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Research Article

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Synthesis of pyrano[2,3-d]pyridine, pyrazolo[3,4-b]pyridine derivatives by microwave irradiation and study of their insecticidal activity

Sunita A. Chaudhari (Patil)[1*], Sandeep R. Patil[2], Vasant M. Patil[2], Sambhaji V. Patil[2], Madhukar N. Jachak[2] and Ashok Desai[3]

[1]*Regional Forensic Science Laboratory, Opposite Vidyut Nagar, Dindori Road, Nashik, to the Government, Home Department, State of Maharashtra, India*
[2]*Organic Chemistry Research Centre, Department of Chemistry, K. T. H. M. College, Gangapur Road Nashik, Maharashtra, India*
[3]*Department of Zoology, K. T. H. M. College, Gangapur Road, Nashik, Maharashtra, India*

ABSTRACT

*5-Amino pyrazole **4**[1] was transformed to pyrazolo pyridine derivatives **7** by microwave irradiation with diethyl malonate. Alternatively it was synthesized by two step process through open chain derivative **6** then it was transformed to **7** by refluxing in biphenyl ether. N- Alkylation reaction on **7** was studied by ethyl bromo acetate and also by microwave irradiation. The pyran ring was annulated on **7** by condensing it with by benzilidine malononitrile. All synthesized compounds were characterized by spectral and analytical methods. It was noted that synthesis and alkylation of **7** was performed in microwave and it is faster than conventional method. The biological activity of compounds **7, 9 and 11** were studied.*

Keywords: Microwave irradiation technique, green approach, 5-amino pyrazole, pyranofused hetrocycles, ethyl bromo acetate, benzilidine malononitrile

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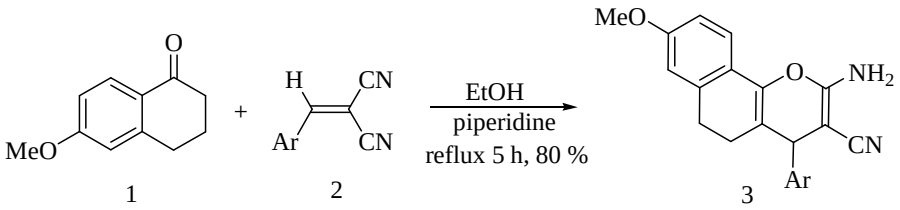
INTRODUCTION

Chromenes have received considerable attention in recent years due to their biological activities [**2**]. Compounds with these ring systems have diverse pharmacological activities such as anticoagulant, anti-cancer, spasmolytic, diuretic, anti-anacaphylactia [**3**]. 2-Amino-4*H*-pyrans can be employed as photoactive materials [4]. Recently the Synthesis of Benzo[*h*]chromene **3** [**5**] was performed by *Michael* addition of 6-methoxy-1-tetralone **1** with benzilidine malononitrile **2.** Pyrazolo[3,4-b]pyridines are promising candidates in organic synthesis due to their significant medicinal activities, such as diagnosis of brain disorder [**6**], treatment of coronary heart disease [**7**], viral disease [**8**], Central nervous system disease [**9**], and showed pharmacological efficacy [**10, 11**]. These literature reports prompted us for synthesis of new pyranofused and pyrazolo fused heterocycles. Herein we have reported synthesis of pyrazolo- [3,4-b]pyridines and pyranofused pyridines and studied their insecticidal activity.



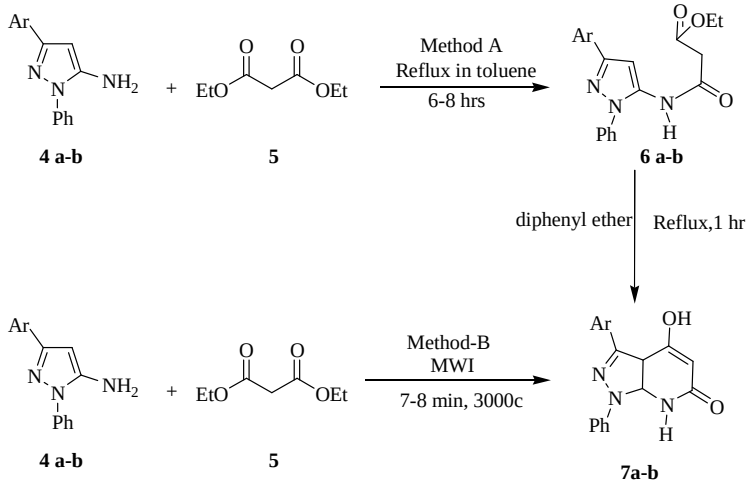
Scheme-1

EXPERIMENTAL SECTION

All the chemicals used in the present work are of AR grade and of the highest purity available.

2.1 General procedure for synthesis of Ethyl 2-[3-(4-Halophenyl)-1-phenyl-1-H-pyrazolo-5-yl-carbamoyl] acetate 6.

A solution of 1-phenyl-3-aryl-5-amino-pyrazole **4 (**0.01 mol) and diethylmalonate **5 (**0.02 mol) in dry toluene (25 ml) was reflux for 6-8 hrs. The reaction was monitor by thin layer chromatography, which was run in acetone. Yellow Solid separated on cooling was filtered dried and recrystallized from ethanol to yield compound **6** with 70 % yield.



Scheme-2

4	Ar
a	p-Cl-C_6H_5
b	p-Br-C_6H_5

2.2 General procedure for synthesis of 3-(4-Halophenyl)-1-phenyl-1-H-pyrazolo[3,4-b]pyri- dine 6 (7H) one.(7)

A. Conventional method: The compound **6** (0.01 mol) further reflux with diphenyl ether (15 ml) for 1 hr. the reaction was monitored by TLC then the solution was poured in ice cold water stir for 15 min the solid obtained was filter and wash 3-4 times by diethyl ether then dried and recrystallized from ethanol to yield pyrazolo pyridine derivative **7** with 68% yield (**Scheme-2**).

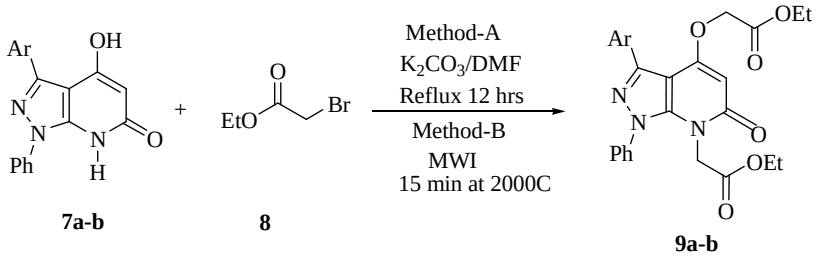
B. Microwave method: A solution of 1-phenyl-3aryl 5-amino pyrazole **4** (0.01 mol) and diethylmalonate **5** (0.02 mol) was placed in Pyrex tube and irradiated in microwave for 7-8 min. The solution was cooled at room temperature. Resulting residue was poured in ice-cold water. The solution stirred for 10 min, yellow solid separated

was filtered on suction, washed with water, dried and recrystallized in ethanol to yield compound **7** in with 85 % yield in one step (**Scheme-2**).

2.3 General procedure for Synthesis of ethyl-2(3,4-Halophenyl-{4-(2ethoxy-2-oxoethoxy)-6-oxo-1-phenyl-1,6-dihydro-7H-pyrazolo[3,4-b]pyridine-7-yl}-acetate (9)

A. Conventional method: Compound **7** (0.01 mol) and ethyl bromoacetate **8** (0.01 mol) in DMF and K_2CO_3 as a base was stir for 12 hrs at room temp under mild condition. Reaction was monitored by thin layer chromatography. After completion of reaction remove solvent under reduce pressure and pour in ice-cold water. Solid separated was filtered, dried and recrystallized in ethanol to yield compound **9** with 78% yield (Scheme-3)

B. Microwave method: Compound **7** (0.01 mol) and ethyl bromoacetate **8** (0.01 mol) was irradiated in microwave for 15 min. at 200 ^{0}C. Reaction mixture was cooled at room temperature and poured in ice cold water solid separated was filtered, dried and recrystallized in ethanol to yield compound **9** with 88% yield (**Scheme-3**).



7a-b **8** **9a-b**

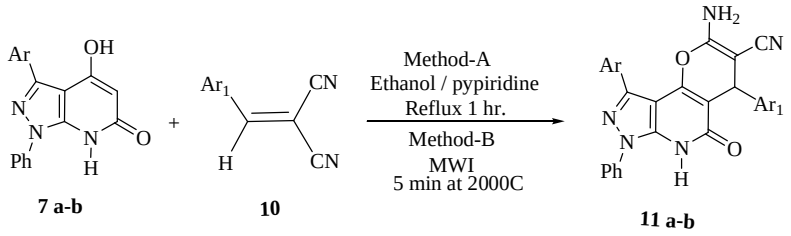
Scheme-3

7, 8	Ar
a	p-Cl-C_6H_5
b	p-Br-C_6H_5

2.4 General procedure for Synthesis of 2-amino-4,9-bis(4-chlorophenyl)-5oxo-7phenyl-4,5,6,7-tetrahydropyrano[2,3-d]pyrazolo[3,4-b]pyridine-3-carbonitrile (11)

A. Conventional method: Compound **7** (0.01moles) and benzylidine malononitrile **10** (0.01 mol) in 20 ml ethanol containing piperidine (0.5ml) was reflux for 1hrs.at 160-180 ^{0}C The solid product that precipitated during reflux was filtered dried and recrystallized from ethanol to give compound **11** with 73 % yield (**Scheme-4**).

B. Microwave method: Compound **7** (0.01moles), benzylidine malononitrile **10** (0.01 mol) and piperidine (0.5ml) was placed in Pyrex tube and then irradiated in microwave at 200 ^{0}c temp, for 4-5 min. After completion of reaction the solid obtain was cooled at room temp. Then the precipitate was filtered dried and recrystallized from ethanol to give compound **11** with 90 % yield (Scheme-4).



7 a-b **10** **11 a-b**

Scheme-4

7,11	Ar	Ar^1
a	p-Cl-C_6H_5	C_6H_6
b	p-Br-C_6H_5	C_6H_6

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 Shimadzu FTIR-408 instrument in KBr pellets. ^{1}H and ^{13}C spectra were recorded on Varian XL -300 spectrometer (300 MHz) in $CDCl_3$. The 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.

3.1 Ethyl-2-[3-(4-chlorophenyl)-1-phenyl-1-H-pyrazolo-5-yl-carbamoyl]-acetate (6a): M.P. 238-239 ^{o}C, Yield: 70%, (1.08 gm), **IR (KBr):** (ν) 3247,3065,1743,1661,1596 1559 cm^{-1}, **^{1}H NMR (CDCl$_3$) δ:** 9.90 (bs,1H,NH), 7.70 (d,2H ArH), 7.60 (d,2H ArH),7.50 (d,5H ArH), 7.15 (S, 1H, ArH), 4.2 (q,2H,CH_2),1.3 (t,3H,CH_3), 1.8 (S,2H,CH_2), **El.Analysis Calculated for $C_{20}H_{18}ClN_3O_3$:** C(59.72), H(5.96), N(11.29), **Found:** C(59.66), H(5.98), N(11.22)

3.2 Ethyl 2-[3-(4-bromophenyl)-1-phenyl-1-H-pyrazolo5-yl-carbamoyl]-acetate (6b): M.P. 240-241 ^{o}C, Yield: 67%, (0.94g), **IR (KBr):** (ν) 3249,3068,1740,1663,1594 1558 cm^{-1}, **^{1}H NMR (CDCl$_3$) δ:** 9.91 (bs,1H,NH), 7.72 (d,2H ArH), 7.61 (d,2H ArH),7.50 (d,5H ArH), 7.15 (S, 1H, ArH), 4.3(q,2H,CH_2),1.3 (t,3H,CH_3), 1.8 (S,2H,CH_2) **El. Analysis Calculated for $C_{20}H_{18}BrN_3O_3$:** C(59.70), H(5.93), N(11.34) **Found:** C(59.74), H(5.95), N(11.28)

3.3 3-(4-chlorophenyl) 4-Hydroxy-1-phenyl -1-H-pyrazolo[3,4,b]pyridine 6 (7H) one (7a)
M.P. 269-270^{o}C (Ethanol), Yield: 68 %, (1.20g) by com. method and 85 % (1.62g) by MW method. **IR (KBr):** (ν) 3369,3070,2923,1643,1592 cm^{-1}, **^{1}H NMR (CDCl$_3$) δ :** 11.7 (bs,1H,OH), 11.12 (bs,1H,NH), 8.30 (d,2H ArH), 8.20(d,2H ArH), 7.60 (m,5H, ArH), 6.0 (S,1H,ArH) **Analysis Calculated for $C_{18}H_{12}ClN_3O_2$:** C(53.74), H(3.76), N(15.67), **Found:** C(53.69), H(3.77), N(15.64)

3.4 3-(4-bromophenyl)-4-Hydroxy-1-phenyl-1-H-pyrazolo[3,4,b]pyridine-6-(7H)-one (7b): M.P. 273-274 ^{o}C (Ethanol), Yield: 69%, (1.18g) by com. method and 84 % (1.73g) by MW method, **IR (KBr):** (ν) 3368,3072,2921,1645,1590 cm^{-1}, **^{1}H NMR (CDCl$_3$) δ:** 11.73 (bs,1H,OH), 11.22 (bs,1H,NH), 8.32 (d,2H ArH), 8.22 (d,2H ArH), 7.63 (m,5H, ArH), 6.2 (S,1H,ArH), **Analysis Calculated for $C_{18}H_{12}BrN_3O_2$:** C(52.84), H(3.68), N(16.97), **Found:** C(52.88), H(3.66), N(15.91)

3.5 Ethyl-2(3,4-chlorophenyl-{4-(2ethoxy-2oxoethoxy)-6-oxo-1-phenyl-1,6-dihydro-7H-pyr- azolo[3,4-b] pyridine-7-yl}-acetate 9a: M.P. 243-244 ^{o}C (Ethanol), Yield: 78%, (1.25g) by com. method and 88 % (1.73g) by MW method**, IR (KBr):** (ν) 2982,1759,1604,1587,1296 cm^{-1}, **^{1}H NMR (CDCl$_3$) δ:** 8.30 (d,2H,ArH,J=8.2 Hz), 8.20 (d,2H ArH J=8.2 Hz), 7.30-7.50(m,5H ArH), 6.2 (S,1H, ArH), 4.90 (S,2H,OCH_2), 4,70(S,2H, CH_2CO), 4.45 (q, 2H CH_2), 4.30 (q, 2H CH_2), 1.40 (t,3H,CH_3),1.20 (t,3H,CH_3), **Analysis Calculated for $C_{26}H_{24}ClN_3O_5$:** C(55.51), H(5.32), N(9.25), **Found:** C(55.55), H(5.29), N(9.22)

3.6 Ethyl-2(3,4-bromophenyl-{4-(2ethoxy-2oxoethoxy)-6-oxo-1-phenyl-1,6-dihydro-7H-pyr- azolo[3,4-b] pyridine-7-yl}-acetate 9b: M.P. 246-247 ^{o}C (Ethanol),Yield: 74%, (1.21g)by con. method, 88% (1.70g)by MW method, **IR(KBr):**(ν) 2980,1758,1603,1588,1294 cm^{-1}, **^{1}H NMR (CDCl$_3$) δ:** 8.32 (d,2H,ArH,J=8.2 Hz), 8.20 (d,2H ArH J=8.2 Hz), 7.30-7.50(m,5H ArH), 6.3 (S,1H, ArH), 4.91 (S,2H,OCH_2), 4,72(S,2H, CH_2CO), 4.44 (q, 2H CH_2), 4.30 (q, 2H CH_2), 1.40 (t,3H,CH_3),1.20 (t,3H,CH_3), **Analysis calculated for $C_{26}H_{24}BrN_3O_5$:**C(55.58),H(4.92), N(9.28), **Found:** C(55.53), H(5.02), N(9.31)

3.7 2-amino-4,9-bis(4-chlorophenyl)-5oxo-7phenyl-4,5,6,7-tetrahydropyrano[2,3-d]pyrazolo [3,4-b]pyridine-3-carbonitrile (11a): M.P. 265-266 ^{o}C (Ethanol), Yield: 73 %, (1.40g) by com. method and 90 % (1.85g) by MW method.**IR (KBr):** (ν) 3470,3308, 3263,3182, 2212,1676,1622,1602 cm^{-1}**, ^{1}H NMR (CDCl$_3$) δ:** 12.10 (bs,1H,NH), 8.14 (d,2H ArH), 8.06(d,2H ArH), 6.92 (S,2H, ArH), 4.61 (S,1H, chiral CH), 7.64 (d,2H, ArH), 7.52 (d, 2H,ArH), 7.2-7.39 (m, 5H ArH) **Analysis Calculated for $C_{28}H_{17}Cl_2N_5O_2$:** C(50.15), H(2.37), N(18.28), **Found:** C(50.09), H(2.32), N(18.24)

3.8 2-amino-4,9-bis(4-bromophenyl)-5oxo-7phenyl-4,5,6,7-tetrahydropyrano[2,3-d]pyrazol- o[3,4-b]pyridine-3-carbonitrile (11b): M.P. 263-264 ^{o}C (Ethanol), Yield: 74 %, (1.45 g) by com. method and 89 % (1.74g) by MW method,**IR (KBr):** (ν) 3472,3306, 3262,3180, 2212,1676,1622,1604 cm^{-1}**, ^{1}H NMR (CDCl$_3$) δ:** 12.10 (bs,1H,NH), 8.13 (d,2H ArH), 8.05(d,2H ArH), 6.92 (S,2H, ArH), 4.61 (S,1H, chiral CH), 7.62 (d,2H, ArH), 7.56 (d,

2H,ArH), 7.2-7.39 (m, 5H ArH) **Analysis Calculated for $C_{28}H_{17}BrCl N_5O_2$:** C(50.18), H(2.35), N(18.23), **Found:** C(50.12), H(2.31), N(18.33)

RESULTS AND DISCUSSION

5-Amino-pyrazole **4** was synthesized by known literature method [1] and utilized for the synthesis of title compounds. Initially 5-amino-pyrazole was condensed with diethyl malonate in toluene to obtained open chain compound **6** then it was transformed to desired pyrazolopyridine derivative **7** by refluxing it in diphenyl ether. The yield of compound **6** and **7** were 70 and 68% respectively. The compound **7** was alternatively synthesized by microwave irradiation. Thus 5-amino- pyrazole **4** and diethyl malonate **5** were heated in microwave at 300 ^{0}C to furnish compound **7** in 85% yields, and the reaction was completed within 7-8 min.

The structure of compound **6** and **7** were confirmed by ^{1}H NMR, ^{1}C NMR, IR and elemental analysis and found to be in agreement with the structure proposed. Compound **7** having hydroxyl and secondary amino group were studied for alkylation reaction. Thus compound **7** on treatment with ethyl bromo acetate yielded compound **9** in good yield, The structure of compound **9** can be confirmed by spectral and analytical method and it is ethyl-2(3,4-Halophenyl-{4-(2-ethoxy-2-oxoethoxy)-6-oxo-1-phenyl-1,6-dihydro-7H-pyrazolo[3,4-b] pyridine-7-yl} acetate **9**. It was observed that both N & O-alkylation compound was took place in alkylation reaction.

Alternatively this alkylation was performed in microwave. Thus compound **7** and ethyl bromo acetate **8** were heated in microwave at 200 ^{0}C yielded compound **9** in excellent yield and in shorter time (Scheme-3). Further pyran ring was annulated on pyrazolopyridine nucleus. Compound **7** on condensation with benzilidine malononitrile in ethanol using pyridine as a base yielded compound **11** in good yield. On the basis of spectral and analytical data structure of **11** is confirmed as 2-amino-4,9-bis(4-halophenyl)-5-oxo-7-phenyl-4,5,6,7-tetrahydropyrano[2,3-d]- Pyrazolo [3,4-b]pyridine-3-carbonitrile (Scheme-4).

Alternatively this condensation was performed by microwave irradiation. Thus compound **7**(0.01 mol) and benzilidine malononitrile **10** (0.01moles) were heated in microwave at 200 ^{0}C furnish compound **11** with excellent yield and within 5 min. Insecticidal activity of compounds **7, 9 and 11** were studied.

5. INSECTICIDAL ACTIVITY OF THE COMPOUND 7 a-b, 9 a-b 11 a-b:

5.1 Bioassay/Method: The insecticidal activity tests were carried out by determination of half lethal concentration (**LC_{50}**) of each compound under investigation. The seeds of chickpea (*Cicer arientinum*) were collected from the local market and dried in oven at 80^{0}C to minimize the moisture and disinfections. Laboratory cultured adult pulse beetle *Sitophilus oryzae* Linn (Temp.28± 2^{0}C, RH-60-75% and L: D photoperiod 13:11) were selected for experimental purpose irrespective sex. Pilot experiments were carried out for determine the lower and higher toxic range of synthetic compounds and then final concentrations were set. The four concentrations of each compound viz-**2, 4, 6** & **8** *ppm* were prepared. 5 drops of each concentrations were smeared with 100 gm disinfested dried chickpea grains and kept in petri dishes; then ten same sized adult beetles were released in each concentration along with control set and mortality was recorded for 24 hours **LC_{50}** values, Regression equation, heterogeneity, variance and fiducial limit were calculated. These bioassays are in accordance with the WHO guidelines and Finney's method [**12, 13**].

5.2 Insecticidal activity of the compound 7 a-b, 9 a-b 11 a-b

The preliminary bioassay indicates that these compounds showed excellent insecticidal activities against the insect *Sitophilus Oryzae*. The results obtained from the present study are summarized in Table No.-1 which indicate LC_{50} values for the synthesized compounds. The X^2 values mentioned in the table suggested that the data are quite heterogeneous. The comparison with the time interval to LC_{50} value, It suggested that 24 hrs LC_{50} values for the entire compound are less i.e. it is more toxic to *Sitophilus oryzae*. So all these compounds are toxic to the insect *Sitophilus oryzae*. However the compounds **9a-b** is appears to be more toxic to *Sitophilus oryzae* because it has less LC_{50} values. Since the cost of pure natural compound is extremely high, it has been advocated that these synthetic pyrazole can be conveniently used for controlling stored grain pests such as *Sitophilus oryzae, Bruchus chinesis, R. domoinica, T. granarium*, agriculture and household pests.

Table No.-1 Data is significant at ≤ 0.05

Sr. No.	Comds.	Time (hrs)	% Mortality					LC_{50}	Regression equation	Heteroginecity (X^2)	Variance	Fiducial limit
			0	2	4	6	8					
1	**7a**	6	0	10	20	20	30	1.402	Y=3.3884 + 1.1496X	0.1107	0.5091	M_1= -0.1459 M_2= 1.5447
	7 b	6	0	10	20	20	30	1.403	Y=3.3886 + 1.1486X	0.1112	0.5094	M_1= -0.1456 M_2= 1.5449
2	**7a**	12	0	20	30	30	40	1.25	Y= 3.8939 + 0.8848X	0.0127	0.4653	M_1= -1.2401 M_2= 1.4338
	7b	12	0	20	30	30	40	1.251	Y= 3.8942 + 0.8852X	0.0129	0.4657	M_1= -1.2401 M_2= 1.4342
3	**7a**	24	0	40	40	50	50	0.903	Y= 4.5348 + 0.4917X	-26.497	0.3727	M1= -1.2408 M_2= -1.1518
	7b	24	0	40	40	50	50	0.903	Y= 4.5353 + 0.4921X	-26.495	0.3724	M1= -1.2413 M_2= 1.1522
1	**9a**	6	0	30	30	40	50	0.995	Y= 4.0769 + 0.9275X	0.1971	0.1682	M_1= -0.8057 M_2= 0.8017
	9 b	6	0	30	30	40	50	0.996	Y= 4.0771 + 0.9273X	0.1974	0.1685	M_1=-0.8059 M_2= 0.8021
2	**9a**	12	0	40	50	60	60	0.577	Y= 4.4697 + 0.9188X	0.027	0.0517	M_1=-0.6843 M_2=0.2071
	9b	12	0	40	50	60	60	0.577	Y= 4.4696 + 0.9191X	0.0273	0.0519	M_1=-0.6847 M_2=0.2075
3	**9a**	24	0	50	50	60	70	0.411	Y= 4.6658 + 0.8144X	0.2917	0.1231	M_1=-1.0741 M_2= 0.3009
	9b	24	0	50	50	60	70	0.411	Y= 4.6662 + 0.8148X	0.2922	0.1235	M_1=-1.0744 M_2= 0.3013
1	**11a**	6	0	20	30	30	40	1.25	Y= 3.8938 + 0.8850X	0.0939	0.465	M_1=-1.2396 M_2= 1.4334
	11b	6	0	20	30	30	40	1.251	Y= 3.8935 + 0.8854X	0.0942	0.4653	M_1=-1.2394 M_2= 1.4338
2	**11a**	12	0	30	40	40	50	0.975	Y= 4.2366 + 0.7833X	0.0837	0.2042	M_1=-0.8966 M_2= 0.8744
	11b	12	0	30	40	40	50	0.976	Y= 4.2368 + 0.7837X	0.084	0.2046	M_1=-0.8969 M_2= 0.8741
3	**11a**	24	0	40	40	50	50	0.903	Y= 4.5593 + 0.4916X	-2.4755	0.3729	M_1=-1.2412 M_2.= 1.1512
	11b	24	0	40	40	50	50	0.903	Y= 4.5596 + 0.4917X	-2.4758	0.3732	M_1=-1.2417 M_2.= 1.1515

CONCLUSION

The synthesis of compound **7, 9** and **11** 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-The waste material is minimum, Reaction time is almost 1000 times less than traditional method, The workups of these reactions are clean and fast & These reactions provide reduction or elimination of the solvent, thereby preventing environmental pollution. The use of microwave afforded compound **7, 9** and **11** with excellent yield and the reaction time is in minute in state of hours. All synthesized compound showed good to excellent insecticidal activity towards the insect *Sitophilus Oryzae.*

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REFERENCES

[1] M. N. Jachak, A. B. Avhale, C. D. Tantak and R. B. Toche, *J. Heterocyclic Chem.*, 42, 1311 (**2005**).
[2] L. Andreani, E. Lapi, *Bull. Chim. Farm.*, *99*, 583, **1960**.

[3] R. Gonzalez, N. Martin, C. Seoane, J. Soto, *J. Chem. Soc., Perkin Trans* 1, 1202, **1985**.
[4] Armesto D., Horspool W., Martin N., Romas A., Seaone C., *J. Org. Chem*. *54*, 3069, **1989**
[5] Jachak M, Kendre D, Avhale A, Toche R, Medhane V.OPPI, vol.38, 313, **2006**
[6] I. Ait, A. Resink and F.Schweighoffer, *U.S.Patent Appl.Publ*.2004219552 (**2004**); *Chem. .Abstr*., 141,388737 (2004).
[7] H.Bischoff and J.Stasch, *PCT Intl. Appl. WO 2003015770 (2003) Chem.Abstr*.,138, 180718 (**2003**).
[8] S. Ludwig, O. Planz, H. Sedlacck and S. Pleschka, *German offen DE 10138912 (***2003***); Chem.Abstr*.,138, 198569 (2003).
[9] A. Feurer, J. Luithle, S.. Wirtz, G. Koenig, J. Stasch, E. Stahl, R. Schreiber, F. Wunder and D. Lang, PCT *Intl. Appl. WO 2004009589 (2004) Chem.Abstr*.,140, 146157 (**2004**).
[10] F.J.Ehlert,P. Ragan, A. Chen,W. R. RocSke and H. I. Yamamura, *Eur. J. pharmacol.*, 78, 249 (**1982**).
[11] Rane,B. S; Deshmukh,S.V; Ghagare, M.G; Rote, R,V; Jachak, M. N. **2012**. *JOCPR*, 2012, 4(7), 3562
[12] Finney, D. J. Probit Analysis. Cambridge University press, Landon, **1971**
[13] Busvin, J.R. *Critical review of techniques Bureax, England*.**1971**, pp 267-282