Journal of Catalysis 319 (2014) 258–264

Contents lists available at ScienceDirect

Journal of Catalysis

journal homepage: www.elsevier.com/locate/jcat

Propargylamine synthesis *via* sequential methylation and C–H functionalization of *N*-methylanilines and terminal alkynes under metal–organic framework $Cu_2(BDC)_2(DABCO)$ catalysis

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ARTICLE INFO

Article history:
Received 15 May 2014
Revised 10 September 2014
Accepted 12 September 2014
Available online 3 October 2014

Keywords:
Metal–organic framework
C–C coupling
Copper-catalyzed
C–H functionalization
Propargylamine

ABSTRACT

A crystalline porous metal–organic framework $Cu_2(BDC)_2(DABCO)$ was synthesized and characterized by X-ray powder diffraction (XRD), scanning electron microscopy (SEM), transmission electron microscopy (TEM), thermogravimetric analysis (TGA), Fourier transform infrared (FT-IR), atomic absorption spectrophotometry (AAS), hydrogen temperature-programmed reduction (H_2-TPR), and nitrogen physisorption measurements. The $Cu_2(BDC)_2(DABCO)$ was used as a heterogeneous catalyst for the direct C–C coupling reaction *via* cascade methylation and C–H functionalization of *N*-methylaniline and terminal alkynes. *tert*-Butyl hydroperoxide also served as the methylating reagent in the transformation, and *N*-methyl-*N*-(3-phenylprop-2-ynyl)benzenamine but not *N*-(3-phenylprop-2-ynyl)benzenamine was produced as the principal product. The Cu-MOF could be recovered and reused several times without a significant degradation in catalytic activity. To the best of our knowledge, the direct oxidative C–C coupling between *N*-methylaniline and alkynes with methylation transformation was not previously mentioned in the literature.

1. Introduction

The potential applications of propargylamine in optical materials, molecular devices, or pharmaceutical are well recognized [1]. Traditional routes to access these molecules often suffer from disadvantages such as harsh conditions, low yields, and limited reaction scope [2]. Nucleophilic addition of alkynyl Grignards to imines or enamines is example in which functional group tolerance is limited and low yields were observed in most cases [3,4]. Therefore, it is interesting to develop more convenient methods for propargylamine synthesis. Recently, the most attractive synthetic route is the use of Mannich-type reaction, a three component procedure of terminal alkynes, formaldehyde, and secondary amines [5]. Transition metals are often employed as catalysts for these two-step reactions. Over the past few decades, many excellent reports have been described using various transition-metal catalysis including copper, gold, and silver [6–8]. However, difficulties in removing catalysts contaminated in final products narrow the application of homogeneous catalytic systems, especially in pharmaceutical industry [9]. As a consequent, a few supported reactions or reactions using heterogeneous catalysts have recently been demonstrated [10,11]. However, the aldehyde-free, oxidative Mannich reactions have not been previously reported under any catalysis.

A new class of crystalline porous materials known as metal–organic frameworks (MOFs) has recently attracted significant attention with potential applications in several areas, including gas storage, sensors, thin films, optics, drug carriers, and catalysis [12–16]. Combining advantages of both organic and inorganic porous materials, MOFs exhibit several special properties such as the ability to tune pore size, high surface areas, well-defined structures, and structural diversity [12,13,17–24]. Although MOFs have just been investigated for application in catalysis, this should be undoubtedly a promising field that will attract further research in the near future [25,26]. Either the active sites could be part of the MOF structure or they could be post-functionalized to the framework [26–29]. Many MOFs have been used efficiently heterogeneous catalysts or catalyst supports for a variety of organic transformations, ranging from carbon–carbon [30–32] to carbon-heteroatom forming reactions [33–37]. Among several popular MOFs, copper-based frameworks previously exhibited high activity in various organic reactions due to their unsaturated open copper metal sites [38–43]. In this work, we present the direct C–C coupling reaction *via* methylation and C–H functionalization of

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http://dx.doi.org/10.1016/j.jcat.2014.09.010
0021-9517/

N-methylaniline and terminal alkynes. Interestingly, *tert*-butyl hydroperoxide was proposed to serve as the methylating reagent in the coupling reaction, and *N*-methyl-N-(3-phenylprop-2-ynyl)benzenamine but not *N*-(3-phenylprop-2-ynyl)benzenamine was produced as the principal product. To the best of our knowledge, this direct oxidative C–C coupling with methylation transformation was not previously mentioned in the literature.

2. Experimental

2.1. Synthesis of the metal–organic framework $Cu_2(BDC)_2(DABCO)$

In a typical preparation [44–47], a mixture of H_2BDC (H_2BDC = 1,4-benzenedicarboxylic acid; 0.506 g, 3.1 mmol), DABCO (DABCO = 1,4-diazabicyclo[2.2.2]octane; 0.188 g, 1.67 mmol), and $Cu(NO_3)_2{\cdot}3H_2O$ (0.8 g, 3.3 mmol) was dissolved in DMF (DMF = *N*,*N*′-dimethylformamide; 80 mL). The mixture was stirred for 2 h, and the resulting solution was then distributed to eight 10 mL vials. The vial was heated at 120 °C in an isothermal oven for 48 h, forming blue crystals. After cooling the vial to room temperature, the solid product was removed by decanting with mother liquor and washed with DMF (3 × 10 mL). Solvent exchange was carried out with methanol (3 × 10 mL) at room temperature. The product was then dried at 140 °C for 6 h under vacuum, yielding 0.57 g of the metal–organic framework $Cu_2(BDC)_2(DABCO)$ as light blue crystals (66% based on 1,4-benzenedicarboxylic acid).

2.2. Catalytic studies

In a typical experiment, a pre-determined amount of the $Cu_2(BDC)_2(DABCO)$ was added to the flask containing a mixture of phenylacetylene (0.11 mL, 1 mmol), *N*-methylaniline (0.22 mL, 2 mmol), *tert*-butyl hydroperoxide (TBHP) (70% in water, 0.41 mL, 3 mmol) as an oxidant, and *n*-hexadecane (0.1 mL) as an internal standard in *N*,*N*-dimethylacetamide (DMA) (4 mL) under an argon atmosphere. The catalyst percentage was calculated based on the molar ratio of copper/phenylacetylene. The reaction mixture was stirred at 120 °C for 180 min. The reaction conversion was monitored by withdrawing aliquots from the reaction mixture at different time intervals, quenching with water (1 mL), drying over anhydrous Na_2SO_4, analyzing by GC with reference to *n*-hexadecane, and further confirming product identity by GC–MS, and ^1H NMR and ^{13}C NMR. To investigate the recyclability of the $Cu_2(BDC)_2(DABCO)$, the catalyst was filtered from the reaction mixture after the experiment, washed with copious amounts of DMA, dried at 140 °C under vacuum in 6 h, and reused if necessary. For the leaching test, a catalytic reaction was stopped after 10 min, analyzed by GC, and filtered to remove the solid catalyst. The reaction solution was then stirred for a further 170 min. Reaction progress, if any, was monitored by GC as previously described.

3. Results and discussion

The Cu-MOF was characterized by several techniques, including XRD, SEM, TEM, TGA, FT-IR, AAS, and nitrogen physisorption measurements (Figs. S11–S18). The $Cu_2(BDC)_2(DABCO)$ was used as a heterogeneous catalyst for the direct C–C coupling reaction *via* C–H functionalization between *N*-methylaniline and phenylacetylene. Initial studies indicated that the $Cu_2(BDC)_2(DABCO)$-catalyzed C–C coupling reaction formed two products, as indicated by GC–MS analysis. The two coupling products were also isolated from the reaction mixture by column chromatography, and their structures were confirmed by ^1H NMR, and ^{13}C NMR. Interestingly, it was found that (A) but not (B) was produced as the principal product of the direct C–C coupling reaction (Scheme 1). Indeed, Li and co-workers previously reported the palladium-catalyzed methylation of arenes by using peroxides, acting as both the methylating reagent and the hydrogen acceptor [48]. Recently, Chen and co-workers also demonstrated the copper-catalyzed *N*-methylation of amides and *O*-methylation of carboxylic acids by using peroxides as the methylating reagents [49]. The fact that (A) was the major product led us to predict that the *tert*-butyl hydroperoxide also served as the methylating reagent.

Effect of reaction temperature on conversion was kinetically investigated. It was observed that the reaction could not proceed at room temperature with no trace amount of product being detected after 180 min. The reaction carried out at 100 °C could afford 37% conversion after 180 min. Increasing the temperature to 110 °C led to a significant enhancement in the reaction rate, reaching 67% conversion after 180 min. The reaction conversion could be improved to 95% after 180 min for the reaction carried out at 120 °C (Fig. 1). It should be noted that the $Cu_2(BDC)_2(DABCO)$-catalyzed C–C coupling reaction could proceed to completion after 180 min at 130 °C. However, the Cu-MOF catalyst was partially decomposed under this condition. It was also found that the temperature exhibited a profound effect on the reaction selectivity (Fig. S19). The reaction carried out at 100 °C produced 29% (A), leaving 71% (B) in the product mixture after 180 min. However, the product distribution changed dramatically at 110 °C, with up to 69% (A) being achieved after 180 min. Increasing the temperature to 120 °C resulted in 80% (A) and 20% (B) in the product mixture.

The effect of catalyst loading with 1 mol%, 3 mol%, 7 mol% $Cu_2(BDC)_2(DABCO)$ catalyst was investigated. Decreasing the catalyst percentage resulted in a drop in the reaction rate, with 88% and 82% conversions being obtained after 180 min for the reaction using 3 mol% and 1 mol% catalyst, respectively (Fig. 2). Similar conversion was obtained when 7% catalyst was employed. Thus, the catalyst loading higher than 5% does not increase the reaction efficiency. Furthermore, only 10% conversion was obtained in the absence of the $Cu_2(BDC)_2(DABCO)$ catalyst, confirming the necessity of using the Cu-MOF as catalyst for the direct C–C coupling reaction. Li and co-workers previously employed 5 mol% CuBr as the catalyst for the direct C–C coupling reaction between *N*,*N*-dimethylaniline and phenylacetylene to form (A) [50]. Furthermore, it was found that the catalyst loading did not significantly affect the selectivity of the reaction (Fig. S20). Moreover, it was observed that using more than two equivalents of *N*-methylaniline was not necessary, while the reaction using one equivalent of the reagent afforded only 79% conversion after 180 min (Fig. 3).

In next study, several oxidants were employed for the transformation, including *tert*-butyl hydroperoxide in water, *tert*-butyl hydroperoxide in decane, di-*tert*-butyl peroxide, dilauroyl peroxide, and $K_2S_2O_8$. The direct C–C coupling reaction was carried out at 120 °C in DMA for 180 min, using two equivalents of *N*-methylaniline, in the presence of three equivalents of the oxidant, at 5 mol% $Cu_2(BDC)_2(DABCO)$ catalyst. Decomposition of starting material was observed when dilauroyl peroxide and $K_2S_2O_8$ were employed. Additionally, no trace amount of the desired product was detected when using oxidants that do not possess methyl group supports our hypothesis about the methylating source. As expected, the reaction using di-*tert*-butyl peroxide as the oxidant also proceeded with difficulty, though 44% conversion was still observed after 180 min. Both *tert*-butyl hydroperoxide in water and *tert*-butyl hydroperoxide in decane were found to be effective, though higher reaction rate was observed for the case of *tert*-butyl hydroperoxide in decane (Fig. 4). A selectivity of 80% to (A) was achieved for the reaction using *tert*-butyl hydroperoxide either in water or in decane as the oxidant. With respect to oxidant, in general, peroxides containing methyl group on the alkyl chain are suitable under tested conditions.