Amidation of Aromatic Amine and Benzoic Acid Under Boric Acid Catalysis

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Synthesis of amides from the condensation reactions between aromatic amines and benzoic acids in the presence of boric acid is described. Aromatic amines include aniline 1,3-phenylenediamine and 1,4-phenylenediamine. Results indicate that the dehydrative amide procedure can be catalyzed by boric acid under mild conditions. The reaction is simple and the catalyst is readily available.

Keywords: Boric acid, Catalysis, Amidation, Aromatic amine, Aromatic acid.

INTRODUCTION

It is well known that amides have been playing an important role in synthetic chemistry, medicinal chemistry and biochemistry. Synthetic amides are usually obtained from amine and pre-activated carboxylic acid derivatives, such as acid chlorides, acid anhydrides and esters¹. There are many advantages to following these traditional ways which include low reaction temperature, short reaction time and satisfactory yields. Of course, there are also some disadvantages of using catalysts. The drawbacks involve the use of toxic reagents and produce of hazardous waste. Thus, direct amide formation between carboxylic acids and amines under ambient conditions has attracted considerable attention. Without additional reagents, a low yield is observed for the reaction of amines and carboxylic acids even under heating. Though DCC, EDC, BOP can be used to a range of coupling syntheses², they are unsuitable for large-scale preparation.

In recent years, employing boron-containing Lewis acids, such as boronic acid and boric acid (**Scheme-I**), as efficient catalysts in amidation reactions has attracted considerable attention³⁻⁵. Compared with boronic acid, boric acid is even low-cost, more readily available and more environmentally friendly. Investigators have done some notable applications of boric acid catalyzed amidation. Tang⁶ employed boric acid to synthesize *N*-benzyl-4-phenylbutyramide from benzylamine and 4-phenylbutyric acid in 88-91 % yield. In the synthesis of bioactive substance pregnenolone-pregnenolone dimmer, it is an easy methodology to produce pregnenolone-derivate *via* pregnenolone hemisuccinate with boric acid catalyst present⁷. Using boric acid as catalyst has developed various active pharmaceutical ingredients (APIs)⁸ and steroid derivatives⁹.

Condensation of aromatic aldehydes and amides using boric acid under thermal and neat microwave irradiation conditions is a convenient method for the symmetrical *N,N'*-alkylidene bisamides¹⁰. It is noteworthy that boric acid has been successfully utilized in multi-component, one-pot condensation reaction of 2-naphthol, aldehydes and amides under solvent-free conditions for the preparation of 1-amidoalkyl-2-naphthols¹¹.

Scheme-I: Boronic acid (a) and boric acid (b)

The scope of boric acid catalyzed amidation has been discussed by Tang in 2012¹². Up to now, the preparation of a range of boric acid catalyzed process for the synthesis of amides by using a mixture of different aliphatic amines-aromatic carboxylic acids or aromatic amines-aliphatic carboxylic acids or aliphatic amines-aliphatic carboxylic acids has been fully reported. But application of aromatic amines and aromatic carboxylic acids for boric acid catalyzed amidation is still not widely known. Herein, we report a simple, economic and efficient method for the synthesis of a series of benzamide derivatives using boric acid as the catalyst (**Scheme-II**).

Scheme-II: General scheme of reaction

EXPERIMENTAL

Boric acid was purchased from Alfa Aesar China (Tianjin) Co., Ltd. All the other reagents were obtained from Sinopharm Chemical Reagent Co., Ltd. All reagents were used as received without further purify.

IR spectra were measured as KBr pellets on a Perkin Elmer Specture one FT-IR Spectrometer in the 4000-400 cm^{-1} region. Routine NMR spectra were recorded on a Varian Mercury 300 spectrometer with ^1H NMR operating at 300 MHz. Melting point were recorded on a WRS-1B digital melting point apparatus (Shanghai precision & scientific instrument Co., Ltd.).

Procedure for the synthesis of the amides

N-phenylbenzamide (1): To a solution of benzoic acid (10 mmol) in toluene (30 mL), boric acid (0.6 mmol) was added. After heated to 100 $^{\circ}\text{C}$, aniline (16 mmol) was added to the mixture in portions. Then, other 20 mL of toluene was added. The above reaction mixture was refluxed for 16 h and water was collected azeotropically in the Dean-Stark trap. The mixture was allowed to cool to room temperature, leading to the precipitation of needle-like solid. The collected solid was successively washed with warm water and dried at room temperature to afford **1** in 47 %, m.p. 162.8-163.5 $^{\circ}\text{C}$. IR (KBr, ν_{max} , cm^{-1}): 3345, 1653, 1600. ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ_{H} : 10.27 (1H, s, NH), 7.95-7.97 (2H, d, ArH), 7.78-7.80 (2H, d, ArH), 7.50-7.62 (3H, m, ArH), 7.33-7.38 (2H, t, ArH), 7.08-7.13 (1H, t, NH).

N,N'-1,4-phenylenebisbenzamide (2): The mixture of benzoic acid (13 mmol) and boric acid (7 mmol) in 30 mL toluene was heated to 60 $^{\circ}\text{C}$. Then 1,4-phenylenediamine (4 mmol), ethanol (5 mL) and toluene (25 mL) were added. The reaction mixture was refluxed for 72 h and water was collected azeotropically in the Dean-Stark trap. The collected solid was successively washed with warm water and ethanol, then dried at room temperature to afford **2** in 76 %, m.p. 342.2-345.1 $^{\circ}\text{C}$. IR (KBr, ν_{max} , cm^{-1}): 3333, 1650, 1602. ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ_{H} : 10.26 (2H, s, NH), 7.95-7.98 (4H, d, ArH), 7.56 (4H, s, ArH), 7.49-7.62 (6H, m, ArH).

N,N'-1,3-phenylenebisbenzamide (3): The mixture of 1,3-phenylenediamine (4 mmol) and boric acid (3 mmol) in mixed 30 mL toluene and 5 mL ethanol was heated to 50 $^{\circ}\text{C}$. After the solid dissolved, benzoic acid (13 mmol) was added. The reaction mixture was refluxed for 48 h and water was collected azeotropically in the Dean-Stark trap. Then, a large number of light gray solid were found in the solution. The collected solid was successively washed with warm water and ethanol. And then dried at room temperature to afford **3** in 63 %, m.p. 244.2-245.1 $^{\circ}\text{C}$. IR (KBr, ν_{max} , cm^{-1}): 3263, 1648, 1602. ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ_{H} : 10.32 (2H, s, NH), 8.34 (1H, s, ArH), 7.96-7.99 (4H, d, ArH), 7.49-7.60 (8H, m, ArH), 7.29-7.35 (1H, t, ArH).

N-4-aminophenylbenzamide (4): A solution of 1,4-phenylenediamine (10 mmol) and boric acid (0.4 mmol) in toluene (30 mL) was heated to 100 $^{\circ}\text{C}$. Then, benzoic acid (10 mmol) and toluene (20 mL) was added to the mixture. The above reaction mixture was refluxed for 16 h and water was collected azeotropically in the Dean-Stark trap. The mixture was allowed to cool to ambient temperature, filtered to get

solid. The product was further purified by recrystallization from mixed solution of ethanol and water. Yield, 56 %, m.p. 126.1-126.5 $^{\circ}\text{C}$. IR (KBr, ν_{max} , cm^{-1}): 3380, 3332, 1646, 1599. ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ_{H} : 9.87 (1H, s, NH), 7.90-7.92 (2H, d, ArH), 7.47-7.57 (3H, m, ArH), 7.36-7.38 (2H, d, ArH), 6.53-6.56 (2H, d, ArH), 4.95 (2H, s, NH).

RESULTS AND DISCUSSION

Direct amide formation between carboxylic acids and amines an important phenomena in organic chemistry¹³. In this study, the most common aromatic amines and benzoic acid were screened. The results are summarized in Table-1. A classical synthetic procedure involves benzoic acid, aromatic amines and boric acid in the flask, equipped with a Dean-Stark apparatus and either toluene or toluene-ethanol as solvent, heated to reflux. In some cases, the addition of ethanol is in order to increase the solubility of certain reactants. Azeotrope was continuously removed from the reaction system. The mechanism of boronic acid catalysis in amide coupling reactions was suggested by Yamamoto *et al.*¹⁴. It can be also applied in explanation of the catalytic behaviour of boric acid (**Scheme-IIIa**). Taking into account the condensation of aromatic aldehydes and amides⁹ in the presence of boric acid as a catalyst, another plausible reaction mechanism for the synthesis under boric acid as an electron acceptor is also supposed (**Scheme-IIIb**). Entries 1 and 4 show that boric acid is capable of catalysis *albeit* at a lower rate (4 %). Boric acid is mildly successful at producing the desired product (N-phenylbenzamide, 47 % yield). This catalytic protocol was successfully applied in amidation of other aromatic diamines. The addition of massive boric acid (75 % mole fraction of diamine) provided the amides in 63 % yield (N,N'-1,3-phenylenebisbenzamide) and 76 % yield (N,N'-1,4-phenylenebisbenzamide). Considering the aromatic amine is less nucleophilic, yields are acceptable.

Scheme-III: Catalytic behaviour of boric acid

Conclusion

We have developed an amidation that allows employing aromatic amine and benzoic acid directly under boric acid catalytic conditions. It is a simple procedure under mild reaction condition and green catalyst, which can be extended to various amidation of aromatic derivative.

TABLE-1
BORIC ACID CATALYZED SYNTHESIS OF *N*-ARYL SUBSTITUTED AROMATIC AMIDES

Entry	Amine	Amide	Solvent	Reaction time (h)	Yield (%)
1			Toluene	16	47
2			Toluene and ethanol	72	76
3			Toluene and ethanol	48	63
4			Toluene	16	56

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