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MW Induced Preparation of Acridin-9-Yl-Bis-Benzothiazol-2-Yl-Amines and Antituberculosis Activity

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ABSTRACT

Preparation of new series of acridin-9-yl-bis-benzothiazol-2-yl-amines have been developed by intra-molecular cyclization of 1-acridin-9-yl-1-benzothiazol-2-yl-3-aryl thiourea with bromine in acetic acid and evaluated for their *in vitro* antibacterial activity against *Mycobacterium tuberculosis* by BACTEC radiometric method. Constitutions of compounds were confirmed by FTIR, ^{1}H-NMR, ^{13}C-NMR spectral methods. Simple work-up procedure and excellent yield of the products are the merits of the route.

Keywords: MW organic reactions, benzothiazole, antituberculosis.

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INTRODUCTION

Organic reactions are accelerated under the influence of microwave conditions[1] have received considerable attention and their use to multi-component reactions[2,3] can be adapted for high-speed parallel synthesis of a library of bioactive compounds. Benzothiazole containing nitrogen and sulphur have been under investigation for a long time because of their important biological properties and atoms constitute the core structure of many pharmacological compounds[4]. Literature survey revealed that amino and chloro group containing benzothiazole shows better anticancer activity[5] and also found to posses the antifungal[6], antimicrobial[7,8], muscle relaxant[9] activities. Most intensively studied 2-aminobenzothiazole one of the privilege structures in medicinal chemistry[10] owing to their utility as imaging agents for β-amyloid, antiparasitics and as photosensitizers[11, 12].

Inspite of many reported method this microwave assisted method is most simple and effective for syntheses 2-substituted benzothiazole in solvent free condition without using catalyst. Our experience in microwave-assisted chemistry of heterocycles[13-14] encouraged us to establish route for an effective preparation of acridin-9-yl-bis-benzothiazol-2-yl-amines in good to excellent yields under microwave condition.

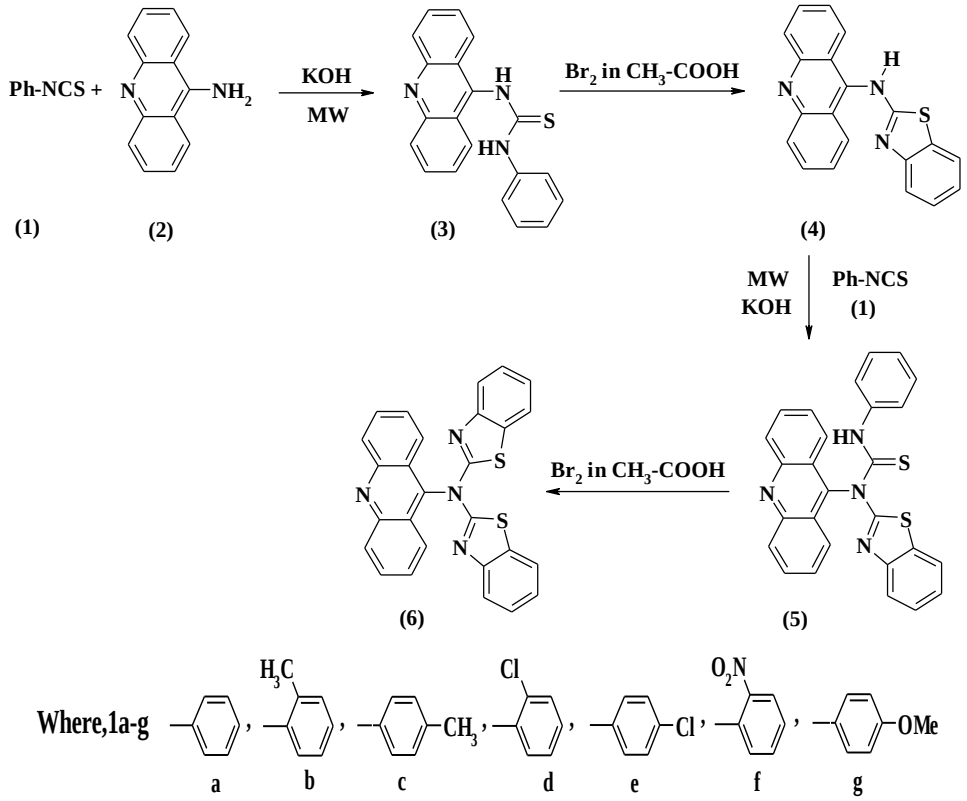
RESULTS AND DISCUSSION

The representative compounds were prepared by intramolecular oxidative cyclization of 1-acridin-9-yl-1-benzothiazol-2-yl-3-aryl thiourea **5a-g** in acetic acid with bromine in acetic acid afforded acridin-9-yl-bis-aryl-benzothiazol-yl-amine **6a-g**. Initially compound 1-acridin-9-yl-3-aryl thiourea **3a-g** is prepared by mixture of 9-aminoacridine hydrochloride **2** and N-aryl isothiocyanate **1a-g** in presence of sodium hydroxide under microwave condition. The significant advantages offered by this procedure are fast reaction, excellent yields of products. The product obtained after usual work-up showed single spot in TLC, recrystallized form absolute alcohol in cold condition. The FTIR spectrum of the compound showed characteristic peak at 1594 cm^{-1}indicated C=N group and ^{1}H-NMR spectrum of the compound indicated signal at 7.4-7.9 ppm and 8-7.3 ppm for the presence of benzothiazole nucleus and acridinyl ring[15] respectively. Antituberculosis assay indicated that compound **7e** was found to be promising against *Mycobacterium tuberculosis* when compared to standard drug rifampin (Table-2).

MATERIALS AND METHOD

Melting points of the representative compounds were determined on a digital melting point apparatus (Veego-VMP) and are uncorrected. The 9-amino acridine (Sigma-Aldrich) and all

chemicals (S. D. Fine) used were of AR grade. Formations of the compounds were checked by TLC. The MW assisted reactions were performed in domestic microwave oven. FTIR spectra of the compounds were recorded on Perkin-Elmer spectrophotometer using KBr disc. ^{13}C-NMR spectra and ^{1}H-NMR spectra were obtained on a Bruker DRX-600 MHz spectrophotometer using TMS as internal standard. Antituberculosis activity of title compounds were studied by BACTEC radiometric method.



Preparation of 1-acridinyl-3-phenyl-thiourea (3a)

1-acridin9-yl-3-phenyl thiourea is prepared by irradiating mixture of 9-aminoacridine hydrochloride **2** (0.01M) and phenyl isothiocyanate **1a** (0.01M) in presence of sodium hydroxide in a microwave oven at 1.5 min. to afford compound **3a**, (80%), m.p. 136^{o}C. This reaction was extended to synthesize other compounds (**3b-g**) using different N-aryl-isothiocyanates **(1b-g)**.

Preparation of N-acridin-9-yl-benzothiazole-2-yl-amines (4a)

The compound N-acridin-9-yl-benzothiazole-2-yl-amines **4a** was prepared by oxidative cyclization of 1-acridinyl-3-phenyl-thiourea **3a** in acetic acid with bromine in acetic acid to afford acidic salt of hydrobromide, which on basification with aqueous ammonia free base N-acridin-9-yl-benzothiazole-2-yl-amines **4a** was obtained, (78%) m.p. 218^{o}C. This reaction was extended to synthesize (**4b-g**) using 1-acridinyl-3-aryl-thioureas **(3b-g)**.

Preparation of 1-acridin-9-yl-1-benzothiazol-2-yl-3-phenyl thiourea (5a)

1-acridin-9-yl-1-benzothiazol-2-yl-3-phenyl thiourea **5a** is prepared by irradiating mixture of N-acridin-9-yl-benzothiazole-2-yl-amines **4a** (0.02M) and phenyl isothiocyanate **1a** (0.02M) in presence of sodium hydroxide in a microwave oven at 1.5 min. to give yellowish solid. The crude solid product obtained was recrystallized from ethanol to afford compound **5a**, (75%), m.p. 128^{o}C. This reaction further extended to synthesize other compounds (**5b-g**) using different N-aryl-isothiocyanates.

Preparation of acridin-9-yl-bis-benzothiazol-yl-amine (6a)

Intra-molecular oxidative cyclization of 1-acridin-9-yl-1-benzothiazol-2-yl-3-phenyl thiourea **5a** in acetic acid with bromine in acetic acid, give yellowish solid acidic to litmus is obtained, on basification with aq. ammonia afforded free base and identified as an acridin-9-yl-bis-benzothiazol-yl-amine **6a**, (83%) m.p. 212-213^{o}C (d). Similarly compounds (**6b-g**) were synthesized using 1-acridin-9-yl-1-benzothiazol-2-yl-3-aryl thioureas **(5b-g)**.

Spectral characterization of compounds 6a-g

6a : IR (KBr), cm^{-1} : 1594 (C=N), 1487 (C=C), 1165 (C-N) ; PMR (DMSO-d_6), ppm : 7.6-7.9 (m, 8H, Acr), 7.3-7.0 (d, 8H, Ar); ^{13}C-NMR (DMSO-d_6), ppm : 124, 134, 140, (Aromatic C-atoms), 156, (C-N).

6b : IR (KBr), cm^{-1} : 3103 (C-H stretch), 1594 (C=N), 1440 (C=C), 1167 (C-N); PMR (DMSO-d_6), ppm : 7.8-8.1 (m, 6H, Acr), 7.4-7.1 (m, 3H, Ar), 2.1 (s, 3H); ^{13}C-NMR (DMSO-d_6), ppm : 124, 137, 140, (Aromatic C-atoms), 154, (C-N).

6c : IR (KBr), cm^{-1} : 3129 (C-H stretch), 1592 (C=N), 1440 (C=C), 1165 (C-N); PMR (DMSO-d_6), ppm : 7.7-7.9 (m, 8H, Acr), 7.4-6.9 (m, 6H, Ar), 2.1 (s, 3H); ^{13}C-NMR (DMSO-d_6), ppm : 127, 135, 140 (Aromatic C-atoms), 157, (C-N).

6d : IR (KBr), cm^{-1} : 3103 (C-H stretch), 1594 (C=N), 1487 (C=C), 1168 (C-N); PMR (DMSO-d_6), ppm : 7.9-8.0 (m, 8H, Acr), 7.2-7.6 (m, 6H, Ar), 2.3 (s, 3H); ^{13}C-NMR (DMSO-d_6), ppm : 124 134, 140 (Aromatic C-atoms), 156, (C-N).

6e : IR (KBr), cm^{-1} : 1595 (C=N), 1487 (C=C), 1165 (C-N); PMR (DMSO-d_6), ppm : 7.9-8.1 (m, 8H, Acr), 7.4-7.7(m, 6H, Ar); ^{13}C-NMR (DMSO-d_6), ppm : 123, 131, 140 (Aromatic C-atoms), 157, (C-N).

6f : IR (KBr), cm^{-1} : 3106 (C-H stretch), 1592 (-NO_2), 1487 (C=C), 1168 (-C-N); PMR (DMSO-d_6), ppm : 7.9-8.1 (m, 8H, Acr), 7.2-7.4 (m, 6H, Ar), 2.3 (s, 3H); ^{13}C-NMR (DMSO-d_6), ppm : 124 136, 140 (Aromatic C-atoms), 158, (C-N).

6g : IR (KBr), cm^{-1} : 1595 (C=N), 1487 (C=C), 1165 (C-N); PMR (DMSO-d_6), ppm : 7.9-8.4 (m, 8H, Acr), 7.5-7.7(m, 6H, Ar), 3.5-3.8 (s, 6H, CH_3); ^{13}C-NMR (DMSO-d_6), ppm : 123, 131, 140 (Aromatic C-atoms), 157, (C-N).

Table 1: Analytical data of synthesized compounds 6a-e

Compds/	Entry R	Mol. Formula	Mol. wt.	Yield %	m.p. ^{0}C (d)
6a	- H	$C_{27}H_{16}N_4S_2$	462	83	212-213
6b	- 4-CH_3	$C_{29}H_{22}N_4S_2$	488	85	226-227
6c	- 6-CH_3	$C_{29}H_{22}N_4S_2$	488	71	188-189
6d	- 4-Cl	$C_{27}H_{14}Cl_2N_4S_2$	528	79	236-237
6e	- 6-Cl	$C_{27}H_{14}Cl_2N_4S_2$	528	87	132-133
6f	- 4-NO_2	$C_{27}H_{14}N_6O_4S_2$	550	96	206-207
6g	- 6-OMe	$C_{29}H_{20}N_4O_2S_2$	520	90	182-183

Antituberculosis activity of compounds 6a-g

All the title compounds were evaluated for their *in-vitro* anti-tubercular screening by BACTEC Radiometric methods for determination of the MIC against *Mycobacterium tuberculosis*. For BACTEC, test compounds solutions were prepared in 10% (v/v) DMSO at a concentration of 10 mM. The medium 7H12 was containing mixture of ^{14}C labelled palmitic acid and mycobacteria inoculated and then incubated at 37^{0}C temperature. The amount of ^{14}C labeled CO_2 reflects the growth of mycobacteria and is expressed in term of the growth index (GI). On addition of test compounds, suppression of growth of *Mycobacterium tuberculosis* have been detected by routine observation. The Growth Index output when compared to the control and standard drug Rifampin of concentration 2 µg/mL).

Table 2: Antituberculosis activity of compounds 6a-g

Compounds / Entry	BACTEC (Concentration in µM)				
	50	25	12.5	6.25	3.125
6a	S	S	S	R	R
6b	S	S	R	R	R
6c	S	S	S	R	R
6d	S	S	S	R	R
6e	S	S	S	S	R
6f	S	S	R	R	R
6g	S	S	R	R	R

S = sensitive R = resistance

CONCLUSION

In conclusion we have provided a simple and efficient method for the preparation of series of acridin-9-yl-bis-benzothiazol-2-yl-amines by intra-molecular ring closure of 1-acridin-9-yl-1-benzothiazol-2-yl-3-aryl thiourea with bromine in acetic acid. These representative compounds

were evaluated for their antibacterial activity against *Mycobacterium tuberculosis* by BACTEC radiometric method. Simple work-up procedure and excellent yield of the products are the merits of the route.

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