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$Cu_3(BTC)_2$ as a viable heterogeneous solid catalyst for Friedel-Crafts alkylation of indoles with nitroalkenes

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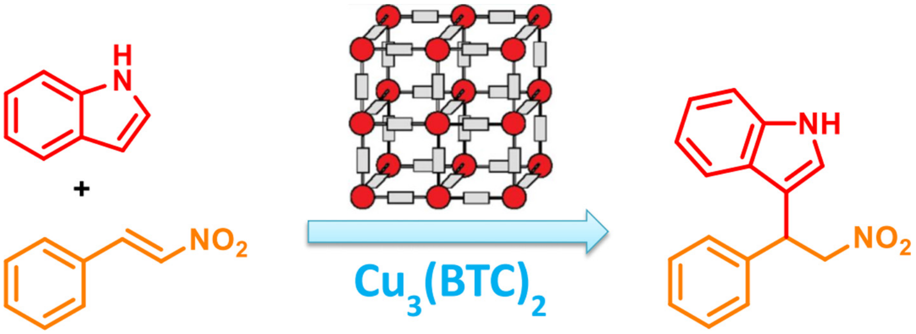
GRAPHICAL ABSTRACT

This manuscript reports the Fridel-Crafts alkylation reaction between indole and β-nitrostyrene using $Cu_3(BTC)_2$ as a reusable solid catalyst under mild reaction conditions.



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ABSTRACT

In the present work, Friedel-Crafts alkylation reaction of indole with β-nitrostyrene is examined using a readily available copper based metal-organic frameworks (MOFs) namely, $Cu_3(BTC)_2$ (BTC: 1,3,5-benzenetricarboxylic acid) as solid catalyst under mild reaction conditions. Among the various catalysts screened for this reaction, $Cu_3(BTC)_2$ exhibits higher activity under the optimized reaction conditions. Besides the absence of leaching of active sites, it is also observed that the catalyst can be reused for four cycles with a minimal decrease in its activity. $Cu_3(BTC)_2$ is used as a catalyst to synthesise a series of heterocyclic compounds with different indole and β-nitrostyrene derivatives in moderate to high yields. The present catalytic system shows comparable activity against to recent reports but the advantage of $Cu_3(BTC)_2$ is that it does not require any post-functionalization and above all it can be readily synthesised, thus contributing to the synthesis of heterocyclic compounds with high biological interest.

1. Introduction

Metal organic Frameworks (MOFs) are a class of porous crystalline materials whose crystal structure is composed between metal ions or inorganic nodes with polydendate organic linkers [1]. They have uniform three dimensional structures with very high surface area, large pore sizes, low density, and have potential applications in gas sorption [2,3], molecular recognition [4], proton conductivity [5], organocatalysis [6–9] and heterogeneous catalysis [10–12]. In addition, MOFs have advantages in their modular synthesis and the porosity can be easily tuned,

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thus, attracting as a solid porous materials for heterogeneous catalysis [13].

The Friedel-Crafts alkylation reactions between indole and β-nitroalkenes such as β-nitrostyrene, are of particular interest since these are the most widely employed approach towards the synthesis of tryptamine derivatives [14]. In contrast to the reactions between β-nitroalkenes and N-alkylated indole derivatives such as 1-methylindole, reactions of unsubstituted indole with β-nitroalkenes are slow, due to the poor nucleophilicity of indole [15,16]. In order to overcome this crucial barrier, as tryptamine derivatives containing non-N substituted indole backbones are important precursors in the synthesis of biologically active alkaloids, such as tryptophan [17,18], neurotransmitters like serotonin [19,20], anti-tumour drugs like lavendamycin [21], and psychedelic compounds such as psilocybin [22]. Hence, the current target is to develop a simple, cost-effective and readily available catalytic system for this organic transformation.

In recent years, the use of mixed linker MOFs has attracted many research groups due to the possibility of attaining different structural motifs which finds extensive applications in heterogeneous catalysis [13]. Hupp and co-workers have developed UiO-67-Squar/bpdc MOF [23], using a combination of unfunctionalized and squaramide appended biphenyl dicarboxylate (bpdc) ligands. It was observed that MOFs with 100% squaramide ligand incorporation showed low catalytic activity which is similar to those MOFs with 100% unfunctionalized bpdc ligand. Furthermore, the reaction of β-nitrostyrene with indole in the presence of UiO-67-Squar/bpdc MOFs with 50% squaramide ligand showed 95% yield of the desired product which was believed to be due to optimal catalytic sites and available MOF porosity. Later, Cohen and co-workers have reported an alternative approach for the synthesis of Cu(dbda) using squaramide ligand [24] and its catalytic activity is examined in the reaction between β-nitrostyrene and indole to afford 99% yield of the desired product after 24 h in chloroform. A (3,24)-connected *rht*-type MOFs, namely, Cu-UBTA containing a urea group was readily prepared between a hexacarboxylate ligand and $Cu(NO_3)_2$ and its activity is tested in the Friedel-Crafts alkylation of *N*-methyl pyrrole or indole with nitroalkenes [25].

HKUST-1 [26] (HKUST stands for Hong Kong University of Science and Technology) also known as $Cu_3(BTC)_2$ has been widely used as heterogeneous catalysts for a variety of reactions [10,27–30], but however, the chemical stability of $Cu_3(BTC)_2$ was reported to be unstable in the aerobic oxidation of thiols [31] and the synthesis of 2-phenylbenzimidazole [32]. Hence, in the present work, we wish to report a simple, robust and readily available $Cu_3(BTC)_2$ as a heterogeneous catalyst for the Friedel-Crafts alkylation between indole and β-nitrostyrene to achieve high yield of the desired product which is comparable to earlier precedents [23,24]. Leaching and reusability experiments further support that $Cu_3(BTC)_2$ is a convenient catalyst for the synthesis of a variety of these biologically interested heterocyclic compounds in moderate to high yields.

2. Results and discussions

The Friedel-Crafts alkylation reaction of indole with β-nitrostyrene is studied by selecting four different MOFs, namely $Cu_3(BTC)_2$, Fe(BTC), Zr(BDC) (BDC: 1,4-benzenedicarboxylate) and Zr(PDC) (PDC: 2,6-pyridinedicarboxylate) based on their wide reactivity and stability in liquid phase reactions [33]. Fe(BTC) contains 21.2% iron content with Fe(III) as nodal metal and tripodal BTC as ligand. It is believed that the crystal structure of Fe(BTC) resembles with MIL-100(Fe) [34] which is an iron(III) carboxylate built up from trimers of iron octahedra sharing a common vertex μ_3-O. The trimers are linked by the BTC ligands in such a way that this leads to the formation of hybrid supertetrahedra thus resulting in two types of mesoporous cages of free apertures of around 25 and 29 Å, accessible through microporous windows of around 5.5 and 8.6 Å [34]. The second MOF in the list is $Cu_3(BTC)_2$ whose crystal structure is constituted by clusters of two copper ions coordinated with four carboxylate groups of BTC defining a paddle-wheel building unit that acts as a structural node held in place by the tripodal BTC linkers [26]. It has a surface area around $1050\ m^2/g$ with 11, 16 and 6 Å pore dimensions. The crystal structure of UiO-66 is constructed between cationic $Zr_6O_4(OH)_4$ nodes formed in situ via hydrolysis of $ZrCl_4$ and BDC linkers with a cubic framework having high crystallinity [35]. In a similar way, Zr(PDC) is also obtained by replacing BDC with PDC as ligand.

The catalytic activity of $Cu_3(BTC)_2$ was assessed in the Friedel-Crafts alkylation between trans-β-nitrostyrene and indole in neat as well as in the presence of various solvents. This reaction resulted in 73% yield of the desired coupling product with $Cu_3(BTC)_2$ as catalyst at 60 °C after 24 h in ethanol (entry 1, Table 1). On the other hand, $Cu_3(BTC)_2$ exhibited 16% yields in acetone and acetonitrile as solvents after 24 h (entries 3–4, Table 1). A considerably high yield was observed when the reaction is performed in chloroform after 24 h using $Cu_3(BTC)_2$ as catalyst (entry 5, Table 1). This result is in good agreement with a recent precedent in where Cu-based MOF exhibited more than 95% yield for the same reaction [24]. In contrast, the same reaction using pre-activated $Cu_3(BTC)_2$ exhibited a significant decrease in the yield to 40% of the desired product (entry 6, Table 1). This may be attributed to the strong adsorption of reactants on the catalyst, thus reducing the population of coordinatively unsaturated sites on $Cu_3(BTC)_2$. The choice of dioxane, THF and DMF as solvents showed poor yields (entries 7–9, Table 1). On the other hand, $Cu_3(BTC)_2$ gave 14% yield of the product in DMSO as solvent (entry 10, Table 1). This is attributed to the diffusion limitations of the reactants to reach the active Lewis acid sites or strong binding of solvent (DMF) with the active sites. In addition, 57% yield of the product was achieved when the reaction was performed in DCM as solvent at room temperature (entry 11, Table 1). A mixture of indole and β-nitrostyrene with $Cu_3(BTC)_2$ exhibited in 98% yield of the desired product in neat conditions without any solvent (entry 12, Table 1). Similarly, $Cu_3(BTC)_2$ resulted in 94% yield of the desired product using 2-propanol as solvent at 80 °C after 24 h (entry 13, Table 1). Here again, a slightly lower yield was observed with pre-activated catalyst (entry 14, Table 1). Under identical conditions, Fe(BTC), Zr(PDC) and Zr (BDC) catalysts showed 45, 39 and 25% yields of the respective product (entries 15–17, Table 1). These data clearly suggest that the activity of $Cu_3(BTC)_2$ is superior compared to other analogous catalysts tested under identical reaction conditions. Furthermore, a blank control in the absence of catalyst detected negligible yield using indole and β-nitrostyrene as substrates in toluene at 55 °C after 24 h (entry 18, Table 1). In contrast, the reaction of indole and β-nitrostyrene using $Cu_3(BTC)_2$ as catalyst afforded 98% yield under the same experimental conditions (entry 19, Table 1). Hence, the optimized reaction conditions to achieve the desired product is using $Cu_3(BTC)_2$ as catalyst in toluene at 55 °C and this protocol is followed for the reusability, leaching experiments and to study the scope of $Cu_3(BTC)_2$ with a wide variety of substrates.

Fig. 1 shows the time-conversion plot for the reaction between indole and β-nitrostyrene at 55 °C in toluene as solvent using $Cu_3(BTC)_2$, Zr(PDC), Zr(BDC) and Fe(BTC) as catalysts. These data suggest that the activity as well as the initial reaction rate of is much higher for $Cu_3(BTC)_2$ than the other three catalysts under identical conditions.

One of the best ways to establish the catalyst stability is to perform heterogeneity of the process. Therefore, leaching experiment was performed for the reaction between indole and β-nitrostyrene under the optimized reaction conditions. As shown in Fig. 2, the