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Tributylhexadecylphosphonium bromide: an efficient reagent system for the one-pot synthesis of 2,4,5-trisubstituted imidazoles

Abstract: The reaction of benzil, an aromatic aldehyde, and ammonium acetate in ethanol at reflux in the presence of tributylhexadecylphosphonium bromide as catalyst affords a 2,4,5-trisubstituted imidazole. The present methodology offers several advantages over the literature methods, including excellent yields, shorter reaction times, environmentally benign milder reaction conditions, cost-effectiveness of catalyst, easy workup, and purification of products by nonchromatographic methods.

Keywords: 2,4,5-trisubstituted imidazoles; aldehyde; benzil; homogeneous catalysis; one-pot synthesis.

DOI 10.1515/hc-2014-0182
Received October 11, 2014; accepted February 2, 2015; previously published online March 26, 2015

Introduction

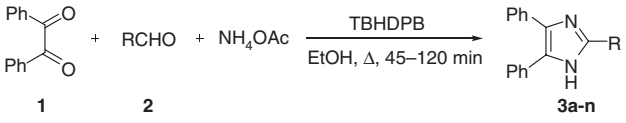
Multicomponent reactions (MCRs) are very important and useful processes in organic synthesis, especially in medicinal and heterocyclic chemistry. In these simple and efficient processes that demonstrate high atom economy and simple procedures [1, 2], usually three or more reactants are mixed together in a simple vessel to produce new compounds that contain portions of all the components. The use of MCRs for synthesis of imidazole and its derivatives has attracted much interest [3–5]. Many derivatives of imidazole are known as fungicides and herbicides, inhibitors of p38 MPA kinase, light-sensitive materials in photography, modular of glucagon receptors, plant growth regulators, and therapeutic agents [6–10].

Imidazole derivatives are most generally prepared by ring construction. One synthetic methodology reported in literature involves ring formation by condensation of an aldehyde, ammonium acetate, and a 1,2-diketone in the presence of a catalyst such as silica sulfuric acid, $InCl_3$, Al_2O_3, acetic acid, $ZrCl_4$ or $NiCl_2$ [9–12]. Other methods, especially for the synthesis of 2,4,5-trisubstituted imidazoles, may involve the use of ionic liquids [13–15]. Most existing methods, however, suffer from several drawbacks, including low yields, formation of by-products, laborious and complex workup, tedious purification, and the use of strong acidic conditions. In this report, we describe a new method that produces a variety of 2,4,5-trisubstituted imidazoles unambiguously, under mild conditions and in good yields.

Results and discussion

In the preliminary experiments, the condensation of benzil (**1**, 1 mmol), ammonium acetate (2 mmol), and benzaldehyde (**2a**, 1 mmol) in the absence of a catalyst in ethanol at ambient temperature and under reflux conditions was attempted. These experiments produced no expected imidazole product **3a** (Scheme 1).

In the presence of 5 mol% of tributylhexadecylphosphonium bromide (TBHDPB) in the absence of any solvent



1 **2** **3a-n**

3a: R = Ph
3b: R = 4-Me-C_6H_4
3c: R = 4-Me_2N-C_6H_4
3d: R = 4-MeO-C_6H_4
3e: R = 3,4-diMeO-C_6H_3
3f: R = 4-HO-C_6H_4
3g: R = 3-HO-C_6H_4
3h: R = 4-Cl-C_6H_4
3i: R = 2-Cl-C_6H_4
3j: R = 4-Br-C_6H_4
3k: R = 4-O_2N-C_6H_4
3l: R = 3-O_2N-C_6H_4
3m: R = Et
3n: R = Me

Scheme 1:

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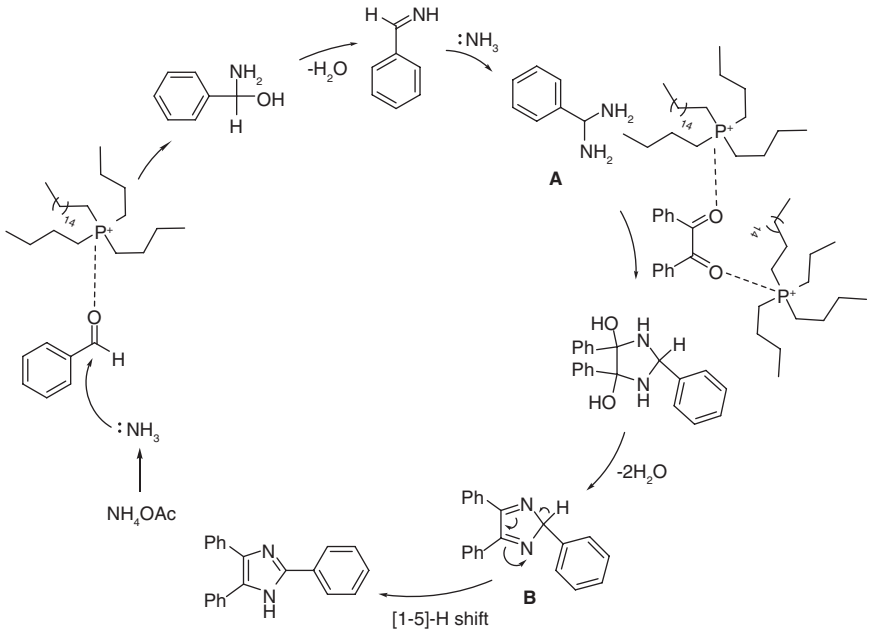

Scheme 2: A plausible mechanism for the formation of 2,4,5 trisubstituted imidazole.

at 60°C after 3 h of heating, the reaction produced compound **3a** in 30% yield. Then the reaction was conducted with varying amounts of the catalyst and in various solvents. Under optimal conditions, the reaction was conducted in ethanol under reflux conditions for 1 h and gave 85% of the desired product **3a**. The remaining products of Scheme 1 were obtained under these optimized conditions. The reaction tolerates electron-donating groups on the aromatic aldehyde to give products **3** in excellent yields. Only good yields are obtained for nitro-substituted benzaldehydes, and even lower yields are observed for aliphatic aldehydes.

A mechanism for the catalytic activity of TBHDPB in the synthesis of trisubstituted imidazole is postulated in Scheme 2. It is suggested that the TBHDPB catalyst facilitates the formation of diamine intermediate **A** by increasing the electrophilicity of the carbonyl group of the aldehyde. Condensation of intermediate product **A** with benzil followed by elimination of water leads to conjugate intermediate **B**, which in turn undergoes rearrangement to the trisubstituted imidazole by a [1, 5] hydrogen shift.

Conclusion

This report describes a simple and efficient one-pot multicomponent methodology for the synthesis of 2,4,5-trisubstituted imidazoles catalyzed by 10 mol% TBHDPB. The availability of the reagent, easy workup, and good yield of the products make the method attractive for the synthesis of various 2,4,5-trisubstituted imidazoles.

Experimental

All products were characterized by comparison of their physical and spectral data (mp, ^{1}H NMR and IR) with those of authentic samples. Melting points were determined in open glass capillaries on a Mettler FP51 melting point apparatus and are uncorrected. The progress of the reactions was followed by thin-layer chromatography (TLC) analysis using silica gel SILG/UV 254 plates.

General procedure for the synthesis of 2,4,5-trisubstituted imidazoles 3a-n

A mixture of benzil (1 mmol), TBHDPB (0.051 g, 0.1 mmol, 10 mol%), and aldehyde (1 mmol) and ammonium acetate (2 mmol) in ethanol (10 mL) was stirred under reflux for 45–120 min. After the completion of reaction, as monitored by TLC analysis, the mixture was cooled to room temperature, diluted with water, and extracted with ethyl acetate. Organic layer was dried over anhydrous $MgSO_4$, and then solvent was removed under reduced pressure. Crude product was washed with *n*-hexane and crystallized from ethanol to obtain the pure product in 30–98% yield.

2,4,5-Triphenyl-1*H*-imidazole (1a) Reaction time 1 h; pale yellow powder; yield 85%; mp 268–270°C (mp 267–269°C) [16].

4,5-Diphenyl-2-p-tolyl-1*H*-imidazole (1b) Reaction time 45 min; white powder; yield 89%; mp 232–234°C (mp 233–235°C) [16].

[4-(4,5-Diphenyl-1*H*-imidazol-2-yl)phenyl]dimethylamine (1c) Reaction time 45 min; pale yellow powder; yield 92%; mp 257–259°C (mp 256–259°C) [16].

2-(4-Methoxyphenyl)-4,5-diphenyl-1*H*-imidazole (1d) Reaction time 45 min; pale yellow powder; yield 98%; mp 230–231°C (mp, 231–233°C) [17].

2-(3,4-Dimethoxyphenyl)-4,5-diphenylimidazole (1e) Reaction time 45 min; pale yellow powder; yield 96%; mp 140–142°C (mp 142°C) [18].

4-(4,5-Diphenyl-1*H*-imidazol-2-yl)phenol (1f) Reaction time 50 min; pale yellow powder, yield 94%; mp 231–233°C (mp 233–235°C) [19].

3-(4,5-Diphenyl-1*H*-imidazol-2-yl)phenol (1g) Reaction time 50 min; pale yellow powder; yield 92%; mp 260–261°C (mp 259°C) [18].

2-(4-Chlorophenyl)-4,5-diphenyl-1*H*-imidazole (1h) Reaction time 75 min; white powder; yield 75%; mp 261–263°C (mp 262–264°C) [20].

2-(2-Chlorophenyl)-4,5-diphenyl-1*H*-imidazole (1i) Reaction time 75 min; white powder; yield 78%; mp 188–190°C (mp 192°C) [18].

2-(4-Bromophenyl)-4,5-diphenyl-1*H*-imidazole (1j) Reaction time 75 min; white powder; yield 79%; mp 189–191°C (mp 190–193°C) [19].

2-(4-Nitrophenyl)-1,4,5-triphenyl-1*H*-imidazole (1k) Reaction time 90 min; bright yellow powder; mp 198–199°C (mp 197–198°C) [19].

2-(3-Nitrophenyl)-1,4,5-triphenyl-1*H*-imidazole (1l) Reaction time 85 min; bright yellow powder; yield 57%; mp 300–301°C (mp 298–303°C) [19].

2-Ethyl-4,5-diphenyl-1*H*-imidazole (1m) Reaction time 2 h; white powder; yield 35%; mp 222–224°C (mp 223–224°C) [21].

2-Methyl-4,5-diphenyl-1*H*-imidazole (1n) Reaction time 2 h; white powder; yield 30%; mp 238–240°C (mp 240–241°C) [16].

Acknowledgments: We are thankful to Islamic Azad University, Ahvaz Branch Research Council.

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