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An efficient boric acid-mediated preparation of α-hydroxyamides

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ABSTRACT

An efficient methodology for the preparation of α-hydroxyamides via boric acid-mediated addition of isonitriles onto aldehydes has been developed. The reaction of isonitriles with α-boronobenzaldehyde takes place under intramolecular catalysis conditions to provide functionalized benzoxaboroles.

1. Introduction

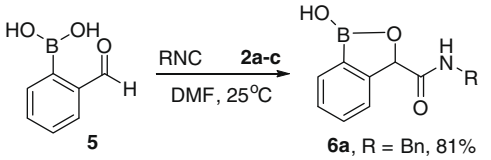
Boric acid is an inexpensive, nontoxic compound, and it is generally considered a green material.[1] It is an excellent precursor for the preparation of various types of organoboranes and is also used as a mild Lewis acid catalyst for several organic transformations.[2] α-Hydroxyamides are important synthetic intermediates in organic synthesis and also serve as valuable agents in medicinal chemistry.[3] The use of isonitriles in three or four component coupling reactions such as Passerini and Ugi is well documented in the literature.[4] The addition of isonitriles onto carbonyl compounds is usually catalyzed by strong protic acids or Lewis acids to provide α-hydroxyamides.[5]

2. Results and discussion

Owing to the aforementioned advantages, we envisaged the utility of boric acid for the direct α-addition of isonitriles onto aldehydes to synthesize α-hydroxyamides (Table 1). For the current study, we chose benzyl, cyclohexyl, and *tert*-butyl isonitriles (**2a–c**) and various types of aldehydes **1a–g** (Table 1). We initiated the optimization of the reaction conditions with propionaldehyde **1a** with benzyl isonitrile **2a**. The reaction was studied in various solvents such as THF, CH_2Cl_2, EtOAc, DMF, DMSO, Dioxane, MeOH, and water with varying amounts of boric acid (10 mol % to one equivalent). DMF as a solvent with one equivalent of boric acid was found to be optimal in obtaining cleaner reaction with good yields. Aliphatic isonitriles **2b**, **2c**, and aliphatic aldehydes were in general found to be more reactive and the reactions were completed in 24 h of stirring at room temperature. Aromatic aldehydes reacted slowly and required almost 48 h of reaction time. Upon completion, the reaction mixture was washed with water, worked up with diethyl ether, and pure products were obtained after silica gel column chromatography.

We also explored the reaction with the ketones 3-pentanone and acetophenone as representative examples. However, the reactions were found to be very sluggish even with two equivalents of boric acid and with an elevated temperature (80 °C).

We then applied the methodology for intramolecular version of the reaction starting with *o*-formyl phenylboronic acid **5**. We envisaged that the proximity of the boronic acid to the formyl group in **5** could lead to a facile reaction with isonitrile under self catalysis mode without any additional boric acid catalysis. This reaction should provide direct access to functionalized cyclic boronic acids (benzoxaboroles) **6**. Indeed, the reaction of boronoaldehyde **5** with isonitrile **2a** in DMF at room temperature took place smoothly without boric acid to provide the product benzoxaborole in 81% yield. Similarly, isonitriles **2b** and **2c** upon reaction with **5** provided the corresponding benzoxaboroles **6b** and **6c,** respec-



6a, R = Bn, 81%
6b, R = ^{t}Bu, 65%
6c, R = Chx, 76%

Scheme 1. Synthesis of α-amido benzoxaboroles.

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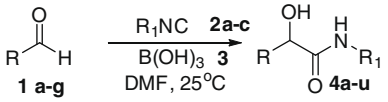
Table 1
Boric acid-mediated addition of isonitriles and aldehydes for the synthesis of α-hydroxyamides



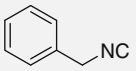
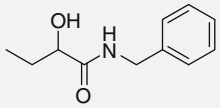
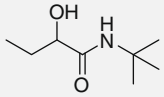
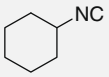
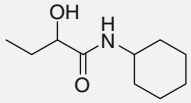
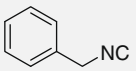
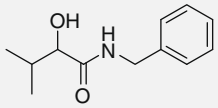
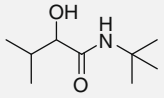
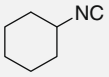
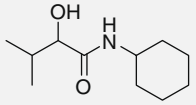
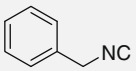
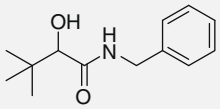
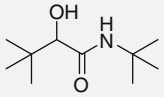
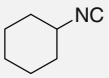
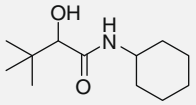
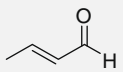
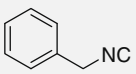
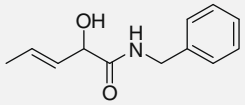
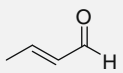
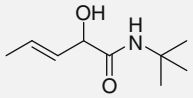
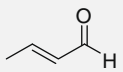
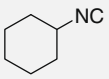
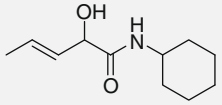
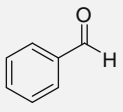
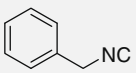
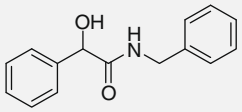
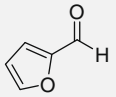
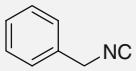
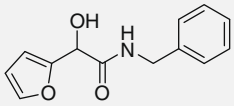
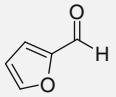
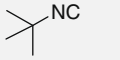
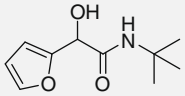
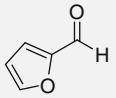
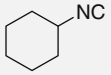
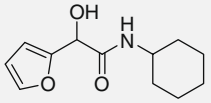
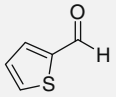
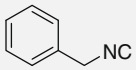
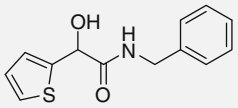
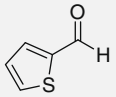
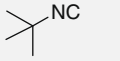
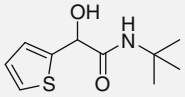
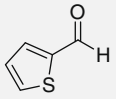
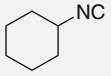
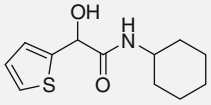
Entry	Aldehyde		Isonitrile		Product		Yield (%)
1	**1a**		**2a**		**4a**		78
2			**2b**		**4b**		74
3			**2c**		**4c**		75
4	**1b**		**2a**		**4d**		70
5			**2b**		**4e**		71
6			**2c**		**4f**		74
7	**1c**		**2a**		**4g**		61
8			**2b**		**4h**		64
9			**2c**		**4i**		72
10	**1d**		**2a**		**4j**		78
11			**2b**		**4k**		74
12			**2c**		**4l**		72
13	**1e**		**2a**		**4m**		82
14	**1e**		**2b**		**4n**		76
15			**2c**		**4o**		80

Table 1 (*continued*)

Entry	Aldehyde	Isonitrile	Product	Yield (%)
16	**1f** 	**2a** 	**4p** 	65
17		**2b** 	**4q** 	68
18		**2c** 	**4r** 	67
19	**1g** 	**2a** 	**4s** 	75
20		**2b** 	**4t** 	72
21		**2c** 	**4u** 	78

tively (Scheme 1). This class of boron compounds have extensive applications in materials chemistry and synthetic chemistry as excellent intermediates for Suzuki cross-coupling reactions.[6] Several of these compounds have also been found to exhibit important antibacterial and antifungal properties.[7]

2.1. Representative procedure for the preparation of hydroxyamide 4a

To a stirred solution of propionaldehyde **1a** (0.14 mL, 2.0 mmol) in 2 mL DMF were added benzyl isonitrile **2a** (0.24 mL, 2.0 mmol), and boric acid (0.12 g, 2.0 mmol) and stirred overnight at room temperature. Upon completion (TLC), the reaction mixture was worked up with water and diethyl ether (3 × 25 mL). The combined organic layers were dried ($MgSO_4$), concentrated in vacuo, and purified by column chromatography (silica gel, hexane/acetone, 4:1) to obtain 0.30 g (78%) of hydroxy amide **4a**. ^{1}H NMR (500 MHz, $CDCl_3$): 7.22–7.32 (m, 5H), 7.18 (bs, 1H), 4.47 (t, J = 4.5 Hz, 1H), 4.42 (dd, J = 4.0, 15.0 Hz, 1H), 4.36 (dd, J = 4.0, 15.0 Hz, 1H),4.05–4.08 (m, 1H), 1.78–1.90 (m, 1H), 1,62–1.72 (m, 1H), 0.95 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): 174.5, 138.2, 128.9, 127.9, 127.7, 73.2, 43.3, 28.1, 9.4; ESI-MS: 216 [$(M+Na)^+$, 100%], 194 $(M+H)^+$.

2.2. Representative procedure for the preparation of benzoxaborole 6b

To a stirred solution of boronoaldehyde **5** (0.3 g, 2.0 mmol) in 2 mL DMF was added *tert*-butyl isonitrile **2a** (0.23 mL, 2.0 mmol), and stirred overnight at room temperature. Upon completion (TLC), the reaction mixture was worked up with water and ethyl acetate (3 × 25 mL). The combined organic layers were dried ($MgSO_4$), concentrated in vacuo, and purified by column chromatography (silica gel, hexane/ethyl acetate, 3:1) to obtain 0.30 g (65%) of benzoxaborole **6b**. (Found: C, 61.53; H, 8.10; N, 6.02%; $C_{12}H_{16}BNO_3$ requires: C, 61.84; H, 6.92; N, 6.01%); ^{1}H NMR (500 MHz, DMSO-d_6): 9.33 (bs, 1H), 7.67 (d, J = 7.2 Hz, 1H), 7.62 (d, J = 7.6 Hz, 1H), 7.36 (t, J = 7.4 Hz, 1H), 7.26 (t, J = 7.4 Hz, 1H), 6.52 (s, 1H), 5.27 (s, 1H), 1.21 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): 169.4, 152.3, 131.3, 130.8, 128.1, 122.9, 80.2, 51.1, 28.9; ESI-MS: 232 [$(M-H)^+$, 100%].

3. Conclusions

In conclusion, we have developed an efficient protocol for the preparation of α-hydroxyamides via boric acid mediated addition of isonitriles onto aldehydes. The reaction in general provides good yields of the products under very mild reaction conditions. We have applied the methodology for an intramolecular version to synthesize functionalized benzoxaboroles. Owing to the importance of hydroxyamides and benzoxaboroles as synthetic intermediates and also as medicinal agents, we believe that the current methodology will find applications in organic and medicinal chemistry.

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