



A Publication  
of Reliable Methods  
for the Preparation  
of Organic Compounds

## Working with Hazardous Chemicals

The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at [http://www.nap.edu/catalog.php?record\\_id=12654](http://www.nap.edu/catalog.php?record_id=12654)). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red "Caution Notes" within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior to performing a reaction, a thorough risk assessment should be carried out that includes a review of the potential hazards associated with each chemical and experimental operation on the scale that is planned for the procedure. Guidelines for carrying out a risk assessment and for analyzing the hazards associated with chemicals can be found in Chapter 4 of Prudent Practices.

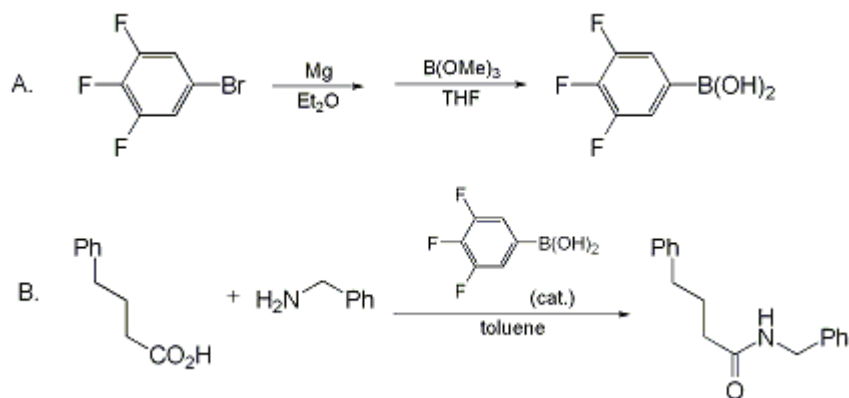
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*September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.*

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## (3,4,5-TRIFLUOROPHENYL)BORONIC ACID-CATALYZED AMIDE FORMATION FROM CARBOXYLIC ACIDS AND AMINES: N-BENZYL-4-PHENYLBUTYRAMIDE

### [ Benzenebutanamide, N-(phenylmethyl)- ]



Submitted by Kazuaki Ishihara<sup>1</sup>, Suguru Ohara<sup>2</sup>, and Hisashi Yamamoto<sup>2</sup>.  
Checked by David T. Amos and Rick L. Danheiser.

### 1. Procedure

*A. (3,4,5-Trifluorophenyl)boronic acid*. A 500-mL, three-necked, round-bottomed flask containing magnesium turnings (1.94 g, 80 mmol) is equipped with a rubber septum, a 20-mL pressure-equalizing dropping funnel fitted with a rubber septum, a Teflon-coated magnetic stirring bar, and a reflux condenser fitted with an argon inlet adapter. The system is flame-dried and flushed with argon. Anhydrous ether (200 mL, Note 1) is introduced to cover the magnesium, a crystal of iodine is added, and the mixture is heated to reflux in an oil bath. The dropping funnel is filled with 1-bromo-3,4,5-trifluorobenzene (8.36 mL, 14.8 g, 70.0 mmol, Note 2) and ca. 1 mL is added to the boiling reaction mixture. After reaction has commenced, the oil bath is removed, and the remainder of the aryl bromide is added slowly at a rate sufficient to maintain reflux (addition time ca. 1 hr). The resulting mixture is stirred for an additional 2 hr. During this period, a flame-dried, 500-mL, single-necked, round-bottomed flask equipped with a Teflon-coated magnetic stirring bar, a rubber septum, and an argon inlet is charged with dry tetrahydrofuran (THF, 50 mL, Note 3) and trimethyl borate (15.7 mL, 14.5 g, 140 mmol, Note 4). The mixture is cooled to 0°C, and the ether solution of (3,4,5-trifluorophenyl)magnesium bromide prepared above is introduced in one portion via a double-ended needle. The reaction mixture is allowed to warm to room temperature, stirred for 1 hr, and then treated with 200 mL of saturated ammonium chloride solution. The organic layer is separated and the aqueous layer is extracted with three 100-mL portions of ethyl acetate. The combined organic layers are washed with brine (100 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The resulting white solid is dissolved in a minimal amount of hot (65°C) ethyl acetate, allowed to cool to room temperature, and then 600 mL of hexane is added. The resulting solution is allowed to stand overnight and then filtered to afford pure (3,4,5-trifluorophenyl)boronic acid as white crystals. Further recrystallization of the mother liquor 3-4 times provides a total of 6.3 g (51%) of (3,4,5-trifluorophenyl)boronic acid (Notes 5 and 6).

*B. N-Benzyl-4-phenylbutyramide*. A flame-dried, 200-mL, single-necked, round-bottomed flask is equipped with a Teflon-coated magnetic stirring bar and a Soxhlet extractor containing a thimble filled with 3 g of calcium hydride and topped with a reflux condenser fitted with an argon inlet (Note 7). The reaction flask is charged with 4-phenylbutyric acid (5.42 g, 33.0 mmol, Note 8), benzylamine (3.28 mL, 30.0 mmol, Note 9), and (3,4,5-trifluorophenyl)boronic acid (52.8 mg, 0.300 mmol) in toluene (60 mL) and then heated in an oil bath. The reaction mixture is brought to reflux (bath temperature 120°C), and

after 16 hr is cooled to ambient temperature and diluted with 80 mL of dichloromethane . The organic layer (Note 10) is washed with 1.0 M hydrochloric acid (HCl, 100 mL) and brine (100 mL), dried over anhydrous magnesium sulfate , filtered, and concentrated under reduced pressure. The resulting yellow residue is recrystallized from ethyl acetate and hexane to provide pure N-benzyl-4-phenylbutyramide (ca. 6-7 g) as white crystals. The mother liquor is concentrated and the residue is purified by flash chromatography on silica gel (Note 11) to provide additional product as a white solid. The total combined yield of N-benzyl-4-phenylbutyramide is 7.11-7.18 g (94-95%, Note 12).

## 2. Notes

1. Ethyl ether was distilled from sodium-benzophenone ketyl before use.
2. 1-Bromo-3,4,5-trifluorobenzene was purchased from Aldrich Chemical Company, Inc. , and used without further purification.
3. Tetrahydrofuran was distilled from sodium-benzophenone ketyl before use.
4. Trimethyl borate was purchased from Tokyo Kasei Kogyo Co., Ltd. or Aldrich Chemical Company, Inc. and used without further purification.
5. The product consists of a mixture of (3,4,5-trifluorophenyl)boronic acid and varying amounts of (3,4,5-trifluorophenyl)boronic anhydride .
6. The submitters obtained the product in 89% yield. (3,4,5-Trifluorophenyl)boronic acid has the following physical properties: TLC  $R_f$  = 0.63 (10:1 ethyl acetate/methanol ); mp 249-252°C, IR (KBr)  $\text{cm}^{-1}$ : 3077, 2359, 1616, 1530, 1217, 1038 ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$ : 4.74-4.82 [br, 0.28 H (for monomer)], 7.35 (t, 0.28 H,  $J$  = 7.0 (for monomer)), 7.77 [t, 1.72 H,  $J$  = 7.9 (for trimer)] ;  $^{13}\text{C}$  NMR (125 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$ : 118.6 (dd,  $J$  = 4.6, 15.0), 130.5-132.6 (br m), 142.2 (dt,  $J$  = 249.8, 15.1), 152.2 (ddd,  $J$  = 249.7, 9.4, 2.3) . Anal. Calcd for  $(\text{C}_6\text{H}_2\text{OBF}_3)_3$ : C, 45.64; H, 1.28. Found: C, 45.32; H, 1.64 (microanalysis was carried out on a sample that was dried at 60-80°C under high vacuum for 2 hr).
7. The submitters used a 10-mL, pressure-equalized addition funnel [containing a cotton plug, calcium hydride (ca. 3 g, lumps), and sea sand (ca. 1 g)] in place of the Soxhlet extractor. The submitters employed calcium hydride (ca. 1-10 mm, No. 068-34) purchased from Nacalai Tesque, Inc. Alternatively, 4Å molecular sieves can be used in place of calcium hydride .
8. 4-Phenylbutyric acid (>99%) was purchased from Tokyo Kasei Kogyo Co., Ltd. or Aldrich Chemical Company, Inc. , and used without further purification.
9. The submitters purchased benzylamine (99%) from Nacalai Tesque, Inc. and used it without further purification. The checkers obtained the amine from Aldrich Chemical Company, Inc. , and distilled it from calcium hydride .
10. The submitters report obtaining a two-phase mixture upon cooling and adding dichloromethane . The organic layer was separated and the aqueous layer was extracted with dichloromethane (80 mL), and treated with 1.0 M aqueous sodium hydroxide solution (100 mL). The combined organic layers were then washed with HCl and brine as described in the procedure.
11. Chromatography was performed using a 3-cm  $\times$  10-cm column packed with 35 g of silica gel (230-400 mesh, No. 9385) purchased from E. Merck Co. The product was eluted with 100 mL of 25% and 200 mL of 33% ethyl acetate-hexane . The checkers observed that N-benzyl-4-phenylbutyramide has a TLC  $R_f$  value of 0.4 in 50% ethyl acetate-hexane .
12. N-Benzyl-4-phenylbutyramide has the following physical properties: mp 79-80°C; IR ( $\text{CH}_2\text{Cl}_2$ )  $\text{cm}^{-1}$ : 1671, 1510, 1460, 1271, 1260 ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$ : 1.96-2.06 (m, 2 H), 2.22 (t, 2 H,  $J$  = 6.9), 2.67 (t, 2 H,  $J$  = 8.0), 4.44 (d, 2 H,  $J$  = 6.0), 5.62 (br, 1 H), 7.15-7.34 (m, 10 H) ;  $^{13}\text{C}$  NMR (75.4 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$ : 28.8, 36.2, 36.4, 44.0, 126.9, 128.1, 128.5, 129.3, 129.4, 129.5, 140.0, 142.8, 175.6 (C=O) . Anal. Calcd for  $\text{C}_{17}\text{H}_{19}\text{NO}$ : C, 80.60; H, 7.56; N, 5.53. Found: C, 80.34; H, 7.67; N, 5.58.

## Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

## 3. Discussion

There are several different routes to carboxamides.<sup>3</sup> In most of these reactions, a carboxylic acid is converted to a more reactive intermediate, e.g. the acid chloride, which is then allowed to react with an

amine. For practical reasons, it is preferable to form the reactive intermediate in situ.<sup>4</sup> Arylboronic acids with electron-withdrawing groups such as (3,4,5-trifluorophenyl)boronic acid act as highly efficient catalysts in the amidation between carboxylic acids and amines.<sup>5</sup> (3-Nitrophenyl)boronic acid and [3,5-bis(trifluoromethyl)phenyl]boronic acid are also effective amidation catalysts and commercially available.

Acyloxyboron intermediates generated from carboxylic acids and boron reagents such as BR<sub>3</sub> (R=C<sub>8</sub>H<sub>17</sub>, OMe),<sup>6a</sup> ClB(OMe)<sub>2</sub>,<sup>6a</sup> HB(OR)<sub>2</sub> (R=i-Pr, t-Am),<sup>6a</sup> BH<sub>3</sub>·Et<sub>3</sub>N (R=Me, Bu),<sup>6b</sup> BF<sub>3</sub>·Et<sub>2</sub>O<sup>6c</sup> and catecholborane<sup>6d</sup> react with amines to furnish amides in moderate to good yield, but only in uniformly stoichiometric reactions. In these amidations, boron reagents transform into inactive boron species after the reaction of acyloxyboron derivatives and amines. However, arylboronic acids with electron-withdrawing substituents at the aryl group can be used to circumvent these difficulties, since they are water-, acid-, and base-tolerant Lewis acids that can generate acyloxyboron species. Their strong Lewis acidity enhances the rate of the generation of acyloxyboron species and their reactivity with amines.

To indicate the generality and scope of (3,4,5-trifluorophenyl)boronic acid-catalyzed amidation, the reaction is examined with various structurally diverse carboxylic acids and primary or secondary amines (Table I). In most cases, the reactions proceed cleanly, and the desired carboxylic amides are obtained in high yields. The catalyst is useful for effecting reaction not only of primary but also of secondary amines with various carboxylic acids. Sterically-hindered 1-adamantanecarboxylic acid is easily amidated at reflux in mesitylene. Aromatic substrates such as anilines and benzoic acid also react well under similar conditions. The catalytic amidation of optically active aliphatic  $\alpha$ -hydroxycarboxylic acids with benzylamine proceeds with no measurable loss (<2%) of enantiomeric purity under conditions of reflux in toluene. However, slight racemization is observed in the case of (S)-(+)-mandelic acid.

In addition, lactams can be prepared by the present technique under heterogeneous conditions although most amino acids are barely soluble in nonaqueous solvents (Table II). Interestingly, (S)-(-)-proline selectively gives the cyclic dimer with no measurable loss of enantiomeric purity.

The proposed mechanism of the boron-catalyzed amidation is depicted in the Figure.<sup>5</sup> It has been ascertained by <sup>1</sup>H NMR analysis that monoacyloxyboronic acid **1** is produced by heating the 2:1 mixture of 4-phenylbutyric acid and [3,5-bis(trifluoromethyl)phenyl]boronic acid in toluene under reflux with removal of water. The corresponding diacyloxyboron derivative is not observed at all. When 1 equiv of benzylamine is added to a solution of **1** in toluene, the amidation proceeds even at room temperature, but the reaction stops before 50% conversion because of hydrolysis of **1**. These experimental results suggest that the rate-determining step is the generation of **1**.

Figure. Proposed Catalytic Cycle

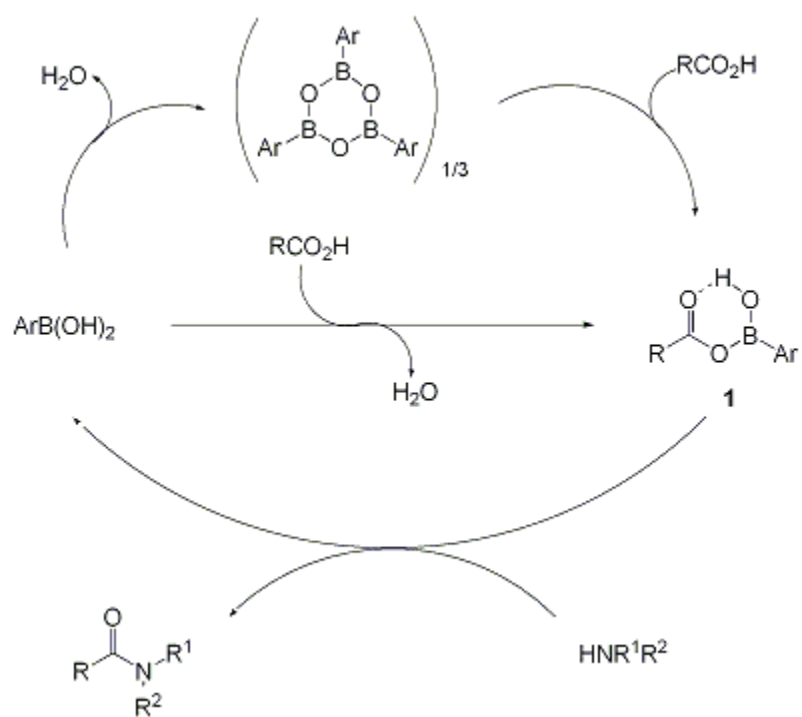

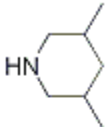


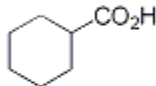
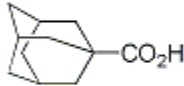

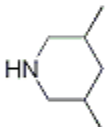
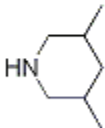
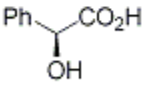
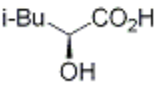
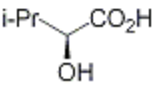


Table 1

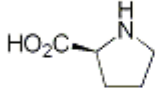
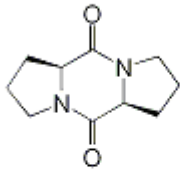

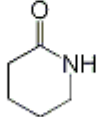

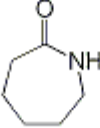
TABLE 1  
 EXAMPLES OF AMIDATION CONDENSATION BETWEEN CARBOXYLIC  
 ACIDS AND AMINES CATALYZED BY (3,4,5-TRIFLUOROPHENYL)BORONIC ACID<sup>a</sup>

Carboxylic Acid	Amine	Solvent	Time (hr)	Yield (%)
		Toluene	48 <sup>b</sup>	96 <sup>b</sup>
	Bu <sub>2</sub> NH	Mesitylene	14.5	99
	PhNH <sub>2</sub>	Mesitylene	4	99
	PhCH <sub>2</sub> NH <sub>2</sub>	Xylene Mesitylene	48 <sup>b</sup> 24 <sup>b</sup>	91 <sup>b</sup> 98 <sup>b</sup>
	PhCH <sub>2</sub> CH <sub>2</sub> NH <sub>2</sub>	Mesitylene	2	92
		Xylene	29	99
PhCO <sub>2</sub> H		Mesitylene	20	95
	PhCH <sub>2</sub> NH <sub>2</sub>	Toluene	10	95 (94% ee)
	PhCH <sub>2</sub> NH <sub>2</sub>	Toluene	10	87 (>98% ee)
	PhCH <sub>2</sub> NH <sub>2</sub>	Toluene	10	96 (>98% ee)

<sup>a</sup>Unless otherwise noted, results taken from reference 5. <sup>b</sup>The reaction was carried out using amines (30 mmol) and carboxylic acids (33 mmol) in the presence of (3,4,5-trifluorophenyl)boronic acid (0.3 mmol) in solvents (60 mL) by heating under reflux with removal of water.

Table II

TABLE II  
LACTAMIZATION REACTION OF AMINOCARBOXYLIC ACIDS  
CATALYZED BY (3,4,5-TRIFLUOROPHENYL)BORONIC ACID<sup>a</sup>

Aminocarboxylic Acid	Solvent	Time (hr)	Product	Yield (%)
	Anisole	11		94
	Xylene	18		20
	Xylene	22		93

<sup>a</sup>Unless otherwise noted, results taken from reference 5.

## References and Notes

1. Research Center for Advanced Waste and Emission Management (ResCWE), Nagoya University, Furo-cho, Chikusa, Nagoya 464-8603, Japan.
2. School of Engineering, Nagoya University, Furo-cho, Chikusa, Nagoya 464-8603, Japan.
3. For a review of the synthesis of amides and related compounds, see: Benz, G. In "Comprehensive Organic Synthesis"; Trost, B. M.; Fleming, I.; Winterfeldt, E., Eds.; Pergamon Press: New York, 1991; Vol, 6, Chapter 2.3, p. 381.
4. For catalytic amidations between carboxylic acids and amines, see: TiCl<sub>4</sub> (a) Nordahl, Å.; Carlson, R. *Acta Chem. Scand., Ser. B.* **1988**, 28; Ti(Oi-Pr)<sub>4</sub> (b) Mader, M.; Helquist, P. *Tetrahedron Lett.* **1988**, 29, 3049; Ph<sub>3</sub>SbO/P<sub>4</sub>S<sub>10</sub> (c) Nomura, R.; Nakano, T.; Yamada, Y.; Matsuda, H. *J. Org. Chem.* **1991**, 56, 4076; Sb(OEt)<sub>3</sub> (d) Ishihara, K.; Kuroki, Y.; Hanaki, N.; Ohara, S.; Yamamoto, H. *J. Am. Chem. Soc.* **1996**, 118, 1569.
5. (a) Ishihara, K.; Ohara, S.; Yamamoto, H. *J. Org. Chem.* **1996**, 61, 4196; (b) Ishihara, K.; Ohara, S.; Yamamoto, H. *Macromolecules* **2000**, 33, 3511; (c) Ishihara, K.; Kondo, S.; Yamamoto, H. *Synlett* **2001**, in press.
6. (a) Pelter, A.; Levitt, T. E.; Nelson, P. *Tetrahedron* **1970**, 26, 1539; (b) Trapani, G.; Reho, A.; Latrofa, A. *Synthesis* **1983**, 1013; (c) Tani, J.; Oine, T.; Inoue, I. *Synthesis* **1975**, 714; (d) Collum, D. B.; Chen, S.-C.; Ganem, B. *J. Org. Chem.* **1978**, 43, 4393.

## Appendix

### Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

(3,4,5-Trifluorophenyl)boronic acid:  
Boronic acid, (3,4,5-trifluorophenyl)- (13); (143418-49-9)

N-Benzyl-4-phenylbutyramide:

Benzenebutanamide, N-(phenylmethyl)- (13); (179923-27-4)

Magnesium (8,9); (7439-95-4)

Iodine (8,9); (7553-56-2)

1-Bromo-3,4,5-trifluorobenzene:  
Benzene, 5-bromo-1,2,3-trifluoro- (13); (138526-69-9)

Trimethyl borate:  
Boric acid, trimethyl ester (8,9); (121-43-7)

4-Phenylbutyric acid:  
Butyric acid, 4-phenyl- (8);  
Benzenebutanoic acid (9); (1821-12-1)

Benzylamine (8);  
Benzenemethanamine (9); (100-46-9)