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

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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.

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] α-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 heterogeneous 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 Mg^{2+} by Al^{3+} 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 Na_2CO_3), 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 ^{1}H-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 $2\theta = 42°$ and 65° can be indexed to the formation of MgO and γ-Al_2O_3 phases and the peak at $2\theta = 36°$ indicates the formation of spinel $MgAl_2O_4$ [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 $MgAl_2O_4$, MgO and γ-Al_2O_3 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 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

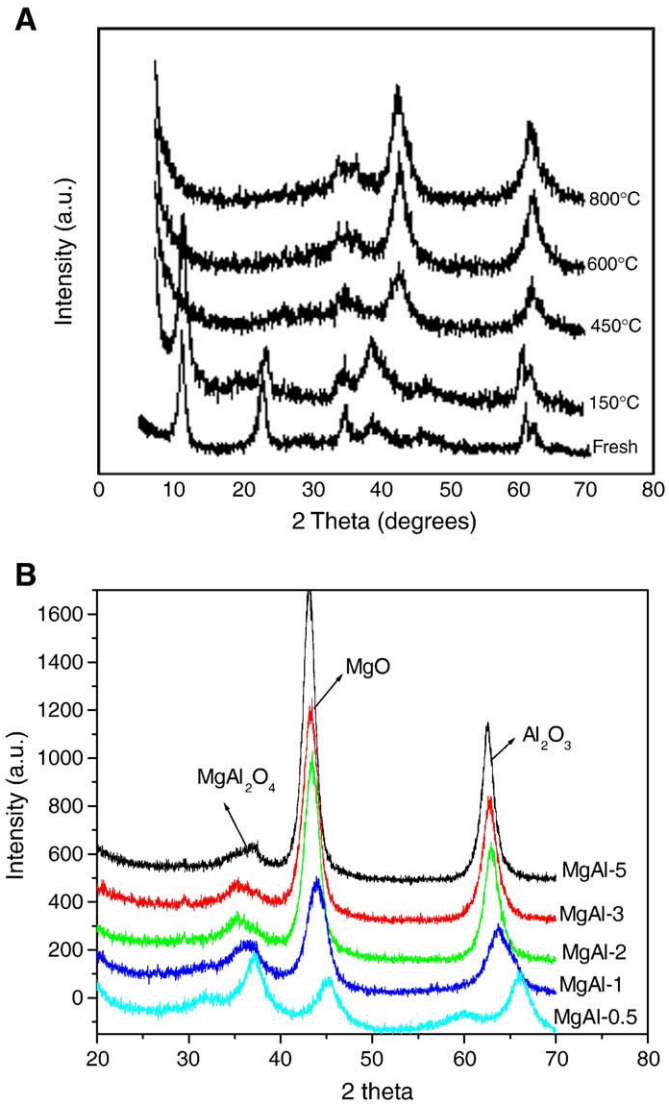
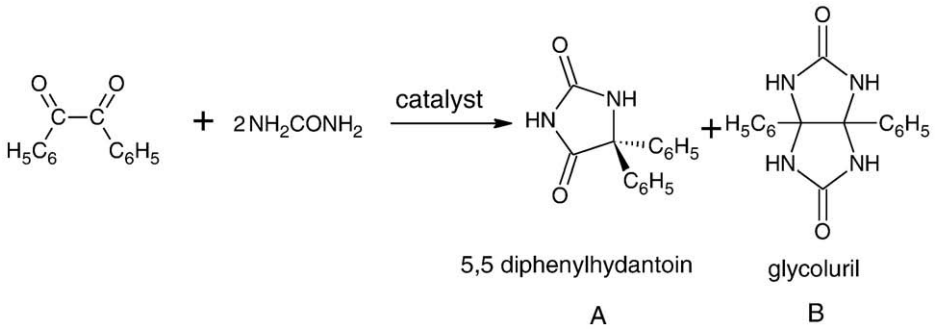


Fig. 1. PXRD patterns of Mg/Al-3 calcined at different temperatures (A) and with different Mg/Al ratio calcined at 873 K (B).



Scheme 1. Synthesis strategy for the production of phenytoin.