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An efficient one-pot synthesis of substituted pyrazolo [3,4 b:4′,3′e]pyridine derivatives via the Hantzch three component condensation using bleaching earth catalyst and their *invitro* Antimicrobial evaluation

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Abstract: A simple and efficient one-pot synthesis of substituted pyrazolo[3,4 b:4',3'e] pyridine derivatives in Polyethylene glycol (PEG-400) as green reaction solvent under microwave irradiation by using basic bleaching earth catalyst (P^H-9.2). The chemical structure of the compounds was confirmed by IR,^{1}H NMR and Mass spectral data. All the compounds of the series screened for their antibacterial and antifungal activity studies. The result revealed that most of the compounds showed good to moderate antimicrobial activity.

Key words: pyridine derivatives , Hantzch three component condensation ,NMR spectral studies, antimicrobial evaluation**.**

Introduction:

Pyrazolo-pyridine and related heterocycles are found to possess a wide application in the field of medicine and agriculture. Industries in the new millennium have widely accepted One of the thrust areas for achieving this target is the use of microwaves[1,2] not only as an alternative energy source but also as a technique to substantially increase yield and reduce reaction time. The pyrazolo heterocycle is a very attractive target in heterocyclic and combinatorial chemistry, as it is a ornamentation in many bioactive natural products[3].The organic compound containing pyrazole nucleus has wide applications in medicinal chemistry as well as considerable interest in the chemotherapeutic activity. Pyrazole and its synthetic analogues have been found to exhibit industrial, agricultural and some biological application[4-8].The ring system plays an important role in many biological processes, and many therapeutic agents contain pyrazole moiety. For example some alkyl, aryl substituted pyrazoles have pronounced sedative action on the central nervous system[9].Certain alkyl pyrazolo-pyridines also showed significant analgesic, antipyretic, bacteriostatic, bactericidal and fungicidal activities[10-12].Most of them involve multistep synthetic reactions including the formation of intermediates

using undesirable harmful chemicals and a major disadvantage of requiring severe conditions in steps like cyclization. So, there is need for simple, efficient, and more general method to synthesize such heterocyclic moieties. Notably, the coupling of three components in a single flask under MWs can be proved as an alternative and more direct strategy to afford pyrazolo [3,4 b:4',3'e] pyridine core. This single flask approach avoids the use of any type of contamination final compounds, employs readily available materials, and has the potential to directly install diverse elements around the pyrazolo[3,4 b:4',3'e] pyridine skeleton.

Reducing or eliminating the use of volatile organic solvents can minimize the generation of waste, which is a requirement of one of the principles of green chemistry[11,12].Recently, poly ethylene glycol (PEG) has been found to be an interesting solvent system. In this respect, and also in continuation of our earlier work[13-15].we have planned to synthesize a series of novel these assets prompted us to prepare some pyrazolo [3,4 b:4',3'e] pyridine derivatives with potential bioactive molecules. In continuation of own work on pyrazole, imidazole as precursors in the synthesis of various heterocycles[16].we have planned to synthesize a series of novel hetero pyrazolo [3,4 b:4',3'e] pyridine derivatives by applying the principles of green chemistry, using PEG-400 as an alternative reaction medium . In recent years, polyethylene glycol (PEG-400) prompted reactions[17-18] 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, ecofriendly nature and economical cost. PEG is non-toxic, non-halogenated, inexpensive potentially recyclable and water soluble which facilitate its removal from reaction product. In view of the diverse therapeutic activity of pyrazolo [3,4 b:4',3'e] pyridine to develop new selective and environmentally benign methodologies using microwave irradiation (MWI), we herein report a one-pot method that allows a three-component coupling reaction of pyrazolone, heteroaldehydes and ammonium acetate by using(PEG-400) as green reaction solvent under microwave irradiation by using basic bleaching earth catalyst (P^H-9.2).

Material and Method:

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-*d6* 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 preparation of substituted pyrazolo [3,4b:4',3'e] pyridine derivatives :

A mixture of pyrazolone (2 mMol), heteroaldehyde (1 mMol) and ammonium acetate (10 mMol) dissolved in PEG-400 as a reaction solvent (10mL) Erlenmeyer flask and subjected to microwave irradiation for 1-2 min with a power of 70% (520watts) at apulse rate of 20sec in a domestic oven[19].After completion of the reaction (checked by TLC), the crude mixture was worked up in ice cold water (100 mL).The yellow precipitate obtained was filtered, washed with water and dried. The crude product was recrystalised from glacial acetic acid to afford final product.

Spectroscopic data of selected compounds:

(3a): IR (KBr) light yellow solid:
736,1086,1345,1461,1595,1636 and 3450 cm-^{1}; ^{1}H NMR (DMSO-*d6*, 300 MHz): δ1.98(s,6H,CH_3), δ2.10(s,3H,CH_3), δ5.12(s,1H,CH),7.15-8.36 (m, 15H, Ar-H), δ 8.68 (s, 1H, -NH) ppm; EIMS (*m/z*): 531 [M+]; Anal. Calcd. For $C_{31}H_{26}ClN_7$: C, 69.98; H, 4.93; N, 18.43% Found: C, 69.86; H, 4.90; N, 18.35%

(3b): IR (KBr) yellow solid:
758,1093,1348,1467,1605, and 3458 cm-^{1}; ^{1}H NMR (DMSO-*d6*,300MHz):δ0.93(s,3H,CH_3(imid)), δ1.35(m,2H,CH_2), δ1.63(m,2H,CH_2),δ2.74(t,2H,CH_2), δ2.10(s,6H,CH_3),δ5.09(s,1H,-CH) 7.05-8.25 (m, 10H, Ar-H), δ 8.62 (s, 1H, -NH), ppm; EIMS (*m/z*): 497[M+]; Anal. Calcd. For $C_{28}H_{28}ClN_7$: C, 67.33; H, 5.67; N, 19.69% Found: C, 67.25; H, 5.60; N, 19.55%

(3d): IR (KBr) yellow solid:
845,1132,1356,1496,1610, and 3442 cm-^{1}; ^{1}H NMR (DMSO-*d6*, 300 MHz): δ2.10(s,6H,CH_3), δ5.04(s,1H,-CH pyri.),7.15-8.46 (m, 14H, Ar-H), δ 8.60 (s, 1H, -NH), ppm; EIMS (*m/z*): 519 [M+]; Anal. Calcd. For $C_{30}H_{22}ClN_5O_2$: C,69.30; H, 4.26; N, 13.47% Found: C, 69.22; H, 4.18; N, 13.35%

(3f): IR (KBr) light yellow solid:
745,1038,1367,1478,1610, and 3478 cm-^{1}; ^{1}H NMR (DMSO-*d6*, 300 MHz): δ2.04(s,6H,CH_3), δ5.10(s,1H,-CH pyri.), 7.25-8.36 (m, 19H, Ar-H+-CH pyrazole), δ 8.69 (s, 1H, -NH), ppm; EIMS (*m/z*): 593[M+]; Anal. Calcd. For $C_{36}H_{28}ClN_7$: C,72.78; H, 4.75; N,16.50% Found: C, 72.66; H, 4.62; N, 15.43%

(3g): IR (KBr) light yellow solid:
812,1120,1390,1468,1590, and 3450 cm-^{1}; ^{1}H NMR (DMSO-*d6*, 300 MHz): δ1.98(s,6H,CH_3), δ5.12(s,1H,-CH pyri.), 7.20-8.35 (m, 19H, Ar-H+-CH pyrazole), δ

8.72 (s, 1H, -NH), ppm; EIMS (*m/z*): 604[M+]; Anal. Calcd. For $C_{36}H_{28}N_8O_2$: C,71.51; H, 4.67; N,18.53% Found: C, 71.45; H, 4.55; N, 18.40%

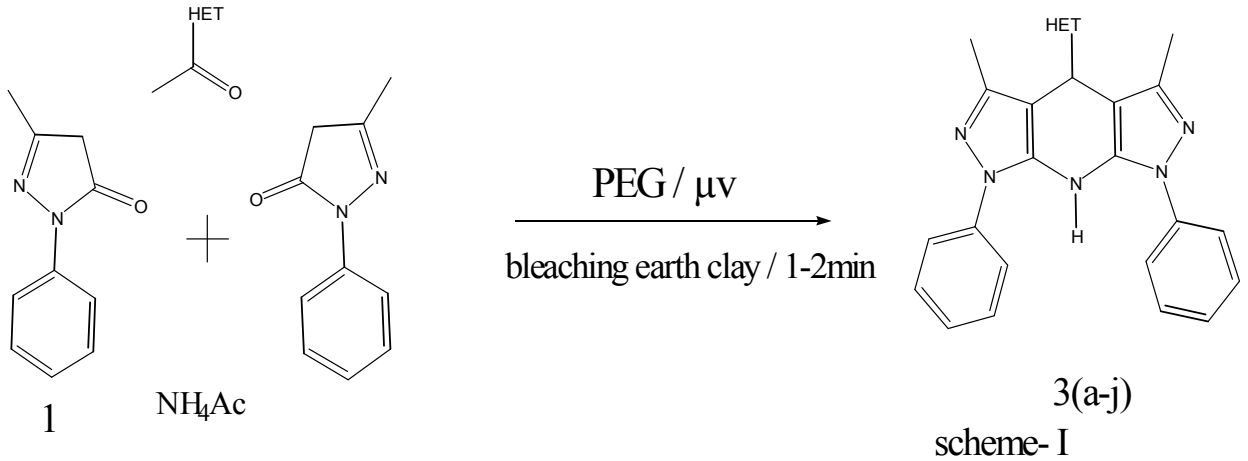
(3h): IR (KBr) light yellow solid:
776,1098,1120,1247,1470,1610, and 3452 cm-^{1}; ^{1}H NMR (DMSO-*d6*, 300 MHz): δ1.98(s,6H,CH_3 Pyrazole), δ1.06(s,3H,CH_3), δ5.08(s,1H,-CH pyri.), 7.28-8.42 (m, 19H, Ar-H+-CH pyrazole), δ 8.64 (s, 1H, -NH), ppm; EIMS (*m/z*): 573[M+]; Anal. Calcd. For $C_{37}H_{31}N_7$: C,77.46; H, 5.45; N,17.09% Found: C, 77.38; H, 5.35; N, 16.92%

Results and Discussion:

As part of our research programme, and in continuation of our work on the development of environmentally friendly methodologies for the preparation of biologically active compounds[18-20], here in we report an efficient synthesis of substituted pyrazolo[3,4 b:4',3'e] pyridine derivatives by using fuller earth catalyst. A homogenous mixture of pyrazolone (2 mMol), heteroaldehyde (1 mMol) and ammonium acetate (10 mMol) dissolved in PEG-400 as a reaction solvent by using bleaching earth catalyst P^H (9.2) was irradiated for 1-2 min at apulse rate of 20sec in a domestic oven (scheme-I) In found excellent yield showing table no.1
The newly synthesized compounds were evaluated for their antibacterial and antifungal Screening. The antibacterial and antifungal activity revealed that most of the showed moderate to good activity. The substitution of pyrazole, imidazole, and chromone moiety attached to the pyridine ring emerged as active in both antibacterial and antifungal evaluation and found to be excellent yield.

Microbiology:

The antimicrobial activities of the synthesized compounds **3(a-j)** were determined by agar well diffusion method[21].The compounds were evaluated for antibacterial activity against, *Escherichia coli* (*MTCC2939) St – Salmonella typhi (MTCC 98), Sa – Staphylococcus aureus (MTCC 96),*and *Bacillus subtilis (MTCC 441).* The antifungal activity was evaluated against *Aspergillus niger* (*MTCC 281*), *Candida albicans(MTCC183* and *Trichoderma viridae (MTCC 167),*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 without compound. The results of antimicrobial data are summarized in Table-2. In comparison with standard antibacterial penicillin, compounds **3b, 3e, 3g** and **3h** found to be active against *Escherichia coli*(*MTCC2939)*. Compounds **3c,3d** were also found to be active against *Staphylococcus aureus (MTCC 96)* Compounds **3a, 3b** and **3j** showed good activity comparatively active against *Bacillus subtilis (MTCC 441)*. As compared with standard antibacterial compounds **3a,3b** and **3g** were observed as active against *Salmonella typhi (MTCC98)*On the other hand, compound **3a, 3c** and **3f** were found to be reduced growth growth activity against *Aspergillus niger* (*MTCC 281*). Compounds **3d**, **3f, 3g, 3i** and **3j** were observed no fungal growth against *Candida albicans (MTCC 183)*. Compounds **3c, 3e, 3h, 3i** and **3j** found to be reduced growth activity against *Trichoderma viridae (MTCC 167).*



scheme- I

Substituted pyrazolo[3,4 b:4',3'e] pyridine derivatives 3(a-j)

Table-1 Physico-chemical data of synthesized compounds :

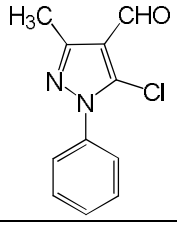
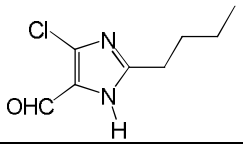
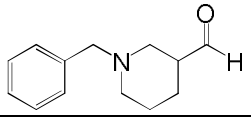
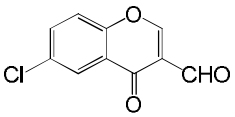
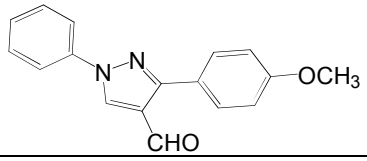
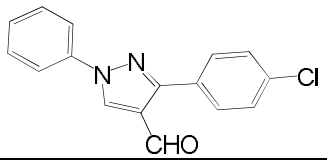
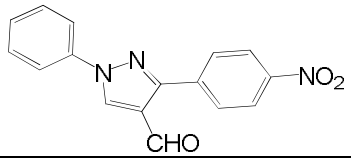
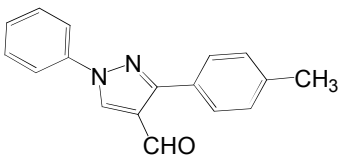
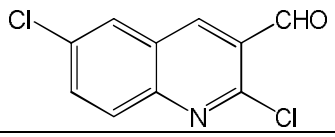
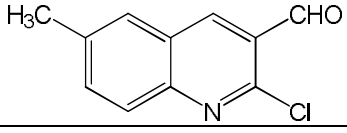
Entry	Product	Het	Yields (%)	Time (sec)	M.P (°C)
1	3a		88	80	175
2	3b		85	100	168
3	3c		82	120	184
4	3d		92	80	164
5	3e		82	120	158
6	3f		85	100	176
7	3g		84	120	163
8	3h		85	100	178
9	3i		90	80	158
10	3j		89	80	162

Table-2: The antimicrobial data of the synthesized Substituted pyrazolo [3,4 b:4',3'e] pyridine derivatives.

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

.a Solvents: DMSO, water, *Escherichia coli (MTCC2939) St – Salmonella typhi (MTCC 98),Sa – Staphylococcus aureus (MTCC 96),Bs – Bacillus subtilis (MTCC 441), An – Aspergillus niger (MTCC 281), and Trichoderma viridae (MTCC 167), Candida albicans (MTCC 183).* –ve -No growth; +ve -Growth of fungi; RD-Reduced growth; NA-Not Applicable

Conclusion:

In conclusion, the present three-component, one step procedure described in this paper is a facile and practical method for the preparation of the title compound. This work is further example of the utility of microwaves in organic synthesis. When conventional thermal procedures requires a considerable reaction time, microwaves irradiation can substitute classical method allowing easy and rapid access to heterocycles,reducing the reaction time from hours to minutes.

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[19] The domestic microwave oven,BPL microwave cooking system model BMO-700T Manufactured by BPL-SANYO utilities and appliances Ltd., Bangalore, india was used in the present studies. The oven has variable time cycles from 1s to 99min and 99s and heating cycles from 155 to 700w of power output which can be varied by selecting power levels ranging from 10 to 100. The overall dimension of the domestic oven is 525(w) × 419(D) × 281 (H) mm with a chamber of 350(w) × 370(D) × 208 (H) mm.The microwave frequency is 50 Hz and oven capacity is 26lit.
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