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A facile four-component sequential reaction in the expedient synthesis of 2-Aryl-5-methyl-2,3-dihydro-1*H*-3-pyrazolones under solvent free by molybdate sulfuric acid (MSA)

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INTRODUCTION

Pyrazolone ring system represent an important class of compounds not only for their theoretical interest but also for their biological activities and because they can constitute the skeleton of dyestuffs and polymers[1,2]. Pyrazolones have gained importance as drug substances in pharmaceutical industry in view of their biological importance. Substituted pyrazolones derivatives are useful antipyretic and analgesic drugs, whilst edaravone (MCI-186) has been used for treating brain and myocardial ischemia. In addition, pyrazolones possess antimicrobial, antifungal, antimycobacterial, antibacterial, anti-inûammatory, antitumor, gastric secretion stimulatory, and antidepressant and anti-ûlarial activities. They also serve as precursors for dyes, pigments, pesticides and chelating agents[3], besides finding applications in the extraction and separation of various metal ions[4-8]. They are also employed in chromatography, petrochemical industry, as laser materials and ^{1}H-NMR shift reagents[9-12].

The synthesis of pyrazolones derivatives is currently of much interest, and various methods have been reported for their synthesis. The development of an environmentally benign methodology for the synthesis of pyrazolones derivatives is of great interest[13-15].

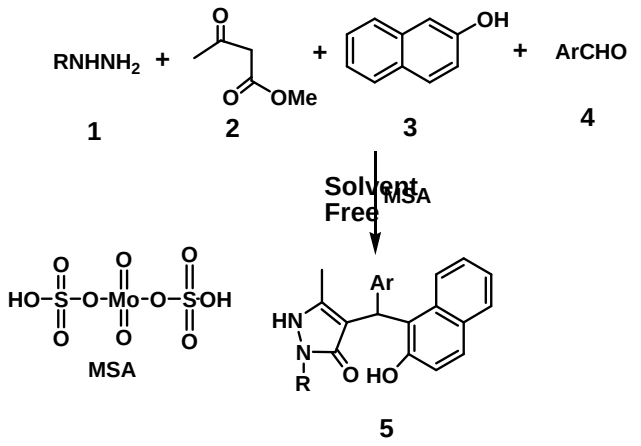
Pyrazolones are traditionally synthesized by treatment of β-keto esters with hydrazine substrates under acidic conditions at elevated temperature[16]. A number of alternative methods have been documented in the literature for the synthesis of these compounds[17]. Recent developments include solid-phase synthesis[18], a two-step reaction of benzoyl hydrazones with silylenolates in the presence of catalytic amounts of Sc(OTf)3[19], one-pot sequential reactions of phenylhydrazine, methyl acetoacetate, aromatic aldehydes and β-naphthol in the presence of catalytic amounts of p-toluenesulphonic acid in water[20], and microwave irradiation and ultrasonic techniques[21,22].

RESULT AND DISCUSSION

In continuation with the search for simple non-hazardous methods and the development of green chemical procedures for the transformations in organic synthesis using[23-26], herein we report a highly versatile, efficient, convergent, four-component sequential protocol for the synthesis of 2-aryl-5-methyl-2,3- dihydro-1*H*-3-pyrazolones (5) from phenyl hydrazine, methyl acetoacetate, aromatic aldehydes and β-naphthol in the presence of catalytic amounts of MSA under solvent free conditions (Scheme 1).

During our investigation, at ûrst, we choose phenyl hydrazine 1 (1 mmol), methyl acetoacetate (1 mmol), β-naphthol (1 mmol) and 4-Chlorobenzaldehyde (1 mmol) under solvent free condition as model reactants and examined the effect of the amount of Molybdate Sulfuric Acid (Scheme 1, TABLE 1). According to this

data, the optimum amount of catalyst was 32 mg as shown in TABLE 1. Further increasing the amount of catalyst did not improve the yield and the reaction time. In order to evaluate the effect of solvent, we examined different solvents (TABLE 1). From the above, it is very clear that the most suitable method, among those examined 32 mg MSA under solvent-free conditions for the reaction to afford a maximum yield of the product.



Scheme 1 : Synthesis of 2-aryl-5-methyl-2,3-dihydro-1*H*-3-pyrazolones (5)

TABLE 1 : The effect of amount of molybdate sulfuric acid and solvent different of (5d)

Entry	Amount Catalyst (mg)	Solvent	Time (min)	Yield [a,b] (%)
1	0	Solvent-free(25°C)	60	0.0
2	32	Solvent-free(25°C)	30	93
3	50	Solvent-free(25°C)	60	55
4	100	Solvent-free(25°C)	65	20
5	32	H_2O(60°C)	60	70
6	50	H_2O(60°C)	180	60
7	100	H_2O(60°C)	184	40
8	32	EtOH(60°C)	180	20
9	32	CH_3CN(60°C)	180	15
10	32	H_2O(reflux)	240	8

[a] **All reactions carried out with phenylhydrazine (1 mmol), methyl acetoacetate (1 mmol), 4-Chlorobenzaldehyde (1 mmol), β-naphthol (1 mmol).** [b] **Yield of isolated product**

A series of 2-aryl-5-methyl-2,3-dihydro-1*H*-3-pyrazolones were prepared in satisfactory yields (TABLE 2).

The sequential reactions presumably proceed through the mechanism depicted in Scheme 2 via the initial reaction of arylhydrazines **(1)** with methyl acetoacetate **(2)** to afford the pyrazolones **(5)**, which could be in equilibrium with their tautomers **(7)**. In another reaction, β -naphthol upon nucleophilic addition to aldehydes with concomitant dehydration presumably results in the formation of α, β-unsaturated ketone **(8)** (*o*-QM). Subsequent *Michael* addition of **(7)** over α, β-unsaturated ketone **(9)** results in formation of pyrazolone **(5)**.

TABLE 2 : Molybdate sulfuric acid catalyzed synthesis of 2-aryl-5-methyl-2,3-dihydro-1*H*-3-pyrazolones (5)

Entry	Product	R	Ar	Reaction Time (min)	Yield (%)[b]	M.p., °C
1	5a	C_6H_5	4-NO_2 C_6H_4	6	91	205-207
2	5b	C_6H_5	3-NO_2 C_6H_4	40	89	161-163
3	5c	C_6H_5	2-NO_2 C_6H_4	50	90	155-157
4	5d	C_6H_5	4-Cl C_6H_4	30	93	174-176
5	5e	C_6H_5	4-BrC_6H_4	40	92	152-154
6	5f	C_6H_5	4-MeO C_6H_4	45	88	183-184
7	5g	C_6H_5	4- Me C_6H_4	35	89	179-181
8	5h	C_6H_5	4- OH C_6H_4	70	86	143-145
9	5i	C_6H_5	C_6H_5	35	90	205-206
10	5j	H	4-NO_2 C_6H_4	10	90	182-184
11	5k	H	3-NO_2 C_6H_4	45	85	169-171
12	5l	H	2-NO_2 C_6H_4	45	87	161-163
13	5n	H	4-Cl C_6H_4	52	82	168-170
14	5m	H	4-MeO C_6H_4	56	84	153-155
15	5o	H	4- Me C_6H_4	53	87	145-147

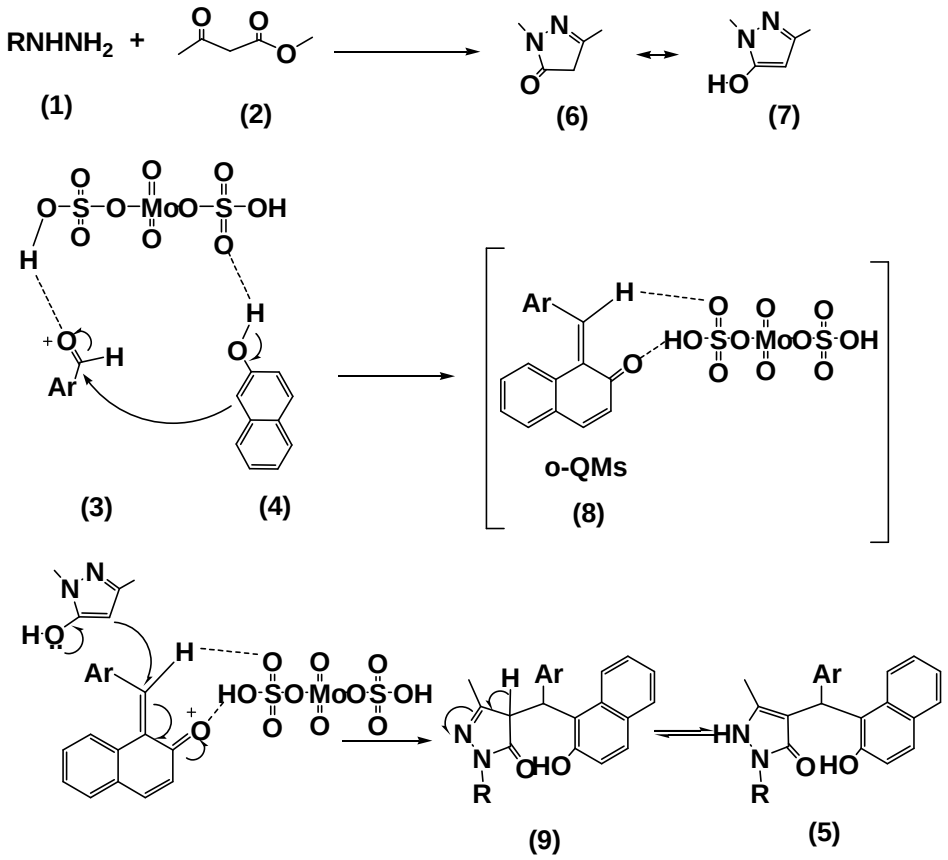
[a]) **Isolated yields**

The electron withdrawing groups (EWD) substituted on benzaldehyde in *o*-QM intermediate increase the rate of 1,4-nucleophilic addition reaction because of alkene LUMO is at lower energy in the neighbouring with-drawing groups than electron donating groups (EDG).[32]

The advantages or the characteristic aspects of the method described in this paper in comparison with other previously reported ones are the following: (i) mild reaction conditions, (ii) one-pot reaction, (iii) satisfactory yields, (iv) green chemical procedures, (v) no waste production, and (vi) reusability of catalyst.

EXPERIMENTAL

To a mixture of phenylhydrazine (1 mmol) and me-



Scheme 2 : Mechanism for the formation 2-aryl-5-methyl-2,3-dihydro-1*H*-3-pyrazolones (5)

thyl acetoacetate (1 mmol) under solvent-free conditions at room temperature for 6-70 min, aromatic aldehyde (1 mmol), β-naphthol (1 mmol) and Molybdate Sulfuric Acid (MSA) (32 mg) were added and stirred for the time given in TABLE 2. After completion of the reaction (TLC), the reaction mixture was extracted with ethanol. After added the amount of aquapura, the solution was heated and decreased after liquidize, catalyst has disported and the pure product 5 has formed quickly in liquid of under grid.

CONCLUSION

In conclusion, the present methodology shows that molybdate sulfuric acid (MSA) is an efficient catalyst in the one-pot synthesis of pyrazolone derivatives under solvent free conditions. The main advantages of the presented protocol are mild, clean and environmentally benign reaction conditions, low costs of the reagents, and high yields of the products. It is believed that this method will be a useful addition to modern synthetic methodologies.

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