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Esmail Rezaei-Seresht^a, Reza Tayebee^a & Mohammad Yasemi^a

^a Department of Chemistry, Faculty of Sciences, Hakim Sabzevari University, Sabzevar, Iran

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KG-60-PIPERAZINE AS A NEW HETEROGENEOUS CATALYST FOR GEWALD THREE-COMPONENT REACTION

Esmail Rezaei-Seresht, Reza Tayebee, and Mohammad Yasemi

Department of Chemistry, Faculty of Sciences, Hakim Sabzevari University, Sabzevar, Iran

GRAPHICAL ABSTRACT



Abstract Piperazine supported on amorphous silica (KG-60-piperazine) as a basic catalyst acts in the Gewald three-component reaction of some aldehydes and ketones with malononitrile as well as ethyl cyanoacetate. The catalyst shows general utility with a variety of starting carbonyl compounds. Moreover, the catalyst can be reused for four additional cycles without significant loss of the activity.

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Keywords 2-Aminothiophenes; Gewald reaction; heterogeneous catalysis; multicomponent reaction

INTRODUCTION

The most convergent and well-established classical approach for the preparation of 2-aminothiophenes is Gewald's three-component reaction.^[1] Depending on the starting substrates and the reaction conditions, four basic versions of the Gewald reaction have been developed.^[1–4] Recently, efficient and convenient modifications to the Gewald reaction have been reported in the literature. For example, Sridhar et al. have carried out the reaction under microwave irradiation.^[5] The microwave-assisted Gewald reaction on solid support was also employed in a solid-phase thiophene synthesis.^[6] The reaction has been performed under microwave irradiation and solvent-free conditions to yield substituted benzo[b]thiophenes in good yields.^[7] Furthermore, a Gewald reaction induced by solar thermal energy

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Address correspondence to Esmail Rezaei-Seresht, Department of Chemistry, Faculty of Sciences, Hakim Sabzevari University, Sabzevar 96179-76487, Iran. E-mail: rezaei_seresht@yahoo.com



Scheme 1. Preparation of catalyst KG-60-piperazine (1).

has been developed for synthesis of 2-aminothiophenes.^[8] Ionic liquids used as solvents in combination with ethylenediammonium diacetate were shown to be very efficient in the case of the Gewald synthesis.^[9] Feroci et al. have developed an electrochemically induced Gewald reaction for synthesis of substituted 2-aminothiophenes.^[10]

Immobilization of catalytically active species on inorganic solid materials enables not only generation of recyclable catalysts but also greater catalytic activities compared with their homogeneous precursors and analogs owing to unique environments of the surfaces.^[11] Catalysts and reagents immobilized upon a range of insoluble supports have been utilized and reported since the late 1960s.^[12] Secondary amines, immobilized on mesoporous FSM-16 silica, have been utilized to obtain substituted 5-ketoaldehydes by direct 1,4-conjugate addition of unmodified aldehydes to vinyl ketones.^[13] Silica gel functionalized with a propylamino moiety [SiO₂-(CH₂)₃-NH₂] was employed in the reaction of different methylene active compounds with aldehydes and ketones for the production of electron-poor olefins.^[14] N,N-Diethylpropylamine supported on amorphous silica (KG-60-NEt₂) has been utilized as a solid and reusable catalyst in the Henry reaction of some nitroalkanes.^[15] Various amines immobilized on acidic silica-alumina surfaces have showed excellent catalytic



Scheme 2. Gewald reaction catalyzed by catalyst 1.

	Starting compounds				
Entry	Compound 2	Compound 3	Gewald product	Yield $(\%)^b$	Mp (°C)
1	2a	3a	CN S	41	102 (104) ^[19]
2	2b	3b	Me S NH ₂	60	45 (46) ^[1]
3	2c	3b	Et S NH2	49	72 (73) ^[1]
4	2d	3a	Me CN Me S NH ₂	46	139 (142) [1]
5	2d	3b	Me COOEt Me S NH ₂	43	91 (91) ^[1]
6	2e	3a	Ph CN S NH ₂	66	140 (142) [5]
7	2e	3b	Ph COOEt	43	97 (98) ^[5]
8	2f	3a	Me S NH2	37	153 (155) [19]
9	2g	3a		47	150 (151) ^[5]
10	2g	3b	CN S NH ₂	42	89 (91) ^[1]

Table 1. Obtained Gewald products in the presence of catalyst 1^a

(Continued)

	Starting compounds				
Entry	Compound 2	Compound 3	Gewald product	Yield $(\%)^b$	Mp (°C)
11	2h	3a		89	143 (144) ^[20]
12	2h	3b	CN S NH ₂	86	115 (115) ^[5]
13	2i	3a	CN S NH ₂	45	124 (126) [21]
14	2i	3b		56	88 (89) ^[5]

Table 1. Continued

^{*a*}Reaction conditions: time = 4 h, temperature = $80 \degree$ C, catalyst = $10 \mod \%$, compound **2** = $20 \mod$ **2** compound **3** = $20 \mod$ **4** = $20 \mod$ **4**

^bIsolated yields. All the products gave satisfactory ¹H NMR and IR spectra.

performance for the Michael reactions of nitrile compounds.^[16] Here, we report a silica-supported piperazine (KG-60-piperazine) as a new heterogeneous catalyst for the Gewald three-component reaction.

RESULTS AND DISCUSSION

It has been already demonstrated that secondary amines such as morpholine and diethylamine excellently catalyze the Gewald reaction.^[17] Therefore, we searched for a suitable amine and found piperazine (1), which was not only was structurally similar to morpholine but also readily immobilized on solid support (silica gel). Piperazine was then immobilized on silica according to a previously described procedure^[18] to yield catalyst KG-60-piperazine (1) (Scheme 1).

To investigate the catalytic activity of 1, the reaction of cyclohexanone with malononitrile and sulfur was selected as a model reaction. At first, mixtures of cyclohexanone (20 mmol), malononitrile (20 mmol), and sulfur (22 mmol) in the presence of different quantities of catalyst 1 were reacted in ethanol at 80 °C for up to 6 h. An experiment was also conducted in the absence of the catalyst. In this case, only very low amounts (<6%) of the Gewald product were formed after 6 h. The results showed that the catalyst significantly improved the yield of the reaction, and the optimum result was observed with 10 mol% of the catalyst after a 4-h reaction time.

The effect of the solvent was also investigated in the reaction. Thus, experiments were run under the conditions previously mentioned ($80 \degree C$, catalyst = $10 \mod \%$,

t = 4 h). In all cases, solutions (20 mmol) of cyclohexanone in solvents hexane, MeOH, dimethylformamide (DMF), dimethylsulfoxide (DMSO), and EtOH were used, and the yields of the reaction were 17, 79, 82, 84, and 89% respectively.

To assess the generality of the method, a number of aldehydes and ketones were reacted in the presence of catalyst 1 to afford the corresponding Gewald products in good to excellent yields (Scheme 2, Table 1). Spectral data for the Gewald products 4 and 5 are available online in the Supplemental Material.

Finally, we faced the problem of catalyst recycling; at the end of the model reaction between cyclohexanone and malononitrile, the catalyst was filtered on a Büchner funnel, washed thoroughly with absolute ethanol and acetone, dried under vacuum for 12 h at room temperature, and reused. The catalyst could be utilized with similar results for at least four additional cycles (reaction: First run 89%; fifth run: 75%).

CONCLUSIONS

We have shown the utilization of KG-60-piperazine as a new heterogeneous and reusable catalyst in the Gewald reaction. It is noteworthy that the catalyst shows general applicability and good to excellent efficiency with all substrates utilized in the reaction.

EXPERIMENTAL

Compounds 2 (20 mmol) and 3 (20 mmol) were dissolved in absolute ethanol (30 mL). Then, sulfur (22 mmol) and catalyst 1 (3.70 g) were added and the mixture was refluxed at 80 °C for 4 h. The reaction mixture was cooled to room temperature and the solid catalyst was filtered off. The solution poured into an ice-water mixture (60 mL) and the precipitation was filtered off, washed with cold water, and dried in vacuo to yield the Gewald products 4 and 5.

Compound **4 h**: Yield, 3.17 g (89%); mp, $143 \degree \text{C}$ (lit.^[20] $144 \degree \text{C}$); IR (KBr, cm⁻¹) 3420, 3320, 2950, 2205, 1631, 1120; ¹H NMR (CDCl₃, 400 MHz) δ 4.64 (s, 2H), 2.49–2.42 (m, 4H), 1.78 (t, 4H); ¹³C NMR (100 MHz, CDCl₃) δ 160.1, 132.3, 120.6, 115.5, 88.6, 24.5, 24.1, 23.4, 22.1.

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