg, 99.0% potency, 95.6% yield).

Received for review March 2, 2004.

OP0499526