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H_2SO_4/Silica gel: An Efficient and Reusable Heterogeneous Catalyst for the Synthesis of Pyrazolo[4,3-e][1,2,4]triazolo[4,3-c]pyrimidines

A. DAVOODNIA
Department of Chemistry, Faculty of Sciences, Islamic Azad University, Mashhad Branch, Mashhad-91735-413, Iran
Fax: (98)(511)8424020; Tel: (98)(511)8435000
E-mail: adavoodnia@yahoo.com; adavoodnia@mshdiau.ac.ir

Sulfuric acid adsorbed on silica gel has been used as an effective and reusable catalyst for the synthesis of pyrazolo[4,3-e][1,2,4]triazolo-[4,3-c]pyrimidines through cyclocondensation of 4-hydrazino-1*H*-pyrazolo[3,4-d]pyrimidines with triethylorthoesters under conventional heating and solvent-free microwave irradiation conditions. The present methodology offers several advantages, such as high yields, short reaction times, mild reaction condition and a recyclable and relatively green catalyst with easy work up.

Key Words: Pyrazolo[4,3-e][1,2,4]triazolo[4,3-c]pyrimidines, H_2SO_4/ Silica gel, Triethylorthoesters, Microwave irradiation.

INTRODUCTION

Solid-supported catalysts have found tremendous popularity in several disciplines of chemistry. These catalysts are reusable, efficient and above all environmentally friendly[1-5]. In past, several researchers have been using acidic silica gel in heterocyclic systhesis[6,7]. On the other hand, in previous work same reported the synthesis of some new pyrazolo[4,3-e][1,2,4]triazolo[4,3-c]pyrimidines under conventional heating and in absence of catalyst[8]. In these conditions the reaction times were relatively high.

In pursuing these studies, in this paper a rapid and efficient synthesis of pyrazolo-[4,3-e][1,2,4]triazolo[4,3-c]pyrimidines (**3a-f**) through cyclocondensation of 4-hydrazino-1*H*-pyrazolo[3,4-d]pyrimidines (**1a-b**) with triethylorthoesters (**2a-c**) catalyzed by sulfuric acid adsorbed on silica gel as an easily available, inexpensive and relatively green catalyst under conventional heating and solvent-free microwave irradiation conditions are reported (**Scheme-I**).

EXPERIMENTAL

Melting points were recorded on an electrothermal type 9100 melting point apparatus. The ^{1}H NMR (100 MHz) spectra were recorded on a Bruker AC 100 spectrometer. The mass spectra were scanned on a Varian Mat CH-7 instrument at 70 eV.

Preparation of the catalyst: Adsorption of sulfuric acid on silica gel: A solution of conc. H_2SO_4 (2 mL) in acetone (20 mL) is added to a dispersion of silica gel 60 (70-230 mesh) (100 g) in acetone (200 mL) and stirred at room temperature for 1 h. The solvent is removed under reduced pressure. A yellow-brown powder is obtained, which can be stored in a desicator for long periods of times without any appreciable loss of activity.

General procedure for the preparation of pyrazolo[4,3-e][1,2,4]triazolo[4,3-c]-pyrimidines (3a-f)

Method A: A mixture of 4-hydrazino-1*H*-pyrazolo[3,4-d]pyrimidines[8] **1a**, **1b** (3 mmol), triethylorthoesters **2a-c** (4 mmol) and H_2SO_4/silica gel (0.5 g) was heated under reflux in ethanol (25 mL) for the indicated time. After the completion of the reaction (monitored by TLC), the solid catalyst was filtered off, the solvent was evaporated to dryness and the crude product was recrystallized from ethanol to give compounds **3a-f** in 76-88 % yields (Table-1).

Method B: The same mixtures as in above were subjected to microwave irradiation at 900 w for the indicated time. After the completion of the reaction (monitored by TLC) the crude product was treated with boiling ethanol and the solid catalyst was filtered off. The filtrate was evaporated to dryness and the residue was recrystallized from ethanol to give compounds **3a-f** in 89-94 % yields (Table-1).

TABLE-1
H_2SO_4 ADSORBED ON SILICA GEL CATALYZED SYNTHESIS OF PYRAZOLO-[4,3-e][1,2,4]TRIAZOLO[4,3-c]PYRIMIDINES (**3a-f**)

Entry	Without the catalyst (reported in ref. 8)		Using the catalyst (Method A)[a]		Using the catalyst (Method B)[b]		m.p. (ºC)
	Time (min)	Yield (%)[c]	Time (min)	Yield (%)[c]	Time (min)	Yield (%)[c]	
3a	360	80	60	88	7	91	260-261
3b	360	74	70	80	7	92	254-256
3c	360	72	75	83	8	90	228-230
3d	360	75	70	84	5	92	237-239
3e	360	70	65	79	6	94	198-200
3f	360	68	75	76	8	89	180-183

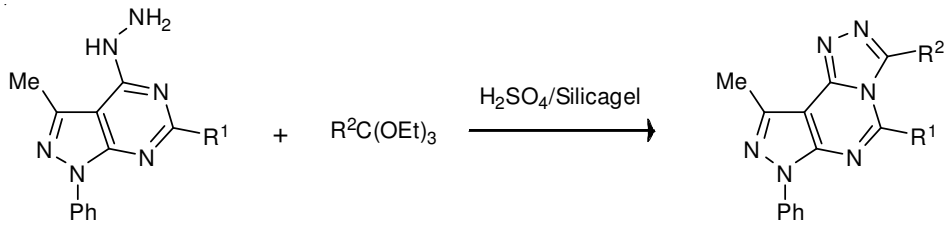
[a]In refluxing ethanol, [b]Under solvent-free microwave irradiation, [c]Isolated yields.

Reusability of the catalyst: At the end of the reaction, the catalyst could be recovered by a simple filtration. The recycled catalyst washed with ethanol, dried at 70 ºC for 1 h and reused in another reaction. The results of the first and subsequent experiments were almost consistent in yields.

RESULTS AND DISCUSSION

First, the preparation of the compounds **3a-f** in refluxing ethanol and in the presence of the solid acid catalyst were explored (**Scheme-I**). Therefore, 4-hydrazino-1*H*-pyrazolo[3,4-d]pyrimidines (**1a**-**b**) were refluxed with triethylorthoesters (**2a-c**)

in ethanol for the indicated time to give the desired three cyclic products **3a-f** in high yields (Table-1, Method A). All products **3a-f** were known and characterized by ^{1}H NMR and Mass spectral data and comparision of their melting points with those of already reported[8]. By comparing the data in Table-1, method A, with previous reported method[8], it can be concluded that the synthesis of compounds **3a-f** in the presence of H_2SO_4/silica gel is faster and the yields are higher.



1a, 1b **2a-c** **3a-f**

1a: R^1 = H
1b: R^1 = Me

2a: R^2 = H
2b: R^2 = Me
2c: R^2 = Et

3a: R^1 = H, R^2 = H
3b: R^1 = H, R^2 = Me
3c: R^1 = H, R^2 = Et
3d: R^1 = Me, R^2 = H
3e: R^1 = Me, R^2 = Me
3f: R^1 = Me, R^2 = Et

Scheme-I

Next, due to our interest in the utilization of microwave irradiation for the synthesis of heterocyclic compounds[6,7,9-11], we tried to extend this non-conventional synthetic method for the synthesis of compounds **3a-f**. Therefore, 4-hydrazino-1*H*-pyrazolo[3,4-d]pyrimidines **(1a-b)** were allowed to interact with triethylorthoesters **(2a-c)** under microwave irradiation at 900 w in solvent-free conditions for the indicated time to give the products **3a-f** in high yields (Table-1, Method B). Table-1 indicates that the microwave irradiation approach is faster and the yields are higher than conventional heating method.

Conclusion

In conclusion, an efficient catalytic procedure for the synthesis of pyrazolo[4,3-e]-[1,2,4]triazolo[4,3-c]pyrimidines through cyclocondensation of 4-hydrazino-1*H*-pyrazolo[3,4-d]pyrimidines with triethylorthoesters using sulfuric acid adsorbed on silica gel as catalyst is reported. The catalyst can be reused after a simple work-up, with a gradual decline of its activity being observed. High yields, short reaction times, simplicity of operation and easy work-up are some advantages of this protocol. On the other hand, microwave irradiation decreased the reaction times and higher product yields were obtained.

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