J IRAN CHEM SOC
DOI 10.1007/s13738-016-0983-y

ORIGINAL PAPER

A green protocol for the one-pot multicomponent Petasis boronic Mannich reaction using ball milling

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Received: 12 December 2015 / Accepted: 25 September 2016

Abstract Solvent-free reactions of salicylaldehyde with various boronic acids and amines were accomplished under ball-milling conditions to achieve the corresponding alkyl- and arylaminophenols in good to excellent yields. This simple protocol offers advantages such as high yields, shorter reaction times, simple workup procedure and eco-friendliness.

Keywords Ball milling · Petasis boronic Mannich reaction · Amines · Boronic acids · Salicylaldehyde

Introduction

Multicomponent reactions (MCRs) have attracted considerable attention in the organic synthesis as they can produce target products in a single operation without isolating the intermediates and thus reducing the reaction times and energy [1, 2]. Additionally, solvent-free reaction is one of the more promising approaches within the area of organic synthesis for their ability to significantly reduce solvent waste [3–10]. Traditionally, solvent-free reactions have been performed using a mortar and pestle, but recently high-speed ball milling (HSBM) has shown to be a more attractive alternative. Ball milling is a technique that works on the same principles as a mortar and pestle. In addition, its mechanical energy is usually enough to facilitate a chemical reaction. Many reports in the literature have shown that HSBM is effective for various organic transformations and for the development of environmentally benign reactions [11–18].

The Petasis boronic Mannich reaction is one of the most fundamental and important synthetic routes for the preparation of α-amino acids [19, 20], secondary and tertiary amines [21] and heterocycles [22, 23]. The most generally applied aldehydes are glyoxylic acid and hydroxy-substituted benzaldehydes particularly salicylaldehydes [24, 25]. In general, the reaction is carried out well with alkenyl boronic acids and electron-rich or neutral aryl and heteroaryl boronic acids. A wide range of amines including secondary amines and hindered primary amines has been employed for this reaction [26]. Petasis boronic Mannich reactions were often carried out in organic solvents such as dichloromethane [27], methanol, acetonitrile, toluene and dioxane. In some reported reactions, hexafluoroisopropanol [28], ionic liquid [29] and water [30, 31] were applied. There are only two examples describing this synthesis under solvent-free conditions using microwave [32] or conventional heating [33]. However, these procedures required either a long reaction time, heat or organic solvents.

In this research, we report the three-component Petasis boronic Mannich reaction of salicylaldehyde with different boronic acids and aliphatic and aromatic amines using ball milling under solvent-free conditions and at room temperature (Scheme 1).

Experimental

The ball mill was a Retsch PM 100 planetary ball mill. Melting points were determined with an Electrothermal Engineering IA9100 in open capillaries and

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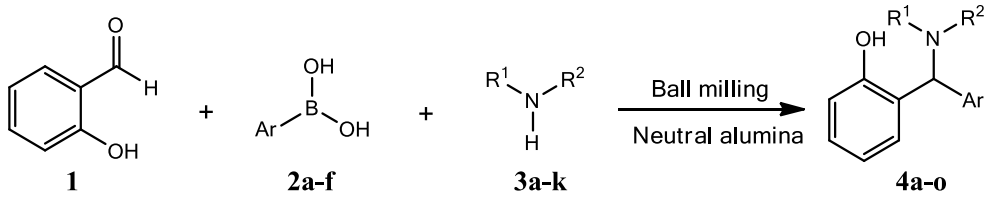
Published online: 04 October 2016



Scheme 1 Preparation of secondary and tertiary aminophenols via Petasis boronic Mannich reaction under ball-milling condition

are uncorrected. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Bruker Ultrashield 400 MHz Avance III spectrometer. The chemical shifts are reported in ppm (δ-scale) relative to TMS, and coupling constants are reported in Hertz (Hz). Mass spectra were obtained at a MSD Agilent 5975C. Elemental analyses were carried out in a CHN Elemental Analyzer LECO 600.

General procedure for the preparation of alkyl- and arylaminophenols (4)

A clean, dry ball-milling vessel was charged with 2 stainless steel grinding balls (10 mm diameter), salicylaldehyde (1 mmol), boronic acid (1 mmol), amine (1 mmol) and neutral alumina (1 gr). The vessel was closed, and the milling was started (milling at 450 rpm). After completion of the reaction, as indicated by TLC, ethyl acetate (2 × 15 mL) was added to the resulting solid mixture. Then, the reaction mixture was filtered and washed with additional ethyl acetate. The combined filtrate and washings were evaporated under reduced pressure to dryness and purified by layer chromatography on silica gel (petroleum ether/ethyl acetate, 9:1). All products were characterized by ^{1}H NMR and ^{13}C NMR spectroscopy. Furthermore, mass spectroscopy was used for new products.

*2-(Morpholino(phenyl)methyl)phenol (**4a**)*

Yield: 92 %; mp: 114–118 °C [33]; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.45–2.49 (m, 2H, 2NCH), 2.62 (br s, 2H, 2NCH), 3.77–3.79 (m, 4H, $2OCH_2$), 4.42 (s, 1H, CH), 6.75 (td, J = 7.4, 1.2 Hz, 1H, Ar), 6.69 (dd, J = 7.6, 1.6 Hz, 1H, Ar), 6.88 (dd, J = 8.4, 1.0 Hz, 1H), 7.14 (ddd, J = 8.4, 7.2, 1.6 Hz, 1H, Ar), 7.25–7.29 (m, 1H, Ar), 7.30–7.34 (m, 2H, Ar), 7.43–7.45 (m, 2H, Ar), 11.74 (s, 1H, OH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 51.7, 66.9, 76.8, 117.0, 119.6, 124.7, 128.1, 128.5, 128.7, 128.9, 129.4, 137.3, 157.7, ppm.

*2-(Phenyl(piperidin-1-yl)methyl)phenol (**4b**)*

Yield: 88 %; mp: 85–88 °C [33]; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.49 (br s, 2H, CH_2), 1.64–1.68 (m, 4H, $2CH_2$), 2.43 (br s, 4H, $2NCH_2$), 4.49 (s, 1H, CH), 6.71 (td, J = 7.2, 1.2 Hz, 1H, Ar), 6.87 (dd, J = 8.0, 1.2 Hz, 1H, Ar), 6.90 (dd, J = 7.6, 1.6 Hz, 1H, Ar), 7.10–7.15 (m, 1H, Ar), 7.26–7.29 (m, 1H, Ar), 7.31–7.35 (m, 2H, Ar), 7.41 (br s, 2H, Ar), 12.60 (br s, 1H, OH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.1, 26.1, 52.5, 76.5, 116.8, 119.0, 125.5, 127.8, 128.3, 128.7, 128.8, 129.2, 139.4, 157.1 ppm.

*2,2′-(Piperazine-1,4-diylbis(phenylmethylene))diphenol (**4c**)*

Yield: 96 %; mp: 270–275 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.34 (br s, 2H, 2NCH), 2.57 (br s, 4H, 4NCH), 3.14 (br s, 2H, 2NCH), 4.44 (s, 1H, CH), 4.74 (s, 1H, CH), 6.71 (td, J = 3.6, 1.2 Hz, 1H, Ar), 6.73 (td, J = 3.6, 1.2 Hz, 1H, Ar), 6.83 (dd, J = 4.2, 1.0 Hz, 1H, Ar), 6.85 (dd, J = 4.2, 1.0 Hz, 1H, Ar), 6.92 (d, J = 1.6 Hz, 1H, Ar), 6.94 (d, J = 1.6 Hz, 1H, Ar), 7.09–7.11 (m, 1H, Ar), 7.12–7.14 (m, 1H, Ar), 7.24–7.26 (m, 2H, Ar), 7.27–7.28 (m, 2H, Ar), 7.30–7.32 (m, 2H, Ar), 7.37–7.41 (m, 4H, Ar), 11.68 (s, 1H, Ar), 11.70 (s, 1H, OH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 50.3, 50.7, 76.0, 76.1, 116.9, 119.5, 119.6, 124.7, 124.8, 128.1, 128.2, 128.5, 128.6, 128.7, 128.8, 128.9, 129.3, 139.0, 139.2, 156.1, 156.2 ppm. MS: *m/z* 450.2 (M^+). Anal. Calcd for $C_{30}H_{30}N_2O_2$ (450.57): C, 79.97; H, 6.71; N, 6.22. Found: C, 79.92; H, 6.75; N, 6.16.

*2-((Dibenzylamino)(phenyl)methyl)phenol (**4d**)*

Yield: 93 %; mp: 122–126 °C [33]; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.43 (d, J = 13.4 Hz, 2H, 2NCHPh), 3.97 (d, J = 13.4 Hz, 2H, 2NCHPh), 5.16 (s, 1H, CH), 6.73 (td, J = 7.4, 1.2 Hz, 1H, Ar), 6.83 (d, J = 7.2 Hz, 1H, Ar), 6.96 (dd, J = 8.0, 1.2 Hz, 1H, Ar), 7.17–7.21 (m, 1H, Ar), 7.29–7.32 (m, 6H, Ar), 7.35–7.39 (m, 4H, Ar), 7.41–7.46 (m, 5H, Ar), 12.30 (s, 1H, OH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 53.8, 68.3, 116.7, 119.0, 124.5, 127.6, 128.2, 128.5, 128.6, 128.8, 129.6, 129.8, 130.6, 135.7, 136.9, 157.5 ppm.

*2-((Benzyl(methyl)amino)(phenyl)methyl)phenol (**4e**)*

Yield: 90 %; mp: 80–83 °C [33]; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.21 (s, 3H, CH_3), 3.60 (br s, 2H, CH_2), 4.75

(s, 1H, CH), 6.77 (td, $J = 7.4$, 1.2 Hz, 1H, Ar), 6.96 (td, $J = 7.8$, 1.2 Hz, 2H, Ar), 7.16–7.21 (m, 1H, Ar), 7.29–7.42 (m, 8H, Ar), 7.53 (d, $J = 7.2$ Hz, 2H, Ar), 12.39 (br s, 1H, OH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 39.1$, 59.6, 75.5, 116.9, 119.2, 125.4, 127.5, 128.1, 128.6, 128.7, 128.8, 129.0, 129.1, 129.3, 137.2, 138.8, 156.9 ppm.

*2-((Benzylamino)(phenyl)methyl)phenol (**4f**)*

Yield: 82 %; mp: 67–71 °C [34]; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.40$ (br s, 1H, NH), 4.64 (d, $J = 15.6$ Hz, 1H, NCHPh), 4.92 (d, $J = 15.6$ Hz, 1H, NCHPh), 5.32 (s, 1H, CH), 6.97 (td, $J = 7.6$, 1.8 Hz, 1H, Ar), 7.09 (d, $J = 6.8$ Hz, 2H, Ar), 7.22–7.26 (m, 1H, Ar), 7.35–7.44 (m, 8H, Ar), 7.53 (d, $J = 7.2$ Hz, 2H, Ar), 12.52 (br s, 1H, OH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 55.3$, 63.2, 117.7, 119.6, 126.7, 128.6, 128.7, 128.8, 128.9, 129.2, 129.3, 130.0, 131.2, 137.6, 138.1, 159.7 ppm.

*2-(Morpholino(m-tolyl)methyl)phenol (**4g**)*

Yield: 90 %; mp: 119–121 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.36$ (s, 3H), 2.47–2.51 (m, 2H, 2NCH), 2.64 (br s, 2H, 2NCH), 3.78–3.79 (m, 4H, $2OCH_2$), 4.41 (s, 1H, CH), 6.76 (td, $J = 7.4$, 1.0 Hz, 1H, Ar), 6.90 (dd, $J = 8.0$, 1.2 Hz, 1H, Ar), 6.99 (dd, $J = 7.6$, 1.6 Hz, 1H, Ar), 7.10 (d, $J = 7.2$ Hz, 1H, Ar), 7.13–7.18 (m, 1H, Ar), 7.22 (t, $J = 7.6$ Hz, 1H, Ar), 7.27 (br s, 2H, Ar), 11.80 (s, 1H, OH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 21.6$, 52.3, 66.9, 76.9, 117.0, 119.6, 124.9, 125.5, 128.6, 128.8, 128.9, 129.1, 129.4, 138.6, 139.3, 156.1 ppm.

*2-((4-(Tert-butyl)phenyl)(morpholino)methyl)phenol (**4h**)*

Yield: 94 %; mp: 130–135 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.29$ (s, 9H, $3CH_3$), 2.53 (br s, 2H, 2NCH), 2.64 (br s, 2H, 2NCH), 3.80 (br s, 4H, $2OCH_2$), 4.45 (s, 1H, CH), 6.75 (t, $J = 3.0$ Hz, 1H, Ar), 6.89 (d, $J = 8.0$ Hz, 1H, Ar), 7.01 (d, $J = 7.2$ Hz, 1H, Ar), 7.15 (t, $J = 7.2$ Hz, 1H, Ar), 7.33 (d, $J = 8.0$ Hz, 2H, Ar), 7.37 (d, $J = 8.0$ Hz, 2H, Ar), 8.74 (br s, 1H, OH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 31.2$, 34.5, 52.2, 66.7, 76.3, 116.9, 119.6, 124.7, 125.8, 128.2, 128.6, 129.4, 135.7, 151.1, 156.0 ppm; MS: *m/z* 325.2 (M^+). Anal. Calcd for $C_{21}H_{27}NO_2$ (325.44): C, 77.50; H, 8.36; N, 4.30. Found: C, 77.54; H, 8.31; N, 4.23.

*2-((4-Methoxyphenyl)(morpholino)methyl)phenol (**4i**)*

Yield: 97 %; mp: 103–107 °C [33]; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.45$–2.47 (m, 2H, 2NCH), 2.61 (br s, 2H, 2NCH), 3.79 (s, 3H, OCH_3), 3.80–3.81 (m, 4H, $2OCH_2$), 4.39 (s, 1H, CH), 6.74 (td, $J = 7.4$, 1.2 Hz, 1H, Ar), 6.84–6.89 (m, 3H, Ar), 6.95 (dd, $J = 7.6$, 1.6 Hz, 1H, Ar), 7.14 (ddd, $J = 8.0$, 7.6, 1.6 Hz, 1H, Ar), 7.35 (d, $J = 8.0$ Hz, 2H, Ar), 11.80 (s, 1H, OH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 52.1$, 55.2, 66.9, 76.0, 114.2, 116.9, 119.5, 125.1, 128.5, 129.3, 129.7, 131.3, 156.0, 159.3 ppm.

*2-((6-Methoxynaphthalen-2-yl)(morpholino)methyl)phenol (**4j**)*

Yield: 96 %; mp: 115–120 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.48$–2.52 (m, 2H, 2NCH), 2.66 (br s, 2H, 2NCH), 3.77–3.79 (m, 4H, $2OCH_2$), 3.91 (s, 3H, OCH_3), 4.56 (s, 1H, CH), 6.75 (td, $J = 7.4$, 1.0 Hz, 1H, Ar), 6.92 (dd, $J = 8.2$, 1.0 Hz, 1H, Ar), 7.01 (dd, $J = 7.6$, 1.6 Hz, 1H, Ar), 7.11 (d, $J = 2.4$ Hz, 1H, Ar), 7.13–7.18 (m, 2H, Ar), 7.60 (d, $J = 8.0$ Hz, 1H, Ar), 7.70 (d, $J = 8.8$ Hz, 1H, Ar), 7.74 (d, $J = 9.2$ Hz, 1H, Ar), 7.77 (br s, 1H, Ar), 11.92 (br s, 1H, OH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 52.3$, 55.3, 66.9, 76.9, 105.6, 117.0, 119.1, 119.6, 124.8, 126.4, 127.5, 127.8, 128.6, 128.7, 129.4, 129.5, 134.2, 134.5, 156.1158.0 ppm; MS: *m/z* 349.1 (M^+). Anal. Calcd for $C_{22}H_{23}NO_3$ (349.42): C, 75.62; H, 6.63; N, 4.01. Found: C, 75.55; H, 6.69; N, 4.07.

*2-((4-Chlorophenyl)(morpholino)methyl)phenol (**4k**)*

Yield: 70 %: mp: 109–112 °C [35]; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.42$–2.45 (m, 2H, 2NCH), 2.58 (br s, 2H, 2NCH), 3.74–3.80 (m, 4H, $2OCH_2$), 4.38 (s, 1H, CH), 6.74 (td, $J = 7.4$, 1.2 Hz, 1H, Ar), 6.87–6.94 (m, 2H, Ar), 7.14 (ddd, $J = 8.0$, 7.6, 1.6 Hz, 1H, Ar), 7.28 (d, $J = 8.4$ Hz, 2H, Ar), 7.38 (d, $J = 8.4$ Hz, 2H, Ar), 11.55 (br s, 1H, OH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 52.1$, 66.7, 76.0, 117.1, 119.7, 124.3, 128.8, 129.0, 129.1, 129.7, 133.8, 137.8, 155.8 ppm.

*2-(Phenyl(phenylamino)methyl)phenol (**4l**)*

Yield: 10 %; Oil; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 4.31$ (br s, 1H, NH), 5.59 (s, 1H, CH), 6.80–6.83 (m, 1H, Ar), 6.85 (td, $J = 7.4$, 1.2 Hz, 1H, Ar), 6.89–6.93 (m, 2H, Ar), 6.98 (dd, $J = 8.0$, 1.6 Hz, 1H, Ar),7.18–7.24 (m, 3H, Ar), 7.30–7.36 (m, 3H, Ar), 7.37–7.41 (m, 3H, Ar), 9.37 (br s, 1H, OH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 72.8$, 114.2, 114.8, 117.1, 118.3, 119.6, 123.9, 127.3, 130.0, 130.3, 130.6, 131.0, 135.2, 154.1, 160.5 ppm.

*4-(((2-Hydroxyphenyl)(phenyl)methyl)amino)benzonitrile (**4m**)*

Yield: 87 %; mp: 84–89 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 4.68$ (br s, 1H, NH) 5.63 (s, 1H, CH), 6.99 (td, $J = 7.5$, 0.9 Hz, 1H, Ar), 7.09–7.11 (m, 1H, Ar), 7.36–7.40 (m, 2H, Ar), 7.43–7.49 (m, 2H, Ar), 7.51–7.55 (m, 1H, Ar),

7.61–7.63 (m, 1H, Ar), 7.66–7.70 (m, 1H, Ar), 7.75 (dd, $J = 7.8$, 1.4 Hz, 2H, Ar), 8.26–8.28 (m, 2H, Ar), 12.52 (s, 1H, OH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 82.2$, 108.6, 116.9, 117.8, 119.3, 126.8, 127.9, 132.6, 133.0, 133.3, 133.8, 134.5, 135.6, 151.2, 161.5, 165.1 ppm. MS: *m/z* 300.1 (M^+). Anal. Calcd for $C_{20}H_{16}N_2O$: C, 79.98; H, 5.37; N, 9.33. Found: C, 79.93; H, 5.34; N, 9.39.

*2-((4-Methoxyphenyl)(phenylamino)methyl)phenol (**4n**)*

Yield: 83 %; mp: 77–81 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.82$ (s, 3H, OCH_3), 4.33 (br s, 1H, NH), 5.57 (s, 1H, CH), 6.82 (d, $J = 7.6$ Hz, 2H, Ar), 6.86–6.95 (m, 5H, Ar), 7.02 (d, $J = 6.8$ Hz, 1H, Ar),7.20–7.25 (m, 3H, Ar), 7.33 (d, $J = 8.4$ Hz, 2H, Ar), 9.51 (br s, 1H, OH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 55.3$, 63.6, 114.4, 116.2, 117.2, 120.2, 120.9, 126.1, 128.6, 128.8, 128.9, 129.3, 133.5, 146.5, 156.4, 159.3 ppm. MS: *m/z* 305.1 (M^+). Anal. Calcd for $C_{20}H_{19}NO_2$: C, 78.66; H, 6.27; N, 4.59. Found: C, 78.60; H, 6.34; N, 4.52.

*2-((4-Methoxyphenyl)((4-nitrophenyl)amino)methyl)phenol (**4o**)*

Yield: 90 %; mp: 150–155 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.50$ (s, 3H, OCH_3), 4.43 (br s, 1H, NH), 5.59 (s, 1H, CH), 7.01 (td, $J = 7.3$, 0.9 Hz, 1H, Ar), 7.08 (d, $J = 8.0$ Hz, 1H, Ar), 7.37–7.41 (m, 2H, Ar), 7.45–7.79 (m, 2H, Ar), 8.09–8.11 (m, 1H, Ar), 8.31–8.35 (m, 2H, Ar), 8.41–8.43 (m, 1H, Ar), 8.54 (d, $J = 8.4$ Hz, 2H, Ar), 12.57 (br s, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 55.3$, 63.6, 117.5, 118.7, 119.5, 121.8, 124.3, 125.2, 130.4, 133.0, 134.5, 139.5, 146.1, 154.2, 161.3, 165.3. MS: *m/z* 349.0 (M^+). Anal. Calcd for $C_{20}H_{18}N_2O_4$: C, 68.56; H, 5.18; N, 8.00. Found: C, 68.51; H, 5.12; N, 7.94.

*5-Methoxy-2-(morpholino(phenyl)methyl)phenol (**4p**)*

Yield: 88 %; mp: 122–124 °C [33]; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.42$–2.60 (m, 4H, $2NCH_2$), 3.73–3.79 (m, 7H, $2OCH_2$, OCH_3), 4.38 (s, 1H, CH), 6.30 (dd, $J = 8.6$, 2.8 Hz, 1H, Ar), 6.43 (d, $J = 2.8$ Hz, 1H, Ar), 6.82 (d, $J = 8.4$ Hz, 1H, Ar), 7.25 (t, $J = 3.4$ Hz, 1H, Ar), 7.30 (t, $J = 7.4$ Hz, 2H, Ar), 7.39 (d, $J = 6.8$ Hz, 2H, Ar), 11.85 (s, 1H, OH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 52.1$, 55.2, 66.9, 76.2, 102.2, 105.9, 117.2, 128.0, 128.5, 128.9, 130.0, 139.5, 157.3, 160.3 ppm.

*2-(Morpholino(phenyl)methyl)-4-nitro-phenol (**4q**)*

Yield: 83 %; mp: 56–58 °C [39]; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.46$–2.61 (m, 4H, $2NCH_2$), 3.77 (br s, 4H, $2OCH_2$), 4.55 (s, 1H, CH), 6.91 (d, $J = 8.8$ Hz, 1H, Ar), 7.31–7.39 (m, 5H, Ar), 7.90 (d, $J = 2.6$ Hz, 1H, Ar), 8.04 (dd, $J = 8.9$, 2.8 Hz, 1H, Ar), 13.24 (br s, 1H, OH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 52.0$, 66.9, 76.3, 117.8, 125.3, 125.4, 126.0, 128.7, 129.1, 129.5, 137.6, 140.7, 163.2 ppm.

Results and discussion

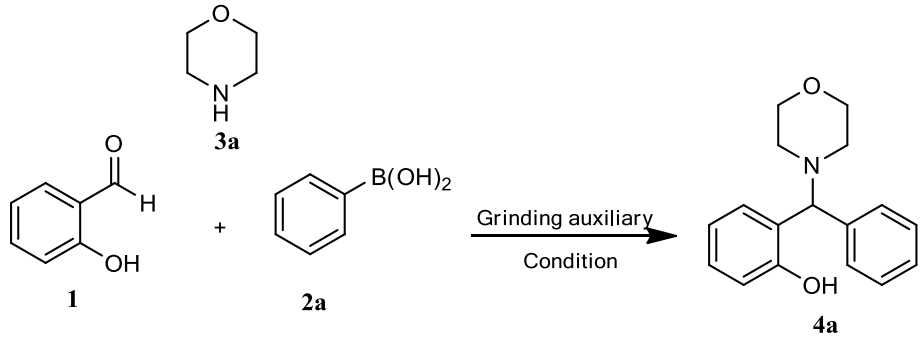
In order to find optimized reaction conditions, the reaction of salicylaldehyde (1 mmol) with phenylboronic acid (1 mmol) and morpholine (1 mmol) was selected as the model reaction. Initially, several milling (grinding) auxiliaries were used in the milling vessels to enable work with small batch sizes. Of these grinding auxiliaries, neutral alumina appears to give the best result (Table 1, entry 1). Using β-Al_2O_3, γ-Al_2O_3 and wet silica gave very low yields of the product (Table 1, entries 2–3 and 6). Silica gel, TiO_2–silica and TiO_2–alumina were also employed in the model reaction as grinding auxiliary, and the product **4a** was formed in 37, 42 and 46 %, respectively (Table 1, entries 4–5 and 7).

After choosing the best grinding auxiliary, to optimize milling speed, various milling speeds from 150 to 550 rpm were investigated. As given in Table 1, increasing the milling speed resulted in increasing the yield of reaction (Table 1, entries 1 and 8–11). It is obvious that the use of higher milling speed results in a significantly higher kinetic energy. Higher kinetic energy, in turn, delivers more energy to the reaction mixture which facilitates the chemical conversion and intense mixing. However, the results showed that 450 rpm was enough to perform good yield of the product.

In order to explore the role of ball milling in this reaction, the model reaction was carried out under solvent-free condition using a mortar and pestle (Table 1, entries 12–14). At room temperature, only a trace amount of the product was formed. A moderate yield was obtained, when the reaction was carried out at 80 °C. These results indicate that the conversion of this reaction is affected by intense mixing of the reactants (ball mill vs. mortar), temperature and milling auxiliary.

After finding the optimized reaction conditions, the scope and generality of this method were further explored with different substrates. As given in Table 2, we initially investigated the reaction of salicylaldehyde and phenylboronic acid with primary and secondary aliphatic amines under optimum conditions which afforded the corresponding products in good to excellent yields (Table 2, entries 1–6). Next, to test the effect of the electronic nature of the substituents, several boronic acids were reacted with salicylaldehyde and morpholine (Table 2, entries 7–11). The results showed that boronic acids bearing more

Table 1 Optimization of reaction conditions for the synthesis of **4a**



Entry	Grinding auxiliary	Milling speed (rpm)	Temperature (°C)	Yield (%)[a]
1	α-Al_2O_3 (neutral)	450	rt	48
2	β-Al_2O_3 (acidic)	450	rt	11
3	γ-Al_2O_3 (basic)	450	rt	Trace
4	TiO_2–Al_2O_3 (1:1)	450	rt	46
5	Silica gel	450	rt	37
6	Wet silica	450	rt	25
7	TiO_2–silica (1:1)	450	rt	42
8	α-Al_2O_3 (neutral)	150	rt	16
9	α-Al_2O_3 (neutral)	250	rt	23
10	α-Al_2O_3 (neutral)	350	rt	42
11	α-Al_2O_3 (neutral)	550	rt	49
12	α-Al_2O_3 (neutral)	–	rt	Trace[b]
13	α-Al_2O_3 (neutral)	–	80	40[b]
14	–	–	80	20[b]

Reaction condition: salicylaldehyde (1 mmol), phenylboronic acid (1 mmol), morpholine (1 mmol), grinding auxiliary (1 gr), 15 min

[a] Isolated yield

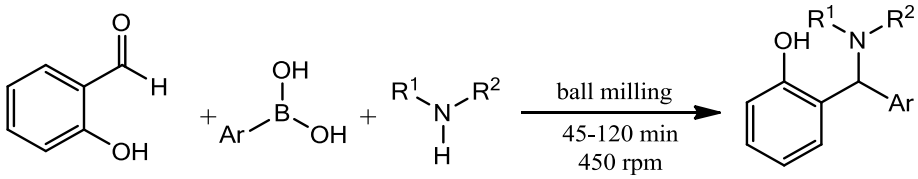
[b] Using mortar and pestle instead of ball mill

electron-donating groups gave higher yields of the corresponding products (Table 2, entries 9–10).

The promising results described above prompted us to test this method on aniline derivatives (Table 2, entries 12–17). To the best of our knowledge, there are no previous reports in the literature about the synthesis of these products through Petasis boronic Mannich reaction. However, the desired products can be obtained via palladium-catalyzed addition of aryl aldehydes with aryl amines and arylboronic acids [36] or via phosphoric acid-catalyzed reduction in *N*-aryl-*ortho*-hydroxybenzophenone ketimines [37]. The reaction of aniline with salicylaldehyde and phenylboronic acid gave only a low yield of the desired product (entry 12). By choosing appropriate reactants, we were able to increase the yield of the reaction. Electron-withdrawing substituted anilines such as 4-cyanoaniline and 4-nitroaniline, which forms more reactive imine intermediate, gave higher yields of the expected products (Table 2, entries 13 and 15). The introduction of a 4-methoxy substituent on the phenylboronic acid, which is known to increase the migrating ability of the aryl substituent [30, 31], afforded also a very good yields of the corresponding products (Table 2, entry 14). In the case of electron-donating substituted anilines such as *p*-anisidine, the formation of imines was observed (Table 2, entry 16), but the aryl migration from the boronic acid to the imine was not observed [38]. Due to the low nucleophilicity of diphenylamine, reactants remained untouched and neither imine nor desired product were formed (Table 2, entry 17). These results are in accordance with the proposed mechanism [31], which consists in the formation of an imine after condensation of salicylaldehyde with a primary amine. After formation a quaternary boronate salt, the boron substituent will be transfer to the imine moiety to yield the secondary amine (Scheme 2).

Furthermore, to test the effect of the substituents on the salicylaldehyde, 4-methoxy and 5-nitro salicylaldehydes

Table 2 Reaction of salicylaldehyde with various boronic acids and amines[a]



1 **2a-f** **3a-k** **4a-o**

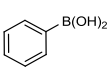
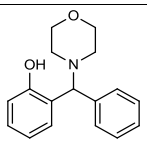
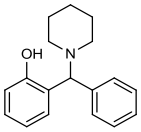
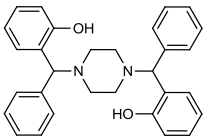
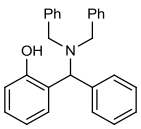
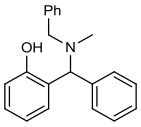
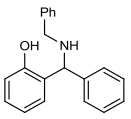
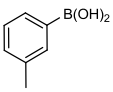
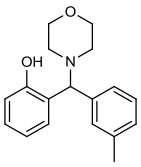
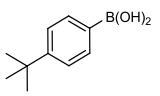
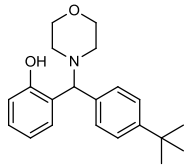
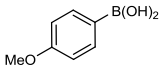
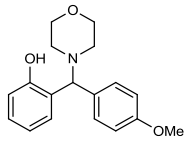
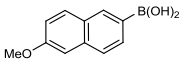
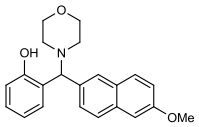
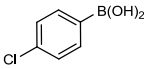
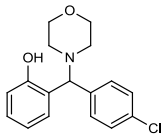
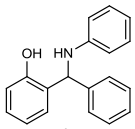
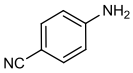
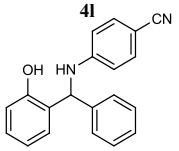
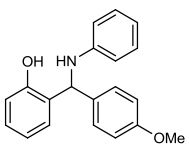
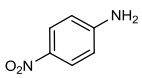
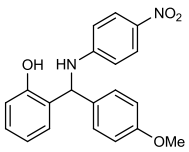
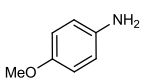
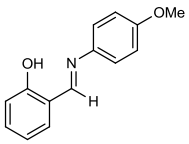
Entry	Boronic acid	Amine	Product	Time (min)	Yield (%)[b]
1	 **2a**	 **3a**	 **4a**	105	92
2	**2a**	 **3b**	 **4b**	105	88
3	**2a**	 **3c**	 **4c**	45	96[c]
4	**2a**	 **3d**	 **4d**	105	93
5	**2a**	 **3e**	 **4e**	120	90
6	**2a**	 **3f**	 **4f**	120	82
7	 **2b**	**3a**	 **4g**	90	90

Table 2 continued

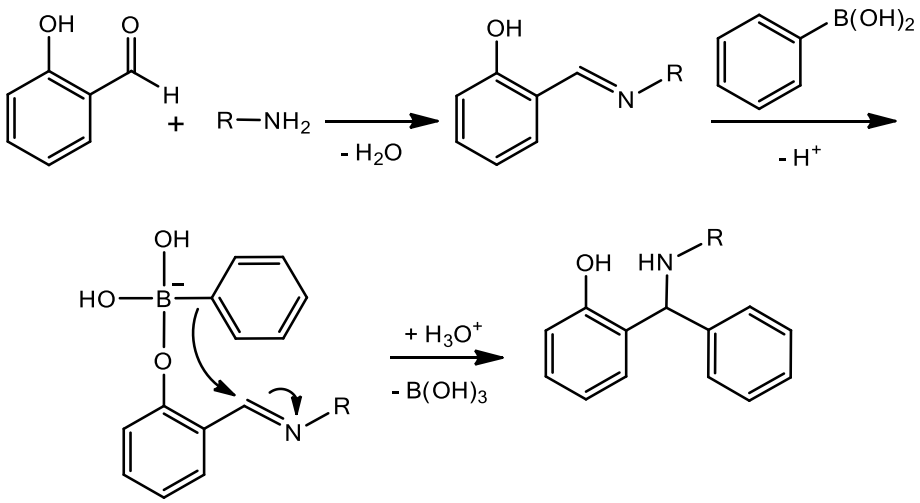
8	 **2c**	**3a**	 **4h**	90	94
9	 **2d**	**3a**	 **4i**	45	97
10	 **2e**	**3a**	 **4j**	60	96
11	 **2f**	**3a**	 **4k**	120	70
12	**2a**	 **3h**	 **4l**	150	10
13	**2a**	 **3i**	 **4m**	120	87
14	**2d**	**3h**	 **4n**	120	83
15	**2d**	 **3j**	 **4o**	105	90
16	**2a**	 **3k**		Imine	
17	**2a**	 **3g**	--	No Reaction	

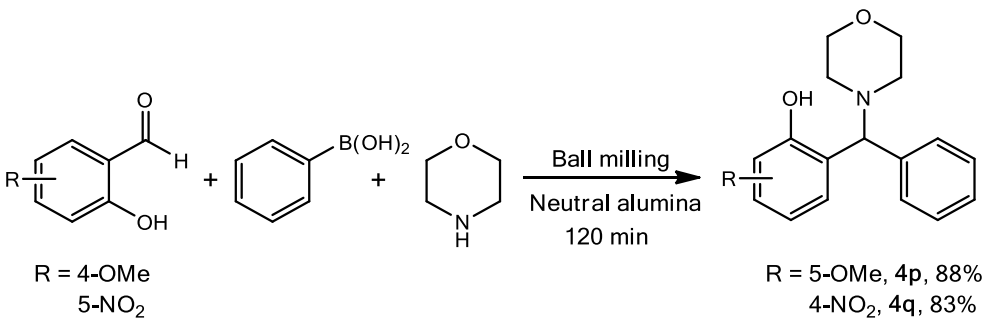
[a] Reaction condition: salicylaldehyde (1 mmol), arylboronic acid (1 mmol), amine (1 mmol), neutral alumina (1 gr), 450 rpm

[b] Isolated yield

[c] Salicylaldehyde (2 mmol), phenylboronic acid (2 mmol), piperazine (1 mmol), neutral alumina (2 gr)

Scheme 2 Mechanism of Petasis boronic Mannich reaction with primary amines





Scheme 3 Reaction of salicylaldehyde derivatives with phenylboronic acid and morpholine using ball milling

were chosen to react with phenylboronic acid and morpholine under ball-milling conditions (Scheme 3). The desired products were obtained in high yields and the substituents had almost no observable influence on the reaction outcome as reported by others [40].

Conclusion

In summary, we have reported a green, efficient and improved three-component reaction for the Petasis boronic Mannich synthesis of secondary and tertiary aminophenols under ball-milling condition. The main advantages of this procedure include high yields, short reaction times, use of various substrates including aniline derivatives, ease of the workup, which make it a useful, attractive and green strategy for the preparation of alkyl and arylaminophenols. Efforts to expand the utility of this method to other Petasis reactions are in progress in our laboratory.

Acknowledgments We gratefully acknowledge the University of Mazandaran for financial support of this work.

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