Arabian Journal of Chemistry (2011) 4, 159–162

King Saud University

Arabian Journal of Chemistry

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ORIGINAL ARTICLE

Nanosized magnesium oxide as a highly effective heterogeneous base catalyst for the rapid synthesis of pyranopyrazoles via a tandem four-component reaction

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Received 9 May 2010; accepted 14 June 2010
Available online 25 June 2010

KEYWORDS

Four-component;
Ethyl 3-alkyl-3-oxo propanoate;
Malononitrile, 6-amino-3-alkyl-4-aryl-5-cyano-1,4-dihydropyrano[2,3-*c*]pyrazole;
6-Amino-3-alkyl-4-aryl-5-cyano-1,4-dihydropyrano[2,3-*c*]pyrazole

Abstract A four-component reaction of hydrazine hydrate or phenyl hydrazine, ethyl 3-alkyl-3-oxo propanoate, aldehydes and malononitrile has been achieved in the presence of nanosized magnesium oxide as a highly effective heterogeneous base catalyst to produce of 6-amino-3-alkyl-4-aryl-5-cyano-1,4-dihydropyrano[2,3-*c*]pyrazole derivatives in excellent yields and in a short experimental time. This method is simple and rapid for focusing a pyrano ring with a pyrazole ring.

1. Introduction

Tandem C–C bond formations are convenient methods for synthesis of heterocyclic compounds from relatively simple starting materials in a convergent way (Tietze et al., 2006; Montgomery, 2004; Miura and Murakami, 2007; Denmark and Thorarensen, 1996; Ji et al., 2008). These transformations are usually operated in one-pot without the need for intermediate workups or purifications. In particular, the development of tandem reactions for the efficient construction of small molecules is an important goal in combinatorial chemistry from the viewpoints of operational simplicity and assembly efficiency. Hence, the development of multi-component reaction protocols for the synthesis of heterocyclic compounds has attracted significant interest from pharmaceutical groups. Pyranopyrazoles are an important class of heterocyclic compounds.

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Peer review under responsibility of King Saud University.
doi:10.1016/j.arabjc.2010.06.032

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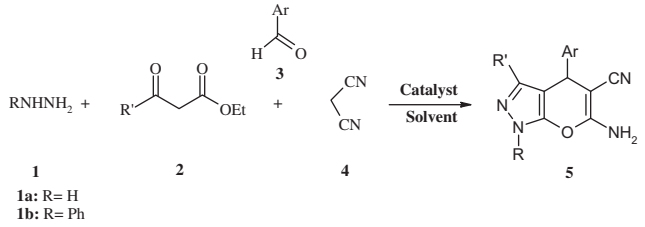
They find applications as pharmaceutical ingredients and biodegradable agrochemicals (Bonsignore et al., 1993; Wang et al., 2000). The first reported pyranopyrazole was synthesized from the reaction between 3-methyl-1-phenylpyrazolin-5-one and tetracyanoethylene (Junek and Aigner, 1973). Various 6-amino-5-cyano-4-aryl-4*H*-pyrazolo[3,4-*b*]pyrans were synthesized by the reaction of arylidienemalononitrile with 3-methyl-pyrazol-ine-5-ones or by the condensation of 4-arylidienepyrazoline-5-one with malononitrile (Wamhoff et al., 1993; Tacconi et al., 1980).

Sharanin Yu et al. (1983) have developed a three-component reaction between pyrazolone, an aldehyde and malononitrile in ethanol using triethylamine as the catalyst. Vasuki and co-workers reported an efficient four-component reaction protocol for the synthesis of pyranopyrazole derivatives in the presence of a catalytic amount of bases such as piperidine, pyrrolidine, morpholine and triethylamine at ambient temperature (Gnanasambandam Vasuki and Kumaravel, 2008). We have recently reported a one-pot three-component synthesis of 5-cyano-1,4-dihydropyrano[2,3-*c*]pyrazole derivatives which were catalyzed by magnesium oxide (MgO) as heterogeneous base catalyst in acetonitrile (Sheibani and Seifi, 2008; Sheibani et al., 2009; Sheibani and Babaei, 2010). Heterogeneous catalysts are advantageous over conventional homogeneous catalysts as they can be easily recovered from the reaction mixture by simple filtration and can be reused after activation, thereby making the process economically viable. Among the heterogeneous basic catalysts, magnesium oxide is a versatile material used as catalyst for several base-catalyzed organic transformations (Hattori, 1995), toxic waste remediation, and as additive in refractory, paint, and superconductor products (Ding et al., 2001).

2. Results and discussion

In the present work, we report an efficient one-pot, four-component reaction protocol for the synthesis of pyranopyrazole derivatives in the presence of nanosized magnesium oxide as a highly effective heterogeneous base catalyst at room temperature. 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 (Scheme 1).

The MgO catalyst is generally prepared by the decomposition of various magnesium salts or magnesium hydroxide [$Mg(OH)_2$, brucite]. However, the MgO formed by this method usually exhibits relatively large grain sizes, inhomogeneous morphologies, and small surface areas. These structural and textural features limit its application as a catalyst. Several novel methods



Scheme 1

such as controlled precipitation, solgel route, sol–gel followed by hypercritical drying, amorphous citrate method, and preparation under hydrothermal conditions, have been reported in literature for preparation of nanosized MgO particles (Wang et al., 1997; Koper et al., 1997). These methods are highly advantageous in terms of the crystallite size and shape, surface area, and surface basic characteristics of the synthesized MgO particles.

The particle size and surface morphology of synthesized MgO by wet chemical procedure depend upon several factors such as the rate of hydrolysis of magnesium salts, temperature, type of base, concentration of the salt, and drying and calcination steps. Proper choice of these parameters can lead to particles of uniform morphology and size. In this study, we have prepared nanosized MgO catalyst on basis of method which was reported by Dalip Kumar and co-workers and used it successfully in the synthesis of dihydropyrano[2,3-*c*]pyrazoles. The treatment of hydrazine hydrate **1a** or phenyl hydrazine **1b**, ethyl 3-alkyl-3-oxopropanoates **2**, aldehydes **3** and malononitrile **4** resulted in 5-cyano-1,4-dihydropyrano[2,3-*c*]pyrazole derivatives **5** in the presence of commercially available MgO and nanosized magnesium oxide (MgO) as base catalysts (Table 1). The catalytic activity of the synthesized nanosized MgO particles was compared with the commercially available MgO catalyst. As shown in Table 1 the activity of the nanosized MgO was much faster as compared to the commercial MgO catalyst. This is in agreement with a recent report where an increase in the initial activity was observed in case of nanoparticles as compared to the bulk catalyst (Valdes-Solis et al., 2006). In order to examine the solvent effect, we used solvents such as water, ethanol and acetonitrile in the four-component reactions of benzaldehyde, hydrazine hydrate **1a** or phenyl hydrazine **1b**, ethyl acetoacetate or ethyl 3-oxo-hexanoate and malononitrile **4** in the presence of nanosized magnesium oxide (MgO) as model reactions to investigate the effects of solvent for preparing compounds **5a** and **5g**, respectively. The four-component condensation in ethanol required relatively longer reaction time and afforded moderate yields of the product. In each case, the substrates were mixed together with 0.05 g catalysts agitated with 10 mL solvent. The results are shown in Table 2. As shown in Tables 1 and 2 yield of the reaction is markedly affected by the catalyst and solvent, and optimum results were obtained when reactions were treated in acetonitrile and in the presence of nanosized magnesium oxide (MgO).

Mechanistically, the reaction occurs via initial formation of arylidenemalononitrile in quantitative yield by the Knoevenagel addition of malononitrile to the aldehyde and followed by loss of water molecules. The Knoevenagel condensations of malononitrile with aldehydes in the presence of magnesium oxide (MgO) as a catalyst have been extensively studied and the rate of these reactions are very fast (Sheibani and Babaei, 2010). The formation of the product **5** is proposed to involve the following tandem reactions: pyrazolone **6** formation by reaction between **1** and **2**, Knoevenagel condensation between **3** and **4**, Michael addition of pyrazolone **6** to arylidenemalononitrile **7**, followed by cyclization and tautomerization (Scheme 2).

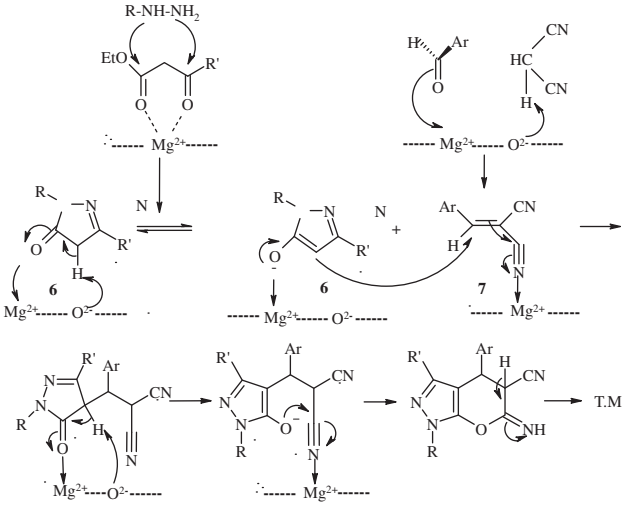
The compounds **5a–o** are known in the literature. The IR spectra and melting point of all known compounds were consistent with those reported in the literature (Sheibani and Babaei, 2010; Peng et al., 2006; Jin et al., 2006). The IR spectra of these compounds showed the presence of CN at region 2235–2238 cm^{-1} and two sharp bands at 3500–3450 and

Table 1 Synthesis of pyranopyrazole derivatives **5a–o** in the presence of MgO.

Compd no.	R	R′	Ar	Commercial MgO		Nanosized MgO		m.p., °C (Ref.)
				Time (min)	Yield (%)	Time (min)	Yield (%)	
5a	H	CH_3	C_6H_5	90	83	10	97	243–245 (Peng et al., 2006)
5b	H	CH_3	2-ClC_6H_4	90	83	12	93	246–248 (Peng et al., 2006)
5c	H	CH_3	4-ClC_6H_4	50	85	5	97	233–235 (Peng et al., 2006)
5d	H	CH_3	3-BrC_6H_4	100	75	17	90	220–222 (Peng et al., 2006
5e	H	CH_3	4-$NO_2C_6H_4$	120	70	25	90	249–252 (Peng et al., 2006)
5f	H	CH_3	4-$CH_3OC_6H_4$	150	70	43	89	208–210 (Peng et al., 2006)
5g	Ph	CH_3	C_6H_5	150	83	12	95	166–168 (Jin et al., 2006
5h	Ph	CH_3	4-$CH_3C_6H_4$	165	85	20	93	176–178 (Jin et al., 2006)
5i	Ph	CH_3	4-$CH_3OC_6H_4$	165	75	15	90	169–170 (Jin et al., 2006)
5j	Ph	CH_3	4-ClC_6H_4	100	87	5	96	144–146 (Jin et al., 2006)
5k	Ph	CH_3	2,4-$Cl_2C_6H_3$	75	88	10	92	182–184 (Jin et al., 2006)
5l	Ph	CH_3	4-BrC_6H_4	175	76	23	88	184–185 (Sheibani and Babaei, 2010
5m	Ph	Propyl	4-ClC_6H_4	100	88	12	92	181–182 (Sheibani and Babaei, 2010)
5n	Ph	*Iso*-propyl	4-ClC_6H_4	100	87	15	93	172–173 (Sheibani and Babaei, 2010)
5o	Ph	*Iso*-propyl	2,4-$Cl_2C_6H_3$	60	85	10	95	188–189 (Sheibani and Babaei, 2010)

Table 2 Solvent effects on the synthesis of compounds **5a** and **5g**.

Compd. no.	Solvent	Time (min)	Yield (%)
5a	H_2O	20	90
5a	CH_3CH_2OH	35	80
5a	CH_3CN	10	97
5g	H_2O	25	85
5g	CH_3CH_2OH	45	75
5g	CH_3CN	12	95



Scheme 2

3390–3380 cm^{-1} due to asymmetric and symmetric vibrations of the NH_2 group. The ^1H and ^{13}C NMR and mass spectra were also in accordance with the proposed structures.

In conclusion, we have described an efficient route for generation of pyranopyrazoles via a tandem four-component reaction in the presence nanosized magnesium oxide (MgO) as a highly effective heterogeneous base catalyst. We believe that the operational simplicity of the present process combined with the efficiency of this method will make it potentially attractive for further library construction.

3. Experimental

The (arylhydrazono)-propan-2-ones **1** were known and prepared according to a general procedure (Koper et al., 1997). Melting points were determined on an Gallenkamp melting point apparatus and are uncorrected. IR spectra were measured on a Mattson 1000 FT-IR spectrometer. ^1H NMR and ^{13}C NMR spectra were recorded on a BRUKER DRX-500 AVANCE spectrometer at 500 and 125.77 MHz, respectively. MS spectra were recorded on a Shimadzu QP 1100EX mass spectrometer operating at an ionization potential of 70 eV. Elemental analyses were performed using a Heraeus CHN-O-Rapid analyzer.

3.1. 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 solution, 0.1 M magnesium nitrate solution was added dropwise with continuous stirring. 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 procedure, the mixture was stirred at room temperature for 12 h, filtered, repeatedly washed with distilled water, dried at 120 °C, and calcined at 500 °C for 2 h (Kumar et al., 2007).

*3.2. General procedure for the preparation of 6-amino-4-aryl-3-alkyl-5-cyano-1,4-dihydropyra-no[2,3-c]pyrazole derivatives (**5a–o**)*

To a stirred solution of hydrazine hydrate 96% (0.107 g, 2 mmol) or phenyl hydrazine (0.216 g, 2 mmol), ethyl 3-alkyl-3-oxopropanoate (2 mmol), aldehyde (2 mmol), malononitrile (0.132 g, 2 mmol) and MgO (50 mg) in acetonitrile (15 mL) were added successively at room temperature with vigorous stirring for the time reported in Table 1 (the progress

of the reaction being monitored by TLC and hexane/ethyl acetate was used as an eluent). After completion of the reaction the catalyst was separated from the reaction mixture by centrifugation. The excess acetonitrile was removed by evaporation and then was poured into ice cold water; the crude product was filtered, dried and recrystallized from 96% ethanol.

3.3. Spectral data for selected compounds

*3.3.1. 6-Amino-5-cyano-3-methyl-4-phenyl-1,4-dihydropyrano[2,3-c]pyrazole (**5a**)*

White crystals, mp. 243–245°C; ν_{max}(KBr): 3450, 3370 (NH_2), 2195 (CN), 1645 (C═N), 1610, 1605 (Ar) cm^{-1}; δ_H (500 MHz, DMSO-d_6): 12.16 (s, 1H, NH), 7.45–7.16 (m, 5H, ArH), 6.95 (s, 2H, NH_2), 4.62 (s, 1H, 4-H), 1.80 (s, 3H, CH_3) ppm.

*3.3.2. 6-Amino-5-cyano-3-methyl-1,4-diphenyl-1,4-dihydropyrano[2,3-c]pyrazole (**5g**)*

Pale yellow crystals, mp. 168–170 °C; ν_{max}(KBr): 3472, 3320 (NH_2), 2205 (CN), 1660 (C═N), 1590 (Ar) cm^{-1}; δ_H (500 MHz, DMSO-d_6): 7.16–7.32 (m, 10H, ArH), 6.95 (s, 2H, NH_2), 4.68 (s, 1H, 4-H), 1.93 (s, 3H, CH_3) ppm.

*3.3.3. 6-Amino-4-(4-chlorophenyl)-5-cyano-1-phenyl-3-propyl-1,4-dihydropyrano[2,3-]pyrazole (**5m**)*

Pale yellow crystals, mp. 181–182 °C; ν_{max}(KBr): 3456, 3312 (NH_2), 2210 (CN), 1656 (C═N), 1586 (Ar) cm^{-1}; δ_H (500 MHz, DMSO-d_6): 7.83–7.30 (9H, m, arom), 7.24 (2H, s, NH_2), 4.73 (1H, s, CH), 2.14 (1H, m, H_a on C_1 of propyl), 2.05(1H, m, H_b on C_1 of propyl), 3.5 (1H, m, H_a on C_2 of propyl), 1.22 (1H, m, H_b on C_2 of propyl), 1.83 (3H, t, CH_3) ppm.

Acknowledgements

The authors express appreciation to the Shahid Bahonar University of Kerman Faculty Research Committee Fund for its support of this investigation.

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