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Microwave assisted cyclization of acridinyl thiourea into dithiazolidines and their antimicrobial study

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ABSTRACT

As a part of systematic investigation of synthesis and biological activity, several [1,2,4]- dithiazolidines were synthesized by cyclization of 1-acridin-9-yl-3aryl-thiourea with N-phenyl-S-chloro-isothiocarbamoyl chloride using microwave radiation. Constitutions of synthesized compounds have been delineated on the basis of chemical transformation, elemental analysis, equivalent weight determination, IR, ^{1}H-NMR and ^{13}C-NMR spectral studies. The title compounds were screened for their antimicrobial activity against the microorganisms like S.typhi, E. coli, B. subtilis, and S. aureus.

Keywords: MW assisted synthesis, [1,2,4]-dithiazolidines, Antimicrobial activity.

INTRODUCTION

A microwave-assisted one-pot cyclo-condensation method has been developed for the synthesis of a series of novel five member ring containing nitrogen and sulphur using an environmentally benign procedure at atmospheric pressure in open vessel [1]. Small ring heterocycles containing nitrogen and sulphur have been under investigation for a long time because of their important properties. Synthesis, structural properties and antimicrobial activities of various [1,2,4]-dithiazolidines have been reported earlier[2]. The literature survey revealed that the [1,2,4]-dithiazolidines have been found to possess potent anti-tumour, anti-tuberculosis[3], anti-diabetic and anti-cancer properties[4]. In view of utility of N-phenyl-S-chloro isothiocarbamoyl chloride in the synthesis of [1,2,4]-dithiazolidines by using 1-acridin-9-yl-3aryl-thiourea [5]. Several decades of intermittent studies exploring the reactions of important heterocycles under microwave conditions and satisfied characterizable levels of the desired heterocycles represent a medicinally and pharmaceutically important class of compounds, because of their diverse range of biological activities [6].

The present paper reports the successful development of synthesis of [1,2,4]- dithiazolidines using N-phenyl-S-chloro-isothiocarbamoyl chloride [7] based on this (Scheme1). This rapid method produced pure products in high yields within few minutes in comparison to a conventional procedure. The method for synthesis of 4-acridin-9-yl-3-arylimino-5-phenylimino-[1,2,4]-dithiazolidines is reported by using microwave irradiation method.

MATERIALS AND METHODS

The melting points of all synthesized compounds were determine on a digital melting point apparatus and were uncorrected. The structures of synthesized compounds were elucidated on the basis of elemental analysis, IR, ^{1}H-NMR and ^{13}C-NMR spectral method. ^{1}H-NMR spectra were recorded with TMS as internal standard using $CDCl_3$ and DMSO-d^6 as solvents. IR spectra recorded on Perkin-Elmer spectrophotometer in the range 4000-400cm^{-1} in nujol hydrocarbon and as KBr pellet. Microwave oven GMG20E 08 SLGX used, Purity of the compounds checked on silica gel-G plates by thin layer chromatography. Starting material (Sigma-Aldrich) and all the chemicals used were of A.R. grade.

Preparation of 1-acridin-9-yl-3-phenyl thiourea (1a) :
The compound 1-acridin-9-yl-3-phenyl thiourea **1a** was prepared by mixing of N-phenyl isothiocyanate (0.02mole) and 9-aminoacridine hydrochloride (0.02mole) in alkaline medium under microwave condition for 1 min., a solid mass was obtained. It was crystallized from ethanol and identified as a 1-acridin-9-yl-3-phenyl thiourea. This reaction was extended to synthesize other substituted thioureas using N-aryl isothiocyanates by reported method.

Preparation of 4-acridin-9-yl-3,5-bis-phenylimino-[1,2,4]-dithiazolidines (4a) :
4-acridin-9-yl-3,5-bis-phenylimino-[1,2,4]-dithiazolidines **4a** can be prepared by treating mixture of 1-acridin-9-yl-3-phenyl thiourea **1a** (0.02mole) with N-phenyl S-chloro isothiocarbamoyl chloride **2** (0.02mole) under microwave in solvent free condition, the reaction was successful in terms of yield and was completed within 2 min. 1-acridin-9-yl-3-phenyl thiourea undergo cyclisation leads to sticky mass, it was repeatedly wash with petroleum ether (40^0-60^0) followed by addition of ethanol, a solid acidic to litmus was isolated. It was crystallized from ethanol (88%) m.p. 184^0C and identified as a 4-acridin-9-yl-3,5-bis-phenylimino-[1,2,4]-dithiazolidine hydrochlorides **3a**.

On basification of **3a** with dilute ammonium hydroxide solution free base 4-acridin-9-yl-3,5-bis-phenylimino-[1,2,4]-dithiazolidine **4a** was obtained, it was crystallized from aqueous ethanol, m.p. 170^0C.

Table 2. Analytical data of MW assisted synthesis of [1,2,4]-dithiazolidines

Entry	R	Mol. wt.	m. p.	Yield
4a	C_6H_5-	462	170 ^{0}C	76 %
4b	*o*-H_3C-C_6H_4-	478	156 ^{0}C	70 %
4c	*m*- H_3C-C_6H_4-	478	154 ^{0}C	72 %
4d	*p*- H_3C-C_6H_4-	478	178 ^{0}C	64 %
4e	*o*-Cl- C_6H_4-	496.5	226 ^{0}C	80 %
4f	*m*-Cl- C_6H_4-	496.5	158 ^{0}C	74 %
4g	*p*-Cl- C_6H_4-	496.5	226 ^{0}C	72 %

Preparation of 4-acridin-9-yl-3,5-bis-phenylimino-[1,2,4]-dithiazolidine (**4a**) :
(Found: C, 68.12; N, 11.28; S, 6.98. Calcd. for $C_{27}H_{18}N_4S_2$: C, 70.12; N, 12.12; S, 7.14%) ; IR : 1550, 1342, 758, 483 cm^{-1} (S-S) [8]; ^{1}H-NMR : δ 7.14-7.46 (10H, m); ^{13}C-NMR : δ 124-128, 38-40;

Preparation of 4-acridin-9-yl-3-phenylimino-5-o-tolylimino-[1,2,4]-dithiazolidine (**4b**) :
(Found: C, 66.91; N, 11.68; S, 12.40. Calcd. for $C_{28}H_{20}N_4S_2$: C, 70.58; N, 11.76; S, 13.44%); IR: 1538, 1332, 763, 458 cm^{-1}; ^{1}H-NMR : δ 6.90-7.39 (9H, m), 2.32 (3H, s); ^{13}C-NMR : δ 124-128, 38-40 (C-N) [9];

Preparation of 4-acridin-9-yl-3-phenylimino-5-m-tolylimino-[1,2,4]-dithiazolidine (**4c**) :
(Found: C, 70.18; N, 11.70 S, 13.21 Calcd for $C_{28}H_{20}N_4S_2$: C, 70.58; N, 11.76; S, 13.44%); IR : 1550, 1338, 755, 470 cm^{-1}; ^{1}H-NMR : δ 6.98-7.40 (9H, m), 2.38 (3H, s); ^{13}C-NMR : δ 126-128, 38-40;

Preparation of 4-acridin-9-yl-3-phenylimino-5-p-tolylimino-[1,2,4]-dithiazolidine (**4d**) :
(Found: C, 66.13; N, 10.89; S, 12.55. Calcd.for $C_{28}H_{20}N_4S_2$: C, 70.58; N, 11.76; S, 13.44%); IR : 1533, 1332, 760, 458 cm^{-1}; ^{1}H-NMR : δ 7.12-7.39 (9H, m), 2.29 (3H, s); ^{13}C-NMR : δ 124-128, 38-40;

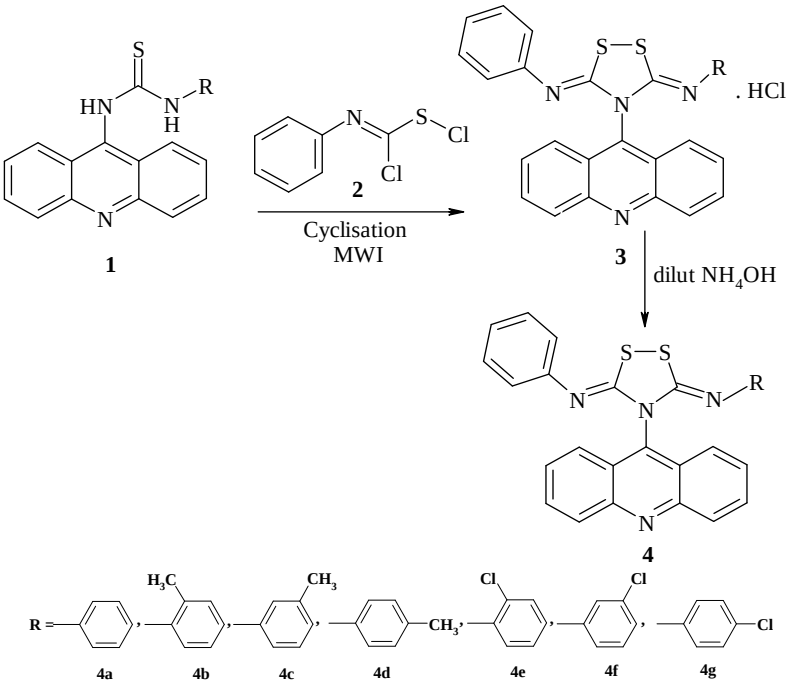
Preparation of 4-acridin-9-yl-3-(2-chlorophenylimino)-5-phenylimino-[1,2,4]-dithiazolidine ***(4e)*** *:*
(Found: C, 64.93; N, 11.18; S, 13.47. Calcd. for $C_{27}H_{17}N_4S_2Cl$: C, 65.32; N, 11.29; S, 12.90%) ; IR : 1550, 1338, 764, 483 cm^{-1}; ^{1}H-NMR : δ 7.22-7.46 (9H, m); ^{13}C-NMR : δ 124-128, 38-40;
Preparation of 4-acridin-9-yl-3-(3-chlorophenylimino)-5-phenylimino-[1,2,4]-dithiazolidine ***(4f)*** *:*

(Found: C, 65.11; N, 11.20; S, 12.86. Calcd. for $C_{27}H_{17}N_4S_2Cl$: C, 65.32; N, 11.29; S, 12.90%) ; IR : 1554, 1358, 751, 480 cm^{-1}; ^{1}H-NMR : δ 7.14-7.46 (9H, m); ^{13}C-NMR : δ 124-128, 38-40;

*Preparation of 4-acridin-9-yl-3-(4-chlorophenylimino)-5-phenylimino-[1,2,4]-dithiazolidine (**4g**) :*
(Found: C, 65.28; N, 11.26; S, 12.73. Calcd. for $C_{27}H_{17}N_4S_2Cl$: C, 65.32; N, 11.29; S, 12.90%) ; IR : 1550, 1340, 758, 483 cm^{-1}; ^{1}H-NMR : δ 7.22-7.46 (9H, m); ^{13}C-NMR : δ 124-128, 38-40;

RESULTS AND DISSCUSION

The parent compound 1-acridin-9-yl-3-aryl-thiourea (**1a)** were prepared by mixing of N-aryl isothiocynate and 9-aminoacridine hydrochloride in alkaline medium under microwave condition for 1 min., a solid mass was obtained. It was crystallized from ethanol and identified as a 1-acridin-9-yl-3-aryl thiourea, which on further treated with N-aryl-S-chloro isothiocarbamoyl chloride (**2)** under microwave radiation for 2min., afforded sticky masses, which on washing with petroleum ether gave granular solids. These were acidic to litmus and on titrimetric analysis identified as 4-acridin-9-yl-3-arylimino-5-phenylimino-[1,2,4]-dithiazolidine hydrochlorides (**3a-g**). These on basification with aqueous ammonium hydroxide solution afforded free bases (**4a-g**) respectively. The Antimicrobial study performed against *S. typhi, E. coli, B. subtilis* and *S. aureus*.



(Scheme 1)

Antimicrobial screening

The antimicrobial activities of all the synthesized compounds **(4a-g)** were performed using Kirby-Bauer method [10] against both gram-positive as well as gram-negative strains like *S. typhi*, *E. coli*, *B. subtilis* and *S. aureus.* The each well (diameter 10 mm) was loaded with 0.1 mL^{-1} of test compound solution in dimethyl sulphoxide, so that concentration of each test compound was 100µg mL^{-1}. The zones of inhibition were recorded in mm after incubation for 24 h at 37^0C. Clear inhibition zone record of the compounds indicated that (**4d**) and (**4g**) were highly active against *E. coli* and moderately active against *S. aureus* and *B. subtilis.* Majority of the compounds were found moderately against *S. typhi*.

To determine minimum inhibitory concentration (MIC), the serial dilution technique [11] was followed using nutrient broth medium. The MIC values of compounds (**4d**) and (**4g**) were determined against *E. coli* and *S. aureus* which were found to be 50 and 65 µg mL^{-1} respectively.

Table 1. Antimicrobial screening results of compounds (4a-g)

Entry	*S.typhi* mm	*E. coli* mm	*B. subtilis* mm	*S. aureus* mm
4a	10	15	13	15
4b	11	16	16	14
4c	10	16	14	15
4d	13	17	15	15
4e	-	13	15	16
4f	14	-	13	-
4g	15	18	13	12
Chloramphenicol	19	22	21	23

CONCLUSION

The present paper have been reported the successful synthesis of 4-acridin-9-yl-3,5-bis-arylimino-[1,2,4]-dithiazolidines (**4a-g**) under mild and clean conditions. This rapid method produced pure products in high yields within few minutes in comparison to a conventional procedure. The advantages of microwave in chemical reactions, such as shorter reaction times, no use of solvents could be of use in industrial applications. Antimicrobial potential study of these compounds revealed that most of the compounds showed promising antibacterial activity against gram positive and gram negative bacteria.

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