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A FAST ONE-POT MULTI-COMPONENT SYNTHESIS OF 3,4-DIHYDROPYRIMIDIN-2(1*H*)-ONES IN THE PRESENCE OF MAGNESIUM OXIDE AS A HIGHLY EFFECTIVE HETEROGENEOUS BASE CATALYST

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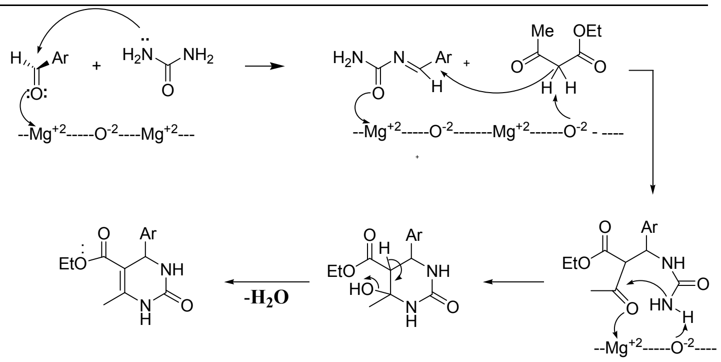
Magnesium oxide (MgO) effectively catalyzes the three-component reaction of aldehydes, urea and ethylacetoacetate to form 3,4-dihydropyrimidin-2(1*H*)-one derivatives. The effect of different kinds of magnesium oxide (MgO) such as commercially available, high surface area and nanosize on the product yield and reaction times under conventional heating have been investigated. The salient features of this method include high conversions, short reaction times, cleaner, reaction profiles, and the use of inexpensive and readily available catalyst.



INTRODUCTION

Polyfunctionalized heterocyclic compounds are the central framework of many drugs.[1,2] That is the reason, the synthesis of such compounds have received considerable attention.

Structures containing such units often play an essential role due to of their biological activity, particularly in cancer and virus research.[3-4] Among these heterocycles, pyrimidine derivatives are an important class in pharmaceutical discovery.[5] Some such compounds are analgesics, antihypertensives, antipyretics, and anti-inflammatory drugs.[6-10] Pyrimidines occur in some pesticides, herbicides, and plant growth regulators.[9] Consequently, synthetic methodologies for synthesis of novel pyrimidines or pyrimidine-fused compounds are of particular interests in the medicinal and agrochemical areas.[10] The simple and direct method for the synthesis of dihydropyrimidinones was first reported by Biginelli in 1893, involving a one-pot condensation of an aldehyde, β-ketoester and urea under strongly acidic conditions.[11] However, it suffers from low yields (20–50%) of products. Therefore, several improved methodologies mainly using Lewis acids,[12,13] triflates,[14] microwave-assisted methodologies[15] and ultrasonic mediated methods[16] have been reported in the literature.

In contrast to the extensive studies involving heterogeneous acid catalysts, fewer efforts have been made to develop heterogeneous base catalysis.[17] Several solid bases have been reported as being effective in this respect, such as zeolites,[18] alkali metals supported on alumina (Na/NaOH/g-Al_2O_3),[19] clay minerals,[20] hydrotalcites (HDT),[21] metal oxides such as magnesium oxide (MgO), and mixed metal oxides, for example magnesium

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lanthanum mixed oxide.[22] Among these solid bases, MgO recently has been studied as a heterogeneous base catalyst for reactions taking place in a liquid phase.[23] More recently we have used magnesium oxide (MgO) as heterogeneous base catalysis in many reactions for preparation of heterocyclic compounds.[24-27] As part of our research program aimed at the synthesis of nitrogen-containing heterocycles,[28,29] we performed the synthesis of 3,4-dihydropyrimidin-2(1*H*)-one derivatives through a three-component reaction in the presence of three kinds of magnesium oxide (MgO) as highly effective heterogeneous base catalysts.

EXPERIMENTAL

General procedures

Ethylacetoacetate, aromatic aldehydes, urea, $Mg(OH)_2$, commercially available MgO and the used solvents were obtained from Merck or Fluka Chemical Co. Melting points were measured on a Gallenkamp melting point apparatus and are uncorrected. IR spectra were measured on a Mattson 1000 FT-IR spectrometer. The proton and carbon NMR spectra were recorded with a BRUKER DRX-500 AVANCE spectrometer at 500 and 125.77 MHz, respectively.

Preparation of high surface area magnesium oxide [MgO]

The catalyst used in this study was obtained by rehydrated $Mg(OH)_2$ at 450°C for 2h.[23] A calcination temperature of 400-500°C gave maximum conversion when the catalyst was calcined above 500°C, the activity of MgO decreased and continued to decrease as the calcinations temperature increased. The maximum surface area was obtained after calcining the samples at 400-500°C.

Preparation of nanosized MgO

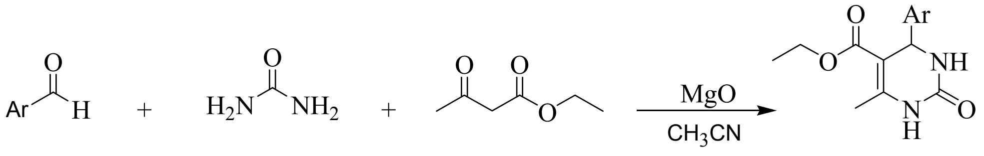
The MgO nanoparticles were synthesized by precipitation of the magnesium hydroxide gels in aqueous solution using $Mg(NO_3)_2$ as salt and liquid ammonia as the precipitating agent. Initially, the pH of 200 mL of distilled water was adjusted to 10.5 by addition of liquid ammonia to this distillated water. A 0.1 M magnesium nitrate solution was added dropwise to the above stirred solution. The rate of addition of the salt solution was kept at 20 mL/h. During the addition, the pH of the mixture decreased due to hydrolysis of the salt. The pH was maintained at 10.5 by controlled addition of liquid ammonia solution. After completion of the precipitation, the mixture was stirred at room temperature for an additional 12 h, filtered, repeatedly washed with distilled water, dried at 120 °C, and calcined at 500 °C for 2 h.[29]

General procedure for 3,4-Dihydropyrimidin-2(1*H*)-Ones

A mixture of an aromatic aldehyde (2 mmol), urea (2mmol), ethylacetoacetate (2mmol) and MgO (50 mg) in CH_3CN (10 ml) was refluxed with stirring for the time reported in Table 2 (the progress of the reaction being monitored by thin layer chromatography (TLC) and hexane/ ethyl acetate was used as an eluent). After completion of the reaction, MgO was removed by filtration and excess CH_3CN was distilled off. The obtained crude product was recrystallized from 96% ethanol to afford the pure product**.**

RESULTS AND DISCUSSION

In the present protocol as exhibited in Scheme **1**, we report an efficient one-pot synthesis of three-component reaction of aldehydes **1**, urea **2** and ethylacetoacetate **3** for the preparation of 3,4-dihydropyrimidin-2(1*H*)-ones **4a-h** in the presence of three different kinds of magnesium oxide (MgO) such as commercially available, high surface area and nanosize as a highly effective heterogeneous base catalyst. This protocol offers flexibility in tuning the molecular complexity and diversity. The reactions proceeded to completion almost instantaneously, and pure product was obtained, without using any chromatographic techniques, simply by recrystallization from ethanol.



4a: Ar = C_6H_5
4b: Ar = 4-MeC_6H_4
4c: Ar = 4-$MeOC_6H_4$
4d: Ar = 4-Cl-C_6H_4
4e: Ar = 2-HOC_6H_4
4f: Ar = 2,4-MeC_6H_3
4g: Ar = 2-$MeOC_6H_4$
4h: Ar = 4-HOC_6H_4

Scheme 1 – Reaction between an aromatic aldehyde, urea and ethylacetoacetatein the present of MgO.

Table 1

Solvent and catalyst effects on the three-component reaction for the synthesis of **4a**

Catalyst (MgO)	Solvent	Time (min)	Yield (%)
commercial	Toluene	200	39
high surface area	Toluene	160	50
nanosize	Toluene	120	65
commercial	Acetonitrile	20	65
high surface area	Acetonitrile	15	85
nanosize	Acetonitrile	10	90
commercial	ethanol	100	40
high surface area	ethanol	45	60
nanosize	ethanol	30	72

Xu and co-workers investigated the reaction of a high-surface-area form of MgO as a catalyst for a number of different Michael additions and Knoevenagel condensations, and it was found that this catalyst is to be very active and reusable.[23] Indeed, the simplicity of the preparation and the ease of reactivation after use may offer sufficient compensation to make MgO the base catalyst of choice even if slightly better yields can be obtained with alternative catalysts.[23]

As shown in Table 1, the yields were markedly affected by the solvent and catalyst. In order to optimize the reaction conditions, we used some polar and non polar solvents in the three-component reaction of benzaldehyde, urea and ethylacetoacetate in the presence of commercially available or high surface area and nanosized magnesium oxide (MgO) as model reactions to investigate the effects of solvent for preparing the product 4a. In each case, the substrates were mixed together with 0.05 g MgO agitated with 10 mL solvent. The results are shown in Table 1. It is noteworthy to mention that the polar solvents such as ethanol or acetonitrile, afford better yields than nonpolar toluene. The optimum results were obtained when reactions were carried out in CH_3CN and in the presence of a catalytic amount of MgO.

On basis of these results in this paper we report in this paper a novel three-component one-pot synthesis of 3,4-dihydropyrimidin-2(1H)-one derivatives **4a-h** in the presence commercially available or high surface area and nanosized magnesium oxide (MgO) as highly effective heterogeneous base catalysts under thermal conditions. The use of larger amounts of catalyst does not have any affect on order to increase the amount of yields. The results of these three-component reactions under thermal conditions were summarized in Table 2.

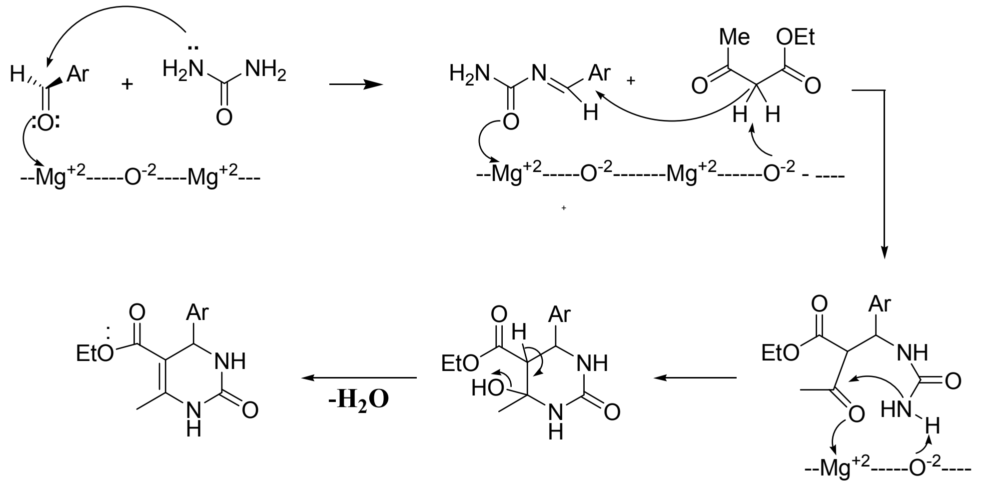
In the plausible mechanism catalyzed by MgO, the initial step is the formation of imine. The MgO coordinates with the nitrogen atom of imine to give an intermediate complex which activates the C=N bond towards nucleophilic addition, complexation of ß-ketoester with MgO increases the nucleophilicity of α-carbon of enolate, facilitating the attack on imine carbon. Attack of free amidic group to ß-cabonyl carbon, results in the formation of six-memberer heterocyclic intermediate which on dehydration gives the desired 3,4-dihydropyrimidin-2(1*H*)-ones (Scheme 2).

Structures **4a-h,** were determined on the basis of their ^{1}H and ^{13}C NMR as well as IR spectroscopic data which showed the presence of carbonyl groups at a region of 1710-1705 and 1650-1645 cm^{-1}. The spectroscopic data of these compounds were comparable with these reported data in the literature.[28]

Table 2

Synthesis of compounds **4a-h** under different reaction conditions

		Thermal conditions		Commercially available MgO		High surface area MgO		Nanosized MgO	
Compd No.	Ar	Time (min)	Yield (%)	Time (min)	Yield (%)	Time (min)	Yield (%)	Time (min)	Yield (%)
4a	C_6H_5	120	50	20	65	15	85	10	90
4b	4-MeC_6H_4	110	50	15	63	10	80	7	88
4c	4-$MeOC_6H_4$	130	52	25	60	15	82	10	90
4d	4-ClC_6H_4	120	51	20	65	15	85	10	92
4e	2-HOC_6H_4	120	49	25	62	20	84	13	91
4f	2,4-MeC_6H_3	120	50	20	64	15	86	10	90
4g	2-$MeOC_6H_4$	110	53	15	65	10	90	7	93
4h	4-HOC_6H_4	150	50	20	60	15	80	11	89



Scheme 2 – Propose mechanism for the synthesis of product **4**, in the present of MgO.

In summary, there is no doubt that MgO is an effective catalyst and provides a new and useful method for the preparation of 3,4-dihydropyrimidin-2(1*H*)-ones by condensation of aldehydes, urea and ethylacetoacetate. The catalysts show environmental friendly character, which is inexpensive and easily obtained. Moreover, the procedure offers several advantages including high yields, operational simplicity, clean reaction conditions and minimum pollution of the environment, which makes it a useful and attractive process for the synthesis of these compounds.

5-(ethoxy carbonyl)-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one **(4a).** Colorless, mp 199-201 °C. IR (KBr, ν_{max}/cm^{-1}): 3242, 3117, 2980, 1722, 1645, 1462, 1388, 1091. ^1H NMR (500 MHz, DMSO-d_6): 9.37(1H, s, NH), 7.31(1H, s, NH), 7.18-7.28 (5H, m, Ar), 5.11 (1H, s, CH), 4.02(2H, q, OCH_2CH_3), 2.27(3H, s, CH_3) 1.12(3H, t, OCH_2CH_3). ^{13}CNMR (125 MHz, DMSO-d6): 164, 150.60, 149, 142.30, 135.20, 130.53, 125.20, 98.25, 57, 54, 18.20, 14.5.

5-(ethoxy carbonyl)-6-methyl-4-(4-methylphenyl)-3,4-dihydropyrimidin-2(1H)-one **(4b).** Colorless, mp 214-216 °C. IR (KBr, ν_{max}/cm^{-1}): 3244, 3112, 2990, 1705, 1649, 1468, 1372, 1223. ^1H NMR (500 MHz, DMSO-d_6): 9.17(1H, s, NH), 7.71(1H, s, NH), 7.12-7.18 (4H, m, Ar), 5.11 (1H, s, CH), 3.95(2H, q, OCH_2CH_3), 2.25(3H, s, CH_3) 1.10(3H, t, OCH_2CH_3). ^{13}CNMR (125 MHz, DMSO-d6): 165.8, 152.60, 148.72, 142.31, 136.82, 129.33, 126.62, 99.91, 59.60, 54.00, 21.11, 18.80, 14.5.

5-(ethoxy carbonyl)-6-methyl-4-(4-methoxyphenyl)-3,4-dihydropyrimidin-2(1H)-one **(4c).** Yellow, mp 195-197 °C. IR (KBr, ν_{max}/cm^{-1}): 3246, 3142, 2990, 1710, 1649, 1466, 1375, 1222. ^1H NMR (500 MHz, DMSO-d_6): 9.42(1H, s, NH), 7.71(1H, s, NH), 7.28-7.33 (4H, m, Ar), 5.11 (1H, s, CH), 4.22(2H, q, OCH_2CH_3), 4.11(2H, q, OCH_2CH_3, Ar) 2.20(3H, s, CH_3) 1.35(3H,t, OCH_2CH_3), 1.45(3H,t, OCH_2CH_3). ^{13}CNMR (125 MHz, DMSO-d6): 166.21, 155.20, 146.14, 142.20, 135.20, 129.00, 99.20, 59.12, 54.20, 22.01, 14.20.

5-(ethoxycarbonyl)-6-methyl-4-(4-cholorophenyl)-3,4-dihydropyrimidin-2(1H)-one **(4d).** Colorless, mp 208-210 °C. IR (KBr, $\nu_{max/}$cm^{-1}): 3244, 3128, 2974, 1705, 1644, 1462, 1384, 1222. ^{1}H NMR (500 MHz, DMSO-d_6): 9.32(1H, s, NH), 7.52(1H, s, NH), 7.22-7.28 (4H, m, Ar), 5.15 (1H, s, CH), 4.20(2H, q, OCH_2CH_3), 2.11(3H, s, CH_3) 1.62(3H,t, OCH_2CH_3), 1.45. ^{13}CNMR (125 MHz, DMSO-d6): 163.32, 152.10, 144.50, 141.20, 136.11, 130.21, 125.00, 97.20, 58.20, 53.00, 21.20, 15.10.

5-(ethoxy carbonyl)-6-methyl-4-(2-hydroxy-phenyl)-3,4-dihydropyrimidin-2(1H)-one **(4e).** Pale Yellow, mp 198-201 °C. IR (KBr, $\nu_{max/}$cm^{-1}): 3256, 3246, 2982, 1705, 1649, 1468, 1385, 1222. ^{1}H NMR (500 MHz, DMSO-d_6): 9.52(1H, s, NH), 7.71(1H, s, NH), 7.35-7.46 (4H, m, Ar), 6.90 (OH), 5.11 (1H, s, CH), 3.82(2H, q, OCH_2CH_3), 2.50(3H, s, CH_3) 1.56(3H,t, OCH_2CH_3). ^{13}CNMR (125 MHz, DMSO-d6): 165.66, 158.15, 146.02, 141.02, 136.20, 129.80, 126.20, 99.20, 59.60, 54.00, 19.20, 14.80.

5-(ethoxy carbonyl)-6-methyl-4-(2,4-dimethyl-phenyl)-3,4-dihydropyrimidin-2(1H)-one **(4f).** Pale Yellow, mp 201-204 °C. IR (KBr, $\nu_{max/}$cm^{-1}): 3244, 3186, 2922, 1710, 1646, 1465, 1365, 1232. ^{1}H NMR (500 MHz, DMSO-d_6): 9.32(1H, s, NH), 7.22(1H, s, NH), 7.10-7.17 (3H, m, Ar), 5.13 (1H, s, CH), 4.02(2H, q, OCH_2CH_3),3.22(3H, s, CH_{3Ar}), 3.12(3H, s, CH_{3Ar}), 2.32(3H, s, CH_3), 1.18(3H,t, OCH_2CH_3). ^{13}CNMR (125 MHz, DMSO-d6): 162.12, 150.11, 149.20, 136.20, 131.20, 125.25, 95.34, 60.53, 54,22, 25.20, 21.11, 18.80, 14.20.

5-(ethoxy carbonyl)-6-methyl-4-(2-methoxy-phenyl)-3,4-dihydropyrimidin-2(1H)-one **(4g).** Yellow, mp 253-255 °C. IR (KBr, $\nu_{max/}$cm^{-1}): 3244, 3122, 2982, 1710, 1649, 1466, 1375, 1222. ^{1}H NMR (500 MHz, DMSO-d_6): 9.44(1H, s, NH), 7.82(1H, s, NH), 7.28-7.33 (4H, m, Ar), 5.11 (1H, s, CH), 4.22(2H, q, OCH_2CH_3), 4.11(2H, q, OCH_2CH_3, Ar) 2.25(3H, s, CH_3) 1.35(3H,t, OCH_2CH_3), 1.45(3H,t, OCH_2CH_3). ^{13}CNMR (125 MHz, DMSO-d6): 165.21, 154.20, 144.15, 141.30, 136.20, 129.14, 98.20, 59.15, 55.25, 21.11, 15.22.

5-(ethoxycarbonyl)-6-methyl-4-(4-hydroxyphenyl)-3,4-dihydropyrimidin-2(1H)-one **(4h).** Red, mp 228-231 °C. IR (KBr, $\nu_{max/}$cm^{-1}): 3246, 3231, 2928, 1705, 1649, 1468, 1385, 1222. ^{1}H NMR (500 MHz, DMSO-d_6): 9.42(1H, s, NH), 7.69(1H, s, NH), 7.25-7.34 (4H, m, Ar), 6.75 (OH), 5.11 (1H, s, CH), 4.13(2H, q, OCH_2CH_3), 2.45(3H, s, CH_3) 1.66(3H,t, OCH_2CH_3). ^{13}CNMR (125 MHz, DMSO-d6): 166.26, 156.12, 145.13, 140.02, 135.21, 129.88, 125.32, 99.18, 59.62, 54.11, 19.14, 14.50.

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