

Efficient Co(II) heterogeneously catalysed synthesis of α -aminonitriles at room temperature *via* Strecker-type reactions†

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Received 27th April 2010, Accepted 7th June 2010

First published as an Advance Article on the web 21st June 2010

DOI: 10.1039/c0gc00047g

An environmentally friendly and highly active mesoporous Co(II) complex on mesoporous SBA-15 material could be used as an easily recoverable catalyst for the synthesis of α -aminonitriles from a wide range of aldehydes/ketones and primary or secondary amines with good to excellent conversions yields at room temperature under solventless conditions. The catalyst can be recovered by simple filtration and could be reused at least 10 times without loss of catalytic activity.

Introduction

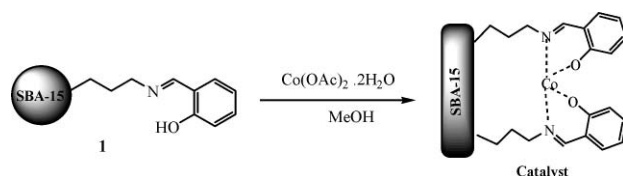
α -Aminonitriles constitute a major class of naturally occurring compounds of great interest due to their useful biological activities and their interconversion to important α -aminoacids (*via* facile hydrolysis). They also have been widely used as the essential building blocks of peptides and proteins synthesis. Numerous synthetic methods have been developed for the synthesis of α -aminonitriles over a century due to the significance and prevalence of this class of compounds.^{1–3}

The Strecker reaction represents one of the most direct and appealing approaches for the preparation of such α -aminonitriles. The process originally involved the addition of ammonia and hydrogen cyanide to acetaldehyde and subsequent hydrolysis of adduct to give alanine, an important aminoacid.⁴ However, classical protocols of the Strecker reaction are sometimes of limited synthetic potential as they often involve harsh conditions, or substrate limitations with side products. With the aim of developing a milder and more convenient approach towards the construction of α -aminonitriles, significant advances have been reported for this important process over the past few years. These have been mostly related to the optimisation of reaction conditions and the use of more challenging substrates including natural products,⁵ the design of novel and more efficient catalytic systems^{6,7} as well as the development of asymmetric Strecker syntheses.^{8,9}

The Strecker reaction with aldehydes has been extensively studied using a wide range of homogeneous and heterogeneous catalysts.^{6–10} However, the three-component Strecker reaction

using ketones is still highly challenging (and even not feasible) for less reactive ketones.^{7–9,11} Zhang *et al.* have recently reported an efficient Brønsted acid catalysed ketone, amine and trimethylsilyl cyanide (TMSCN) Strecker type reaction, using phosphoric acid derived catalysts.⁷ Good to excellent yields of products were obtained using simple ketones as substrates in the reaction. However, the protocol suffered from important drawbacks including the use of high catalyst loadings (10 mol%) of a catalyst that needs to be recovered by flash chromatography and long reaction time (typically 24–48 h). Other extensively reported Lewis acid and base catalysts^{6–10} often required high catalyst loadings, some of them are difficult to separate, or recovered and recycles. The use of ketimines as substrates in Strecker-type cyanation reactions has been restricted to a few selected examples, and mostly related to asymmetric processes,^{8,9} due to their inferior electrophilic character compared to aldimine counterparts, thus remaining a significant challenge in organic chemistry.⁹

Our aim was to develop more efficient and environmentally friendly catalytic processes. Recently we have reported the application of a simple and efficient Co(II) complex supported on mesoporous SBA-15 (Scheme 1) in a wide range of important reactions including aerobic oxidations,¹² chemoselective deprotection of acetates,¹³ acetylation of alcohols¹⁴ and C-heteroatom bond forming reactions.¹⁵ This hybrid Co/SBA-15 catalyst, featuring advantages from both heterogeneous and homogeneous systems, was found to be highly active and selective in the reported organic transformations with low catalyst loadings, offering a versatile and greener approach to more efficient heterogeneous catalytic process.



Scheme 1 Structure of the supported Co(II) catalyst.^{12–15}

Aiming to bridge the gap between the use of such versatile heterogeneous catalysts and the transformation of ever challenging organic substrates for efficiency-improved catalytic processes, herein we report a simple, eco-friendly and most convenient synthetic pathway towards α -aminonitriles from a variety of aldehydes, ketimines and ketiminium salts using Co/SBA-15 as catalyst at room temperature. To the best of our knowledge, this is the first example for the synthesis of α -aminonitriles from ketiminium salts as substrates.

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† Electronic supplementary information (ESI) available: Experimental and spectral data. See DOI: 10.1039/c0gc00047g

Table 1 Effect of amount of Co/SBA-15 catalyst on product yields in the three-component Strecker reaction of benzaldehyde, pyrrolidine and TMSCN

Entry	Catalyst loading (mol%)	Time/h	Yield (%) ^{a,b}
1	—	24	8
2	5	2	99
3	3	2	99
4	2	2	99
5	1	2	99
6	0.5	2	70
7	1	1	99
8	1	0.5	75

^a For the reaction of benzaldehyde, pyrrolidine, and TMSCN at room temperature. ^b Isolated yield. Reaction conditions: 1.1 mmol TMSCN, 1 mmol benzaldehyde, 1 mmol pyrrolidine, 1 mol% catalyst, RT.

Experimental

Materials preparation

Co/SBA-15 was prepared as previously reported.¹⁵ The catalyst had a surface area of 448 m² g⁻¹, with a pore size of 3.6 nm and 0.77 mL g⁻¹ mesoporous pore volume, and Co loading was found to be 0.3 mmol g⁻¹. Metal content in the materials was determined using inductively coupled plasma (ICP) in a Philips PU 70000 sequential spectrometer equipped with an Echelle monochromator (0.0075 nm resolution). Samples were digested in HNO₃ and subsequently analyzed by ICP (for more details see ESI†).

Results and discussion

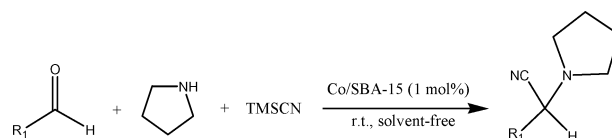
Initially, experiments were performed to optimize the reaction conditions for the Strecker reaction using aldehydes as substrates. We therefore conducted a systematic investigation using Co/SBA-15 as heterogeneous catalyst for a model of three-component Strecker reaction with benzaldehyde and pyrrolidine and TMSCN at room temperature (RT) under solvent-free conditions (Scheme 1). Among the cyanide sources, TMSCN was chosen due to its nature as effective, relatively safe and easily-handled cyanation reagent compared to HCN and alkali cyanides.

In a typical reaction run, TMSCN (1.1 mmol) was added to a mixture of the aldehyde (1 mmol), amine (1 mmol) and catalyst Co/SBA-15 (34 mg; ~1 mol% Co/SBA-15) in a 25 mL sealed tube and the mixture was stirred with 500 rpm at room temperature for the appropriate time as indicated in Table 1. After the completion of the reaction (monitored by TLC), the mixture was diluted with ethyl acetate and filtrated to obtain the crude product. In some cases, the crude product was purified by column chromatography on silica gel to afford the pure α-aminonitrile in good to excellent yields.

As the three-component reaction seemed to work quite well, we were particularly interested in investigating the catalyst loading to achieve the most efficient process using the catalyst as low as possible. The reaction did not progress in the absence of catalyst even after 24 h (Table 1). Quantitative conversion of starting material could be obtained by using 1 mol% of the catalyst. By using lower quantities of catalyst gave low yields of

the products (*ca.* 70%) after 1 h. (Table 1, entry 6). A further decrease in reaction time (to 0.5 h) resulted in an incomplete reaction, and as a result, only 75% yield was obtained (Table 1, entry 8).

With the optimized condition in hand, and to explore the scope and limitations of the protocol, we examined the reaction of various aldehydes and amines in the presence of Co/SBA-15 under solvent-free conditions (Scheme 2, Tables 2 and 3). The corresponding products were obtained in excellent yields (90–97%), regardless of the nature and position of the substituents and/or aliphatic/aromatic nature of the amines. The protocol was also amenable to a range of amines (Table 3), and excellent yields to products obtained in reasonable reaction times at room temperature, typically 1–5 h.

**Scheme 2** Three-component Strecker reaction of various aldehydes, pyrrolidine and TMSCN catalyzed by Co/SBA-15**Table 2** Three-component Strecker reaction of various aldehydes, pyrrolidine and TMSCN catalyzed by Co/SBA-15 at RT

Entry	R ¹	Time/h	Yield(%) ^a
1	phenyl	1	99
2	4-nitrophenyl	1	99
3	3-nitrophenyl	2.5	95
4	4-chlorophenyl	3	98
5	(3-phenyl)propyl	4.5	92
6	1-naphthyl	4.5	92

^a Isolated yields. Reaction conditions: 1.1 mmol TMSCN, 1 mmol aldehyde, 1 mmol pyrrolidine, 1 mol% catalyst, RT.

Table 3 Three-component Strecker reaction of aldehydes, amines and TMSCN catalyzed by Co/SBA-15 at RT

Entry	R ¹	Amine	Time/h	Yield(%) ^a
1	Ph	piperidine	1	99
2	4-(NO ₂)C ₆ H ₄	piperidine	1	99
3	3-(Cl)C ₆ H ₄	piperidine	2.5	95
4	PhCH ₂ CH ₂	piperidine	4	97
5	CH ₃ (Ph)CH	piperidine	4	95
6	1-naphthyl	piperidine	5	90
7	ph	morpholine	1.5	99
8	4-(NO ₂)C ₆ H ₄	morpholine	1.5	99
9	3-(NO ₂)C ₆ H ₄	morpholine	3	96
10	4-(Cl)C ₆ H ₄	morpholine	3.5	94
11	4-(NO ₂)C ₆ H ₄	1-phenyl ethylamine	4	92
12	4-(NO ₂)C ₆ H ₄	2-butylamine	1.5	98
13	4-(NO ₂)C ₆ H ₄	diethylamine	1.5	98
14	4-(Cl)C ₆ H ₄	diethylamine	3	97

^a Isolated yields. Reaction conditions: 1.1 mmol TMSCN, 1 mmol aldehyde, 1 mmol amine, 1 mol% catalyst, RT.

Encouraged by these good results and realizing the importance of synthesis of α -aminonitriles from less reactive substrates (e.g. ketones), we then decided to explore the Co/SBA-15 catalysed cyanation of a variety of ketimines and ketiminium salts under the optimized conditions. These interesting and more challenging compounds were employed as substrates instead of ketones. As compared to the fast formation of the imine intermediates in the Strecker reaction (first step, from the reaction between the aldehyde/ketone and the amine), the cyanation of such intermediate formed (second step, nucleophilic attack of the cyanide reagent to the imine) is believed to be the rate determining step of the whole process.⁷

Prior to these reported studies, efficient, clean and eco-friendly heterogeneously catalysed methodologies employing ketimines/ketiminium salts as substrates were considered a significant challenge, particularly, for the asymmetric cyanation of ketimines.^{8,9} In a typical cyanation experiment, TMSCN (1.2 mmol) was added to the ketimine or ketiminium salt (1 mmol) and Co/SBA-15 catalyst (34 mg; ~1mol% Co/SBA-15) in a sealed tube at 40 °C, and the mixture was stirred at appropriate time (Table 4).

Similarly, as reported before, after completion of the reaction, the mixture was diluted with ethyl acetate and filtrated to obtain the crude product, and was purified by column chromatography on silica gel to afford the pure related α -aminonitriles.

In some cases where starting materials were solid, a few drops of solvent (e.g. ethyl acetate) were added to ensure that the reactants are thoroughly mixed.

Preliminary investigations showed that the rates of the reaction in the cyanation of ketimines and ketimine salts were significantly affected by the temperature of reaction, and a remarkable increase in yields observed at 40 °C compared to room temperature. Interestingly, a further increase in temperature (from 40 to 60 °C) did not have any influence in the yields and similar yields were obtained for those reported at 40 °C. Therefore, the experiments were conducted at 40 °C as optimum temperature of reaction in order to maximise the yields (Table 4). In general, excellent yields of products were obtained in all cases at various reaction times (typically between 3 to 12 h) depending on the substituent of the parent ketones (Table 4). Yields were slightly reduced for ketones with larger chains. However, the reported methodology was amenable to both aromatic and aliphatic (cyclic and acyclic) substituents, giving almost quantitative yields in all cases. Interestingly, ketiminium salts (Table 4, entries 1–6) provided improved yields of products at significantly reduced reaction time (typically 3 h) compared with ketimines (Table 4, entries 7–12).

These findings are in good agreement with the cyanation mechanism recently proposed by Zhang *et al.* for the phosphoric acid catalysed Strecker reaction of ketones, amines and TMSCN.⁷ Ketimines obtained as intermediates in the Strecker reaction (starting materials in this work) can be protonated by the catalyst (in our case the Co/SBA-15 material has been shown to have some interesting Lewis acidity) to produce a more electrophilic and activated iminium ion which subsequently attacked by the nucleophilic cyanide reagent to give the final α -aminonitrile product. Thus, the use of already activated ketiminium salts provided improved yields at shorter reaction time.

Table 4 TMSCN cyanation of ketimines and ketiminium ions catalyzed by Co/SBA-15 at 40 °C

Entry	Substrate	Product	Time/h	Yields(%) ^a
1			3	95
2			3	95
3			3	98
4			3.5	98
5			2.5	99
6			6	92
7			10	87
8			12	88
9			12	90
10			10	95
11			12	92
12			12	90

The rates of reaction could also be improved under microwave irradiation (from hours to minutes) and there is also scope for the extension of the ketimine protocol to a catalytically enantioselective methodology, as many products from Table 4 have chiral centers. These investigations are currently ongoing in our laboratories and will be the subject of a future publication.

For practical applications, lifetime of heterogeneous systems and the levels of reusability are very important factors. A set of experiments were planned to investigate the reusability of the catalyst for the three-component Strecker reaction of benzaldehyde, pyrrolidine and TMSCN under optimized conditions. The reaction was carried out under similar conditions. After completion of the first reaction with 99% yield, the catalyst was recovered by filtration, washed with ethanol and dried at 70 °C for 30 min. Then the used catalyst was employed in another reaction run with fresh reactants under the similar conditions. Co/SBA-15 showed excellent recoverability and reusability over 10 successive runs under the same conditions to the first run. No

detectable metal traces in solution (<0.5 ppm) were determined by ICP of the final reaction mixture, confirming the strong coordination and stability of cobalt in the catalyst that prevented metal leaching during/after the reaction.

Conclusions

A highly active Co/SBA-15 versatile catalyst was employed in the Strecker reaction. The catalyst possesses the ability to catalyze both the Strecker reaction for a variety of aldehydes, and amines as substrates as well as the cyanation of ketimines and ketimine salts with TMSCN in good to excellent yields. The catalyst can be successfully recycled over 10 times with no significant loss of catalytic activity. As a result of its high efficiency and activity, as well as recyclability and low catalyst loading, the catalyst system described herein is foreseen to have an excellent future for a range of applications in the synthesis of fine chemicals.

Acknowledgements

FR is grateful to Payame Noor University for partial support and MRS gratefully acknowledges Sharif University of Technology for funding and support.

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