This article was downloaded by: [Duke University Libraries] On: 11 July 2012, At: 11:24 Publisher: Taylor & Francis Informa Ltd Registered in England and Wales Registered Number: 1072954 Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK



# Organic Preparations and Procedures International: The New Journal for **Organic Synthesis**

Publication details, including instructions for authors and subscription information:

http://www.tandfonline.com/loi/uopp20

## A CONVENIENT REDUCTION OF HIGHLY FUNCTIONALIZED AROMATIC CARBOXYLIC ACIDS TO ALCOHOLS WITH BORANE-THF AND BORON TRIFLUORIDE-ETHERATE

M. H. Chen<sup>a</sup>, E. lakovleva<sup>a</sup>, S. Kesten<sup>a</sup>, J. Magano<sup>a</sup>, D. Rodriguez<sup>a</sup>, K. E. Sexton<sup>a</sup>, J. Zhang<sup>a</sup> & H. T. Lee<sup>a</sup> <sup>a</sup> Pfizer Global Research & Development, Ann Arbor Laboratories, 2800 Plymouth Road, Ann Arbor, MI, 48105, USA

Version of record first published: 11 Feb 2009

To cite this article: M. H. Chen, E. Iakovleva, S. Kesten, J. Magano, D. Rodriguez, K. E. Sexton, J. Zhang & H. T. Lee (2002): A CONVENIENT REDUCTION OF HIGHLY FUNCTIONALIZED AROMATIC CARBOXYLIC ACIDS TO ALCOHOLS WITH BORANE-THF AND BORON TRIFLUORIDE-ETHERATE, Organic Preparations and Procedures International: The New Journal for Organic Synthesis, 34:6, 665-670

To link to this article: http://dx.doi.org/10.1080/00304940209355791

### PLEASE SCROLL DOWN FOR ARTICLE

Full terms and conditions of use: <u>http://www.tandfonline.com/page/terms-and-conditions</u>

This article may be used for research, teaching, and private study purposes. Any substantial or systematic reproduction, redistribution, reselling, loan, sub-licensing, systematic supply, or distribution in any form to anyone is expressly forbidden.

The publisher does not give any warranty express or implied or make any representation that the contents will be complete or accurate or up to date. The accuracy of any instructions, formulae, and drug doses should be independently verified with primary sources. The publisher shall not be liable for any loss, actions, claims, proceedings, demand, or costs or damages whatsoever or howsoever caused arising directly or indirectly in connection with or arising out of the use of this material.

### A CONVENIENT REDUCTION OF HIGHLY FUNCTIONALIZED AROMATIC CARBOXYLIC ACIDS TO ALCOHOLS WITH BORANE-THF AND BORON TRIFLUORIDE-ETHERATE

Submitted by (12/04/01)

M. H. Chen,\* E. Iakovleva, S. Kesten, J. Magano, D. Rodriguez, K. E. Sexton, J. Zhang and H. T. Lee

Pfizer Global Research & Development, Ann Arbor Laboratories 2800 Plymouth Road, Ann Arbor, MI 48105, USA

The reduction of carboxylic acids to the corresponding alcohols has been performed with a variety of metal hydrides and complex metal hydrides, such as LiAlH<sub>4</sub>, and its alkoxy derivatives,<sup>1</sup> NaBH<sub>4</sub>-Lewis acids,<sup>2</sup> boranes<sup>3</sup> and combinations of borane-Lewis acids.<sup>4</sup> The selective reduction of highly functionalized aromatic carboxylic acids with borane complexes is still not very well studied in the literature. During the recent synthesis of an important neurodegeneration inhibitor and its analogs, large quantities of key intermediate 3-hydroxy-4-nitrobenzyl alcohol (2) were needed. Compound 2 could be obtained from the reduction 3-hydroxy-4-nitrobenzoic acid (1). Most of the known reducing reagents, such as LiAlH<sub>4</sub>,<sup>5</sup> BH<sub>3</sub>-THF,<sup>3b</sup> BH<sub>3</sub>-Me<sub>2</sub>S,<sup>6</sup> NaBH<sub>4</sub>/I<sub>2</sub>,<sup>7</sup> CICO<sub>2</sub>*i*-Bu/NaBH<sub>4</sub>,<sup>8</sup> and *i*-Bu<sub>2</sub>AlH,<sup>9</sup> gave incomplete (0–60% conversion) reaction.<sup>10</sup> However, the reduction of compound 1 with the combination of BH<sub>3</sub>-THF and BF<sub>3</sub>-Et<sub>2</sub>O gave complete conversion and 91% isolated yield of alcohol 2. A thorough on-line literature search showed no previous examples using this combination for the reduction of functionalized aryl carboxylic acids to the corresponding benzyl alcohols. This encouraged us to further study this reagent in reduction reactions.

The reaction we now report involves the addition of a 1.0 M solution of  $BH_3$ -THF in THF to a mixture of benzoic acid and  $BF_3$ - $Et_2O$  in THF at ambient temperature and under an inert atmosphere. Hydrogen gas evolves immediately. The reaction mixture is then stirred at ambient temperature overnight. After quenching with methanol, the crude product is purified by recrystallization or chromatography. The results of the reaction are summarized in Table 2. This reduction tolerates a variety of functional groups on the benzoic acids such as nitro, hydroxy, chloro, bromo, trifluoromethyl, thio, cyano and methyl ester. Very good to excellent yields were obtained from the reduction of these highly functionalized compounds. The reduction of 3-hydroxy-4-methyl-2-nitrobenzoic acid gave both low conversion and yield. This may be due to the electron-withdrawing nitro group *ortho* to the carboxylic acid, as discussed by Brown and coworkers.<sup>3b</sup> Diacids were reduced to the corresponding diols when 4 eq of borane-THF and 2 eq of  $BF_3$ - $Et_2O$  were applied. Attempted partial reduction of the diacid with one half of the borane-THF complex unfortunately led to a low yield (42%) of the desired reduction product, together with some diol and recovered diacid. A highly halogenated acid (5-bromo-2,3,4-trifluorobenzoic acid also gave a good yield of the reduction product. Aliphatic acids, which

#### **OPPI BRIEFS**

are well known to be more easily reduced than their aromatic counterparts, are expected to undergo this transformation under these conditions and an example is provided in the last entry of Table 2, where the keto group was reduced as well. The reduction of 3-hydroxy-4-nitrobenzoic acid (1) with  $BH_3$ -SMe<sub>2</sub>/BF<sub>3</sub>-Et<sub>2</sub>O using the literature conditions<sup>4</sup> gave alcohol **2** in 66% yield, which is much lower than our result (91%).



Entry	Acid (mmols)	BH <sub>3</sub> -THF (mmols)	$BF_3$ -Et <sub>2</sub> O (mmols)	Vield %
	(11111015)	(11111013)	(minois)	
1	10	20	5	63
2	10	20	10	91
3	10	20	15	90
4	10	20	20	82
5	10	5	10	No Reaction
6	10	10	10	No Reaction
7	10	15	10	59
8	10	25	10	77

**Table 1.** Reactant Ratio Study for the Reduction of 1 to 2

The best ratio of reactants for the reduction of 3-hydroxy-4-nitrobenzoic acid was determined and the results are listed in Table 1. No reaction occurred when less than 1.5 eq. of BH<sub>3</sub>-THF was used (entries 5, 6). With a fixed amount of BH<sub>3</sub>-THF (2.0 eq.) and less than 1.0 eq. (entry 1) or more than 1.5 eq. (entry 4) of BF<sub>3</sub>-Et<sub>2</sub>O lower yields were obtained. Similar yields resulted when 1.0 or 1.5 eq. of BF<sub>3</sub>-Et<sub>2</sub>O was used. When the amount of BF<sub>3</sub>-Et<sub>2</sub>O (1.0 eq.) was fixed, the best result was obtained when 2.0 eq. of BH<sub>3</sub>-THF (entry 8) was applied. We found that the optimum ratio is acid: BH<sub>3</sub>-THF : BF<sub>3</sub>-Et<sub>2</sub>O = 1 : 2 : 1. We also carried out this reduction in hexane (60% yield), ethyl acetate (61% yield), diethyl ether (70% yield) and methylene chloride (79% yield). THF gave the best result (91% yield), possibly due to the greater solubility of the acid in this solvent.

In conclusion, we have developed a useful method to convert aromatic carboxylic acids to their corresponding benzylic alcohols using the combination of borane-THF and boron trifluorideetherate complex. A wide variety of functional groups can be tolerated with these mild reaction conditions. The facile reaction experimental conditions, the ease of work-up, and the excellent yields of the isolated products indicate that the reduction of benzoic acids with this methodology is a useful and convenient method for the preparation of highly functionalized benzyl alcohols.

#### **OPPI BRIEFS**

Entry	Acid	Product <sup>a</sup>	% Yield	mp (°C)	Lit. mp(°C)
1		CH <sub>2</sub> OH VO <sub>2</sub> OH	91	93-94	<b>90-92</b> <sup>11</sup>
2			93	92-93	97 <sup>12</sup>
3			96	60-62	66 <sup>13</sup>
4	CO <sub>2</sub> H	CI CH2OH	85	87-89	90-91 <sup>14</sup>
5	CO <sub>2</sub> H	CH <sub>2</sub> OH CF <sub>3</sub>	97	Oil	Oil <sup>15</sup>
6	CO <sub>2</sub> H NO <sub>2</sub> OH		24b	70-71	c
7	CO2H CO2H	Снаон	95	56-58	57 <sup>16</sup>
8	CO2H CO2Me	CH <sub>2</sub> OH CO <sub>2</sub> Me	82	Oil	Oil <sup>17</sup>
9		CN CH2OH	68	76-77	<b>Ref</b> . <sup>18</sup>
10	S S CO2H	CH2OH S S CH2OH	75	136-137	141-142 <sup>19</sup>
11	Br F F	Br F	96	Oil	d
12			89	133-135	55.5-57 <sup>20</sup>

Table 2. Reduction of Substituted Benzoic Acids with BH.	-THF/BF.	-Et_O
	1111/21	~

Entry	Acid	Product <sup>a</sup>	% Yield	mp (°C)	Lit. mp(°C)
13	F CO2H	F CH2OH	88	154-155	e
14	СО <sub>2</sub> Н ОМе	СН₂ОН ОМе	86	Oil	Oil <sup>21</sup>
15	°, ⊂CO2H	CT CH	91	Oil <sup>22</sup>	f

Table 2. Continued...

a) All structures are confirmed by NMR, IR, and MS. Solid products were recrystallized from hexane-EtOAc, and liquid products were purified by flash chromatography (silica gel, hexane-EtOAc).
b) Recovered acid: 29%. c) Calcd. For C<sub>8</sub>H<sub>9</sub>NO<sub>4</sub>: C, 52.46; H, 4.95; N, 7.65. Found: C, 52.07; H, 4.77; N, 7.55. d) Calcd. For C<sub>7</sub>H<sub>4</sub>BrF<sub>3</sub>O: C, 34.89; H, 1.67; F, 23.65; Br, 33.16. Found: C, 35.02; H, 1.61; F, 23.75; Br, 33.38. e) Calcd. For C<sub>13</sub>H<sub>11</sub>FN<sub>2</sub>O<sub>3</sub>: C, 59.54; H, 4.23; N, 10.68; F, 7.24. Found: C, 59.26; H, 4.07; N, 10.54; F, 7.12. f) Calcd. For C<sub>16</sub>H<sub>16</sub>O: C, 85.68; H, 7.19. Found: C, 85.60; H, 7.11.

#### **EXPERIMENTAL SECTION**

The acids, BH3-THF and BF3-Et2O were obtained from Aldrich Chemical Co. and used as received. THF was obtained from Burdick & Jackson and freshly distilled from sodium. Melting points were determined with a Thomas Hoover apparatus and are uncorrected. <sup>1</sup>H NMR spectra were recorded on a Varian-Gemini-400 in CDCl<sub>3</sub> as both solvent and internal standard.

General Procedure for the Reduction of Acids to Alcohols.- To a solution of the substituted aromatic acid (10 mmol) in dry THF (50 mL, 0.2 M), at ambient temperature, under nitrogen atmosphere, was added boron trifluoride diethyl etherate (10 mmol), followed by the addition of borane-tetrahydrofuran complex (1.0 M solution in THF, 20 mmol) over 5 min. The mixture was stirred at ambient temperature for 18 hrs and then quenched by the careful addition of methanol until the gas evolution ceased and then with water (20 mL). The mixture was evaporated *in vacuo* and the residue was extracted with ethyl acetate (3 x 50 mL) and the combined organic extracts were washed with brine and dried over MgSO<sub>4</sub>. The crude product was purified by recrystallization or flash chromatography.

#### REFERENCES

 (a) For a summary of the literature, see N. G. Gaylord, "Reduction with Complex Metal Hydrides", p 322, Interscience, New York, NY, 1956. (b) H. C. Brown, P. M. Weissman and N. M. Yoon, J. Am. Chem. Soc., 88, 1458 (1966). (c) H. C. Brown and P. M. Weissman, J. Am. Chem. Soc., 78, 6714 (1965).

- (a) H. C. Brown and B. C. Subba Rao, J. Am. Chem. Soc., 78, 2582 (1956). (b) ) H. C. Brown and B. C. Subba Rao, J. Am. Chem. Soc., 82, 681 (1960). (c) S. Kano, Y. Tanaka, E. Sugino, and S. Hibino, Synthesis, 695 (1980).
- (a) H. C. Brown, P. Heim and N. M. Yoon, J. Am. Chem. Soc., 92, 1637 (1970). (b) N. M. Yoon, C. S. Pak, H. C. Brown, S. Krishnamurthy and T. P. Stocky, J. Org. Chem., 38, 2786 (1973).
- (a) C. F. Lane, H. L. Myatt, J. Daniels and H. B. Hopps, J. Org. Chem., 39, 3052, (1974). (b) G. A. Smith and R. E. Gawley, Org. Syn., 63, 136 (1984).
- 5. R. F. Nystrom, and W. G. Brown, J. Am. Chem. Soc., 69, 2548 (1947).
- (a) R. O. Hutchins and F. Cistone, Org. Prep. Proc. Int., 13, 227 (1981). (b) G. A. Smith and R. E. Gawley, Org. Syn., 63, 136 (1984).
- 7. J. V. B. Kanth and M. J. Periasamu, Org. Chem., 56, 5964 (1991).
- 8. K. Ishizumi, K. Koga and S.-I. Yamada, Chem. Pharm. Bull., 16, 492 (1968).
- 9. N. M. Yoon and Y. S. Gyoung, J. Org. Chem., 50, 2443 (1985).
- The ratios of unreacted acid (1) and alcohol (2) in the final reaction mixtures were determined by HPLC and are as follows (1:2): LAH: 56:44; BH<sub>3</sub>-THF: 36:64; BH<sub>3</sub>-Me<sub>2</sub>S: 37:63; NaBH<sub>4</sub>/I<sub>2</sub>: 100:0; CICO<sub>2</sub>*i*-Bu/NaBH<sub>4</sub>: 100:0; and *i*-Bu<sub>2</sub>AlH: 84:26.
- 11. R. S. Selivanov, S. V. Kulikov and A. I. Ginak, Russ. J. Org. Chem., 32, 394 (1996).
- 12. R. Stoermer and K. Behn, Chem. Ber., 34, 2455 (1901).
- 13. R. Fuchs and D. M. Carlton, J. Org. Chem., 43, 3151 (1978).
- D. S. Kemp, R. I. Carey, J. C. Dewan, N. G. Galakatos, D. Kerkman and, S-L. Leung, J. Org. Chem., 54, 1589 (1989).
- 15. R. Fuchs and D. M. Carlton, J. Amer. Chem. Soc., 85, 104 (1963).
- 16. C. Mettler, Chem. Ber., 39, 2933 (1906).
- M. H. Chen, J. G. Davidson, J. T. Freisler, E. Iakovleva and J. Magano, Org. Prep. Proced. Int., 32, 381 (2000).
- J. M. Fevig and M. L. Quan, WO 9806694. Even though this compound was included in this patent, no melting point was reported.
- 19. R. Grice and L. N. Owen, J. Chem. Soc., 1947 (1963).
- R. Fuchs and D. M. Carlton, J. Org. Chem., 27, 1520 (1962). The very large difference in melting point with respect to the reported value is most likely due to the impurities present in the latter as stated by the authors.

#### **OPPI BRIEFS**

- 21. T. Oku, H. Kayakiri, S. Satoh, Y. Abe, Y. Sawada, T. Inoue and H. Tanaka, WO 8000563.
- 22. The keto group was also redued to the alcohol as expected according to: E. Breuer, *Tetrahedron Lett.*, 20, 1849 (1967). Dehydration took place upon work-up of the reaction to give the conjugated alkene, regardless of the conditions used to quench it (methanol or water). From the <sup>1</sup>H NMR spectrum, a 1/6.5 *cis/trans* ratio was determined.