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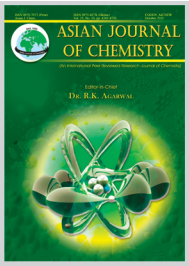

Montmorillonite K10 as an Efficient and Reusable Catalyst for the Synthesis of Substituted Pyrazolo[3,4-*d*]pyrimidin-4-ones Under Solvent-Free Conditions

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A green and efficient method for the synthesis of pyrazolo[3,4-*d*]pyrimidin-4-ones through heterocyclization reaction of 5-amino-1-phenyl-1*H*-pyrazole-4-carboxamides with orthoesters using Montmorillonite K10, as an effective and reusable catalyst, under solvent-free conditions is described. The present methodology offers several advantages, such as a simple procedure with an easy work-up, short reaction times, high yields and the absence of any volatile and hazardous organic solvents. Furthermore, the products could be separated simply from the catalyst and the catalyst could be recycled and reused with only slight reduction in its catalytic activity.

Key Words: Pyrazolo[3,4-d]pyrimidin-4-ones, 5-Amino-1-phenyl-1*H*-pyrazole-4-carboxamides, Orthoesters, Solvent-free condition.

INTRODUCTION

The principles of green chemistry have been introduced to eliminate or at least to reduce the use of hazardous materials, such as H_2SO_4 or H_3PO_4 in chemical processes. The use of homogeneous acid catalysts has some major limitations including no possible reuse, difficulty of products separation, air and moisture sensitivity and low product selectivity[1]. As a result, one of the challenges in the field of catalysis is to replace this homogeneous acid catalysts by a non-toxic, non-corrosive, easy to handle and environmentally friendly heterogeneous catalyst. Thus, the development and use of solid green catalysts are very important in organic syntheses.

Clays function as efficient catalysts for various organic transformations due to their Brønsted and Lewis acidities in both their natural and ion-exchanged forms[2]. Montmorillonite K10 (M-K10) is a layered alumino-silicate with a dioctahedral layer sandwiched between two tetrahedral layers. It is insoluble in common organic solvents, causes low corrosion and shows environmental acceptability. Due to strong catalytic activity as Bronsted acid, M-K10 clay has been used extensively as a catalyst Friedel-Crafts reaction[3,4], Michael reaction[5,6], Diels-Alder reaction[7], synthesis of fused heterocycles[8,9], synthesis of homoallylic silyl ethers[10], synthesis of amidoalkyl naphthols[11] and Hantzsch synthesis of 1,4-dihydropyridines[12]. M-K10 has also been used in many microwave reactions under liquid phase as well as in solvent-free conditions[13].

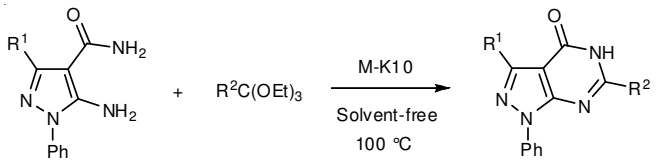
Pyrazolo[3,4-*d*]pyrimidins are a large group of heterocycles with diverse and interesting biological activities. These compounds are reported to possess significant vasodilatory[14], fungicidal[15,16], herbicidal[17-19] and antimicrobial[20-22] activities. Also, a number of these compounds are known to inhibit enzymes such as Bruton's tyrosine kinase[23], phosphodiesterase[24], adenosine deaminase[25] and plasmodium falciparum PfPK7 protein kinase[26]. The routes to pyrazolo[3,4-*d*]pyrimidins mainly involve cyclocondensation of suitably functionalized pyrimidines or pyrazoles with different electrophiles and nucleophiles such as isocyanates[27], methylhydrazine in combination with aldehydes[28], thiophosgene in combination with amines[29], allylamine, ammonium and ethylenediamine[30] and orthoesters[31].

Due to our interest in the synthesis of heterocyclic compounds[31-39] and in continuation of our previous works on the applications of reusable catalysts in organic reactions[40-50], we wish to report here a solvent-free synthesis of pyrazolo[3,4-*d*]pyrimidin-4-ones by heterocyclization reaction of 5-amino-1-phenyl-1*H*-pyrazole-4-carboxamides with orthoesters using M-K10 clay as an effective heterogeneous catalyst (**Scheme-I**).

EXPERIMENTAL

Melting points were recorded on a Stuart SMP3 melting point apparatus. The IR spectra were obtained using a Tensor 27 Bruker spectrophotometer as KBr disks. The ^{1}H NMR (500 MHz) spectra were recorded with a Bruker DRX500 spectrometer.

General procedure for the synthesis of pyrazolo[3,4-*d*]pyrimidin-4-ones (3a-f): A mixture of 5-amino-1-phenyl-1*H*-pyrazole-4-carboxamides (**1a** or **1b**) (1 mmol), orthoesters



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 Synthesis of pyrazolo[3,4-*d*]pyrimidin-4-ones catalyzed by M-K10

(**2a-c**) (1.5 mmol) and M-K10 (0.01 g) was heated in the oil bath at 100 ºC for 7-30 min. The reaction was monitored by thin-layer chromatography (TLC). Upon completion, the reaction mixture was cooled to room temperature, hot ethanol (15 mL) was added and filtered to remove the catalyst. The catalyst was washed with a small portion of hot ethanol (5 mL). The combined filtrate was reduced by half and allowed to stand at laboratory temperature for 0.5 h. The precipitated solid was collected by filtration and recrystallized from ethanol to give compounds **3a-f** in high yields. All the products were known and characterized by IR and ^{1}H NMR spectral data and by comparision of their melting points with those of authenticated samples.[31]

Recycling and reusing of the catalyst: Due to the fact that the catalyst was insoluble in hot ethanol, it could therefore be recycled by a simple filtration. The separated catalyst was washed with hot ethanol, dried at 80 ºC under vacuum for 2 h and reused in another reaction. The catalyst could be used at least three times with only slight reduction in its catalytic activity.

RESULTS AND DISCUSSION

The starting materials 5-amino-1-phenyl-1*H*-pyrazole-4-carboxamides **1a** and **1b** were prepared according to the literature method[51]. At first, the synthesis of compound **3e** was selected as a model reaction to optimize the reaction conditions. The reaction was carried out by heating a mixture of 5-amino-3-methyl-1-phenyl-1*H*-pyrazole-4-carboxamide (**1b**) (1 mmol) and triethyl orthoacetate (**2b**) (1.5 mmol) under various amount of the catalyst and at different temperatures under solvent-free conditions (Table-1). It was found that the yield of compound **3e** was strongly affected by the catalyst amount and reaction temperature. In the absence of M-K10, compound **3e** was obtained in relatively low yield after 1 h (entry 1), whereas good results were obtained in the presence of M-K10 (entries 2-7). The best result was obtained when the reaction was run at 100 ºC in the presence of 0.01 g of M-K10 (entry 5).

The reaction was also carried out in various solvents (Table-2). As shown in this table, in comparison to conventional methods the yield of the reaction under solvent-free conditions is higher and the reaction time is shorter.

In order to evaluate the generality of this model reaction we then prepared a range of pyrazolo[3,4-*d*]pyrimidin-4-ones under the optimized reaction conditions. The results are summarized in Table-3. In all cases the reaction gives the products in high yields and in short reaction times under solvent-free conditions. In comparison to the previous report[31], in the present methodology the yields of the products are higher and the reaction times are much shorter.

TABLE-1
EFFECT OF M-K10 AMOUNT AND TEMPERATURE ON THE MODEL REACTION[a]

Entry	Catalyst (g)	T (ºC)	Time (min)	Yield (%)[b]
1	None	100	60	43
2	0.005	100	20	72
3	0.01	50	15	83
4	0.01	80	10	87
5	0.01	100	7	89
6	0.05	100	7	90
7	0.1	100	7	89

[a]5-Amino-3-methyl-1-phenyl-1*H*-pyrazole-4-carboxamide (**1b**) (1 mmol) and triethyl orthoacetate (**2b**) (1.5 mmol) under solvent-free conditions. [b]Isolated yields

TABLE-2
SYNTHESIS OF COMPOUND **3e** IN THE PRESENCE OF M-K10 (0.01 g) IN DIFFERENT SOLVENTS[a]

Entry	Solvent	T (ºC)	Time (min)	Yield (%)[b]
1	H_2O	Reflux	5 (h)	Trace
2	EtOH	Reflux	80	75
3	CH_2Cl_2	Reflux	45	65
4	$CHCl_3$	Reflux	60	50
5	Solvent-free	100	7	89

[a]5-Amino-3-methyl-1-phenyl-1*H*-pyrazole-4-carboxamide (**1b**) (1 mmol) and triethyl orthoacetate (**2b**) (1.5 mmol). [b]Isolated yields.

The reusability of M-K10 was also investigated. For this purpose, the same model reaction was again studied under optimized conditions. After the completion of the reaction, the catalyst was recovered according to the procedure mentioned in experimental section and reused for a similar reaction. As shown in Fig. 1, the catalyst could be used at least three times with only slight reduction in the catalytic activity.

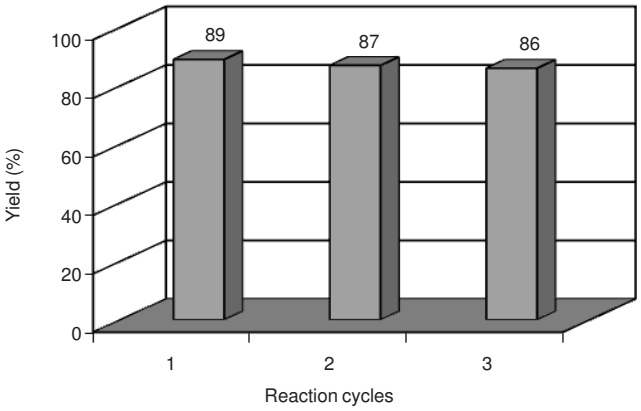
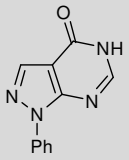
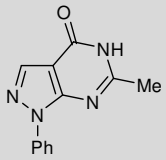
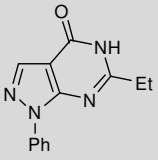
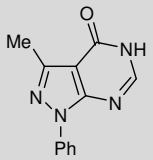
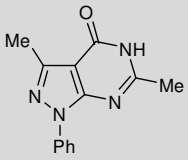
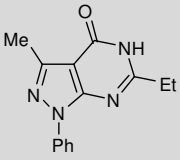


Fig. 1. Reusability of M-K10 for model reaction

Conclusion

Montmorillonite-K10 clay as a solid acid showed high catalytic activity in the synthesis of pyrazolo[3,4-*d*]pyrimidin-4-ones. This procedure offers several advantages including mild reaction conditions, high yields, short reaction times, ease of workup, which makes it a useful and attractive protocol for

TABLE-3
SYNTHESIS OF PYRAZOLO[3,4-d]PYRIMIDIN-4-ONES **3a-f** USING M-K10 AS CATALYST[a]

Entry	R^1	R^2	Products[b]	Time (min)	Yields (%)[c]	m.p. (ºC)	
						Found	Reported
1	H	H	 **3a**	12	85	290-291	294-296 [31]
2	H	Me	 **3b**	10	85	287-289	296-298 [31]
3	H	Et	 **3c**	30	78	289-291	291-293 [31]
4	Me	H	 **3d**	8	88	269-271	271-273 [31]
5	Me	Me	 **3e**	7	89	298-300	298-300 [31]
6	Me	Et	 **3f**	25	83	258-260	262-264 [31]

[a]5-Amino-1-phenyl-1*H*-pyrazole-4-carboxamide (**1a** or **1b**) (1 mmol), orthoester (**2a-c**) (1.5 mmol) and M-K10 (0.01 g) at 100 ºC under solvent-free conditions; [b]All the products were characterized by IR and ^{1}H NMR spectral data and by comparison of their melting points with those of authenticated samples; [c]Isolated yields

the synthesis of these compounds. Furthermore, the catalyst can be recycled after a simple work-up and used at least three times with only slight reduction in its catalytic activity. It has also all advantages devoted to solvent-free reactions namely environmentally friendly conditions.

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