Catal Lett (2008) 126:275–279
DOI 10.1007/s10562-008-9603-5

High Surface Area MgO as a Highly Effective Heterogeneous Base Catalyst for Three-Component Synthesis of Tetrahydrobenzopyran and 3,4-Dihydropyrano[c]chromene Derivatives in Aqueous Media

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Received: 20 February 2008 / Accepted: 24 July 2008 / Published online: 4 November 2008

Abstract Magnesium oxide (MgO) as a highly effective heterogeneous base catalyst effectively catalyzes the three component reaction of aryl aldehydes, malononitrile and α-hydroxy or α-amino activated C–H acids such as 1,3-cyclohexanedione, dimedone, 4-hydroxy-6-methylpyrone, 4-hydroxycoumarin, 1,3-dimethylbarbituric acid and 1,3-dimethyl-6-amino uracil to the formation of the corresponding pyran annulated heterocyclic systems. The catalyst is inexpensive and easily obtained, stable and storable, easily recycled and reused for several cycles with consistent activity.

Keywords Magnesium oxide (MgO) · Malononitrile · Tetrahydrobenzopyran · Three-component reaction

1 Introduction

In recent years, 4*H*-pyrans and its derivatives have attracted strong interest due to their useful biological and pharmacological properties, such as anticoagulant, spasmolytic, anticancer, antianaphylactin agents [1]. Some 2-amino-4*H*-pyrans can be employed as photoactive materials [2]. Furthermore, substituted 4*H*-pyrans also constitute a structural unit of a series of natural products [3]. Considering the importance of these compounds, many methods for the synthesis of tetrahydro-4H-benzo-[b]-pyran derivatives have been reported successively. The conventional synthesis involves the condensation of dimedone with aromatic aldehyde and malononitrile under refluxing in acetic acid [4] or the bicomponent condensation of dimedone with α-cyanocinnamonitriles in the presence of ethanolic piperidine [5]. A number of methods have been reported for the synthesis of these compounds in the presence catalyst like 1,1,3,3-*N*,*N*,*N*′,*N*′-tetramethylguanidinium trifluoro acetate (TMGT) as an ionic liquid [6], diammonium hydrogen phosphate, (DAHP) [7], hexadecyldimethylbenzyl ammonium bromide [8] or by electrochemical reactions [9] or using microwave hating in the solid state [10] in organic solvents i.e. ethanol, methanol or in water [4–8]. However, most of rely on multi step reactions and each of the above methods has its own merits. However, these procedures have drawbacks, which involve reacting at high temperature, using of expensive catalyst, the low yield or commercially unavailable.

2 Experimental

Malononitrile, aldehydes and α-hydroxy or α-amino activated C–H acids were commercially available, obtained from Merck Chemical Co. and used without further purification. Melting points were obtained with a Gallenkamp melting point apparatus. IR spectra were recorded on a Mattson 1000 FT-IR spectrometer.

2.1 Catalyst Preparation

The catalysts used in this study were obtained by rehydrated $Mg(OH)_2$ at 450 °C for 2 h. 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 calcination temperature increased. The maximum surface area was obtained after calcining the samples at 400–500 °C [11, 12].

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2.2 General Experiment

2.2.1 *General Procedure for the Preparation of Tetra-Hydrobenzopyran and 3,4-Dihydropyrano [c]Chromene Derivatives*

A mixture of aldehyde **1** (2 mmol), malononitrile **2** (2 mmol), α-hydroxy or α-amino activated C–H acids (2 mmol) and MgO (0.25 g) in H_2O (40 mL) and ethanol (10 mL) was refluxed with stirring for the time reported in Table 3 (the progress of the reaction being monitored by TLC and was used hexane/ethyl acetate as an eluent). When the reaction was completed as indicated by TLC, the crude product **4** was precipitated from the reaction mixture by cooling, and the solid was filtered and recrystallized with ethanol to get pure product.

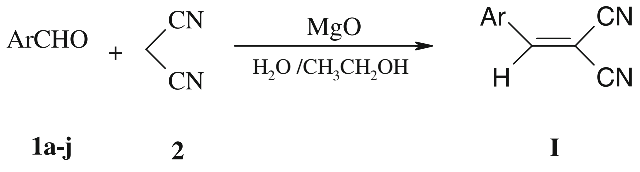
2.3 Knoevenagel Condensation

The reactions were carried out in a standard round bottom glass flask equipped with a vertical condenser under thermal conditions. Reactions were performed with arylaldehydes **1** (2 mmol), malononitrile **2** (2 mmol) and MgO (0.05 g) in H_2O (40 mL) and ethanol (10 mL) was refluxed with stirring for the specified time (Table 1).

2.4 Michael Addition

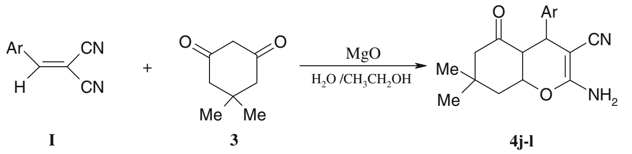
Reactions were performed with benzylidenemalononitrile **I** (2 mmol) and dimedone (2 mmol) by using MgO (0.2 g) as a base catalyst in H_2O (40 mL) and ethanol (10 mL) was refluxed with stirring for the appropriate time (Table 2). The product **4** was precipitated from the reaction mixture by cooling, and the solid was filtered and recrystallized from ethanol.

Table 1 Knoevenagel condensation of aldehydes with malononitrile catalyzed by MgO



Com. No.	Ar	Time (min)	Yield (%)	M.P. (°C)
Ia	C_6H_5	7	94	82–83
Ib	4-$MeOC_6H_4$	8	93	113–115
Ic	4-$NO_2C_6H_4$	5	96	160
Id	3-$NO_2C_6H_4$	6	95	100–102
Ie	2,4-ClC_6H_3	5	96	141–143
If	4-ClC_6H_4	6	95	156–158

Table 2 Michael additions of **I** with dimedone catalyzed by MgO

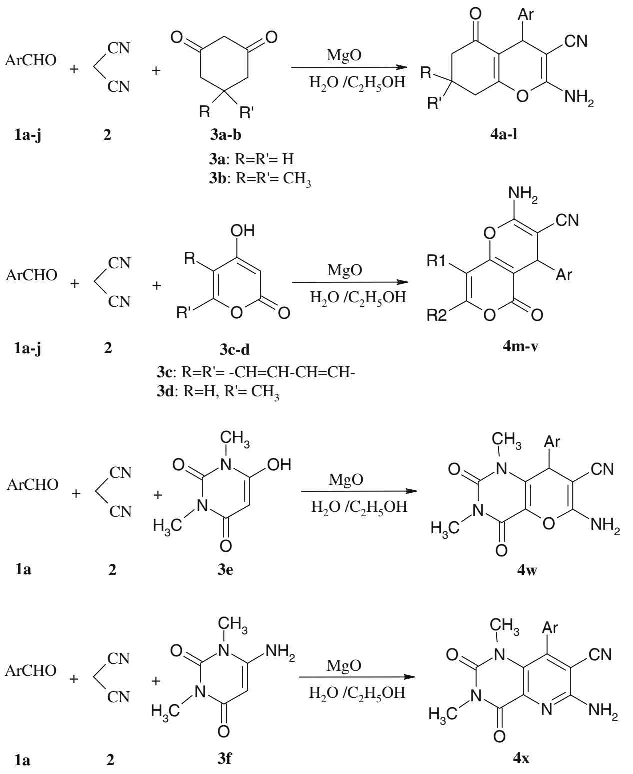


Compd No.	Ar	Time (min)	Yield (%)
4g	C_6H_5	25	94
4h	4-$MeOC_6H_4$	28	92
4i	4-$NO_2C_6H_4$	20	97
4j	3-$NO_2C_6H_4$	20	96
4k	2,4-ClC_6H_3	20	97
4l	4-ClC_6H_4	20	95

3 Results and Discussion

As part of our continued interest [13, 14] in the development of highly expedient methods for the synthesis of heterocyclic compounds of biological importance, we report here a very simple and highly efficient method for the synthesis of pyran annulated heterocyclic systems 4a–x via a three-component reaction of an aldehyde **1**, malononitrile **2** and a α-hydroxy or an α -amino activated C–H acid such as 1,3-cyclohexanedione **3a**, dimedone **3b**, 4-hydroxycoumarin **3c**, 4-hydroxy-6-methylpyrone **3d**, 1,3-dimethylbarbituric acid **3e**, 1,3-dimethyl-6-amino uracil **3f** and in the presence high surface area MgO as a highly effective heterogeneous base catalyst (Scheme 1).

In recent years, there has been increasing emphasis on the design and use of environmentally friendly solid acid and base catalysts to reduce the amount of toxic waste and by products arising from chemical processes prompted by stringent environment protection laws [15]. In contrast to the extensive studies involving heterogeneous acid catalysts, fewer efforts have been made to develop heterogeneous base catalysts [16]. Several solid bases have been reported as being effective in this respect such as zeolites[17], alkali metals supported on alumina (Na/NaOH/γ-Al_2O_3) [18], clay minerals [19], hydrotalcites (HDT) [20], metal oxides such as magnesium oxide (MgO) and mixed metal oxides, for example magnesium–lanthanum mixed oxide [21]. Amongst these solid bases, magnesium oxide (MgO) has recently been studied the most [11]. Magnesium oxide (MgO), obtained using a novel but simple procedure, was systematically investigated as a heterogeneous base catalyst for reactions taking place in the liquid phase, specifically the Michael addition and the Knoevenagel condensation. The catalytic activity of MgO for both Knoevenagel condensation and Michael additions



Scheme 1

(active methylene compounds such as malononitrile and 1,3-dicarbonyl compounds with *α*,*β*-unsaturated carbonyl compounds) was found to compare favourably with previous studies using more complicated and expensive catalysts [11]. 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 [11].

Since the three-component reaction of malononitrile, aromatic aldehydes and 1,3-dicarbonyl compounds involve both Knoevenagel condensation and Michael addition. We have separately studied also the effect of catalytic activity of MgO on the Knoevenagel condensation of malononitrile **2** and aldehydes **1** to afford the *α*-cyanocinnamonitrile **I** derivatives and Michael addition of active methylene of 1,3-dicarbonyl compounds such as dimedone with *α*-cyanocinnamonitriles **I** in same conditions. The catalyst plays a crucial role in the success of the reaction in terms of the rate and the yields. Our observations are recorded on Tables 1 and 2.

Multicomponent reactions (MCRs) by virtue of their convergence, productivity, ease of execution and generally high yields of products have attracted considerable attention from the point of view of combinatorial chemistry [22]. The first MCR was described by Strecker in 1850 for the synthesis [23] of amino acids. However, in the past decade there have been tremendous development in three- and four-component reactions and great efforts continue to be made to develop new MCRs [24].

Table 3 Solvent effects on the three-component reaction for the synthesis of **4a** and **4b** in the presence of MgO

Compd No.	Solvent	Time (min)	Yield (%)
4a	Toluene	120	65
4b	Toluene	150	63
4a	Acetonitrile	60	78
4b	Acetonitrile	90	74
4a	Ethanol	45	87
4b	Ethanol	40	85
4a	H_2O/C_2H_5OH	27	94
4b	H_2O/C_2H_5OH	30	92

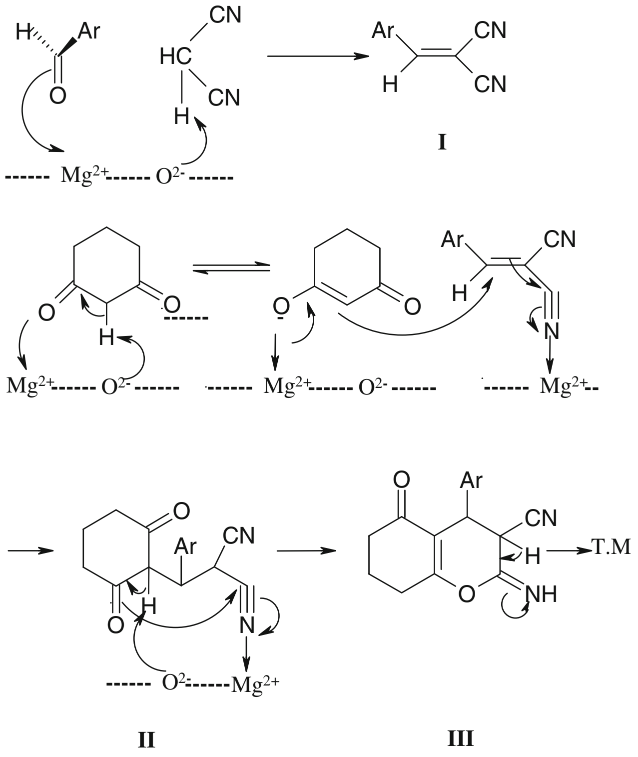
In order to optimize the reaction conditions, we used some polar and non polar solvents in the three-component reaction of benzaldehyde, malononitrile and dimedone 3b or 4-hydroxycoumarin 3c in the presence magnesium oxide (MgO) as model reactions to investigate the effects of solvent for preparing compounds 4a and 4b, respectively. In each case, the substrates were mixed together with 0.25 g MgO agitated with 10 mL solvent. The results are shown in Table 3. It is noteworthy to mention that the polar solvents such as water and ethanol or acetonitrile, which afford better yields than nonpolar ones, and the mixture of water and ethanol is the most effective solvent.

On basis of these results we report in this paper a novel three-component one-pot synthesis of functionalised tetrahydrobenzo[b]pyran, pyrano[2,3-d]- and pyrido[2,3-d]pyrimidine derivatives in the presence high surface area MgO as a highly effective heterogeneous base catalyst under thermal conditions. The results of these three-component reactions under thermal conditions were summarized in Table 4.

A reasonable mechanism for the formation of the product **4** is outlined in Scheme 2. The Knoevenagel reaction occurs via an initial formation of *α*-cyanocinnamonitrile deriva-tives **I**, from the condensation of aromatic aldehydes **1** and malononitrile **2**. A mechanism for the Knoevenagel condensation has been proposed by Moison [25] as shown in Scheme 2. The methylene of **3** is activated by MgO and reacts with the electrophilic C=C double bond in **I** giving intermediate **II**. The latter is then cyclized by nucleophilic attack of the OH group on the cyano (CN) moiety, giving intermediate **III**. Finally, the expected product is afforded by tautomerization. The catalytic activity of MgO for both Michael additions and Knoevenagel condensation was found to compare favourably with previous studies using more complicated and expensive catalysts.

Table 4 Three-component process for the synthesis of 4a–x in the presence high surface area MgO

Compd No.	Ar	*β*-Diketones	Time (min)	Yield (%)	M. P. observed (°C)	M. P. reported (°C)
4a	C_6H_5	3a	27	94	229–231	230–232 [9]
4b	4-$MeOC_6H_4$	3a	30	92	190–192	192–194 [9]
4c	4-$NO_2C_6H_4$	3a	22	96	235–237	234–236 [9]
4d	3-$NO_2C_6H_4$	3a	22	95	201–203	202–204 [9]
4e	2,4-ClC_6H_3	3a	22	96	221–223	223–225 [9]
4f	4-ClC_6H_4	3a	22	95	225–227	224–226 [9]
4g	C_6H_5	3b	30	92	226–228	227–229 [9]
4h	4-$MeOC_6H_4$	3b	33	90	194–196	194–196 [9]
4i	4-$NO_2C_6H_4$	3b	25	95	177–179	178–180 [9]
4j	3-$NO_2C_6H_4$	3b	25	94	213–215	212–214 [9]
4k	2,4-ClC_6H_3	3b	25	95	116–118	115–117 [9]
4l	4-ClC_6H_4	3b	25	93	236–238	237–239 [9]
4m	C_6H_5	3c	32	89	257–259	256–258 [8]
4n	4-$MeOC_6H_4$	3c	35	87	241–243	240–242 [8]
4o	4-$NO_2C_6H_4$	3c	30	92	257–259	258–260 [8]
4p	3-$NO_2C_6H_4$	3c	30	91	263–265	262–264 [8]
4q	2,4-ClC_6H_3	3c	30	92	256–258	257–259 [8]
4r	4-ClC_6H_4	3c	30	91	263–265	263–265 [8]
4s	C_6H_5	3d	34	87	222–224	223–225 [7]
4t	4-$MeOC_6H_4$	3d	37	85	201–203	200–202 [7]
4u	4-$NO_2C_6H_4$	3d	30	90	212–214	211–213 [7]
4v	3-$NO_2C_6H_4$	3d	30	89	235–237	234–236 [7]
4w	C_6H_5	3e	32	89	206–208	205–207 [7]
4x	C_6H_5	3f	34	87	286–288	285–287 [7]



Scheme 2

Recently, Chunli Xu et al. reported a simple method for the preparation of MgO [11], a catalyst that exhibits a high activity for base-catalyzed reactions. The experimental results showed that an optimal calcination temperature in the range 400–500 °C gives poorly crystalline, high surface area MgO that can be regenerated by washing, and then reused.

4 Conclusion

In summary, there is no doubt that MgO is an effective catalyst and provides a new and useful method to synthesis of pyran annulated heterocyclic systems by condensation of aldehydes, α-hydroxy or α-amino activated C–H acid compounds and malononitrile. 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.

Acknowledgments The authors express their gratitude to the Shahid Bahonar University of Kerman Faculty Research Funds for its support of this investigation. We are also grateful to Professor K. Saidi at the Shahid Bahonar University of Kerman for helpful comments and suggestions.

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