Organic Syntheses

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). 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.

The procedures described in *Organic Syntheses* are provided as published and are conducted at one's own risk. *Organic Syntheses, Inc.*, its Editors, and its Board of Directors do not warrant or guarantee the safety of individuals using these procedures and hereby disclaim any liability for any injuries or damages claimed to have resulted from or related in any way to the procedures herein.

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.

BORIC ACID CATALYZED AMIDE FORMATION FROM CARBOXYLIC ACIDS AND AMINES:
N-BENZYL-4-PHENYLBUTYRAMIDE
(Benzenebutanamide, *N*-(phenylmethyl)-)
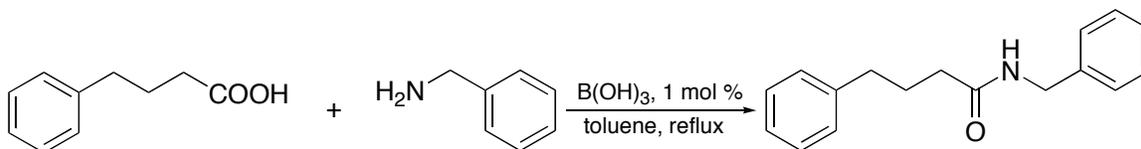
Submitted by Pingwah Tang.[1]
Checked by Helga Krause and Alois Fürstner.

Discussion Addendum *Org. Synth.* **2012**, *89*, 432

1. Procedure

N-Benzyl-4-phenylbutyramide. A flame-dried, 200-mL, three-necked, round-bottomed flask is equipped with two glass stoppers, a vacuum-jacketed Dean-Stark trap topped with a reflux condenser fitted with a nitrogen inlet, and a Teflon-coated magnetic stirring bar. The reaction vessel is charged with 4-phenylbutyric acid (4.92 g, 30 mmol) (Note 1), boric acid (0.020 g, 0.30 mmol) (Note 2), and 88 mL of toluene (Note 3). To the stirred colorless reaction mixture is added benzylamine (3.32 g, 31 mmol) (Note 4) in one portion. The reaction mixture is heated at reflux for 16 h and ca. 0.6 mL of water is collected in the Dean-Stark trap (Notes 5, 6, 7, 8). The mixture is allowed to cool to ambient temperature and then is poured with stirring into 500 mL of hexanes leading to the immediate precipitation of a white solid. Stirring is continued for an additional 30 min and then the precipitate is filtered off with suction through a sintered glass filter funnel. The collected solid is successively washed with two 60-mL portions of hexanes and two 60-mL portions of distilled water (Note 9) and then is dried in vacuo at room temperature for 12 h to afford 6.90 g (91%) of *N*-benzyl-4-phenylbutyramide as a white solid (Notes 10, 11).

2. Notes

1. 4-Phenylbutyric acid (99%) was purchased from Aldrich Chemical Company and used as received.

2. Boric acid (99.999%) was purchased from Aldrich Chemical Company and used as received.

3. Toluene (99.8% anhydrous, water <0.001%, evaporation residue <0.005%) was purchased from Aldrich Chemical Company and used as received. The capacity of the receiver in the Dean-Stark trap was 28 mL. The initial amount of toluene placed in the flask was 88 mL. Upon heating to reflux, 28 mL of toluene was distilled from the flask and collected in the receiver. The remaining volume of toluene in the reaction flask was ca. 60 mL, corresponding to an approximately 0.50M concentration of the reactants.

4. Benzylamine (redistilled 99.5+ %) was purchased from Aldrich Chemical Company and used without further purification.

5. The theoretical amount of water is 0.54 mL.

6. TLC analysis indicated that the reaction was complete. TLC was performed on pre-coated plates with silica gel 60 F_{254} purchased from EM Sciences (Merck) using hexanes/ethyl acetate (1/1) as the eluent.

7. HPLC analysis indicated that the reaction was complete. HPLC was conducted utilizing Perkin-Elmer's Series 200 autosampler and pump with either a Perkin-Elmer Series 200 or Applied Biosystems 785A UV/Vis detector (both monitoring at $\lambda = 220$ nm). Phenomenex's Kromasil 5 micron C18 column (50 mm x 4.6 mm) fitted with Phenomenex's C18 (ODS, Octadecyl) security guard cartridges (4 mm x 3 mm) were utilized with a 3 mL/min flow-rate. The solvent system consisted of mixtures of acetonitrile and water, containing 0.1% (v/v) trifluoroacetic acid, with the gradient starting at 5% acetonitrile and increasing to 95% over 10.5 min.

8. GC analysis indicated that the reaction was complete. Gas chromatographic analyses were performed on a Agilent 6890N GC system equipped with a 30-m 5% polyphenyl methyl siloxane capillary column (0.32 mm i.d.). Helium was used as the carrier gas, and the flow rate was kept constant at 7.7 mL/min. The retention time was measured under the following conditions: injector temperature: 250 °C; initial temperature of the

column: 150 °C; increment rate 8 °C/min to 200 °C. After being kept at 200 °C for 8.0 min, the temperature was raised to 290 °C at an increment rate of 8 °C/min.

9. The water wash removes residual boric acid. Elemental analysis of the final product indicated that boron content was less than 0.005%.

10. The filtrate (wash liquor) contained some white solid which was collected, triturated with ca. 5 mL of heptane, and dried to provide additional 0.35-0.50 g of pure product as a white solid (0.4-0.7%). Analytical data (TLC, GC, HPLC and elemental analysis) indicated that this crop has a purity of ≥ 95%.

11. The amide was obtained in 88-91% yield in different runs. The product has the following physico-chemical properties: GC: R_t: 10.31 min (Note 8); HPLC: R_t: 5.63 min (Note 7); TLC R_f: 0.40 (Note 6); mp 78-80 °C; IR (Kbr) cm^{-1} 3293, 3085, 3029, 2944, 1632, 1550, 1453, 1236, 1155, 1080, 1027, 724, 695; ^{1}H NMR (300 MHz, DMSO-d$_6$) δ: 1.76-1.87 (m, 2 H), 2.15 (t, 2 H, $J = 7.2$), 2.55 (t, 2 H, $J = 7.5$), 4.26 (d, 2 H, $J = 6.0$), 7.16-7.33 (m, 10 H), 8.30 (br, 1 H); ^{13}C NMR (75.6 MHz, DMSO-d$_6$) δ: 27.1, 34.6, 34.7, 41.9, 125.7, 126.6, 127.1, 128.20, 128.23, 128.27, 139.7, 141.7, 171.7. Anal. calcd for $C_{17}H_{19}NO$: C, 80.60; H, 7.56; N, 5.53. Found: C, 80.29; H, 7.53; N, 5.47; B < 0.005.

Waste Disposal Information

All toxic materials were disposed in accordance with "Prudent Practices in the Laboratories"; National Academy Press; Washington, DC, 1965

3. Discussion

Many procedures for the formation of carboxylic acid amides are known in the literature. The most widely practiced method employs carboxylic acid chlorides as the electrophiles which react with the amine in the presence of an acid scavenger. Despite its wide scope, this protocol suffers from several drawbacks. Most notable are the limited stability of many acid chlorides and the need for hazardous reagents for their preparation (thionyl chloride, oxalyl chloride, phosgene, etc.) which release corrosive and volatile by-products. Moreover, almost any other functional group in either reaction partner needs to be protected to ensure chemoselective amide formation.[2] The procedure outlined above presents a convenient and catalytic alternative to this standard protocol.

Although there are several reports in the literature on boron-mediated amide formations, the boron reagents had to be used in stoichiometric amounts.[3-9] Recently, Yamamoto et al. presented the first truly catalytic method allowing for a direct amide formation from free carboxylic acids and amines as the reaction partners.[10-12] Best results were obtained by using phenylboronic acids bearing electron withdrawing substituents in the *meta*- and/or *para*-positions such as 3,4,5-trifluorophenylboronic acid or 3,5-bis(trifluoromethyl)boronic acid as the catalysts.

During the course of our discovery program directed to small molecules for drug delivery, it was discovered that cheap, readily available, non-toxic, and environmentally benign boric acid, $B(OH)_3$, also constitutes a highly effective catalyst for direct amide formation. Benzylamines and cyclic aliphatic amines such as piperidines react smoothly. In most cases, the use of 5 mol% of $B(OH)_3$ is sufficient for obtaining excellent yields. Likewise, aniline derivatives afford the corresponding amides without incident even if they are hardly nucleophilic due to the presence of electron withdrawing substituents on the arene ring; in such cases, however, the amount of $B(OH)_3$ has to be increased to ca. 25% to ensure complete conversion. The scope of the method is illustrated by the examples compiled in Tables 1 and 2. Particularly noteworthy are the operational simplicity of this new method which might therefore qualify for large-scale preparations, as well as the excellent chemoselectivity profile that can make

protection/deprotection sequences obsolete. This is illustrated by the examples shown below.
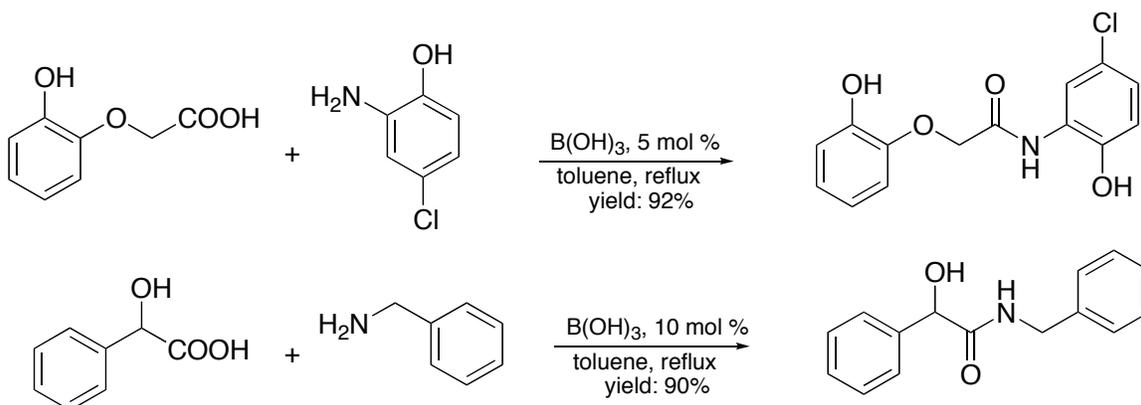
It is proposed that the boric acid reacts with the carboxylic acid to form a mixed anhydride as the actual acylating agent.[9,13] Upon reaction with an amine, this intermediate forms the desired carboxamide and regenerates the catalytically active boric acid.

Table 1

$$\text{Carboxylic acid} \quad + \quad \text{Amine} \quad \xrightarrow[\text{reflux}]{\text{B(OH)}_3} \quad \text{Carboxamide}$$

Entry	Carboxylic acid	Amine	Carboxamide	Solvent	Time (hr)	Isolated Yield
1	HO–O, Ph (4-phenylbutanoic acid)	H₂N–Ph (benzylamine)	Ph...N(H)–Ph amide	Heptane	15	99
2	HO–O, Ph	H₂N–C₆H₅ (aniline)	Ph...C(O)N(H)–C₆H₅	Toluene	15	92
3	HO–O, Ph	3,5-dimethylpiperidine (HN)	Ph...C(O)–N(piperidine)	Toluene	15	95
4	cyclohexanecarboxylic acid	H₂N–CH₂Ph	cyclohexyl-C(O)N(H)-benzyl	Toluene	15	95
5	cyclohexanecarboxylic acid	H₂N–C₆H₅	cyclohexyl-C(O)N(H)-C₆H₅	Toluene	15	83
6	2-hydroxyphenoxyacetic acid	2-amino-4-chlorophenol	amide product	Toluene	16	92
7	C_2H_5–O–CH₂CO₂H (ethoxyacetic acid)	2-amino-4-chlorophenol	amide product	Toluene	4	90
8	mandelic acid (OH, CO₂H)	H₂N–CH₂Ph	amide product	Xylene	15	90
9	benzoic acid	3,5-dimethylpiperidine (HN)	amide product	o-Xylene	20	85
10	acetic acid (CH₃CO₂H)	2-amino-4-chlorophenol	**No carboxamide produced**	Toluene	16	0
11	$EtO_2C\text{-}C_6H_{10}$–CO₂H	4-amino-3-hydroxy-methylbenzoate	$EtO_2C_6H_{10}$...amide, CO_2CH_3	Toluene	16	80
12	cyclohexanecarboxylic acid	ethyl 4-aminobenzoate (NH₂, CO₂Et)	amide, CO_2Et	Toluene	16	60

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Table II

$$R^*O_2C\text{-}(R_3)\text{-}CO\text{-}OH \;+\; H\text{-}N(R')(R) \xrightarrow[\text{Toluene, reflux}]{B(OH)_3,\; 5\;mol\,\%} R^*O_2C\text{-}(R_3)\text{-}CO\text{-}N(R')(R)\quad \mathbf{2}$$

$$\xrightarrow[\text{(2) H}^+]{\text{(1) Saponification}} HO_2C\text{-}(R_3)\text{-}CO\text{-}N(R')(R)\quad \mathbf{3}$$
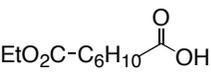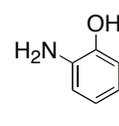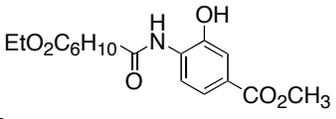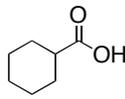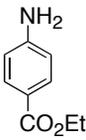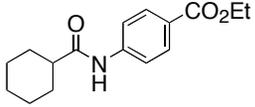
Entry	Carboxylic acid	Amine	HO₂C–(R₃)–CO–N(R')(R)	Reaction Time (hr)	Yield % of 3
1	EtO₂C–C₆H₁₂–COOH	2-aminophenol	HOOC–C₆H₁₂–CONH–(2-hydroxyphenyl)	16	75
2	EtO₂C–C₄H₈–COOH	2-amino-5-methylphenol	HOOC–C₄H₈–CONH–(hydroxy-methylphenyl)	4	77
3	EtO₂C–C₈H₁₆–COOH	2-amino-5-methylphenol	HOOC–C₈H₁₆–CONH–(hydroxy-methylphenyl)	4	78
4	EtO₂C–C₇H₁₄–COOH	2-amino-6-methylphenol	HOOC–C₇H₁₄–CONH–(hydroxy-methylphenyl)	4	77
5	EtO₂C–C₄H₈–COOH	2-amino-4-methylphenol	HOOC–C₄H₈–CONH–(hydroxy-methylphenyl)	4	78
6	MeO₂C–C₃H₆–COOH	2-amino-4-chlorophenol	HOOC–C₃H₆–CONH–(chloro-hydroxyphenyl)	16	72
7	EtO₂C–C₄H₈–COOH	2-amino-4-chlorophenol	HOOC–C₄H₈–CONH–(chloro-hydroxyphenyl)	16	70
8	EtO₂C–C₆H₁₂–COOH	2-amino-4-chlorophenol	HOOC–C₆H₁₂–CONH–(chloro-hydroxyphenyl)	16	57
9	MeO₂C–CH₂–CH(CH₃)–CH₂–COOH	2-amino-3,5-dichloro-4-methylphenol	HOOC–CH₂–CH(CH₃)–CH₂–CONH–(dichloro-methyl-hydroxyphenyl)	16	68
10	MeO₂C–CH₂–CH(CH₃)–CH₂–COOH	2-amino-5-methylphenol	HOOC–CH₂–CH(CH₃)–CH₂–CONH–(methyl-hydroxyphenyl)	16	70
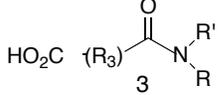
Several important generalizations emerge from the study of the boric acid catalyzed amidation of carboxylic acids and amines.

(1)   In most cases, 5 mol% of the catalyst is sufficient to catalyze the amidation. In all cases, the reactions proceed cleanly in high yields to the expected carboxamides.

(2)   No or little side reactions either with the unprotected hydroxy group present in the phenylamines, or with the unprotected hydroxyl group present in the carboxylic acids are observed. The catalytic amidation of unprotected α-hydroxycarboxylic acids also proceeds well under similar conditions.

(3)   The present method is successfully applicable to aromatic amines, which are less nucleophilic and less reactive. It works well with phenylamines, even bearing deactivating groups such as carboxylic acid ester moieties; in these cases we use 25 mol% of boric acid to drive the reaction to completion.

(4)   The catalyst employed in the reactions, boric acid, is inexpensive and commercially available. Boric acid is a "green" catalyst. By virtue of the simplicity of the process, the operation is easy to conduct. Therefore, it is amenable for large-scale preparations.

(5)   The catalytic amidation is an atom-economical process because it maximizes the incorporation of all materials used in the process into the final product. Therefore, it allows organic molecule architects for the quick building of molecular complexity.

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Appendix
Chemical Abstracts Nomenclature (Registry Number)

N-Benzyl-4-phenylbutyramide: Benzenebutanamide, N-(phenylmethyl)-;
     (179923-27-4)

4-Phenylbutyric acid: Benzenebutanoic acid; (1821-12-1)

Boric acid: Boric acid (H_3BO_3); (10043-35-3)

Benzylamine: Benzenemethanamine; (100-46-9)