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Tandem Oxidative Isocyanide-Based Cycloaddition Reactions in the Presence of MIL-101(Cr) as a Reusable Solid Catalyst

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Abstract

The tandem oxidative three-component synthesis of two types of the heterocycles such as furans and imidazopyridines, *via* isocyanides [1+4] cycloaddition reactions in the presence of MIL-101(Cr) under aerobic conditions are reported. When the 4-toluenesulfonylmethyl isocyanide was used, an unexpected [3+2] cycloaddition reaction of isocyanides with aldehydes accomplished and dihydrophenyloxazoles and phenyloxazoles produced. These syntheses were successfully carried out using a wide scope of the substrates.

Keywords: Tandem Oxidative, Isocyanide, Cycloaddition, MIL-101(Cr), Aerobic Oxidation,

1. Introduction

Reengineering approach is one of the most efficient tools to provide the new route for simplifying the prominent organic reactions.[1] This concept defined as the analysis and redesign of the reaction conditions based on the changing in the starting materials such as replacing one of the reaction components with two or more simple and readily available materials, [2] and in situ providing the starting material (tandem process).[3, 4] In the last two decades, many types of the reengineering approaches in the organic transformations were reported based on tandem oxidative or reductive processes.[5-8] Very recently, Liu et al. reported a tandem cycloaddition/reductive reaction for synthesis of pyrrolo[2,3-b]quinolones with nitrochalcones.[3] Jayaram et al. redesigned the synthesis of the benzimidazoles and benzodiazepines wherein the starting reactant primary/secondary alcohol is oxidized to generate aldehyde/ketone in situ and then reacted with a diamine to provide the desired product.[9]

Multicomponent reactions (MCRs) are powerful tools for the synthesis of complex biologically relevant molecules.[10, 11] The atom economy of MCRs, their convergent character, operational simplicity, and the structural diversity and complexity of the resulting molecules make chemistry using them exceptionally useful for discovery and optimization processes in the pharmaceutical industry. MCRs, especially isocyanide-based MCRs (IMCRs), allow fast and selective methods

for the synthesis of large libraries of organic molecules simply by varying each component through a chain of consecutive elementary transformations.[12, 13]

In the recent years, MOFs have been considered as very interesting, multifunctional materials with prominent properties such as high surface area, large and accessible cages, and tunable pores.[14-18] These materials have a wide range of applications including gas storage,[19] separation,[20] sensing,[21] and catalysis.[22, 23] Metal-organic frameworks offer many opportunities as heterogeneous catalysts, particularly for organic reactions in the liquid phase.[24, 25] Among this class of material, MIL-101 is primarily regarded as a catalyst for organic processes. Many reports have been presented using MIL-101 families, such as chromium and iron as solid catalysts for green hydrogenation of benzaldehyde[26] and nitrobenzene,[27] water oxidation,[28] photochemical oxidation of organic pollutant[29], and auto-oxidation of benzylic hydrocarbon.[30]

In an attempt to continue efforts toward IMCRs and the development of efficient heterogeneous catalysts for synthesized heterocyclic compounds, [31-35] herein, aimed to redesign the synthesis of furans and imidazo[1,2-a]pyridines *via* the tandem oxidative/cycloaddition reaction starting from alcohols in the presence of the MIL-101(Cr). In the first tandem synthesis reaction, the benzaldehyde derivatives were provided by *in-situ* oxidation of benzyl alcohol derivatives. It was condensed with an activated C-H acid through the Knoevenagel reaction, followed by a treatment of isocyanides, to provide the furan derivatives *via* a [1+4]-cycloaddition reaction (Scheme 1, reaction A). The second reaction was carried out *via* a domino reaction of 2-aminopyridines and isocyanides with benzaldehyde derivatives that were provided from the oxidation of benzyl alcohols (Scheme 1, reaction B).



Scheme 1. Tandem oxidative-three-component reactions (a) tandem oxidative-GBB reactions (b)

2. Experimental

2-1. Typical procedure for oxidation of bezyl alcohol using MIL-101(Cr)

Benzyl alcohol (0.108 g, 1.00 mmol) was added to a two-necked flask containing MIL-101(Cr) (0.030 g, 0.04 mmol), KOH (0.020 g, 0.360 mmol) and acetonitrile (2.00 mL). The reaction mixture was stirred under air blowing for 2 h at 80 °C. The progress of the reaction was followed by TLC. Upon completion, the reaction mixture was filtered and the filtrate was analyzed by GC.

2-2. Typical procedure for tandem oxidative synthesis of ethyl 5-(cyclohexylamino)-2methyl-4-phenylfuran-3-carboxylate (4k)

The mixture of benzyl alcohol (2.50 mmol) with mentioned catalytic systems in the acetonitrile (2.00 mL) was stirred for 15 min under air blowing at 80 °C and followed by addition of ethyl acetoacetate (0.12 g, 1.00 mmol) and cyclohexyl isocyanide (0.11 g, 1.00 mmol). The progress of the reaction was monitored by TLC. After the compellation of the reaction, the catalyst was separated by filtering and the solvent was evaporated. The solid residue was washed with deionized water and crystalized in ethanol: methylene chloride (2:1).

2-3. Typical procedure for tandem oxidative synthesis of *N*-cyclohexyl-2-phenylimidazo[1,2-a]pyridin-3-amine (6a)

A mixture of benzyl alcohol (2.50 mmol) with mentioned catalytic systems in the acetonitrile (3 mL) was stirred under air blowing at 80 °C. The solution of 2-amino pyridine (0.10 g, 1.00 mmol) and cyclohexyl isocyanide (0.11 g, 1.00 mmol) in acetonitrile (2 mL) were added to the reaction mixture and followed by stirring at 80 °C. The progress of the reaction was monitored by TLC. After the compellation of the reaction, the catalyst was separated by filtering and the solvent was evaporated. The solid residue was washed with deionized water and crystalized in ethanol.

3. Results and discussion

The synthesized MIL-101(Cr) was characterized using FT-IR, XRD, SEM and BET techniques. The X-ray powder diffraction pattern and FT-IR spectrum of the MIL-101 (Cr) are shown in Figs. 1S and 2S (Supporting Information, SI), respectively. The results are in good agreement with previous reports.[18, 27] The SEM image of MIL-101 (Cr) (Fig. 3S) showed that the dimensions of the MIL-101(Cr) crystals range from 0.3 up to 0.9 μ m. The cubic symmetry of MIL-101(Cr) is reflected in the shape of the crystals. The specific surface area of the samples was measured using a BET method with N₂ adsorption-desorption at -196 °C. The BET surface was around 1835 m² g⁻¹. The total pore volume of MIL-101(Cr) was estimated to be 89 cm³ g⁻¹, with an average pore diameter of 1.93 nm.

In the first stage of this study, aerobic oxidation of benzyl alcohol to benzaldehyde by MIL-101(Cr) was investigated. During the preliminary studies with MIL-101 (Cr), aerobic oxidation of benzyl alcohol was carried out in various polar and nonpolar solvents such as water, dimethylsulfoxide, *N*,*N*-dimethylformamide, toluene, 1,2-dichlorobenzene, n-hexane, and acetonitrile in the presence of KOH under reflux conditions (Table 1, entries 1-7). In all cases moderate to high yield of product was observed except for water and n-hexane. Acetonitrile was selected as the best solvent. Next, various inorganic bases and different amount of MIL-101(Cr) were used in the model reaction in acetonitrile. Notably, the reaction failed to produce any product in the absence of base at ambient or mild temperatures, and only trace amount was obtained at high temperatures. As indicated in Table 3, the best conditions for the oxidation of benzyl alcohol *via* MIL-101(Cr) were determined as 0.03 g catalyst [0.04 mmol of MIL-101(Cr)], 0.12 mmol of Cr] and 0.02 g of KOH in acetonitrile at 80 °C after 1 h. Using this approach, some derivatives of benzaldehyde, such as 4-NO₂, 4-Cl, 4-CH₃ and 4-(CH₃)₂CH, were produced (Table 2).

Table 1 Optimization of benzyl alcohol aerobic oxidation conditions^a

Entry	Gram of MIL-101(C	r) (mmol %) Solvent	Base (g)	Temperature (°C)	Time (h)	Yield (%) ^b
1	0.03 (0.04 mmol)	Water	KOH (0.02)	100	6	Trace
2	0.03 <mark>(0.04 mmol)</mark>	Dimethylsulfoxide	KOH (0.02)	170	2	53
3	0.03 <mark>(0.04 mmol)</mark>	N,N-Dimethylformamide	KOH (0.02)	140	2	47
4	0.03 <mark>(0.04 mmol)</mark>	Toluene	KOH (0.02)	110	1	90
5	0.03 <mark>(0.04 mmol)</mark>	1,2-dichlorobenzene	KOH (0.02)	180	1	24
6	0.03 <mark>(0.04 mmol)</mark>	n-Hexane	KOH (0.02)	65	12	Trace
7	0.03 <mark>(0.04 mmol)</mark>	Acetonitrile	KOH (0.02)	80	2	92
8	0.01 <mark>(0.014 mmol)</mark>	Acetonitrile	-	r.t.	24	Trace ^c
9	0.02 <mark>(0.028 mmol)</mark>	Acetonitrile	-	r.t.	24	Trace
10	0.03 (0.04 mmol)	Acetonitrile	-	r.t.	24	Trace
11	0.03 <mark>(0.04 mmol)</mark>	Acetonitrile	-	50	6	Trace
12	0.03 <mark>(0.04 mmol)</mark>	Acetonitrile	-	80	6	Trace
13	0.03 <mark>(0.04 mmol)</mark>	Acetonitrile	$K_2CO_3(0.13)$	80	6	Trace
14	0.03 <mark>(0.04 mmol)</mark>	Acetonitrile	$Cs_2CO_3(0.32)$	80	6	Trace
15	0.03 <mark>(0.04 mmol)</mark>	Acetonitrile	NaOH (0.03)	80	2	67
16	0.03 <mark>(0.04 mmol)</mark>	Acetonitrile	KOH (0.05)	80	2	92
17	0.03 <mark>(0.04 mmol)</mark>	Acetonitrile	KOH (0.05)	r.t	2	32
18	0.03 <mark>(0.04 mmol)</mark>	Acetonitrile	KOH (0.03)	80	2	92
19	0.03 (0.04 mmol)	Acetonitrile	KOH (0.01)	80	2	43

^a1.0 mmol of benzyl alcohol under air blowing. ^bYield determined by GC analysis. ^cTrace: <10 %





After optimization the oxidation reaction of benzyl alcohols, the progress of model reactions was monitored by GC analysis during 2 h, and yield as a function of time is illustrated in Fig. 1.



Fig. 1 Yield of aerobic oxidation of benzyl alcohol as a function of time.

In continuation, using the results of the previous experiments of oxidation of benzyl alcohol derivatives, this study was aimed to carry out tandem oxidative IMCRs in the presence of MIL-101(Cr) and KOH under optimum oxidation conditions. The reactions of *N*,*N*-dimethyl barbituric acid, cyclohexyl isocyanide and benzyl alcohol under aerobic oxidation conditions were chosen as models for reaction **A**. The reaction results showed these systems to have good ability in the synthesis of 6-(cyclohexylamino)-1,3-dimethyl-5-phenylfuro[2,3-d]pyrimidine-2,4(1H,3H)-dione, as the desired product had high yields after 1 h. With the obtained optimal conditions, the substrate scope of the tandem oxidative IMCRs was investigated. As shown in Fig. 2, a series of β -dicarbonyl compounds **2** were employed to react with five different isocyanides **3** and benzyl alcohols, under the optimized reaction conditions. As shown in Table 3, all reactions were proceeded smoothly, affording the expected furan derivatives (**4a-r**) in good yields. The structure of some selected products (**4c**, **d** and **e**) was deduced from the physical properties characterized by ¹H NMR and ¹³C NMR spectra (Fig. 5S-10S, SI).



Fig. 2 Scope of the substrates for tandem oxidative reactions A.



Table 3 Tandem oxidative-three component reactions A^a

^aReaction conditions: 1 (2.5 mmol), 2 (1.0 mmol), 3 (1.0 mmol), MIL-101(Cr),(0.03 g, 0.04 mmol), KOH, (0.036 mmol), acetonitrile (5 ml), 80 °C and air blowing. Isolated yield.

According to the excellent performance of this catalytic system for synthesizing fully substituted furan derivatives *via* tandem oxidative reaction, the same process was extended to preparing imidazopyridines by tandem oxidative reaction (reaction **B**). For this purpose, 2-aminopyridine **5** and cyclohexyl isocyanide **3** were reacted with benzyl alcohol under oxidation conditions. These reactions were accomplished in less than 1 h. As shown in Table 4, using this method, six derivatives of imidazopyridines were synthesized using various isocyanides, benzyl alcohols and 2-aminopyridines and characterized with physical properties and ¹H NMR and ¹³C NMR spectra for some selected compound (**6c** and **e**, see the experimental section).



Table 4 Tandem oxidative-three component reactions B^a

^aReaction conditions: 1 (2.5 mmol), 5 (1.0 mmol), 3 (1.0 mmol), MIL-101(Cr),(0.03 g, 0.04 mmol), KOH, (0.036 mmol), acetonitrile (5 ml), 80 °C and air blowing. Isolated yield.

When the 4-toluenesulfonylmethyl isocyanide was used in this reaction, unexpectedly the desired product (2-phenyl-3-(tosylmethyl)imidazo[1,2-a]pyridine) did not produce. Instead, 5-phenyl-4-tosyl-4,5-dihydrooxazole **7a** was formed. 2-Aminopyridine did not participate in the reaction. In order to clarify the role of 2-aminopyridine in this process, the reaction was examined in the absence of 2-aminopyridine which the reaction completely quenched. Next, in the same reaction conditions, the reaction in the absence of MIL-101(Cr) was examined with benzaldehyde, and the product **7a** was successfully obtained. These results confirmed the catalytic role of 2-aminopyridine in this process. It is notable that the oxidation of benzyl alcohol was repeated in the presence of 2-aminopyridine on the oxidation process. This can be caused by its basic character or interaction with the reaction intermediates. Four derivatives of 4-tosyl-4,5-dihydrooxazole **7a-d** were synthesized.



Table 5 Tandem oxidative synthesis of 5-phenyl-4-tosyl-4,5-dihydrooxazoles

As a parallel investigation, the 4-toluenesulfonylmethyl isocyanide was used in the reaction **A**. The *N*,*N*-dimethylbarbituric acid was not reacted, and the two component reaction participated as same as the reaction **B**. However, the reaction was not produced the product **7a**, instead the 5-phenyloxazole was obtained through the more 4-toluenesulfonic acid elimination reaction on **7a**. Similarly, four derivatives of the 5-phenyloxazole **8a-d** were synthesized.

Table 6 Tandem oxidative synthesis of 5-phenyloxazoles



Recyclability of the catalyst MIL-101(Cr) was examined in the oxidation of benzyl alcohol and two tandem oxidative reactions that discussed above for five consecutive cycles. The results show that only minor decreases were observed in the reaction yield (Fig. 3).



Fig. 3 Recyclability of MIL-101(Cr) for five cycles using oxidation of benzyl alcohol and model synthesis reactions of 4k and 6a.

The stability of the catalyst was investigated by comparison of the FT-IR and XRD analysis of the as-prepared (fresh) and recovered catalyst. X-ray powder diffraction patterns of MIL-101(Cr) are shown in Fig. 4S. The diffraction peaks are in good agreement with other published results.[36, 37] In the case of recovered catalyst, which was above 99.5%, the characteristic MIL-101(Cr) pattern appeared, and no obvious peaks from impurities can be observed. Similarly, the FTIR spectra of the catalysts confirmed that the MIL-101(Cr) structure and its activity remain intact[37] after recovery. According to these results, MIL-101(Cr) is conveniently and reusable recoverable during these processes. Finally, quantitative analysis of products by atomic absorption spectroscopy showed less than 1 ppm chromium contamination.

The possible mechanism for the oxidation of benzyl alcohol, under mentioned conditions, is shown in Scheme 2. In the second steps of the tandem reactions, MIL-101(Cr) can act as a catalyst to increase the rate of reactions. To clarify the proposed mechanism, the model reactions for the two tandem cases mentioned above were repeated using benzaldehyde in the presence of

MIL-101 under optimized conditions. The results were compared with similar reactions that were carried out in the absence of MIL-101(Cr). These results show low reaction times with higher yields for catalyst cases, compared to catalyst-free reactions, and support the proposed mechanism (Table 7).





Entry	MIL-101(Cr)	Temperature	T (h)	Product	Yield
	(g)	(°C)			(%)
1	0.05	80	0.33	4a	96
2	0	80	5.00	4a	82
3	0.05	80	0.5	6a	91
4	0	80	12	6a	10>

Reaction condition: **1** (1 mmol), **2** or **5** (1 mmol) and **3** (1 mmol) in acetonitrile (5 ml) at 80 °C. Isolated yield.





Scheme 2. Proposed mechanism

In summary, an innovative approach for the tandem synthesis of the fully substituted furans, imidazo[1,2-a]pyridines, 5-phenyl-4-tosyl-4,5-dihydrooxazoles and 5-phenyloxazoles was designed based on the *in situ* aerobic oxidation of benzyl alcohols to corresponding benzaldehydes in the presence of the MIL-101(Cr). A variety of these heterocycles was synthesized in high yields under mild reaction conditions in a single step.

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