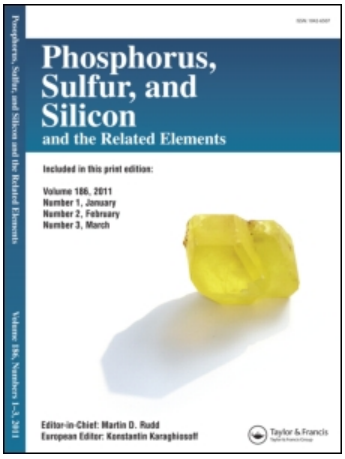

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

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To cite this Article Dandia, Anshu , Upreti, Mani , Saha, Mitali and Shivpuri, Asha(1998) 'ONE-POT SYNTHESIS OF A NOVEL TETRACYCLIC RING SYSTEM: BENZOPYRANO-1,2,4-TRAZOL0[3,4-B][1,3,4] THIADIAZEPINES AND THEIR ANTIFUNGAL ACTIVITY', Phosphorus, Sulfur, and Silicon and the Related Elements, 143: 1, 115 — 124
To link to this Article: DOI: 10.1080/10426509808045490
URL: http://dx.doi.org/10.1080/10426509808045490

Phosphorus, Sulfur and Silicon, 1998, Vol. 143, pp. 115-124
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ONE-POT SYNTHESIS OF A NOVEL TETRACYCLIC RING SYSTEM: BENZOPYRANO-1,2,4-TRIAZOLO[3,4-B][1,3,4] THIADIAZEPINES AND THEIR ANTIFUNGAL ACTIVITY

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(Received 01 July, 1998; In final form 30 September, 1998)

A series of novel 11-alkyl-2-chloro-6a, 7-dihydro-6H-7(4-aryl)-6-phenyl[1]benzopyrano-1,2,4-triazolo[3,4-b]benzothiadiazepines(IV) have been synthesized by the reaction of 4-amino-5-alkyl-3-mercapto-1,2,4-triazoles (I) with (E)-6-chloro-3-(4-chloro/methoxybenzylidene)flavanones (IIa/b) in refluxing toluene, containing piperidine as catalyst. The compounds have been characterized on the basis of elemental and spectral studies and have been screened *in vitro* for antifungal activity against *Rhizoctonia solani*, *Fusarium oxysporum* and *Colletotrichum capsici*. All the compounds have shown excellent activity against these pathogens.

Keywords: Triazolothiadiazepines; antifungal activity; spectral studies

INTRODUCTION

Since the 1,5-benzothiazepines are important compounds in drug research, their numerous representatives are well known in the literature and different procedures have been introduced for their preparation[1–3]. One of the most important calcium channel blocking agents, currently in clinical use, is "Diltiazem", a 1,5-benzothiazepine-2-one analogue, which has found wide application in the treatment of various forms of hypertension[4],

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arrhythmia[5], angina pectoris[6], artereosclerosis[7] and myocardial infection[8]. The patented drug "Clinitiazem", an 8-chloro analogue has proved to be a more potent antihypertensive than "Diltiazem"[9].

The origin of the 1,5-benzothiazepine class of compounds can be traced back to the analogous 1,4-and 1,5-benzodiazepine class of compounds, which are currently in use as effective psychopharmacological agents all over the world[10,11]. A survey of the literature indicated that the incorporation of an additional heterocyclic moiety to the benzothiazepine[12] or analogous benzodiazepine[13] ring system may serve as a further pharmacophore, enhancing potential bioactivity of the compounds. In the course of the pharmacological evaluation of these 1,5-benzothiazepines, it was observed that the compounds having a 1,4-benzothiazepine ring fused with the bioactive thiophene or triazole[14] moiety, instead of the aromatic moiety lead to the formation of thiophenothiazepines and triazolothiadiazepines, which have been reported to possess diverse range of bioactivity.

Flavanones[15,16] are important intermediates for the synthesis of biologically active flavones and isoflavones. A number of diflavones, diflavonols have been shown to exhibit significant antifeedant activity. Nevertheless, no report has been cited so far, regarding the reaction of aminomercaptotriazoles with 3-arylidene flavanones. However, Prasad[17] reported the reaction of aminomercaptotriazoles with substituted chalcones in pyridine, containing a small amount of acetic acid, leading to the synthesis of 4-amino-3-(1,3-diaryl-3-oxo-1-mercapto)-5-phenyl-s-triazoles in 40–50% yield, instead of the expected thiadiazepines.

Hence, as a part of our continuing interest on the synthesis of biodynamic benzothiazepines[18,20] and other sulfur and nitrogen containing heterocycles[21–23], an attempt has been made for the first time, to fuse the bioactive thiadiazepine nucleus with triazole and benzopyran rings in a one-pot procedure.

RESULTATS AND DISCUSSION

The one-pot synthesis of novel 11-alkyl-2-chloro-6a, 7-dihydro-6H-7-(4-aryl)-6-phenyl[1]benzopyrano-1,2,4-triazolo[3,4-b][1,3,4] benzothiadiazepine (IV) has been carried out be refluxing 5-alkyl-4-amino-3-mercaptotriazoles (I) with (E)-6-chloro-3-(4-chloro/

methoxybenzylidene)flavanones (II) in dry toluene, containing piperidine as catalyst, with azcotropica removal of water (Scheme-1).

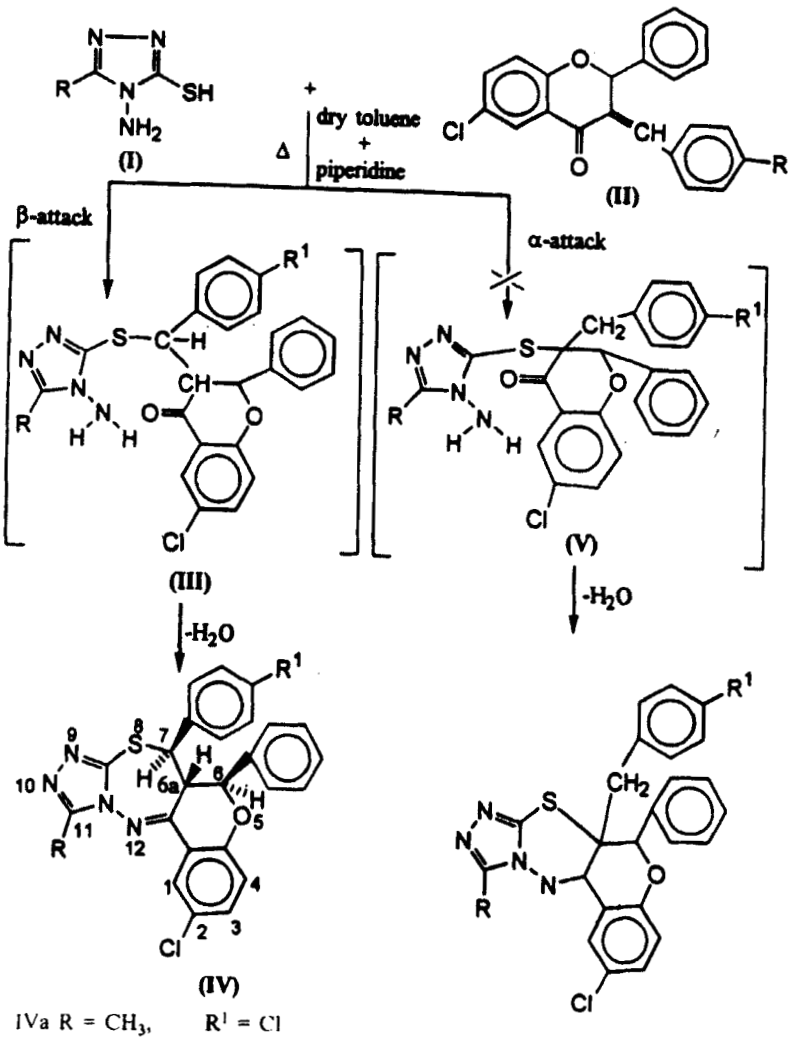
The 6-chloro-3-(4-chloro/methoxybenzylidene)flavanone (IIa,b) were prepared by acid catalyzed condensation of 4-chloro/methoxy benzaldehydes with 6-chloroflavanone, while the latter compound was synthesized by the reaction of 5-chloro-2-hydroxyacetophenone with benzaldehyde in ethanol in the presence of 50% NaOH.

The first step is a nucleophilic attack by the sulphydryl group on the β-carbon atom of the double bond of arylidene flavanone, which is rendered electrophilic due to vinyl-carbonyl conjugation. It has been observed that when substitutents are present in an α,β-unsaturated ketone, only the nucleophilic addition of the mercapto group to the β-carbon atom takes place, followed by condensation of the carbonyl group with the aromatic primary amine to give a seven membered ring system[24–26]. The presence of the basic catalyst piperidine, makes available a strong nucleophile by the abstraction of a proton from sulphydryl group of aminomercaptotriazoles, and thus mechanistically rules out the possibility of the formation of V & VI.

IR spectra of arylidene flavanones (IIa, b) showed characteristic absorptions at 1680–1670 cm^{-1} (>C=O) and at 1620–1625 cm^{-1} due to (C=C) stretching. PMR spectra displayed absorption signals as doublets at δ 6.9–7.2 (>CH) and at δ 7.2–7.4 (>C-CH)[27] ppm. IR spectra of the title compounds (IVa-f) showed a sharp absorption at 1610–1595 cm^{-1}, due to C=N stretching of the seven-membered heterocyclic ring system[28]. The disappearance of absorption bands at 1680–1670 cm^{-1} (>C=O). 1630–1625 (C=C) and 3400–3300 cm^{-1} ($-NH_2$) rules out the possibility of the formation of the open Michael type adduct contradicting the observations of Prasad et.al.[17] in the reaction of (I) with chalcones in pyridine containing acetic acid.

In the ^{1}HNMR spectrum, a doublet was observed at δ 3.9–3.95 (J=12.4–12.8 Hz) assigned for H-7 proton[29]. Another doublet at δ 3.46–3.5 (J=1.3–1.7 Hz) assigned to H-6 proton, while a comparatively weak double doublet at δ 3.17–3.20 ppm was observed due to the bridgehead H-6a proton[29]. The absence of $-CH_2$ protons signal further rules out the probability of structure V & VI.

This pattern of proton absorption is in conformity with the observations made by Leval[29] for benzopyrano benzothiazepines obtained by the reaction of 2-aminothiophenol with benzylidene flavanone. In the mass spec-



(I) (II) (III) (IV) (V) (VI)

IVa R = CH_3, R^1 = Cl
IVb R = CH_3, R^1 = OCH_3
IVc R = C_2H_5, R^1 = Cl
IVd R = C_2H_5, R^1 = OCH_3
IVe R = C_3H_7, R^1 = Cl
IVf R = C_3H_7, R^1 = OCH_3

SCHEME I

tra, compound IVf under electron impact gave its molecular ion peak at m/z 517(2.4%) and other peaks at 397(4.4%), 365(14.2%), 362(22.1%), 328(2.4%), 307(2.7%), 238(2.5%), 230(2.7%), 167(2.4%). In the case of IVa molecular ion peak was not observed, but the other peaks were observed at m/z 379 (32.1%), 347(3.7%), 271(7.6%), 257(4.7%).

The synthesized compounds were screened for antifungal activity against three pathogenic fungi, namely *Rhizoctonia solani,* causing root rot of okra, *Fusarium oxysporum,* causing wilt of mustard and *colletotrichum capsici* causing leaf spot and fruit rot of chilli. In the pot trial experiment, it was found that IVf having $-OCH_3$ group showed maximum germination (70%) indicating that, it is most effective in controlling the growth of pathogen. "Baynate" and "Thiram" recommended as standard fungicide as seed dressers to control this disease are also having -N-C-S linkage, similar to the synthesized compounds, which is responsible for their antifungal activity.

EXPERIMENTAL

Melting points, determined on a Toshniwal point apparatus, are uncorrected. IR were recorded in KBr on a Perkin-Elmer spectrophotometer model 577(ν_{max} in cm^{-1}). ^1H NMR were recorded on a Jeol FX 400Q in $CDCl_3$ solvent, at 300.13 MHz using TMS as internal standard. The FAB mass spectra were recorded on a Jeol 102 mass spectrometer. Purity of the compounds was checked by tlc on silica gel plates.

5-Chloro-2-hydroxy acetophenone[30], 6-chloroflavanone[31] and 4-amino-5-alkyl-3-mercaptotriazoles[32] have been prepared following literature methods.

6-Chloro-3-(4-arylidene)-flavanones (II)

Equimolar quantities of 6-chloroflavanone (0.01 mole) and 4-chloro/methoxy benzaldehydes (0.01 mole) were dissolved in dry ethanol (50ml). Hydrogen chloride gas was passed to the reaction mixture till saturation, which was then kept at room temperature for 24 hrs The solid obtained was filtered off, dried and recrystallised from dry methanol.

IIa: m.p. 128–30°C; Yield 65% (found : C, 70.23; H, 3.62; $C_{22}H_{14}O_2Cl_2$ requires C, 69.47; H, 3.68%). **IIb** : m.p. 85°C; yield 56% (found C, 73.92; H, 4.49; $C_{23}H_{17}O_3Cl$ requires C, 73.40; H, 4.52%).

11-Alkyl-2-chloro-6a,7-dihydro-6H-7-(4-aryl)-6-phenyl[1]benzopyrano-1,2,4-triazolo[3,4-b][1,3,4]benzothiadiazepines (IVa-f)

A mixture of 4-amino-5-alkyl-3-mercaptotriazole I (0.001 mole) and 6-chloro-3-(4-methoxy/chlorobenzylidene) flavanone II (0.001 mole) in dry toluene (5ml) containing dry piperidine (5ml) was refluxed for 60–65 hours, with azeotropical removal of water formed. Progress of the reaction was monitored by tlc. The solvent was removed under reduced pressure and the resultant solid was recrystallised from dry methanol.

Compound IVa

$C_{25}H_{18}N_4OSCl_2$: ^{1}HNMR ($CDCl_3$) : δ 3.19 (dd, 1H, H-6a), 3.49 (d, 1H, J=1.5 Hz, H-6), 3.92 (d, 1H, J=12.5 Hz, H-7) 2.1 (s, 3H, C<u>H</u>$_3$), 6.9–8.08 (m, Ar-<u>H</u>) ; MS m/z (%) 379 (32.1) 347 (3.7) 271 (7.6) 257 (4.7).

Compound IVb

$C_{26}H_{21}N_4O_2SCl$: ^{1}HNMR ($CDCl_3$); δ 3.20 (dd, 1H, H-6a), 3.48 (d, 1 H, J=1.7 Hz, H-6), 3.9 (d, 1H, J=12.8 Hz, H-7) 2.2 (s, 3H, C<u>H</u>$_3$), 3.83 (s, 3H,-OC<u>H</u>$_3$), 3.83 (s, 3H,-OC<u>H</u>$_3$), 6.86–8.1 (m, Ar<u>H</u>).

Compound IVc

$C_{26}H_{20}N_4OSCl_2$: ^{1}HNMR ($CDCl_3$) : δ 3.18 (dd, 1H, H-6a), 3.5 (d, 1H, J=1.3 Hz, H-6), 3.9 (d, 1H, J=12.5 Hz, H-7), 1.35 (t, 2H, -CH_2-C<u>H</u>$_3$), 2.8 (q, 3H, -C<u>H</u>$_2$-CH_3), 7-8.15 (m, Ar-<u>H</u>).

Compound IVd

$C_{27}H_{23}N_4O_2SCl$: ^{1}HNMR ($CDCl_3$) δ 3.17 (dd, 1H, H-6a), 3.46 (d, 1H, J=1.5 Hz, H-6), 3.94 (d, 1H, J=12.6 Hz, H-7), 1.37 (t, 2H, -CH_2-C<u>H</u>$_3$), 2.84 (q, 3H,C<u>H</u>$_2$-CH_3), 2.84 (q, 3H, -C<u>H</u>$_2$-CH_3), 3.85 (s, 3H,-OC<u>H</u>$_3$), 7–8.05. (m, Ar-<u>H</u>).

Compound IVe

$C_{27}H_{22}N_4OSCl_2$: ^{1}HNMR ($CDCl_3$) : δ 3.18 (dd, 1H, H-6a), 3.47 (d, 1H, J=1.6 Hz, H-6), 3.95 (d, 1H J=12.6 Hz, H-7), 1.1 (t, 3H,-CH_2-CH_2-CH_3), 1.5 (m, 2H,-CH_2-CH_2-CH_3), 2.2 (t, 2H, -CH_2-CH_2-CH_3), 6.8–8.2 (m, Ar-H).

Compound IVf

$C_{28}H_{25}N_4O_2SCl$: ^{1}HNMR ($CDCl_3$) : δ 3.19 (dd, 1H, H-6a), 3.48 (d, 1H J=1.5 Hz, H-6), 3.94 (d, 1H, J=12.6 Hz, H-7), 1.2 (t, 3H, -CH_2-CH_2-CH_2). 1.7 (m, 2H,-CH-CH_2-CH_3), 2.28 (t, 2H, -CH_2-CH_2-CH_3), 3.86 (s, 3H,-OCH_3), 7–8.1 (m, Ar-H); MS m/z (%) : 517 (M^+ + 1, 2.4) 365 (14.2) 362 (22.1) 328 (2.4) 307 (2.7) 238 (2.5) 230 (2.7) 167 (2.4).

TABLE I Analytical and Physical data of IVa-f

Compd. no.	*R*	*R^1*	*M.P. (°C)*	*Yield (%)*	*Mol. Formula*	*Found (Calcd) %*			
						C	*H*	*N*	*S*
IVa	CH_3	Cl	116	54	$C_{25}H_{18}N_4OSCl_2$	60.95 (60.97)	3.62 (3.65)	11.34 (11.38)	6.52 (6.50)
IVb	CH_3	OCH_3	112	49	$C_{26}H_{21}N_4O_2SCl$	63.89 (63.86)	4.32 (4.29)	11.42 (11.46)	6.52 (6.55)
IVc	C_2H_5	Cl	113	42	$C_{26}H_{20}N_4OSCl_2$	61.56 (61.53)	3.97 (3.94)	11.01 (11.04)	3.29 (6.31)
IVd	C_2H_5	OCH_3	122	51	$C_{27}H_{23}N_4O_2SCl$	64.49 (64.47)	4.59 (4.57)	11.17 (11.14)	6.40 (6.36)
IVe	C_3H_7	Cl	121	50	$C_{27}H_{22}N_4OSCl_2$	62.22 (62.18)	4.18 (4.22)	10.72 (10.74)	6.12 (6.14)
IVf	C_3H_7	OCH_3	135	45	$C_{28}H_{25}N_4O_2SCl$	65.08 (65.05)	4.86 (4.84)	10.82 (10.84)	3.23 (6.19)

Antifungal activity : It was done by two methods

(i)Poison plate technique[33]

The compounds synthesized were dissolved in acetone and compounds were prepared in 1000 and 500 ppm concentrations. Potato-dextrose-agar medium was prepared in flasks and sterilized. To this medium, a requisite

quantity of solution was added and then the medium was poured into petriplates in three replication. A culture of test fungus was grown on PDA for 6–7 days. Small disc (4 mm) of the fungus culture was cut with a sterile corkborer and transferred asceptically, upside-down in the centre of petridishes containing the medium and fungicides. Plates were incubated at 25°C ± 1°C for 6-days. Colony diameter were measured and data was statistically analysed (Table II).

TABLE II Effect of concentrations of different chemicals on the mean radial growth (cms) of different fungus *in vitro*

Compd. no.	*Rhizoctonia solani*		*Fusarium axysporum*		*Colletotrichum capsici*	
	1000 ppm	*500 ppm*	*1000 ppm*	*500 ppm*	*1000 ppm*	*500 ppm*
IVa	1.08*	1.75	1.58	1.83	1.33	2.17
IVb	2.58	1.50*	1.50	3.92	2.58	3.67
IVc	1.83	2.58	2.25	4.25	1.75	3.25
IVd	2.08	7.67	2.92	5.00	1.50	3.58
IVe	6.67	8.25	1.08*	1.67	0.75*	1.25*
IVf	1.92	3.83	1.25	1.58*	2.50	4.08
CHECK	9.00	9.00	8.17	8.17	7.33	7.33
CD 1%	1.22	1.02	0.77	1.14	1.03	1.08

* Min value
— At par with min. value.

(ii)Pot trial method[34]

White seeded sorghum grains were soaked in water for about 12 hours. 160gm of the soaked kernels were placed in 500ml flasks, and 20ml of water was added to each. The material was autoclaved twice on successive days before inoculation. After sterilization, fungus bits were inoculated in each flask and flasks were kept for 10-days at 25–27°C. 100 seeds of okra were taken for one treatment of each compound. Inoculum was added @ 2g/kg of soil, 3-days prior to sowing. Sowing was done after 3-days and germination data were recorded after 7,15,25 days of sowing. Suitable checks were maintained and the data was statistically analysed (Table III).

TABLE III Evaluation of triazolothiadiazepine derivatives as seed dressers against *Rhizoctonia solani* causing root rot of okra (in pot trial)

Compd. no.	*Percent germination 7 DAS*	*Plant stand 25 DAS*
IVa	42.00	58.00
IVb	46.00	54.00
IVc	37.00	63.00
IVf	70.00	30.00
Baynate (0.2%)	98.00	64.00
Thiram (0.3%)	79.00	68.00
Check with inoculum	10.00	6.00
Check without inoculum	90.00	81.00

DAS – Days after sowing.

Acknowledgements

Financial assistance from State D.S.T, Jaipur is gratefully acknowledged.

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