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A CONVENIENT SYNTHESIS AND BIOCIDAL ACTIVITY OF (N-ALKYL/ARYL SULPHONAMIDO)-4H-BENZ [d] OXAZIN-2-ONE DERIVATIVES

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Keywords:

CSI, Cycloaddition, bis-electrophilic, Chlorosulphonyl isocyanate, Sulphonamide, benzoxazines, fungicides, herbicides

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ABSTRACT: Compounds with a 2(H)-1, 4-benzoxazin-3(4H)-one skeleton have attached the attention of phytochemistry researchers since 2, 4-dihydroxy-(2H)-1,4-benzoxazin-3(4H) and 2,4-dihydroxy-7-methoxy-(2H)-1,4-benzoxazin-3(4H)-one were isolated from plants belonging to the Poaceae family. These compounds exihibit interesting properties11 such as phytotoxic, antimicrobial12, antifeedent, antifungal and insecticidal properties. The reaction of CSI with 2-Chlorobenzyl alcohol result in N-chlorosulphonyl derivatives, which show antibacterial potency. Futher, N-chlorosulphonyl derivatives can be easily cyclofunctionalized. This cyclofunctionalization has been exploited in the synthesis of the title compounds (3). Thus, the title compound being oxygen analogues of 1, 3-thiazine derivatives together with N-sulphonamide moiety could be expected to exhibit enhanced bioactivities14-18.

INTRODUCTION: Chlorosulphonyl isocyanate (CSI) undergoes cyclo addition reaction with alcohols, thiols, phenols and amines[1]. Many heterocyclic compounds have been synthesised from readily available starting materials by using the high reactivity of CSI and its bis-electrophilic character. Some N-substituted oxazolidine-2ones[2,3] have been found to display antibacterial and antifungal activity. 1, 3-Thiazine nucleus has been very extensively used for designing various pharmacological agents of Agro-Chemicals[4-8]. The reaction of CSI with 2-Chlorobenzyl alcohol result in N-chlorosulphonyl derivatives, which show antibacterial potency[9]. Futher, N-chlorosulphonyl derivatives can be easily cyclofunctionalized. This cyclofunctionalization has been exploited in the synthesis of the title compounds (3).

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Thus, the title compound being oxygen analogues of 1, 3-thiazine derivatives together with N-sulphonamide moiety[14] could be expected to exhibit enhanced bioactivities.

MATERIAL AND METHODS: (N-Alkyl/Aryl sulphonamide)-4H-Benz [d]oxazin-2-ones (3) synthesised by the cyclization N-(2-chlorobenzyloxy carbonyl) sulphonyl chloride (2) and substituted alkyl/aryl amines, in presence of triethylamine. N-(2-chlorobenzyloxy carbonyl) sulphonyl chloride was prepared by the reaction of 2-chloro benzyl alcohol and CSI. Three of the compounds (3d, 3e and 3i) displaced the invitro fungitoxicity equivalent to that of a commercial fungicide Mancozeb against *Cephalosporium saccharii* and *Aspergillus niger* at 100 ppm concentration and herbicidal activity equivalent to that of a commercial herbicide 2,4-D against barnyard grass, Velvet leaf and Foxtail green.

Melting points were determined in open glass capillary and are uncorrected. The IR spectra in KBr recorded on a Perkin Elmer-993 infrared spectrophotometer (γ_{max} Cm^{-1}). The PMR spectra

were recorded on Varian EM (200 MHz) spectrometer in DMSO-d_6 using TMS as an internal reference. Chemical shift are expressed in δ-ppm. Procedure for each step has been described.

N - (2-chlorobenzyloxycarbonyl) sulphonyl chloride (2): This was prepared according to the method of Montero et al. Thus, 2-chlorobenzyl alcohol (0.1 M) and CSI (0.1 M) were stirred at room temperature in dichloromethane (25 mL) for 3 hrs. The stirred mixture poured into ice-water, the solid thus obtained was washed with water and crystallized from ethanol.

Yield 68%, m.p. 105^{0}C. Rf = 0.62; CH_2Cl_2: MeOH: AcOH (10:5:2). IR (KBr) γ_{max} Cm^{-1}: 1245, 1190 (C-O-C), 1680 (C=O), 3320 (-NH) (SO_2Cl). PMR (DMSO-d_6): δ 2.98 (d, 2H, CH_2), 7.12 – 7.92 (m 4H, ArH), 9.24 (s, 1H, -NH).

N-(4-Chlorophenyl sulphonamide)-4H-benz [d] oxazin-2-one (3d) - N-(2-Chlorobenzyloxy carbonyl sulphanyl chloride (0.01 M) and 4-chloro aniline (0.014 M) were stirred at 50-60^{0}C in dichloromethane for 5 hrs. Yellowish crystalline solid obtained was further cyclised qualitatively in the presence of triethylamine to desire product. The product poured into water and the solid thus obtained crystallise with ethanol and dried.
Yield 57%, m.p. 160^{0}C, Rf = 0.60, CH_2Cl_2: MeOH: AcOH (10:5:2). IR (KBr) γ_{max} $Cm^{-1:}$ 1350 (-SO_2NH), 1720 (C=O cyclic). PMR (DMSO-d_6): 7.62 – 8.32 (m, 8H, ArH).

The physical characterization data of other compounds are recorded in **Table 1**.

TABLE 1: PHYSICAL CHARACTERISATION DATA OF COMPOUND (3).

Compound (3)	R / Ar	Yields (%)	m.p. (^{0}C)
a	C_2H_5	58	128
b	C_3H_7	52	132
c	C_6H_5	58	145
d	4-ClC_6H_4	57	160
e	2,4-$Cl_2C_6H_3$	62	205
f	4-$NO_2C_6H_4$	50	168
g	4-$CH_3C_6H_4$	53	149
h	2-$CH_3C_6H_4$	48	158
i	2-ClC_6H_4	45	178

Fungicidal Activity- The fungicidal activity of each compound was evaluated against *C. sacchari* and *A. niger* by Agar growth technique[10] at 100 ppm and 10 ppm concentration. The inhibitory activity of commercial fungicide Mancozeb was also tested against above mentioned fungi for comparison. The fungicidal activity of the tested compound is recorded in **Table 2**.

TABLE 2: BIOCIDAL ACTIVITY OF COMPOUND (3)

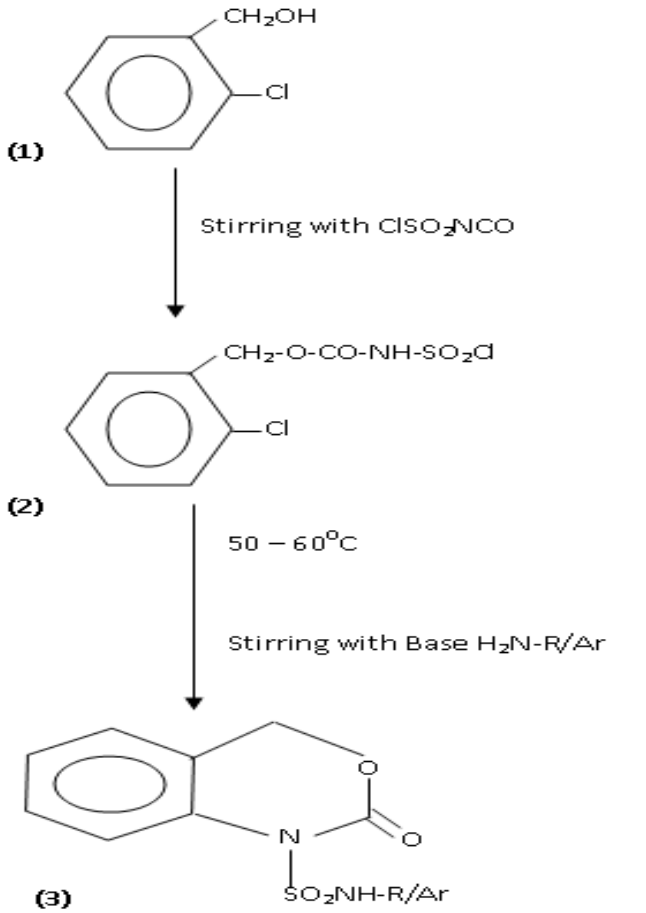
	Fungicidal Activity Against				Herbicidal activity against					
	C. saccharii		*A. niger*		Siol Treatment			Foliar Treatment		
	100ppm	10ppm	100ppm	10ppm	B.g.	V.l.	F.g.	B.g.	V.l.	F.g.
3a	52	38	52	22	2	2	1	1	1	1
3b	53	32	50	38	2	2	2	2	1	1
3c	68	40	63	38	3	2	2	2	2	1
3d	100	76	98	65	5	4	5	4	3	3
3e	100	72	96	60	4	4	5	3	4	4
3f	93	68	80	52	5	5	5	4	5	4
3g	72	53	70	40	3	3	2	3	3	3
3h	78	51	72	41	4	2	4	2	2	2
3i	96	70	88	53	4	5	4	4	3	4
Mancozeb	100	78	100	75	*	*	*	*	*	*
2,4-D	*	*	*	*	5	5	5	5	5	5

Herbicidal Activity: Barnyard grass, Velvet leaf and Foxtail green were tested. This test was achieved by pre-emergence application at 5 Kg ha^{-1} of each compound, as aqueous emulsion in 5% DMF and 0.15% surfactant mixture {poly (oxyethelene) styryl phenyl ether; calcium dodecyl benzene sulphonate and xylene}. 10 mL of this solution was sprayed on the soil surface of polyethylene pots were maintained at 25^{0}C in a green house for 3 weeks. The herbicidal activity was determined by rating the level of plant response.

Foliar treatment – Barnyard grass, Velvet leaf and Foxtail green were tested. The test was achieved by foliar spray 5 Kg ha^{-1} of each compound, in aqueous emulsion in 7% acetone and 0.3% surfactant mixture. 4 mL of this emulsion was

sprayed on to the foliage of 8-10 days old 9 plants grown in polyethylene pots (10 cm x 10 cm). This experiments was conducted in a green house for 2 weeks and phytotoxic activity was determined by the above method **(Table 2).**

SCHEME - 1



RESULTS AND DISCUSSIONS:

Fungicidal Activity- The fungicidal activity of the test compounds revealed moderate toxicity to both the test fungi and toxicity decreased upon dilution. The fungitoxicity of the test compounds may be due to presence of >C=O group and $–SO_2NH$ group, toxophoric importance of which is well known. The compounds 3d, 3e, 3f and 3i showed potent fungitoxicity of appreciable order, may be due to presence of –Cl and $-NO_2$ group in aryl moiety, which is additive function to the activity of these compounds.

Herbicidal Activity – The herbicidal data indicates that the compounds 3d, 3e and 3f were promising herbicides. A perusal of structure of these compounds indicates that some of them had at least one polar group i.e. –Cl, NO_2 etc. This indicates that presence of chloro substituent imparted herbicidal power to this series of compounds. The two compounds 3d, 3f were most active and their activity was comparable to the commercial herbicide 2, 4-D. Further screening of the two compounds a wider range of herbs is suggested.

CONCLUSIONS: The fungitoxicity of the test compounds may be due to presence of >C=O group and $–SO_2NH$ group, toxophoric importance of which is well known. The compounds **3d**, **3e**, **3f** and **3*i*** showed potent fungitoxicity of appreciable order of Mancozeb M-45. The two compounds **3d**, **3f** were most active and their activity was comparable to the commercial herbicide 2, 4-D.

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