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## An efficient method for the multicomponent synthesis of multisubstituted pyridines, a rapid procedure using Au/MgO as the catalyst

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#### ABSTRACT

Au/MgO proved to be a highly efficient and reusable catalyst for multicomponent coupling reactions at 70 °C. The synthesized multisubstituted pyridines were obtained in high yields and in short reaction times. With facile work-up, the novel catalyst can be readily recovered after the reaction and reused without any loss of its catalytic activity.

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Eco-efficient and eco-friendly methodologies for heterocyclic chemistry are vital for the continued preparation of functional organic molecules and materials.<sup>1</sup> For the sake of economic outlook and pollution prevention, multicomponent reactions (MCRs) are very attractive research endeavors in organic synthesis due to the formation of C—C and C-heteroatom bonds in one pot.<sup>2</sup> This approach has garnered considerable interest, as it addresses the fundamental principles of synthetic efficiency and reaction design arising from minimization of waste, time, energy, and cost. Minimizing the consumption of auxiliary substances, energy, and time required in achieving separations, results in significant economic and environmental benefits owing to the new strategies for recycling heterogeneous solid catalysts.<sup>2a,b</sup>

Assembling N-heterocycles is important in synthetic organic chemistry. The synthesis of polysubstituted pyridines is of particular interest because such compounds constitute partial or complete structures of many natural products and organic functional materials, as well as in many synthetic compounds of pharmaceutical interest.<sup>3</sup> Additionally, 2-amino-3-cyanopyridine derivatives (Fig. 1) have raised considerable attention as potent inhibitors of HIV-1.<sup>4</sup>

The development of highly efficient methods for the preparation of polysubstituted pyridine derivatives is of considerable

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**Figure 1.** Polysubstituted pyridines with adjacent amino and nitrile functionalities having diverse pharmacological properties.

interest. Most of the existing synthetic routes to pyridines are based on reactions between amines and carbonyl compounds.<sup>5</sup> Despite the numerous studies and methods that have appeared in the literature, most of the protocols still suffer from one or more important limitations such as long reaction times, low yields, use of toxic solvents,<sup>6</sup> high temperatures, or microwave assistance.<sup>7</sup> However, a straightforward and efficient one-pot synthesis of multisubstituted pyridine structures is often a challenge. So there is still a great demand to develop new approaches to multifunctionalized pyridines. The reported use of MgO supported Au catalysts for oxidation and coupling reactions<sup>8</sup> has prompted our choice of catalyst. To our knowledge, no reports are available in

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Table 1
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Screening of reaction conditions for the four-component reaction

Entry	Product	Catalyst	Amount	Solvent	Temp (°C)	Time (h)	Yield <sup>a</sup> (%)
1	5a	-	_	EtOH	rt	9	b
2	5a	-	-	EtOH	70	7	30
3	5a	[Bmim]BF <sub>4</sub>	8 drops	-	rt	9	b
4	5a	[Bmim]BF <sub>4</sub>	8 drops	-	70	8	с
5	5a	PTSA	30.0 mg	EtOH	70	8	с
6	5a	CF3COOH	1.0 ml	EtOH	70	8	с
7	5a	Au/MgO	10.0 mg	EtOH	70	4	75
8	5a	Au/MgO	20.0 mg	EtOH	70	2	94
9	5a	Au/MgO	30.0 mg	EtOH	70	2	95
10	7a	-	_	EtOH	70	6	b
11	7a	Au/MgO	20.0 mg	EtOH	70	3	86

<sup>a</sup> Isolated yields.

<sup>b</sup> Product not found.

<sup>c</sup> Trace.

the literature on the synthesis of polysubstituted pyridines by using Au/MgO catalysts. In view of this, we have studied the onepot synthesis of highly substituted pyridines from commonly available starting materials by employing this catalyst.

We have previously reported new routes to small heterocyclic compounds bearing, in particular, amino groups at the 2 position and a carbonitrile group at the 3 position of the heterocycle, via the reaction of various aromatic aldehydes, malononitrile, ketones, and ammonium acetate and using different catalysts.<sup>2</sup> In the current study, we initially carried out the model reaction of benzaldehyde, malononitrile, a ketone (two examples), and ammonium acetate with various Brønsted and Lewis acids in ethanol (Table 1). Excellent results (Table 1, entries 8 and 11) were obtained with the composite Au/MgO, serving as a heterogeneous catalyst, at reflux temperature (70 °C). With Au/MgO established as the catalyst of choice, and based on our past experience,<sup>2b,c</sup> ethanol was chosen as the solvent for this multicomponent, one-pot transformation. After systematic screening, we established that Au/MgO and ethanol under reflux give a good yield of product in a short reaction time (Schemes 1 and 2). The formation of multisubstituted pyridines can be rationalized by the initial formation of arylidenemalononitrile (A) as an intermediate via the standard Knoevenagel condensation. This is followed by the Michael type addition of ketone 2 to the activated double bond of the arylidene. Intramolecular cyclization of these adducts and subsequent oxidation yielded target products **5a-g** (Scheme 3).

Examination of the results summarized in Table 1 shows that the reaction time in the absence of the catalyst was longer and the product yield was only 30%. The presence of the catalyst resulted in a 95% product yield in two hours. The nature of the Au/MgO catalyst, particularly its acidic/basic properties and binding of the substrate to the active sites acquired due to sparsely distributed Au, seems to play an important role in enhancing the performance of this catalyst in this multicomponent reaction. An important advantage of heterogeneous catalysis is that it can be







Scheme 2. Four-component synthesis of multisubstituted pyridine derivatives 7a-d.

recovered and reused. The recovery of Au/MgO was accomplished easily by filtration. A series of experiments was performed using the recycled catalyst in the synthesis of **5a**. Studies showed that the recycled catalyst can be reused at least five times without significant loss (<2%) of activity (Fig. 2). All the reactions were carried out under identical conditions. The maintained activity of the catalyst is an extremely important parameter which reflects the nonpoisoning of the surface. Higher surface areas favor adsorption of reaction molecules and the small particle size is advantageous for minimal internal diffusion resistance of molecules, thereby increasing the catalytic performance of heterogeneous catalysts.

From the results shown in Table 2, it is evident that spatiallyhindered aldehydes (2-methoxy, 2-bromo, and 2-chloro substituted) gave the desired products. Table 2 shows that a wide-range of aldehydes gave good to excellent yields of the desired products. This method has further scope due to the absence of harmful organic solvents. The Au/MgO catalyst combination also enhanced the rate of the reaction resulting in reduced reaction times. The synthesized multisubstituted pyridines were fully characterized by FTIR, <sup>1</sup>H NMR, <sup>13</sup>C NMR, and mass spectrometry. The IR spectra of the products showed, symmetrical and unsymmetrical NH<sub>2</sub> stretching in the region between 3307 and 3330 cm<sup>-1</sup> and the CN stretching vibration of the nitrile group appeared in the region between 2210 and 2215 cm<sup>-1</sup>. The <sup>1</sup>H NMR spectra in CDCl<sub>3</sub> showed one singlet signal around  $\delta$  = 4.96–5.14 due to the NH<sub>2</sub> protons and all the compounds were further examined by <sup>15</sup>N NMR (GHSQC) to confirm the presence of the -NH<sub>2</sub> group in their structure (Supplementary data).

To investigate the morphology of the used catalysts, SEM analysis was performed (Fig. 3). The micrograph reveals particles with uniform size and shape, reflecting the morphologies of highly crystalline mesoporous materials. SEM-EDX shows (Fig. 1 in Supplementary data) the presence of gold nanoparticles on the surface of the support.

The TEM images (Fig. 4) of the catalyst show that the lattice edges of the MgO and Au nanoparticles are clearly visible on the

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Scheme 3. Plausible reaction mechanism for the formation of compounds 5a-g.



Figure 2. Reusability studies on the Au/MgO catalyst for the synthesis of 5a.

Table 2 Multicomponent reaction for the synthesis of multisubstituted pyridines 5a-g and 7a-d

Entry	Product	R	Time (h)	Yield <sup>a</sup> (%)
1	5a	Н	2.0	94
2	5b	$4-OCH_3$	2.5	90
3	5c	4-Br	2.0	92
4	5d	2-Cl	1.5	95
5	5e	2-Br	2.0	88
6	5f	$2-OCH_3$	3.0	85
7	5g	4-N(CH <sub>3</sub> ) <sub>2</sub>	2.0	95
8	7a	Н	3.0	86
9	7b	4-OCH <sub>3</sub>	3.5	80
10	7c	4-Br	3.0	84
11	7d	2-Cl	3.0	82

<sup>a</sup> Isolated yields.

surface of MgO. In high resolution, the particles appeared to be of an irregular circular shape, as has previously been described in the literature.<sup>9</sup> The darker parts of the images show the presence of gold particles dispersed evenly on the surface with sizes of approximately 30–40 nm, which is slightly larger than similarly synthesized nanoparticles.<sup>10</sup>

The surface area was calculated using the BET equation and from the physical adsorption and desorption isotherms of  $N_2$ . The catalyst showed a type-IV isotherm, which indicates the mesoporous



Figure 3. SEM image of the Au/MgO catalyst.



Figure 4. TEM image of the Au/MgO catalyst.

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Figure 5. BET surface area and pore size of Au/MgO.



Figure 6. Powder X-ray diffractogram of Au/MgO.

nature of the catalyst (Fig. 5). Data show that the surface area is closely related to the Au molar fraction. The surface area for the catalyst was found to be 87.8  $m^2/g$ , which is double the surface area for a catalyst previously synthesized using a similar method.<sup>10</sup> The pore volume was found to be 0.51 cm<sup>3</sup>/g.

The XRD spectrum of 5% Au loaded on MgO is shown in Figure 6. The powder XRD diffraction patterns of the prepared catalyst show d-spacing values of 3.27, 2.31, 1.88, 1.63, and 1.46 Å for  $2\theta$  angles of 19, 38.9, 46.2, 53.2, and 63.6°, respectively. The d-spacing phases correlated with the ICDD file numbers are 01-078-0430, 01-076-0667, and 4-0796 for Au-MgO phases respectively. The support phases, that is, Au and MgO, correlate well with reported values.<sup>11</sup>

In summary, we have synthesized highly substituted pyridines in excellent yields, with the use of Au loaded on MgO as a catalyst in a one-pot, multicomponent system by employing simple starting materials. The present protocol offers advantages in terms of higher yields, short reaction times, and no column chromatography is needed. Paramount is the use of the heterogeneous catalyst which can be easily recovered and reused. The proposed method should be a valuable addition to methods for synthesizing polysubstituted pyridines. Further studies on the sustainable applications of this catalyst to other chemical reactions are underway in our laboratory.

#### Preparation of Au(III) stock solution

With continuous stirring, HAuCl<sub>4</sub> (3 ml) was added to H<sub>2</sub>O (50 ml) in a pre-weighed beaker containing a stir bar. The beaker equipped with a thermometer, was then placed on a hot-plate and was heated to a temperature of 90 °C. The solution was left to stir for 6 h at a constant temperature to concentrate the solution. Evaporation of the solution resulted in orange microcrystals (2.053 g) and the wet crystals were then dissolved in H<sub>2</sub>O/EtOH mixture (9:1) and made up to 50 ml to attain a stock solution with a concentration of 0.0873 M.

#### **Catalyst preparation**

The preparation of gold on magnesium oxide (MgO) support was undertaken via a wet impregnation method.<sup>10</sup> To achieve a 5% Au/MgO loading, 5 ml of the Au(III) stock solution containing 0.133 g of gold was added to a beaker containing MgO (2.525 g) in double-distilled H<sub>2</sub>O (10 ml). The mixture was allowed to stir for a period of 3 h with continual analysis. The resultant mixture was then filtered under vacuum and washed with H<sub>2</sub>O (3 × 5 ml). The purple powder was collected and dried at 130–140 °C overnight. It was then calcined in the presence of air, at 450 °C for 5 h which yielded the pink-colored 5% Au/MgO catalyst.

# Typical procedure for the synthesis of multisubstituted pyridine derivatives catalyzed by Au/MgO (5a-g/7a-d)

Freshly distilled benzaldehyde (2.0 mmol) in EtOH (3 ml) at room temperature, malononitrile (2.0 mmol), cycloheptanone/ ethyl methyl ketone (4.0 mmol), ammonium acetate (3.0 mmol), and Au/MgO (20.0 mg) were added to a round-bottomed flask equipped with a magnetic stir bar and a condenser. The mixture was heated at 70 °C for the time specified in Table 2. The reaction progress was monitored by TLC (EtOAc/hexane = 3:7). After completion of the reaction, the mixture was cooled to room temperature and extracted with EtOAc. After filtering the Au/MgO solid, the solvent layer was washed with H<sub>2</sub>O, dried over anhydrous Na<sub>2</sub>-SO<sub>4</sub>, and the solvent was removed to obtain a precipitate which was recrystallized from EtOH to give the pure target compound **5** or **7**. The recovered Au/MgO solid was washed with CH<sub>2</sub>Cl<sub>2</sub>, dried under reduced pressure, and reused.

#### **Compound 5a**

Off-white solid: mp 227–228 °C (lit.,<sup>6</sup> 225–226 °C); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 1.47–1.52 (2H, m), 1.69–1.82 (4H, m), 2.46 (2H, t, *J* = 5.4 Hz), 2.92 (2H, t, *J* = 5.5 Hz), 5.11 (2H, s, NH<sub>2</sub>), 7.21–7.49 (5H, m); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  26.18, 28.03, 28.97, 31.98, 39.67, 89.33, 116.94, 126.42, 128.38, 128.60, 128.68, 136.85, 153.11, 157.22, 167.96; IR (KBr, cm<sup>-1</sup>): 3316 (NH<sub>2</sub>), 2212 (CN); MS (ESI), *m*/*z* = 286 (M+Na, 100%); Anal. Calcd (C<sub>17</sub>H<sub>17</sub>N<sub>3</sub>): C, 77.54; H, 6.51; N, 15.96. Found: C, 77.62 H 6.49, N 15.98.

#### **Compound 7a**

Off-white solid: mp 240–241 °C (lit.,<sup>12</sup> 243–244 °C); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 1.95 (3H, s, –CH<sub>3</sub>), 2.44 (3H, s, –CH<sub>3</sub>), 5.05 (2H, s, NH<sub>2</sub>), 7.23–7.50 (5H, m); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  15.30, 23.72, 89.72, 116.80, 119.69, 128.33, 128.64, 128.77, 136.79, 153.86, 157.23, 161.57; IR (KBr, cm<sup>-1</sup>): 3330 (NH<sub>2</sub>), 2211 (CN); MS (ESI), *m*/*z* = 224 (M+1, 100%); Anal. Calcd (C<sub>14</sub>H<sub>13</sub>N<sub>3</sub>): C, 75.31; H, 5.87; N, 18.82. Found: C, 75.37; H, 5.89; N, 18.78.

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#### Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.05. 089.

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