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Synthesis and Antimicrobial Activity of 1,3-Thiazines

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Nitrochalcones react with thiourea or diphenylthiourea in alkaline medium to give 1,3-thiazines in 3 h and yields are found to be 50–60%. The same reaction was carried out in DMSO medium in presence of sodium methoxide and it was interesting to find that the reaction takes place in 15 min and gives better yield. 1,3-Thiazines possess antibacterial and antifungal properties when assayed against the test organisms.

INTRODUCTION

It was reported that thiourea reacts with mesityl oxide in acetic acid medium to give 2-imino-6H-2,3-dihydro-1,3-thiazines and 2-thioxo tetrahydro pyrimidine[1]. Similarly 6-hydroxy-4-methoxy-5-aryl-acryloyl benzo(b) furans react with thiourea in alkaline medium afforded corresponding to 1,3-thiazines[2]. 1,3-Thiazines act as potential fungicides[3]. Literature survey indicates that 1,3-thiazines were not prepared from nitrochalcones; therefore it was thought interesting to carry out these reactions and to find microbial activities against test organism as antibacterial and antifungal agents.

EXPERIMENTAL

2-Hydroxy-5-methyl-3′-nitrochalcone (1a) (0.01 mol) and thiourea (0.02 mol) dissolved in ethanol (30 ml). To this aqueous KOH solution (0.02 mol) was added. The reaction mixture was refluxed for 3 h, cooled, diluted with water and acidified with 1 : 1 HCl. The product obtained was crystallised from ethanol to get compound (2a) m.f. $C_{17}H_{15}N_3O_3S$, m.pt. 245°C, yield 60%, % analysis: Found (Calcd.) N = 12.52 (12.35), S = 9.50 (9.41); R_f value in benzene is 0.45.

It gives brown colouration with neutral $FeCl_3$ solution indicating the presence of free phenolic –OH group and deep blue colouration with conc. H_2SO_4 showing the absence of $-\overset{\overset{O}{\|}}{C}-CH=CH$ linkage.

IR (Nujol) bands (cm^{-1}): 3440 (–OH), 1620 (>C=N), 2800–3000 (C–H), 1585 (–NH), 1540 and 843 (Ar–NO_2), 1268 (C–N). PMR ($CDCl_3$): 2.5 (S, 3H,

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Ar–CH_3), 3.25 (d, 1H, –C–CH–S); 5.24 (d, 1H, –C=CH, 6.52–7.33 (m, 7H, Ar–H); 8.03 (S (br), 2H, N-H), 11.55 δ (S, 1H, Ar–OH)

From analytical data, spectral data and chemical analysis the compound 2a assigned a structure as 4-(2′-hydroxy-5′-methyl)-6-(3-nitrophenyl)-2-imino-6H,2,3-dihydro-1,3-thiazines.

The other thiazines are prepared by the same method as listed in Table 1.

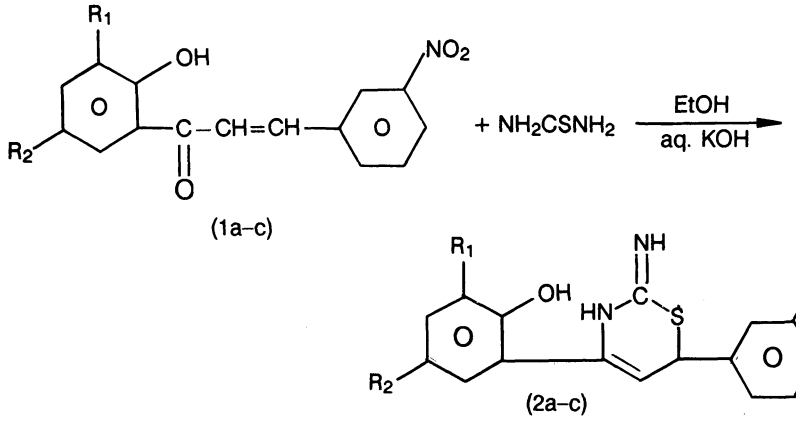
2-Hydroxy-5-methyl-3′-nitrochalcone (1a) (0.01 mol) and diphenyl thiourea (0.02 mol) dissolved in ethanol (30 ml). To this aqueous KOH solution (0.02 mol) was added. The reaction mixture was refluxed for 3 h, cooled, diluted with water and acidified with 1 : 1 HCl. The product obtained was crystallised from ethanol to get 4-(2′-hydroxy-5′-methyl)-6-(3-nitrophenyl)-2-imino-6H,2,3 diphenyl-1,3-thiazines (3a), m.pt. 161°C, yield 63%. R_f in benzene is 0.81.

IR (Nujol) bands (cm^{-1}): 3348 (–OH), 1663 (>C=N), 1510 (Ar–NO_2), 1042 (C–N), 1320 (O–H bending). PMR ($CDCl_3$): 2.30 (S, 3H, Ar–CH_3), 3.20 (d, 1H, –C–CH–S), 5.15 (d, 1H, –CC=CH–), 6.2 to 7.76 (m, 17 H, Ar-H), 10.42 δ (S, 1H, Ar-OH).

The other 1,3-thiazines are prepared by the same method listed in Table 1.

Modified Method

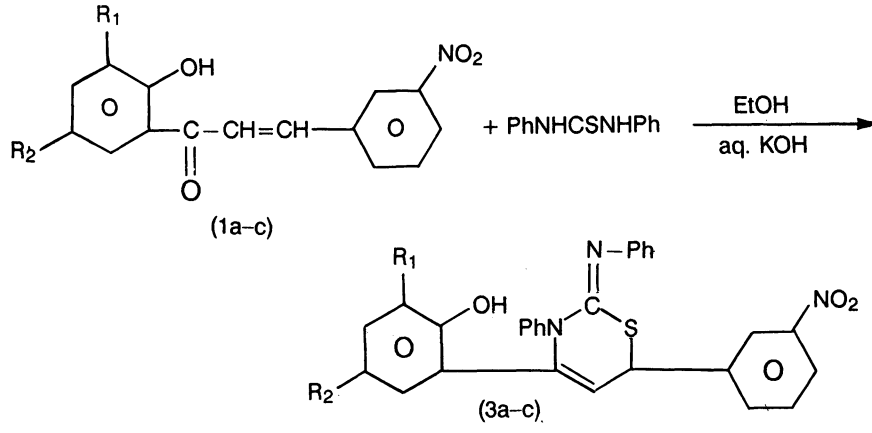
Nitrochalcones (1a-c) (0.01 mole) and thiourea (0.02 mol) or diphenyl thiourea (0.02 mol) was dissolved in DMSO (25 ml) containing a little sodium methoxide (0.01 g). The reaction mixture was refluxed for 15 min, cooled, diluted with water and acidified with 1:1 HCl. The product thus obtained was crystallised from ethanol to get (2a-c) and (3a-c), yield 80–90%.



2a: R_1 = H; R_2 = CH_3; 2b: R_1 = NO_2; R_2 = CH_3; 2c: R_1 = H; R_2 = Cl

Antimicrobial Activity

For testing the antimicrobial activity, the compounds 2a-c and 3a-c were assayed against the test organisms *Salmonella typhi, Salmonella paratyphi, Proteus vulgaris, Xanthomonas* spp, *Fusarium solanii* and *Botrytis cincera*. The



3a: $R_1 = H$; $R_2 = CH_3$; 3b: $R_1 = NO_2$; $R_2 = CH_3$; 3c: $R_1 = H$; $R_2 = Cl$;

minimum inhibitory concentration (MIC) values were determined by serial dilution method[4]. These compounds were insoluble in water and hence dissolved in methanol. The comparative study of MIC values of 1,3 thiazines is given in Table 1.

TABLE 1
MINIMUM INHIBITORY CONCENTRATION OF COMPOUNDS (MIC IN %)

Compound	S. typhi	S. paratyphi	P. vulgaris	X. spp.	F. solanii	B. cinerea	M.pt (°C)	Yield in Ethanol %	Yield in DMSO %	R_f Value in benzene
2a	0.03	0.032	0.02	0.03	0.03	0.032	254	60	80	0.45
2b	0.02	0.02	0.02	0.022	0.027	0.02	174	58	75	0.55
2c	0.04	0.04	0.02	0.04	0.032	0.038	184	55	72	0.48
3a	0.06	0.075	0.069	0.05	0.096	0.113	161	62	75	0.81
3b	0.09	0.07	0.09	0.07	0.07	0.087	179	62	75	0.67
3c	0.075	0.06	0.05	0.05	0.062	0.07	111	60	80	0.78

All thiazines show good inhibitory activities against both fungal and bacterial species. The MIC values of compound 2a range from 200–300 microgm ml^{-1}, 2b have range 200 microgm ml^{-1}, 2c have range 200–400 microgm ml^{-1}. Addition of phenyl group resulted in lowering the activities of compound 3a-c. The MIC values of compound 3a range from 600–1130 microgm ml^{-1}, 3b have range 700–900 microgm ml^{-1} and 3c have range 500–750 microgm ml^{-1}.

All bacterial species used in present investigation are known human pathogens. *Salmonella typhi* causes typhoid, and *Salmonella paratyphi* causes paratyphoid in human beings. *Proteus vulgaris* is known for causing urinary track infections. The fungal species used in the present investigation are known plant pathogens. The compound synthesised may find application in therapeutic

purpose in human diseases and may also help in controlling plant diseases provided they are nontoxic to human body and plant body.

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