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An efficient one-pot synthesis of 2, 4, 6-triaryl pyridines and their in vitro antimicrobial activity

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Abstract

A simple and efficient synthesis of 2,4,6-triaryl pyridines is described by the one-pot condensation of substituted acetophenones, 1-phenyl-3-(4'-hydroxy/chloro phenyl) pyrazol-4-carboxaldehyde, ammonium acetate and solid sodium hydroxide in polyethylene glycol (PEG-400) as green reaction solvent. The newly synthesized compounds were evaluated for their antibacterial and antifungal activity.

Keywords: PEG-400, substituted acetophenones, 1-phenyl-3-(4'-hydroxy/chlorophenyl) pyrazol-4-carboxaldehyde, ammonium acetate, antimicrobial activity;

INTRODUCTION

Pyridine derivatives have occupied a unique position in medicinal chemistry. The naturally occurring B6-vitamins pyridoxine, pyridoxal, pyridoxamine and codecarboxylase contain a pyridine nucleus. Due to their JI-stacking ability, some pyridines are used in supramolecular chemistry. In addition, many pyridines are reported as antimalerial, anesthetic, anticonvulsant, antiepileptic, antioxidant, fungicidal, antibacterial, antiparasitic activities [1-4].

Pyridines with a 2,4,6-triaryl substitution pattern (Krohnke pyridines) [5] have been synthesized using various methods and procedures. Traditionally, these compounds have been prepared through the reaction of N-phenacylpyridinium salts with α, β-unsaturated ketones in the presence of NH_4OAc [5-6]. However, the pyridinium salts and the unsaturated ketones have to be synthesized first, so this method is relatively expensive. Several improved methods and procedures have been developed for the synthesis of these pyridines such as solvent-free reaction

between acetophenones, benzaldehydes, and NH_4OAc in the presence of sodium hydroxide [7], and the one-pot reaction of acetophenones, benzaldehydes, and NH_4OAc without catalyst under microwave irradiation [8].

Knowing these chemical and pharmacological importances of the Krohnke pyridines, it was planned to synthesize some new Krohnke type mono-pyridines under the frame of green chemistry. In recent years, polyethylene glycol (PEG-400) prompted reactions [9-12] have attracted the attention of organic chemists due to their solvating ability and aptitude to act as a phase transfer catalyst, negligible vapor pressure, easy recyclability, ease of work-up, eco-friendly nature and economical cost. PEG is non-toxic, non-halogenated, inexpensive potentially recyclable and water soluble which facilitate its removal from reaction product.

MATERIALS AND METHODS

Experimental:

Melting points were uncorrected and determined in an open capillary tube. IR spectra were recorded on FTIR Shimadzu spectrometer. ^{1}H NMR spectra were recorded in DMSO-d_6 on Avance 300 MHz spectrometer using TMS as an internal standard. The mass spectra were recorded on EI-Shimadzu-GC-MS spectrometer. Elemental analyses were performed on a Carlo Erba 106 Perkin-Elmer model 240 analyzer.

General procedure for the synthesis of 2, 4, 6-triaryl pyridines 3(a-j)

Substituted acetophenone **1** (2 mmol) was added to a suspension of crushed NaOH (2.5 mmol) in polyethylene glycol (15 mL) and stirred at 0 ^{o}C for 10 min. 1-Phenyl-3-(4′-hydroxy/chloro phenyl)-pyrazol-4-carboxaldehyde **2** (1 mmol) was added by stirring and the suspension left standing at 0 ^{o}C for 2 hours. Every 15 minutes the suspension was stirred with spatula. After 2 hours ammonium acetate (5 gm, excess) was added and the suspension heated at 100 ^{o}C for 2 hours. After completion of the reaction (TLC), the reaction mixture was cooled at room temperature and poured in ice cold water (100 mL). The resultant solid was filtered, washed with ice cold water (50 ml) followed by cool ethanol (10 ml) to give the corresponding product.

Spectroscopic data of selected compounds

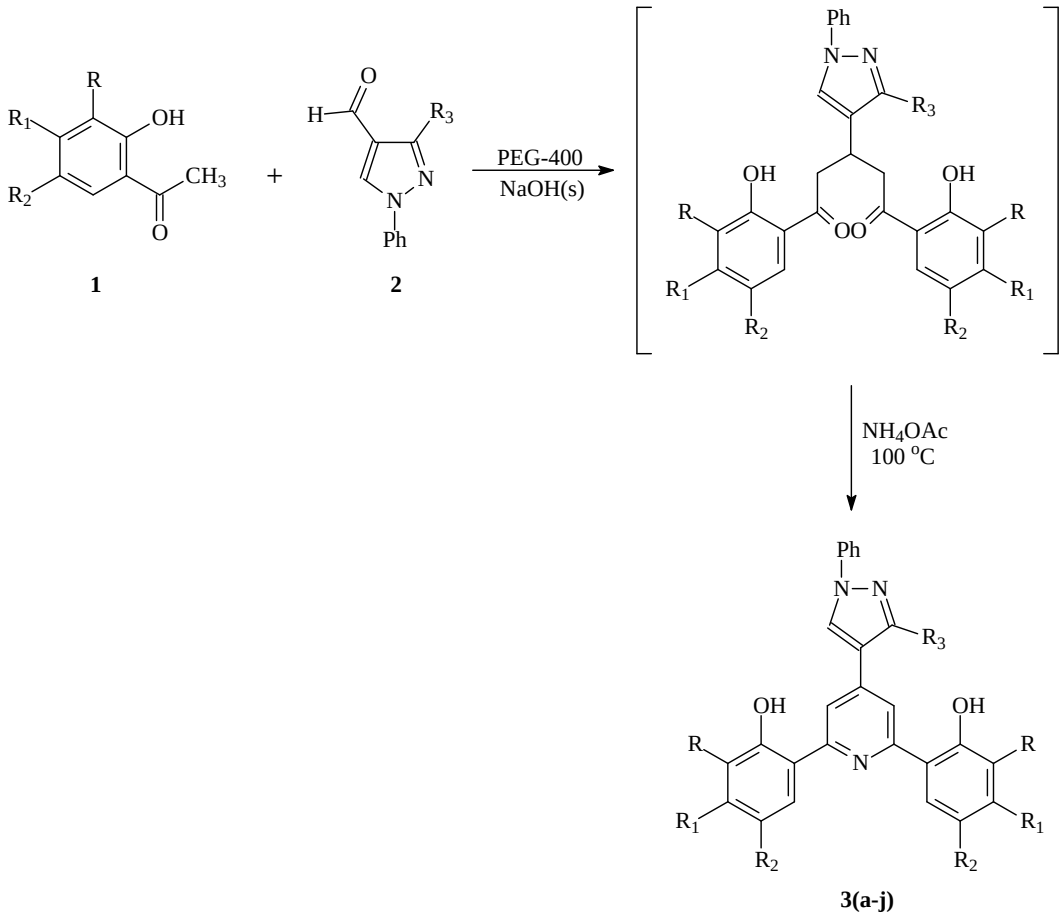
(**3b**)**:**IR (KBr): 3176, 3089,1598 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 6.95-8.35 (m, 13H, Ar-H), δ 8.78 (s, 2H, Ar-H), δ 8.92 (s, 1H, H-5 of pyrazole), δ 10.85 (s, 1H, -OH), δ 12.48 (s, 2H, -OH) ppm; EIMS (*m/z*): 724 (M^+); Anal. Calcd. For $C_{32}H_{19}O_3N_3Cl_2Br_2$: C, 53.07, H, 2.64; N, 5.81%. Found: C, 53.18; H, 2.58; N, 5.89%

(**3f**)**:**IR (KBr): 3282, 3151,1596 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 6.98-8.21 (m, 15H, Ar-H), δ 8.91 (s, 2H, Ar-H), δ 9.45 (s, 1H, H-5 of pyrazole), δ 12.32 (s, 2H, -OH) ppm; EIMS (*m/z*): 584 (M^+); Anal. Calcd. For $C_{32}H_{20}O_2N_3Cl_3$: C, 65.71, H, 3.45; N, 7.18%. Found: C, 65.78; H, 3.56; N, 7.11%

(**3j**)**:**IR (KBr): 3149, 3072,1602 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.31 (s, 3H, CH_3), δ 6.98-8.34 (m, 13H, Ar-H), δ 8.62 (s, 2H, Ar-H), δ 8.95 (s, 1H, H-5 of pyrazole), δ 11.81 (s, 2H, -OH) ppm; EIMS (*m/z*): 612 (M^+); Anal. Calcd. For $C_{34}H_{24}O_2N_3Cl_3$: C, 66.63, H, 3.95; N, 6.86%. Found: C, 66.52; H, 3.88; N, 6.98%

RESULTS AND DISCUSSION

As part of our research programme, and in continuation of our work on the development of environmentally friendly methodologies using polyethylene glycol (PEG-400) as a reaction solvent for the preparation of biologically active compounds [13-15], herein we report an efficient synthesis of Krohnke type mono-pyridines. The one-pot condensation of substituted acetophneones **1**, 1-phenyl-3-(4'-hydroxy/chloro phenyl) pyrazol-4-carboxaldehyde **2**, ammonium acetate using solid sodium hydroxide in polyethylene glycol (PEG-400) as reaction solvent to afford the corresponding Krohnke mono-pyridines **3(a-j)** (Scheme-1) in good yield. The newly synthesized compounds were evaluated for their antibacterial and antifungal activity.



Scheme-1: Synthesis of Krohnke type mono-pyridine derivatives 3(a-j)

The formation of the products were proceed through the 1,5-dione intermediate. The formation of the 1,5-dione involved the condensation of 2:1 molar ratio of substituted acetophenone and aromatic aldehyde. However, the isolation of 1,5-dione intermediate can be avoided with the pyridine derivative accessible in one-pot condensation, whereby excess of ammonium acetate was added. The newly synthesized compounds confirmed by the spectral analysis and were evaluated for their antibacterial and antifungal activity.

Table-1: Physical data of Krohnke mono-pyridine derivatives 3(a-j)

Entry	Product	R	R_1	R_2	R_3	Yield (%)	M.P. (°C)
1	3a	H	H	Cl	4-hydroxy phenyl	85	210
2	3b	Br	H	Cl	4-hydroxy phenyl	80	180
3	3c	I	H	Cl	4-hydroxy phenyl	78	170
4	3d	I	H	CH_3	4-hydroxy phenyl	85	220
5	3e	I	CH_3	H	4-hydroxy phenyl	72	212
6	3f	H	H	Cl	4-chloro phenyl	80	162
7	3g	Br	H	Cl	4-chloro phenyl	85	180
8	3h	I	H	Cl	4-chloro phenyl	82	175
9	3i	H	OH	H	4-chloro phenyl	80	202
10	3j	H	CH_3	Cl	4-chloro phenyl	78	232

The antimicrobial activities of the synthesized compounds **3(a-j)** were determined by agar well diffusion method [16]. The compounds were evaluated for antibacterial activity against *Escherichia coli*, *Salmonella typhi*, *Staphylococcus aureus* and *Bacillus subtilis*. The antifungal activity was evaluated against *Aspergillus niger*, *Aspergillus flavus*, and *Penicillium chrysogenum* were procured from Institute of Microbial technology (IMTech), Chandigarh, India. The antibiotic penicillin (25µg/mL) and nystatin (25µg/mL) was used as reference drug for antibacterial and antifungal activity, respectively. Dimethyl sulphoxide (1%, DMSO) was used a control with out compound.

Table-2: The antimicrobial data of the synthesized pyridine derivatives 3(a-j)

Product	Bacteria (Zone of inhibition in mm)				Fungi (Growth)		
	Ec	St	Sa	Bs	An	Af	Pc
3a	08	11	09	11	+ve	+ve	RD
3b	12	10	--	10	RD	RD	-ve
3c	10	08	15	10	-ve	-ve	RD
3d	06	11	12	08	+ve	+ve	+ve
3e	11	12	10	10	RD	RD	RD
3f	13	14	13	09	RD	-ve	-ve
3g	10	11	08	12	RD	RD	RD
3h	08	11	12	06	RD	-ve	RD
3i	12	11	14	11	RD	RD	RD
3j	10	08	10	09	-ve	+ve	+ve
Penicillin	16	15	18	14	NA	NA	NA
Nystatin	NA	NA	NA	NA	-ve	-ve	-ve

Ec-*Escherichia coli*; St-*Salmonella typhi*; Sa-*Staphylococcus aureus*; Bs-*Bacillis subtilis*; An-*Aspergillus niger*; An-*Aspergillus flavus*; Pc-*Penicillium chrysogenum*; -ve-No growth; +ve-Growth of fungi; RD-Reduced growth; NA-Not Appilcable

The results of antimicrobial data are summarized in Table-2. In comparison with standard antibacterial penicillin, compounds **3b**, **3f**, and **3i** found to be active against *E. coli*. Compounds **3c**, **3f**, and **3i** were also found to be active against *S. aureus*. Compounds **3a**, **3b**, **3c**, **3g** and **3i** showed good activity comparatively active against *B. subtillis*. As compared with standard antibacterial compounds **3a**, **3d**, **3e**, **3f**, **3g**, **3h** and **3i** were observed as active against S. typhi. On the other hand, compound **3b**, **3e**, **3f**, **3g**, **3h** and **3i** were found to be reduced growth activity against *A. niger*. Compounds **3d**, **3f** and **3h** were observed no fungal growth against *A. flavus*. Compounds **3a**, **3c**, **3e**, **3g**, **3h** and **3i** found to be reduced growth activity aginst *P. chrysogenum*.

CONCLUSION

In summary, we have described a simple and efficient method for the synthesis of 2,4,6-triaryl pyridines by the one-pot condensation of substituted acetophenones, 1-phenyl-3-(4'-hydroxy/chloro phenyl) pyrazol-4-carboxaldehyde, ammonium acetate using solid sodium hydroxide in polyethylene glycol (PEG-400) as green reaction solvent. The newly synthesized compounds were confirmed by the spectral analysis and further evaluated for their antimicrobial activity. The antibacterial and antifungal activity revealed that most of the compounds showed moderate to good activity. The substitution of hydroxyl group in position 2 and presence of halo groups in 3 and 5 positions emerged as active in both antibacterial and antifungal screening

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