Journal of Saudi Chemical Society (2016) xxx, xxx–xxx

King Saud University

Journal of Saudi Chemical Society

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ORIGINAL ARTICLE

Highly efficient transition metal-free coupling of acid chlorides with terminal alkynes in [bmim]Br: A rapid route to access ynones using $MgCl_2$

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Received 3 May 2016; revised 8 June 2016; accepted 13 June 2016

KEYWORDS

α,β-Acetylenic ketone;
Acid chloride;
Alkyne;
C–C coupling reaction;
Ionic liquid;
Magnesium chloride

Abstract A simple, mild, highly efficient and transition metal-free protocol for synthesis of ynones in an ionic liquid is described. In this approach, the coupling reaction of different acid chlorides with terminal alkynes was efficiently carried out using 0.05 mol% $MgCl_2$ in the presence of triethylamine in [bmim]Br at room temperature to afford the corresponding ynones in good to excellent yields. This method is highly efficient for various acid chlorides and alkynes including aliphatic, aromatic, and heteroaromatic substrates bearing different functional groups. The influence of some parameters in this reaction including type of ionic liquid, base and catalyst has been discussed.

1. Introduction

Ynones (α,β-acetylenic ketones) have received considerable interest due to their widespread occurrence in natural products, bioactive molecules and pharmaceuticals [1–3]. The bifunctional electrophilic nature of ynones has led to their extensive utilization in organic and medicinal chemistry. Ynones are known as reactive Michael acceptors and hence, they often serve as beneficial three-carbon building blocks for the synthesis of diverse heterocycles [1,4–7]. Since the enormous practical applications found for ynones, many synthetic approaches were developed to afford a plenty of ynones [1]. To this end, the classical methods to access ynones involve palladium-catalyzed carbonylative Sonogashira coupling of aryl bromides with terminal alkynes or the metalated derivatives [8–11], direct oxidative nucleophilic addition of an aldehyde to a metal acetylide [12,13] or alkyne [14], oxidation of the propargylic alcohol derivatives [15,16], α-oxidation of an alkyne [17,18], and the palladium-catalyzed coupling reaction of carboxylic acids with terminal alkynes or metal acetylides [19–23]. Recently, the addition of terminal alkynes or metalated derivatives to nitriles [24,25], gold catalyzed dehydrogenative Meyer–Schuster-like rearrangement of propargylic pivalates [26], and palladium-catalyzed carbonylative Sonogashira coupling of aryl bromides via tert-butyl isocyanide insertion [27] have also been reported to produce ynones. Up to now, among different approaches established so far to access ynones, the palladium catalyzed coupling of terminal alkynes with acid chlorides has been extensively used due to protocol's diversity, wide functional group tolerance, mild

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Peer review under responsibility of King Saud University.

Production and hosting by Elsevier

http://dx.doi.org/10.1016/j.jscs.2016.06.001

Please cite this article in press as: M.N. Soltani Rad, Highly efficient transition metal-free coupling of acid chlorides with terminal alkynes in [bmim]Br: A rapid route to access ynones using $MgCl_2$, Journal of Saudi Chemical Society (2016), http://dx.doi.org/10.1016/j.jscs.2016.06.001

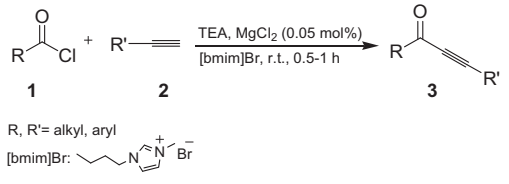
conditions, and high yields [28–30]. However, the uses of expensive palladium catalysts, the difficulties in purification, and separation of the metal–ligand complexes from the main products, have restricted the applicability of this approach. Therefore, developing an efficient and convenient palladium-free protocol for readily achieving the ynones is of great significance. To this end, the use of metal salts such as Cu(I) [31,32] and Zn(II) [33] salts has been reported to achieve the coupling reaction of alkynes with acid chlorides. The reaction of diverse alkynyl organometallic reagents with acid chlorides has also been developed as an alternative method for production of ynones [1]. Recently, Taylor and Bolshan developed the synthesis of ynones from acid chlorides and potassium alkynyltrifluoroborate salts in the presence of BCl_3 [34]. Feng and coworkers reported the decarboxylative alkynylation of α-keto acids for synthesis of ynones under transition metal-free conditions [35]. Although procedures utilizing the alkynyl organometallic reagents achieve the ynones in satisfactory yields; however, the preparation of the starting substrates is often expensive and cumbersome. Moreover, Cu(I) salts catalyzed alkyne-alkyne homocoupling side reaction results in lower yields of the desired ynone. Hence, there is a substantial need for establishing a convenient, practical, and efficient protocol for synthesis of ynones.

Ionic liquids (ILs) have unique properties such as low vapor pressure, high thermal stability, extreme of polarity, ability to dissolve a wide range of materials, non-flammability, non-corrosivity, and recyclability. Due to their green credentials, ionic liquids proved to be an excellent environmentally benign reaction media to substitute the toxic and hazardous solvents in organic reactions [36]. Up to now, the structurally diverse ionic liquids have been extensively employed in different organic reactions [37]. As an instance, the synthesis of ynones via palladium-catalyzed carbonylative Sonogashira coupling of aryl bromides with terminal alkynes has been reported in room temperature ionic liquids (RTILs) [38,39]. In this connection, the direct transition metal-free coupling of terminal alkynes with acid chlorides in ionic liquid would be a highly advantageous strategy. However, to the best of our knowledge, there has been no report yet on this attractive approach. Hereby, we would like to report a very mild, environmentally benign, cheap and highly efficient synthetic methodology for gaining ynones through the transition metal-free coupling of acid chlorides with terminal alkynes using $MgCl_2$ in the presence of triethylamine (TEA) in [bmim]Br at room temperature (Scheme 1).

2. Experimental

2.1. General

All chemicals were purchased from either Fluka or Merck. Solvents were purified and stored over 3 Å molecular sieves.



Scheme 1 Coupling of acid chlorides with terminal alkynes using $MgCl_2$ in [bmim]Br.

Reactions were followed by TLC using SILG/UV 254 silica-gel plates. Column chromatography was performed on silica gel 60 (0.063–0.200 mm, 70–230 mesh; ASTM). Melting points were measured using Electrothermal IA 9000 melting point apparatus in open capillary tubes and are uncorrected. Elemental analyses were performed on a Perkin-Elmer 240-B micro-analyzer. IR spectra were obtained using a Shimadzu FT-IR-8300 spectrophotometer. ^{1}H- and ^{13}C-NMR spectrum was recorded on Brüker Avance-DPX-250 spectrometer operating at 250/62.5, respectively. Chemical shifts are given in δ relative to tetramethylsilane (TMS) as an internal standard, coupling constants *J* are given in Hz. Abbreviations used for ^{1}H NMR signals are: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad and etc. GC/MS was performed on a Shimadzu GC/MS-QP 1000-EX apparatus (*m*/*z*; rel.%). High resolution mass spectra (HRMS) were obtained on a Jeol JMS 700 high resolution mass spectrometer.

2.2. Synthesis of Ynones (*3a–3p*)

To a round bottom flask (50 mL), was added a mixture of acid chloride (10 mmol), alkyne (12 mmol), TEA (12 mmol), and anhydrous $MgCl_2$ (0.5 mmol, 0.05 mol%) in [bmim]Br (10 mL). The reaction mixture was stirred at room temperature for the appropriate time (Table 4). The mixture was then diluted with water (150 mL) and extracted with $CHCl_3$ (2 × 50 mL). The organic layer was separated, dried (Na_2SO_4) and evaporated in vacuo. The crude product was purified by short column chromatography on silica gel eluting with a mixture of hexane/AcOEt.

2.2.1. 1,3-Diphenylprop-2-yn-1-one (*3a*)

Column chromatography (Hexane/AcOEt, 15:1) yielded 1.93 g (94%). Yellow liquid. IR (film): 2195 (C≡C), 1648 (C=O). ^{1}H-NMR ($CDCl_3$, 250 MHz): 8.20 (*d*, *J* = 8.1, 2 H); 7.78 (*d*, *J* = 8.1, 2 H); 7.70–7.49 (m, 6 H). ^{13}C-NMR ($CDCl_3$, 62.5 MHz): 176.1; 136.7; 133.9; 132.4; 130.8; 129.5; 128.9; 128.2; 119.6; 93.1; 87.2. MS: 206 (16.1, M^+). Anal. calc. for $C_{15}H_{10}O$: C 87.36, H 4.89; found: C 87.30, H 4.96. HRMS (EI$^+$): *m*/*z* [M]$^+$ calcd for $C_{15}H_{10}O$: 206.0732; found: 206.0731.

2.2.2. 3-(4-Methoxyphenyl)-1-phenylprop-2-yn-1-one (*3b*)

Column chromatography (Hexane/AcOEt, 15:1) yielded 2.17 g (92%). White solid. M.p. 68–70 °C. IR (KBr): 2198 (C≡C), 1644 (C=O). ^{1}H-NMR ($CDCl_3$, 250 MHz): 8.15 (*d*, *J* = 8.2, 2 H); 7.68–7.50 (m, 5 H); 6.97 (*d*, *J* = 8.2, 2 H); 3.85 (s, 3 H). ^{13}C-NMR ($CDCl_3$, 62.5 MHz): 177.4; 161.0; 137.5; 134.5; 133.2; 130.1; 128.0; 115.1; 113.8; 97.9; 88.3; 54.1. MS: 236 (17.8, M^+). Anal. calc. for $C_{16}H_{12}O_2$: C 81.34, H 5.12; found: C 81.45, H 5.24. HRMS (EI$^+$): *m*/*z* [M]$^+$ calcd for $C_{16}H_{12}O_2$: 236.0837; found: 236.0837.

2.2.3. 3-(4-Nitrophenyl)-1-phenylprop-2-yn-1-one (*3c*)

Column chromatography (Hexane/AcOEt, 15:1) yielded 2.38 g (95%). Orange solid. M.p. 147–149 °C. IR (KBr): 2201 (C≡C), 1647 (C=O). ^{1}H-NMR ($CDCl_3$, 250 MHz): 8.29 (*d*, *J* = 8.0, 2 H); 8.17 (*d*, *J* = 8.0, 2 H); 7.90 (*d*, *J* = 8.0, 2 H); 7.70–7.53 (m, 3 H). ^{13}C-NMR ($CDCl_3$, 62.5 MHz): 178.1; 149.8; 137.9; 135.0; 133.1; 128.9; 128.6; 126.9; 124.0;

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