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Animal bone meal as an efficient catalyst for crossed-aldol condensation

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ABSTRACT

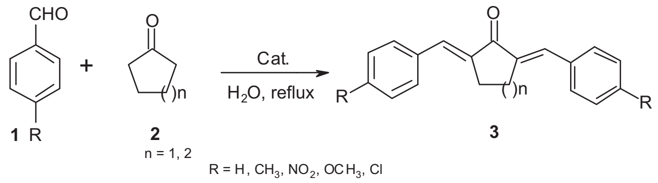
α,α′-Bis(substituted benzylidene)cycloalkanones were efficiently prepared from cycloalkanones and benzaldehydes in water by using animal bone meal (ABM) or ABM modified as a catalyst. It is shown that ABM modified can be quantitatively recovered and be reused effectively for many times. A comparison of catalytic activity of these catalysts is discussed.

1. Introduction

The crossed-aldol condensation is an effective way of synthesizing of α,α′-bis(substituted benzylidene)cycloalkanones as precursors for the synthesis of bioactive pyrimidine derivatives.[1–3] These compounds have gained a lot of attention due to their uses as agrochemical, pharmaceutical and perfume intermediates and as liquid crystal polymer units.[4–7] Among these reactions, the aldol condensation is useful for the formation of carbon–carbon bonds in many kinds of carbonyl compounds.[8–10] Crossed-aldol can be operated with the aid of strong acids or bases.[2,11]

Improvements have been achieved by application of KF supported reagents under microwave mediation[12] and ultra-sound irradiation.[13] Lewis acid catalysis using $Yb(OTf)_3$,[14] iodotrimethylsilane,[15] $TiCl_3(SO_3CF_3)$,[16] $RuCl_3$,[17] Pd/C-Me_3SiCl,[18] $SOCl_2$,[19] SmI_3,[20] I_2,[21] LiOH,[22] KOH,[23,24] TMSCl,[25] $LiClO_4$, $TMSNEt_2$,[26] TCT,[27] SiO_2–OK,[28] or $FeCl_3$[29] in ionic liquids are also employed.

Numerous organic reactions have been carried out in solid/liquid heterogeneous media. Therefore, several types of catalysts or solid supports have been studied as basic catalysts, we can mention fluorapatite,[30] diphosphate $Na_2CaP_2O_7$,[31] natural phosphate,[32] and hydroxyapatite.[33]



Scheme 1. Crossed-aldol condensation catalyzed by ABM or Na/ABM.

Our group has recently developed the preparation and use of animal bone meal (ABM) as a natural catalyst for C–S bond formation by thia-Michael addition.[34] This new natural heterogeneous method led to β-sulfinyl adduct in very high yields after only a few minutes.

In continuation of our research program concerning the development of this natural catalyst, we report in this paper an efficient catalyst for crossed-aldol condensation affording α,α′-bis(substituted benzylidene)cycloalkanones (Scheme 1).

A comparison of catalytic activity of two catalysts (ABM and Na/ABM) was also realized.

2. Experimental

2.1. Preparation of catalysts ABM, Na/ABM

Animal bones were collected from nearby butcher shops. All of the attached meat and fat were removed and cleaned from the bones. The bones were then washed several times with tap water

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and left in open air for several days to get rid of odors. Later, they were transferred to the oven at 80 °C for drying. The dried bones were crushed and milled into different particle sizes in the range 45–200 μm then calcined for 2 h at 800 °C. The residue was washed with water and was used after drying for 24 h at 80 °C. The residue was washed with water and was dried overnight at 100 °C in a conventional drying oven, and then calcined at a heating rate of 2 °C/min to 400 °C, and kept at this temperature for 4 h. The resulting material was denominated ABM. The catalysts obtained were characterized by X-ray diffraction (Fig. 1).

The modified bones Na/ABM was prepared by impregnating the bones with an aqueous solution of sodium nitrate.[35] The weight ratio used was $NaNO_3$/bones = 1/2. The mixture was stirred vigorously at room temperature, evaporated to dryness, dried, and calcined at 800 °C for 2 h. The new catalysts obtained were characterized by X-ray diffraction (Fig. 2).

Elemental analysis of ABM showed high levels of phosphate (56.3%) and calcium (36.8%), with a Ca/P ratio of 1.55, compared with small amounts of magnesium (3.72%), carbon (0.17%), hydrogen (0.15%), and nitrogen (0.36%). Only the strong characteristic phosphate bands were observed in IR spectra. X-ray diffraction analysis confirmed the presence of hydroxyapatite.

A mixture of aldehyde (2 mmol) and ketone (1 mmol) in H_2O (5 mL) was well stirred in the presence of 0.1 g ABM or Na/ABM catalyst under reflux conditions until completion of the reaction. The reaction mixture was filtered and the catalyst was washed with dichloromethane (2 × 5 mL). After concentrating the filtrate under reduced pressure, the precipitate was recrystallized from ethyl acetate (column chromatography was not required). Isolated yields of products were above 90%. Physical and spectral characterization of the products was confirmed by comparison with available literature data.[13–15,25]

In this Letter, we wish to report a simple, efficient, and practical method for the preparation of bis(arylmethylidene)cycloalkanones in excellent yields using an inexpensive and recyclable ABM modified catalyst.

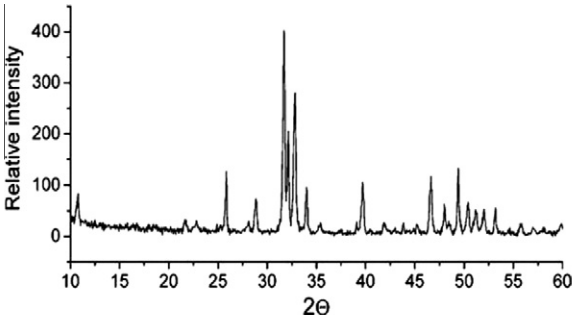


Figure 1. X-ray diffraction patterns of ABM.

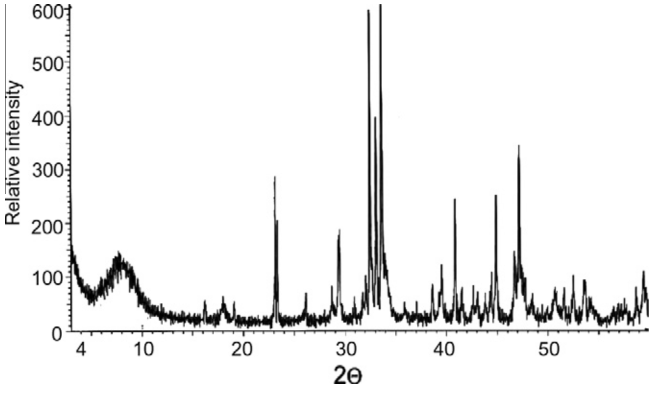


Figure 2. X-ray diffraction patterns of Na/ABM.

The reaction was carried out under reflux conditions by taking 1:2 mole ratios of cycloalkanones and aldehydes in water in the presence of modified bones to give the desired bis(arylmethylidene)cycloalkanones[36] in excellent yields (Table 1). *Under similar conditions in the absence of the bones, only the starting material was regenerated, thus highlighting the role of this catalyst.*

When acetone is used as a ketone only the starting material is regenerated.

In general, the use of ABM as the heterogeneous catalyst in the crossed-aldol condensation has allowed the isolation of our products in satisfactory yields (Table 1). The reactions are relatively slow.

Under similar conditions, the use of ABM doped with $NaNO_3$ decreases remarkably the reaction time and the attempted products were isolated in good yields only after few minutes (10–20 min) (Table 1).

The *EE* geometry of the double bonds in the above compounds (**3a–j**) was based on earlier literature reports. It is reported that the vinylic protons are in proximity to the carbonyl group which exerted an anisotropic effect, resulting in the downfield shifting and overlapping of the vinylic protons with the aromatic protons, and appearance of vinylic protons in the region of δ 7.15–7.95 ppm is an indication of such compounds with *E*-configuration and in the region of δ 6.8 ppm indicates *Z*-configuration. As for example, the olefinic protons of *Z*-2-phenyl methylenecyclohexanones and *Z*-2-phenyl methylene-6,6-diphenyl cyclohexanones are generally observed at δ 6.27 and 6.22 ppm.[23]

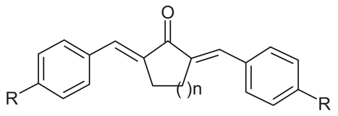
The *EE* geometry of the two double bonds was further substantiated by NOE experiment on a prototype compound (**3c**). The vinylic proton at δ 7.8 ppm showed NOE with the aromatic *ortho* protons and at the same time it did not show any NOE with the methylene protons at C-3 (δ 2.7 ppm) (Fig. 3).

When the reactions were examined in different organic solvents such as methanol, toluene, chloroform, water and THF, we found that water is the best solvent due to high yields and shorter reaction times (Table 2).

It has been shown that of the five solvents used, water gave the highest yield for the desired product (Table 2, entry 5). When THF or toluene was used as the solvent, the reaction could not be completed after reflux or stirring for 10 min and we have obtained a mixture of starting materials and final products. Moreover, using water as the reaction medium made the separation process much

Table 1

Condensation of various aromatic aldehydes with cyclic ketones in the presence of modified bones



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Entry	*n*	Product	Yields/time (min) ABM	Yields/time (min) Na/ABM
1	2	**3a** (R = H)	76/75	96/20
2	2	**3b** (R = Cl)	81/45	94/10
3	2	**3c** (R = NO_2)	87/45	91/10
4	2	**3d** (R = OCH_3)	83/75	90/15
5	2	**3e** (R = CH_3)	83/45	92/10
6	1	**3f** (R = H)	87/45	98/10
7	1	**3g** (R = Cl)	72/50	91/10
8	1	**3h** (R = NO_2)	81/45	92/10
9	1	**3i** (R = OCH_3)	86/45	97/15
10	1	**3j** (R = CH_3)	84/45	93/10

The analytical data were identical to those reported in the literature.[26,27]

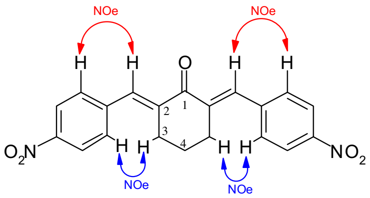

Figure 3. NOE in *EE* geometry.

Table 2
Effect of solvent on the synthesis of **3f** catalyzed by Na/ABM

Entry	Solvent	Reaction time (min)	Isolated yield (%)
1	THF	10	38
2	Toluene	10	22
3	Methanol	10	45
4	Chloroform	10	66
5	Water	10	98

Reaction conditions: solvent (2 mL), benzaldehyde (2 mol), cyclopentanone (1 mmol), and Na/ABM (0.1 g).

easier than using other solvents. For example, with water as the solvent, the product could be obtained with high purity through simple filtration and rinsing of the filtrates with a little amount of dichloromethane.

However, when toluene, THF, chloroform, and methanol were used as solvents, a homogenous mixture of product and starting materials was obtained at the end of the reaction; this product has the same stereoselectivity of the product obtained when we use water as the solvent. We clearly show that water increases the catalytic activity of both ABM alone and with Na/ABM, in all cases.[37]

After filtration of the product, Na/ABM was recovered quantitatively by simple filtration and regenerated by calcination at 400 °C for several hours for each new reuse. Investigations of benzaldehyde and cyclopentanone as model substrates showed that successive reuse of the recovered catalyst in the same reaction gave the product in yield almost as high as that of the first round (Table 3).

It should be noted that even in the sixth round, reuse of the catalyst recovered can produce the corresponding product **3f** in fairly good yield.

To obtain further evidence we studied the effects of different catalysts on the condensation reaction of *p*-chlorobenzaldehyde with cyclohexanone. The results of this study are presented in Table 4.

Comparison of the results obtained by our method with some of those reported shows the efficiency of this method because of shorter reaction times, high yields, and application of an inexpensive and readily available catalyst.

In conclusion, the present method is an efficient and selective procedure for the synthesis of α,α′-bis(substituted benzylidene)cycloalkanones from cyclic ketones with aromatic aldehydes in refluxing water.

A simple procedure and the use of water as a solvent are expected to contribute to the development of more benign crossed-aldol reactions. The ABM is a new, inexpensive, and attractive solid support which can contribute to the development of catalytic processes and reduced environmental problems and it is the first use of this material as the catalyst.

Table 3
Studies on the reuse of Na/ABM in the synthesis of product **3f**

Round	Yield	Na/ABM recovered (%)
1	98	99
2	95	96
3	94	96
4	89	98
5	89	96
6	84	96

Table 4
Comparison of the condensation reaction of *p*-chlorobenzaldehyde and cyclohexanone in the presence of different catalysts

Entry	Catalyst	Time (min)	Yield (%)
1	Na/ABM	10	94
2	$TiCl_3{\cdot}SO_3CF_3$	120	96[16]
3	SiO_2–OK	180	88[28]
4	I_2	270	94[21]
5	TCT	16	90[27]
6	$Yb(OTf)_3$	720	95[14]
7	$RuCl_3$	720	94[17]

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36. *General procedure for the synthesis of product* **3**. A mixture containing (1.0 mmol) of cyclohexanone and (2.0 mmol) of benzaldehyde in water and Na/ABM (0.1 g) was stirred at reflux until completion of the reaction. The reaction mixture was filtered and the catalyst was washed with CH_2Cl_2 (2×5 mL). After concentrating of the filtrate under reduced pressure, the residue was subjected to recrystallization (EtOAc).
Spectral data of **3a**: IR (KBr): δ max cm^{-1} 3071, 1721, 1603; ^1H NMR ($CDCl_3$) δ (ppm) 7.33–7.50 (m, 10H), 7.25 (s, 2H), 2.90 (t, 4H, $J = 3.5$ Hz), 1.74–1.85 (m, 2H); ^{13}C NMR ($CDCl_3$) δ (ppm) 28.4, 128.3, 128.5, 130.3, 136.3, 136.9, 190.4.
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