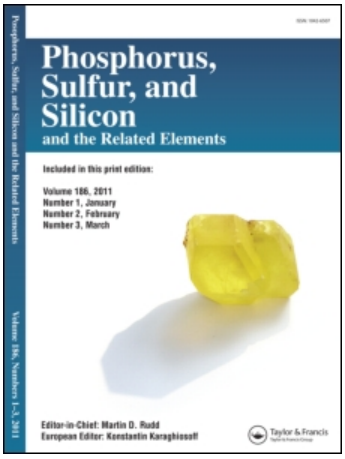

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

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Online publication date: 27 October 2010

To cite this Article Holla, B. Shivarama , Bhat, K. Subrahmanya and Shetty, N. Suchetha(2003) 'Synthesis of Some New Fluorine Containing Thiadiazolotriazinones as Potential Antibacterial Agents', Phosphorus, Sulfur, and Silicon and the Related Elements, 178: 10, 2193 — 2199
To link to this Article: DOI: 10.1080/713744567
URL: http://dx.doi.org/10.1080/713744567

Phosphorus, Sulfur, and Silicon, 178:2193–2199, 2003

ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/10426500390228864

SYNTHESIS OF SOME NEW FLUORINE CONTAINING THIADIAZOLOTRIAZINONES AS POTENTIAL ANTIBACTERIAL AGENTS

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(Received February 19, 2003; accepted April 24, 2003)

2,4-dichloro-5-fluorophenyl, 4-fluoro-3-(Phenoxy)phenyl, 4-fluorophenyl groups are known pharmacophores and can be used in the synthesis of new biologically active molecules. Therefore, 4-amino-6-arylmethyl-3-mercapto-1,2,4-triazin5(4H)-ones ***1*** *are condensed with 3-phenoxy-4-fluoro-benzoic acid, 2,4-dichloro-5-fluorobenzoic acid, and 4-fluorobenzoic acid* ***2*** *to give 7-substituted-3-arylmethyl-4H-1,3,4-thiadiazolo[2,3-c]-1,2,4-triazin-4-ones* ***3****. Phosphorous oxychloride was used as cyclizing agent. All the newly synthesized compounds* ***3a-l*** *was screened for their antibacterial activities. Most of them showed promising activity in the range of 10 μg/mL concentrations.*

Keywords: Antibacterial activity; fluoroheterocycles; thiadiazolotriazinones

Several thiadiazoles find important application in medicine, agriculture, and industry. Triazinones also are used as effective herbicides and fungicides.[1–4] In continuation on our studies on the synthesis of biologically active thiadiazolotriazinones[5] and in an attempt to significantly improve their antibacterial activity, we considered substitution at C-7 position by fluorophenyl moieties. Our earlier attempt of modifying the structure by halophenylfuranyl moiety significantly enhanced their antibacterial activity.[6] It has been reported that substitution of hydrogen or methyl group in a biologically active unit by a fluorine or trifluromethyl group enhances the biological activity.[7] It was hoped

We would like to thank RSIC, IIT Madras for spectral data. KSB is thankful to CSIR, New Delhi for the award of Junior Research Fellowship. We are also thankful to Rallies India Ltd., Bangalore for gift sample of 4-fluoro-3-phenoxybenzaldehyde.

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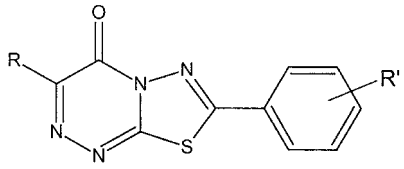
that these compounds (Structure **3**), would improve the antibacterial activity due to the introduction of 2,4-dichloro-5-fluorophenyl, 4-fluoro-3-(Phenoxy)-phenyl, and 4-fluorophenyl substitutions at position-7 of thiadiazolotriazinones. Further it is known that incorporation of fluorine atom in the ring modifies its properties by enhancing the solubility and thermal stability.[8–9]



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RESULTS AND DISCUSSION

For the present work four 6-arylmethyl-4-amino-3-mercapto-1,2,4-triazin-6(4H)-ones (R = 4-chlorobenzyl, piperanylbenzyl, 2,4-dichlorobenzyl) were prepared by condensing the respective azalactones with thiocarbohydrazide or by reaction of arylpyruvic acid with thiocarbohydrazide.[10] The 6-*tert*-butyl-4-amino-3-mercapto-1,2,4-triazin-5(4H)-one was obtained commercially used after recrystallization from ethanol. The required 4-fluoro-3-phenoxy-benzoic acid was prepared from its aldehyde by oxidation using hydrogen peroxide/acetic acid mixture. 2,4-Dichloro-5-fluorobenzoic acid was prepared from 2,4-dichloro-5-fluoro acetophenone by haloform reaction, whereas 4-fluorobenzoic acid was obtained commercially. The triazinones were then condensed with fluorine containing acids in the presence of phosphorous oxychloride-acetonitrile/dry toluene to afford 7-(substituted phenyl)-3-arylmethyl/*tert*-butyl-4H-1,3,4-thiadiazolo[2,3-*c*]-1,2,4-triazin-4-ones in 75–90% yield. Formation of these thiadiazolotriazinones was confirmed by elemental analysis, IR, ^{1}H NMR, and mass spectral data. In the IR spectrum of compound **3b** showed characteristic absorptions at 3100(Ar—CH str.), 2960(CH_3 str.), 1680(C=O str.), 1445(C=N str.), 1200(C=O str.), 1110 (C—F str.) in conformity with the structure assigned. The ^{1}H NMR spectrum showed a singlet at δ 1.5 integrating for 9 protons assigned to *t*-butyl group. The multiplets observed in the range 7.3–7.9, integrating for 8 protons were due to aromatic protons. The mass spectrum of compound showed molecular ion peak at *m/z* 396, followed by fragment ion at *m/z* 381 due to loss of methyl group from molecular ion. An intense peak observed at *m/z* 231

was due to the formation of 4-fluoro-(3-phenoxy)-thiobenzoyl cation. A peak at *m/z* 187 and 77 was assigned to 4-fluoro-(3-phenoxy)-phenyl and phenyl cation respectively. The physical data of these compounds are given in Table I. Spectral data for some of the compounds are given in Table II.

Antibacterial Activity

All the newly synthesized compounds were screened for their in vitro antibacterial activity against *Escherichia coli, Pseudomonas aeruginosa, Klebsiella sp*, and *staphylococcus aureus* Smith according to serial dilution technique.[11] Nitrofurazone was used as the standard drug. All the tested compounds (Table III) showed good to moderate antibacterial activities against tested bacterial strains. It is interesting to note that the compounds are selective against *staphylococcus aureus* and *Klebsiella sp*. However, none of the compounds are active against pathogenic bacteria *Pseudomonas aeruginosa* at lesser than 50 μg/ml concentrations. Comparing the antibacterial activities of these compounds with our earlier work,[5] it is evident that the introduction of fluorophenyl moiety significantly enhanced the antibacterial activities.

EXPERIMENTAL

Melting points were taken in open capillary tubes and are uncorrected. The IR spectra in KBr disc were recorded on a Shimadzu FT IR

TABLE I Characterization Data of Thiadiazolotriazinones (**3a-l**)

Comp no.	R	R′	M.P (°C)	Yield (%)	Mol. form.
3a	$C(CH_3)_3$—	4-F—	188–90	85	$C_{14}H_{13}FN_4OS$
3b	$C(CH_3)_3$—	4-F-3-(OC_6H_5)—	134–35	85	$C_{20}H_{17}FN_4O_2S$
3c	$C(CH_3)_3$—	2,4-Cl_2-5-F—	148–50	80	$C_{14}H_{11}Cl_2FN_4OS$
3d	4-Cl—C_6H_4—CH_2—	4-F—	208–10	90	$C_{17}H_{10}ClFN_4OS$
3e	4-Cl—$C_6H_4CH_2$—	4-F-3-(OC_6H_5)—	184–85	78	$C_{23}H_{14}ClFN_4O_2S$
3f	4-Cl—C_6H_4—CH_2—	2,4-Cl_2-5-F—	166–67	76	$C_{17}H_8Cl_3FN_4OS$
3g	3,4-O_2CH_2—C_6H_3—CH_2—	4-F—	205–05	80	$C_{18}H_{11}FN_4O_3S$
3h	3,4-O_2CH_2—C_6H_3—CH_2—	4-F-3-(OC_6H_5)—	192–93	75	$C_{24}H_{15}FN_4O_4S$
3i	3,4-O_2CH_2—C_6H_3—CH_2—	2,4-Cl_2-5-F—	156–58	78	$C_{18}H_9Cl_2FN_4O_3S$
3j	2,4-Cl_2—C_6H_3—CH_2—	4-F—	176–78	82	$C_{17}H_9Cl_2FN_4OS$
3k	2,4-Cl_2—C_6H_3—CH_2—	4-F-3-(OC_6H_5)—	142–44	80	$C_{23}H_{13}Cl_2FN_4O_2S$
3l	2,4-Cl_2—C_6H_3—CH_2—	2,4-Cl_2-5-F—	186–87	80	$C_{17}H_7Cl_4FN_4OS$

[a] Compounds showed satisfactory microanalysis.
[b] Reported yields are after recrystallization.
[c] The compounds were crystallized from ethanol + dioxan mixture.

TABLE II Spectral Characterization Data of the Compounds (**3b**, **3i**, and **3k**)

Compd no.	IR (cm^{-1})	^1H NMR (δ, ppm)	Mass (EIMS, *m/z*)
3b	3100(Ar—CH str.), 2960(CH_3 str.), 1680(C=O str.), 1445(C=N str.), 1200(C=O str.), 1110 (C—F str.)	1.5(s, 9H, —$C(CH_3)_3$, 7.3–7.9(m, 8H, Ar—H)	*m/z*: 396(M^+), 381(M+ −15, loss of methyl group), 231(4-fluoro-(3-phenoxy)-thiobenzoyl cation), 183(4-fluoro-(3-phenoxy)-phenyl cation), 77(phenyl cation)
3i	3150(Ar—CH str.), 2965(CH_2 str.), 1680 (C=O str.), 1445 (C=N str.), 1240(C—O str.), 1180(C—F str.), 1040/890(C—Cl str.)	4.1(s, 2H, —CH_2—), 4.9(s, 2H, O—CH_2—O), 7.3–7.9(m, 5H, Ar—H)	—
3k	3150(Ar—CH str.), 2975(CH_2 str.), 1680(C=O str.), 1460 (C=N str.), 1260(C—O str.), 1180 (C—F str.), 840/790 (C—Cl str.)	4.4(s, 2H, —CH_2—), 7.2–7.9(m, 11H, Ar—H)	*m/z*: 463(M^+ −35, loss of Chlorine), 231(4-fluoro-(3-phenoxy)-thiobenzoyl cation), 77(phenyl cation)

[a]Higher Ar—CH stretch may be due to the presence of fluorine in the ring.
[b]Recorded using DMSO-d_6 or $CDCl_3$ as solvents.

TABLE III Antibacterial Activity Data of Triazinothiadiazoles (MIC in μg/ml) (**3a-l**)

Compd no.	Bacteria tested			
	E. coli	*P. aeruginosa*	*S. aureus*	*Klebsiella sps.*
3a	—	—	4	200
3b	—	—	4	100
3c	50	—	10	100
3d	50	—	20	200
3e	20	100	10	100
3f	20	100	10	100
3g	20	100	20	50
3h	20	—	10	50
3i	20	50	10	50
3j	10	50	10	20
3k	10	50	20	50
3l	10	50	10	50

[a]Indicates the bacteria is resistant to the compounds at the maximum tested concentration, i.e., at 200 μg/ml.
MIC = Minimum Inhibitory Concentration.

spectrophotometer. ^{1}H NMR spectra were recorded in $CDCl_3$-DMSO-d_6 on a Bruker AC-300F (300 MHz) NMR spectrometer using TMS as an internal standard. The mass spectra were recorded on a JEOL-JMS D-300 mass spectrometer operating at 70 eV. Purity of the compounds was checked by thin layer chromatography (TLC) on silica gel plates using a hexane: chloroform (4:1) solvent system. Iodine was used as the visualizing agent. Triazinones were prepared according to literature method.[10]

General Procedure for the Preparation of 4-Fluoro-3-phenoxy Benzoic Acid

4-Fluoro-3-phenoxy benzaldehyde (0.01 mmol) in 10 ml of alcohol was added excess hydrogen peroxide and catalytic amount of acetic acid. The reaction mixture was refluxed on a water bath for 4 h. The excess of solvent was distilled off. The reaction mixture was cooled, washed with cold water, and the separated solid was filtered and dried. It was recrystallized from ethanol. m.p. 126°C, yield 100%.

General Procedure for the Preparation of 2,4-Dichloro-5-fluorobenzoic Acid

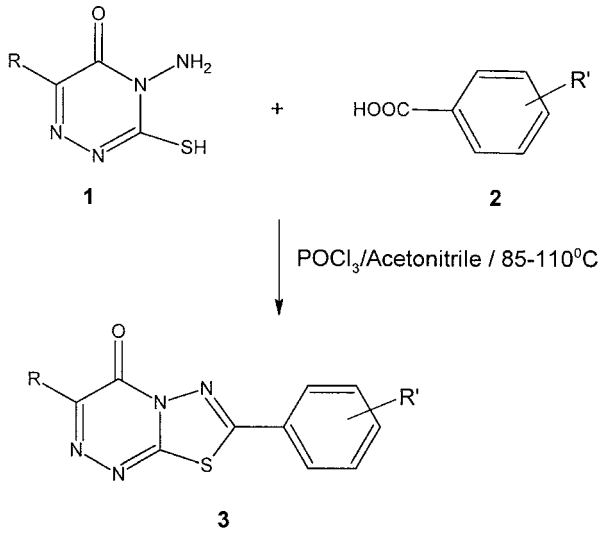
2,4-Dichloro-5-fluoro acetophenone (0.01 mmol) was dissolved in minimum amount of ethanol. To it excess of Sodium hydroxide solution (pH is maintained at 8–10) was added and chlorine gas was passed for 6 h. The solution was made acidic. The separated solid was filtered, washed with cold water and dried. Yield of 2,4-dichloro-5-fluorobenzoic acid is nearly quantitative, m.p: 144°C.

Preparation of 4-Amino-6-arylmethyl-3-mercapto-1,2,4-triazin-5(4H)-ones **1**

To a solution of thiocarbohydrazide (1.06 g, 0.01 mmol) in warm water (30 ml) was added dropwise a solution of arylpyruvic acid (0.01 mmol) in ethanol with stirring. The reaction mixture was stirred on a water bath for 2 h. The solid product thus separated was filtered and recrystallized from ethanol to give triazinones **1**. Their physical data is in agreement with the values reported by us earlier.[10]

General Procedure for the Preparation of 7-(Substituted phenyl)-3-arylmethyl/tert-butyl-4H-1,3,4-thiadiazolo-[2,3-c]-1,2,4-triazin-4-ones **3**

To a mixture of triazinones (0.01 mmol), 4-fluoro-3-phenoxy benzoic acid/2,4-Dichloro-5-fluorobenzoic acid/4-fluorobenzoic acid (0.012 mmol) in 20 ml of dry Acetonitrile/toluene was added 50 ml of phosphorous oxychloride was added drop wise. The mixture was



3a:R=$C(CH_3)_3$- ,R'=4-F-, **3b**:R=$C(CH_3)_3$, R'=4-F-3-(OPh)-,

3c: R=$C(CH_3)_3$- ,R'= 2,4-Cl_2-5-F- **3d**: R=4-Cl-C_6H_4-CH_2- R'= 4-F-

3e: R=4-Cl-C_6H_4-CH_2- R'= 4-F-3-(OPh)- **3f**: R=4-Cl-C_6H_4-CH_2- R'= 2,4-Cl_2-5-F- **3g**: R= 3,4-O_2CH_2-C_6H_3-CH_2- R'= 4-F-

3h:R= 3,4-O_2CH_2-C_6H_3-CH_2- R'=4-F-3-(OPh)- **3i**: R= 3,4-O_2CH_2-C_6H_3-CH_2- R'= 2,4-Cl_2-5-F- **3j**: R= 2,4-Cl_2-C_6H_3-CH_2- R'= 4-F-

3k: R= 2,4-Cl_2-C_6H_3-CH_2- R'= 4-F-3-(OPh)- **3l**: R= 2,4-Cl_2-C_6H_3-CH_2- R'= 2,4-Cl_2-5-F-

SCHEME 1 Condensation of triazinones **1** with fluorobenzoic acids **2**.

refluxed on an oil bath for 6 h. Excess of phosphorous oxychloride was removed by distillation under reduced pressure. The reaction mixture was cooled and poured onto crushed ice. The resulting solid product was filtered, washed with sodium bicarbonate solution (2%), followed by cold water. It was dried and recrystallized from dioxan and ethanol mixture. The yield and characterization data of thiadiazolotriazinones prepared according to this method are given in Table I.

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