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Research Article

ALUM ($KAl(SO_4)_2.12H_2O$) CATALYZED ONE-POT SYNTHESIS OF N-PHENYL PYRAZOLES AND THEIR ANTIBACTERIAL SCREENING

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ABSTRACT

Alum ($KAl(SO_4)_2.12H_2O$) catalyzed one-pot cyclocondensation of 1,3-dicarbonyl with phenyl hydrazines in aqueous media with simple string at room temperature to obtain N-phenyl pyrazoles. The products obtained in good to moderate yields with simple work up procedure. The compound **3a** was investigated in-vitro against Gram +ve and Gram –ve bacteria at different concentrations and compared with standard drug ciprofloxacin.

Keywords: Alum, N-phenyl pyrazoles, Water.

INTRODUCTION

Pyrazoles are useful synthons and building blocks for many heterocyclic products and they can act as a binucleophile, with wide range biological activities[1,2]. Pyrazole nucleus have been commercialized as herbicides, insecticides, and drugs like lonazolac, fipronil, Viagra, celecoxib, and many others. The 1-alkyl or aryl-1H-pyrazole unit has been broadly reported in previous studies[3,4]. It is used in numerous drugs, like herbicides by JV485 (Monsanto Bayer), Nipyraclofen (Bayer CropScience) and Pyraflufen-ethyl (Japan, Idametsu). Some representative examples are used in commercial products, such as Tebufenpyrad, an acaricide[5], and Ethiprole[6] (Bayer CropScience), for lepidopterans insects. Owing to their diverse and major properties, the discovery of environmentally benign, efficient and practical approaches for the construction and functionalization of pyrazole cores, especially in a regioselective manner, has always been an active field of research of high impact in synthetic chemistry[7].

Recently many organic reactions are been carried out in water which is readily available, non-toxic, inexpensive and eco-friendly solvent. Here we are interested to use alum ($KAl(SO_4)_2.12H_2O$) which is also non-toxic, easy handling, eco-friendly and inexpensive catalyst which is previously been reported as effective catalyst for the synthesis of 5-arylidene-2,4-thiazolidinedione[8], coumarins[9], anthraquinone[10], dihydropyrimidine[11] and trisubstituted imidazoles[12].

EXPERIMENTAL SECTION

General Procedure for the synthesis of N-phenyl pyrazoles

1,3-dicarbonyl (**1**) (13.8 mmol)and phenyl hydrazine (**2**) (13.8 mmol) and water (5 mL)

and were mixed in round bottom flask (RBF) and to that alum 20 mol% was added. The mixture was stirred at room temperature for appropriate time (Table 3 entries **3a-g**). The progress of reaction was monitored using TLC. After completion of the reaction mass was poured on crushed ice. The obtained solid was filtered, washed with water and dried. The crude compound was crystallized using DMF-Ethanol. In some cases after pouring the reaction mass on crushed ice, oily drops were obtained (**Table 2,** entry **3a**, **3c** and **3g**) then the liquid products were extracted by using ethyl acetate and sodium chloride. The obtained organic layers were dried by dehydrating agent, sodium sulfate and distilled out to obtain the products.

Compound **3a**: Yield 94%; light yellow liquid; bp 141-142℃. FTIR Model RZX (Perkin Elmer) cm^{-1}: 1518 (C=N str., Pyrazolyl); 1199 (C-N str.); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.13 (t, 1H, Pyrazolyl), 7.67 (d, 1H, Pyrazolyl), 7.76 (d, 1H, Pyrazolyl), 7.59-7.62 (m, 5H, Ar-H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ 141.03, 140.12, 129.40, 126.81, 126.35, 119.02, 107.66 ppm;MS (ESI, m/z): calcd for $C_9H_8N_2$ ($M + H^+$) 144.0687; found: 145.1508.

Table 1: Screening of solvents for the synthesis of 1-phenyl-1H-pyrazole (3a)[a]

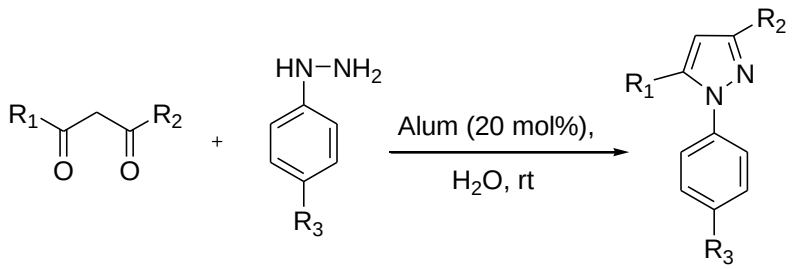
Entry	Solvents	Catalyst (20 mol %)	Time (min)	Yield (%)[b]
1	THF	Alum	140	40
2	DMSO	Alum	120	45
3	CH_2Cl_2	Alum	120	30
4	DMF	Alum	120	40
5	CH_3CN	Alum	90	35
6	Dioxane	Alum	90	48
7	Toluene	Alum	90	50
8	MeOH	Alum	70	62
9	EtOH	Alum	70	65
10	H_2O	Alum	60	93

[a]Reaction conditions: acetylacetone (**1a**)(13.8 mmol) and phenyl hydrazine (**2a**) (13.8 mmol) at room temperature.
[b]Isolated yield.

Table 2: Effect of concentrations of alum for the synthesis of 1-phenyl-1H-pyrazole (3a)[a]

Entry	Alum (mol %)	Time (min)	Yield (%)[b]
1	5	80	65
2	10	80	73
3	15	50	80
3	**20**	**60**	**93**
4	25	60	93

[a]Reaction conditions: acetylacetone (**1a**)(13.8 mmol) and phenyl hydrazine (**2a**) (13.8 mmol) in water at room temperature. [b]Isolated yield.



(**1a-g**) (**2a-g**) (**3a-g**)

Where,

R_1 & R_2 = -H, -CH_3, -^{t}Bu

R_3 = -H, -Cl, -Br, -I, -OCH_3

Scheme. Alum catalyzed synthesis of N-phenyl pyrazole

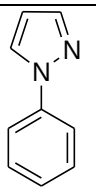
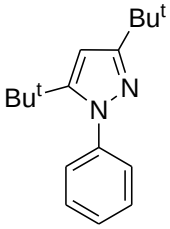
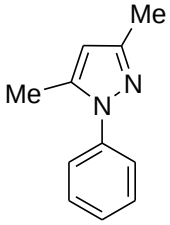
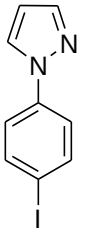
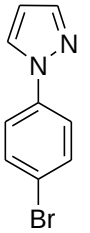
ANTIBACTERIAL ACTIVITY

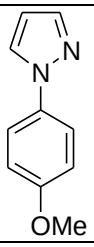
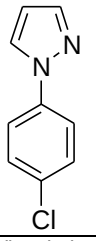
The procedure for antibacterial screening was repeted as given in our previous published research papers[13, 14]. Here, compound 1-phenyl-1H-pyrazole (**3a**) was screened for in-vitro antimicrobial activity using agar disc-diffusion method against two gram positive bacterial strains, Staphylococcus aureus and Bacillus subtilis and two gram negative strains, Escherichia coli and Pseudomonas aeruginosa. Ciprofloxacin was used as standard drug. **3a** compound was found to give no activity against selected strains. The results obtained are given in (**Table 4**).

RESULTS AND DISCUSSION

The model reaction (**3a**) was performed for the optimization of reaction conditions. The reaction is carried out by reacting acetylacetone (**1a**) (13.8 mmol) and phenyl hydrazine (**2a**) (13.8 mmol) at room temperature to give 1-phenyl-1H-pyrazole. Different solvents like tetrahydrofuran (THF), dimethyl sulfoxide (DMSO), dichloromethane (CH_2Cl_2), dimethylformamide (DMF), acetonitrile (CH_3CN), Dioxane, Toluene, methanol, ethanol and water were screened at appropriate temperature. Among the solvents used water gave excellent.

Table 3: Synthesis of substituted N-phenyl pyrazoles (3a-g)[a]

Compound	R	R^1	R^2	Product	Yield (%)[b]	M. P./B.P (°C)
3a	H	H	H		93	b.p;141-142
3b	H	Bu^t	Bu^t		88	m.p;106-108
3c	H	Me	Me		90	b.p;144-145
3d	p-I	H	H		85	m.p.;90-91
3e	p-Br	H	H		86	m.p;69-76

3f	p-OMe	H	H		90	b.p;279-281
3g	p-Cl	H	H		78	m.p;89-92

[a]Reaction conditions: 1,3-dicarbonyl (**1a-g**) (13.8 mmol)and phenyl hydrazine (**2a-g**) (13.8 mmol) in water at room temperature. [b]Isolated yield.

Yield as compared to other solvents as given in (**Table 1**, entries 1-9) thus water is the best medium for reaction (**Table 1**, entry 10).This could be because of the catalyst alum having better solubility in water. Then the effect of concentrations of catalyst alum was determined at different concentration like 5, 10,15,20,25. Here we got good yield at 20 mol% of alum is sufficient for the good result (**Table 2**, entry 3). Thus the reaction using water as a medium and catalyst alum 20 mol% at room temperature gave satisfactory yield. And thus the methodology was developed and used for further derivative synthesis of 2-aryl-1H-pyrazole (**Table 3**). Using this methodology, reactions were completed in shorter time with higher yields.

The compound (**3a**) 1-phenyl-1H-pyrazole was screened for in-vitro antimicrobial activity using agar disc-diffusion method against two gram positive bacterial strains, *Staphylococcus aureus* and *Bacillus subtilis* and two gram negative strains, *Escherichia coli* and *Pseudomonas aeruginosa*. Ciprofloxacin was used as standard drug and the data obtained from antibacterial study is given in Table 4:The compound (3a) does not show any activity any activity against bacterial strains.

Table 4: Antibacterial Activity of 3a

Sr. No.	Conc. µg/mL	Zone of inhibition in mm							
		Gram +ve				Gram -ve			
		3b							
		Pathogen – Staphylococcus aureus		Pathogen – Bacillus subtilis		Pathogen – Escherichia Coli		Pathogen – Pseudomonas aeruginosa	
		Replicate 1	Replicate 2	Replicate 1	Replicate 2	Replicate 1	Replicate 2	Replicate 1	Replicate 2
1	125	-	-	-	-	-	-	-	-
2	250	-	-	-	-	-	-	-	-
3	500	-	-	-	-	-	-	-	-
4	1000	-	-	-	-	-	-	-	-
Standard Ciprofloxacin									
1	125	31	31	27	27	26	26	27	27
2	250	35	36	29	29	28	28	32	32
3	500	40	41	30	31	29	31	36	34
4	1000	44	45	32	33	30	33	38	39

CONCLUSION

In conclusion, we have developed a green and efficient method for the synthesis of 1-aryl-1H-pyrazoles using alum as catalyst and water as unique medium. The reaction is carried out at room temperature. Antibacterial screening of **3a** compound was found to give no activity against selected strains. Further studies on the biological activities of the products and application of this methodology to other interesting heterocycles are underway in our laboratory.

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