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COMPARISON OF CONVENTIONAL AND MICROWAVE–ASSISTED SYNTHESIS OF 3-THIO-4-ARYL-5-PHENYLIMINO-[1,2,4]-DITHIAZOLIDINES

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ABSTRACT

Series of 3-thio-4-aryl-5-phenyl-imino-[1,2,4]-dithiazolidines have been synthesised by the interaction of ammonium aryl dithiocarbamates with N-phenyl-S-chloro isothiocarbamoyl chloride under microwave irradiation followed by the basification with dilute ammonium hydroxide solution. These compounds were synthesized also by conventional heating for comparison. Initially ammonium aryl dithiocarbamates have been prepared by the interaction of different amines with carbondisulphide and ammonium hydroxide. Constitution of synthesized compounds have been delineated on the basis of chemical transformation elemental analysis, equivalent weight determination, IR and ^{1}H-NMR spectral studies. The title compounds were evaluated for their antimicrobial activity against the microorganisms like *S. typhi, E. coli, B. subtilis* and *S. aureus.*

KEYWORDS: Synthesis, antimicrobial activity, substituted-[1,2,4]-dithiazolidines.

I. INTRODUCTION

Microwave-assisted synthesis is a branch of green chemistry. Microwave-assisted synthesis has gained much attention in recent years. Microwave irradiation-assisted chemical transformations are pollution free, eco-friendly and offer high yields together with simplicity in processing and handling.

Synthesis, structural properties and bactericidal activities of various [1,2,4]-dithizolidines have been reported earlier.[1-5] The literature has been enriched with progressive finding about the synthesis of [1,2,4]-dithizolidines by using the reagent N-phenyl-S-chloro isothiocarbamoyl chloride.[6-9] and by oxidative cyclization using bromine and iodine.[10,11] [1,2,4]-dithizolidines have been also found to have potent anti-inflammatory and anti-tumor properties as they down regulate the NF-kB transcription factor.[12] In view of the utility of N-phenyl-S-chloro isothiocarbamoyl chloride in the synthesis of heterocyclic compounds and as a part of wider programme to provide alternative routes of synthesis both by conventional and microwave assisted, the method for synthesis of substituted 3-thio-4-aryl-5-phenyl-imino-[1,2,4]-dithiazolidines are reported.

II. MATERIALS AND METHOD

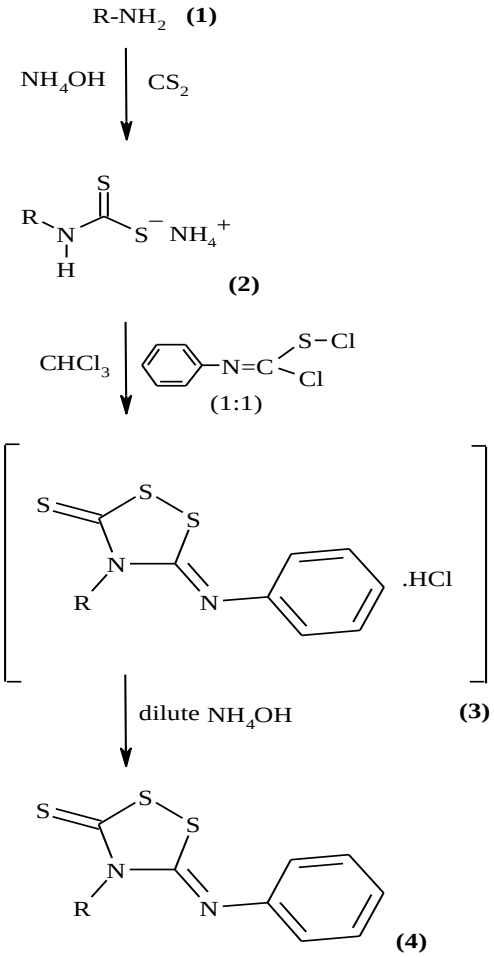
The melting points of all synthesized compounds were recorded using hot paraffin-bath and are uncorrected. Chemicals used were of A.R. grade.[1] H-N.M.R. spectra were recorded with TMS as internal standard using $CDCl_3$ and DMSO-d_6 as solvents. IR spectra were recorded on Perkin-Elmer spectrophotometer in the range 4000-400 cm^{-1} in nujol mull and as KBr pellets. Purity of the compounds was checked on silica gel-G plates by TLC.

Synthesis of ammonium phenyl dithiocarbamate (2a)
The compound ammonium phenyl dithiocarbamate (2a) was prepared by dropwise addition of aniline (1a) (9 ml) in ice cold mixture of ammonia (15 ml, density 0.88) and carbondisulphide (7.5 ml) followed by the vigorous shaking. The reaction mixture was allowed to stand for 30 minute, heavy precipitate of ammonium phenyl dithiocarbamate (2a) separates out. This reaction was extended to synthesize other substituted dithiocarbamates (2b-g) using different amines (1b-g) by reported method.[13]

Synthesis of 3-thio-4-phenyl-5-phenyl-imino-[1,2,4]-dithiazolidine (4a)
Ammonium phenyl dithiocarbamate (2a) (0.01 mol) was suspended in chloroform (15 ml). To this a solution of *N*-phenyl-*S*-chloro isothiocarbamoyl chloride (0.01 mol) in chloroform was added. The reaction mixture was microwaved at 1800W for 2 Min.30Sec. The evolution of hydrogen chloride gas was observed and chloroform was evaporated, a sticky mass was obtained. It was repeatedly washed with petroleum ether ($40\text{-}60^{0}$) followed by addition of ethanol, a solid acidic to litmus was isolated, crystallized from ethanol (80%), m.p. 149^{0} and identified as 3-thio-4-phenyl-5-phenyl-imino-[1,2,4]-dithiazolidine hydrochloride (3a).

Similarly, other compounds (3b-g) were prepared from (2b-g): 3b (75%), m.p. 167^0; c (70%), m.p. 184^0; d (75%), m.p. 181^0; e (85%), m.p. 174^0; f (70%), m.p. 188^0; g (80%), m.p. 193^0.

On basification of (3a) with dilute ammonia solution a free base (4a) was obtained, it was crystallized from aqueous ethanol, m.p. 130^0 (Found: C, 55.48; H, 3.28; N, 9.19; S, 31.66. Calcd. for $C_{14}H_{10}N_2S_3$: C, 55.62; H, 3.31; N, 9.28; S, 31.78%); ν_{max} 1550 (C=N), 1342 (C-N), 1239 (C=S), 758 (C-S), 483 cm^{-1} (S-S); δ ($CDCl_3$+DMSO-d_6) 7.14-7.46 (10H, m, Ar-H).[14,15] Similarly, free base (4b) was prepared from (3b): 4b, m.p. 149^0 (Found: C, 56.82; H, 3.73; N, 8.73; S, 30.32. Calcd. for $C_{15}H_{12}N_2S_3$: C, 56.96; H, 3.79; N, 8.86; S, 30.37%); ν_{max} 1538 (C=N), 1332 (C-N), 1263 (C=S), 763 (C-S), 458 cm^{-1} (S-S); δ ($CDCl_3$+DMSO-d_6) 6.90-7.41 (9H, m, Ar-H), 2.32 (3H, s, Ar-CH_3). This reaction was extended to synthesize other free bases (4c-g): 4c, m.p. 152^0 (Found: C, 56.70; H, 3.76; N, 8.81; S, 30.23. Calcd. for $C_{15}H_{12}N_2S_3$: C, 56.96; H, 3.79; N, 8.86; S, 30.37%); d, m.p. 158^0 (Found: C, 56.93; H, 3.69; N, 8.63; S, 30.38. Calcd. for $C_{15}H_{12}N_2S_3$: C, 56.96; H, 3.79; N, 8.86; S, 30.37%); e, m.p. 160^0 (Found: C, 49.52; H, 2.60; N, 8.21; S, 28.42. Calcd. for $C_{14}H_9N_2S_3Cl$: C, 49.92; H, 2.67; N, 8.32; S, 28.52%); f, m.p. 159^0 (Found: C, 49.63; H, 2.64; N, 8.29; S, 28.47. Calcd. for $C_{14}H_9N_2S_3Cl$: C, 49.92; H, 2.67; N, 8.32; S, 28.52%); g, m.p. 161^0 (Found: C, 49.88; H, 2.55; N, 8.30; S, 28.31. Calcd. for $C_{14}H_9N_2S_3Cl$: C, 49.92; H, 2.67; N, 8.32; S, 28.52%).



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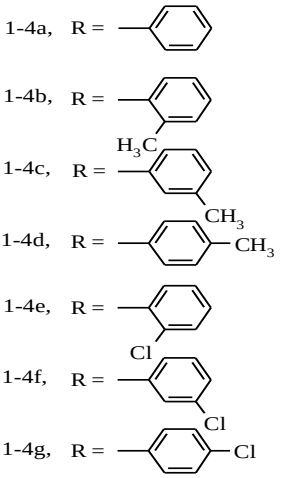

Scheme I

Table 1: Yields, Melting Points And Total Reaction Time For Synthesised [1,2,4]-Dithiazolidines (For All Synthesis 180 W Mw Was Used).

Compound	% Yield		MP (^{O}c)		Total Reaction Time	
	Conventional	MW	Conventional	MW	Conventional	MW
1-4a	78	80	129	130	2h.10 min.	4min. 30 s.
1-4b	70	75	147	149	2h.15 min.	5min. 20 s.
1-4c	65	70	150	152	2h.10 min.	4min. 40 s.
1-4d	72	75	157	158	2h.15 min.	4min. 50 s.
1-4e	80	85	159	160	2h.10 min.	4min. 30 s.
1-4f	68	70	160	159	2h.15 min.	4min. 40 s.
1-4g	74	80	160	161	2h.10 min.	4min. 50 s.

Antimicrobial Activity

The synthesized compounds (4a-g) were screened for their antibacterial activity using cup plate diffusion method.[16,17] The bacterial organisms used included both gram-positive as well as gram-negative strains like *S. typhi, E. coli, B. subtilis* and *S. aureus*. Sensitivity plates were seeded with a bacterial innoculum of $1x10^6$ CIU ml^{-1} and each well (diameter 10 mm) was loaded with 0.1 ml of test compound solution (1000 µg ml^{-1}) in dimethylformamide, so that concentration of each test compound was 100 µg ml^{-1}. The zones of inhibition were recorded after incubation for 24 h at 37^0, using Vernier caliper. Inhibition zone record of the compounds clearly indicated that 4d and 4g were highly active against *E. coli* and moderately active against *S. aureus*. Majority of the compounds were found inactive against *S. typhi* and *B. subtilis*.

To determine minimum inhibitory concentration (MIC), the serial dilution technique,[18] 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 80 and 75 µg ml^{-1} respectively.

III. RESULTS AND DISCUSSION

The compounds ammonium aryl dithiocarbamates (2a-g) were prepared by dropwise addition of different amines (1a-g) (0.6 mole) in ice cold mixture of ammonia (15 ml, density 0.88) and carbondisulphide (7.5 ml) followed by the vigorous shaking. The reaction mixtures were allowed to stand for 30 minute, heavy precipitate of ammonium aryl dithiocarbamates (2a-g) separates out.

Compounds (2a-g) were then reacted with *N*-phenyl-*S*-chloro isothiocarbamoyl chloride in boiling chloroform for 2 h. The evolution of hydrogen chloride gas was clearly noticed as tested with moist blue litmus paper. Cooling the reaction mixture and distilling off chloroform afforded sticky masses, which on washing with petroleum ether gave granular solids. These were acidic to litmus and on titrimetric analysis identified as 3-thio-4-aryl-5- phenylimino-[1,2,4]-dithiazolidine hydrochlorides (3a-g). These on basification with aqueous ammonia solution afforded free bases (4a-g) respectively.

All the Dithiazolidines derivatives were synthesized by both conventional synthesis (above method) and microwave- assisted synthesis (Table-1) and compared.

The synthesized compounds (4a-g) were screened for their antibacterial activity using cup plate diffusion method. The bacterial organisms used were *S. typhi, E. coli, B. subtilis* and *S. aureus*. Inhibition zone record of the compounds indicated that 4d and 4g were highly active against *E. coli* and moderately active against *S. aureus*. Majority of the compounds were found inactive against *S. typhi* and *B. subtilis*. The MIC values of compounds 4d and 4g were determined against *E. coli* and *S. aureus*, which were found to be 80 and 75 µg ml^{-1} respectively.

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