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A rapid construction of 1,3,2-benzodiazaborininones [R–B(aam)] from boronic acids and anthranilamides†

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A simple, efficient and mild methodology for the synthesis of 1,3,2-benzodiazaborininones [R–B(aam)] from boronic acids and anthranilamides on ethyl acetate is described. A series of 1,3,2-benzodiazaborininones were prepared in moderate to excellent yields at room temperature without dehydrating agents, metal catalysts, corrosive acids or other additives. Meanwhile, a multi-gram scale reaction is also performed to ensure the scalability of the reaction, and the product can be conveniently isolated by simple filtration.

Introduction

Organoboron compounds play an important role in drug synthesis, medicinal chemistry, and biochemistry.[1–6] For example, boronic esters have been developed as triggers for ROS-activated prodrugs for the treatment of cancer patients in recent years.[7,8] They also have been regarded as especially popular organometallic reagents[9,10] for constructing carbon–carbon and carbon–heteroatom bonds, owing to their broad availability and their compatibility with a multitude of functional groups.[11,12] At the same time, Boron(B)–nitrogen(N)-containing heteroaromatic compounds continue to arouse interest in the fields of materials chemistry[13–15] and fluorescence imaging.[16–20] Since Suginome reported on boron-masking strategy in Suzuki–Miyaura coupling (SMC) using 1,8-diaminonaphthalene (danH_2)[21–24] and *N*-methyliminodiacetoxy (mida)[25–29] as boron-masking groups, iterative SMC has been widely used in the synthesis of complex oligoaromatic hydrocarbons and natural products (Fig. 1). Besides, other protected boron moieties[30,31] were successively reported later such as 1,3,2-benzodiazaborininones [R–B(aam)].[32–35] Furthermore, the unique advantage of B(aam) is that it can serve as an ortho-directing group in catalytic Ar–H silylation[34] (Fig. 2) and it plays an important role in the stereoselective borohydride reaction of alkynes catalyzed by iridium.[36] Therefore, the synthesis of compound R–B(aam) is of great significance.

Conventional methods for constructing R–B(aam) reported in the literature include the following synthetic protocols: condensation reaction of boric acids with anthranilamide (aam-H_2) in high temperature (110 °C)[37] or Ni/Pd-catalyzed.[38] Besides, the synthesis of these compounds by the reaction of potassium phenyltrifluoborate with aam-H_2 (ref. 39) and the reaction of Ar–X with (pin)B–B(aam) (pin = pinacol ester) catalyzed by Pd[40] (Fig. 3). Although high yields can be achieved using these methods, several factors must be considered, including strict reaction conditions that always involve high temperatures, long reaction times, and complicated combinations of reagents. From the green chemistry point of view, the use of green catalysts[41,42] or catalyst-free reactions is the mainstream. There is still a great need to develop simple, efficient, clean and high-yield methods to synthesize these compounds.

In our previous work, R–B(dan), oxdiazobium compound, dioxazobium compound and oxdiazobium compound were synthesized by a simple method[43,44](Fig. 4). At the same time, the green synthesis of borazine heterocycles should be further expanded. Herein, we report an efficient protocol for the synthesis of R–B (aam) in ethyl acetate without any other catalysts or additives (Fig. 4).

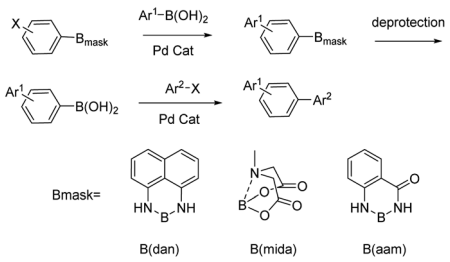

Fig. 1 Iterative Suzuki–Miyaura coupling using masked haloarylboronic acids for selective synthesis of oligoarenes.

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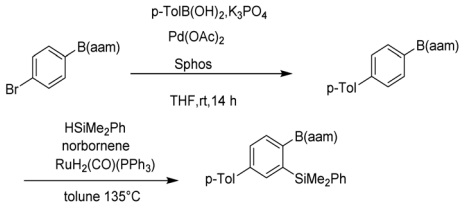


Fig. 2 Boron-masking strategy with B(aam).

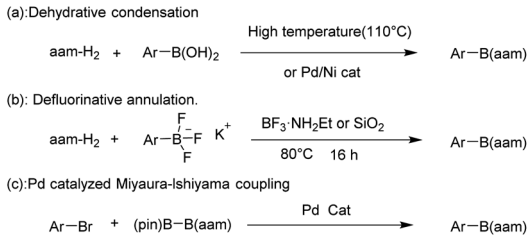


Fig. 3 Common methods for the synthesis of R–B(aam).

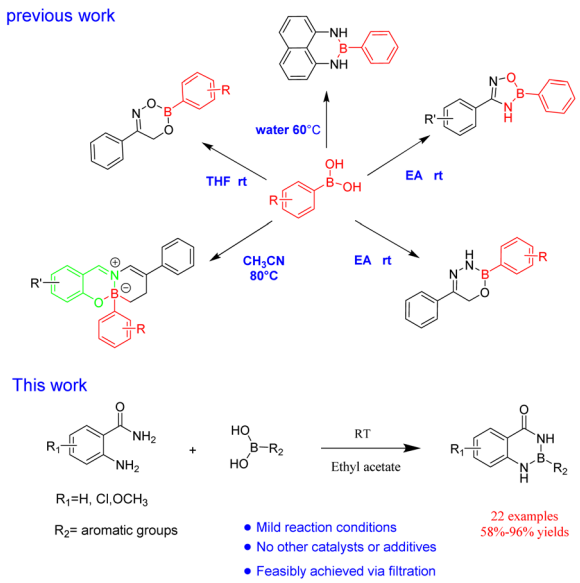
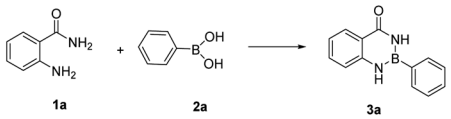


Fig. 4 The synthesis of R–B(aam).

Results and discussion

In our initial trials, we first carried out the reaction of amm-H_2 with phenylboronic using $TiCl_4$ as a dehydrating agent in the tetrahydrofuran (THF) at room temperature for 4 h. The product **3a** was obtained in 93% yield (Table 1, entry 1), The structure of the product was established by NMR analysis. To our delight, the yield of the product was 90% in the absence of $TiCl_4$ at room temperature (Table 1, entry 2). Then the reaction was carried out in different solvents (including ethanol, methanol, *N*,*N*-Dimethylformamide (DMF), ethyl acetate, *etc.*) for 0.5 h (Table 1, entries 3–12) revealed that the highest yield (70%) was obtained in ethyl acetate (Table 1, entry 7). The yields increased gradually with extended reaction times (Table 1, entries 13–15), and an

Table 1 Optimization of reaction conditions[a]



Entry	Catalyst	Solvent	Temp	Time (h)	Yield[b] (%)
1	$TiCl_4$	THF	RT[c]	4	93
2	—	THF	RT[c]	4	90
3	—	THF	RT[c]	1	50
4	—	Ethanol	RT[c]	1	62
5	—	Methanol	RT[c]	1	61
6	—	DMF	RT[c]	1	30
7	—	Ethyl acetate	RT[c]	1	70
8	—	DMSO	RT[c]	1	20
9	—	Water	RT[c]	1	15
10	—	Dichloromethane	RT	1	68
11	—	Chloroform	RT	1	61
12	—	Ether	RT	1	60
13	—	Ethyl acetate	RT[c]	1.5	78
14	—	Ethyl acetate	RT[c]	2	82
15	—	Ethyl acetate	RT[c]	3	93
16	—	Ethyl acetate	RT[c]	3.5	93
17	—	Ethyl acetate	RT[c]	4	93
18	—	Ethyl acetate	40 °C	3	93
19	—	Ethyl acetate	60 °C	3.5	93

[a] Reaction condition: **1** (1 mmol), **2** (0.83 mmol), $TiCl_4$ (16 mol%), solvent (3 mL). [b] Isolated yield for column chromatography. [c] RT: room temperature.

excellent yield of Ar–B(aam) was generated in 93% (Table 1, entry 15) as the reaction times was increased to 3 hours. Interestingly, the desired product **3a** was precipitated from the ethyl acetate (Fig. 5) and could be isolated by simple filtration in 75% yield (93% yield for column chromatography). But with the increase of reaction time and temperature continuously, the reaction failed to give the expected yield (Table 1, entries 16–19). The optimum conditions were chosen for 3 h at room temperature (RT) in this reaction system. It was worth nothing that the progress of the reaction was monitored by TLC (DCM : EA = 10 : 1) in all the cases (Fig. 6).

With the optimized reaction conditions in hand, substituted anthranilamides **1** with boronic acids **2** were used to investigate the scope of the reaction. Results were displayed in Table 2. Various phenylboronic acids containing different substituent

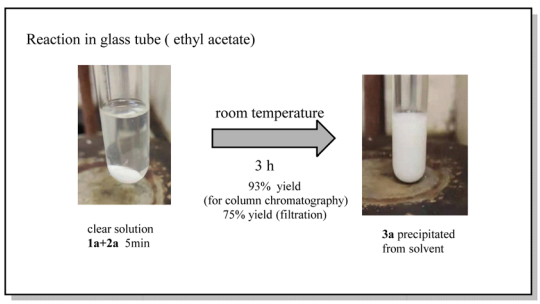


Fig. 5 Reaction phenomenons and results.

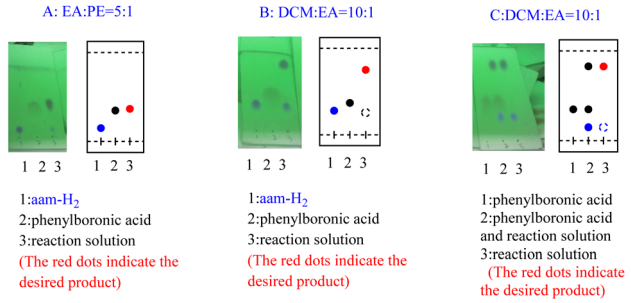
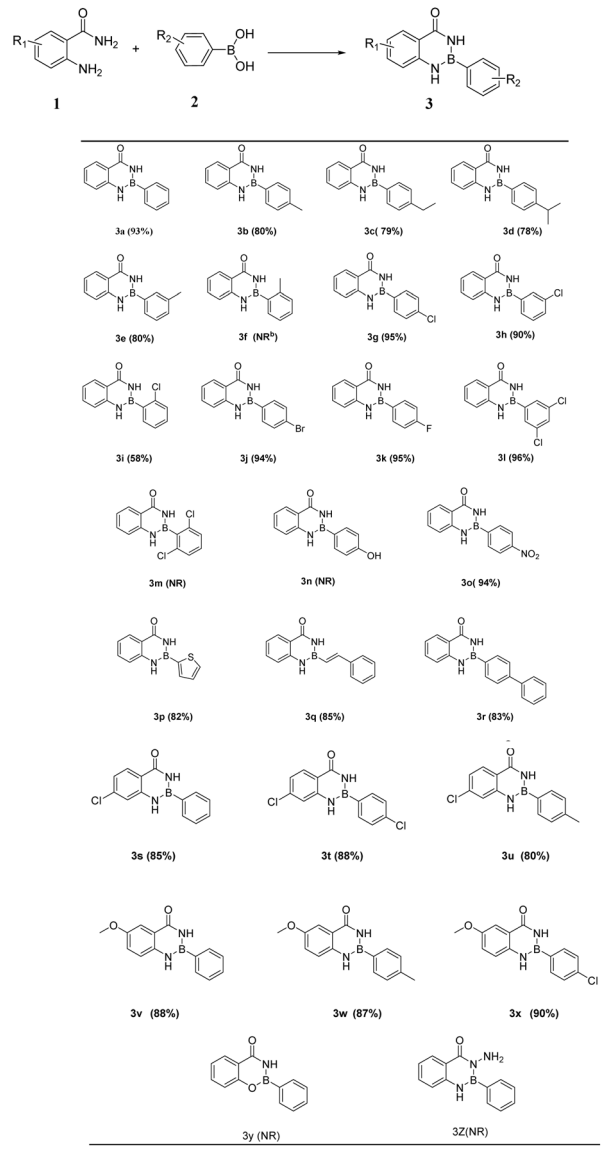


Fig. 6 The progress of the reaction was monitored by TLC.

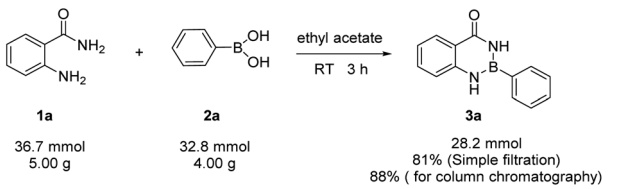
Table 2 Substrate scope for the synthesis of Oxadiazaborole 3[a,b]



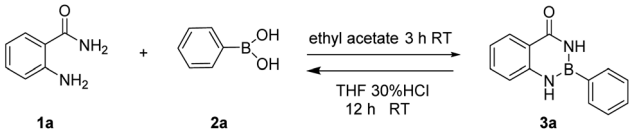
[a] Reaction conditions: **1** (1 mmol),**2** (0.83 mmol), ethyl acetate (3 mL), 3 h, RT (room temperature), yields refer to isolated yield for column chromatography. [b] NR: no reaction.

on the *para*-position, such as methyl, ethyl, isopropyl and halogen groups, and the product (Table 2 **3b-3d**, **3g**, **3j**, **3k**) was obtained in high yield of 80–95%. Moreover, one or two different groups were introduced into the *meta*-position of phenylboronic acid, and the yield of the product (Table 2 **3e**, **3h**, **3l**) also was 80–96%. Similarly, the reaction was also applicable to boric acid containing different aromatic groups, such as 4-vinylphenylboronic acid, 2-thiopheneboronic acid and 4-biphenylboronic acid, and could still proceed smoothly in 82–85% yield (Table 2 **3p-3r**). However, it should be noted that a halogen in the *ortho*-position of phenylboronic acid (Table 2 **3i**) gave the target product only in 58%. Especially, phenylboronic acid couldn't react with aam-H_2 when it contains a methyl group at the *ortho*-position (Table 2 **3f**), which indicates that steric hindrance has a great influence. And boronic acids bearing strong electron-withdrawing substituents such as nitro underwent the reaction smoothly to afford target product **3o**. Nevertheless, product formation was not observed when the strong electron-donating substituents such as hydroxyl group were attached (Table 2 **3n**). Thus, the electronic effects of substituents on the phenylboronic acid showed obvious influence on the reaction outcome. To further examine the substrate scope of the reaction, anthranilamides with substituents on benzene ring were employed. All products (Table 2 **3s-3x**) were afforded in good yields followed by the same procedure. In addition, anthranilic acid hydrazide and salicylamide do not react with phenylboronic acid.

The gram-scale reaction was also carried out to demonstrate the practicability of the methodology (Scheme 1). The aam-H_2 (5.00 g, 36.7 mmol) was treated with phenylboronic (4.00 g, 32.8 mmol) in ethyl acetate (100 mL). As expected, the product Ar–B(aam) **3a** was obtained in 88% yield (6.42 g, by column chromatography purification) which indicted the scalability of the reaction. Furthermore, the desired product could be isolated by simple filtration in 81% yield (5.96 g). Therefore, with merit of simplicity, convenience and quickness, this method can be applied in industrial production. Moreover, Hydrolysis reaction of Ar–B(aam) were performed as follows (Scheme 2) from the reaction conditions found in the literature.[21,45]



Scheme 1 Multi-gram scale reaction of aam-H_2 with phenylboronic acid.



Scheme 2 Hydrolysis reaction of Ar–B(aam).

Conclusions

We have developed a mild and efficient protocol for the synthesis of R–B(aam) through the reaction of boric acids with anthranilamides. Moderate to excellent yields of the products were obtained for 3 h at room temperature without any catalysts or other additives. The multi-gram scale reaction was also found that the product in was afforded excellent yields successfully, and the product can be conveniently isolated by simple filtration. Considering the potential importance of the R–B(aam) in SMC reactions and materials science, the newly developed green methodology will be efficacious to chemists and industrialists.

Conflicts of interest

There are no conflicts to declare.

Notes and references

1 S. J. Baker, J. W. Tomsho and S. J. Benkovic, *Chem. Soc. Rev.*, 2011, **40**, 4279–4285.
2 S. Kuwano, Y. Hosaka and T. Arai, *Org. Biomol. Chem.*, 2019, **17**, 4475–4482.
3 F. Meng, K. P. McGrath and A. H. Hoveyda, *Nature*, 2014, **513**, 367–374.
4 G. R. Mereddy, A. Chakradhar, R. M. Rutkoski and S. C. Jonnalagadda, *J. Organomet. Chem.*, 2018, **865**, 12–22.
5 T. Ogiyama, M. Yamaguchi, N. Kurikawa, S. Honzumi, Y. Yamamoto, D. Sugiyama and S. Inoue, *Bioorg. Med. Chem.*, 2016, **24**, 3801–3807.
6 C. Xu, H. Li, Z. Wang, X. Lou and W. Fu, *Monatsh. Chem.*, 2014, **145**, 767–773.
7 Y. Ai, O. N. Obianom, M. Kuser, Y. Li, Y. Shu and F. Xue, *ACS Med. Chem. Lett.*, 2019, **10**, 127–131.
8 X.-M. Jiang, X.-R. Liu, A. Chen, X.-Z. Zou, J.-F. Ge and D.-W. Gao, *Eur. J. Org. Chem.*, **2022**, e202101463.
9 A. Yuasa, K. Nagao and H. Ohmiya, *Beilstein J. Org. Chem.*, 2020, **16**, 185–189.
10 T. Wakamatsu, K. Nagao, H. Ohmiya and M. Sawamura, *Beilstein J. Org. Chem.*, 2015, **11**, 2444–2450.
11 T. Ohe, N. Miyaura and A. Suzuki, *Synlett*, 1990, 221–223.
12 W. J. Teo, X. X. Yang, Y. Y. Poon and S. Z. Ge, *Nat. Commun.*, 2020, **11**, 8.
13 R. N. Dhital and H. Sakurai, *Asian J. Org. Chem.*, 2014, **3**, 668–684.
14 X. Y. Lu, C. T. Yang, J. H. Liu, Z. Q. Zhang, X. Lu, X. Lou, B. Xiao and Y. Fu, *Chem. Commun.*, 2015, **51**, 2388–2391.
15 L.-J. Xiao, L. Cheng, W.-M. Feng, M.-L. Li, J.-H. Xie and Q.-L. Zhou, *Angew. Chem., Int. Ed.*, 2018, **57**, 461–464.
16 K. Boknevitz, J. S. Italia, B. Li, A. Chatterjee and S. Y. Liu, *Chem. Sci.*, 2019, **10**, 4994–4998.
17 P. G. Campbell, A. J. V. Marwitz and S.-Y. Liu, *Angew. Chem., Int. Ed.*, 2012, **51**, 6074–6092.
18 F. Lindl, S. Lin, I. Krummenacher, C. Lenczyk, A. Stoy, M. Mueller, Z. Lin and H. Braunschweig, *Angew. Chem., Int. Ed.*, 2019, **58**, 338–342.
19 W. M. Wan, D. Tian, Y. N. Jing, X. Y. Zhang, W. Wu, H. Ren and H. L. Bao, *Angew. Chem., Int. Ed.*, 2018, **57**, 15510–15516.
20 P. Zhao, D. O. Nettleton, R. G. Karki, F. J. Zecri and S. Y. Liu, *ChemMedChem*, 2017, **12**, 358–361.
21 N. Iwadate and M. Suginome, *J. Organomet. Chem.*, 2009, **694**, 1713–1717.
22 N. Iwadate and M. Suginome, *Org. Lett.*, 2009, **11**, 1899–1902.
23 N. Iwadate and M. Suginome, *J. Am. Chem. Soc.*, 2010, **132**, 2548.
24 H. Noguchi, K. Hojo and M. Suginome, *J. Am. Chem. Soc.*, 2007, **129**, 758–759.
25 G. R. Dick, E. M. Woerly and M. D. Burke, *Angew. Chem., Int. Ed.*, 2012, **51**, 2667–2672.
26 E. P. Gullis and M. D. Burke, *J. Am. Chem. Soc.*, 2007, **129**, 6716–6717.
27 C. He and X. Pan, *Macromolecules*, 2020, **53**, 3700–3708.
28 D. M. Knapp, E. P. Gillis and M. D. Burke, *J. Am. Chem. Soc.*, 2009, **131**, 6961.
29 J. Q. Li, A. S. Grillo and M. D. Burke, *Acc. Chem. Res.*, 2015, **48**, 2297–2307.
30 S. Darses and J.-P. Genet, *Chem. Rev.*, 2008, **108**, 288–325.
31 G. A. Molander and N. Ellis, *Acc. Chem. Res.*, 2007, **40**, 275–286.
32 H. Ihara, M. Koyanagi and M. Suginome, *Org. Lett.*, 2011, **13**, 2662–2665.
33 S. Kamio, I. Kageyuki, I. Osaka and H. Yoshida, *Chem. Commun.*, 2019, **55**, 2624–2627.
34 M. Koyanagi, N. Eichenauer, H. Ihara, T. Yamamoto and M. Suginome, *Chem. Lett.*, 2013, **42**, 541–543.
35 S. Kamio, I. Kageyuki, I. Osaka and H. Yoshida, *Chem. Commun.*, 2019, **55**, 2624–2627.
36 H. Yoshida, M. Kimura, H. Tanaka, Y. Murashige, I. Kageyuki and I. Osaka, *Chem. Commun.*, 2019, **55**, 5420–5422.
37 S. S. Chissick, M. J. S. Dewar and P. M. Maitlis, *J. Am. Chem. Soc.*, 1961, **83**, 2708–2711.
38 H.-J. Wang, M. Zhang, W.-J. Li, Y. Ni, J. Lin and Z.-H. Zhang, *Adv. Synth. Catal.*, 2019, **361**, 5018–5024.
39 G. H. M. Davies, A. Mukhtar, B. Saeednia, F. Sherafat, C. B. Kelly and G. A. Molander, *J. Org. Chem.*, 2017, **82**, 5380–5390.
40 S. Kamio, I. Kageyuki, I. Osaka, S. Hatano, M. Abe and H. Yoshida, *Chem. Commun.*, 2018, **54**, 9290–9293.
41 S. P. Ding, M. J. Hulsey, H. An, Q. He, H. Asakura, M. Gao, J. Y. Hasegawa, T. Tanaka and N. Yan, *CCS Chem.*, 2021, **3**, 1814–1822.
42 M. J. Hülsey, B. Zhang, Z. Ma, H. Asakura, D. A. Do, W. Chen, T. Tanaka, P. Zhang, Z. Wu and N. Yan, *Nat. Commun.*, 2019, **10**, 1330.
43 Q. Kuang, X. Hu, Y. Li, S. Shang, X. Huang, S. Liao, Y. Song, W. Ma, S. Li, A. Liu, X. Liu, X. Zhang and J. Yuan, *Org. Biomol. Chem.*, 2022, **20**, 6413–6417.
44 S. Liao, X. Hu, Y. Li, X. Wang, D. Li, Q. Wang, Y. Wang, X. Huang, P. Xu, H. Wu, X. Li and J. Yuan, *Tetrahedron*, 2021, **90**, 132205.
45 H. Noguchi, K. Hojo and M. Suginome, *J. Am. Chem. Soc.*, 2007, **129**, 758–759.