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ORIGINAL PAPER

Copper-catalysed synthesis of 3,5-disubstituted isoxazoles enabled by pyridinyl benzimidazol (PBI) as a bidentate *N*-chelating ligand under mild conditions

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Abstract
In this paper, we introduced pyridinyl benzimidazol (PBI) as an easy-to-handle and bidentate *N*-chelating ligand that promote clean synthesis of 3,5-disubstituted isoxazoles in the presence of copper acetate as catalyst. This catalytic approach initiates with the hydroxyamination of aldehydes followed by chlorination and then generation of nitrile oxide which subsequently undergoes click-type [3 + 2]-dipolar cycloaddition with alkynes to give isoxazoles. This method provides an alternative green process to construct isoxazole derivatives.

Keywords Isoxazole derivatives · Pyridinyl benzimidazol (PBI) · Bidentate ligand · Cycloaddition reaction

Introduction

Design and efficient synthesis of biologically active molecules have emerged as a tremendous challenge in medicinal chemistry.

Heterocyclic compounds are frequently found in natural products and functional material. Among the several heterocycles, isoxazole derivatives are attractive frameworks that present in many bioactive compounds including anti-infective, antitumor, cardiovascular [1–3], antituberculosis [4], anti-inflammatory [5], antibacterial [6], anti-HIV [7], anticancer [8] and nervous system agents [1–3].

They are also core structures of some pesticides and insecticides that have agrochemical properties including herbicidal and soil fungicidal activity [9].

Isoxazoles are also indispensable as they participate as intermediates in the synthesis of numerous natural products [10, 11].

Regarding their prevalence, numerous research studies have been carried out on the synthesis of isoxazoles and their derivatives [12, 13].

The main strategy that has been employed generally to prepare isoxazole derivatives is the [3 + 2] dipolar cycloaddition of alkenes or alkynes with nitrile oxides [14–17].

The nitrile oxide 1,3-dipole is generated in situ from the corresponding primary nitroalkanes [18, 19] and hydroximoyl chlorides [20].

The reactions of hydroxylamine with 1,3-dicarbonyl compounds [21], α,β-unsaturated carbonyl compounds [22] and α,β-unsaturated nitriles have also been reported [23]. Additionally, the alternative approaches such as the reaction of an oxime-derived dianion with an ester [24] or amide [25] also provide isoxazoles.

Ring systems which contain nitrogen atom have been widely used as ligands in organometallic chemistry.

Benzimidazole as a typical heterocyclic ligand with nitrogen as the donor atom is frequently used in organometallic chemistry. In particular, 2-(2-pyridinyl)-1*H*-benzimidazole can be described as donor ligand because two nitrogen atoms of the benzimidazole and pyridine moieties participate in coordination. Organometallic complexes containing benzimidazolic ligands are effectively used in coordination chemistry [26–28].

Some of these complexes have been applied as highly active catalysts for organic reactions such as *N*-arylation of indoles [29] and olefin epoxidation [30].

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As a continuation of our previous work [31–39] on the preparation of some new heterocyclic compounds, herein we report our recent research into the green and three-step regioselective synthesis of isoxazole derivatives from aldehydes and alkynes, under a mild condition in water, whereupon nitrile oxide intermediates are generated in situ and further reacted without isolation.

Experimental section

Instrumentation, analyses and starting material

NMR spectra were recorded on a Bruker Avance DPX-250 (^{1}H NMR at 250 MHz and ^{13}C NMR at 62.5 MHz) spectrometer in pure deuterated solvents with TMS as an internal standard. IR spectra were obtained using a Shimadzu FT-IR 8300 spectrophotometer. Mass spectra were determined on a Shimadzu GCMS-QP 1000 EX instruments at 70 or 20 eV. Elemental analyses were performed with a Thermo Finnigan CHNS-O 1112 series analyser. Melting points determined in open capillary tubes in a Buchi-535 circulating oil melting point apparatus. The purity determination of the substrates and reaction monitoring were accomplished by TLC on silica gel PolyGram SILG/UV 254 plates. Column chromatography was carried out on short columns of silica gel 60 (70–230 mesh) in glass columns (2–3 cm diameter) using 15–30 g of silica gel per g crude mixture. Chemical materials were purchased from Fluka, Aldrich and Merck. The used activated carbon was also purchased from Merck (Atr. No. 9631, 0.3–0.05 mm).

General procedure

General procedure for the preparation of imidoyl chlorides

10 mmol of aldehyde was dissolved in 10 mL of H_2O/EtOH (v/v) 1/1) mixture by stirring in a 100-mL round-bottomed flask. The solution was cooled to 0 °C, and 10 mmol of hydroxylamine hydrochloride was added to this solution. Then 25 mmol of NaOH as a 50% solution in water was added dropwise. The reaction mixture is allowed to warm slowly to room temperature and stirred for 1 h. The solution was extracted with chloroform, and the aqueous phase was acidified to pH 6 by adding concentrated HCl while keeping the temperature below 30 °C and extracted with chloroform to give the oxime products in 90–97% yield. For chlorination of oxime, 1.8 mmol of *N*-chlorosuccinimide (NCS) was added in one portion to a solution of 10 mmol of oxime in DMF (10 mL). A slight increase in the reaction temperature shows the beginning of the reaction. A small amount of HCl gas can be bubbled through the solution when the reaction does not start. In the case of the electron-deficient oximes for starting the reaction, the mixture is heated to 45 °C. The remaining 8.2 mmol of NCS was added in small portions while keeping the temperature below 35 °C (below 60 °C for electron-deficient oximes). The mixture was then stirred at room temperature for 1 h and quenched with water and extracted with chloroform (3 × 10 mL) to give the imidoyl chloride products in 72–93% yield.

General procedure for the synthesis of isoxazoles from nitrile oxides and alkynes

To a stirred solution of imidoyl chloride (1 mmol) and alkyne (1 mmol) in H_2O (5 mL), pyridinyl benzimidazole (1 mol%), copper(II)acetate (1 mol%) and K_2CO_3 (2 mmol) were added. The resulting solution was stirred at room temperature for 3 h. After the completion of the reaction, it was diluted with water, and the solid off-white isoxazole product was filtered off.

3-(4-Chlorophenyl)-5-phenylisoxazole (1) White solid, m.p: 177–178 °C. IR (KBr): 3114 (m), 1612 (s), 1489 (s), 1446 (s), 1425 (s), 1383 (s), 1093 (s), 1015 (s), 950 (s), 838 (s), 815 (s), 760 (s), 693 (s), 517 (s) cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 6. 80 (s, 1H), 7.44–7.52 (m, 5H), 7.79–7.88 (m, 4H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 97.3, 125.8, 127.2, 128.0, 128.2, 129.0, 129.2, 130.3, 136.0, 161.8, 168.3. Mas *m/z* (%) 257 (M^++2, 2.8), 256 (M^++1, 7.5), 255 (M^+, 10.5), 105 (100.0), 77 (41.1). Anal. calcd. for $C_{15}H_{10}ClNO$ (255.699): C 70.46 H 3.94; found: C 79.81, H 4.97.

3,5-Diphenylisoxazole (2) White solid, m.p: 121 °C. IR (KBr): 3114 (m), 3049 (m), 1593 (s), 1573 (s), 1463 (s), 1461 (s), 1402 (s), 950 (s), 820 (s), 764 (s), 700 (s), 555 (s), 529 (m) cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 6.83 (s, 1H), 7.43–7.53 (m, 6H), 7.83–7.90 (m, 4H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 97.5, 125.8, 126.8, 128.3, 128.7, 128.9, 129.0, 130.0, 130.2, 130.6, 131.0, 163.0, 170.4. Mas *m/z* (%) 223 (M^++2, 3.5), 222 (M^++1, 15.2), 221 (M^+, 20.0), 178 (25.6), 144 (12.7), 105 (100.0), 77 (72.5), 51 (22.3). Anal. calcd. for $C_{15}H_{11}NO$ (221.254): C 81.43 H 5.01; found: C 79.81, H 4.97.

3-(4-Methoxyphenyl)-5-phenylisoxazole (3) White solid, m.p: 120 °C. IR (KBr): 3110 (m), 2942 (m), 1613 (s), 1572 (s), 1529 (s), 1492 (s), 1447 (s), 1434 (s), 1295 (s), 1250 (s), 1178 (s), 1027 (s), 836 (s), 817 (s), 761 (s), 691 (s), 537 (s) cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.88 (s, 3H), 6.78 (s, 1H), 7.00 (dd, 2H, J_1 = 6.8 Hz, J_2 = 2.5 Hz), 7.41–7.53 (m, 3H), 7.74–7.89 (m, 4H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 55.3, 97.3, 112.1, 114.3, 121.6, 125.8, 126.4, 127.5, 128.2, 128.6, 129.0, 130.1, 161.0, 162.6, 170.1. Mas *m/z* (%) 253 (M^++2, 2.0), 252 (M^++1, 12.9), 251 (M^+, 16.1), 105

(100.0), 77 (56.0). Anal. calcd. for $C_{16}H_{13}NO_2$ (251.280): C 76.48 H 5.21; found: C 79.81, H 4.97.

3-(4-Isopropylphenyl)-5-phenylisoxazole (4) White solid, m.p: 111 °C. IR (KBr): 3111 (m), 2966 (s), 2962 (s), 1615 (s), 1567 (s), 1492 (s), 1447 (s), 1431 (s), 1387 (s), 1056 (s), 948 (s), 839 (s), 820 (s), 768 (s), 694 (s), 555 (s) cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): $\delta = 1.29$ (d, 6H, $J = 9.6$ Hz), 2.92–3.03 (m, 1H), 6.82 (s, 1H), 7.35 (d, 2H, $J = 8.3$ Hz), 7.44–7.52 (m, 3H), 7.80 (d, 2H, $J = 8.6$ Hz), 7.82–7.87 (m, 2H). ^{13}C NMR (62.5 MHz, $CDCl_3$): $\delta = 23.9$, 34.0, 97.4, 125.8, 126.6, 126.8, 127.0, 127.5, 129.0, 130.1, 151.0, 162.9, 170.2. Mas *m/z* (%) 265 (M^++2, 5.3), 264 (M^++1, 24.1), 263 (M^+, 38.5), 248 (40.6), 186 (2.1), 105 (100.0), 77 (41.1). Anal. calcd. for $C_{18}H_{17}NO$ (263.334): C 82.10 H 6.51; found: C 79.81, H 4.97.

3-(4-Methylphenyl)-5-phenylisoxazole (5) White solid, m.p: 131 °C. IR (KBr): 3117 (m), 1614 (s), 1570 (s), 1492 (s), 1447 (s), 1426 (s), 1188 (m), 1117 (m), 1075 (s), 947 (s), 830 (s), 765 (s), 684 (s), 524 (s) cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): $\delta = 2.41$ (s, 3H), 6.80 (s, 1H), 7.24–7.30 (m, 2H), 7.45–7.47 (m, 2H), 7.49 (t, 2H, $J = 1.9$ Hz), 7.77 (dd, 1H, $J_1 = 8.2$ Hz, $J_2 = 2.3$ Hz), 7.80–7.87 (m, 2H). ^{13}C NMR (62.5 MHz, $CDCl_3$): $\delta = 21.4$, 97.4, 125.8, 126.3, 126.7, 127.5, 129.0, 129.6, 130.1, 140.1, 162.9, 170.2. Mas *m/z* (%) 237 (M^++2, 3.2), 236 (M^++1, 13.1), 235 (M^+, 19.3), 158 (10.6), 105 (100.0), 77 (53.8). Anal. calcd. for $C_{16}H_{13}NO$ (235.281): C 81.68 H 5.57; found: C 79.81, H 4.97.

3-(3,5-Dimethoxyphenyl)-5-phenylisoxazole (6) White solid, m.p: 110 °C. IR (KBr): 3005 (m), 2940 (m), 1612 (s), 1572 (s), 1526 (s), 1493 (s), 1460 (s), 1430 (s), 1257 (s), 1200 (s), 1171 (s), 1143 (s), 1022 (s), 947 (s), 861 (s), 760 (s), 690 (s), cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): $\delta = 3.93$ (s, 3H), 3.96 (s, 3H), 6.79 (s, 1H), 6.94 (dd, 1H, $J_1 = 8.3$ Hz, $J_2 = 2.6$ Hz), 7.35 (dd, 1H, $J_1 = 8.3$ Hz, $J_2 = 1.9$ Hz), (m, 4H), 7.81–7.86 (m, 2H). ^{13}C NMR (62.5 MHz, $CDCl_3$): $\delta = 56.0$, 97.3, 109.2, 110.5, 119.9, 125.8, 127.4, 129.0, 130.1, 150.6, 162.7, 170.2. Mas *m/z* (%) 283 (M^++2, 6.7), 282 (M^++1, 44.1), 281 (M^+, 74.9), 204 (11.4), 179 (13.2), 105 (100.0), 77 (37.2). Anal. calcd. for $C_{17}H_{15}NO_3$ (281.306): C 72.58 H 5.37; found: C 79.81, H 4.97.

***N,N*-dimethyl-4-(5-phenyl-3-isoxazolyl)aniline (7)** White solid, m.p: 127–128 °C. IR (KBr): 3399 (m), 3217 (m), 2949 (m), 2839 (m), 1740 (s), 1609 (s), 1506 (s), 1412 (s), 1376 (s), 1338 (s), 1163 (s), 1056 (m), 950 (s), 777 (m), 681 (m), 595 (s) cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): $\delta = 2.82$ (s, 6H), 5.93 (s, 1H), 6.95 (dd, 2H, $J_1 = 1.8$ Hz, $J_2 = 8.5$ Hz), 7.55–7.56 (m, 2H), 7.59–7.61 (m, 2H), 7.73–7.75 (m, 3H). ^{13}C NMR (62.5 MHz, $CDCl_3$): $\delta = 43.2$, 97.8, 119.1, 126.7, 126.9, 127.0, 129.5, 130.3, 139.9, 168.0, 177.9. Mas *m/z* (%) 265 (M^++1, 4.8), 264 (M^+, 10.7), 236 (19.4), 152 (18.7), 123 (24.6), 97 (60.3), 57 (100.0). Anal. calcd. for $C_{17}H_{16}N_2O$ (264.322): C 77.25 H 6.10; found: C 79.81, H 4.97.

Ethyl 4-(5-phenyl-3-isoxazolyl)benzoate (8) White solid, m.p: 138 °C. IR (KBr): 2988 (m), 1735 (s), 1449 (s), 1295 (s), 1270 (s), 1126 (s), 1109 (s), 1025 (s), 950 (s), 864 (s), 774 (s), 759 (s), 688 (s), 679 (s) cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): $\delta = 1.20$ (trp, 3H, $J = 7.1$ Hz), 4.18 (qr, 2H, $J = 7.9$ Hz), 6.64 (s, 1H), 7.23–7.29 (m, 3H), 7.60–7.64 (m, 2H), 7.71 (d, 2H, $J = 7.5$ Hz), 7.92 (d, 2H, $J = 6.7$ Hz). ^{13}C NMR (62.5 MHz, $CDCl_3$): $\delta = 14.3$, 61.2, 97.5, 125.8, 126.7, 127.2, 129.0, 130.1, 130.4, 131.7, 133.2, 162.2, 166.0, 170.8. Mas *m/z* (%) 295 (M^++2, 5.5), 294 (M^++1, 26.8), 293 (M^+, 34.0), 248 (17.5), 105 (100.0), 77 (26.6). Anal. calcd. for $C_{18}H_{15}NO_3$ (293.317): C 73.71 H 5.15; found: C 79.81, H 4.97.

3-(2,4-Dichlorophenyl)-5-phenylisoxazole (9) White solid, m.p: 96 °C. IR (KBr): 3162 (w), 3058 (w), 1598 (s), 1553 (s), 1487 (s), 1450 (s), 1400 (s), 1364 (s), 1106 (s), 1055 (s), 954 (s), 934 (s), 865 (s), 821 (s), 750 (s), 680 (s), 539 (s), 456 (s) cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): $\delta = 6.98$ (s, 1H), 7.36 (dd, 1H, $J_1 = 10$ Hz, $J_2 = 2$ Hz), 7.45–7.51 (m, 3H), 7.53 (d, 1H, $J = 2$ Hz), 7.75 (d, 1H, $J = 8.5$ Hz), 7.81–7.99 (m, 2H). ^{13}C NMR (62.5 MHz, $CDCl_3$): $\delta = 100.5$, 125.8, 127.5, 127.7, 128.6, 129.0, 130.9, 131.7, 132.7, 133.6, 136.2, 160.6, 170.0. Mas *m/z* (%) 292 (M^++2, 3.3), 291(M^++1, 5.7), 290 (M^+, 3.7), 289 (11.3), 105 (100.0), 77 (44.4). Anal. calcd. for $C_{15}H_9Cl_2NO$ (290.143): C 62.09 H 3.13; found: C 79.81, H 4.97.

3-(4-Nitrophenyl)-5-phenylisoxazole (10) White solid, m.p: 222 °C. IR (KBr): 3114 (m), 1572 (m), 1530 (s), 1489 (m), 1449 (s), 1356 (s), 1344 (s), 1114 (m), 951 (m), 863 (s), 814 (s), 772 (s), 695(s) cm^{-1}. ^1H NMR (250 MHz, DMSO-d_6): $\delta = 7.55$–7.57 (m, 3H), 7.73 (s, 1H), 7.90–7.92 (m, 2H), 8.18 (d, 2H, $J = 6.5$ Hz), 8.39 (d, 2H, $J = 6.5$ Hz). ^{13}C NMR (62.5 MHz, DMSO-d_6): $\delta = 97.3$, 115.6, 124.3, 125.7, 126.5, 127.7, 128.6, 129.0, 130.1, 135.3, 148.6, 161.1, 171.5. Mas *m/z* (%) 268 (M^++2, 2.8), 267 (M^++1, 10.5), 266 (M^+, 13.7), 105 (100.0), 77 (48.8). Anal. calcd. for $C_{15}H_{10}N_2O_3$ (266.252): C 67.67 H 3.79; found: C 79.81, H 4.97.

5-Phenyl-3-(2-thienyl)isoxazole (11) White solid, m.p: 119–120 °C. IR (KBr): 3117 (m), 1615 (m), 1576 (s), 1489 (m), 1446 (s), 1425 (s), 1344 (m), 1071 (m), 949 (s), 916 (s), 851 (s), 755 (s), 750 (s), 745 (s), 667 (s), 614 (s), 517 (m) cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): $\delta = 6.68$ (s, 1H), 7.36–7.42 (m, 4H), 7.51 (dd, 1H, $J_1 = 1.1$ Hz, $J_2 = 5.0$ Hz), 7.71 (dd, 1H, $J_1 = 1.2$ Hz, $J_2 = 2.9$ Hz), 7.74–7.78 (m, 2H). ^{13}C NMR (62.5 MHz, $CDCl_3$): $\delta = 97.8$, 119.8, 124.6, 125.8,

126.0, 129.0, 130.2, 134.5, 145.5, 158.8, 170.1. Mas *m/z* (%) 229 (M^++2, 2.5), 228 (M^++1, 13.3), 227 (M^+, 13.5), 105 (100.0), 77 (56.5). Anal. calcd. for $C_{13}H_9NOS$ (227.283): C 68.70, H 3.99; found: C 79.81, H 4.97.

5-(Bromomethyl)-3-(4-chlorophenyl)isoxazole (12) White solid, m.p: 116 °C. IR (KBr): 3135 (m), 3039 (m), 2979 (m), 1606 (s), 1429 (s), 1290 (s), 1228 (s), 1100 (s), 1016 (s), 934 (s), 834 (s), 811 (s), 666 (s), 569 (s), 498 (s) cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 4.51 (s, 2H), 6.59 (s, 1H),7.42 (dd, 2H, J_1 = 6.6 Hz, J_2 = 2 Hz), 7.71 (dd, 2H, J_1 = 9.0 Hz, J_2 = 2.4 Hz). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 18.5, 101.8, 127.0, 128.0, 129.3, 136.3, 161.8, 168.3. Mas *m/z* (%) 274 (M^++2, 8.1), 273 (M^++1, 15.5), 272 (M^+, 11.3), 178 (100.0), 150 (30.6), 127 (13.4), 111 (35.7), 75 (38.2), 51 (13.2). Anal. calcd. for $C_{10}H_7BrClNO$ (272.525): C 44.07 H 2.59; found: C 79.81, H 4.97.

5-(Chloromethyl)-3-(4-chlorophenyl)isoxazole (13) White solid, m.p: 105 °C. IR (KBr): 3140 (m), 3020 (m), 2973 (m), 1610 (s), 1510 (s), 1440 (s), 1275 (s), 1175 (s), 1090 (s), 1015 (s), 939 (s), 885 (s), 824 (s), 812 (s), 709 (s), 677 (s), 500 (s) cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 4.64 (s, 2H), 6.61 (s, 1H), 7.44 (dd, 2H, J_1 = 6.6 Hz, J_2 = 1.9 Hz), 7.73 (dd, 2H, J_1 = 6.5 Hz, J_2 = 1.9 Hz). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 34.4, 100.3, 101.7, 127.0, 128.0, 129.2, 136.3, 161.7, 168.3. Mas *m/z* (%) 230 (M^++2, 12.3), 229 (M^++1, 18.6), 228 (M^+, 14.9), 227 (18.9), 178 (100.0), 150 (46.1), 111 (29.3), 75 (37.2), 51 (12.6). Anal. calcd. for $C_{10}H_7Cl_2NO$ (228.074): C 52.66 H 3.09; found: C 79.81, H 2.95.

3-(4-Chlorophenyl)-5-[(4-methylphenoxy)methyl]isoxazole (14) White solid, m.p: 122 °C. IR (KBr): 3130 (m), 2921 (m), 1617 (s), 1600 (s), 1500 (s), 1420 (s), 1373 (s), 1294 (s), 1248 (s), 1182 (s), 1100 (s), 1013 (s), 949 (s), 922 (s), 834 (s), 820 (s), 786 (s), 512 (s), 492 (s) cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 2.30 (s, 3H), 5.15 (s, 2H), 6.61 (s, 1H), 6.89 (d, 2H, J_1 = 8.6 Hz), 7.12 (d, 2H, J_1 = 8.6 Hz), 7.37–7.45 (m, 2H), 7.74 (d, 2H, J_1 = 8.5 Hz). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 20.5, 61.5, 101.1, 114.6, 127.3, 128.1, 129.5, 130.1, 131.3, 136.1, 155.7, 161.5, 169.1. Mas *m/z* (%) 301 (M^++2, 13.0), 300 (M^++1, 21.7), 299 (M^+, 26.5), 192 (46.4), 139 (15.3), 107 (100.0), 77 (39.5). Anal. calcd. for $C_{17}H_{14}ClNO_2$ (299.751): C 68.12 H 4.71; found: C 79.81, H 4.97.

2-{[3-(4-Chlorophenyl)-5-isoxazolyl]methyl}-1,2-benzisothiazol-3(2*H*)-one 1,1-dioxide (15) White solid, m.p: 186 °C. IR (KBr): 3482 (m), 3141 (w), 3093 (w), 2923 (w), 1750 (s), 1611 (m), 1431 (s), 1331 (s), 1302 (s), 1268 (s), 1185 (s), 1090 (m), 923 (m), 754 (s), 588 (s), 513 (s) cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 5.08 (s, 2H), 6.66 (s, 1H), 7.40 (dd, 2H, J_1 = 6.7 Hz, J_2 = 1.7 Hz), 7.71 (dd, 2H, J_1 = 6.7 Hz, J_2 = 1.7 Hz), 7.87–7.97 (m, 3H), 8.10 (d, 1H, J = 1.5 Hz). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 33.6, 102.0, 121.3, 125.6, 128.1, 129.2, 134.7, 135.3, 136.2, 160.6, 162.9, 166.1. Mas *m/z* (%) 376 (M^++2, 6.0), 375 (M^++1, 9.9), 374 (M^+, 14.8), 178 (100.0), 150 (33.9), 111 (16.4), 77 (16.6). Anal. calcd. for $C_{17}H_{11}ClN_2O_4S$ (374.799): C 54.48, H 2.96; found: C 79.81, H 4.97.

[3-(4-Chlorophenyl)-5-isoxazolyl]methanol (16) White solid, m.p: 96 °C. IR (KBr): 3305 (s), 3147 (w), 2943 (w), 1608 (s), 1572 (m), 1511 (m), 1456 (s), 1440 (s), 1373 (s), 1275 (w), 1161 (w), 1095 (s), 1082 (s), 1061 (s), 1013 (m), 925 (s), 836 (s), 829 (s), 800 (s), 684 (m), 517 (m) cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 2.9 (s, 1H), 4.80 (s, 2H), 6.52 (s, 1H), 7.40 (dd, 2H, J_1 = 6.7 Hz, J_2 = 1.8 Hz), 7.69 (dd, 2H, J_1 = 6.7 Hz, J_2 = 1.9 Hz). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 56.4, 99.9, 127.2, 128.0, 129.2, 136.2, 161.5, 172.3. Mas *m/z* (%) 211 (M^++2, 10.1), 210 (M^++1, 25.7), 209 (M^+, 26.1), 178 (100.0), 150 (54.8), 111 (39.7), 75 (44.3) 50 (13.8). Anal. calcd. for $C_{10}H_8ClNO_2$ (209.629): C 57.30 H 3.85; found: C 79.81, H 4.97.

2-[3-(4-Chlorophenyl)-5-isoxazolyl]-2-propanol (17) White solid, m.p: 96–98 °C. IR (KBr): 3350 (m), 2993 (m), 1601 (s), 1568 (s), 1509 (m), 1456 (m), 1442 (s), 1405 (s), 1264 (s), 1223 (s), 1190 (s), 1090 (s), 1014 (s), 967 (s), 925 (s), 802 (s), 623 (s) cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 1.64 (s, 6H), 2.66 (s, 1H), 6.44 (s, 1H), 7.40 (dd, 2H, J_1 = 1.8 Hz, J_2 = 4.8 Hz), 7.70 (dd, 2H, J_1 = 1.8 Hz, J_2 = 8.5 Hz). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 29.0, 69.2, 97.3, 127.4, 128.0, 129.2, 136.0, 161.3, 178.8. Mas *m/z* (%) 240 (M^++2, 5.4), 239 (M^++1, 8.6), 238 (M^+, 16.1), 222 (28.0), 178 (47.0), 152 (35.8), 111 (20.3), 85 (22.4), 59 (100.0). Anal. calcd. for $C_{12}H_{12}ClNO_2$ (237.682): C 60.64, H 5.09; found: C 79.81, H 4.97.

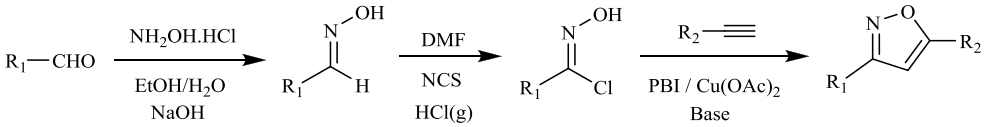
Result and discussion

2-(2-Pyridinyl)-1*H*-benzimidazole (PBI) was prepared from the reaction between 2-pyridylaldehyde and 1,2-phenylenediamine in the presence of copper nanoparticles on activated carbon (Cu/C) as a heterogeneous catalyst [34].

We then examined the effect of the nitrogen-based ligand for the synthesis of isoxazoles in the reaction of aldehydes with alkynes using $Cu(OAc)_2$ as a catalyst without any reducing agent.

Firstly, a three-step approach to the synthesis of isoxazoles has been examined: (1) preparation of the aldoximes, (2) formation of the imidoyl chlorides and (3) [3 + 2] cycloaddition reactions (Scheme 1). The nitrile oxides required for this methodology are readily prepared from

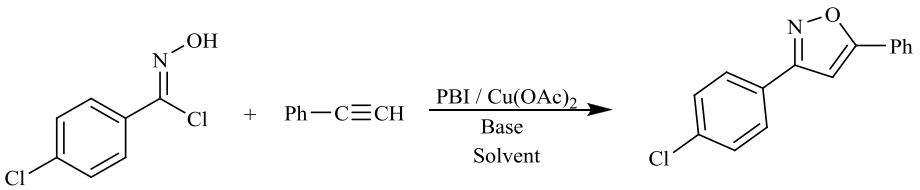
Scheme 1 3,5-Disubstituted isoxazoles prepared from aldehydes



aldehydes. To this end, an aldehyde is first converted to the corresponding aldoxime via reaction with hydroxylamine chloride and sodium hydroxide in an ethanol/water mixture at room temperature. The aldoxime is transformed to the corresponding imidoyl chlorides using *N*-chlorosuccinimide in DMF. Finally, alkyne reacted with nitrile oxide, which was generated in situ by dehydrohalogenation of imidoyl chloride in the presence of catalytic amount of PBI/copper (II) acetate, an appropriate base and solvent to affording isoxazoles.

In the beginning, the 4-chlorobenzaldehyde was chosen as a selected substrate for the synthesis of imidoyl chloride.

Table 1 Optimization of the reaction conditions



Entry	Catalyst	Condition	Time (h)	Yield (%)
1	$Cu(OAc)_2$/PBI	CH_2Cl_2/K_2CO_3	3	18
2	$Cu(OAc)_2$/PBI	$DMSO/K_2CO_3$	3	12
3	$Cu(OAc)_2$/PBI	$Acetone/K_2CO_3$	3	16
4	$Cu(OAc)_2$/PBI	THF/K_2CO_3	3	41
5	$Cu(OAc)_2$/PBI	CH_3CN/K_2CO_3	3	53
6	$Cu(OAc)_2$/PBI	$Dioxane/K_2CO_3$	3	65
7	$Cu(OAc)_2$/PBI	$PEG\ 300/K_2CO_3$	3	79
8	$Cu(OAc)_2$/PBI	$EtOH/K_2CO_3$	3	90
9	$Cu(OAc)_2$/PBI	H_2O/K_2CO_3	3	95
10	$Cu(OAc)_2$/PBI	H_2O/K_3PO_4	3	9
11	$Cu(OAc)_2$/PBI	$H_2O/NaHCO_3$	3	68
12	$Cu(OAc)_2$/PBI	H_2O/Cs_2CO_3	3	15
13	$Cu(OAc)_2$/PBI	H_2O/Et_3N	3	83
14	$Cu(OAc)_2$/PBI	H_2O/NaOH	3	0
15[a]	$Cu(OAc)_2$/PBI	H_2O/K_2CO_3	3	95
16[b]	$Cu(OAc)_2$/PBI	H_2O/K_2CO_3	3	76
17[c]	$Cu(OAc)_2$/PBI	H_2O/K_2CO_3	3	95
18[d]	$Cu(OAc)_2$/PBI	H_2O/K_2CO_3	3	80
19	CuI/PBI	H_2O/K_2CO_3	3	83
20	CuBr/PBI	H_2O/K_2CO_3	3	79
21	CuCl/PBI	H_2O/K_2CO_3	3	71
22	$Cu(OAc)_2$	H_2O/K_2CO_3	3	75
23	–	H_2O/K_2CO_3	3	0

Reaction conditions: 4-chloro-*N*-hydroxybenzenecarboximidoyl chloride (1 mmol), phenyl acetylene (1 mmol), Cu(II)/PBI (1 mol%), K_2CO_3 (2 mmol)

[a] K_2CO_3 (3 mmol)

[b] K_2CO_3 (1 mmol)

[c] $Cu(OAc)_2$/PBI (2 mol%)

[d] $Cu(OAc)_2$/PBI (0.5 mol%)

Table 2 Substrate scope for the synthesis of isoxazole derivatives

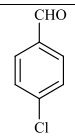
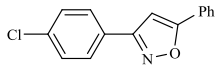
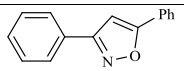
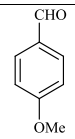
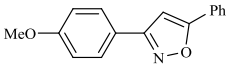
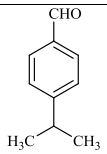
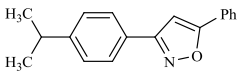
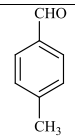
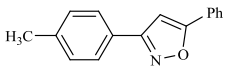
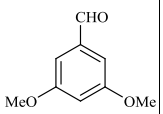
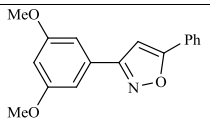
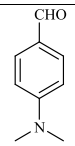
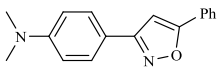
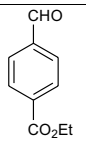
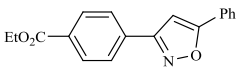
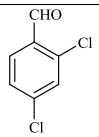
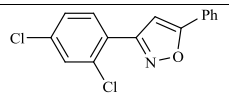
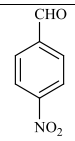
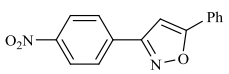
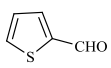
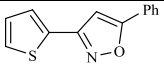
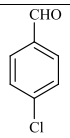
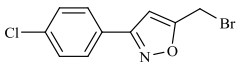
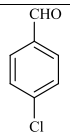
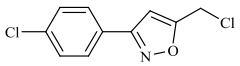
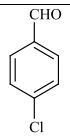
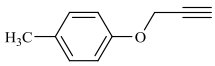
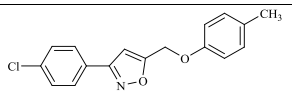
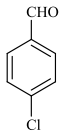
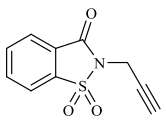
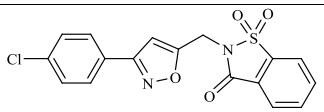
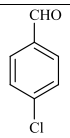
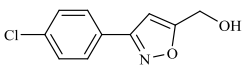
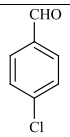
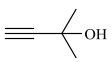
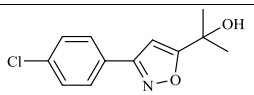
Entry	Aldhyde	Alkyne	Product	Yield (%)[a]
1			 **1**	95
2			 **2**	90
3			 **3**	90
4			 **4**	85
5			 **5**	87
6			 **6**	90
7			 **7**	90
8			 **8**	80
9			 **9**	89
10			 **10**	80
11			 **11**	92

Table 2 (continued)

12			 **12**	89
13			 **13**	88
14			 **14**	82
15			 **15**	78
16			 **16**	75
17			 **17**	81

Reaction conditions: aldehyde (1 mmol), alkyne (1 mmol), Cu(II)/PBI (1 mol%), K_2CO_3 (2 mmol) a) K_2CO_3 (3 mmol)

[a]Isolated yields

In order to optimize the reaction conditions for the isoxazole synthesis, a model reaction using 4-chloro-*N*-hydroxybenzenecarboximidoyl chloride (prepared in situ from corresponding aldehyde) and phenyl acetylene was screened in detail (Table 1).

All the reactions were proceeded at room temperature.

Our studies commenced with a survey of solvents with the goal of identifying effective conditions. When 4-chloro-*N*-hydroxybenzenecarboximidoyl chloride (1 mmol) and phenyl acetylene (1 mmol) were treated with 1 mol% of Cu(II)/PBI, K_2CO_3 (2 mmol) in dichloromethane at room temperature for 3 h, the expected reaction proceeded to give the corresponding isoxazole in 18% yield (Table 1, entry 1).

Replacement of DMSO and acetone with CH_2Cl_2 (Table 1, entries 2, 3) did not give an improved outcome, while the formation of corresponding product was markedly improved when using the same reaction conditions in THF, CH_3CN, dioxane, PEG 300 and EtOH (Table 1, entries 4–8).

The best result was observed under 1 mol% of Cu(II)/PBI catalysis in H_2O at room temperature in the presence of 2 mmol K_2CO_3 (Table 1, entry 9).

Next, the influence of the base on the result of the model reaction was studied. For this purpose, equimolar amounts of 4-chloro-*N*-hydroxybenzenecarboximidoyl chloride and phenyl acetylene were reacted in H_2O with a twofold excess of K_3PO_4, $NaHCO_3$, NaOH, Cs_2CO_3 and Et_3N, respectively. With K_3PO_4 as the base the yield dropped to 9% (Table 1, entry 10). The yields obtained with $NaHCO_3$, Cs_2CO_3 and Et_3N amounted to 68, 15 and 83%, respectively (Table 1, entries 11–13). Conversely, the extent of the [3 + 2] cycloaddition reaction between alkynes and nitrile oxides dramatically fell when NaOH was used as a base in H_2O (Table 1, entry 14). Increasing the stoichiometry of K_2CO_3 to 3 equiv had shown no useful improvement (Table 1, entry 11), whereas the yield of product decreased to 76%, when the amount of K_2CO_3 was reduced to 1 equiv (Table 1, entry 16).

Improvement in the yield was not observed by increasing the loading of the catalyst to 2 mol% (Table 1, entry 17), whereas decreasing the catalyst loading to 0.5 mol% resulted in a lower yield of the product (Table 1, entry 18). CuI, CuBr and CuCl can also be utilized in the cycloaddition process. However, the use of these copper salts in H_2O resulted in lowered yields (Table 1, entries 19–21). Without PBI, the yield of the reaction was decreased to 75% (Table 1, entry 22). Other attempt to carry out this reaction without any catalyst was unsuccessful (Table 1, entry 23).

After the extensive screening of reaction conditions, we concluded that the most efficient set of conditions employs 1.0 equiv of imidoyl chloride, 1.0 equiv of alkyne, 2.0 equiv of K_2CO_3 and 1 mol% of Cu(II)/PBI in H_2O at room temperature.

On the basis of these screening results, to demonstrate the scope of this reaction, a series of hydroximoyl chlorides were reacted with various terminal alkynes at room temperature in the presence of 1 mol% of Cu(II)/PBI and K_2CO_3 as the base for 3 h (Table 2). The results are summarized in Table 2. As shown, almost all reactions proceeded to completion in 3 h and the corresponding products were obtained in good to excellent yields.

Substrates bearing electron-donating substituents on the phenyl ring provided the corresponding products in high yields (Table 2, entries 3–7).

However, introducing a bulky isopropyl group into the parent aldehyde provided 85% yield of the desired isoxazole (**4**), perhaps because of the relatively decreased water solubility (Table 1, entry 4).

Next, different electron-withdrawing substituents on the phenyl ring were tested with the catalytic system (Table 1, entries 8–10).

When aldehyde bearing an ester group was employed, the tandem reaction also successfully underwent (Table 2, entry 8).

It should be emphasized that the isoxazole derivative containing a thiophene ring was obtained in 92% yield under similar reaction conditions (Table 2, entry 11).

We next explored the possibility of employing aliphatic terminal alkynes as the substrate to react with imidoyl chloride under the standard conditions. The corresponding isoxazoles were obtained in good to high yields (Table 2, entries 12–17).

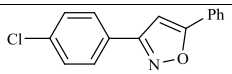
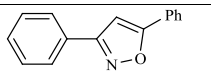
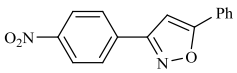
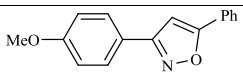
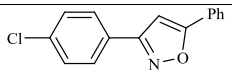
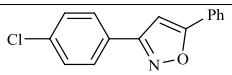
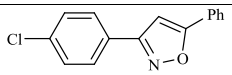
Propargyl bromide and chloride were reacted under the standard conditions. The corresponding products **12** and **13** were obtained in 89 and 88% yields, respectively.

Moreover, synthesized alkyl terminal alkynes from 4-methyl phenol and saccharin were also found to be suitable reaction partners with the model compound in the reaction (Table 2, entries 14–15).

In addition, propargylic alkynes could also react with 4-chlorobenzaldehyde to afford the corresponding products **16** and **17** in 75 and 80% yields, respectively (Table 2, entries 16–17).

Moreover, our catalytic system worked well under gram-scale reaction conditions: reaction of 50 mmol of

Table 3 Comparison of protocols for the synthesis of isoxazole derivatives

Entry	Condition	Product	Yield (%)	Time (h)	Ref.
1	K_2CO_3, MeOH/H_2O, 60 °C		54	10	[40]
2	Cu/$CuSO_4$, t-BuOH:H_2O(1:1)		72	4	[14]
3	$CuSO_4.5H_2O$, 2 mol%, Sodium ascorbate, 10 mol%, $KHCO_3$, H_2O/t-BuOH, r.t		74	4	[41]
4	$PdCl_2(PPh_3)_2$ (1 mol%), DMF-H_2O		54	37	[42]
5	CrO_2, MeCN, 80 °C		85	2	[43]
6	Clay-Cu(II) (15 mol%), r.t		76	6	[44]
7	PBI / $Cu(OAc)_2$(2 Mol%)		95	3	This work

4-chlorobenzaldehyde with phenyl acetylene gave the corresponding products **1** in 90% yield.

The literature reports for the synthesis of 3,5-disubstituted isoxazole derivatives in the presence of various catalysts are listed in Table 3. The results demonstrate that the present protocol is indeed superior to several of the other protocols. The 3-(4-chlophenyl)-phenylisoxazole is produced in 3 h and 95% isolated yield using the present protocol. Most of the other protocols listed take either longer time for completion or use high temperature. Also, this protocol was employed to give 3,5-diphenylisoxazole, 3-(4-nitrophenyl)-5-phenylisoxazole and 3-(4-methoxyphenyl)-5-phenylisoxazole, in comparison with other procedure, in shorter reaction time with excellent isolated yields. So, $Cu(OAc)_2$ in the presence of pyridinyl benzimidazole (PBI) as a bidentate *N*-chelating ligand can be considered as an efficient catalyst in the synthesis of 3,5-disubstituted isoxazole derivatives.

In conclusion, we have reported a highly regioselective tandem reaction that involves catalytic system 1,3-dipolar cycloaddition of alkynes with nitrile oxides. This catalytic system provides an efficient method for the synthesis of isoxazole derivatives.

The synthetic value of the developed methodology was demonstrated by the efficient preparation of a representative range of aldehydes and alkynes including gram-scale synthesis of isoxazole derivatives.

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