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A heterogeneous strong basic Mg/La mixed oxide catalyst for efficient synthesis of polyfunctionalized pyrans

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Abstract

An efficient synthesis of polyfunctionalized 4*H*-pyrans is carried out in one pot through condensation of an aldehyde, malononitrile, and an active methylenic diketo compound using a heterogeneous strong basic Mg/La mixed oxide catalyst. The protocol offers advantages in terms of higher yields, short reaction times, and mild reaction conditions, with reusability of the catalyst.

Keywords: Pyrans; Mg/La mixed oxide; Three component reaction; Diketo esters

1. Introduction

The synthesis of polyfunctionlized 4*H*-pyrans group is attractive to researchers as it is a constituent of various natural products.[1,2] The main interest in the 4*H*-pyran group is due to its biological and pharmacological[3] activities. These compounds are used as anti-coagulants, anticancer agents, spasmolytics, anti-anaphylactics, etc.[4,5] The pharmacological activities exhibited by these compounds are mainly due to the presence of different heterocyclic ring systems. Generally, 5-substituted-2-amino-4-aryl-3-cyano-6-methyl-4*H*-pyrans are prepared from arylidenemalononitriles and activated methylene compounds in the presence of organic bases.[6,7] Moreover, these compounds can be used in various applications as cognitive enhancers for the treatment of neuro degenerative diseases, including Alzheimer's disease, as well as for the treatment of schizophrenia and myoclonus. Also a number of 2-amino-4*H*-pyran derivatives are useful as photoactive materials.[8] Thus, in view of their wide utility, researchers have synthesized the 4*H*-pyran unit using different methods including radiative and non-radiative techniques such as microwave and ultrasonic irradiation.[9] In addition, the one-pot synthesis of 4*H*-pyrans has been reported using TMG-[bmim][X] and [2-aemim][PF_6] as catalysts under microwave irradiation.[10,11] A few reports exist in the literature using organic bases[12–14] as catalysts, for example, tetrabutylammonium bromide, (*S*)-proline, rare earth perfluorooctanoates, and hexadecyltrimethylammonium bromide for the synthesis of 4*H*-pyrans in one-pot reactions. All of these catalysts have merits, while some are disadvantaged by limitations such as harsh reaction conditions, low yields, tedious work-ups, and poor recyclability. Thus, the development of a suitable solid base catalyst for the efficient synthesis of 4*H*-pyrans in a single step still remains an attractive goal to researchers. From both economical and environmental point of views, the use of nontoxic solvents and nonmetallic catalysts is very promising. In the past few years, the synthesis of solid base catalysts derived from alkali earth metallic precursors has played a prominent role in the field of heterogeneous catalysis. Solid base catalysts have several advantages over homogeneous organic basic catalysts, such as easy recovery of the catalyst, simple product isolation, and recyclability. Thus, the heterogeneous solid base catalysts have been recognized as potential alternatives to homogeneous organic basic catalysts.

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In an effort to design various solid base catalysts for the synthesis of polyfunctionalized pyran derivatives, we have identified that the Mg/La catalyst efficiently catalyzes the one-pot condensation of an aldehyde, malononitrile, and a ketoester (Scheme 1). Mg/La mixed oxide catalysts are reusable basic catalysts, and the presence of La enhances the basicity of the catalyst. The Mg/La mixed oxides are used as catalysts for various organic transformations.[15–20] The present catalyst leads to 4*H*-benzopyran derivatives in high yields within short reaction times at the reflux temperature of methanol. To the best of our knowledge, this is the first heterogeneous strong basic Mg/La catalyst for the synthesis of 4*H*-pyrans under mild reaction conditions.

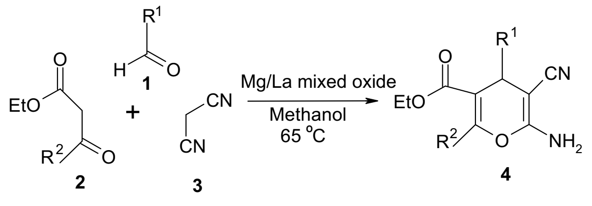
2. Preparation of the Mg/La catalyst

The Mg/La catalyst was prepared by a co-precipitation method while maintaining the pH of the solution at pH 10. In a typical method, 10.55 g of $Mg(NO_3)_2$ and 4.45 g of $La(NO_3)_3$ (corresponding to a Mg/La molar ratio of 3:1) were dissolved in 500 ml of water. The solution was precipitated by adding a mixture of 1 M KOH and 0.25 M K_2CO_3 as a precipitating agent at a constant pH of 10. After the completion of precipitation, the catalyst solution was washed several times with deionized water and filtered. The obtained catalyst was dried at 120 °C for 12 h and finally calcinated at 650 °C for 4 h.

3. Catalytic activity measurements

In a typical experiment 0.05 g of catalyst was added to a mixture of 140 mg of *p*-benzaldehyde (1 mmol), 72.6 mg of malononitrile (1.1 mmol), and 143 mg of ethyl acetoacetate (1.1 mmol) in 2 mL of methanol. The reaction mixture was stirred under reflux and the progress of the reaction was monitored by TLC. After completion, the catalyst was separated from the reaction mixture by centrifugation. The excess methanol was removed by evaporation and the resultant 4*H*-pyran derivative was isolated by column chromotagraphy. The structure of the compound was determined by ^1H NMR spectroscopy and the results were comparable with the reported data.

The separated catalyst was washed with methanol and dried at 120 °C for 2 h. The dried catalyst was reused for the recycling experiments.



Scheme 1. Synthesis of polyfunctionalized 4*H*-pyrans via one-pot condensation of an aldehyde, malononitrile, and ethyl acetoacetate using Mg/La mixed oxide.

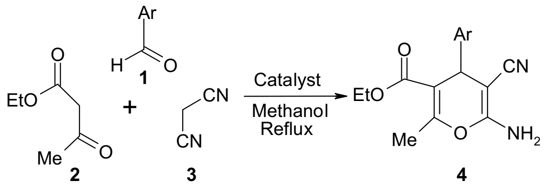
4. Catalyst characterization methods

The physical properties of the Mg/La catalyst were studied by X-ray diffraction, temperature programmed desorption (TPD) of CO_2 to determine the total basicity of the catalyst and by Brunauer, Emmett, Teller (BET) surface area measurements. These results are provided in Supplementary data.

The Mg/La catalyst was studied along with other known solid base catalysts using the reaction of 4-chlorobenzaldehyde, malononitrile, and ethyl acetoacetate in 2 mL of methanol as a model system for the synthesis of the corresponding 4*H*-pyrans. The results are summarized in Table 1. The results show that the three component reactions catalyzed by commercial MgO and KF/Al_2O_3 proceed in longer reaction times and afforded moderate product yields. The Mg–Al hydrotalcite and $Mg–Al–CO_3$ catalysts exhibited good activity requiring a 3–4 h reaction time. It is interesting to note that the Mg/La catalyst catalyzes the present reaction in high yield within a short reaction time compared to the other solid base catalysts. It appears that the basicity of the catalyst plays a prominent role. In the literature,[15–20] it has been reported that the Mg/La catalyst possesses strong basic sites compared to other solid base catalysts. The presence of La_2O_3 in proximity to MgO leads to enhanced basicity. The presence of strong basic sites in the Mg/La catalyst was confirmed by CO_2 TPD measurements (see Supplementary data). The presence of a strong CO_2 desorption peak at high temperature ($\sim T_{max}$ 600–700 °C) in the CO_2 TPD profile indicates the presence of strong basic sites.

The present method was extended to various aldehydes **1**, malononitrile **2**, and several active methylene components **3** in the presence of a catalytic amount of Mg/La to give the desired pyrans[21] **4**. The results are presented in Table 2 and indicate that aldehydes bearing electron-withdrawing groups react more quickly than their

Table 1
Synthesis of benzopyran **4** using various solid base catalysts[a]

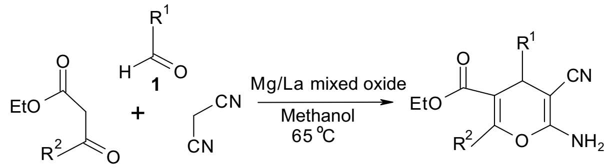


Ar = 4-ClC$_6$H$_4$

Entry	Catalyst	Time (h)	Yield **4** (%)
1	MgO (commercial)	5	67
2	KF/Al_2O_3	5	74
3	Mg–Al (hydrotalcite)	3	82
4	$Mg–Al–CO_3$	4	64
5	Mg–La mixed oxide	1	92

[a] Reaction conditions: 4-chlorobenzaldehyde (1 mmol); malononitrile (1.1 mmol); ethyl acetoacetate (1.1 mmol); temperature 65 °C; yields were determined by ^1H NMR spectroscopy.

Table 2
Mg/La catalyzed synthesis of 4*H*-pyrans derivatives[a]



Entry	R^1	R^2	Time (h)	Yield[b] (%)
1	Ph	Me	1	83
2	4-NO$_2$-C$_6$H$_4$	Me	1	88
3	3-NO$_2$-C$_6$H$_4$	Me	1	86
4	4-Cl–C$_6$H$_4$	Me	1	92, 89[c]
5	4-CN–C$_6$H$_4$	Me	1	90
6	4-OH–C$_6$H$_4$	Me	2	79
7	4-Me–C$_6$H$_4$	Me	1.5	87
8	4-OMe–C$_6$H$_4$	Me	1.5	82
9	4-CH$_3$-COO–C$_6$H$_4$	Me	3	60
10	CH$_3$-CH$_2$	Me	3	52
11	4-TBDMSO–C$_6$H$_4$	Me	1.5	35
12	4-Cl–C$_6$H$_4$	CH$_2$COOEt	1	87
13	4-Me–C$_6$H$_4$	CH$_2$COOEt	1	76
14	4-OH–C$_6$H$_4$	CH$_2$COOEt	1.5	15
15	C$_6$H$_5$	OEt	1.5	78

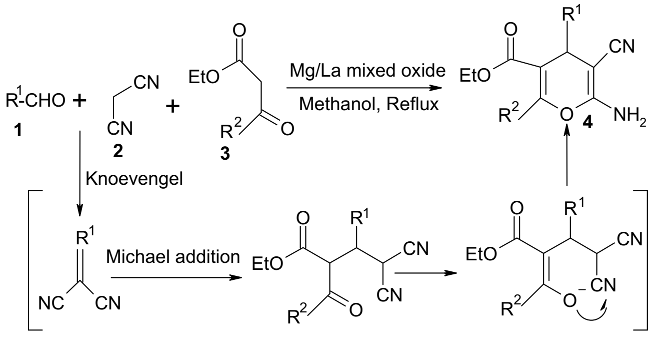
[a] Reaction conditions: aldehyde derivative (1 mmol); malononitrile (1.1 mmol); active methylene diketo compound (1.1 mmol).

[b] Yields were determined by ^{1}H NMR spectroscopy.

[c] Yield obtained after the fourth recycle.

electron-donating aldehyde counterparts. For example, aromatic aldehydes such as 4-chloro, 4-nitro, 3-nitro, and 4-cyano benzaldehydes (entries 2–5) react quickly with high product yields in comparison to 4-hydroxy, 4-methyl, 4-methoxy, and 4-acetoxy benzaldehyde derivatives[22] (entries 6–9). The catalyst also exhibited good activity with an aliphatic aldehyde (entry 10). The present catalyst was also studied by varying the active methylenic derivative[22] (entries 12–15). Recycling experiments were performed using the Mg/La catalyst for the synthesis of 5-ethoxycarbonyl-2-amino-4-(4-chlorophenyl)-3-cyano-6-methyl-4*H*-pyran (Table 2, entry 4). These recycling experiments show that the Mg/La catalyst catalyzes the reaction with consistent activity even after four cycles.

The mechanism of the present reaction (Scheme 2) initially proceeds by Knoevenagel condensation, as the catalyst possesses strong basic sites, which promotes the reaction by abstracting a proton from the active methylene component. As a result, an alkene intermediate may form with the aldehyde. This in turn reacts with 1,3-diethyl acetone dicarboxylate/ethyl acetoacetate/diethyl malonate via Michael addition to give the polyfunctionalized 4*H*-pyrans **4**.



Scheme 2. A plausible mechanism of 4*H*-pyran synthesis.

In summary, an efficient heterogeneous strong basic Mg/La catalyst is reported for the synthesis of 4*H*-pyran derivatives in a three component condensation reaction of an aldehyde, malononitrile, and a ketoester. Advantages of the strategy include simple catalyst preparation, mild reaction temperature, easy recovery, and reusability of the catalyst with consistent activity and short reaction times.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.02.154.

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21. The new compounds were analyzed by ^{1}H NMR, ^{13}C NMR, ESI-MS, and elemental (CHNS) analysis. 5-Ethoxycarbonyl-2-amino-4-(4-acetoxyphenyl)-3-cyano-6-methyl-4*H*-pyrans (Table 2, entry 9): Mp: 216–217 °C; ^{1}H NMR (400 MHz, DMSO-d_6, ppm) δ 1.033 (t, 3H). 2.24 (s, 3H), 3.37 (s, 3H), 3.96 (q, 2H), 4.30 (s, 1H), 6.95 (br s, 1H), 7.07 (d, 2H), 7.15 (d, 2H); ^{13}C NMR (400 MHz, DMSO-d_6, ppm) δ 14.27, 18.75, 21.38, 38.78, 57.58, 60.78, 107.67, 120.27, 122.32, 128.72, 142.91, 149.74, 157.37, 159.06, 165.94, 169.77; ESI-MS *m*/*z*: 342 (M^{+}); CHNS analysis: C, 63.5; H: 5.4, N, 8.2.

    5-Ethoxycarbonyl-2-amino-4-ethyl-3-cyano-6-methyl-4*H*-pyrans (Table 2, entry 10): Mp: 185–186 °C; ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ 1.14 (t, 3H), 1.28 (t, 3H), 2.61 (s, 3H), 3.52 (m, 2H), 3.72 (t, 1H), 4.14 (q, 2H), 5.71 (br s, 2H); ^{13}C NMR (400 MHz, CDCl$_3$, ppm): δ 13.96, 14.18, 31.89, 41.18, 46.39, 60.33, 61.57, 110.62, 114.80, 146.08, 165.93, 168.43; ESI-MS *m*/*z* 236 (M^{+}); CHNS analysis: C, 61.3; H, 7.1; N, 11.2.

    5-Ethoxycarbonyl-2-amino-4-(4-(*tert*-butyldimethylsilyloxy)phenyl)-3-cyano-6-methyl-4*H*-pyrans (Table 2, entry 11): Mp: 141–142 °C; ^{1}H NMR (400 MHz, DMSO-d_6, ppm) δ 0.15 (s, 6H), 1.01 (s, 9H), 1.18 (t, 3H), 2.28 (s, 3H), 2.28 (s, 3H), 3.44 (br s, 2H), 4.04 (q, 2H), 4.22 (s, 1H), 6.76 (d, 2H), 7.01 (d, 2H); ^{13}C NMR (400 MHz, DMSO-d_6, ppm): δ −4.03, 14.27, 18.42, 26.04, 38.58, 59.93, 61.28, 112.86, 114.63, 120.11, 128.95, 138.32, 154.36, 156.62, 166.01, 168.95; ESI-MS *m*/*z* 414 (M^{+}); CHNS: C, 63.65, H, 7.4, N, 7.1.
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