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[bmim]BF₄/[Cu(Im¹²)₂]CuCl₂ as a novel catalytic reaction medium for click cyclization

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ABSTRACT

Herein, a new application of an ionic liquid containing copper (I), ([Cu(Im¹²)₂]CuCl₂), is introduced. This ionic liquid was used as an efficient catalyst for the click cyclization between organic azides and terminal alkynes in various solvents. Then, the mixture of [bmim]BF₄/[Cu(Im¹²)₂]CuCl₂ was used as a green catalytic medium for the multicomponent click synthesis of 1,4-disubstituted-1*H*-1,2,3-triazoles from α-halo ketones. The reactions were performed efficiently in this mixture and excellent yields were obtained in all cases. This catalytic reaction medium was recycled five times without significant loss of activity.

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1. Introduction

Multicomponent reactions (MCRs) are one of the most important concepts in modern synthetic organic chemistry. MCRs have received significant demand as a direct route for the synthesis of diverse compounds and compound libraries [1–5]. For example, multicomponent Cu(I)-catalyzed 1,3-dipolar azide–alkyne cycloaddition (CuAAC) leads to a diversity of 1,4-disubstituted 1,2,3-triazole compounds; this is best known as the click reaction [6]. Many kinds of copper (I) catalysts have been reported for CuAAC reactions. However, some of these catalysts have serious drawbacks. For instance, some of the reported catalysts suffer from their instability or high tendency toward oxidation, which leads to catalytic inactivity. In some cases, the formation of undesired alkyne–alkyne coupling and other by-products are ob-

served in their presence [7,8]. Almost all of them are applicable and suitable for certain kinds of solvents. For example, simple coordination complexes of Cu(P(O-Me)₃)₃Br [9] and Cu(PPh₃)₃Br [10,11] are often used in reactions in organic solvents, in which cuprous salts have limited solubility. A report describes the bis(phosphine) complex Cu(PPh₃)₂OAc as an excellent catalyst for the CuAAC reaction in toluene and dichloromethane [12]. In situ-prepared Cu (I) from Cu (II), using sodium ascorbate was introduced by Fokin et al. for click cyclization in water [6]. Although the immobilization of copper (I) salts on various supports makes them recoverable and somewhat more stable than their free copper (I) salt counterparts, the leaching of the catalysts from support into the reaction mixture leads to product contamination and catalyst deficiency during the recycling process.

Click chemistry principles are consistent with the goals of green chemistry, focusing on minimizing the hazard and maximizing the efficiency of any chemical choice. They have attracted an enormous amount of interest over the past decade [13].

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Although CuAAC reactions can often be carried out in water as a green solvent, the solubility of organic azide and acetylene reactants can sometimes be a serious obstacle in using this reaction medium. In particular, a phase transfer catalyst or elevated temperatures seems to be necessary when organic azides are prepared in situ from their halide forms. Using ionic liquids as a reaction medium can overcome these problems. The user-friendly and adjustable properties of ionic liquids have prompted numerous applications as environmentally benign reaction media, catalysts [14], task-specific reagents [15], and chirality transfer media [16]. From this perspective, combining the synthetic potential of MCRs with the dual properties of room temperature ionic liquids (RTILs) as solvents and catalysts has resulted in the development of new and promising eco-compatible organic transformations [17]. Recently, a diversity of ionic liquids containing copper (I) and (II) have been synthesized and were used as catalysts for the oxidative carbonylation of alkanols to dialkyl carbonates [18,19]. This paper aims to introduce new application for the ionic liquid containing copper (I), $[\text{Cu}(\text{Im}^{12})_2]\text{CuCl}_2$, and demonstrates that the mixture of 1-butyl-3-methylimidazolium tetrafluoroborate ($[\text{bmim}]\text{BF}_4$)/ $[\text{Cu}(\text{Im}^{12})_2]\text{CuCl}_2$ is a versatile, recyclable catalytic reaction medium for multicomponent Huisgen preparation of 1,4-disubstituted 1,2,3-triazoles, adapted with the principles of green chemistry.

2. Experimental

2.1. Materials and methods

All α -halo ketones, ionic liquids and other chemicals were purchased from Fluka and Merck in high purity, and $[\text{Cu}(\text{Im}^{12})_2]\text{CuCl}_2$ was synthesized according to the literature [18]. All of the triazole compounds were prepared using our procedure. Their spectroscopic data were recorded on a BOMEM MB-Series 1998 FT-IR spectrophotometer, Bruker Avance DPX 500 MHz and DPX 400 MHz spectrometers using TMS as internal standard. Mass spectral analyses were made on an Agilent HP 5973 Network Mass Selective Detector. The analyzer made its determination according to the ASTM method. Elemental analyses were performed on a Thermo Fin-nigan CHNS-O analyzer, 1112 series.

2.2. Preparation of $[\text{Cu}(\text{Im}^{12})_2]\text{CuCl}_2$

To a Schlenk flask charged with CuCl (1.21 g, 12.22 mmol), a solution of 1-dodecylimidazole (3.06 g, 12.95 mmol) in CH_3CN (5 mL) was added. It was placed in an ultrasonic bath at room temperature for 30 min. The solvent was evaporated in vacuo and the precipitate was washed with ether and dried under vacuum to give $[\text{Cu}(\text{Im}^{12})_2]\text{CuCl}_2$ as a fine crystalline colorless solid; anal. calc. for $\text{C}_{30}\text{H}_{56}\text{Cl}_2\text{Cu}_2\text{N}_4$: C 53.72, H 8.41, N 8.35%; found: C 53.87, H 8.58, N 8.45%; mp 73 °C (Lit. [18] 73 °C), decomp. 281.4 °C. IR (cm^{-1}): 3122, 3050, 2950, 2847, 1690, 1615, 1520, 1466, 1442, 1399, 1357, 1288, 1240, 1110, 1053, 1039, 1028, 1006, 962, 895, 845, 760, 730, 655, 500, 442.

2.3. General procedure for the synthesis of 1,4-disubstituted-1H-1,2,3-triazoles using $[\text{Cu}(\text{Im}^{12})_2]\text{CuCl}_2$ as a catalyst

$[\text{Cu}(\text{Im}^{12})_2]\text{CuCl}_2$ (0.07 g, 0.1 mmol) was added to a round-bottomed flask containing $[\text{bmim}]\text{BF}_4/\text{H}_2\text{O}$ 1:1 (8 mL), α -halo ketone (1 mmol), terminal alkyne (1 mmol) and sodium azide (1.2 mmol). The reaction mixture was stirred at room temperature for 20 min. The organic phase was extracted with ethyl acetate (2×8 mL), washed with brine, dried over anhydrous Na_2SO_4 , filtered and concentrated in vacuo. The solid residual was recrystallized in hot ethanol to give pure crystals of the product. In some cases, water was added dropwise to precipitate the pure product (Table 3, entries 6–8). The aqueous phase was kept for the next runs. The pure products were dried under vacuum at room temperature, which resulted in 80–89% yields.

2.4. Typical procedure for multicomponent synthesis of 2-(4-{4-[1-(2-oxo-2-phenylethyl)-1H-1,2,3-triazol-4-yl]phenyl})-1H-1,2,3-triazol-1-yl-1-phenyl-1-ethanone

$[\text{Cu}(\text{Im}^{12})_2]\text{CuCl}_2$ (0.14 g, 0.2 mmol) was added to a round-bottomed flask containing $[\text{bmim}]\text{BF}_4/\text{H}_2\text{O}$ 1:1 (16 mL), 1,3-diethynylbenzene (1 mmol), phenyl acetylene (2 mmol) and sodium azide (2.4 mmol). The reaction mixture was stirred at room temperature for 20 min (Table 3, entry 11b). The organic phase was extracted with ethyl acetate (2×16 mL), washed with brine, dried over anhydrous Na_2SO_4 , filtered and concentrated in vacuo. The solid residual was recrystallized in hot ethanol to give pure crystals of the product. The latter was dried under vacuum at room temperature as a white solid crystal [20] (0.360 g, 80%). IR (cm^{-1}): 1696 (CO), 1226, 686; $^1\text{H-NMR}$ (500 MHz DMSO-d_6) δ 8.64 (2H, s, CH triazole), 8.44 (1H, s), 8.13–8.12 (4H, m), 7.87 (2H, q, $J = 2.33$ Hz), 7.76 (2H, t, $J = 4.95$ Hz), 7.64 (4H, t, $J = 5.17$ Hz), 7.58 (1H, t, $J = 5.17$ Hz), 6.30 (4H, s, COCH_2); $^{13}\text{C-NMR}$ (125 MHz DMSO-d_6) δ 193.0, 146.9, 135.1, 135.0, 132.2, 130.5, 129.9, 129.1, 125.5, 122.7, 56.9; anal. calcd. for $\text{C}_{28}\text{H}_{20}\text{N}_6\text{O}_2$: C 69.63, H 4.49, N 18.74%; found: C 69.22, H 5.56, N 18.81.

1-phenyl-2-(4-phenyl-1H-1,2,3-triazole-1-yl)-1-ethanone (1b of Table 3, 89%, white solid crystals) [21]: IR (cm^{-1}): 1704 (CO), $^1\text{H-NMR}$ (400 MHz, DMSO-d_6): δ 8.54 (1 H, s), 8.11 (2H, d; $J = 8.10$ Hz), 7.90–7.88 (2H, m), 7.78–7.74 (1H, m), 7.63 (2H, t; $J = 7.7$ Hz), 7.47 (2H, t; $J = 7.7$ Hz), 7.38–7.34 (1H, m), 6.28 (2H, s). $^{13}\text{C-NMR}$ (100 MHz, DMSO-d_6): δ 192.7 (CO), 146.8, 134.8, 134.6, 131.2, 129.5, 129.4, 128.7, 128.4, 125.6, 123.5, 56.5. HRMS (CI): MH^+ , $\text{C}_{12}\text{H}_{12}\text{BrN}_3\text{O}_2$ requires 263.2939, found: 263.3413.

1-(4-phenyl-1H-1,2,3-triazole-1-yl)acetone (5b of Table 3, white solid crystals). IR (cm^{-1}): 1710 (CO), $^1\text{H-NMR}$ (500 MHz, CDCl_3): δ 7.88–7.87 (3H, m), 7.46 (2H, t, $J = 7.50$ Hz), 7.40–7.36 (1H, m), 5.28 (2H, s), 2.30 (3H, s). $^{13}\text{C-NMR}$ (125 MHz, CDCl_3): δ 199.61 (CO), 148.64, 130.77, 129.30, 128.74, 126.22, 121.55, 58.96, 27.66. HRMS (CI): MH^+ , $\text{C}_{12}\text{H}_{12}\text{BrN}_3\text{O}_2$ requires 201.2, found: 201.2.

1-(4-bromophenyl)-2-[(4-(1-hydroxyethyl)-1H-1,2,3-triazole-1-yl)]-1-ethanone (7b of Table 3, 0.191 g, 83%, white solid crystals) [21]. IR (cm^{-1}): 3417 (OH), 1704 (CO), 1599, 1497, 1250 cm^{-1} ; $^1\text{H-NMR}$ (400 MHz DMSO-d_6) δ 8.37 (1H, s, CH triazole), 7.95 (2H, d, $J = 8.6$ Hz), 7.79 (2H, d,

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