

Synthesis of Some 3-(Substituted Phenyl)-1,2,4-Triazolo-6-[Alkyl/Halide/Alkoxy Substituted Phenyl]-[3,4-b] [1,3,4] Thiadiazoles

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Condensation of 3-(substituted)-4-amino-5-mercapto-1,2,4-triazole and alkyl/alkoxy/halide substituted carbonyl chloride in presence of phosphoryl chloride yields 3-(substituted phenyl)-1,2,4-triazolo-6-(substituted phenyl)-[3,4-b] [1,3,4] thiadiazoles. Their structures have been established by chemical analysis and spectral data.

Key Words: Synthesis, Substituted thiadiazoles.

INTRODUCTION

The survey of literature revealed that s-triazolo [3,4-b] [1,3,4] thiadiazoles, an interesting fused system of s-triazole and 1,3,4-thiadiazole rings, has received much attention during recent years on account of its prominent utilization as antifungal, anti-inflammatory, anti-viral, analgesic and anthelmintic agent¹⁻⁴. During past years considerable evidence has been accumulated to demonstrate the efficacy of 1,3,4-thiadiazolein inducing antibacterial, amebicidal, antifungal, insecticidal, CNS depressant and antitumor activities when fused to an s-triazolo ring system. El-Khawass *et al.*⁵ have reported the anthelmintic activity of a series of triazolothiadiazoles which are structurally and isosterically related to tetramisole, the established anthelmintic agent, against third stage larvae of *Acylostoma caninum*. The observations quoted are encouraging enough to stimulate further investigation in this direction.

EXPERIMENTAL

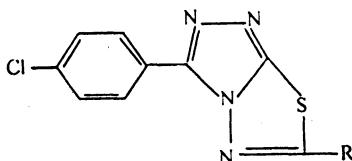
Infrared spectra (KBr) were recorded on FT-IR spectrophotometer and PMR spectra on a R24-B Hitachi (60 MHz) spectrophotometer using TMS as an internal standard.

Preparation of title compounds: A mixture of crude aminothiolo (0.01 mole) and the appropriate substituted carbonyl chloride (0.01 mole) in phosphoryl chloride (20 mL) was refluxed for 5 h. The excess phosphoryl chloride was

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removed under reduced pressure and the residue was added to crushed ice. The mixture was stirred at room temperature for 1 h, during which time the solution was gradually neutralized with solid sodium bicarbonate. The precipitated solid product was filtered, washed with diluted aqueous solution of sodium bicarbonate (20%) and water. The collected solid was dried and crystallized⁶; m.p. and yield obtained for each compound are mentioned in Table-1.

TABLE-1
3-(*p*-CHLOROPHENYL)-1,2,4-TRIAZOLO-6-(SUBSTITUTED PHENYL)-[3,4-*b*] [1,3,4]
THIADIAZOLE



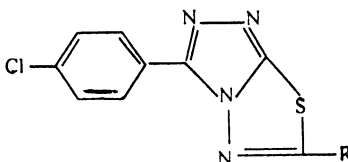
Substituents (R)	Yield (%)	m.p. (°C)	% Found (Required)		
			C	H	N
4-Fluorophenyl	50	≥ 250°C	54.16 (54.46)	2.15 (2.45)	16.64 (16.94)
2-Fluorophenyl	55	183–85°C	54.06 (54.46)	2.05 (2.45)	16.54 (16.94)
3,4-Dichlorophenyl	56	83–84°C	42.96 (43.06)	1.61 (1.91)	13.19 (13.33)
Cyclopropyl	45	98–100°C	45.60 (45.99)	2.89 (3.19)	17.58 (17.88)
4-Methoxyphenyl	59	196–98°C	55.65 (56.05)	2.91 (3.21)	16.05 (16.35)
Cinnamoyl	57	193–95°C	59.86 (60.26)	2.94 (3.24)	16.34 (16.54)
Cyclohexyl	60	132–34°C	56.33 (56.69)	4.40 (4.40)	17.23 (17.63)
Thiophenyl	61	98–101°C	48.57 (48.97)	1.99 (2.19)	17.28 (17.58)
3,4-Dimethoxy phenyl	52	217–219°C	54.36 (54.76)	3.18 (3.48)	14.83 (15.03)
N,N-Diethyl	53	148–150°C	50.43 (50.73)	4.35 (4.55)	22.36 (22.76)
N,N-Dimethyl	60	168–70°C	49.51 (49.71)	3.46 (3.76)	20.99 (21.09)
4-Trifluoromethyl phenyl	61	228–30°C	50.05 (50.45)	1.70 (2.10)	14.31 (14.71)

PMR spectrum of 3-(*p*-chlorophenyl)-3,6-(substituted phenyl)-[3,4-*b*] [1,3,4]thiadiazole showed the following absorptions: a triplet at δ 1.30–1.40 and a

quartet at 3.49–3.56 due to the ethyl protons of $-\text{CH}_2\text{CH}_3$. Aromatic protons appear as a duplet between δ 7.40–8.25.

Prepared compounds were subjected to antitubercular testing; moderate activity was observed for all fluorosubstituted compounds. In antibacterial testing compounds **5**, **6**, **8**, **10**, **11** and **12** showed moderate activity. No promising results were observed when tested for antifungal testing. All compounds were screened by tube dilution method. All compounds were also screened for *in vivo* anthelmintic activity against *Hymenolepis nana* in albino mice described by Agrawal *et al.*⁷ Anthelmintic screening showed variable results. Three substitutions, *i.e.*, cinnamoyl, 4-trifluoromethyl and 3,4-dichlorophenyl, seem to be very active, *i.e.*, per cent efficacy is more than 70% as mentioned in Table-2.

TABLE-2
ANTHELMINTIC ACTIVITY OF 3-(*p*-CHLOROPHENYL)-1,2,4-TRIAZOLO-6-
(SUBSTITUTED PHENYL)-[3,4-b][1,3,4] THIADIAZOLES

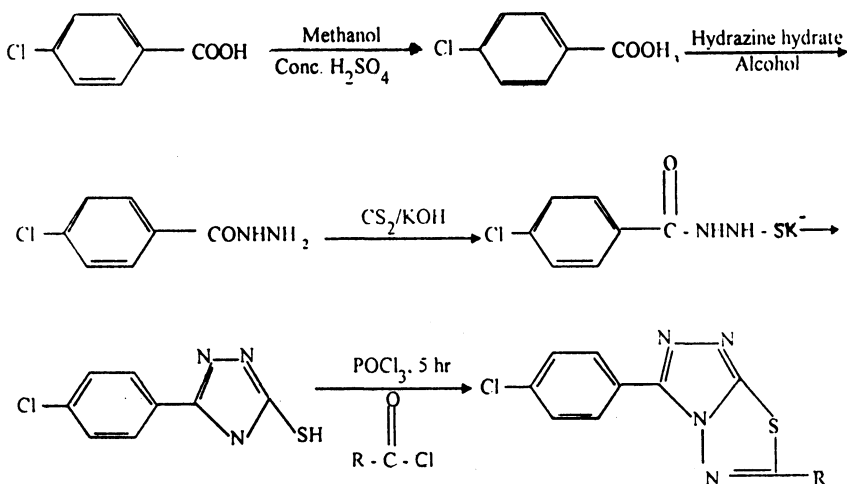


Substituents (R)	% efficacy (Single dose 250 mg/kg)
N, N-Diethyl	58.18
N, N-Dimethyl	50.00
Cinnamoyl	73.63
4-Methoxy phenyl	61.81
4-Trifluoromethyl phenyl	75.45
3,4-Dimethoxy phenyl	60.90
2-Fluorophenyl	61.81
4-Fluorophenyl	60.00
3,4-Dichlorophenyl	72.72
Cyclopropyl	64.54
Thienyl	65.45
Cyclohexyl	62.72

RESULTS AND DISCUSSION

p-Chloromethyl benzoate was prepared by esterification of *p*-chlorobenzoic acid in the presence of concentrated sulphuric acid in methanol. This *p*-chloromethyl benzoate was then reacted with hydrazine hydrate to give hydrazide of the *p*-chloromethyl benzoate which further gave potassium salt by reacting

with potassium hydroxide forming triazole. This aminothiole further by reaction with different substituted acid chlorides in presence of phosphoryl chloride gave rise to [3,4-b] [1,3,4] thiadiazole. During this reaction the mixture was stirred at room temperature for 1 h and the solution was gradually neutralized with sodium carbonate. Precipitated product was filtered, washed with diluted aqueous solution of sodium bicarbonate and water. TLC examination of this product showed the presence of only a single component. In all cases studied, the chromatogram showed only one product.



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