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The use of potassium alkynyltrifluoroborates in Mannich reactions[☆]

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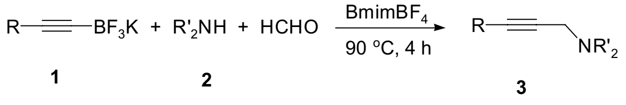
Abstract—Potassium alkynyltrifluoroborates react with amines and salicylaldehydes in the presence of benzoic acid to generate highly functionalized amines. Ionic liquids such as butylmethylimidazolium tetrafluoroborate ($BmimBF_4$) are suitable solvents for the reaction.

The Petasis reaction is a modern variation of the Mannich reaction involving an amine, a carbonyl compound, and an organoborane.[1] The method has attracted considerable interest because the three-component process is applicable to a variety of boronic acids, amines, and carbonyl compounds such as α-ketoacids,[2,3] α-hydroxyaldehydes,[4] and salicylaldehydes.[5] α-Heterocyclic aldehydes have also been shown to participate.[6] Examples of the Petasis reaction involving alkenylboronates and arylboronates, are well documented but alkynylboron derivatives have not been utilized.

Alkynylboronic esters are stronger Lewis acids than aryl and alkenylboronate esters and are easily hydrolyzed.[7] Therefore, their use in organic reactions can be problematic. However, alkynylboronate salts are hydrolytically stable and readily participate in a number of carbon–carbon bond forming reactions.[8] Recently, Molander and Genet independently reported Suzuki–Miyaura cross-coupling reactions using air stable potassium alkynyltrifluoroborates, which can be easily synthesized from corresponding alkynyllithium reagents.[9] It is becoming apparent that trifluoroborate derivatives can be successfully used in place of boronate esters.[9,10] We have discovered that potassium alkynyltrifluoroborates are suitable reagents for carrying out Mannich reactions in ionic liquid media.

Ionic liquids have emerged as alternative solvents because they have essentially no vapor pressure and provide good solubility for a wide range of organic, inorganic, and organometallic compounds.[11] In continuation our studies focused on organoboron reactions in room temperature ionic liquids,[12] we examined the reaction of potassium alkynyltrifluoroborate salts with formaldehyde and various amines in butylmethylimidazolium tetrafluoroborate ($BmimBF_4$). Propargylamines, **3**, were obtained in high yields (Scheme 1). The resultant products are of biological interest because they are selective inhibitors of the rat squalene epoxidase enzyme.[13]

In an initial study, the reaction of salicylaldehyde with potassium 1-hexynyltrifluoroborate and dibenzylamine in $BmimBF_4$ produced only 10% of desired product



R	Amine	Yield (%)
n-Butyl	Dibenzylamine	92
n-Butyl	Morpholine	90
Phenyl	Piperidine	83

Scheme 1.

Keywords: Potassium alkynyltrifluoroborates; Mannich reaction; Ionic liquids; Butylmethylimidazolium tetrafluoroborate; Propargylamines.

[☆] Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2003.11.049

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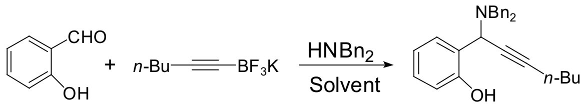
(Table 1, entry 1). We then found that the addition of 1 equiv of benzoic acid increased the reaction yields dramatically (Table 1, entry 2). The benzoic acid presumably catalyzes the condensation of the aldehyde with the amine to generate an iminium ion, which then reacts more efficiently with the borate salt.[14] The reaction was most efficient in $BmimBF_4$ and DMF; whereas, THF, acetonitrile, 1,4-dioxane, and ionic liquids such as BmimBr, $BmimPF_6$ were less effective.[15]

The reactions of a variety of alkynyltrifluoroborates and carbonyl compounds were then investigated (Table 2). Benzaldehyde derivatives lacking an *o*-hydroxy substituent were found to be unreactive. The reaction is limited to secondary amines, but both aliphatic and aromatic alkynyltrifluoroborates participate. Under the reaction conditions utilized, no heterocycle formation was observed.[5a]

Table 1. Three-component Mannich reaction in various solvents[a,b]



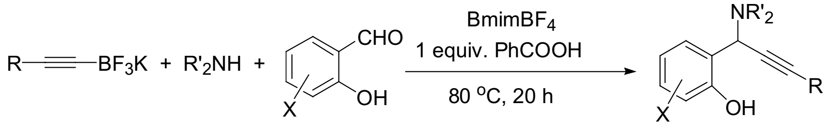
Entry	Solvent	Isolated yield (%)
1	$BmimBF_4$	10[c]
2	$BmimBF_4$	81
3	BmimBr	17
4	$BmimPF_6$	41
5	DMF	73
6	THF	6
7	1,4-Dioxane	11
8	Acetonitrile	0

[a] Reactions carried out at 80 °C for 20 h.

[b] One equivalent of benzoic acid was added to the reaction.

[c] Reaction run in the absence of benzoic acid.

Table 2. Three-component condensation of potassium alkynyltrifluoroborates, amines, and salicylaldehydes



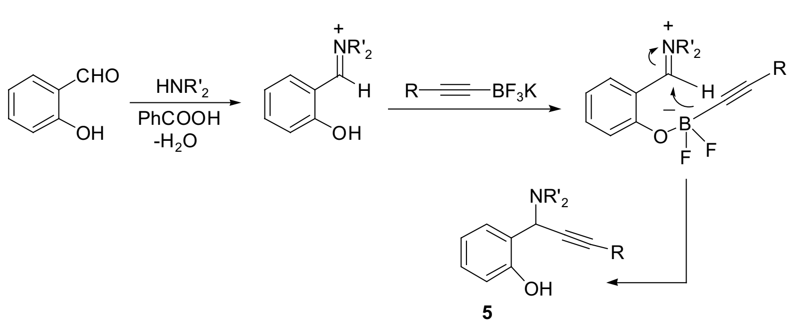
1 2 4 5

Entry	R	Amine (**2**)	X	Yield (%)[a]
1	*n*-Butyl	Dibenzylamine	H	81
2	*n*-Butyl	Dibenzylamine	5-NO_2	83
3	*n*-Butyl	Morpholine	H	76
4	*n*-Butyl	Morpholine	3-Me	63
5	*n*-Butyl	Morpholine	5-*t*-Bu	76
6	*n*-Butyl	Morpholine	5-Cl	53
7	Phenyl	Dibenzylamine	H	81
8	Phenyl	Morpholine	5-NO_2	79
9	*p*-Tolyl	Morpholine	5-NO_2	78
10	*tert*-Butyl	Morpholine	H	72
11	1-Cyclohexenyl	Morpholine	H	78
12	1-Cyclohexenyl	Tetrahydroisoquinoline	H	58[b]
13	Trimethylsilyl	Morpholine	H	55[c]

[a] Isolated yields.

[b] DMF was used as solvent.

[c] The trimethylsilyl group was removed under the reaction conditions.



5

Scheme 2.

The mechanism of the reaction presumably involves the initial formation of an iminium ion. Coordination of the borate moiety with the phenolate oxygen[10a] would form an intermediate, **6**, that would deliver the propargylamine (Scheme 2).[5]

In conclusion, the efficient benzoic acid promoted, three-component coupling of potassium alkynyltrifluoroborates, amines, and salicylaldehydes in ionic liquid media has been achieved. The process is simple and generates functionalized propargylamines in good yields. The products, **5**, can be utilized as precursors to a variety of functionally substituted heterocycles.[16]

Supplementary data

Reaction procedure, ^{1}H and ^{13}C and analytical data. This supplementary data is available online with the paper in ScienceDirect.

Acknowledgements

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15. Typical experimental procedure: To a mixture of salicylaldehyde (1 mmol) and dibenzylamine (1 mmol) in BmimBF$_4$ (800 mg), potassium 1-hexynyltrifluoroborate (1 mmol) and benzoic acid (1 mmol) were added. The mixture was stirred at 80 °C for 20 h, the product was extracted into diethyl ether (3 × 5 mL), the solvent removed, and the crude product purified by column chromatography (silica gel).
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