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Ruthenium-exchanged FAU-Y zeolite catalyzed improvement in the synthesis of 6*H*-indolo[2,3-*b*]quinolines

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ABSTRACT

Ruthenium-exchanged FAU-Y zeolite (RuY) was used as a recyclable catalyst for preparation of 6*H*-indolo[2,3-*b*]quinolines from the reaction of indole-3-carbaldehyde with aryl amines in refluxing dioxane. Under the above mentioned conditions, reasonable yields of the desired products with different substituents on the quinoline ring were obtained.

1. Introduction

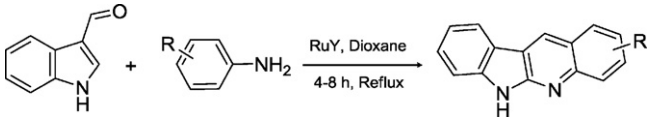
The development of new efficient synthetic methods leading to indole derivatives continues to receive much attention in organic synthesis because of their biological activities [1,2]. Various indole derivatives occur in many pharmacologically and biologically active compounds [3]. Among them, 6*H*-indolo[2,3-*b*]quinoline is the precursor to cryptotakieine (neocryptolepine) alkaloid [4–7], one of the major metabolites out of thirteen alkaloids isolated from *Cryptolepis sanguinolenta* [8,9], which proved to be an effective DNA intercalator [10–12]. Various methyl derivatives of such systems display biological properties such as antimuscarinic, antibacterial, antiviral, antimicotic and antihyperglycemic [13–15].

We have recently reported the preparation of oxindoles form electrophilic substitution reaction of indoles with isatin-derived imines under ruthenium catalysis [16]. During preparation of the aldimine precursor from indole-3-carbaldehyde and aniline for a similar reaction, we observed that a trace amount of an unknown side product was formed. Meanwhile, Parameswaran et al. reported the preparation of 6*H*-indolo[2,3-*b*]quinolines from the reaction of indole-3-carbaldehyde with aryl amines in the presence of a catalytic amount of iodine [17]. Characterization of the aforementioned side product revealed its 6*H*-indolo[2,3-*b*]quinoline structure. This prompted us to evaluate the catalytic potential of ruthenium towards preparation of 6*H*-indolo[2,3-*b*]quinolines. Literature survey showed that the reported methods on this type of synthesis have drawbacks such as multi step procedure, long reaction times, unsatisfactory yields and use of toxic solvents [17–19]. Ruthenium species, on the other hand, are well known to catalyze a variety of organic transformations [20]. In continuation of our recent work on indole derivatives and catalytic reactivity of ruthenium [21–25], we now describe an improvement in the synthesis of 6*H*-indolo[2,3-*b*]quinolines, using ruthenium-exchanged FAU-Y zeolite (RuY) as a recyclable heterogeneous catalyst (Scheme 1).

Table 1
Effect of catalyst on the yield of 6*H*-indolo[2,3-*b*]quinoline.

Entry[a]	Catalyst	Loading[b]	Yield[c] (%)
1	No catalyst	0	0
2	RuY	0.05	40
3	RuY	0.1	65
4	RuY	0.25	65
5	HY	0.1	38
6	NaY	0.1	0
7	Ru-NaY	0.1	58
8	Ru-AlMCM-41	0.1	45

[a] The reaction was carried out according to general experimental procedure. Conditions: dioxane, 4 h, reflux.
[b] g of catalyst per mmol of aldehyde.
[c] Isolated yields.



Scheme 1. RuY catalyzed synthesis of 6*H*-indolo[2,3-*b*]quinolines.

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Table 2
Effect of solvents on the yield of 6*H*-indolo[2,3-*b*]quinoline.

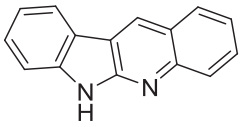
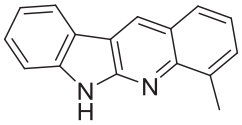
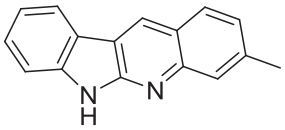
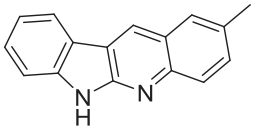
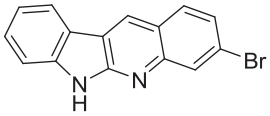
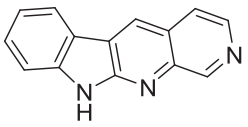
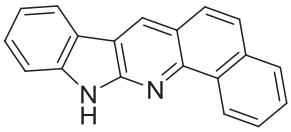
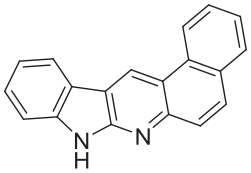
Entry[a]	Solvent	Temperature[b] (°C)	Yield[c] (%)
1	1,2-Dichloroethane	84	35
2	THF	66	5
3	Dioxane	RT	0
4	Dioxane	105	65
5	C_2H_5OH	78	36

[a] The reaction was carried out according to general experimental procedure (0.1 g RuY, 4 h).
[b] Reflux conditions.
[c] Isolated yields.

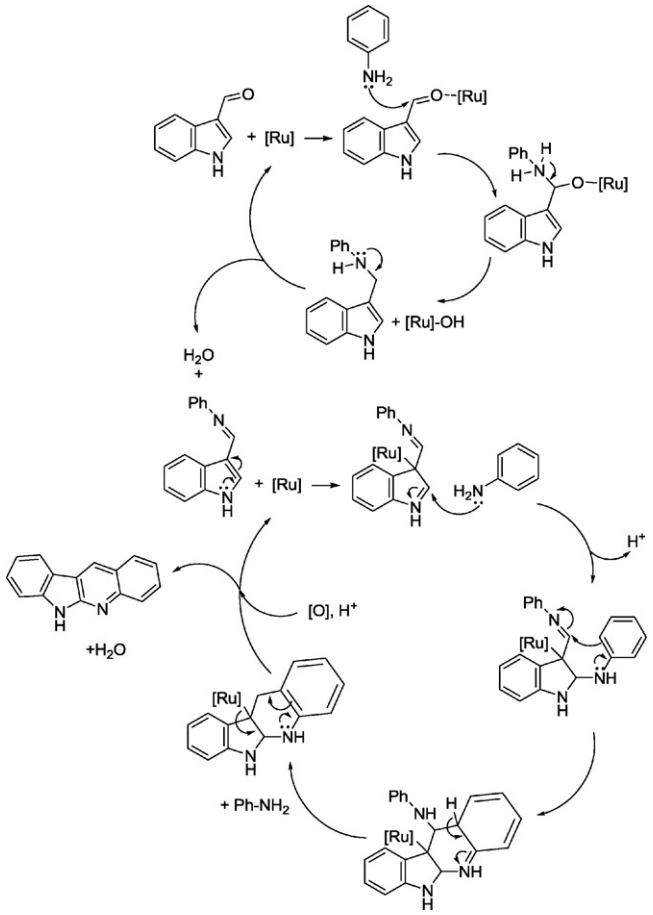
2. Results and discussion

First of all, using indole-3-carbaldehyde and aniline as substrates, the reaction conditions were optimized with respect to catalyst-type and loading, choice of solvent and temperature. The effect of catalyst-type and loading on the yield of product is summarized in Table 1.

Table 3
RuY catalyzed synthesis of 6*H*-indolo[2,3-*b*]quinolines.

Entry[a]	Amine	Product[b]	Time (h)	Yield[c]
1	Aniline		4	65
2	*o*-Toluidine		6	55
3	*m*-Toluidine		6	50
4	*p*-Toluidine		6	55
5	3-Bromoaniline		6	53
6	3-Aminopyridine		8	39
7	α-Naphthylamine		5	68
8	β-Naphthylamine		5	73

[a] The reaction was carried out according to general experimental procedure (0.1 g RuY, dioxane, reflux).
[b] Identified by comparison with authentic samples [11,17,19].
[c] Isolated yield.



Scheme 2. Proposed mechanistic pathway for the RuY catalyzed formation of 6*H*-indolo[2,3-*b*]quinoline.

As it is shown, in the absence of catalyst, no formation of the desired product was observed (entry 1), and the optimum loading was found to be 0.1 g RuY per mmol of the aldehyde substrate (entry 3). In order to further explore the role of different acid sites (Lewis and Bronsted) in the reaction, a comparison was also made between NaY, ruthenium-exchanged NaY (Ru-NaY) and ruthenium-exchanged mesoporous AlMCM-41 (Ru-AlMCM-41). In situ DRIFT (pyridine adsorption) measurements were used to determine the acidity of the catalysts. Correlation between DRIFT signals and coordination site of pyridine (Lewis or Bronsted acid sites which are responsible for the catalytic activity of zeolites) is well reported [26–28]. As it is shown in Table 1, the yield of product increases in the order NaY < HY < Ru-NaY < RuY, which is the same order of the increasing Lewis acid site density of the catalysts. Ru^{3+} ion-exchanged HY zeolite showed better activity than the parent HY zeolite owing to its higher Lewis acidity. Mesoporous AlMCM-41 (Si/Al ratio of 39) when ion-exchanged with Ru^{3+}, however, showed lower activity (entry 8). This may be due to lower cation exchange capacity of the AlMCM-41 [29]. Higher activity of microporous RuY, on the other hand, may be attributed to its lower Si/Al ratio and higher external surface acid sites.

Solvent screening experiments showed that the yields were solvent dependent (Table 2, entries 1–5) and the best solvent was found to be refluxing dioxane (105 °C, entry 4).

With the optimized conditions in hand (Scheme 1), an array of anilines was used to explore generality of the reaction. Typical results are shown in Table 3. Treatment of indole-3-carbaldehyde (1 mmol) with aniline (1 mmol) in refluxing dioxane (5 mL) in the presence of Ru^{3+} exchanged FAU-Y zeolite (RuY, 0.1 g, activated at

Table 4
Reaction of indole-3-carbaldehyde and aniline in presence of the recycled catalyst in successive runs.

Run[a]	Catalyst:aldehyde ratio	Time (h)	Yield[b] (%)
1	0.1 g:1 mmol	4	65
2	”	4	63
3	”	4	63
4	”	4	61
5	”	4	60

[a] Conditions: RuY, dioxane, reflux.
[b] Isolated yields.

550 °C for 3 h) after 4 h, gave 6*H*-indolo[2,3-*b*]quinoline in 65% isolated yield. With regard to the amine moiety, the present protocol is noteworthy because naphthyl amines, as well as other substituted anilines participated in the reaction.

Although the precise mechanism of the reaction awaits further studies, the following proposed mechanistic pathway (Scheme 2) rationalizes the formation of a quinoline ring on an indole backbone.

In order to evaluate reusability of the solid catalyst, the reaction of indole-3-carbaldehyde and aniline was carried out in presence of the recycled catalyst (see Section 4) in successive runs. These results are shown in Table 4.

As it is shown, only 5% loss of efficiency in terms of the product yield was observed after five runs, which promises minimization of the waste.

3. Conclusion

In conclusion, we have developed a convenient method for preparation of indoloquinolines. Highlights of the present work are:

i) Application of RuY as a heterogeneous catalyst resulted in more efficiency in terms of reaction time, temperature and yield.
ii) Reusability of the solid acid catalyst is also, noticeable.

4. Experimental

4.1. General

IR spectra were recorded on a Shimadzu FTIR-8400S spectrometer. ^{1}H NMR spectra were obtained on a Bruker DRX-400 Avance spectrometer and ^{13}C NMR spectra were obtained on a Bruker DRX-100 Avance spectrometer. Chemical shifts of ^{1}H and ^{13}C NMR spectra were expressed in ppm downfield from tetramethylsilane. DRIFT spectra were recorded in a Nicolet Avatar 360 FT-IR spectrophotometer equipped with a high temperature vacuum chamber. Melting points were measured on a Büchi Melting Point B-540 instrument and are uncorrected. Elemental analyses were made by a Carlo-Erba EA1110 CNNO-S analyzer and agreed with the calculated values.

4.2. Materials

Na-form of FAU-Y zeolite was converted into the H-form by repeated ion-exchange with 1 M NH_4NO_3 solution and subsequent calcination of the resulting filtered material in air at 550 °C. The Ru^{+3} ion-exchanged zeolite (RuY), was obtained by stirring HY with 0.05 M ruthenium chloride hydrate (15 mL per g of zeolite) overnight and subsequent filtration and calcination at 550 °C. AlMCM-41 with a Si/Al ratio of 39 was synthesized and characterized according to the literature [30]. For the ion exchange with Ru^{3+} a “slurry-filtration-wash” cycle [30] was applied using a 0.05 M ruthenium chloride hydrate solution in water (15 mL per g of zeolite). All other materials were purchased from Merck and used without further purification.

4.3. General procedure for the RuY catalyzed formation of 6H-indolo[2,3-b]quinolines

Indole-3-carbaldehyde (1 mmol) and RuY (0.1 g) were added to a solution of arylamine (1 mmol) in dioxane (10 mL) and the mixture was refluxed for the appropriate time (Table 3). After completion of the reaction (as indicated by TLC), the mixture was filtered and the catalyst washed thoroughly with dioxane, then filtered and dried. The combined washings and filtrate were concentrated in vacuum. The crude product was purified by preparative TLC (*n*-hexane/ethyl acetate: 10/4). The recovered catalyst was reactivated at 550 °C.

4.4. Selected spectroscopic data for 6H-indolo[2,3-b]quinoline

Yellow solid, m.p. 343–345 °C, IR (KBr): υ (cm^{-1}); 3144, 1616, 1460, 1405, 1230; ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C): δ = 11.70 (s, 1H, NH), 9.05 (s, 1H), 8.27 (d, J = 7.8 Hz, 1H), 8.11 (d, J = 8.1 Hz, 1H), 7.98 (d, J = 8.4 Hz, 1H), 7.72 (m, 1H), 7.45–7.58 (m, 3H), 7.27 (m, 1H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6, 25°C): δ = 153.36, 146.80, 141.95, 130.31, 129.13, 128.68, 128.00, 127.45, 124.15, 123.20, 122.28, 120.76, 120.14, 118.38, 111.39 ppm. Anal. Calcd for $C_{15}H_{10}N_2$: C, 82.55; H, 4.62; N, 12.84; found: C, 82.51; H, 4.60; N, 12.84.

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