



One-step three-component reaction among organoboronic acids, amines and salicylaldehydes

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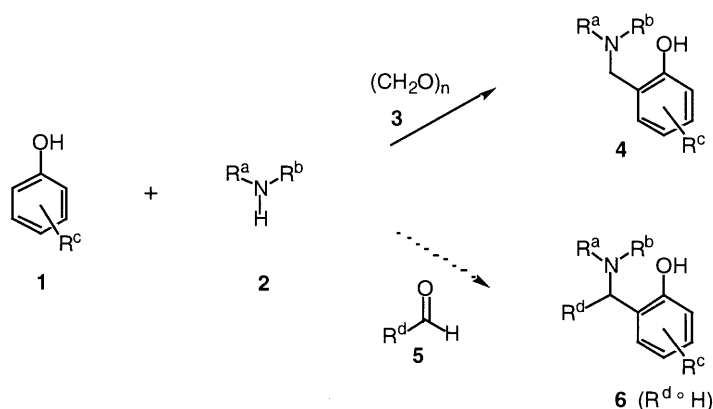
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Abstract—Alkenyl, aryl and heteroaryl boronic acids react with amines and salicylaldehydes in a single step to give novel aminophenol derivatives. © 2001 Published by Elsevier Science Ltd.

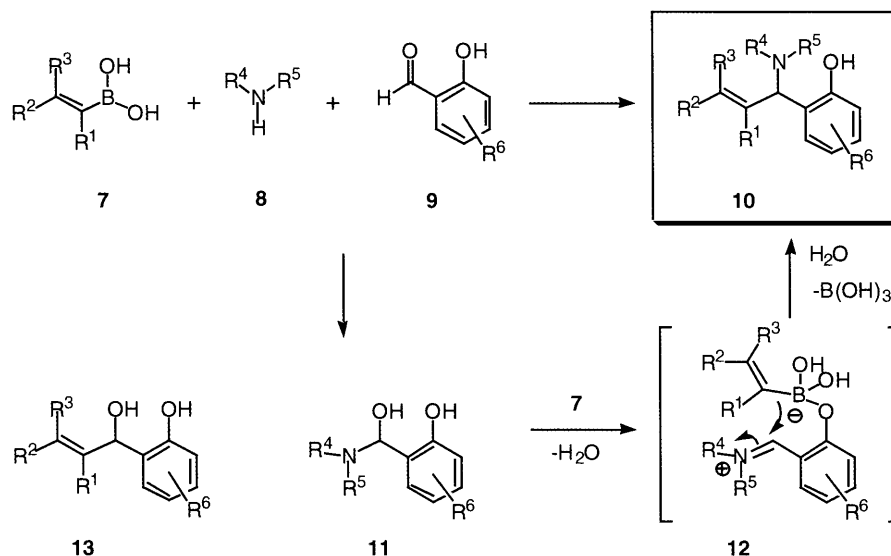
Functionalized arylalkylamines and aminoalkylphenols are attractive structures for the development of pharmaceuticals and agrochemicals. While simple derivatives of this type (**4**) are well known because they are readily available via one-step Mannich reactions¹ of phenols (**1**), amines (**2**) and paraformaldehyde (**3**), more substituted derivatives (**6**) are generally not directly accessible in this manner,² particularly with non-activated aldehydes (**5**) (Scheme 1). Consequently, some stepwise approaches have been developed for this purpose.³ Herein, we describe a novel approach to molecules of this type via the one-step reaction among organoboronic acids (**7**), amines (**8**) and salicylaldehydes (**9**).

Based on the concept that organoboronic acids are weakly electrophilic molecules that can be transformed into transient nucleophilic species, we have recently introduced a number of new reactions of these versatile and synthetically valuable molecules.^{4,5} Among the reactions we have reported is a novel one-step multi-component process^{5b-d} involving the condensation of alkenyl, aryl or heteroaryl boronic acids (**7**) with amines (**8**) and certain carbonyl compounds, such as α -keto acids and α -hydroxy aldehydes, leading to α -amino acids^{5b,c} and β -amino alcohols,^{5d,e} respectively. Herein, we report that the analogous one-step reaction with salicylaldehydes (**9**) affords the corresponding aminomethylphenol derivatives (**10**). The mechanism of



Scheme 1.

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Scheme 2.

this process presumably involves the initial reaction among the amine and the carbonyl to give an aminol intermediate (**11**), which reacts with the organoboronic acid to generate a transient species such as (**12**), leading to the product (**10**) via irreversible carbon–carbon bond formation (Scheme 2).

A key feature of this process that makes possible its multicomponent nature is that the direct addition of **7** to **9** to afford **13** does not take place readily under the reaction conditions. Indeed, compounds **13** do not form even with more reactive boronic acids, higher temperatures or prolonged reaction times.

A number of boronic acids, amines and carbonyl compounds were investigated for this reaction (Scheme 3). Several types of alkenyl (**14**), aryl (**15**, **16**) and heteroaryl (**17–20**) boronic acids gave the expected products (**36–49**) in variable yields (not optimized). We examined a number of amines and found that the reaction is more general with secondary amines (e.g. **22–26**), while primary amines (e.g. **21**) afford the expected products in modest yields when more reactive boronic acids are employed (e.g. **43**⁶).

Among the carbonyl compounds used, salicylaldehydes (**27–29**) worked well in most cases, while other benzaldehyde derivatives lacking an *o*-hydroxy substituent (**30–33**) were not effective in this process. This is consistent with the intermediacy of a species such as **12**. The corresponding *o*-hydroxy acetophenone as well as several polyhydroxy derivatives (e.g. **34**, **35**) were also ineffective, probably due to the suppressed reactivity of the carbonyl moiety.

The examples shown in Scheme 3 were performed by stirring the three components in ethanol at room tem-

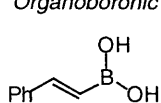
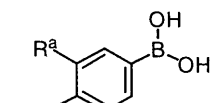
perature over 24–36 h. Other polar solvents, such as methanol and acetonitrile were also effective in this process, while the reaction was slower in dichloromethane or toluene. The indicated yields are of purified products, after flash column chromatography. All products gave satisfactory spectroscopic and analytical data.

Typical experimental procedure: To a mixture of salicylaldehyde (**27**, 122 mg, 1.0 mmol) and morpholine (**26**, 87 mg, 1.0 mmol) in ethanol (10 mL), was added (*E*)-2-phenylethenyl boronic acid (**14**, 148 mg, 1.0 mmol) and the solution was stirred at room temperature while monitored by TLC (10% ethyl acetate in hexanes). After the completion of the reaction (24 h) the solvent was evaporated and the product was isolated by flash chromatography using 10% ethyl acetate in hexanes to give the product **37** (260 mg, 88%).⁷

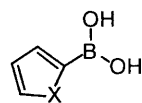
In summary, we have shown that functionalized Mannich-like products can be directly obtained in one-step from organoboronic acids, amines and salicylaldehydes. Further manipulations of the adducts of this process may lead to a variety of cyclic products.⁸ Additional variations and synthetic applications of this chemistry are currently being explored.

Acknowledgements

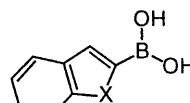
We thank Ilia A. Zavialov for his help and suggestions. We also gratefully acknowledge the National Institutes of Health (grant GM 45970) for support of this research and the Loker Hydrocarbon Research Institute for a Harold Moulton Graduate Fellowship to S.B.

Organoboronic Acids**14**

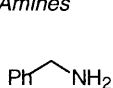
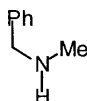
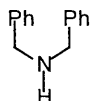
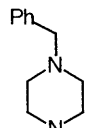
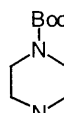
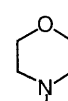
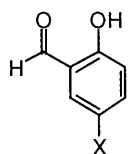
15, R = H
16, R = OMe



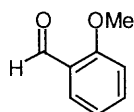
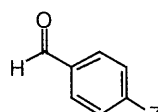
17, X = S
18, X = O



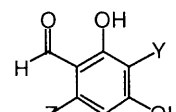
19, X = S
20, X = O

Amines**21****22****23****24****25****26***Salicylaldehydes*

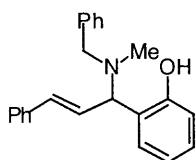
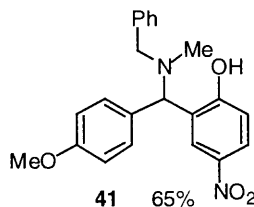
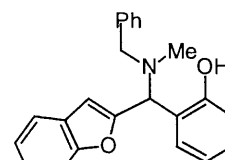
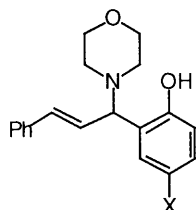
27, X = H
28, X = Br
29, X = NO₂

**30**

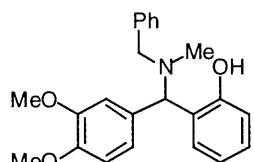
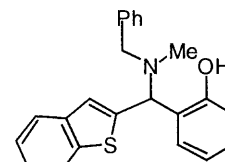
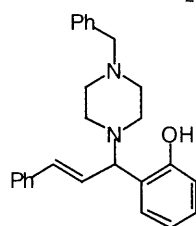
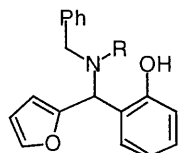
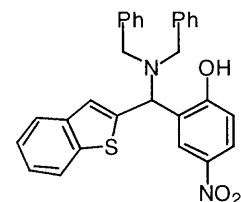
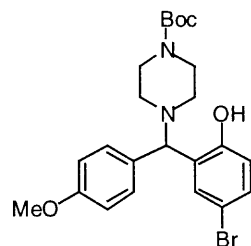
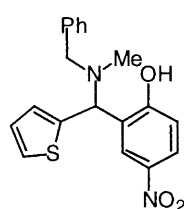
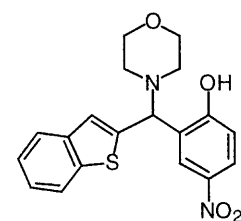
31, R = H
32, R = OH
33, R = F



34, Y = OH, Z = H
35, Y = H, Z = OH

Products**36** 81%**41** 65%**46** 52%

37 X = H 88%
38 X = NO₂ 40%

**42** 70%**47** 50%**39** 58%**43** R = H 32%**44** R = Me 79%**48** 70%**40** 63%**45** 66%**49** 62%

Scheme 3.

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3. For some examples, see: (a) Katritzky, A. R.; Abdel-Fattah, A. A. A.; Tymoshenko, D. O.; Belyakov, S. A.; Ghiviriga, I.; Steel, P. J. *J. Org. Chem.* **1999**, 64, 6071. (b) Palmieri, G. *Eur. J. Org. Chem.* **1999**, 805. (c) Grumbach, H. J.; Arend, M.; Risch, N. *Synthesis* **1996**, 883.
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6. Methanol was used as the solvent in this case.
7. Data for **37**: ^1H NMR (250 MHz, CDCl_3) δ 7.44–6.65 (m, 9H), 6.55 (d, 15.8 Hz, 1H), 6.29 (dd, 15.6 Hz, 9.5 Hz, 1H), 3.99 (d, 9.3 Hz, 1H), 3.74 (bm, 4H), 2.59 (bm, 4H). ^{13}C NMR (62.5 MHz, CDCl_3) δ 156.3, 136.0, 133.9, 128.9, 128.6, 128.5, 128.0, 126.5, 125.9, 123.9, 119.7, 116.6, 74.0, 66.8, 51.1. HRMS-Cl calculated for $\text{C}_{19}\text{H}_{22}\text{NO}_2$ ($\text{M}+\text{H}^+$) 296.1572, found 296.1648.
8. For a novel application see: Wang, Q.; Finn, M. G. *Org. Lett.* in press.