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A ONE POT MULTICOMPONANT SYNTHESIS OF NOVEL PYRAZOLO[3,4 B]PYRIDINE DERIVATIVES BY MICROWAVE IRRADIATION TECHNIQUES

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ABSTRACT

Green reagents in multi-component reaction are of increasing importance in organic and medicinal chemistry. 5-Amino pyrazole **5** was synthesized by known literature method and utilized for the synthesis of target compounds. 5- Amino pyrazole **5** was transformed to pyrazolo pyridine derivatives **10** by cyclocondensing three fold mixture of 5-aminopyrazole **5**, aroyl acetonitrile **9** and Het.aryl aldehydes **8** by using basic catalyst triethyl amine and ethanol as a solvent. Alternatively it was synthesized by microwave irradiation technique; If the same reaction mixture was irradiated in microwave oven without any catalyst and solvent we obtained same product with maximum yield. It was observed that the compound obtained by both the method is one and the same and this can be confirmed by taking TLC, m.p., mix m.p., IR, ^{1}H NMR and elemental analysis. All synthesized compounds were characterized by spectral and analytical methods.

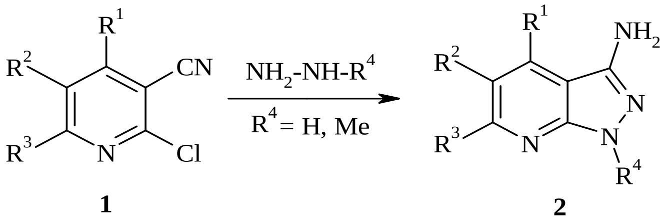
KEYWORDS: Microwave irradiation technique, 5-amino pyrazole, one pot reaction and multicomponant reaction

INTRODUCTION

An environmentally benign process [1] for the synthesis of biologically active compound under microwave irradiation is the recent trend in the organic synthesis [2]. Synthesis of heterocyclic compound using microwave irradiation is good ecofriendly, less expensive and maintains high efficiency of the product. These green reagents in multi-component reaction [3] are of increasing importance in organic and medicinal chemistry. The pyrazolo [3,4] pyridines as aza analogues of indazoles[4] are attractive targets in organic synthesis. Pyrazolo[3,4-*b*] pyridine derivatives were first synthesized by Ortoleva in 1906 [5]. They showed number of interesting pharmacological activities such as hypotensive[6], hypoglycemic [7,8], cyatostatic [9], psychotropic agents [10] and as coronary vasodilators [11,12] or neurodegenerative diseases [13], cytotoxic [14] or antiviral [15] activity. These compounds are also act as potential purine antagonists [16], anti-asthmatic [17], anti-allergic [18], anti tumor [19] and anti-bacterial [20]. There are generally two methods for the synthesis of pyrazolo[3,4-*b*]pyridine derivatives [21], I) pyrazole ring is annulated on pyridine ring and II) Pyridine ring is annulated on pyrazole ring.

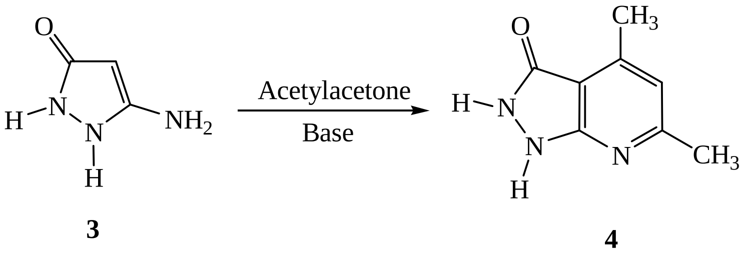
I) Pyrazole ring annulated on pyridine ring:

1) By condensation of 2-chloro-3-cyano pyridines **1** with hydrazine or substituted hydrazines gave pyrazolo[3,4-*b*]pyridine derivatives **2** [22].

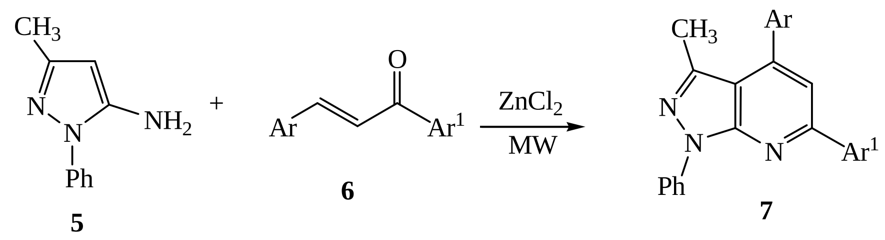


II) Pyridine ring annulated on pyrazole ring

Reaction of pyrazolone **3** with acetyl acetone under basic condition gave pyrazolo[3,4-*b*]pyridines **4** [23].



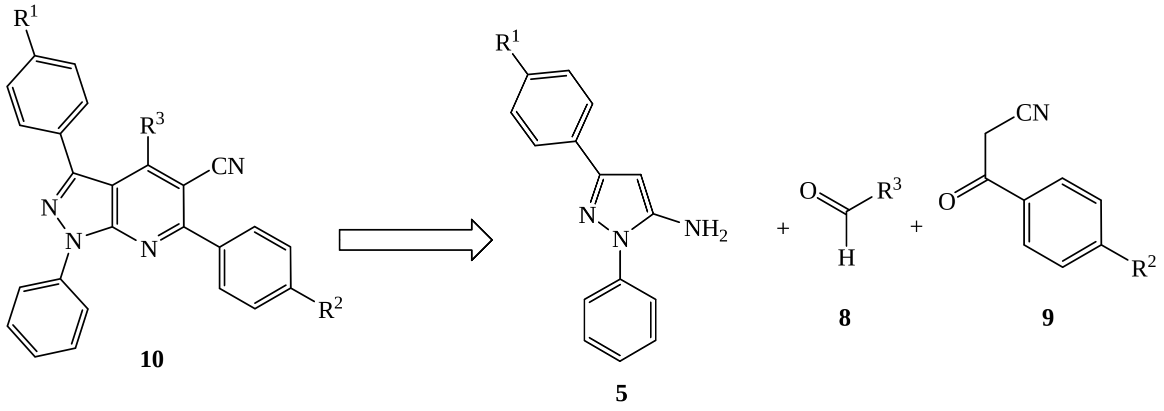
Recently X. Zou *et. al.* [24] reported the synthesis of pyrazolo[3,4-*b*]pyridine derivatives **7** by reaction of 5-aminopyrazole **5** with chalcone **6** in presence of $ZnCl_2$, under MW irradiation.



These literature reports prompted us to develop a new method for the synthesis of pyrazolo pyridine.

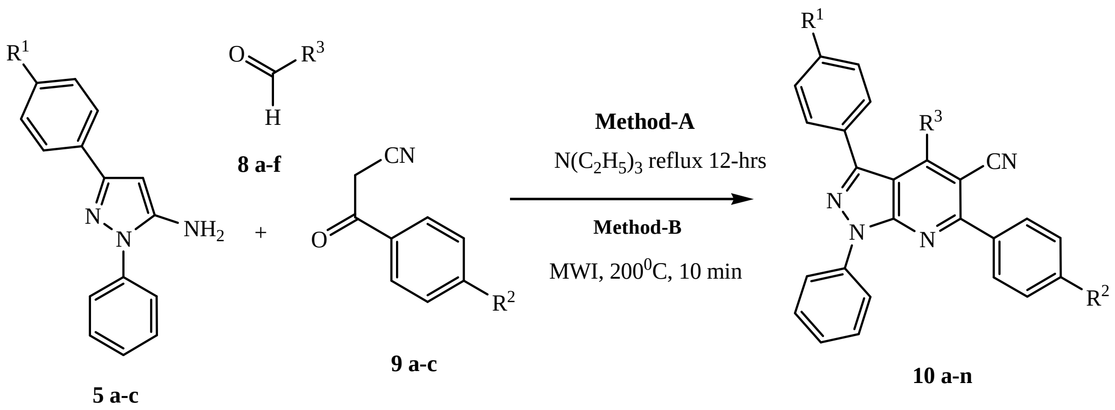
A One pot synthesis of Pyrazolo[3,4-*b*]pyridine derivatives

Synthesis of pyrazolo[3,4-*b*] pyridine derivatives **10** can be performed by cyclocondensing three fold mixture of 5-aminopyrazole **5**, aroyl acetonitrile **9** and aryl/Het. aldehydes **8** by using microwave oven.



RESULTS AND DISCUSSION

Pyrazolo[3,4-*b*]pyridine nucleus were synthesized by Quiroga and co-workers [25,26] using 5-aminopyrazoles and chalcones derived from benzoylacetonitrile/ malono nitrile with aromatic aldehydes by *Michael* addition. We have adopted different strategy for synthesis of these compounds. In our method we condensed 5-aminopyrazole **5**, hetero/aryl aldehydes **8** and benzoylacetonitriles **9** in one pot in which prior synthesis of chalcone is not required and with different substitution patterns.



Scheme-1

10	R^1	R^2	R^3	10	R^1	R^2	R^3
a	Cl	Cl	4-FC_6H_4	**h**	CH_3	Cl	4-ClC_6H_4
b	Cl	Br	4-FC_6H_4	**i**	CH_3	CH_3	4-(thien-2-yl)
c	Cl	Br	4-CNC_6H_4	**j**	CH_3	CH_3	4-(2-furyl)
d	Cl	Cl	4-ClC_6H_4	**k**	CH_3	CH_3	4-[3-(4-chlorophenyl)-1-phenyl-1*H*-pyrazol-4-yl]
e	Cl	Cl	4-BrC_6H_4	**l**	CH_3	CH_3	4-[3-(4-chlorophenyl)-1-phenyl-1*H*-pyrazol-4-yl]
f	CH_3	CH_3	H	**m**	CH_3	CH_3	4-$OMeC_6H_4$
g	CH_3	CH_3	4-FC_6H_4	**n**	CH_3	CH_3	4-$(OMe)_2C_6H_3$

5-Amino pyrazole **5** was synthesized by known literature method and utilized for the synthesis of target compounds. One pot Cyclocondensation of p-bromo benzoylacetonitriles **9b** (1 mmole**)**, 5-aminopyrazole **5a** (1 mmole) and 4-fluorobenzaldehydes **8a** (1 mmole) was refluxed in ethanol (20 ml) at 120^0C temperature for 12 hrs in presence of basic catalyst triethyl amine (1 ml) furnished buff coloured solid. The solid obtained was collected by filtration, wash with ethanol, dried and recrystalized from DMF to furnish the respective compounds with good yield (64%).

Alternatively if the same reaction mixture was irradiated in microwave at 200^0C for 10 min., without any solvent furnished the desired product **10 b** with excellent yield (83%). It was observed that the compound obtained by both the method is one and the same and this can be confirmed by taking TLC, m.p., mix m.p., IR, ^{1}H NMR and elemental analysis.

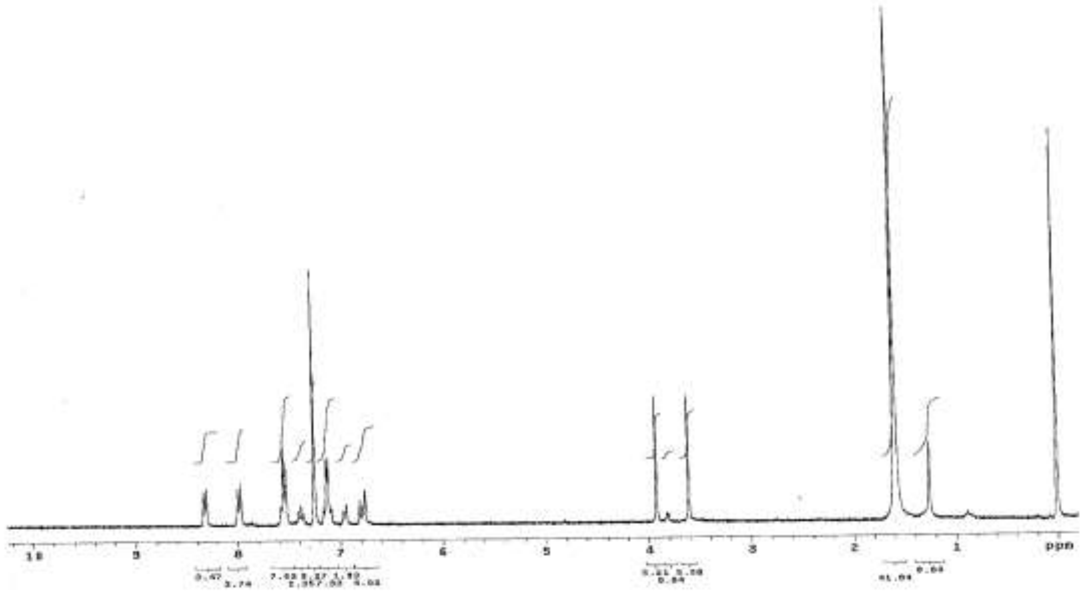
Spectral analysis

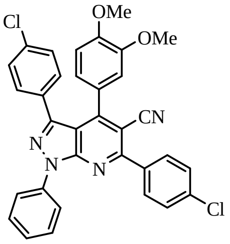
The IR spectrum of **10b** showed band at 2227 cm^{-1} for CN group. The ^{1}H NMR spectrums ($CDCl_3$) of this solid showed multiple at δ 7.02-7.11 for four aromatic protons. Doublet at δ

7.16 (*J*= 8.7Hz) for two aromatic protons and multiplet between δ 7.29-7.36 for two aromatic protons. The triplet at δ 7.41 (*J*=8.4Hz) for one aromatic proton and triplet at δ 7.57 (*J*=8.1Hz) for two aromatic protons. Two doublets at δ 7.74 (*J*= 8.4Hz) and at δ 7.94 (*J*= 8.4Hz) corresponded four protons of p-substituted benzene ring at C_3. The doublet at δ 8.35 (*J*=8.1Hz) corresponded to two aromatic protons. (Spectrum No.-2.2, Page No. 12) The elemental analysis agreed with molecular formula $C_{31}H_{17}BrClFN_4$. On the basis of above spectral and analytical data structure **10b** was assigned to this compound and it is 6-(4-Bromophenyl)-3-(4-chlorophenyl)-4-(4-fluorophenyl)-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile, 28b Analogously compound **10a-n** was characterized by spectral and analytical data, which is given in experimental section.

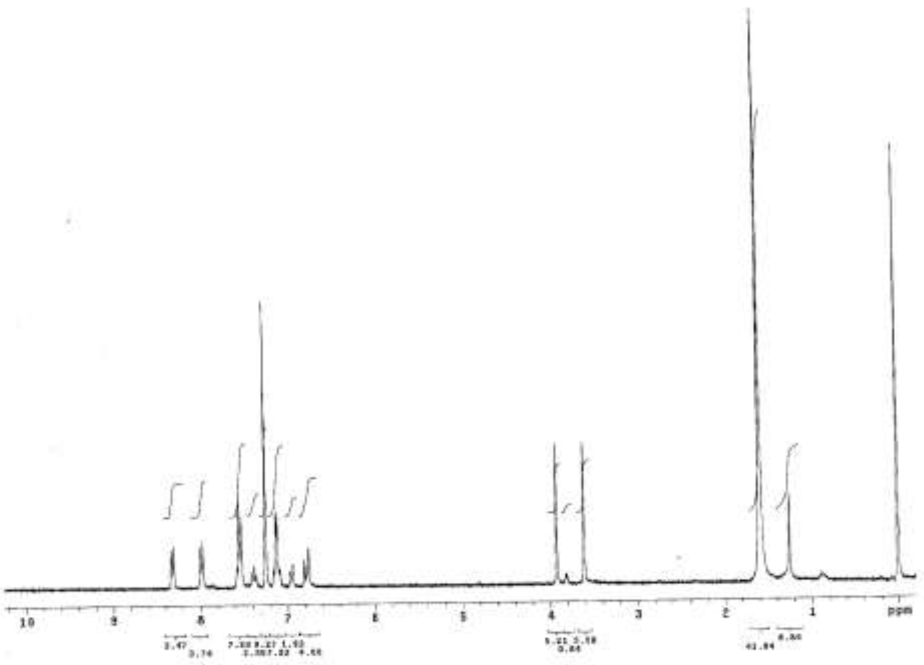
Comparative Study of Conventional method and microwave method

Parameters	**Method A**	**Method B**
Reaction time	12 hrs	10 min
Yield in %	64%	83 %
Yield in gm	0.73 gm	0.90 gm
Melting point	280-281 °C	280-281 °C
Solvent use	**Ethanol**	**Solvent Free**
Amt. of solvent	20ml	---





IR spectra of 3,6-bis(4-chlorophenyl)-4-(3,4-dimethoxyphenyl)-1-phenyl-1H-pyrazolo[3,4-b]pyridine-5-carbonitrile (10 n)



^{1}HNMR spectra of 3,6-bis(4-chlorophenyl)-4-(3,4-dimethoxyphenyl)-1-phenyl-1H-pyrazolo[3,4-b]pyridine-5-carbonitrile (10n)

EXPERIMENTAL

Melting points were determined on a Gallenkamp melting point apparatus, Mod.MFB-595 in open capillary tube and are uncorrected. FT-IR spectra were recorded on Schimadzu FTIR-408 instrument in KBr pellets. ^{1}H and ^{13}C spectra were recorded on Varian XL -300 spectrometer (300MHz) in $CDCl_3$ and DMSO. Chemical shifts are reported in ppm with respect to tetra methyl silane as an internal standard. Elemental analyses were carried out on Hosli CH analyzer and are within ± 0.4 of theoretical percentages. The progress of the reaction was monitored by thin layer chromatography (TLC, 0.2 mm silica gel 60 F 254 ,Merck plates) and visualized using UV light(254 and 366 nm) for detection. Microwave assisted synthesis was carried out in an Emery synthesizer single wave microwave cavity producing controlled irradiation at 2450 MHz, the temp was measured with IR sensor on the outside of reaction vessels. All commercial grade chemicals were purchased from S.D. Fine chemicals India and used without further purification while solvents were purified by standard literature procedures.

General procedure for synthesis of compound 10 a-n

A. Conventional Method

A mixture of 5-aminopyrazole **5a** (0.54g, 2mmole), 4-chlorophenylacetonitrile **9a** (0.36g, 2mmole) and 4-fluorobenzaldehyde **8b** (0.25g, 2mmole) was refluxed in ethanol (10ml) in presence of catalytic amount of triethylamine (1ml) for 12 hours. The reaction mixture after cooling was stirred in ice cold water to remove excess of impurities formed during the reaction. The solid obtained was collected by filtration and washed with water, dried and recrystalized from ethanol-DMF (7:3). The solid obtained to yield compound **10a.** Analogously compounds **10b-n** was prepared. Crystallized all compounds from mixture of ethanol-*DMF* (7:3).

B. By Microwave Method

A mixture of 5-aminopyrazole **5a** (0.54 g, 2 mmole), 4-chlorophenylacetonitrile **9a** (0.36 g, 2 mmole) and 4-fluorobenzaldehyde **8b** (0.25 g, 2 mmole) was irradiated in microwave at 200^0C for 10 min. The reaction mixture after cooling was stirred in ice cold water to remove impurity formed during the reaction. The solid obtained was collected by filtration and washed with water, dried and recrystalized from ethanol-DMF (7:3). The solid obtained was to yield **10a.** Analogously compounds **10b-n** was prepared. Recrystallized all compounds from mixture of ethanol-*DMF* (7:3).

Characterization of Compound 10a-n

3,6-Bis(4-chlorophenyl)-4-(4-fluorophenyl)-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile, 10a

M.P. 280-281 °C; Yield: 72 %, (0.77g) **IR :** 2221, 1520, 1453 cm^{-1}

^{1}H NMR(DMSO-d_6) : δ: 7.02-7.50 (m, 9H, ArH), 7.62 (d, 2H, ArH), 7.76 (d, 2H, ArH), 7.98 (d, 2H, ArH), 8.42 (d, 2H, ArH) ppm.

Analysis calculated for $C_{31}H_{17}Cl_2FN_4$: **Calcd:** C,69.54; H, 3.20; N, 10.46

Found: C, 69.70; H, 3.45; N, 10.58

6-(4-Bromophenyl)-3-(4-chlorophenyl)-4-(4-fluorophenyl)-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile, 10b

M.P. 284-285 ^{o}C; Yield: 74 %, (0.86g) **IR :** 2223, 1521, 1455 cm^{-1}

^{1}H NMR(CDCl$_3$) : δ: 7.02-7.11 (m, 4H, ArH), 7.16 (d, *J*=8.7 Hz, 2H, ArH), 7.29-7.36 (m, 2H, ArH), 7.41 (t, *J*=8.4 Hz, 1H, ArH), 7.57 (t, *J*=8.1 Hz, 2H, ArH), 7.74 (d, *J*=8.4 Hz, 2H, ArH), 7.94 (d, *J*=8.4Hz, 2H, ArH), 8.35 (d, *J*=8.1 Hz, 2H, ArH) ppm.

Analysis calculated for $C_{31}H_{17}BrClFN_4$: **Calcd:** C,64.21; H, 2.95; N, 9.66

Found: C, 64.38; H, 2.67; N, 9.79

6-(4-Bromophenyl)-3-(4-chlorophenyl)-4-(4-cyanophenyl)-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile, 10c

M.P. 325-326 ^{o}C; Yield: 69 %, (0.81g) **IR :** 2219, 1524, 1458 cm^{-1}

^{1}H NMR(DMSO-d$_6$) : δ: 7.03-7.14 (m, 4H, ArH), 7.39-7.74 (m, 8H, ArH), 7.89-8.24 (m, 5H, ArH) ppm.

Analysis calculated for $C_{32}H_{17}BrClN_5$: **Calcd:** C,65.49; H, 2.92; N, 11.93

Found: C, 65.71; H, 3.17; N, 12.18

3,4,6-Tri(4-chlorophenyl)-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5- carbonitrile, 10d

M.P.280-281 ^{o}C; Yield: 66 %, (0.73g) **IR**: 2220, 1520, 1451 cm^{-1}

^{1}H NMR(DMSO-d$_6$) : δ: 7.15-7.74 (m, 11H, ArH), 7.84-8.24 (m, 6H, ArH) ppm.

Analysis calculated for $C_{31}H_{17}Cl_3N_4$: **Calcd**: C,67.47; H, 3.10; N, 10

Found :C, 67.65; H, 3.27; N, 10.36

3,6-Bis(4-Chlorophenyl)-4-(4-bromophenyl)-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile, 10e

M.P: 263-264 ^{o}C; Yield: 76 %, (0.77g) **IR :** 2225, 1519, 1454 cm^{-1}

^{1}H NMR(DMSO-d$_6$) : δ: 7.02 (d, 2H, J=8.7, ArH), 7.12 (d, 2H, J=8.4, ArH), 7.21 (m, 4H, ArH), 7.36 (t, 1H, J=7.2, ArH), 7.53 (m, 4H, ArH), 7.96 (d, 2H, J=8.4, ArH), 8.29 (d, 2H, J=8.7, ArH) ppm.

Analysis calculated for $C_{25}H_{14}Cl_2N_4$: **Calcd:** C,62.44; H, 2.87; N, 9.40

Found: C, 62.52; H, 3.91; N, 9.36

3,6-Bis(4-Methylphenyl)-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile, 10f

M.P - 235-236 °C; Yield: 70 %, (0.56g) IR **:** 2224, 1523, 1456 cm^{-1}

^{1}H NMR($CDCl_3$) : δ: 2.56 (s, 6H, $2CH_3$), 7.39-7.51 (m, 9H, ArH), 7.55(m,2H,ArH), 7.74(d,2H,ArH), 7.95 (d,2H,ArH), 8.42 (d,2H, ArH) ppm.

Analysis calculated for $C_{27}H_{20}N_4$: **Calcd:** C,80.97; H, 5.03; N, 13.99

Found: C, 80..98; H, 5.24; N, 14.23

3,6-Bis(4-Methylphenyl)-4-(4-fluorophenyl)-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile, 10g

M.P: 234-235 °C; Yield: 71 %, (0.70g) **IR :** 2223, 1521, 1453 cm^{-1}

^{1}H NMR($CDCl_3$) : δ: 2.48 (s, 6H, $2CH_3$), 7.02-7.63 (m, 11H, ArH), 7.74(d, 2H, J=8.4Hz, ArH), 7.94 (d, 2H, J=8.7Hz, ArH), 8.35(d, 2H, J=8.4Hz, ArH) ppm.

Analysis calculated for $C_{33}H_{23}FN_4$**: Calcd:** C,80.14; H, 4.69; N, 11.33

Found: C, 80.11; H, 4.67; N, 11.48

4,6-Bis(4-Chlorophenyl)-3-(4-methylphenyl)-1-phenyl-1*H*-pyrazolo[3,4-*b*] pyridine-5-carbonitrile, 10h

M.P: 258-259 °C; Yield: 69 %, (0.73g) **IR :** 2219, 1522, 1455 cm^{-1}

^{1}H NMR(DMSO-d_6) : δ: 2.47 (s, 3H, CH_3), 6.99-7.56 (m, 12H, ArH), 7.92(d, 2H, J=8.4Hz, ArH), 8.32 (d, 2H, J=8.4Hz, ArH) ppm.

Analysis calculated for $C_{32}H_{20}Cl_2N_4$: **Calcd:** C,72.32; H, 3.79; N, 10.54

Found: C, 72.51; H, 3.97; N, 10.72

3,6-Bis(4-Methylphenyl)-1-phenyl-4-thien-2-yl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile, 10i

M.P.- 221-222 °C; Yield: 73 %, (0.70g) **IR :** 2218, 1524, 1452 cm^{-1}

^{1}H NMR($CDCl_3$) : δ: 2.49 (s, 6H, $2CH_3$), 6.54 (m, 1H, ArH), 7.10 (m, 1H, ArH), 7.17-7.55 (m, 8H, ArH), 7.67 (d, 2H, J=8.4Hz, ArH), 7.85 (d, 2H, J=8.4Hz, ArH) 8.25 (d, 2H, ArH) ppm.

Analysis calculated for $C_{31}H_{22}N_4S$: **Calcd**: C, 77.15; H, 4.59; N, 12.61

Found: C, 77.34; H, 4.68; N, 12.68

3,6-Bis(4-Methylphenyl)-4-(2-furyl)-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile, 10j

M.P.- 238-239 °C; Yield: 71 %, (0.66g) **IR** : 2218, 1521, 1456 cm^{-1}

^{1}H NMR(CDCl$_3$) : δ: 2.41 (s, 6H, 2CH$_3$),6.97(d, 2H, ArH), 7.12-7.57 (m, 14H, ArH), 7.67(d, 2H, J=8.4Hz, ArH), 7.84 (m, 3H, ArH), 8.31 (d, 2H, J=8.4Hz, ArH) ppm.

Analysis calculated for $C_{31}H_{22}N_4O$: **Calcd:** C,79.81; H, 4.75; N, 12.01

Found: C, 79.94; H, 4.85; N, 12.08

3,6-Bis(4-Methylphenyl)-4-[3-(4-chlorophenyl)-1-phenyl-1*H*-pyrazol-4-yl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile, 10k

M.P.- 244-245 °C; Yield: 70 %, (0.91g) **IR :** 2221, 1519, 1460 cm^{-1}

^{1}H NMR(CDCl$_3$) : δ: 2.44 (s, 3H, CH$_3$),6.89 (m, 4H, ArH), 7.16-7.44(m, 12H, ArH), 7.60 (m, 4H, ArH), 8.03 (d, 2H, J=8.4Hz, ArH), 8.36 (s, 1H, ArH) ppm.

Analysis calculated for $C_{42}H_{29}ClN_6$: **Calcd:** C,77.23; H, 4.47; N, 12.87

Found: C, 77.43; H, 4.64; N, 12.94

3-(4-chlorophenyl-6-(4-Methylphenyl)-4-[3-(4-chlorophenyl)-1-phenyl-1*H*-pyrazol-4-yl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile, 10l

M.P.- 278-279 °C; Yield: 73 %, (0.98g) **IR** : 2221, 1521, 1458 cm^{-1}

^{1}H NMR(DMSO-d$_6$) : δ: 7.02 (d, 2H, J=8.7Hz ArH), 7.12 (d, 2H, J=8.4Hz ArH), 7.21 (m, 4H, ArH), 7.36 (t, 1H, J=7.2Hz, ArH), 7.53 (m,4H,ArH), 7.96 (d, 2H, J=8.4Hz, ArH) 8.29 (d, 2H, J=7.8Hz, ArH) ppm.

Analysis calculated for $C_{41}H_{26}Cl_2N_6$: **Calcd:** C,73.11; H, 3.89; N, 12.48

Found: C, 73.26; H, 3.96; N, 12.64

3,6-bis(4-chlorophenyl)-4-(3-methoxyphenyl)- 1-phenyl-1H **-pyrazolo[3,4-*b*]pyridine-5-carbonitrile, 10m**

M.P.- 284-285°C; Yield: 76 %, (0.98g) **IR :** 2928, 2220, 1521, 1595, 1285 cm^{-1}

^{1}H NMR(CDCl$_3$) : δ: 3.6 (S, 3H,OCH$_3$), 6.8(S,1H,Ar-H), 6.9(d,2H,Ar-H), 7.10(m,3H,Ar-H), 7.19(d,2H,Ar-H), 7.3(d,2H,Ar-H), 7.6(m,3H,Ar-H), 7.90(d,2H,Ar-H), 8.32(d,2H,Ar-H),

Analysis calculated for $C_{32}H_{20}Cl_2N_4O$: **Calcd**: C,70.21; H, 3.68; N, 10.23

Found: C, 70.28; H, 3.66; N, 10.27

3,6-bis(4-chlorophenyl)-4-(3,4-dimethoxyphenyl)- 1-phenyl-1H **-pyrazolo[3,4-*b*]pyridine-5-carbonitrile, 10n**

M.P.- 288-289°C; Yield: 81 %, (0.98g) **IR :** 2923, 2217, 1743, 1597, 1266-1300 cm^{-1}

^{1}H NMR($CDCl_3$) : δ: 3.6 (S, 3H,OCH_3), 3.9 (S, 3H,OCH_3), 6.8 (d, 2H,Ar-H), 6.9 (d, 1H,Ar-H), 7.2 (m, 2H,Ar-H), 7.3 (m, 2H,Ar-H), 7.4 (t, 1H,Ar-H), 7.58 (m, 4H,Ar-H), 7.99 (d, 2H,Ar-H), 8.33(d, 2H,Ar-H).

Analysis calculated for $C_{33}H_{22}Cl_2N_4O_2$: **Calcd:** C, 68.64; H, 3.84; N, 12.28
Found: C, 68.60; H, 3.96; N, 12.24

CONCLUSION

The syntheses of compound 10 a-n are novel and reproducible. Microwave irradiation has recently been used as an efficient technique to increase reaction rates. Thus, we attempted to take advantage of this technique to decrease the reaction time and to increase yield of the product. As this technique is solvent free, it avoids the environmental pollution, so our approach is ecofriendly.

The distinct advantage of this solvent free protocol are-

1. The waste material is minimum.
2. Reaction time is almost 1000 times less than traditional method.
3. The workups of these reactions are clean and fast.
4. These reactions provide reduction or elimination of the solvent, thereby preventing environmental pollution.

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