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Indole cyanation *via* C–H bond activation under catalysis of Ru(III)-exchanged NaY zeolite (RuY) as a recyclable catalyst

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Abstract

Selective 3-cyanation of indoles was achieved under heterogeneous catalysis of Ru(III)-exchanged NaY zeolite (RuY) as a recyclable catalyst, in combination with $K_4[Fe(CN)_6]$ as a nontoxic, slow cyanide releasing agent. Under the aforementioned conditions, good yields of the desired products were obtained.

Keywords: Cyanation; Indole; Zeolite; Heterogeneous; Catalysis

1. Introduction

Indole-containing structures have widespread occurrence in many pharmacologically and biologically active compounds [1–4]. Aromatic nitriles are also, important building blocks of pharmaceuticals, dyes and agrochemicals [5]. Cyanation of the aromatic rings, were classically achieved by Rosenmund–von Braun reaction [6] and Sandmeyer reaction [7], where CuCN was used as cyanide source. In recent years, most attention has been paid to the metal-catalyzed cyanation of aryl halides or cyanation *via* C–H bond activation of arens [8–10]. In this context, various –CN sources have been used such as MCN (M = Cu, K, Na, Zn), $K_4[Fe(CN)_6]$ [11,12], and more recently, CH_3NO_2 [13], $(CH_3)_2NCHO + NH_3$ [14], DMSO + NH_4HCO_3 [15], and DMF [16]. Little attention, however, has been paid to the direct cyanation of indoles through C–H bond activation. Recently, we have been involved in the study of the chemistry of indoles and ruthenium species as catalyst [17–20]. Limitations associated with recent reports on the direct cyanation of indoles [15,16,21–24], prompted us to evaluate the catalytic activity of Ru(III)-exchanged NaY zeolite (RuY), as a catalyst for this reaction. In this contribution, we now describe regioselective 3-cyanation of indoles under heterogeneous catalysis of Ru(III)-exchanged NaY zeolite (RuY) as a recyclable catalyst, in combination with $K_4[Fe(CN)_6]$ as a nontoxic, slow cyanide releasing agent (Scheme 1).

2. Experimental

IR spectra were recorded on a Shimadzu FTIR-8400S spectrometer. ^{1}H NMR and ^{13}C NMR spectra were obtained on a Bruker DRX-400 (or DRX-100) Avance spectrometer. Chemical shifts were expressed in ppm downfield from

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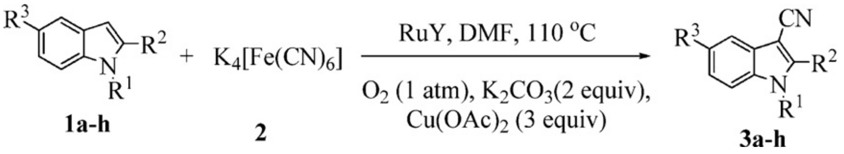


Scheme 1. RuY catalyzed direct 3-cyanation of indoles.

tetramethylsilane. Melting points were measured on a Büchi Melting Point B-540 instrument. The BET specific surface areas were determined by nitrogen adsorption at liquid nitrogen temperature on a Sibata SA-1100 surface area analyzer. X-ray diffraction measurements were recorded by a D8 Bruker Advanced diffractometer with Cu-Kα radiation.

The Na-form of Y zeolite was converted into the H-form by repeated ion-exchange with 1 mol/L NH_4NO_3 solution and subsequent calcination of the resulting filtered material in air at 550 °C. For the ion exchange with Ru^{3+} a ‘‘slurry-filtration-wash’’ cycle [25], was applied using a 0.05 M ruthenium chloride solution in water (15 mL per g of zeolite). The resulting material then heated overnight at 550 °C.

2-Methylindole (1 mmol, 131 mg), RuY (0.30 g), $K_4[Fe(CN)_6]$ (1 equiv.), $Cu(OAc)_2$ (3 equiv.), K_2CO_3 (2 equiv.) and dry DMF were charged into a two-neck round-bottom flask connected to a condenser under a current of O_2. The flask was then heated in an oil bath at 110 °C for the appropriate time (Table 2). After completion of the reaction (as indicated by TLC), the mixture was filtered and the catalyst washed thoroughly with ethyl acetate, then filtered and dried. The filtrate was extracted with ethyl acetate (3 × 10 mL) and the combined washings and extracts were washed with water, dried over anhydrous sodium sulfate, and then concentrated in vacuum. The crude product was purified by preparative TLC (n-hexane/ethyl acetate: 10/3). The filtered catalyst was washed with hot DMF and hot water to remove inorganic waste and the recovered catalyst was reactivated at 550 °C.

*Selected characterization data for 1,2-dimethyl-1H-indole-3-carbonitrile (**3g**)*: White solid, mp: 85–88 °C, IR (KBr, cm^{-1}); 740, 1053, 1254, 1410, 1475, 1544, 2204, 2850, 2924. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ 2.56 (s, 3H), 3.67 (s, 3H), 7.21–7.30 (m, 3H), 7.65 (d, 1H, $J = 7.1$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ 11.94, 30.11, 84.79, 109.73, 116.49, 118.88, 121.92, 122.90, 126.95, 136.18, 145.60. Anal. Calcd. for $C_{11}H_{12}N_2$: C, 76.71; H, 7.02; N, 16.27; found: C, 76.71; H, 7.04; N, 16.27.

3. Results and discussion

First of all, using 2-methylindole as substrate, the reaction conditions were optimized with respect to catalyst-type and loading, cyanide source, choice of solvent and temperature. The effect of catalyst-type and loading on the yield of product is summarized in Table 1.

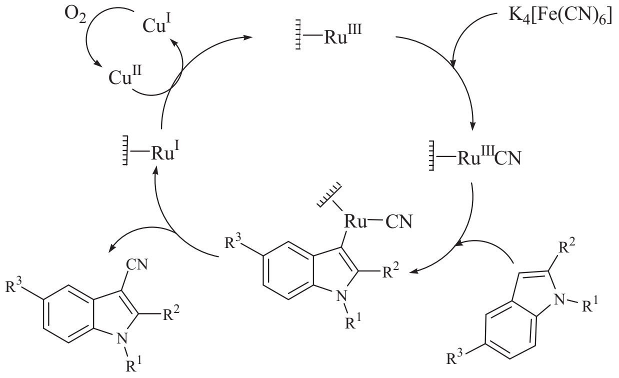
As it is shown, in the absence of catalyst, no formation of the desired product was observed (entry 1). It was also found, that the presence of O_2 (1 atm.) and $Cu(OAc)_2$ (3 equiv.) was necessary to promote the reaction. This may be

Table 1
The effect of catalyst type and loading on the cyanation of 2-methylindole.

Entry [a]	Catalyst	Particle size (μm)	BET surface area (m^2/g)	Pore volume (cm^3/g)	Catalyst loading (g per mmol of indole)[b]	Yield (%)
1	No catalyst	–	–	–	0	0
2	RuY	0.5	628	0.282	0.15	45
3	RuY	”	”	”	0.30	70
4	RuY	”	”	”	0.50	71
5	NaY	”	635	0.284	0.15	0
6	NaY	”	”	”	0.30	3
7	NaY	”	”	”	0.50	3
8	HY	”	647	0.285	0.15	2
9	HY	”	”	”	0.30	7
10	HY	”	”	”	0.50	6

[a] The reaction was carried out according to general experimental procedure.

[b] Ru content was found to be 6.57% by ICP method.



Scheme 2. A plausible mechanistic pathway for the RuY catalyzed 3-cyanation of indoles.

attributed to a second redox cycle, which regenerates Ru(III) species (Scheme 2). In presence of these additives, the best catalyst was found to be RuY, in an optimum loading of 0.30 g per mmol of 2-methylindole (entry 3). Parent NaY zeolite and its acidic form (HY) on the other hand, were not as effective as RuY.

Other physico-chemical properties of the zeolites are also, embedded in Table 1. As it is shown, a correlation between the reaction yield and the particle size, pore size, acidity and BET surface areas of the zeolites could not be established (entries 2–10). This may decline the Lewis-acid role of the catalyst and strengthen a plausible mechanistic pathway, based on transmetalation of CN^- from $K_4[Fe(CN)_6]$ to Ru(III), electrophilic ruthenation at the C3 position of indole and then reductive elimination of the product [21]. Reduced Ru(I) species, then undergo oxidation to regenerate Ru(III) by a second Cu(II)/Cu(I) cycle in the presence of O_2 (Scheme 2).

Solvent screening experiments showed that the yields were solvent dependent and the best solvent was found to be DMF (110 °C). Finally, in order to minimize the formation of homocoupling side products [21], K_2CO_3 was used as an additive which resulted in the best conditions. With the optimized conditions in hand (Scheme 1), various indoles were used and indicated the generality and scope of the reaction. Typical results are shown in Table 2. Treatment of 2-methylindole (1 mmol, 131 mg) with $K_4[Fe(CN)_6]$ (1 equiv.) in the presence of Ru(III)-exchanged NaY zeolite (RuY, 0.30 g, activated at 550 °C for 3 h) at 110 °C for 6 h gave 2-methylindole-3-carbonitrile in 70% isolated yield (entry 1). Addition of $Cu(OAc)_2$ (3 equiv.) and K_2CO_3 (2 equiv.) however, was necessary to promote the reaction and to minimize the formation of uncharacterized side products. The reaction can be used for cyanation of substituted indoles with either electron donating or electron withdrawing groups (Table 2, entries 2–8). The same regioselectivity toward cyanation of C3 was observed in each case. In order to evaluate reusability of the catalyst, the reaction was carried out in presence of the recycled catalyst (see Section 2) in successive runs. Only 15% loss of efficiency in terms of the product yield was observed after five runs, which promises minimization of the waste.

Table 2
RuY catalyzed direct 3-cyanation of various indoles with $K_4[Fe(CN)_6]$.

Entry[a]	Indole	Product	Time (h)	Yield[b] (%)
1	$R^1 = H, R^2 = Me, R^3 = H$	2-Methyl-*1H*-indole-3-carbonitrile **3a**	6	70
2	$R^1 = Me, R^2 = H, R^3 = H$	1-Methyl-*1H*-indole-3-carbonitrile **3b**	6	71
3	$R^1 = H, R^2 = H, R^3 = H$	Indole-3-carbonitrile **3c**	10	63
4	$R^1 = H, R^2 = H, R^3 = Br$	5-Bromo-*1H*-indole-3-carbonitrile **3d**	11	61
5	$R^1 = H, R^2 = H, R^3 = OMe$	5-Methoxy-*1H*-indole-3-carbonitrile **3e**	8	66
6	$R^1 = H, R^2 = Ph, R^3 = H$	2-Phenyl-*1H*-indole-3-carbonitrile **3f**	7	64
7	$R^1 = Me, R^2 = Me, R^3 = H$	1,2-Dimethyl-*1H*-indole-3-carbonitrile **3g**	4	77
8	$R^1 = H, R^2 = H, R^3 = Cl$	5-Chloro-*1H*-indole-3-carbonitrile **3h**	12	63

[a] All products were characterized by ^1H NMR, ^{13}C NMR and IR data.
[b] Isolated yields.

4. Conclusions

In conclusion, we have developed a more convenient method for 3-cyanation of indoles. The present protocol has several advantages such as milder reaction conditions, higher yields, lower reaction times and reusability of the catalyst.

Acknowledgments

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