MICROWAVE ASSISTED SYNTHESIS OF 6-ARYL-2-METHYL-3-[BENZOTHIAZINYLPYRIDINYL / 2-AMINOPYRIMIDINYL / 2-AMINOTHIAZOLYL / TRIAZOLOTHIADIAZINYL]PYRIDINES

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Abstract : A number of new 6-Aryl-2-methyl-3-[benzothiazinylpyridinyl / 2-amino pyrimidinyl / 2-aminothiazolyl and triazolothiadiazinyl] pyridines (4 - 7) have been synthesized under microwave irradiation conditions.

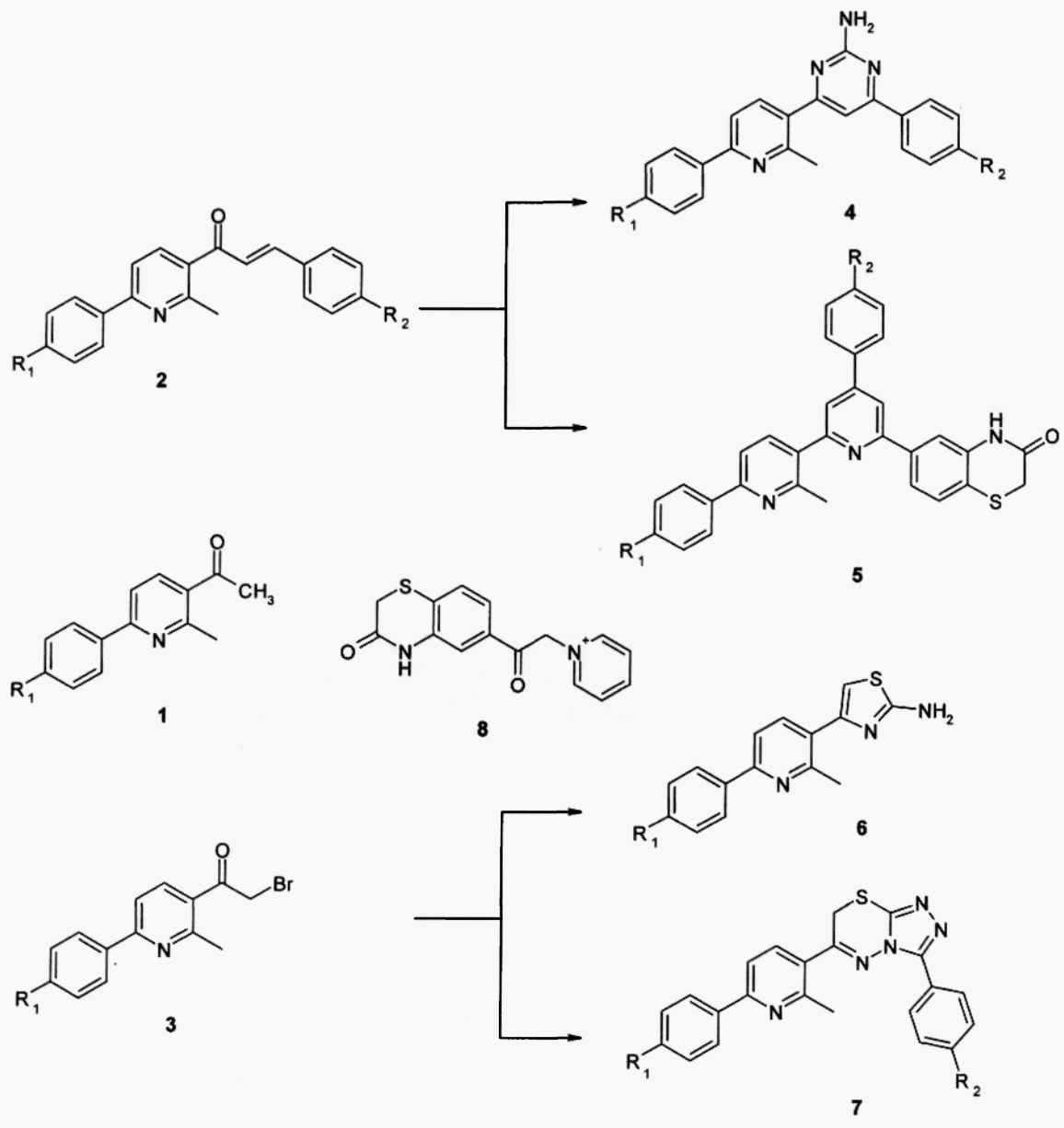
Introduction

Pyridine ring forms an important pharmacophore with its presence in a number of natural and pharmaceutical products[1]. Certain functionally substituted pyridines have been reported as potent inhibitors of the human immunodeficiency virus type I (HIV-I) reverse transcriptase[2]. Diarylpyridines like *Etoricoxib* has been introduced as a selective COX-2 inhibitor[3]. In continuation of our work on diaryl heterocycles[4] for biological evaluation, we report herein the synthesis of some new heterocyclic substituted pyridines under microwave conditions.

Thus microwave irradiation of various enaminoketones with acetyl acetone in presence of acetic acid and ammonium acetate gave the starting 2-methyl-6-aryl-3-acetylpyridines **1** in good yields and shorter reaction times of 5-7 minutes when compared to conventional heating[5] for 5-6 hrs. **1** were reacted with araldehydes in presence of sodium methoxide to get the chalcones **2** in good yields. Bromination of **1** with bromine in acetic acid in presence of HBr gave the 3-bromoacetyl-2-methyl-6-arylpyridines **3**. The structures of **2** & **3** are established based on their spectral data.

Reaction of chalcones **2** with guanidine hydrochloride in presence of sodium ethoxide gave the corresponding 6-pyridinyl-2-aminopyrimidines **4**. Reaction of **2** with 3-oxo-2H[1,4]-benzothiazine-3,4-dihydro-6-acetyl pyridinim salt **8** in refluxing acetic acid in presence of ammonium acetate gave the pyridinyl benzothiazinyl pyridines **5** under Kröhnke's conditions[6]. 4-Pyridinyl-2-aminothiazoles **6** and 6-pyridinyl triazolothiadiazines **7** were obtained by reaction of bromoacetyl derivative **3** with thiourea and 4-amino-8-mercapto. 1,2,4-Triazoles under Hantschz reaction conditions (**Scheme-1**). Also keeping in view of the advantages of microwave irradiation in reduction of reaction timings and ecofriendly nature[7], all the condensation reactions were

carried out under microwave irradiation condition and the reactions were completed within 5 minutes when compared to 2-4 hrs under conventional heating (**Table –1**).



Scheme-1

The structures of the reaction products **4**, **5**, **6** & **7** were based on their IR, ^{1}H-NMR and mass spectra. All the products exhibited characteristic singlet for 2-methyl group around δ 2.75 apart from pyridine and aromatic protons. In addition compounds **5** & **7** are characterized by the presence of $-SCH_2$ around δ 3.5 & 4.8 respectively. 2-Aminopyridmidine protons in **4** and 2-aminothiazolyl protons in **6** appeared around δ 5.2 and δ 4.8. C_5-thiazole proton in **6** appeared around δ 6.57.

Experimental Section

Melting points were determined in open capillaries and are uncorrected. The purity of all the compounds was routinely checked by TLC on silica gel coated plates. IR spectra were recorded on KBr pellets on a Perkin Elmer system 2000 FT IR spectrometer. ^{1}H-NMR spectra on a Varian 200 MHz instrument with TMS as an internal standard and chemical shifts expressed in δ ppm. Mass spectra were recorded on Hewelett Packard mass spectrometer operating at 70eV.

2-Methyl-6-aryl-3-acetylpyridines (1): Microwave irradiation condition
A mixture of 3-dimethylamino-1-phenyl-prop-2-en-1-one (0.01 mol) and acetyl acetone (0.01 mol), ammonium acetate (0.06 mol) acetic acid (10 ml) taken in a Erlenmeyer flask was irradiated for 6 minutes in 6 x 1 with 1 minute interval using domestic microwave oven. At the end of the reaction as monitored by TLC, it was poured onto ice. The separated solid was filtered, washed with water, dried and recrystallized form ethanol to give pure **1** as crystalline solids.

1-(6-Aryl-2-methylpyridin-3-yl)-3-aryl-2-propen-1-ones 2: General procedure
A mixture of **1** (0.01 mol) and aromatic aldehyde (0.01 mole) was added to a solution of sodium (0.02 mole) in methanol. The reaction mixture was stirred at room temperature until the disappearance of starting materials as monitored by TLC. The solution was neutralized and the separated solid was filtered, washed with water followed by methanol to give pure **2** as crystalline solids.

The melting points and yields of different **2**, prepared are given below.

2a R_1 = H, R_2 = Cl, 114°C, 72% **2b** R_1 = H, R_2 = F, 120°C, 73%
2c R_1 = R_2 = Cl, 138°C, 76% **2d** R_1 = Cl, R_2 = F, 95°C, 73%
2e R_1 = R_2 = F, 132°C, 74%

^{1}H-NMR ($CDCl_3$) **2b**: δ 2.74 (s, 3H), 7.1(m, 3H), 7.40-7.64(m, 7H), 7.85(d, 1H), 8.07(m, 2H).

6-Aryl-2-methyl-3-bromoacetylpyridine 3: General procedure

To a mixture of **1** (0.01 mole), hydrobromic acid (0.5 ml) and acetic acid (5 ml), bromine (0.01 mol) was added drop wise keeping the temperature below 25°C. It was stirred for additional 2 hrs, checked for completion of the reaction. The separated solid was filtered washed with acetone. It was taken up in minimum amount of water and neutralized with a cold solution of $NaHCO_3$. It was filtered and recrystallized from hexane to give pure **3** as crystalline solids.

The melting points and yields of different **3**, prepared are given below.

3a R_1 = H, 93°C, 66% **3b** R_1 = Cl, 115°C, 61% **3c** R_1 = F, 107°C, 63%

^{1}H-NMR($CDCl_3$) **3c**: δ 2.83(s, 3H), 4.43(s, 2H), 7.17(m, 2H), 7.61(d, 1H), 8.12(m, 3H).

6-Aryl-2-methyl-3-(2-amino-4-arylpyrimidin-6-yl)pyridines 4: Microwave condition

A mixture of **2** (0.01 mole), guanidine hydrochloride (0.01 mol) and sodium ethoxide in absolute ethanol (60 ml) taken in an Erlenmeyer flask was irradiated in a domestic micro oven for 1.5 minutes. The residue was diluted with water (100 ml), acidified with acetic acid, the separated solid was filtered, washed with water, dried and recrystallised from methanol to give **4** as pure crystalline solid.

Compounds **4a-e** were similarly prepared and their physical and spectral data are presented in **Table 1**.

6-Aryl-2-methyl-3-[4-aryl-6-(3-oxo-1,4-benzothiazin-6-yl)pyrid-2-yl]pyridines 5: Microwave condition

A mixture of **2** (0.01 mol), 3-oxo-2H-[1,4]benzothiazin-3,4-dihydro-6-acetylpyridinim salt (**8**, 0.01 mol), ammonium acetate (0.06 mol) and acetic acid (50 ml) taken in an Erlenmeyer flask was irradiated in a domestic micro oven for 4-5 minutes. At the end of the reaction as monitored by TLC, the reaction mixture was cooled, filtered, washed with water, dried and recrystallized from DMF – methanol to give pure **5** as crystalline solid.

Compounds **5a-e** were similarly prepared and their physical and spectral data are presented in **Table 1**.

6-Aryl-2-methyl-3-(2-amino-3-thiazol-4-yl)pyridines 6: Microwave condition

A mixture of **3** (0.01 mol), thiourea (0.01 mol) in ethanol (50 ml) was irradiated for 1.5 minutes, The residue was neutralized with $NaHCO_3$ solution, the separated solid was filtered washed with water, dried and recrystallized from ethanol to give pure **6** as crystalline solid.

Compounds **6a-c** reported in **Table 1** were similarly prepared.

6-Aryl-2-methyl-3-[3-aryl-7H-[1,2,4]triazolo[3,4-b]thiadiazin-6-yl]pyridines 7: Microwave condition

A mixture of **3** (00.01 mole) 4-amino-3-mercapto-5-aryl-1,2,4-triazole (0.01 mol) in ethanol (50 ml) was irradiated for 1 minute. The residue was neutralized with $NaHCO_3$ solution, the separated solid was filtered, washed with water, dried and recrystallised from, DMF – Methanol to give pure **7** as crystalline solid.

Compounds **7a-c** reported in **Table 1** were similarly prepared.

Synthesis of 4, 5, 6 & 7 under conventional heating

All the above reactions were carried out under conventional heating for comparison and the results are presented in **Table 1**.

Table-1: Characterization data of compounds 4 - 7

Compd	R_1	R_2	Method				M. p (°C)	Mol. Formula	^{1}H NMR δ ppm $CDCl_3$ / DMSO-d_6
			Microwave		Conventional				
			Time (min)	Yield (%)	Time (hr)	Yield (%)			
4a	H	Cl	1.5	57	3 hr	53	193	$C_{22}H_{17}ClN_4$	2.75(s, 3H), 5.24(s, 2H), 7.13(m, 3H), 7.46(m, 2H), 7.64(m, 1H), 7.82(m, 2H), 8.05(m, 4H)
4b	H	F	1.5	60	3.5	55	171	$C_{22}H_{17}FN_4$	2.70(s, 3H), 5.13(s, 2H), 7.13(m, 3H), 7.46(m, 2H), 7.67(m, 1H), 7.82(m, 2H), 8.06(m, 4H)
4c	Cl	Cl	1.5	58	3	54	196	$C_{22}H_{16}Cl_2N_4$	2.73(s, 3H), 5.24(s, 2H), 7.15(m, 3H), 7.47(m, 2H), 7.64(m, 1H), 7.82(m, 2H), 8.04(m, 4H)
4d	Cl	F	1.5	58	4	52	205	$C_{22}H_{16}ClFN_4$	2.69(s, 3H), 5.26(s, 2H), 7.15(m, 3H), 7.45(m, 2H), 7.62(m, 1H), 7.81(m, 1H), 8.05(m, 4H)
4e	F	F	1.5	65	4	61	221	$C_{22}H_{16}F_2N_4$	2.74(s, 3H), 5.23(s, 2H), 7.14(m, 3H), 7.44(m, 2H), 7.61(m, 1H), 7.82(m, 1H), 8.04(m, 4H)
5a	H	Cl	4	76	4	71	260	$C_{31}H_{22}ClN_3OS$	2.75(s, 3H), 3.51(s, 2H), 7.37-7.56(m, 6H), 7.89-7.97(m, 4H), 8.08-8.17(m, 6H), 10.67(s, 1H)
5b	H	F	4.5	78	4	72	>300	$C_{31}H_{22}FN_3OS$	2.76(s, 3H), 3.52(s, 2H), 7.38-7.56(m, 6H), 7.90-7.98(m, 4H), 8.08-8.18(m, 6H), 10.67(s, 1H)
5c	Cl	Cl	5	73	3.5	70	278	$C_{31}H_{21}Cl_2N_3OS$	2.76(s, 3H), 3.53(s, 2H), 7.41-7.58(m, 5H), 7.91-7.97(m, 4H), 8.08-8.17(m, 6H), 10.67(s, 1H)
5d	Cl	F	4.5	76	3.5	72	>300	$C_{31}H_{21}ClFN_3OS$	2.77(s, 3H), 3.52(s, 2H), 7.41-7.58(m, 5H), 7.90-7.96(m, 4H), 8.08-8.16(m, 6H), 10.67(s, 1H)
5e	F	F	4.5	79	4	75	>300	$C_{31}H_{21}F_2N_3OS$	2.76(s, 3H), 3.52(s, 2H), 7.41-7.58(m, 5H), 7.91-7.96(m, 4H), 8.08-8.16(m, 6H), 10.67(s, 1H)
6a	H	-	1	64	1.5	60	181	$C_{15}H_{13}N_3S$	2.74(s, 3H), 4.81(bs, 2H), 6.57(s, 1H), 7.43(m, 5H), 7.52(d, 1H), 7.92(d, 1H)

Table-1 (Continued): Characterization data of compounds 4 - 7

Compd	R_1	R_2	Method				M. p (°C)	Mol. Formula	^{1}H NMR δ ppm $CDCl_3$ / DMSO-d_6
			Microwave		Conventional				
			Time (min)	Yield (%)	Time (hr)	Yield (%)			
6b	Cl	-	1	68	1.5	63	242	$C_{15}H_{12}ClN_3S$	2.73(s, 3H), 4.82(bs, 2H), 6.58(s, 1H), 7.24(m, 2H), 7.53(d, 1H), 7.91(d, 1H), 8.17(m, 2H)
6c	F	-	1.5	69	1	65	191	$C_{15}H_{12}FN_3S$	2.74(s, 3H), 4.83(bs, 2H), 6.58(s, 1H), 7.23(m, 2H), 7.52(d, 1H), 7.92(d, 1H), 8.18(m, 2H)
7a	H	Cl	1	68	1	62	223	$C_{22}H_{16}ClN_5S$	2.66(s, 3H), 4.81(s, 2H), 7.32(m, 2H), 7.57(m, 3H), 7.99(m, 2H), 8.21(m, 3H), 8.44(d, 1H)
7b	Cl	Cl	1	67	1	62	235	$C_{22}H_{15}Cl_2N_5S$	2.67(s, 3H), 4.82(s, 2H), 7.32(m, 2H), 7.57(m, 2H), 7.99(m, 2H), 8.21(m, 3H), 8.44(d, 1H)
7c	F	Cl	1	75	1	71	240	$C_{22}H_{15}ClFN_5S$	2.65(s, 3H), 4.81(s, 2H), 7.32(m, 2H), 7.57(m, 2H), 7.96(m, 2H), 8.19(m, 3H), 8.46(d, 1H)

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