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Journal of Molecular Catalysis A: Chemical 246 (2006) 39–42

JOURNAL OF MOLECULAR CATALYSIS A: CHEMICAL

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Short communication

Zinc bromide supported on hydroxyapatite as a new and efficient solid catalyst for Michael addition of indoles to electron-deficient olefins

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Received 19 September 2005; received in revised form 11 October 2005; accepted 12 October 2005
Available online 21 November 2005

Abstract

Zinc bromide supported on hydroxyapatite (Zn-HAP) in presence of acetonitrile as solvent was found to be a very efficient heterogeneous catalyst to promote the synthesis of 3-substituted indoles from Michael addition of indoles to α,β-unsaturated ketones. The substitution on the indole nucleus occurred exclusively at the 3-position and *N*-alkylation products have not been observed. Moreover, the catalyst was readily recovered by simple filtration and could be reused with only minor decrease in its catalytic activity.

Keywords: Hydroxyapatite; Zinc bromide; Heterogeneous catalysis; 3-Substituted indoles; Michael addition

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1. Introduction

Due to their biological activities, indole derivatives continue to receive much attention in organic synthesis [1,2]. Various indole derivatives occur in many pharmacologically and biologically active compounds [3,4]. Among them, 3-substituted indoles are important building blocks for the synthesis of biologically active compounds and natural products [5].

Michael additions promoted by Lewis acid catalysts are one of the most important carbon–carbon bond-forming reactions in organic synthesis. There are several different metal-based Lewis acid catalysts for these Michael reactions [6,7]. However, the acid-catalyzed conjugate addition of indoles requires careful control of acidity to prevent side reactions such as dimerisation and polymerization. For this reason, the need of cheaper solid catalysts is desirable which secure catalytic activity, low toxicity, moisture and air tolerance. Generally, heterogeneous solid acids are advantageous over conventional homogeneous acid catalysts as they can be easily recovered from the reaction mixture by simple filtration and can be reused after or without activation making the process economically viable. In many cases, heterogeneous catalysts can be recovered with only minor changes in activity and selectivity so that they can be used in continuous flow reactions.

Recently, hydroxyapatite (HAP) has attracted wide attention due to its use as macroligand for different catalytic active centers. Indeed, Kaneda and co-workers demonstrated the utility of HAP as a solid support for Ru, Pd and La species to perform many organic transformations [8–10]. Moreover, Sebti et al. [11–13] has developed a new family of heterogeneous catalysts based on apatite structures that can be used directly or after activation by several methodologies to promote organic reactions. Thus, these materials have been used successfully in Knoevenagel reaction [14,15], Friedel–Crafts alkylation [16], the synthesis of chalcones [17], and Michael addition [18,19].

Herein, we designed and developed a method involving $ZnBr_2$ supported on hydroxyapatite (Zn-HAP) for Michael addition of indoles **1** to α,β-unsaturated ketones **2** to synthesize 3-substituted indoles **3** (Scheme 1).

2. Experimental

2.1. Preparation of the catalyst (HAP and Zn-HAP)

The synthesis of hydroxyapaptite [$Ca_{10}(PO_4)_6(OH)_2$] is carried out by co-precipitation method [20,21] (Scheme 2). An

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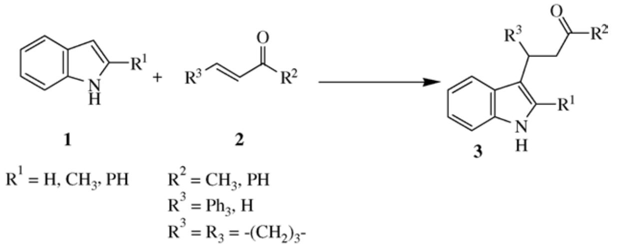
doi:10.1016/j.molcata.2005.10.012



Scheme 1.

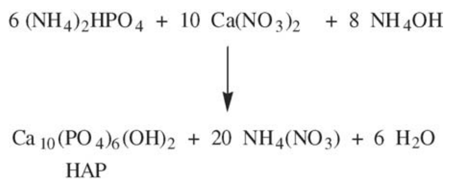
amount of 250 ml of an aqueous solution containing 7.92 g of diammonium phosphate, maintained at a pH greater than 12 by addition of ammonium hydroxide (70 ml), was dropped under constant stirring into 150 ml of an aqueous solution containing 23.6 g of calcium nitrate [$Ca(NO_3)_2 \cdot H_2O$]. The suspension was refluxed for 4 h. The obtained HAP was filtered, washed with doubly distilled water, dried overnight at 80 °C and calcined in air at 800 °C for 1 h before use. HAP (10 g) was stirred with aqueous zinc bromide (2.25 g in 25 ml water) at room temperature for 2 h and then evaporated to dryness under reduced pressure. The obtained catalyst Zn-HAP was dried overnight at 100 °C before use.

2.2. Reaction procedure

To a solution of indole derivative **1** (1 mmol) and electron-deficient olefin **2** (1 mmol) in acetonitrile (2 ml) was added the catalyst (see Tables 1 and 2 for amount). The mixture was refluxed for a period of time as indicated in Tables 1 and 2. After completion of the reaction, the resulting mixture was filtered and the catalyst washed with ethyl acetate (5 ml). After the removal of the solvents under reduced pressure, the crude product was purified by a column chromatography on silica gel (eluant:hexane/EtOAc 8:2) to afford the corresponding 3-alkylated indoles which were identified by ^1H and ^{13}C NMR data.

3. Results and discussion

The structure of the obtained hydroxyapatite was confirmed by X-ray diffraction, infrared spectroscopy and chemical analysis. The hydroxyapatite crystallizes in the hexagonal system with the space group $P6_{3/m}$. The lattice parameters of the prepared HAP are in excellent agreement with standard data: $a = 6.883$ Å and $c = 9.422$ Å. Surface area of the calcined HAP was determined by the BET method from the adsorption–desorption isotherm of nitrogen at its liquid temperature (77 K), and was found to be $S = 35\ m^2\ g^{-1}$. The total pore volume was calculated by the BJH method at $P/P_o = 0.98$ ($V_T = 0.157\ cm^3\ g^{-1}$).

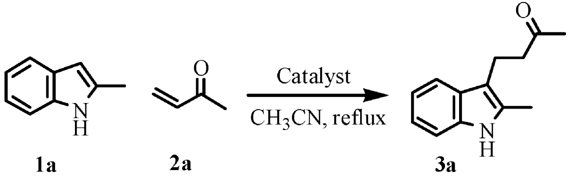


$$6\,(NH_4)_2HPO_4 + 10\ Ca(NO_3)_2 + 8\ NH_4OH \longrightarrow \underset{\text{HAP}}{Ca_{10}(PO_4)_6(OH)_2} + 20\ NH_4(NO_3) + 6\ H_2O$$

Scheme 2.

Table 1

Michael addition of 2-methyindole to methyl vinyl ketone in the presence of HAP and Zn-HAP supported catalyst



1a **2a** **3a**

Entry	Catalyst	Yield (%)[a]
1	Without	No reaction
2	HAP	25
3	$ZnBr_2$	90[b]
4	Zn-HAP	98
5	Zn-HAP	77[c]
6	Zn-HAP	75[d]

2-Methyindole (1 mmol), methyl vinyl ketone (1 mmol), catalyst (0.1 g), acetonitrile (2 ml), reflux, 4 h.

[a] Based on isolated yield.

[b] $ZnBr_2$, the same mass contained in 0.1 g of Zn-HAP.

[c] Yield after second cycle. The catalyst was recovered, washed and dried at 100 °C before use.

[d] Yield after third cycle.

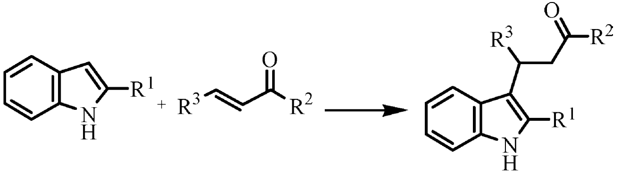
The XRD pattern of Zn-HAP is similar to that of HAP. The modification of HAP by $ZnBr_2$ impregnation does not change the crystalline structure of the obtained solid catalyst (Zn-HAP). The intensity of typical diffraction peaks did not significantly change indicating no disorganization of the HAP structure. It is to be mentioned that no $ZnBr_2$ phase was detected on the doped material, indicating that $ZnBr_2$ was highly dispersed in the solid support. The acidic activity of Zn-HAP has been already demonstrated in Friedel–Crafts alkylation [16].

In the effort to develop a better catalytic system, the catalytic activity of hydroxyapatite alone was checked in Michael addition of 2-methyindole to methyl vinyl ketone in acetonitrile under reflux (Table 1, entry 2). Low yield was obtained when using non-activated hydroxyapatite (25%).

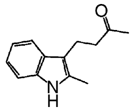
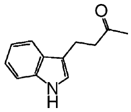
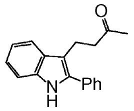
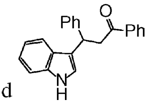
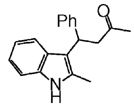
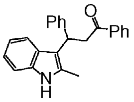
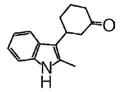
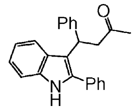
In previous research, it was demonstrated that the doping of phosphates, both synthetic and natural [22,23] by zinc halide, increases the activity of the solid. This strategy was evaluated in the synthesis of **3a** (Table 1, entry 4). Total yield was obtained with only 0.1 g of catalyst (Zn-HAP). Otherwise, we have carried out the same reaction in presence of $ZnBr_2$ alone using the same quantity contained in 0.1 g of Zn-HAP, and the obtained yield was 90% (Table 1, entry 3). However, the use of homogeneous zinc bromide catalyst in Michael addition may bring about a series of troublesome problems such as separation of product, recovery of the catalyst and serious corrosion caused by $ZnBr_2$, plus potential danger in handling and waste disposal. The introduction of such reagent on solid supports can circumvent some of these problems and provide an attractive alternative in organic synthesis in view of the selectivity, ease of manipulation and catalyst recovery.

The use of solid catalyst is especially interesting when it can be used several times. This reuse gives the catalyst an advantage

Table 2
Conjugate addition of indoles to electron-deficient olefins using Zn-HAP as catalyst in presence of acetonitrile



1 2 3

Product	*R*[1]	*R*[2]	*R*[3]	Time (h)	Yield (%)[a,b]
 3a	CH_3	CH_3	H	4	98
 3b	H	CH_3	H	4	89
 3c	Ph	CH_3	H	20	98
 3d	H	Ph	Ph	24	70
 3e	CH_3	CH_3	Ph	24	18
				36	78[c]
 3f	CH_3	Ph	Ph	24	95
 3g	CH_3	$-(CH_2)_3-$		24	95
 3h	Ph	CH_3	Ph	24	21
				36	69[c]

[a] *Conditions:* Indoles (1 mmol), electron-deficient alkenes (1 mmol), catalyst (0.1 g) and reflux in acetonitrile (2 ml).

[b] Yields of isolated products. Products were identified by ^1H and ^{13}C NMR data.

[c] Reaction carried out in presence of 0.3 g of catalyst (Zn-HAP).

compared to other catalysts. Thus Zn-HAP was recovered by simple filtration, washed with acetone and dried overnight at 100 °C and reused at least twice (Table 1, entries 5 and 6). The reused catalyst gives good results in **3a** with only minor decrease in its catalytic activity.

In order to check the general character of this methodology, the addition of different indole derivatives to electron-deficient alkenes were tested in presence of Zn-HAP (Table 2). In general, good to excellent yields were obtained except for **3e** and **3h**. One solution for this problem would be the use of a greater amount of catalyst. Indeed, the use of 0.3 g of Zn-HAP led to 78 and 69% yield for **3e** and **3h**, respectively.

Generally, the reactions are clean and the products are obtained in high yields without the formation of any side products such as *N*-alkylation products. This important result provided a remarkable contrast to similar reactions under palladium catalysis, where *N*-alkylation was predominant [24].

4. Conclusion

The results obtained in the preparation of 3-substituted indoles demonstrate the potential application of hydroxyapatite as inorganic macroligand for Lewis acid catalyst. The supported catalyst (Zn-HAP) can be easily recovered and reused with only minor decrease in its catalytic activity. The high reactivity of Zn-HAP coupled with its ease of use and reduced environmental problems makes it attractive as an alternative to homogeneous acidic reagents.

Acknowledgements

This work was supported by a Georg Forster Fellowship of the Alexander von Humboldt Foundation for R.T. The authors would like to thank also the group of Chemical Engineering of Chemnitz University of Technology for experimental support.

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