

Ionic liquid accelerated Petasis reaction: A green protocol for the synthesis of alkylaminophenols

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Abstract

Ionic liquids are found to accelerate the Petasis boronic acid–Mannich reaction of aldehyde, secondary amine and aryl boronic acid under mild conditions to afford the corresponding alkylaminophenols in high yields. The remarkable features of this procedure are improved yields, enhanced reaction rates and ease of recyclability of ionic liquids (ILs). The recovered ionic liquid can be reused for four to five times without apparent loss of activity.

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Keywords: Ionic liquids (ILs); Petasis–Mannich reaction; Alkylaminophenols

1. Introduction

The Petasis boronic–Mannich reaction is a powerful and convenient synthetic route for the preparation of α -amino acids and heterocycles [1–6]. The most commonly used aldehydes are glyoxylic acid and hydroxy-substituted benzaldehydes particularly salicylaldehydes [7]. In general, the reaction works well with alkenyl boronic acids and electron rich or neutral aryl and heteroaryl boronic acids. The range of amines such as secondary amines, hindered primary amines, anilines and hydrazines has been used for this reaction [8,9]. Generally, the reaction requires stirring at room temperature for periods of 24 h or more. In some cases, microwave activation or refluxing conditions have been employed to achieve reasonable conversion [10]. The most commonly used solvents are dichloromethane, toluene, ethanol and acetonitrile. Recently, hexafluoroisopropanol has been used to accelerate the Petasis–Mannich reaction [11]. However, many of these procedures require either a long reaction time or microwave activation and in addition they demand routine aqueous work-up.

In recent times, ionic liquids have emerged as alternative reaction media for the immobilization of transition metal-based catalysts, Lewis acids and enzymes [12,13]. They are being used

as green solvents because they are non-volatile, recyclable, non-explosive, ease of handling, thermally robust, and in addition they are compatible with various organic and organometallic compounds. They are referred to as ‘designer solvents’ as their properties such as hydrophilicity, hydrophobicity, Lewis acidity, viscosity and density can be altered by the fine-tuning of parameters such as the choice of organic cation, inorganic anion and the length of alkyl chain attached to an organic cation [14,15] (Fig. 1).

These structural variations offer flexibility to the chemist to devise the most idealized solvent, catering to the needs of any particular process. As a result of their green credentials and potential to enhance reaction rates and selectivities, ionic liquids are finding increasing applications in organic synthesis [16]. However, there have been no reports on the use of ionic liquids to promote the Petasis reaction.

2. Results and discussion

In this article, we wish to report the use of ionic liquids as recyclable solvents for the Petasis–Mannich reaction of aryl boronic acids, 2-hydroxy aryl aldehydes and secondary amines to afford alkylaminophenols in high yields under mild and neutral conditions (Scheme 1).

Treatment of 2-hydroxy benzaldehyde with morpholine and *p*-phenyl phenylboronic acid in 1-butyl-3-methylimidazolium

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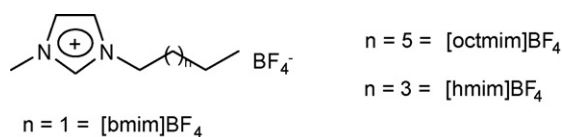


Fig. 1. Chemical structure of representative ionic liquids.

tetrafluoroborate [bmim]BF₄ at room temperature over a period of 3 h resulted in the formation of **4a** in 80% yield. The reaction proceeded efficiently at room temperature without the need of any additional promoters. The product was easily isolated by simple extraction with diethyl ether. The rest of the ionic liquid was further washed with ether and reused in successive runs. Encouraged by the results obtained in the model reaction, we turned our attention to various aryl boronic acids and secondary amines. Interestingly, a wide range of aryl boronic acids underwent smooth Mannich type coupling reaction with imines formed *in situ* from salicylaldehydes and secondary amines. In most cases, the reactions proceeded smoothly at room temperature with high efficiency. Ionic liquids are stable with amines and water that exist during imine formation and also effectively activate the imines to undergo coupling. The experiments were performed in both hydrophilic [bmim]BF₄ and hydrophobic [bmim]PF₆ ionic liquids. Among these solvents, [bmim]BF₄ was found to be effective in terms of conversion. Aryl imines, formed *in situ* from salicylaldehydes and secondary amines, exhibit enhanced reactivity in the ionic liquid thereby reducing the reaction times and improving the yields significantly. For instance, treatment of *p*-phenyl phenylboronic acid with salicylaldehyde and pyrrolidine in [bmim]BF₄ afforded the corresponding alkyl amino phenol **4c** in 82% yield within 3.5 h whereas the same reaction in methanol gave the desired product in 60% after 12 h. In addition, the ionic liquid was easily recovered after the reaction and reused several times without loss of activity, even after the fourth cycle the product **4c** was obtained with similar yield and purity to that obtained in the first cycle. The use of ionic liquids as reaction media for this transformation helps to avoid the necessity of high temperature or microwave activation or long reaction times. To know the effect of ionic liquid in this transformation, the reaction was carried out in dichloromethane both in the presence of 10 mol% [bmim]BF₄ ionic liquid and in the absence of ionic liquid. High conversions were obtained in a short reaction time in the combined solvent system, i.e. 10 mol% [bmim]BF₄ in dichloromethane. Other polar organic solvents such as methanol and acetonitrile were also used to study the effect of ionic liquids in this transformation. In these solvents, the reactions proceeded only at

high temperature (70–80 °C) and also took longer reaction times (12–24 h) to afford comparable yields. The scope and generality of this method is illustrated with respect to various aryl boronic acids, 2-hydroxy benzaldehydes and a wide range of secondary amines and the results are presented in Table 1.

3. Experimental

Melting points were recorded on Buchi R-535 apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer FT-IR 240-c spectrophotometer using KBr optics. ¹H NMR spectra were recorded on Gemini-200 and Varian Bruker-300 spectrometer in CDCl₃ using TMS as internal standard. Mass spectra were recorded on a Finnigan MAT 1020 mass spectrometer operating at 70 eV.

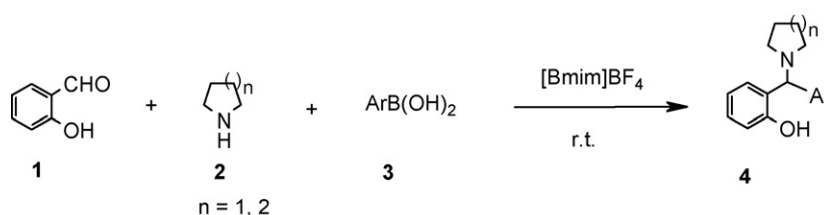
3.1. Typical procedure

A mixture of aryl boronic acid (1 mmol), secondary amine (1 mmol) and salicylaldehyde (1 mmol) in [bmim]BF₄ ionic liquid (2 mL) was stirred at room temperature (for few reactions temperature was raised to 80 °C) for the appropriate time (see Table 1). After complete conversion, as indicated by TLC, the reaction mixture was extracted with ether (3 × 10 mL). The combined organic extracts were concentrated in vacuo and the resulting product was purified by column chromatography on silica gel (Merck, 100–200 mesh, ethylacetate:hexane, 0.5:9.5) to afford pure product.

3.1.1. Spectroscopic data for selected compounds

4a: 2-[1,4-Oxazinan-4-yl(4-phenylphenyl)methyl]phenol: White viscous liquid, IR (KBr): ν_{max} : 3029, 2928, 2855, 2360, 1746, 1590, 1485, 1401, 1253, 1117, 1000, 935, 875, 757, 697, 567, 519 cm⁻¹; ¹H NMR (200 MHz, CDCl₃): δ 11.41 (s, 1H), 7.20–7.70 (m, 9H), 7.15 (t, J_{1-2} = 7.5 Hz, 1H), 6.90 (d, J_{1-2} = 7.0 Hz, 1H), 6.70 (d, J_{1-2} = 7.0 Hz, 1H), 6.62 (d, J_{1-2} = 7.5 Hz, 1H), 4.40 (s, 1H), 3.70 (s, 4H), 2.30–2.70 (m, 4H). FAB mass: m/z : 346 (M + 1), 307, 279, 259, 215, 192, 154, 107, 57.

4b: 2-[4-Methylhexahydro-1-pyridinyl(2-naphthyl)-methyl]phenol: White viscous liquid, IR (KBr): ν_{max} : 2921, 2357, 1595, 1466, 1254, 854, 766, 477 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.70–7.80 (m, 4H), 7.53–7.61 (s, 1H), 7.38–7.42 (m, 2H), 7.06 (t, J_{1-2} = 7.6 Hz, 1H), 6.86 (d, J_{1-2} = 7.0 Hz, 1H), 6.82 (d, J_{1-2} = 7.0 Hz, 1H), 6.62 (t, J_{1-2} = 7.6 Hz, 1H), 4.58 (s, 1H), 1.93–2.20 (m, 2H), 1.57–1.77 (m, 2H), 1.21–1.41 (m, 5H), 0.98 (d, 3H). FAB mass: m/z : 332



Scheme 1.

Table 1
Petasis multi-component coupling reaction in ionic liquid [bmim]BF₄



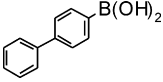
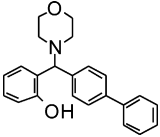


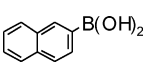
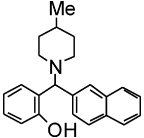


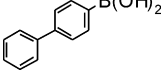
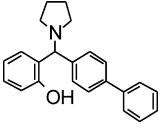

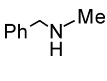
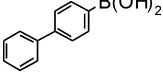
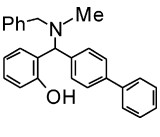


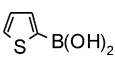
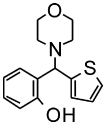


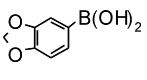
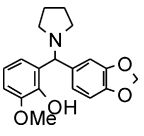

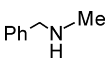
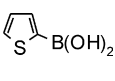
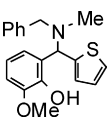

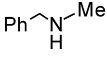
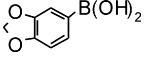
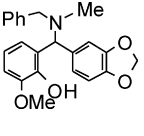

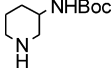
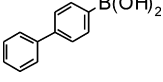
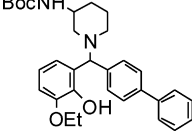

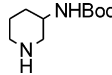
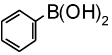
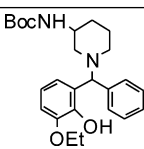
Entry	Salicylaldehyde, 1	Amine, 2	Boronic acid, 3	Product, ^a 4	Time (h); temperature (°C)	Yield (%) ^b
a					3.0; RT	80
b					4.0; 80	79
c					3.5; RT	82
d					4.0; RT	80
e					5.0; 80	75
f					3.0; RT	80
g					4.0; 80	76
h					3.0; RT	70
i					5.0; RT	85

Table 1 (Continued)

Entry	Salicylaldehyde, 1	Amine, 2	Boronic acid, 3	Product, ^a 4	Time (h); temperature (°C)	Yield (%) ^b
j					3.0; RT	70

^a All products were characterized by ¹H NMR, IR and mass spectroscopy.

^b Isolated and unoptimized yields.

(M + 1), 307, 289, 273, 260, 245, 233, 215, 202, 179, 167, 154, 137, 124, 107, 100, 77, 69, 55.

4c: 2-[4-Phenylphenyl(tetrahydro-1H-1-pyrrolyl)methyl]phenol: Yellow viscous liquid, IR (KBr): ν_{\max} : 2967, 2816, 2236, 1591, 1482, 1405, 1328, 1254, 1117, 1032, 890, 838, 758, 697, 628, 561 cm^{-1} ; ¹H NMR (400 MHz, CDCl₃): δ 11.83 (s, 1H), 7.40–7.58 (m, 5H), 7.32 (t, J_{1-2} = 7.5 Hz, 2H), 7.25 (d, J_{1-2} = 7.5 Hz, 2H), 7.05 (t, J_{1-2} = 7.5 Hz, 1H), 6.92 (d, J_{1-2} = 7.0 Hz, 1H), 6.79 (d, J_{1-2} = 7.0 Hz, 1H), 6.66 (t, J_{1-2} = 7.5 Hz, 1H), 4.35 (s, 1H), 2.40–3.71 (m, 4H), 2.82 (s, 4H); mass: m/z : 329 (M⁺), 259, 236, 176, 154, 109, 95, 81, 69, 55.

4d: 2-Benzyl(methyl)amino(4-phenylphenyl)methylphenol: Colorless viscous liquid, IR (KBr): ν_{\max} : 3433, 2925, 2853, 1730, 1597, 1480, 1399, 1252, 1116, 1009, 836, 754, 700, cm^{-1} ; ¹H NMR (200 MHz, CDCl₃): δ 11.3 (s, 1H), 7.42–7.60 (m, 5H), 7.18–7.41 (m, 9H), 6.99–7.19 (m, 2H), 6.70 (m, 2H), 4.70 (s, 1H), 3.47–3.60 (q, J_{1-2} = 12.8 Hz, J_{2-3} = 5.2 Hz, J_{1-3} = 18.8 Hz, 2H), 2.10 (s, 3H); FAB mass: m/z : 380 (M + 1), 259, 136, 91, 69, 57.

4e: 2-[1,4-Oxazinan-4-yl(2-thienyl)methyl]phenol: White solid, m.p. 145–148 °C, IR (KBr): ν_{\max} : 2960, 2918, 2850, 1588, 1481, 1405, 1255, 1153, 1117, 999, 920, 876, 792, 757, 657, 611, 502; ¹H NMR (300 MHz, CDCl₃): δ 11.2 (s, 1H), 7.16–7.26 (m, 2H), 7.12 (d, J_{1-2} = 4.9 Hz, 1H), 7.03–7.1 (t, J_{1-2} = 7.1 Hz, 1H), 6.86 (d, J_{1-2} = 7.9 Hz, 1H), 6.78 (d, J_{1-2} = 7.5 Hz, 1H), 6.64–6.72 (t, J_{1-2} = 7.1 Hz, 1H), 4.50 (s, 1H), 3.70 (m, 4H), 2.46–2.62 (m, 2H), 2.34–2.44 (m, 2H); FAB mass: m/z : 275 (M + 1), 189, 147, 95, 81.

4. Conclusion

In summary, ionic liquid was found to be an effective reaction medium for the three-component coupling of aryl boronic acids,

aldehydes and secondary amines to produce a variety of alkylaminophenols. Aryl boronic acids show significant increase in reactivity thereby reducing the reaction times and improving the yields substantially. The simple experimental and product isolation procedures combined with ease of recovery and reuse of this novel reaction media is expected to contribute to the development of green process for Petasis boronic–Mannich reaction.

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