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Boric Acid Catalyzed Amidation in the Synthesis of Active Pharmaceutical Ingredients

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Abstract:

Application of a boric acid catalyzed process for the synthesis of the carboxamides, key reaction intermediates in the preparation of various active pharmaceutical ingredients (APIs), has been explored.

Introduction

A plethora of procedures for the formation of carboxamides is precedented in the literature.[1] The most explored method incorporates acid chlorides as electrophiles that react with the amines in the presence of an acid scavenger. Despite its versatility, this method has limitations because there are many unstable acid chlorides and they also require hazardous reagents for their preparation (thionyl chloride, oxalyl chloride, phosgene, etc.). To achieve the chemoselective amidation, mineral acid-labile functional groups, present in either reaction partners, need to be masked with hydrolysis-benign protecting groups.

There are other common routes for carboxamide synthesis, for example, (a) activation of carboxylic acids using 1-hydroxybenzotriazole (HOBt) and *N*,*N*′-dicyclohexylcarbodiimide (DCC), (b) treatment of carboxylic acids with ammonium chlorides, tertiary amine, and coupling agents typically used in peptide synthesis, and (c) utilization of acyl azolides and *N*-acylimidazoles as efficient acylating reagents to react with amines. These methods were found to be incompatible with practice at industrial scale because of their exothermic nature, use of basic catalysts, high pressure, and poor selectivity. Other disadvantages include insolubility of starting materials, competitive hydrolysis of the activated carboxyl group, and removal of dicyclohexyl urea by product obtained in the DCC-HOBt-mediated amidation process. The concerned disadvantageous factors categorize these methods as eco-unfriendly and warrant the development of a catalytic and mild process for amidation.

Yamamoto et al. reported the first boron reagent based catalytic method that allows direct amide formation from free carboxylic acids and amines as the reaction partners.[2] A phenylboronic acid derivative bearing electron-withdrawing substituents in the *m*- and *p*-positions was found to be the catalyst of choice for these kinds of transformations.

Tang's work[3] featured the use of cheap, readily available, nontoxic, and eco-friendly boric acid, $B(OH)_3$, as a highly effective catalyst, which proved to be superior to other known catalysts involved in the amidation process.

To our surprise, despite the proven potential of boric acid as a catalyst, it has not been explored extensively for amidation, particularly in API syntheses. Herein, we report the application of a boric acid catalyzed amidation procedure in the synthesis of a large number of APIs.

Results and Discussions

The present study is mainly focused on the formation of carboxamides present in various API intermediates. To investigate the versatility of this process, we chose aliphatic as well as aromatic acids or amines for amidation. A classical synthetic procedure is followed to prepare the amide intermediate, which involves acid, amine derivatives, and boric acid (catalytic amounts, 10 mol%) in the flask, equipped with a Dean–Stark apparatus and either toluene or xylene as solvent, heated to reflux. The liberated water was continuously removed from the reaction. It was observed that aromatic acids or amines require a longer time and higher temperatures, while aliphatic acids and amines require a relatively shorter time and lower temperatures for the completion of reactions. Additionally, the boric acid catalyzed amidation has several advantages over other processes in terms of eliminating byproducts, minimizing the number of impurities, and affording products in good yields and purity. The results are summarized in Table 1.

It was surprising that we did not observe bis-amidation due to presence of the primary and secondary amine functionalities in **3e** (entry e; alfuzosin intermediate). The resulting amidation to afford **1e** appears to be chemose-

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(1) (a) Kelly, S. E.; LaCour, T. G. *Synth. Commun.* **1992**, *22*, 859. (b) Tani, J.; Oine, T.; Inoue, I. *Synthesis* **1975**, 714. (c) Trapani, G.; Reho, A.; Latrofa, A. *Synthesis* **1983**, 1013. (d) Pelter, A.; Levitt, T. E.; Nelson, P. *Tetrahedron* **1970**, *26*, 1539. (e) Collum, D. B.; Chen, S.-C.; Ganem, B. *J. Org. Chem.* **1978**, *43*, 4393. (f) Pelter, A.; Levitt, T. E. *Tetrahedron* **1970**, *26*, 1545. (g) Carlson, R.; Lundstedt, T.; Nordahl, A.; Prochazka, M. *Acta Chem. Scand., Ser. B* **1986**, *40*, 522. (h) For mixed anhydride: Srinivas, P.; Gentry, E. J.; Mitscher, L. A. 223rd American Chemical Society National Meeting, Division of Organic Chemistry, Orlando, FL, April 7–11, 2002, Poster session 237. (i) Dale, D. J.; Dunn, P. J.; Golightly, C.; Hughes, M. L.; Levett, P. C.; Pearce, A. K.; Searle, P. M.; Ward, G.; Wood, A. S. *Org. Process Res. Dev.* **2000**, *4*, 17–22.

(2) (a) Ishihara, K.; Ohara, S.; Yamamoto, H. *J. Org. Chem.* **1996**, *61*, 4196. (b) Ishihara, K.; Kondo, S.; Yamamoto, H. *Synlett* **2001**, *9*, 1371. (c) Ishihara, K.; Ohara, S.; Yamamoto, H. *Org. Synth.* **2004**, *X*, 80.

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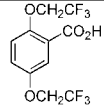
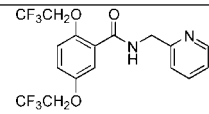
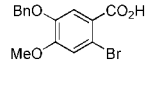
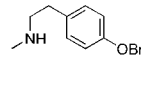
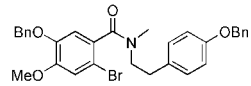
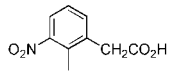
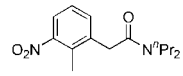
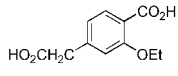
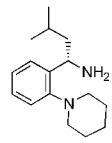
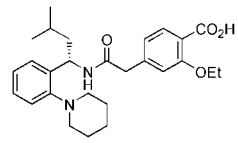
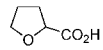
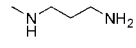
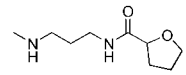
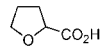
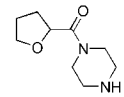
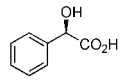
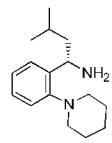
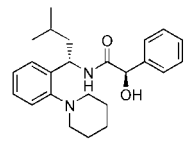
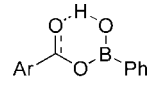
Table 1. **Boric or Phenyl Boronic Acid Catalyzed Synthesis of Various APIs' Intermediate**

entry (API)	acid 2a-i	amine 3a-i	carboxamide 1a-i	solvent / time	catalyst (0.1 eq.)	yield/ HPLC purity (%)
a (Flecanide)				Toluene / 6 h	$B(OH)_3$	87/98
b (Galanthamine)				o-Xylene / 30 h	$PhB(OH)_2$	86/99
c (Ropinarole)				Toluene / 50 h	$PhB(OH)_2$	44/92
d (Repaglinide)				Toluene / 18 h	$B(OH)_3$	72/96[a]
e (Alfuzosin)				Toluene / 4h	$B(OH)_3$	95/94[b]
f (Terazosin				Toluene / 11 h	$B(OH)_3$	75/95[b]
g (Chiral acid/amine combination)		 3d		Toluene / 20 h	$B(OH)_3$	60/95[a]

[a] Chiral purity. [b] GC.

lective. The synthesis of **1f** was accomplished in 75% yield employing strictly 1 equiv of **3f**, however, the use of piperazine (**3f**) as a symmetrical amine partner made the reaction nonchemoselective, and as expected, we were able to detect 1–2% of the bis-amidation product. Synthesis of ropinarole intermediate (**1c**) was low yielding because the boiling point of amine partner, di-n-propyl amine **3c** happened to be similar to the boiling point of the toluene. In the due course of the reaction, a certain quantity of **3c** might have azeotropically distilled out, which causes the lowering of the yield of **1c** (44%). In the synthesis of **1g**, we isolated the product in 60% yield, and the remaining starting material was found to be unreacted. Phenyl boronic acid activates the carboxylic acid moiety by reducing the electron density at the carbonyl function, which makes the intermediate **4** more prone to amine nucleophilic substitution to facilitate the transformation in moderate to good yield (see entries **1b** and **1c**).



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Xylene was preferred over toluene in one case (**1b**) to provide a higher temperature because the reaction was not efficient in toluene or in combination with boric acid. In a control amidation experiment, that is, transformation without boric acid or its derivative as a catalyst, none of the acid and base partners afforded amide except the **2d** and **3d** combination that provided **1d** in 10% conversion. In the synthesis of **1d** and **1g**, no racemization was observed.

Experimental Section

The ^1H spectra were recorded in $CDCl_3$ and DMSO-d_6, using a Varian Gemini 200 MHz FT NMR spectrometer; the chemical shifts are reported in δ ppm relative to TMS. The solvents and reagents were used without further purification.

***N*-(2-Pyridinelmethyl)-2,5-bis(2,2,2-trifluoroethoxy)benzamide, 1a.** To a solution of 2,5-bis-(2,2,2-trifluro-ethoxy) benzoic acid (**2a**, 10 g, 31.4 mmol) in toluene (300 mL) was added boric acid (1.91 g, 3.14 mmol). To this mixture was added pyridin-2-methylamine (**3a**, 3.39 g, 31.4 mmol) in one portion.

(4) Ray, A. K.; Patel, H. K. V.; Merai, S. V.; Patel, M. R. PCT Int. Appl., 2002; p 17; CODEN: PIXXD2 WO 2002004419, A2 20020117.

The reaction mixture was refluxed for 6 h and water was collected azeotropically in the Dean–Stark trap. The mixture was allowed to cool to ambient temperature and then poured with stirring into 700 mL of *n*-hexane, leading to the immediate precipitation of a white solid. Stirring was continued for an additional 30 min, and then the precipitate was filtered off. The collected solid was successively washed with 2 × 50 mL portions of hexanes and 2 × 60 mL portions of water and dried under vacuum at room temperature for 12 h to afford 11.5 g of **1a** in 87% yield as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.30–4.79 (m, 6H), 6.97 (d, 1H, J = 9.1 Hz), 7.12 (dd, 1H, J = 8.9, 3.0 Hz), 7.23 (dd, 1H, J = 7.2, 5.4 Hz), 7.33 (d, 1H, J = 9.1 Hz), 7.69 (dd, 1H, J = 7.8, 1.7 Hz), 7.80 (d, 1H, J = 3.5 Hz), 8.60 (d, 1H, J = 4.4 Hz), 8.59 (bs, 1H).

5-Benzyloxy-*N*-[2-(4-benzyloxy-phenyl)-ethyl]-2-bromo-4-methoxy-*N*-methyl-benzamide, 1b. To a solution of 5-benzyloxy-2-bromo-4-methoxy-benzoic acid (**2b**, 50 g, 1.48 mmol) in *o*-xylene (850 mL) was added phenylboronic acid (1.8 g, 0.148 mmol). The reaction mixture was heated to 120 °C and [2-(4-benzyloxy-phenyl)-ethyl] methylamine was added (**3b**, 44.69 g, 1.48 mmol) in one portion. The reaction mixture was refluxed for 30 h and water was collected azeotropically in the Dean–Stark trap. The reaction mass was distilled off under reduced pressure, and the obtained crude was dissolved in methanol (50 mL) at reflux temperature. To the resulting clear solution was added 5% alkaline methanol (150 mL) at same reflux temperature, and the solution was stirred for 1 h at reflux and 4 h at 0–5 °C. The solid obtained was filtered and washed with 2 × 50 mL portions of methanol and dried under vacuum at 60 °C for 6 h to afford 71.4 g of **1b** in 86% yield as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.61 (t, 2H, J = 4.0 Hz), 3.10 (t, 2H, J = 4.0 Hz), 3.30 (s, 3H), 3.81 (s, 3H), 4.98 (d, 2H, J = 12.0 Hz), 5.02 (s, 2H), 6.90 (s, 1H), 6.98 (d, 1H, J = 8.0 Hz), 7.18–7.48 (m, 14H).

2-(2-Methyl-3-nitro-phenyl)-*N*,*N*-dipropyl-acetamide, 1c.[6] To a solution of 2-methyl-3-nitrophenyl acetic acid (**2c**, 30.0 g, 153.7 mmol) in toluene (800 mL) was added phenylboronic acid (4.0 g, 32.7 mmol), and the solution was heated to 40 °C. To this mixture was added *N*,*N*-dipropylamine (**3c**, 46.6 g, 461.4 mmol) in one portion at 40 °C. The reaction mixture was refluxed for 50 h, and water was collected azeotropically in the Dean–Stark trap. The mixture was allowed to cool to ambient temperature, a 10% Na_2CO_3 solution was added (200 mL), and the mixture was stirred for 25–30 min. The above organic layer was washed with saturated NaCl solution (200 mL) and dried over Na_2SO_4. The final organic layer was then distilled off under reduced pressure to afford 18.6 g of the **1c** in 44% yield as syrup. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.80–1.08 (m, 6H), 1.38–1.90 (m, 4H), 2.35 (s, 3H), 3.20–3.48 (m, 4H), 3.75 (s, 2H) 7.14–7.77 (m, 3H).

***S*-(+)-2-Ethoxy-4-(2-((3-methyl-1-(2-(1-piperidinyl)phenyl)-butyl)amino)-2-oxoethyl) Benzoic Acid, 1d.**[7] To a solution of 4-carboxymethyl-2-ethoxy-benzoic acid (**2d**, 5.0 g, 22.3 mmol) in toluene (100 mL) was added boric acid (0.375 g, 6.0 mmol). To this mixture was added *S*-(+)-3-methyl-1-(2-piperidin-1-yl-phenyl)-butyl amine (**3d**, 5.9 g, 20.29 mmol) in one portion. The reaction mixture was refluxed for 18 h and water was collected azeotropically in the Dean–Stark trap. The mixture was allowed to cool to ambient temperature, filtered to remove the boric acid present in the reaction mass, and washed with toluene (5 mL). The combined filtrates were concentrated, and the obtained residue was triturated with *n*-heptane (100 mL), resulting in 6.6 g of **1d** in 72% yield as a fine solid. ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.89 (m, 6H), 1.35 (t, 3H, J = 7.4 Hz), 1.40 (t, 3H, J = 7.4 Hz), 1.40–1.80 (m, 6H), 1.60 (q, 2H, J = 7.4, 7.4 Hz), 1.70 (m, 1H), 2.63 (m, 1H), 2.91 (m, 2H), 3.50 (s, 2H), 4.00 (m, 2H), 5.35 (m, 1H), 6.81 (d, 1H, J = 6.8 Hz), 6.83 (s, 1H), 7.0–7.3 (m, 4H), 7.72 (d, 1H, J = 8.2 Hz).

Tetrahydrofuran-2-carboxylic Acid (3-Methylamino-propyl)-amide, 1e. To a solution of tetrahydro-2-furoic acid (**2e**, 20.0 g 172.4 mmol) in toluene (300 mL) was added boric acid (1.06 g, 17.24 mmol). To this mixture was added *N*-methyl 1,3-propylenediamine (**3e**, 15.17 g, 172.4 mmol) in one portion. The reaction mixture was refluxed for 4 h and water was collected azeotropically in the Dean–Stark trap. The mixture was allowed to cool to 40–45 °C, filtered to remove the boric acid present in the reaction mass, and then further cooled to 25–35 °C. After stirring for 1 h at 25–35 °C, toluene was decanted, and then the resulting crude material was dissolved in methanol (50 mL). Distillation afforded 30.6 g of **1e** in 95% yield as syrup. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.64–1.70 (m, 2H), 1.73 (bs, 1H), 1.82–1.90 (m, 2H), 2.00–2.05 (m, 1H), 2.18–2.27 (m, 1H), 2.40 (s, 3 H), 2.57–2.64 (m, 2H), 3.26–3.34 (m, 2H), 3.80–3.85 (m, 1H), 3.86–3.91 (m, 1H), 4.30 (dd, 1H, J = 8.4, 5.7 Hz), 7.22 (bs, 1H).

Terrazosin Intermediate, 1f.[8] To a solution of tetrahydro-2-furoic acid (**2f**, 20 g, 172.4 mmol) in toluene (800 mL) was added boric acid (1.06 g, 17.24 mmol). To this mixture was added piperazine (**3f**, 14.82 g, 172.4 mmol) in one portion. The reaction mixture was refluxed for 11 h and water was collected azeotropically in the Dean–Stark trap. The mixture was allowed to cool to 40–45 °C, filtered to remove the boric acid present in the reaction mass, and then further cooled to 25–35 °C. After stirring for 1 h at 25–35 °C, toluene was decanted, and the resulting crude material was dissolved in methanol (50 mL), followed by distillation, which afforded 23.6 g of **1f** in 75% yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.89–1.92 (m, 1H), 1.94–2.08 (m, 2H), 2.23–2.27 (m, 1H), 2.45 (s, 1H), 2.86–2.92 (m, 4H), 3.48–3.58 (m, 2H), 3.61–3.69 (m, 2H), 3.86–3.91 (m, 1H), 3.93–4.00 (m, 1H), 4.62 (dd, 1H, J = 7.3, 5.4 Hz).

Chiral Acid/Amine Derived Amide, 1g. To a solution of *R*-(+)-mandelic acid (**2g**, 10.0 g, 65 mmol) in toluene (300 mL)

(5) Radoslav, V.; Dikran, K.; Grigor, S.; Maja, C.; Ioncho, V.; Stojan, P.; Gunther, S.; Ludger, E.; Klaus, K.; Wolf-Rainer, A.; William, S. S. *Tetrahedron.* **1989**, *45*, 3329–3345.

(6) DeMarinis, R. M., Jr.; Sumanth, G. G.; Hall, R. F.; Franz, R. G.; Webster, C.; Huffman, W. F.; Schwartz, M. S.; Kaiser, C.; Ross, S. T.; Wilson, J. W.; Hieblet, P. *J. Med. Chem.* **1986**, *29*, 939–947.

(7) Kolla, N.; Elati, C. R.; Vankawala, P. J.; Gangula, S.; Sajja, E.; Anjaneyulu, Y.; Bhattacharya, A.; Sundaram, V.; Mathad, V. T. *Chimia* **2006**, *29*, 1–4.

(8) Chou, W. C.; Tan, C. W.; Chen, S. F.; Hao, K. *J. Org. Chem.* **1998**, *63*, 10015–10017.

was added boric acid (0.4 g, 6.5 mmol). To this mixture was added *S*-(+)-3-methyl-1-(2-piperidin-1-yl-phenyl)-butyl amine (**3d**, 16.0 g, 65 mmol) in one portion. The reaction mixture was refluxed for 20 h and water was collected azeotropically in the Dean–Stark trap. The reaction mass was distilled off and triturated with *n*-heptane (300 mL), and the obtained solid was filtered and dried under vacuum at 50 °C to afford 15 g of **1g** in 60% yield as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.87 (d, 3H, J = 6.4 Hz), 0.94 (d, 3H, J = 6.4 Hz), 1.30–1.80 (m, 11H), 2.60–2.77 (m, 1H), 2.82–2.97 (m, 1H), 4.77 (t, 1H, J = 7.6 Hz), 5.12 (s, 1H), 7.20–7.40 (m, 7H), 7.47 (d, 2H, J = 6.8 Hz), 8.1 (bs, 1H). MS (ES) calcd for $C_{24}H_{32}N_2O_2$ (M^+), 380.52; found ($M^+ + H$), 381.00.

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