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One step liquid phase heterogeneous synthesis of phenytoin over MgAl calcined hydrotalcites

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1. Introduction

Phenytoin (5,5-diphenylhydantoin) is a useful pharmacological compound and widely prescribed as an anticonvulsant agent, treatment of grand mal, psychomotor epilepsy ulcers, epidermolysis bullosa, inflammatory conditions [1–4] and for the treatment of many more diseases including HIV [1,2]. Conventionally, phenytoin and its derivatives are synthesized by well known Bucherer-Bergs reaction [3]. In the past, many homogeneous methods were developed to synthesize hydantoin and their derivatives [4] such as α -amino amides with triphosgene [5], amino acids with acetic anhydride and ammonium thiocyanate (thiophenytoin), carbodiimides with α , β unsaturated carboxylic acids, nitriles with organometallic reagents. $[6-8] \alpha$ -amination of esters by Cu(I) [9] and reaction of aldehydes and ketones with gallium (III) triflate salts [10]. In addition, microwave synthesis, solid phase technologies [11,12] and the esoteric syntheses of hydantoins involving complex rearrangements [13,14] have also been reported for the synthesis of phenytoins. Very recently, the synthesis of 5,5-diphenyl-2,4-imidazolidinedione (phenytoin) derivatives were reported using Almonds [15]. However, the use of homogeneous reagents for the synthesis of phenytoins limits their practical utilization because of the difficulties associated with the product purification, to overcome the effluent treatment problems and for environmental concerns. But no heterogeneous system has been reported so far for the synthesis of phenytoins. Therefore, the development of heterogeneous catalytic system for this one step selective conversion is strongly encouraged. Among various hetero-

ABSTRACT

Heterogeneous liquid phase synthesis of phenytoin (5,5-diphenylhydantoin) was carried out over MgAl calcined hydrotalcites for the first time under environmental friendly conditions. The catalytic activity results showed very high conversion (80–95%) and selectivity (90–95%) of the desired product phenytoin over MgAl calcined hydrotalcites. The calcined hydrotalcites can be recycled without further loss in the activity and the possible mechanism of the reaction is also proposed.

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geneous catalysts, hydrotalcites (HTs) otherwise referred as Layered Double Hydroxides have received a tremendous attentions due to their potential use as catalysts, ion exchange, adsorption and petrochemical applications [16]. Structurally, these materials can be perceived with the structure of brucite Mg (OH)₂ lattice wherein an isomorphous substitution of Mg²⁺ by Al³⁺ occurs and the resulting excess positive charge is compensated by anions occupying the interlayer space along with water molecules. The basic properties of Mg/Al hydrotalcites and their calcined forms have been effectively utilized for many base catalyzed transformations [17,18]. In our earlier work, we have also exploited copper containing ternary hydrotalcites for selective oxidation/hydroxylation of aromatics [19]. In order to explore the basic properties of the hydrotalcites, we report for the first time the potential use of M (II)/Al (where M (II) = Mg, Ni, Co, Zn) calcined hydrotalcites for the liquid phase synthesis of phenytoins under environmental friendly conditions.

2. Experimental

All chemicals were used from Sigma Aldrich without further purification. The hydrotalcites were prepared by the low supersaturation technique. Two solutions; solution (I) containing the desired amount of metal nitrates and solution (II) having precipitating agents (i.e., NaOH and Na₂CO₃), were added simultaneously, while maintaining the pH around 9–10 under stirring at room temperature. The addition took around 100 min and the final pH of the solution was adjusted to 10. The samples were aged at 338 K for 18 h, filtered, washed with hot water (until total absence of nitrates and sodium in the washing liquids), dried in an air oven at 353 K for 12 h and the solids synthesized were hand ground. In all cases, the atomic ratio between the divalent and trivalent cations was varied between 5:1 and 1:5. The samples were

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named as M (II) M (III)-HT. Similarly ternary hydrotalcites M(II)M'(II) Al-HT, M(II)/M'(II)=3 and (M(II)+M'(II))/Al=3) with different combinations of co-bivalent metal ions were also synthesized to compare the activity and selectivity. The fresh (as synthesized) samples were calcined at different temperatures to obtain the mixed oxides with varying acid–base properties.

2.1. Catalytic activity studies and product extraction

Typically, 2 mmol of benzil, 4 mmol of urea and 15 ml of solvent (methanol) were mixed at desired temperature (298-373 K) and different amount of catalyst (10-500 mg) was added at once to the previously stirred reaction mixture in the glass reactor. The course of the reaction was monitored by TLC by taking samples periodically for 24 h. The product confirmation was also done by gas chromatography after considering the response factors of the authentic samples. After the completion of the reaction, the catalyst was vacuumed filtered and solvent was removed under reduced pressure to isolate the product A (Scheme 1) and unreacted benzil by solvent extraction method (discussed in detail in supplementary information 1.2) to account for the mass balance. Finally, the product (A) was recrystallized with ethanol, dried and weighed to calculate the isolated yield. The product extraction was little difficult due to the solubility constraints of the product with the reactants and therefore comparatively low yield of product (A) was obtained. Similarly benzil was also isolated from the reaction mixture and the total conversion is estimated on the basis of benzil reacted. The melting point of the recrystallized product was found to be 293–294 °C (literature m.p. – 294–295 °C). The IR (υ KBr) and ¹H-NMR spectra of the sample are in agreement with the authentic (Supplementary information (SI)).

3. Results and discussions

Fig. 1A showed the powder X-ray diffraction (PXRD) pattern of the MgAl-3 calcined at different temperatures (150, 400, 600 and 800 °C) according to the thermal decomposition pattern of hydrotalcites [16]. The MgAl-3 is chosen based on the catalytic activity results (discussed in catalytic activity studies). The peak at $2\theta = 42^{\circ}$ and 65° can be indexed to the formation of MgO and γ -Al₂O₃ phases and the peak at $2\theta = 36^{\circ}$ indicates the formation of spinel MgAl₂O₄ [20]. Fig. 1B showed the PXRD pattern of different atomic composition of Mg and Al calcined at 600 °C. The spectrum also indicates the formation of spinel MgAl₂O₄, MgO and γ -Al₂O₃ phases irrespective of Mg/Al composition. The formation of spinel phase is facilitated more with the samples having higher concentration of Mg contents.

Basic strength of the calcined MgAl hydrotalcite was qualitatively determined by using Hammett indicators. 1 ml of Hammett indicator was added to 25 mg of the samples and diluted with 10 ml of methanol. The reaction mixture was equilibrated for 4 h and after the equilibration, color of the catalyst was noted (Table 1). The soluble basicity was also determined by titration method using 0.02 mol/l anhydrous methanol



Fig. 1. PXRD patterns of Mg/Al-3 calcined at different temperatures (A) and with different Mg/Al ratio calcined at 873 K (B).

solution of benzoic acid. The calcined hydrotalcite (Mg/Al-3) was stirred vigorously in 50 ml distilled water for 1 h and the solution was filtered. The filtrate was then titrated with benzoic acid. The soluble basicity was found to be 0.64 mmol/g which is in agreement with the values reported earlier [21,22]. The details of the basicity measurement are given in (SI, 1.1). By knowing the universal basic properties of the calcined



Table 1	
Basic strength of MgAl hydrotalcites calcined at 873 K.	

Catalyst	Base strength
Mg/Al 5	$12 < pK_{BH+} < 18.5$
Mg/Al 3	$18.4 < pK_{BH+} < 26.5$
Mg/ Al 2	$11 < pK_{BH+} < 18.4$
Mg/Al 1	$11 < pK_{BH+} < 18.4$
Mg/Al 0.2	$11 < pK_{BH+} < 15$

hydrotalcites, in the present report, emphases are mainly devoted to the catalytic studies.

3.1. Catalytic studies

3.1.1. Effect of different bivalent metals in binary M (II)/Al hydrotalcites The catalytic activity on the fresh (as synthesized) binary hydrotalcites with M (II)/Al-3 (where M (II) = Ni, Zn, Co, Cu) (SI, Table S1) showed very low conversion, yield and the selectivity of the desired product A. It is generally known that the thermal decomposition of hydrotalcites at 873 K results in the formation of mixed oxides with enhanced basic properties (M(II)-O-Al) and hence the catalytic activity was tested on all the binary calcined M(II)Al-HTs. Table 2 showed very high conversion, yield and selectivity of the product (A) in all the calcined hydrotalcites indicating the influence of enhanced acidic-basic properties (Bronsted or Lewis) [23-25] compared to the fresh hydrotalcites. In order to see the influence of different atomic compositions of different bivalent metal ions in M(II)/Al on the catalytic activity and selectivity (Table S2, SI), the results concluded that highest conversion (94%), yield (73%) and the selectivity (95%) of the product (A) was obtained on the Mg/Al-3 mixed oxides (Table 3). A careful analysis of the catalytic results on the calcined Mg/Al series revealed that the catalytic activity increased with increase in the Mg contents up to Mg/Al-3 and then decreased with further increase in the Mg concentration at Mg/Al-5. The high activity of Mg/Al-3 can be attributed to the more basicity and high surface area compared to Mg/Al-5 calcined hydrotalcites (Tables 1 and 3). It is to be mentioned here that no conversion was obtained in the blank reaction (without catalyst) and very low conversion and selectivity of the desired product (A) was obtained on commercial MgO, Al₂O₃ (basic) and KOH further indicate the necessity of the mixed oxides (both acid-base properties) in controlling the selectivity of the product (Scheme 2, proposed mechanism). In order to see the effect of calcined ternary hydrotalcites, the catalytic activity was studied on calcined ternary hydrotalcites but very low conversion of phenytoins was observed (SI, Table S3) compared to binary calcined hydrotalcites. These

Table 2

Variation of total conversion, product selectivity and product yield over different catalysts (hydrotalcites, M(II)AI used are calcined at 873 K).

Catalyst	Conversion ^a (%)	Product selectivity (%)		ct selectivity Isolated yield ^b (%)
		A	В	
Blank	0	-	-	-
MgO	60	71	29	44
Al ₂ O ₃ (basic)	15	80	20	9
KOH	80	73	22	61
Mg/Al-3	94	95	5	73
Ni/Al-3	44	92	8	31
Zn/Al-3	40	90	10	27
Cu/Al-3	18	89	11	12
Co/Al-3	5	90	10	-

Reaction conditions: benzil - 420 mg, urea - 240 mg, solvent - methanol, catalyst weight - 50 mg, temp. - 338 K, reaction time - 24 h.

^a Based on the benzil reacted.

^b Based on isolated phenytoin (A).

Table 3

Variation of the yield of phenytoin over different Mg/Al compositions calcined at 873 K (conditions as in Table 2).

Mg/Al ratio	Conversion ^a (%)	Product selectivity (%)		Isolated yield ^b (%)	Surface area (m ² /g)
		A	В		
0.2	20	94	6	17	304
1	28	93	7	19	171
2	40	95	5	26	117
3	94	95	5	73	152
5	70	92		53	41

^a Based on the benzil reacted.

^b Based on isolated phenytoin (A).

results are similar to the earlier reports and may be due to the formation of different mixed oxide phases (not shown) responsible for activity and selectivity [26]. Hence calcined Mg/Al-3 catalyst was selected for further detailed catalytic studies. Screening of different solvents (SI, Fig. S1) indicates that the maximum conversion is achieved using methanol as a solvent. It seems that the conversion of the desired product phenytoin depends directly on the polarity and the nature (protic or aprotic) of the solvent because the hydride transfer is considered to be easier in protic solvent. Similarly the reaction temperature (Fig. 2) and the catalyst weight (SI, Fig. S2) were optimized for better activity and selectivity.

3.1.2. Effect of calcinations temperature

The calcinations temperature plays an important role in altering the acid–base properties of the mixed oxides (Mg–O–Al). Therefore the catalyst (Mg/Al-3) was calcined at different temperature (423 K, 723 K, 873 K, and 1073 K) in order to seek for better activity and selectivity (Table 4). It was observed that the catalytic conversion and the yield of the desired product increased with increase in the calcinations temperature up to 873 K and slightly decreased at 1073 K under our experimental conditions. These results clearly demonstrate the generation of different acidic–basic properties of the mixed oxides generated at different calcinations temperatures responsible for this reaction. Hence the catalyst calcined at 873 K was chosen for further studies.

3.1.3. Time-on-stream studies (TOS)

The time-on-stream studies (Fig. 3) were carried out using calcined Mg/Al-3 and KOH to compare the activity and selectivity of the desired product. The catalytic results on Mg/Al-3 catalyst indicated that the product conversion as well as yield of the product increased with increasing time and the reaction was completed within 10 h with 95% selectivity of the product (A). However, the reaction was allowed to proceed further for 24 h to check the formation of secondary products or the inter conversion of the product(s). But, no difference in the activity and selectivity was noted indicating that the product formed is quite stable under our experimental conditions. On the other hand the initial kinetics of the reaction was observed slightly faster with KOH but the conversion and the selectivity of the product (A) decreased significantly after 6 h of the reaction time (Fig. 4), with the formation of other side products (Scheme 1, product B) clearly indicating the necessity of both the acid-base properties (solid support) to control the product selectivity (Scheme 2).

3.1.4. Effect of substrate: urea molar ratio

Table 5 showed that the conversion as well as yield increased with increase in the molar concentration of urea up to 1:2 with 95% selectivity of the desired product (A). However, the conversion decreased with further increase in the ratio (1:3) without significantly affecting the selectivity. These results are opposite to the results observed under homogeneous conditions and therefore the present catalyst MgAl-HTlc



Scheme 2. Plausible mechanism.

[27] and hence offers a significant advantages over homogeneous systems in controlling the selectivity of the product [28].

3.1.5. Reusability of the catalysts

In order to see the reusability of the catalysts, the catalyst after the reaction was filtered, washed thoroughly first with methanol, acetone and finally with water. The catalyst was dried, calcined at 873 K and finally subjected to fresh reaction. No difference in the activity and selectivity was noted. Subsequently the catalyst was repeated for three cycles without significant loss in the activity indicating the non-leaching behavior of metal oxides from the catalyst during the course of reaction.

3.1.6. Plausible mechanism of the reaction

The probable reaction mechanism is proposed in Scheme 2. Initially the nucleophilic substitution on carbonyl carbon by urea



Fig. 2. Variation of total conversion with the reaction temperature over MgAl-3 catalyst (Conditions as in Table 2).

Table 4

Variation of calcination temperature on the yield of the phenytoin over Mg/Al-3 catalyst (conditions as in Table 2).

forms an intermediate (X) followed by ring closure via proton

abstraction in presence of Mg–O–Al mixed oxide. We believe that the selectivity of the desired product (A) is controlled by the relative

Calcination temp. (K)	Conversion ^a (%)	Isolated yield ^b (%)	Product selectivity (%) (A)
423	24	15	95
723	86	61	95
873	94	73	95
1073	83	63	90

^a Based on the benzil reacted.

^b Based on product phenytoin (A).



Fig. 3. Variation of total conversion with reaction time over KOH and MgAl calcined hydrotalcites (conditions as in Table 2).



Fig. 4. Variation of product selectivity of phenytoin with the reaction time over KOH and MgAl-3 calcined hydrotalcites (conditions as in Table 2).

Table. 5

Effect of the molar ratio (benzil:urea) on the yield of phenytoin over Mg/Al-3 catalyst (conditions as in Table 2).

Molar ratio (benzil:urea)	Conversion ^a (%)	Isolated yield ^b (%)	Product selectivity (A) (%)
1:1	57	44	95
1:2	94	73	95
1:3	78	57	90

Based on the benzil reacted.

Based on product phenytoin (A).

stability of the cyclic intermediate (Y) in the presence of the acidic sites on the solid support. Additionally, the presence of this solid support follows the pathway (I) and prevents the reaction pathway (II) which might be possible in homogeneous conditions (KOH). Therefore, the formation of the desired product should essentially proceed via pathway (I) followed by pinacol-rearrangement. Overall the selectivity of the desired product depends on the competitive reaction pathways (I) and (II). Furthermore, the solid support prevents the attack of urea molecule leading to the formation of product (B).

4. Conclusions

In conclusion, MgAl calcined hydrotalcites were reported for the first time as heterogeneous catalyst for the synthesis of 5,5diphenylhydantoin under milder reaction conditions. The catalytic activity results based on the yield and selectivity of the desired product are beneficial over homogeneous catalysts generally employed for this interesting synthesis. Moreover, the use of calcined hydrotalcites may pave the new pathways for the synthesis of hydantoin derivatives with multifunctional substitutions for which the efforts are currently underway.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.catcom.2010.05.004.

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