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Microwave-Assisted Synthesis of Novel 1,3,4-Thiadiazolyl-Substituted 1,2,4-Triazines as Potential Antitubercular Agents

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A series of triazines have been synthesized starting from 5-alkyl-1,3,4-thiadiazole-2-thioles (**1a–d**). On reaction with ethyl bromoacetate in the presence of anhydrous K_2CO_3 under microwave irradiation (MWI), these yielded corresponding esters (**2a–d**) which on hydrazinolysis under MWI produced (5-alkyl-1,3,4-thiadiazol-2-yl sulfanyl) acetohydrazides (**3a–d**). The reaction of **3a–d** with ω-bromoacetophenone under MWI yielded 6-aryl-3-[(5-alkyl-1,3,4-thiadiazol-2-yl sulfanyl)methyl]-1,2,4-triazines (**4a–h**). All the synthesized triazines showed *in vitro* antitubercular activity.

INTRODUCTION

1,2,4-Triazines have been associated with diverse pharmacological activities such as antihypertension and inhibition of platelets (*1*) and antileukemic (*2*) and anti-inflammatory (*3*) activities. Thiadiazoles are also well known for their antibacterial activity (*4*).

There is considerable interest in the rapid synthesis of a variety of heterocyclic compounds under MWI (*5*). In continuation of our work on microwave-assisted synthesis (*6–8*) of pharmacologically active heterocycles (*9*, *10*) we thought that it was worthwhile to develop a rapid synthesis of title compounds and to screen the products for antitubercular activity. The synthesis entails the union of two biologically active nuclei, viz. triazine and thiadiazole.

EXPERIMENTAL

The melting points were determined on an electrothermal apparatus and are uncorrected. IR spectra (ν_{max} in cm^{-1}) were recorded on a Perkin–Elmer Spectrophotometer Model 599 using KBr. ^1H NMR spectra were recorded on an FT NMR Hitachi R-600 instrument using $CDCl_3$ + DMSO-d_6 as solvent and Me_4Si as internal standard (chemical shifts in δ ppm). Microwave irradiations were carried out in a Padmini Essentia oven, Model Brownie at 2450 MHz, and a power of 700 W was used for each sequence of irradiation.

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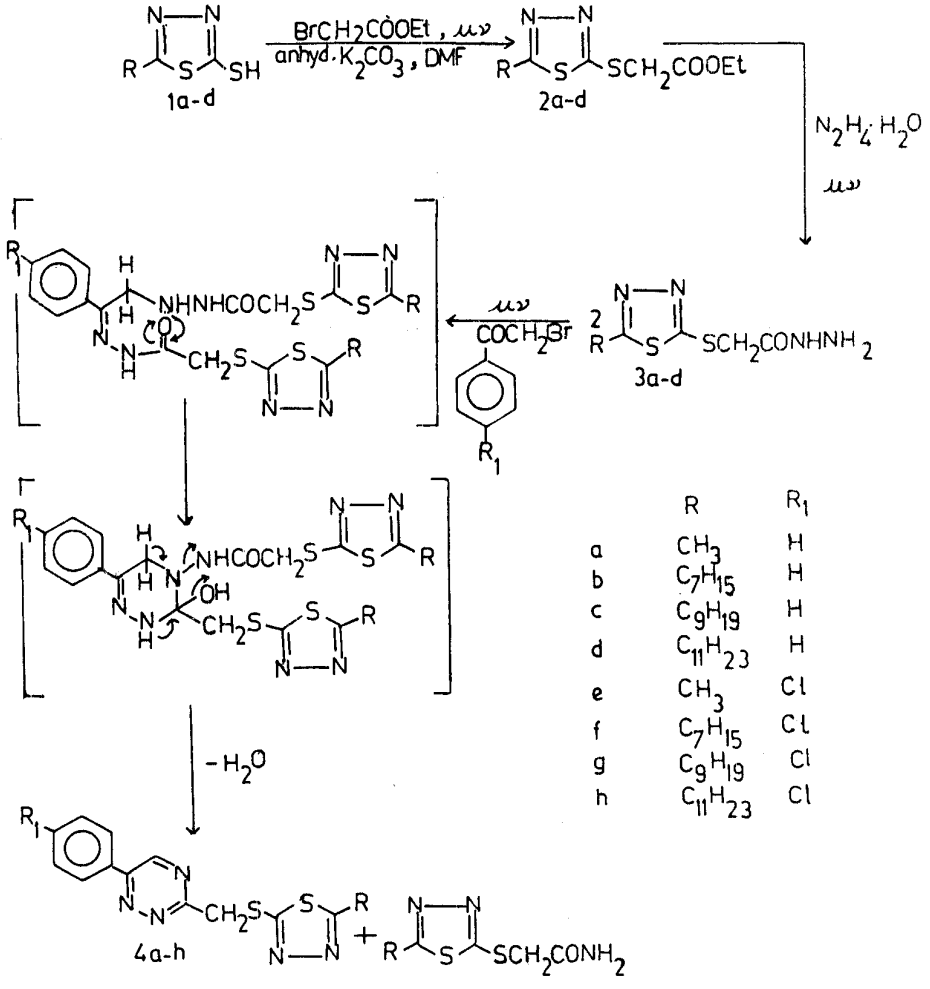

SCHEME 1

*5-Alkyl-1,3,4-thiadiazole-2-thioles (**1a–d**)*

These compounds were prepared according to the literature (*7*).

*Ethyl(5-alkyl-1,3,4-thiadiazol-2yl Sulfanyl) Acetates (**2a–d**)*

To a solution of **1a–d** (0.01 mol) in DMF (5 ml) in an Erlenmeyer flask, anhydrous K_2CO_3 (0.5 g) and ethyl bromoacetate (0.01 mol) were added. The reaction mixture was subjected to MWI for a period of 2–3 min at 2450 MHz. The inorganic salt was filtered in hot water and the filtrate was cooled, diluted with an excess of ice-cold water (100 ml), and extracted with CH_2Cl_2. The organic layer was washed with water (2×50 ml), dried over Na_2SO_4 (anhyd.) and evaporated to get the products.

TABLE 1
Physical and Analytical Data of Compounds (**2a–d, 3a–d, 4a–h**)

Compound	mp (°C)	Yield (%)	Analysis found (calcd) (%)		
			C	H	N
2a[7]	—	86	38.62(38.53)	4.51(4.58)	12.84(12.84)
2b	—	83	51.59(51.66)	7.24(7.28)	9.24 (9.27)
2c	—	82	54.58(54.54)	7.81(7.88)	8.56 (8.48)
2d	—	83	57.06(56.98)	8.31(8.38)	7.86 (7.82)
3a[7]	126	85	29.45(29.41)	3.96(3.92)	27.42(27.42)
3b	117–118	79	45.86(45.83)	6.98(6.94)	19.12(19.44)
3c	105–117	78	49.31(49.37)	7.51(7.59)	17.78(17.72)
3d	95–96	77	52.38(52.33)	8.18(8.14)	16.21(16.28)
4a	178–179	84	51.88(51.83)	3.61(3.65)	23.21(23.26)
4b	161–163	76	59.12(59.22)	6.05(5.97)	18.08(18.18)
4c	154–155	74	61.11(61.02)	6.61(6.54)	16.91(16.95)
4d	143–144	75	62.51(62.59)	7.08(7.03)	15.95(15.87)
4e	173–174	86	46.59(46.50)	2.91(2.98)	20.82(20.86)
4f	158–159	79	54.38(54.35)	5.25(5.24)	16.61(16.69)
4g	151–152	77	56.24(56.31)	5.74(5.81)	15.71(15.64)
4h	138–139	76	58.11(58.04)	6.79(6.31)	14.61(14.72)

*(5-Alkyl-1,3,4-thiadiazol-2yl Sulfanyl) Acetohydrazides (**3a–d**)*

A solution of **2a–d** (0.01 mol) and hydrazine hydrate (99%, 0.01 mol) in absolute ethanol was subjected to MWI for 1.5–2.0 min. The reaction mixture was cooled, and the solid was separated, filtered, dried, and recrystallized with ethanol.

*6-Aryl-3-[(5-alkyl-1,3,4-thiadiazol-2yl sulfanyl)methyl]-1,2,4-triazine (**4a–d**)*

A mixture of **3a–d** (0.02 mol) and phenacyl bromide (*12*)/4-chlorophenacyl bromide (0.01 mol) in DMF (5 ml) was subjected to MWI for 5–6 min. The reaction mixture was cooled and poured over crushed ice; the solid was separated, filtered, washed with water, and recrystallized with a DMF–EtOH mixture.

BIOLOGICAL ACTIVITY

The compounds were screened at 100 and 50 μg/ml concentrations for their *in vitro* antitubercular activity by twofold serial dilutions against *Mycobacterium tuberculosis* ATCC 27294. The desired concentrations of each compound were prepared aseptically with the help of their respective solvents. Sterilized Middlebrook's 7H10 (Difco) medium was dispensed in tubes and OADL (oleic albumin dextrose catalase) was added to each medium tube. Aseptically, 0.1 ml of each concentration of compound was added into the medium.

Fresh growth of *M. tuberculosis* ATCC 27294 was harvested, homogenized, and