$[Cu_2(BDC)_2(BPY)]$ as Excellent Catalyst for The Synthesis of Pyrazine Derivatives

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Abstract

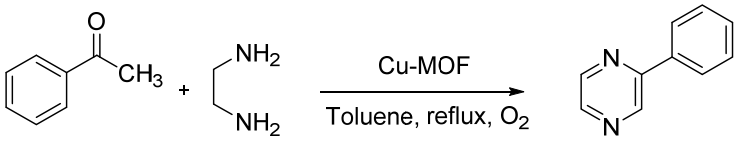
A nano mesoporous metal-organic framework $Cu_2(BDC)_2(BPY)$ (BDC=1,4-benzenedicarboxylate, BPY= 4,4'-bipyridine) could be employed as a heterogeneous catalyst for the copper-catalyzed oxidative C–H/N–H coupling between simple ketones and diamines to form pyrazines. The $Cu_2(BDC)_2(DABCO)$ offered higher catalytic activity than common copper salts such as CuCl, CuBr and CuI.

Keywords: Pyrazine, Oxidative- Coupling**,** Cu-MOFs, $Cu_2(BDC)_2(BPY)$

1. Introduction

Compounds containing N-heterocyclic moieties are a class of privileged compounds that have found numerous applications as pharmaceuticals. Pyrazines are important components of aroma fragrances [1], potential pharmacophore of a large number of biologically active substances [2-6] and widely used as agrochemicals [7-9]. Pyrazines are a vital class of heterocyclic compounds present in nature and are also synthesized in the laboratory since 1876 [10-12]. Different synthetic methods have been adopted to prepare these biologically important heterocyclic derivatives [13-16]. In particular, pyrazine derivatives exhibit wide range of pharmaceutical activities as anti-inflammatory [18], anticancer [19], antidiabetic [17] and diuretic [20] Pyrazine derivatives are important class of compounds with diverse biological and cytotoxic activities and clinical applications. For example, methoxy pyrazines are relevant components of aromas of many fruits, vegetables, and wines; methyl phenyl derivatives of dihydropyrazines inhibit the growth of Echerichia coli by generating hydroxyl and carbenecentered radicals that cause DNA strand breakage and alkylpyrazines have been recognized as flavor components in foods, as pheromones in various insect species [7, 8], and as versatile synthetic intermediates. Pyrazine derivatives are known for use as relaxing cardiovascular and uterine smooth muscle, antithrombotic, anti-aggregation, COX-2

inhibiting, and analgesic effects [21] Because of the wide variety of applications associated with the pyrazine moieties, their synthesis has remained the goal of many research groups over the years. Herein, we effort to report for the first time a convenient, more efficient and green method for the synthesis of pyrazine catalyzed by Cu-MOFs (Scheme 1).



Scheme 1. Synthesis of pyrazine derivatives catalyzed by $Cu_2(BDC)_2BPY$

The past decade has seen explosive growth in the preparation, characterization, and study of materials known as metal-organic frameworks (MOFs). These materials are constructed by joining metal-containing units [secondary building units (SBUs)] with organic linkers, using strong bonds (reticular synthesis) to create open crystalline frameworks with permanent porosity [22]. MOFs have exceptional porosity and a wide range of potential uses including gas storage, separations, and catalysis [23]. In particular, applications in energy technologies such as fuel cells, supercapacitors, and catalytic conversions have made them objects of extensive study, industrial-scale production, and application [23–24].

2. Experimental

All reagents including organic linker H_2BDC, metal salt $Cu(OAc)_2.H_2O$, 1,4-benzenedicarboxylate (BDC, 99%), 4,4'-bipyridine (BPY), acetophenone derivatives and ethylene diamine were obtained from commercially available sources such as Sigma–Aldrich and Merck without any purification. ^{1}H and ^{13}C-NMR spectra were measured ($CDCl_3$) with a Bruker DRX-500 AVANCE spectrometer at 500.13 and 125.8 MHz, respectively.

General Procedure for synthesis of 2-Phenylpyrazine:

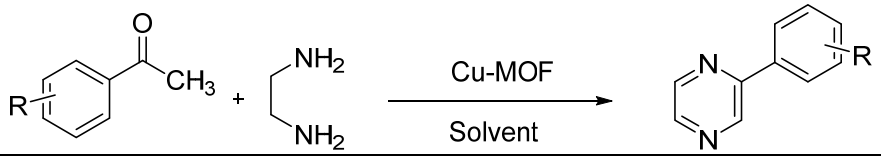
$[Cu_2(BDC)_2$ (BPY)] was synthesized by method are reported in literature [25]. Acetophenone (120 mg, 1 mmol), C_2H_4 $(NH_2)_2$ (120 mg, 2 mmol) and [Cu_2 $(BDC)_2BPY$] (0.02 g) were added to a round-bottom flask in Toluene (10 ml) in an inert oxygen atmosphere. Further, the reaction mixture was stirred at 120°C for 20 hours. After Completion of the reaction confirmed by TLC, catalyst was filtered and the solvent was

evaporated at reduced pressure to afford the crude product. Crude product was purified by column chromatography (EtOAc: Hexane (1:3)). White solid, Isolated yield = 52%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.01 (d, J = 1.1 Hz, 1H), 8.60 – 8.64 (m, 1H), 8.46 (d, J = 2.6 Hz, 1H), 7.92 -8.02 (m, 2H), 7.37-7.67 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.2, 144.1, 142.9, 142.4, 136.3, 130.0, 129.1, 127.0.

3. Results and Discussion

The $[Cu_2(bdc)_2(bpy)]$ was used as a selective and heterogeneous catalyst for the oxidative-coupling reaction of acetophenone with ethylene diamine to form corresponding pyrazines as the principal product (scheme 1). Aiming to optimize the reaction conditions, an initial experiment was conducted by using the reaction of acetophenone as a model substrate with ethylene diamine under metal-free conditions or by using variable amounts of catalyst in the temperature of 110-120°C. In addition, to choose the best oxidant for this reaction, O_2 and *t*-BuOOH were evaluated. Reviews of various reaction conditions are summarized in Table 1.

Table 1. Optimization of the Reaction Conditions



Entry	Catalyst (Cu-MOF) (mg)	Oxidant	Solvent	Time (h)	T (°C)	Yield (%)
1	-	Air	Toluene	24	110	NR
2	20	Air	Toluene	24	110	22
3	-	TBHP	Toluene	24	110	NR
4	20	Air	DMF	24	120	25
5	10	TBHP	DMF	24	120	53
6	20	TBHP	Toluene	24	110	45
7	20	TBHP	DMF	24	120	52
8	30	TBHP	DMF	24	120	50
9	40	TBHP	DMF	24	120	52

As shown in Table 1, It is also worth mentioning that no reaction was observed between acetophenone with ethylene diamine in the absence of either catalyst or oxidant and no product detected (Table 1, entry 1 and 3). We found that reaction was carried out by air as oxidant in only 22% yield. Thus, it can be concluded that TBHP exhibited the best performance in the $[Cu_2(bdc)_2(bpy)]$ catalyzed oxidative coupling reaction. Moreover, experimental results revealed that the solvent exhibited a significant effect on the

reaction rate. In DMF as a solvent the yield of reaction increased. The results indicated that changing amounts of catalyst from 10mg to 40mg do not have any significant effect in yield of reaction (Table 1, entry 4-5). Therefore, under the optimized conditions, we investigated the reaction of various types of acetophenone with ethylene diamine. Interestingly, in all of the conversions, oxidation-sensitive and versatile groups remain intact. Along these lines, electron-donating, electron-withdrawing groups could smoothly decrease the yield of the reaction.

4. Conclusions

In summary, we have described that $Cu_2(BDC)_2(BPY)$ can be used as an available and environmentally friendly Catalyst for synthesis of pyrazine derivatives. The advantages of this procedure, good yield, easy work up, recovery and reusability of the catalyst.

Acknowledgements

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