

Research paper

An insight on the influence of surface Lewis acid sites for regioselective C–H bond C₃-cyanation of indole using NH₄I and DMF as combined cyanide source over Cu/SBA-15 catalyst



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ABSTRACT

The Cu dispersed on mesoporous SBA-15 has demonstrated the regioselective C–H bond C₃-cyanation of indoles by in-situ generation of –CN using DMF and NH₄I in presence of O₂. Pyridine adsorbed diffuse reflectance infrared spectroscopy (DRIFTS) results revealed that surface Cu²⁺ species are acting as Lewis acid sites in the in-situ generation of cyano- group for the synthesis of indole nitriles. A direct correlation between Cu metal surface area and the indole nitrile yields are established and the dual role of copper is substantiated by N₂O titration and XPS techniques. The 10 wt%Cu/SBA-15 demonstrated superior performance when compared to Pd, Ru supported on SBA-15. The 10 wt%Cu/SBA-15 catalyst showed consistent activity and selectivity after the 4th cycle.

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1. Introduction

The derivatives of indole nitriles exhibit broad range of biological activities and they are present in many agrochemicals, dyes, pharmaceuticals and natural products as a backbone of their structural frameworks and are also widely used in organic synthesis [1]. Additionally, 3-cyanoindoles are key intermediates for the preparation of functional groups, such as aldehydes, amines, ketones, amidines, amides, tetrazoles and their carboxyl derivatives [2]. Notably, 3-cyanosubstituted indoles are core structures in many biologically active compounds currently being developed as estrogen receptor ligands, hepatitis C virus inhibitors, or therapeutic agents for cardiovascular diseases [3,4]. Aryl nitriles are generally prepared from classical organic transformations, such as Sandmeyer [5] and Rosenmund-von Braun reaction [6], which are pre-functionalized starting materials for the cyanation of aryldiazonium salts or aryl halides by stoichiometric amounts of CuCN. However, these reactions suffer from the toxic CuCN source at high temperature with prolonged times and also multiple procedures.

Recently, the transition-metal-catalyzed cyanation of aryl halides [7], borons [8] or mesylates provide a promising alternative

to the cyanation reactions [9]. In these procedures, several cyano sources were employed e.g. metal cyanides (NaCN, KCN, CuCN, TMS-CN, K₄[Fe(CN)₆]), BnCN, t-BuNC, electrophilic CN⁺ reagents (NCTs, BrCN), and combined cyano sources (NH₄I/DMF, DMF, NH₄HCO₃/DMSO, TMEDA/(NH₄)₂CO₃). Metal cyanides are frequently used as cyanide sources in various organic transformations. Nevertheless, almost all these methods suffer from limitations. An important issue to be resolved is the high affinity of the cyanide ion for the transition metal, which often results in rapid deactivation of catalyst. Moreover, most of the cyano sources, in particular NaCN, KCN and CuCN have notorious toxicity. For example Zn(CN)₂ leads to heavy metal waste and Me₃SiCN is sensitive to moisture and easily liberates hydrogen cyanide. Although K₄[Fe(CN)₆] is exceptionally nontoxic, its slow solubility in organic solvent limits its usage. Acetone cyanohydrins [10] would greatly decrease the utility of the aforementioned transformations. To this end, a number of CN-containing small organic molecules such as cyanohydrins [11], CH₃CN [12], as well as molecule without a CN group such as formamide [13], DMF [14] and nitromethane [15] have been shown to be effective CN sources for aromatic cyanation reactions. In addition, more complicated strategies for generating a CN group from combined sources have been reported to achieve aromatic cyanation reactions, e.g., DMF + NH₃ [16], DMF + NH₄I [17], DMF + NH₄HCO₃ [18,19]. However, the search for methods using safer and easy handling CN sources remains highly desirable. C–H

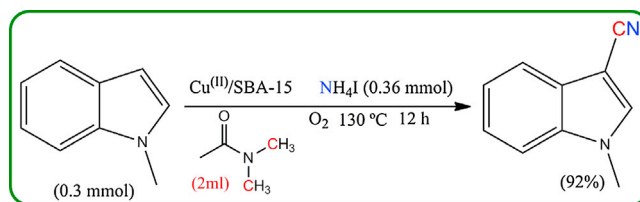
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activation of sp^2 centres presents unique challenges. Selective and direct cyanation of highly abundant C–H bonds of (hetero) arenes has emerged as a powerful tool to achieve atom and step economy in organic synthesis. Most of these processes involve either the use of expensive noble metals or non-eco-friendly reagents. Therefore, the development of inexpensive acidic metal catalysts for the selective cyanation of indoles has become a topic of interest.

In this investigation, SBA-15 has been chosen as the support material for various metals such as Cu, Ru, Pd and Ni are examined for the regioselective C₃-cyanation of indole. In the comparative analysis, Cu/SBA-15 demonstrated a better nitrile yield than the Ru/SBA-15, Ni/SBA-15 and Pd/SBA-15 catalysts thus showing economic viability of the catalyst. A significant amount of work on cyanation reactions has been reported by Chang and co-workers. They have used DMF and ammonia or ammonium salts as the combined 'CN' source to realize the cyanation of the carbon–hydrogen (heteroatom) bond [20]. Cyanation of aromatic halides by employing ammonium bicarbonate and DMF (or) DMSO as the combined 'CN' source was also achieved [18,20]. These methods for cyanation reactions involve the combined 'CN' source composed of DMF or DMSO which provides the 'C' unit of 'CN', while the 'N' unit comes from ammonia or ammonium salts. We have examined the cyanation of aromatic C–H bonds by using a combination of NH_4HCO_3 and DMSO as the 'CN' source over a Pd(II) on Mg–La mixed oxide [21]. Recently, we have explored supported copper catalyst for the cyanation of arenes using NH_4HCO_3 and *N,N*-dimethylformamide as a CN source [22]. Transition-metal-catalyzed direct C–H activation and functionalization has become a powerful tool in organic synthesis [23]. In particular, the building of C–C and C-heteroatom bonds directly from two simple carbon–hydrogen (C–H) bonds or C–H and H–Nu (Nu=B, O, N, S) bonds provides an unusually attractive pathway by virtue of its step economy, lower cost, and a decrease in waste production [24]. Jianbo Wang and co-workers reported the Pd-catalyzed cyanation using $K_4[Fe(CN)_6]$ as cyanating agent and selectively introduce a cyano group into the 3-position of indoles with high efficiency [25]. Khorshidi showed the selective 3-cyanation of indoles was achieved under Ru catalyst [26]. Chaitanya and Anbarasan demonstrated the Rh catalyzed cyanation of indoles [27]. Yang et al. reported the Lewis acid catalyzed direct cyanation of indoles [28]. Shen and co workers reported the Cu-catalyzed cyanation of indoles using acetonitrile as a cyano source [29].

In recent years, mesoporous silica materials have attracted the catalysis community because of mesoporous silica (SBA-15) exhibits interesting textural properties, such as thick framework walls, uniform-sized pores (4–30 nm), large specific surface areas (above $1000\text{ m}^2\text{ g}^{-1}$), high thermal stability and diffusion limitations and is widely used as catalyst supports, drug delivery materials [30–32], SBA-15 supported metals have revealed excellent activity and stability of the catalytic oxidation of organic compounds [33,34] and catalytic transfer hydrogenation and cyclization [35]. Herein, we report SBA-15 supported Cu catalysts for the selective 3-cyanation of indole C–H bonds by using a combination of NH_4I and DMF as the 'CN' source in the presence of oxygen is an attractive, atom-economic and environmentally benign oxidant due to the fact that it is cheap, widely available (20vol% of air) and clean (only water as by-product) to provide indole nitriles in good yields (Scheme 1). The Cu loaded SBA-15 samples are characterized by BET-surface area, powder X-ray diffraction (XRD), H_2 -temperature programmed reduction (H_2 -TPR), NH_3 -temperature programmed desorption (NH_3 -TPD), transmission electron microscopy (TEM), N_2O pulse titration for Cu metal surface area, X-ray photoelectron spectroscopy (XPS), pyridine adsorbed diffuse reflectance Fourier transformed infrared spectroscopy (DRIFTS).



Scheme 1. Cyanation of *N*-methylindole.

2. Experimental section

2.1. Catalyst preparation

The mesoporous siliceous SBA-15 support was prepared according to the procedure reported by Zhao et al. [36]. In a typical method, using 2.0 g Pluronic P123 tri-block co-polymer surfactant dissolved in 15 g water, followed by the addition of 60 g of 2 M HCl. Under constant stirring, 4.25 g TEOS was added and the mixture was stirred continuously for 24 h at 40 °C. The gel mixture was then subjected to heat treatment in an autoclave at 100 °C for 48 h. After filtration, the obtained gel was dried in an air oven at 80 °C for 12 h. The dried SBA-15 solid was calcined in air flow at 550 °C for 8 h. The resultant mesoporous silica (SBA-15: conformed by powder XRD) was used as support. A series of copper loadings e.g. 2.5, 5, 7.5, 10 and 12.5 wt% were prepared by wet impregnation method using $Cu(NO_3)_2 \cdot 3H_2O$ as copper precursor. The solid was dried in an oven at 100 °C for 12 h and subsequently calcined at 450 °C for 5 h in static air. The elemental analysis of prepared catalysts is investigated using atomic absorption spectroscopy and the results are listed in Table S1. The complete details on the characterization of the catalysts are given in Supporting Information.

2.2. Catalyst activity studies

A 10 mL round bottom flask was charged with *N*-methylindole (40 mg, 0.3 mmol), Cu/SBA-15 (150 mg), NH_4I (0.36 mmol), DMF (2 mL) and O_2 as oxidizing agent. The round bottom flask was kept for stirring at 130 °C. After 12 h of run, the reaction was monitored by TLC; 5 mL of ethyl acetate was added to the reaction mixture. The catalyst was separated by centrifugation followed by the treatment of the reaction mixture with 10 mL of brine solution. The organic layer is separated by ethyl acetate (3 × 5 mL). The combined ethyl acetate extract was dried with anhydrous Na_2SO_4 and it was concentrated under reduced pressure. The pure product was isolated by flash column chromatography on silica gel using ethyl acetate-hexane (3:1) as an eluent (pale yellow oil, 92% yield). The catalyst was washed with distilled water for several times then dried in an oven at 100 °C and used for the next cycle. Following the similar procedure the cyanation reaction was tested for 3 recycles.

3. Results and discussion

3.1. Powder X-ray diffraction (XRD)

The low angle XRD patterns of pure SBA-15 and Cu loaded SBA-15 samples are displayed in Fig. 1A. The XRD pattern of parent SBA-15 exhibited a well-resolved sharp intense diffraction peak at $2\theta = 0.8^\circ$ along with two other low intense peaks at $2\theta = 1.59^\circ$ and 1.8° corresponding to the (100), (110) and (200) reflections respectively which can be indexed to a mesoporous 2D hexagonal pore structure. However, there is no major change observed in the structure of SBA-15 in Cu loaded samples suggesting hexagonal structure is intact and stable.

Fig. 1B shows the wide angle XRD patterns of parent SBA-15 and calcined Cu/SBA-15 samples. The broad X-ray diffraction peak at

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