Organic Process Research & Development **2008,** *12,* 785–786

Technical Notes

Solving a Scale-Up Problem in the *O*-Alkylation of Isovanillin Under Phase-Transfer Catalysis Conditions

Bogdan K. Wilk,* Nalukui Mwisiya, and Jean L. Helom

Wyeth Research, Chemical Development, 401 North Middletown Road, Pearl River, New York 10965, U.S.A.

Abstract:

The alkylation of isovanillin with cyclopentyl bromide in the presence of potassium carbonate and a phase-transfer catalyst in THF is investigated. Successful completion of the reaction depends on the particle size of potassium carbonate.

Introduction

3-(Cyclopentyloxy)-4-methoxybenzaldehyde (**1**) is a key intermediate in the synthesis of PDE IV inhibitors used for the treatment of asthma, inflammatory disorders, and depression.[1] To support the development of Filaminast (PDA-641), it was necessary to synthesize multikilogram quantities of aldehyde **1**. Initially, it was prepared by alkylation of isovanillin **2** with cyclopentyl bromide (**3**) in *N,N*-dimethylformamide (DMF) at 65−100 °C, in the presence of anhydrous K_2CO_3. The reaction mixture was filtered, and DMF was removed *in vacuo*. The resulting concentrate was diluted with toluene and washed with aqueous NaOH to remove residual isovanillin **2**, and the aqueous phase was extracted with toluene. The combined organic extracts were washed with water and dried. Following evaporation of toluene, the crude oil was then dissolved in tetrahydrofuran (THF). Since the next step in the synthetic sequence was the addition of MeMgCl in THF,[2] it was highly desirable to be able to also run the alkylation of isovanillin **2** in THF.

A process was designed and successfully scaled up in which isovanillin **2** was alkylated in the presence of Bu_4NBr and anhydrous K_2CO_3 in refluxing THF (Scheme 1). To minimize the side reaction (elimination of HBr), bromide **3** was added in two portions: 1 equiv at the beginning of the reaction and another 0.5 equiv after 6 h. Upon filtration, the solution of **1** in THF was used directly in the next step, the Grignard addition.[2] This new, high throughput process assures high conversion of isovanillin **2** and eliminates both aqueous workup and solvent replacement.

Results and Discussion

During a second pilot-plant run, an unexpected problem was encountered with the reaction completion as an aliquot taken after 5 h at reflux showed 38% of unreacted isovanillin **2**, higher than the expected 20−25% observed in earlier batches. After an additional 8 h at reflux, 31% of **2** remained, instead of the expected 0−3%. An examination of the batch records showed that the stirring rate and the quality of carbonate used were different from prior batches. Specifically the stirring was slower, and the carbonate was milled by a different process.

Increasing the stirring rate and refluxing the reaction mixture for additional 3 h, did not decrease the amount of residual isovanillin **2**. K_2CO_3 used in this batch (carbonate **A**) had been milled on FitzMill J pulverizer with 20 mesh screen, whereas the carbonate in earlier, successful batches had been milled on a larger, speed-controlled FitzMill model D with 40 mesh screen. Therefore, additional carbonate was milled on FitzMill D with 40 mesh screen (carbonate **B**) and added to the batch. After 16 h at reflux, the level of **2** decreased to 13%. With more carbonate **B** added to the batch and additional 17 h at reflux, the amount of **2** eventually decreased to 5%. It was satisfactory for batch completion; however, it was still higher than in previous batches.

The quality of carbonate **A** used in this batch and the former batches (carbonate **B**) was similar in terms of physical characteristics. Both materials were 78% above 50 mesh. Subsequent

* Author to whom correspondence may be sent. E-mail: wilkb@wyeth.com

(1) (a) Lombardo, L. J. Eur. Pat. 0470805, 1992. (b) Lombardo, L. J. *Curr. Pharm. Des.* **1995**, *1*, 255. (c) Heaslip, R. J.; Lombardo, L. J.; Golankiewicz, J. M.; Ilsemann, B. A.; Evans, D. Y.; Sickels, B. D.; Mudrick, J. K.; Bagli, J.; Weichman, B. M. *J. Pharm. Exp. Ther.* **1994**, *268*, 888. (d) Cavalla, D.; Frith, R. *Curr. Med. Chem.* **1995**, *2*, 561. (e) Ashton, M. J.; Cook, D. C.; Fenton, G.; Karlsson, J.-A.; Palfreyman, M. N.; Raeburn, D.; Ratcliffe, A. J.; Souness, J. E.; Thurairatnam, S.; Vicker, N. *J. Med. Chem.* **1994**, *37*, 1696. (f) Honda, T.; Ishikawa, F.; Kanai, K.; Sato, S.; Kato, D.; Tominaga, H. *Heterocycles* **1996**, *42*, 109. (g) Cook, D. C.; Jones, R. H.; Kabir, H.; Lythgoe, D. J.; McFarlane, I. M.; Pemberton, C.; Thatcher, A. A.; Thompson, D. M.; Walton, J. B. *Org. Process Res. Dev.* **1998**, *2*, 157. (h) Anada, M.; Mita, O.; Watanabe, H.; Kitagaki, S.; Hashimoto, S. *Synlett* **1999**, *11*, 1775. (i) Langlois, N.; Wang, H.-S. *Synth. Commun.* **1997**, *27*, 3133. (j) Brackeen, M. F.; Cowan, D. J.; Stafford, J. A.; Schoenen, F. J.; Veal, J. M.; Domanico, P. L.; Rose, D.; Strickland, A. B.; Verghese, M.; Feldman, P. L. *J. Med. Chem.* **1995**, *38*, 4848. (k) Alexander, R. P.; Warrellow, G. J.; Eaton, M. A. W.; Boyd, E. C.; Head, J. C.; Porter, J. R.; Brown, J. A.; Reuberson, J. T.; Hutchinson, B.; Turner, P.; Boyce, B.; Barnes, D.; Mason, B.; Cannell, A.; Taylor, R. J.; Zomaya, A.; Millican, A.; Leonard, J.; Morphy, R.; Wales, M.; Perry, M.; Allen, R. A.; Gozzard, N.; Hughes, B.; Higgs, G. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1451. (l) Christensen, S. B.; Guider, A.; Forster, C. J.; Gleason, J. G.; Bender, P. E.; Karpinski, J. M.; DeWolf, W. E., Jr.; Barnette, M. S.; Underwood, D. C.; Griswold, D. E.; Cieslinski, L. B.; Burman, M.; Bochnowicz, S.; Osborn, R. R.; Manning, C. D.; Grous, M.; Hillegas, L. M.; O'Leary Bartus, J; Ryan, M. D.; Eggleston, D. S.; Haltiwanger, R. C.; Torphy, T. J. *J. Med. Chem.* **1998**, *41*, 821.

(2) Wilk, B. K.; Helom, J. L.; Coughlin, C. W. *Org. Process Res. Dev.* **1998**, *2*, 407.

10.1021/op800058n CCC: $40.75
Published on Web 05/30/2008

Scheme 1

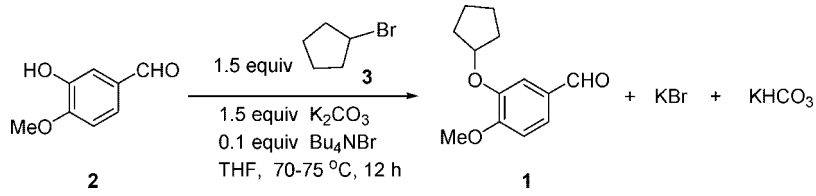

Table 1. **Product 1 distribution (HPLC area %) in the alkylations of 2 with 3.**

entry		1	2
1	**A**, Bu_4NBr	92.9	7.0
2	**A**, mortar-ground, Bu_4NBr	99.8	0
3	**B**, Bu_4NBr	88.5	11.6
4	**B**, activated at 105 °C, Bu_4NBr	88.9	10.8
5	**C**, Bu_4NBr	99.9	0
6	**C**, w/o Bu_4NBr	54.8	21.4
7	325-mesh powder, Bu_4NBr	99.8	0
8	granular, Bu_4NBr	62.1	36.9

Table 2. **Comparison of potassium carbonate particle size distribution, specific surface area, product 1 and residual substrate 2 distribution (HPLC area %).**

	potassium carbonate	D90 [μm]	specific surface [m^2/g]	1	2
1	**C**	29	1.02	99.9	0
2	325-mesh, powder	48	0.71	99.8	0
3	**A**	521	0.05	89.7	10.1
4	**B**	536	0.07	89.3	10.5
5	granular	570	0.02	60.5	38.8

experiments using various types of carbonates were conducted (Table 1) on a 0.3 mol scale under similar conditions (equipment, reagents, time, stirring rate). Carbonate **A** gave incomplete alkylation (entry 1; Table 1). However, when mortar-ground, it gave quantitative conversion of isovanillin **2** (entry 2). Carbonate **B** also gave incomplete alkylation (entry 3). Its activation at 105 °C did not increase its performance (entry 4). A finer carbonate **C**, obtained on FitzMill D with 80 mesh screen (entry 5) and the commercial 325-mesh carbonate (45 μm; entry 7), both gave quantitative conversions of **2**. Granular carbonate (entry 8), however, left 37% of unreacted **2**.

Addition of a phase-transfer catalyst is important. As shown in entry 6, when carbonate **C** was used in the absence of Bu_4NBr, the result was a low conversion of **2**. Even though, Bu_4NBr does not solubilize K_2CO_3,[3] with a pK_a of **2** at 8.9,[4] ion pairs (Bu_4N^+ ArO^-) are likely to form because the deprotonation of the phenol occurs at the surface of the carbonate.[3] During the reaction, K_2CO_3 is converted to KBr and $KHCO_3$.[5,6]

All carbonates used in the studies were submitted for particle scanning (Table 2). Direct correlation was found between K_2CO_3 particle size and the conversion of **2**. The carbonates with particle size D90: 30−50 μm gave quantitative conversion of **2**, whereas those with larger particles (D90: 520−570 μm) resulted in incomplete conversion.

Conclusions

Isovanillin **2** underwent nearly quantitative *O*-alkylation with cyclopentyl bromide **3** in the presence of K_2CO_3 and a phase-transfer catalyst (Bu_4NBr) in refluxing THF. A high throughput process was developed, allowing telescoping of the alkylation step to the subsequent step with a Grignard reagent. Both an aqueous workup and a solvent switch were eliminated. Direct correlation was found between K_2CO_3 particle size and the conversion of **2**. More stringent specifications were put in place.

Experimental Section

The pilot-plant materials were used, except the 325-mesh K_2CO_3 (Aldrich), granular K_2CO_3 (J.T. Baker), $KHCO_3$ (EM Science), and $K_2CO_3 \cdot 1.5\ H_2O$ (Aldrich). Particle size distribution was determined in isopropanol on a Malvern instrument. HPLC scans were obtained on a Hitachi D-6000 instrument with Partisil 5 μm, ODS-3, 4.6 mm × 250 mm column (Whatman); phosphate buffer (pH 3.5)/acetonitrile, 3:2 v/v; flow 1.0 mL/min; wavelength 226 nm.

Pilot-Plant Synthesis of 1. A mixture of **2** (45.0 kg), THF (115 kg), Bu_4NBr (9.6 kg), and milled K_2CO_3 (61.2 kg) was refluxed for 1.5 h in a 100-gal glass-lined vessel with agitation at 125 rpm. The vessel content initially thickened then thinned before reaching reflux. After cooling to 40 °C, **3** (44.1 kg) was added, and reflux continued for 5 h. A second batch of **3** (21.9 kg) was added and the mixture refluxed for additional 9 h. When all starting material was consumed (HPLC), the mixture was cooled to 25 °C, and solids were removed by filtration on a 0.25 m^2 Rosenmund filter. The filter cake was washed with THF (4 × 18 kg). The combined filtrate and wash were used as such in the next pilot-plant step.[2]

Acknowledgment

We thank Wyeth Research Analytical Department for the support. Helpful and stimulating discussions with Drs. M. Kolb, J. Potoski, and A. Pilcher are highly appreciated.

Received for review March 11, 2008.

OP800058N

(3) Dehmlow, E. V.; Dehmlow, S. S. *Phase Transfer Catalysis*; Verlag Chemie: Boca Raton, FL, 1983; pp 42, 92.
(4) Robinson, R. A.; Kiang, A. K. *Trans. Faraday. Soc.* **1955**, *51*, 1398.
(5) Bicarbonates form stable ion pairs (Bu_4N^+ HCO_3^-) that are well soluble in organic solvents (*cf.* ref 3). In fact, potassium bicarbonate ($KHCO_3$) gave conversion similar to that with potassium carbonate.
(6) A typical potassium carbonate contains 0.04−0.1% KOH along with 0.1−0.9% water. Nevertheless, the Cannizzaro by-product was not observed. Lock, G. *Chem. Ber.* **1929**, *62B*, 1177. Addition of water (0.1 equiv) had no effect on the conversion of **2**; yet surprisingly, potassium carbonate sesquihydrate ($K_2CO_3 \cdot 1.5\ H_2O$) gave complete conversion of **2**, but the reaction mixture turned very dark.