RJC

RASĀYAN *J. Chem.*
Vol. 5 | No.2 | 177-182 | April-June | 2012
ISSN: 0974-1496 | CODEN: RJCABP
http://www.rasayanjournal.com

MICROWAVE ASSISTED SYNTHESIS OF N- [4-(5-ARYL-1*H*/ PHENYL-PYRAZOL -3-YL)-PHENYL]- BENZENESULFONAMIDES

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ABSTRACT

A series of N-[4-(5-aryl-1*H*/phenyl-pyrazol-3-yl)-phenyl]-benzenesulfonamides have been synthesized under conventional heating conditions and microwave irradiation. Under conventional heating conditions, titled compounds were synthesized by the action of hydrazine hydrate/ phenyl hydrazine on N-[4-(2,3-dibromo-3-aryl-propanoyl)-phenyl]benzenesulfonamide in ethanol in presence of catalytic amount of piperidine. Under microwave irradiation, reaction proceeds smoothly without use of any catalyst in shorter time with better yields. IR, ^{1}H NMR and Mass spectra were used to validate the identity of all the synthesized compounds.

Keywords: Benzenesulfonamides, Chalcone-dibromides, Microwave Assisted synthesis and Pyrazoles.

INTRODUCTION

Synthetic organic chemistry requires consumption of energy. Microwave-assisted organic synthesis (MAOS) continues to be a popular theme within the realm of organic and medicinal chemistry community. Since 1986, microwave heating has emerged as a powerful technique to promote a variety of chemical reactions[1,2].

Sulfonamide compounds, identified as chemotherapeutic agents, possess broad spectrum of biological properties[3]. Amongst the many five membered heterocycles, pyrazoles have received a considerable attention over past few decades. Their wide range of biological activities has made them popular synthetic inhibitors for different enzymes and pathways[4]. Furthermore, diarylpyrazoles have been identified as key pharmacophore in antimicrobial[5], analgesic[6] and anti-inflammatory agents[7] (Figure 1). 5-Amino- 1-(4-methylphenyl) pyrazole bearing phenylsulfonamide moiety at 4 position has been tested as an NPY5 antagonist[8] (Figure 1). Numerous methods for the synthesis of 1,3,5-substituted pyrazoles are known[9]. Azarifar *et al.* synthesized 1,3,5-triarylpyrazoles in 90-96% yields by oxidative aromatization using trichloroisocyanuric acid under microwave irradiation[10].

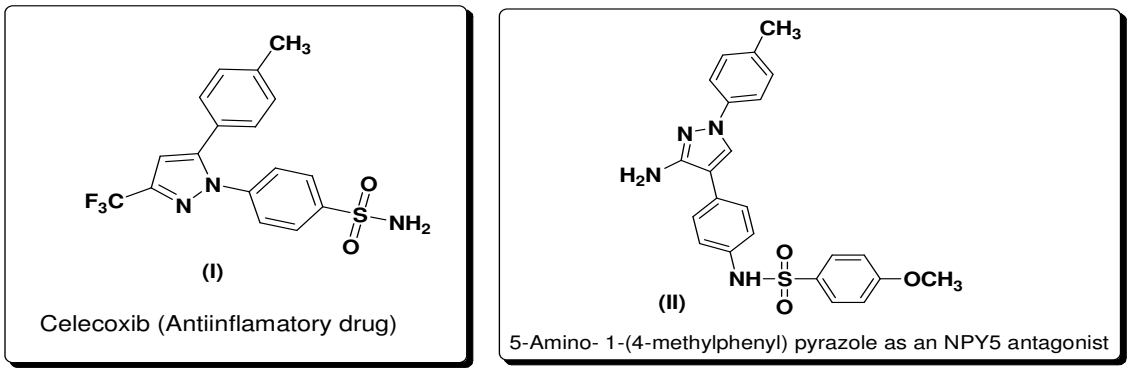


Fig.-1: Pharmacologically active pyrazoles

Heller *et al*, reported the condensation of propane 1,3-dione derivatives and phenyl hydrazine in toluene using LiHMDS in 43% yield[11]. Minis, reported the synthesis of pyrazoles which involves the direct C-C coupling by Grignard and Suzuki coupling[12]. Pyrazoles can also be obtained by oxidation of pyrazoline derivatives with I_2 in DMSO[13] or p-iodobenzene diacetate (PIDA)[14]. Bishop *et al* reported the synthesis of 1,3,5-substituted pyrazoles from acetylenic ketone and hydrazines[15].
Most frequently used method for the synthesis of pyrazoles is the action of hydrazine on 1,3-diketones[16] or flavones[17] in various solvents like ethanol, acetic acid, DMSO and triethanolamine[18]. Chalcone-dibromides and chalcone epoxides have also been proved as useful synthons for synthesis of 3,5-diarylpyrazoles[19]. However, these methods have been used in the synthesis of only a limited number of analogues.
Prompted by these observations, and in continuation to our endevaur on the synthesis of pyrazolyl benzenesulfonamides[20], we herein report the synthesis of N-[4-(5-aryl-1*H*/phenyl-pyrazol-3-yl)-phenyl]benzenesulfonamide under conventional heating conditions and microwave irradiation.

EXPERIMENTAL

All common reagents and solvents were used as obtained from commercial suppliers without further purification. All melting points were taken in open capillary in silicon oil bath and are uncorrected. Homogeneity of the synthesized compounds was checked on pre-coated TLC plates & spots were visualized using UV chamber. IR spectra were recorded in 1% KBr on Perkin-Elmer PARAGON 1000 spectrometer. ^1H NMR spectra were recorded on Brucker spectrometer (300 & 500 MHz) using TMS as internal standard. Mass spectra were recorded on Brucker micrOTOF-Q spectrometer.

General procedure for synthesis of 2a-d

To a suspension of N-[4-(3-aryl-acryloyl)-phenyl]-benzenesulfonamide **1a-d** (10 mmol) in acetic acid (10mL), solution of Bromine in acetic acid (30% v/v) was added dropwise with constant stirring until the reaction mixture appears dark brown. It was stirred for half an hour at room temperature. The solid obtained was filtered and washed with petroleum ether to get **2a-d**.

N-[4-(2,3-Dibromo-3-phenyl-propanoyl)-phenyl]benzenesulfonamide 2a

M.p. 168° C. IR (KBr) (ν max in cm^{-1}): 3237 (NH), 1685(C=O), 1331 & 1145 (SO_2 asymm. & symm.), 546 (C-Br); ^1H NMR ($CDCl_3$) δ (ppm) : 5.61-5.64 (d, 1H, J= 12 Hz) & 5.66-5.72 (d, 1H, J=12 Hz), 7.19-7.85(m, 14H, Ar-H); MS (ESI): m/z 521.9 (M+H).

N-{4-[2,3-Dibromo-3-(4-methoxyphenyl)-propanoyl]-phenyl}benzenesulfonamide 2b

M.p. 150°C. IR (KBr) (ν max in cm^{-1}): 3208 (NH), 1688(C=O), 1330 & 1172 (SO_2 asymm.& symm.), 555 (C-Br); ^1H NMR ($CDCl_3$) δ (ppm) : 3.83 (s, 3H, -OCH_3), 4.82-4.86 (d,1H, J= 12 Hz) & 4.97-5.01 (d, 1H, J=12 Hz) , 6.91-7.95 (m, 13H, Ar-H); MS (ESI): m/z 551.9 (M+H).

N-{4-[2,3-Dibromo-3-(4-chlorophenyl)- propanoyl]-phenyl}benzenesulfonamide 2c

M.p. 165°C. IR (KBr) (ν max in cm^{-1}): 3250 (NH), 1685(C=O), 1341 & 1160 (SO_2 asymm.& symm.), 567 (C-Br); ^1H NMR (DMSO-d_6) δ (ppm) : 5.73-5.75 (d,1H, J= 11 Hz) & 6.51-6.53 (d,1H, J=11 Hz) , 7.22-8.14 (m,13H,Ar-H), 11.11(s,1H,NH); MS (ESI): m/z 557.8 (M+H).

N-{4-[2,3-Dibromo-3-(4-fluorophenyl)- propanoyl]-phenyl}benzenesulfonamide 2d

M.p. 115°C. IR (KBr) (ν max in cm^{-1}): 3270 (NH), 1683(C=O), 1339 & 1159 (SO_2 asymm.& symm.), 592 (C-Br); ^{1}H NMR ($CDCl_3$) δ (ppm) : 5.59-5.63 (d,1H, J= 12 Hz) & 5.66-5.70 (d,1H, J=12 Hz) , 7.09-8.02 (m,13H,Ar-H); MS (ESI): m/z 539.6 (M-H).

General Procedure for synthesis of N-[4-(5-aryl-1*H*/phenyl-pyrazol-3-yl)-phenyl]-benzenesulfonamide 3a-d/4a-d

Method A: Conventional heating

1-(4-phenylsulphonamidophenl)-3-aryl-2,3-dibromopropanone **(2a-d)** (25 mmol), hydrazine hydrate/phenyl hydrazine (37.5 mmol) and 2-3 drops of piperidine was refluxed in ethanol medium

(25mL) until the TLC reported the consumption of starting material i.e. for 6-8 hrs. The reaction mixture was cooled and poured into aq. HCl (1M, 30 mL). The solid obtained was filtered, dried & purified by crystallization / column chromatography using proper eluent to get **3a-d/4a-d**.

Method B: Microwave Irradiation

1-(4-phenylsulphonamidophenl)-3-aryl-2,3-dibromopropanone **(2a-d)** (25 mmol), hydrazine hydrate/ phenyl hydrazine (37.5 mmol) and ethanol (2 mL) was irradiated with Microwave irradiation for 5-6 minutes. Then ethanol (10 mL) was added to it and it was stirred at room temp for 10 minutes. The reaction mixture was poured into crushed ice. The solid obtained was filtered, dried & purified by crystallization / column chromatography using proper eluent to get 3**a-d/ 4a-d**.

N-[4-(5-Phenyl-1*H*-pyrazol-3-yl)-phenyl]benzenesulfonamide 3a

M.p. 245°C. IR (KBr) (ν max in cm^{-1}): 3260 (NH), 1619(C=N), 1337 & 1164 (SO_2 asymm. & symm.); ^1H NMR (DMSO-d_6) δ (ppm) :6.78 (s, 1H, =CH of pyrazole), 7.08-7.80 (m, 14H, Ar-H), 10.46 (s, 1H, SO_2NH); MS (ESI): m/z 376.1 (M+H) .

N-[4-(5-(4-Methoxyphenyl)-1*H*-pyrazol-3-yl)-phenyl]benzenesulfonamide 3b

M.p. 275°C. IR (KBr) (ν max in cm^{-1}): 3262 (NH), 1611(C=N), 1333 & 1159 (SO_2 asymm. & symm.); ^1H NMR (DMSO-d_6) δ (ppm) : 3.72 (s, 3H, -OCH_3), 6.93 (s, 1H, =CH of pyrazole), 6.97-7.77 (m, 13H, Ar-H), 10.4 (s, 1H, SO_2NH), 13.1 (s,1H, NH); MS (ESI): m/z 406.1 (M+H).

N-[4-(5-(4-Chlorophenyl)-1*H*-pyrazol-3-yl)-phenyl]benzenesulfonamide 3c

M.p. 230°C. IR (KBr) (ν max in cm^{-1}): 3238 (NH), 1611(C=N), 1332 & 1158 (SO_2 asymm. & symm.); ^1H NMR ($CDCl_3$) δ (ppm) :6.95 (s, 1H, =CH of pyrazole), 7.0-8.2 (m, 13H, Ar-H), 10.2 (s, 1H, SO_2NH); MS (ESI): m/z 410.1 (M+H).

N-[4-(5-(4-Fluorophenyl)-1*H*-pyrazol-3-yl)-phenyl]benzenesulfonamide 3d

M.p. 280°C. IR (KBr) (ν max in cm^{-1}): 3248 (NH), 1603(C=N), 1333 & 1160 (SO_2 asymm. & symm.); ^1H NMR (DMSO-d_6) δ (ppm) : 7.03(s,1H,=CH of pyrazole), 7.06 -8.16 (m, 13H,Ar-H), 10.41 (s, 1H, SO_2NH), 11.12 (s,1H,NH); MS (ESI): m/z 394.1 (M+H).

N-[4-(1,5-Diphenyl-pyrazol-3-yl)-phenyl]benzenesulfonamide 4a

M.p. 225°C. IR (KBr) (ν max in cm^{-1}): 3255(NH), 1652(C=N), 1333 & 1161 (SO_2 asymm. & symm.); ^1H NMR (DMSO-d_6) δ (ppm) : 7.04 (s, 1H, =CH of pyrazole), 7.06-8.05 (m, 19H, Ar-H), 10.52 (s, 1H, SO_2NH); MS (ESI): m/z 452.1443 (M+H) and 474.1273 (M+Na).

N-[4-(5-(4-Methoxyphenyl)-1-acetyl-pyrazol-3-yl)-phenyl]benzenesulfonamide 4b

M.p. 175° C. IR (KBr) (ν max in cm^{-1}): 3245 (NH), 1669(C=N), 1335 & 1162 (SO_2 asymm. & symm.); ^1H NMR (DMSO-d_6) δ (ppm) : 3.81 (s,3H, -OCH_3), 6.80 (s, 1H, =CH of pyrazole), 6.82-8.00 (m, 18H, Ar-H), 10.40 (s, 1H, SO_2NH); MS (ESI): m/z 482.1538 (M+H).

N-[4-(5-(4-Chloro-phenyl)-1-acetyl-pyrazol-3-yl)-phenyl]benzenesulfonamide 4c

M.p. 215°C. IR (KBr) (ν max in cm^{-1}): 3239 (NH), 1596 (C=N), 1329 & 1158 (SO_2 asymm. & symm.); ^1H NMR (DMSO-d_6) δ (ppm) : 6.69 (s, 1H, =CH of pyrazole), 7.02-8.02 (m, 18H, Ar-H), 10.40 (s, 1H, SO_2NH); MS (ESI): m/z 486.2 (M+H) and 484.1 (M-H).

N-[4-(5-(4-Fluoro-phenyl)-1-acetyl-pyrazol-3-yl)-phenyl]benzenesulfonamide 4d

M.p. 275° C. IR (KBr) (ν max in cm^{-1}): 3336 (NH), 1596 (C=N), 1333 & 1160 (SO_2 asymm. & symm.); ^1H NMR (DMSO-d_6) δ (ppm) : 6.65 (s,1H, =CH of pyrazole), 6.75-7.90 (m, 18H, Ar-H), 9.90 (s, 1H, SO_2NH); MS (ESI): m/z 470.1 (M+H).

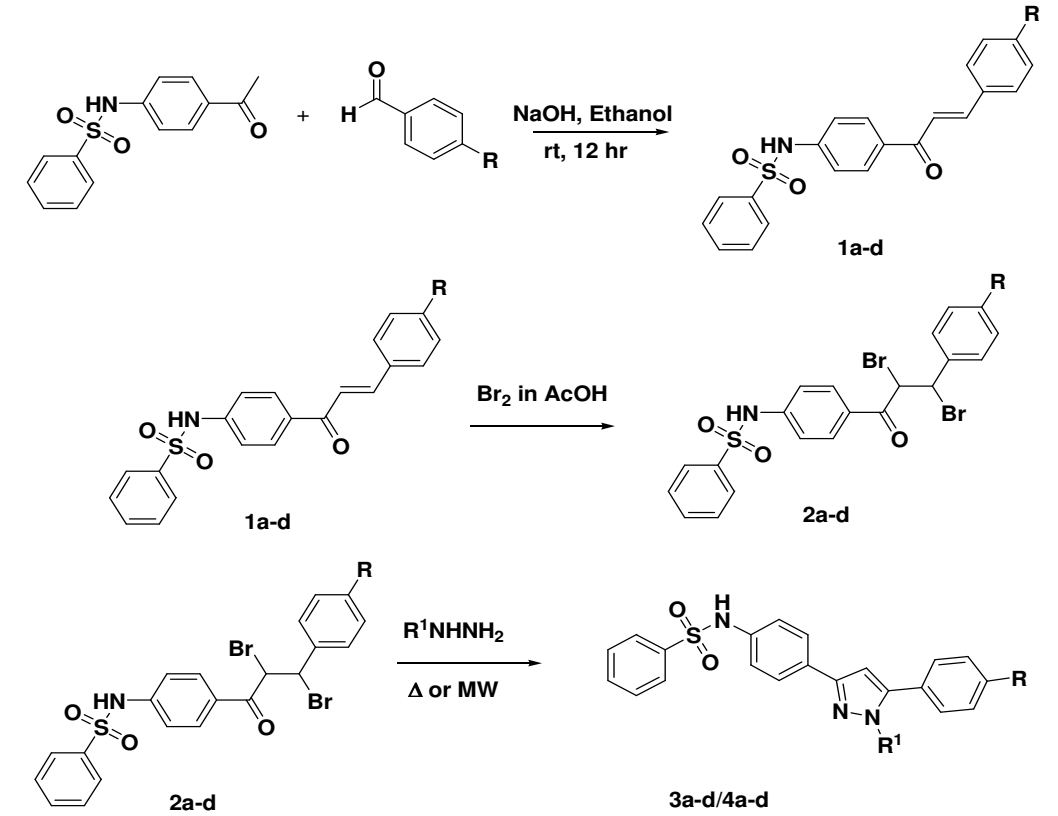
RESULTS AND DISCUSSION

The key intermediate N- [4-(3-aryl-acryloyl)-phenyl]benzenesulfonamide **1a-d** were prepared by Claisen-Schmidt condensation of N-(4-acetyl-phenyl)benzenesulfonamide with aromatic aldehydes in presence of NaOH / ethanol in good yields[21]. Compounds **1a-d** were treated with Br_2/AcOH to give N-[4-(2,3-dibromo-3-aryl-propanoyl)-phenyl]-benzenesulfonamide **2a-d** (Scheme-1).

Compounds **2a-d** were refluxed with hydrazine hydrate in ethanol in presence of catalytic amount of piperidine to get **3a-d**.

We further synthesized N-[4-(5-aryl-1-phenylpyrazol-3-yl)-phenyl]benzenesulfonamide **4a-d** by refluxing **2a-d** with phenyl hydrazine in ethanol in presence of catalytic amount of piperdine.

To demonstrate the utility of microwave heating in the synthesis of the titled compounds, we attempted the successful synthesis of **3a-d/ 4a-d** from **2a-d** using ethanol as a solvent. This method appeared to be rapid, efficient and economical. The reaction was found to proceed smoothly with better yields under microwave irradiation within 5-6 minutes whereas under reflux conditions, 6-8 hrs were required (Table-1).



R= -H, -OCH_3, -Cl, -F

Scheme-1: Synthesis of pyrazolyl benzenesulfonamides

Table-1: Synthesis of N-[4-(5-aryl-1*H*/phenyl-pyrazol-3-yl)-phenyl]benzenesulfona- mide under conventional heating conditions and microwave irradiation

Entry	R	R^1	Conventional Heating		Microwave Irradiation	
			Time	% Yield	Time (min)	% Yield[a]
3a	H	H	6 h	71	5 min	82
3b	OCH_3	H	7h	58	5 min	76
3c	Cl	H	7h	74	6 min	81
3d	F	H	8h	63	5 min	79
4a	H	Ph	6h	69	6 min	80

4b	OCH_3	Ph	8h	68	5 min	76
4c	Cl	Ph	7h	71	5 min	82
4d	F	Ph	8h	67	5 min	81

[a] -Isolated Yield

ACKNOWLEDGEMENTS

The author is thankful to the University Grants Commission (WRO), Pune (F. No. 47 – 046 / 47) for providing financial assistance.

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[RJC-925/2012]