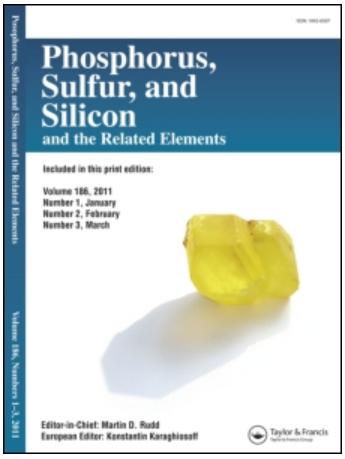

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

Synthesis of Some New 2-(4-Methoxybenzothiazol-2'-yl amino)-4-(2-chloro-4-trifluoromethylanilino)-6-(substituted thioureido)-1,3,5-triazine as Antifungal Agents

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Online publication date: 28 December 2009

To cite this Article Sareen, Vineeta , Khatri, Vineeta , Jain, Prakash and Sharma, Kanti(2010) 'Synthesis of Some New 2-(4-Methoxybenzothiazol-2'-yl amino)-4-(2-chloro-4-trifluoromethylanilino)-6-(substituted thioureido)-1,3,5-triazine as Antifungal Agents', Phosphorus, Sulfur, and Silicon and the Related Elements, 185: 1, 140 — 146
To link to this Article: DOI: 10.1080/10426500902717754
URL: http://dx.doi.org/10.1080/10426500902717754

Phosphorus, Sulfur, and Silicon, 185:140–146, 2010

ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/10426500902717754

SYNTHESIS OF SOME NEW 2-(4-METHOXYBENZOTHIAZOL-2′-YL AMINO)-4-(2-CHLORO-4-TRIFLUOROMETHYLANILINO)-6-(SUBSTITUTED THIOUREIDO)-1,3,5-TRIAZINE AS ANTIFUNGAL AGENTS

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2,4,6-Trichloro 1,3,5-triazine was selectively reacted with new nucleophilic reagents such as 4-methoxy-2-aminobenzothiazole, 2-chloro-4-trifluoromethyl-aniline, and phenylsubstituted thiourea in alkaline medium to give 2-(4-methoxybenzothiazol-2′-ylamino)-4-(phenylthioureido)-6-(substitutedthioureido)-1,3,5-triazines. The structures of these compounds were confirmed by IR, ^{1}H NMR, ^{19}F NMR, mass spectral data, and elemental analysis. The compounds show fungicidal activity against **Alternaria alternata, Aspergillus niger,** ***and*** **Macrofomina.**

Supplemental materials are available for this article. Go to the publisher's online edition of **Phosphorus, Sulfur, and Silicon and the Related Elements** ***to view the free supplemental file.***

Keywords Fungicidal activity; 2-(4-methoxybenzothiazol-2′-ylamino)-4-(2-chloro-4-trifluoromethylanilino)-6-chloro-1,3,5-triazine; 2-(4-methoxybenzothiazol-2′-ylamino)-4-(2-chloro-4-trifluorophenylanilino)-6-(4-fluorophenyl thioureido)-1,3,5-triazine; 2-(4-methoxybenzothiazol-2′-ylamino)-4,6-dichloro-1,3,5-triazine

INTRODUCTION

It has been observed that the benzothiazole nucleus is associated with a broad spectrum of biological activities such as antimicrobial,[1–4] anti-inflammatory,[5] etc. Similarly s-triazine derivatives have attained significance in agriculture as herbicides[6] and fungicides.[6] They are also used for the treatment of HIV infection.[7]

We thought it would be interesting to construct a system that may combine these biolabile[8,9] rings together in a molecular framework to see the additive effects towards antifungal activities. Further, the fluorinated derivatives are also prepared to enhance the biological activity.[10]

Received 8 July 2008; accepted 2 December 2008.

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RESULTS AND DISCUSSION

In continuation of our work on triazines,[11,12] we have synthesized some new fluorinated derivatives of 2,4,6-trisubstituted 1,3,5-triazine with enhanced fungicidal activity. The fungicidal activity was evaluated against *Alternaria alternata*, *Aspergillus niger*, and *Macrophomina*. Three chlorine atoms of 2,4,6-trichloro-1,3,5-triazine (cyanuric chloride) have been replaced subsequently by 2-amino-4-methoxybenzothiazole (which in turn is prepared by condensing p-methoxyaniline with ammonium thiocyanate,[11] 2-chloro-4-trifluoromethyl aniline, and substituted thioureas in alkaline medium selectively to give the title compound **4** (Scheme 1).

2-(4-Methoxybenzothiazol-2′-ylamino)-4,6-dichloro-1,3,5-triazine **2** was prepared by treating cyanuric chloride in acetone with 2-amino-4-methoxy benzothiazol **1** at 0–5°C and stirring for 3 h. The second chlorine atom of **2** was replaced by 2-chloro-4-trifluoromethylaniline at 35–45°C in acetone by constant stirring for 3 h to give 2-(4-methoxybenzothiazol-2′-ylamino)-4-(2-chloro-4-trifluoromethylanilino)-6-chloro-1,3,5 -triazine **3**. The third chlorine atom of **3** was replaced by different substituted thioureas at 85–90°C in acetone to give 2-(4-methoxybenzothiazol-2′-ylamino)-4-(2-chloro-4-trifluoromethyl- anilino)-6-(substituted thioureido)-1,3,5-triazine **4**.

2,4,6-Trichloro-1,3,5-triazine derivatives (cyanuric chloride) react selectively with nucleophilic reagents.[13] Cyanuric chloride is a weak base. If one of its chlorines is replaced by -NHR, R, or SR, the basicity is increased because of the electron releasing effect of these groups substituted at α-positions of the ring nitrogen atoms.

Compound **2** showed the presence of >NH group in both its IR spectrum 3150 cm^{-1} and ^1H NMR spectrum, which showed a broad singlet at δ 9.8 (>NH).

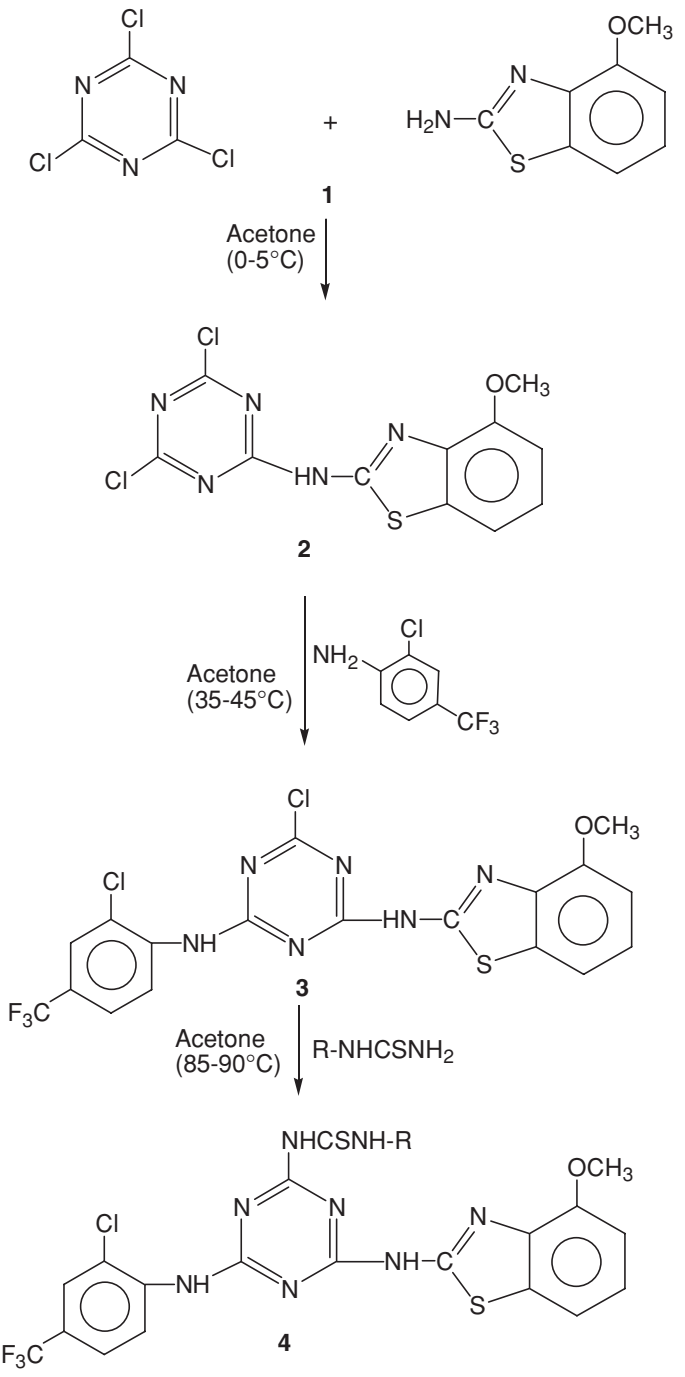
The IR spectrum of compound **3** showed peak at 3150 cm^{-1} (broad band for >NH) and its ^1H NMR shows peak at δ 8.8 (a singlet for two >NH protons). Further in ^{19}F NMR it shows peak at δ −5 to −10 ppm for $\geq C-CF_3$ group. Mass spectrum shows M^+ at m/z 487. Compound **4a** showed peaks at 3120 (>NH, broad), 3050 (>NHCSNH<), and 1115 (CS) cm^{-1} in IR spectrum. ^1H NMR show peaks at δ 8.9 (brs, two, >NH), δ 4.8 (>NHCSNH<), δ 6.5–7.8 ppm for aromatic protons, and δ 3.4 ppm (s, $-OCH_3$). In ^{19}F NMR, peaks at δ −5 to −10 for $\geq C-CF_3$ and −30 to −40 ppm for $\geq C-CF$ group were observed. Finally, mass spectrum of **4a** shows M^+ at m/z 619.5.

FUNGICIDAL ACTIVITY

Compounds **4a–i** were screened for fungicidal activity against *Alternaria alternata*, *Aspergillus niger*, and *Macrophomina* using the agar diffusion technique.[14] (See the Supplemental Materials online for more detailed information.)

EXPERIMENTAL

Purity of all the compounds was checked on silica gel G plates using iodine vapor as the detecting agent. Melting points were determined in open capillary tubes using Gallenkamp melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin Elmer 577 spectrophotometer in KBr pellets. ^1H NMR spectra (chemical shifts in δ ppm) were recorded at 89.99 MHz using GEOL (model AL-300) apparatus with TMS as



Scheme 1 *(Continued)*

4a; R = 4-FC_6H_4 **4e**; R = 2-$OCH_3C_6H_4$

4b; R = 2-FC_6H_4 **4f**; R = 2-$CH_3C_6H_4$

4c; R = 2-$CF_3C_6H_4$ **4g**; R = 2-$NO_2C_6H_4$

4d; R = 4-ClC_6H_4 **4h**; R = C_6H_5

4i; R = $CH_2 = CH–CH_2–$

Scheme 1 (Continued)

the internal standard. In ^{19}F NMR spectra, TFA was taken as an external standard. The mass spectra were recorded on Kratos MS-30 and MS-50 spectrometer operating at ionization potential of 70 ev.

2-(4-Methoxybenzothiazol-2′-ylamino)-4,6-dichloro-1,3,5-triazine (2)

To 2,4,6-trichloro-1,3,5-triazine (18.4 g, 1 mmol) dissolved in acetone (100 mL) cooled at 0°C, 4-methoxy-2-aminobenzothiazole (18.0 g, 1 mmol) dissolved in acetone (100 mL) was added with stirring of NaOH (4.0 g, 1 mmol) in water (50 mL). The mixture was stirred for 3 h then poured into ice water and acidified with dil HCl. The resulting solid was washed with acetone, dried, and recrystallized from ethanol. Mp 204°C, yield (78%), IR (KBr) ν_{max}: 3160 (>NH); 1380(−OCH_3); ^1H NMR($CDCl_3$): 9.8 (s, 1H, >NH 6.5–6.8 (m, 3H, aromatic), 3.8 (s, 3H, −OCH_3), MS: 328 (m/z). (Found C, 40.27, H, 2.16, N, 21.26, s, 9.79, $C_{11}H_7N_5Cl_2OS$ requires C, 40.24, H, 2.13, N, 21.34, S, 9.75%).

2-(4-Methoxybenzothiazol-2′-ylamino)-4-(2-chloro-4-trifluoromethylanilino)-6-chloro-1,3,5-triazine (3)

A solution of **2** (3.26 g, .0.1 mmol) dissolved in acetone (100 mL) was added to 2-chloro-4-trifluoroaniline (19.5 g, 1 mmol) in acetone (100 mL) slowly with stirring followed by the addition of NaOH (4.0 g, 1 mmol) in water (50 mL). The reaction mixture was stirred for 3 h at 35–45°C, then poured in ice water and acidified with dil HCl. The resulting solid was washed with acetone, dried, and recrystallized from ethanol. Mp 180°C, yield (74%); IR (KBr) ν_{max}: 3130 (>NH), 1350 (−OCH_3), ^1H NMR: 8.8 (s, 2H >NH), 6.4–6.8 (m, 6H, aromatic), 3.8 (s, 3H, −OCH_3), ^{19}F NMR: (−5) to (−10) (≥C−F), MS: 487 (m/z). (Found C, 44.33, H, 2.31, N, 17.35, S, 6.54, $C_{18}H_{11}N_6Cl_2F_3OS$ requires C, 44.35, H, 2.25, N, 17.24, S, 6.57%).

2-(4-Methoxybenzothiazol-2′-ylamino)-4-(2-chloro-4-trifluoromethylanilino)-6-(4-fluorophenylthioureido)-1,3,5-triazine (4a)

To a solution of **3** (4.85 g, 0.1 mmol) in acetone (50 mL), 4-fluorophenylthiourea (1.55 g, 0.1 mmol) and NaOH (0.1 mmol) in water (10 mL) were added, and the mixture was refluxed at 85–90°C for 2 h. It was poured into water acidified with dil HCl, and the resulting

Table I Physical and analytical data of the compounds **4a–i**

Compound	Yield (%)	Mp (°C) range	Mol. formula (mol. wt.)	Analytical found (Calcd.)			
				C	H	N	S
4a	62	172	$C_{25}H_{17}N_8S_2ClOF_4$ (619.5)	48.31 (48.34)	2.71 (2.73)	18.00 (18.04)	10.29 (10.31)
4b	65	166	$C_{25}H_{17}N_8S_2ClOF_4$ (619.5)	48.32 (48.34)	2.70 (2.73)	18.00 (18.04)	10.28 (10.31)
4c	70	176	$C_{26}H_{17}N_8S_2ClOF_6$ (669.5)	46.50 (46.53)	2.50 (2.53)	17.67 (17.70)	9.52 (9.54)
4d	60	180	$C_{25}H_{17}N_8S_2Cl_2OF_3$ (635)	47.00 (47.09)	2.63 (2.66)	17.55 (17.50)	10.00 (10.04)
4e	50	189	$C_{26}H_{20}N_8S_2Cl_2OF_3$ (643.5)	49.30 (49.32)	3.12 (3.16)	17.67 (17.70)	10.09 (10.11)
4f	60	179	$C_{26}H_{20}N_8S_2ClOF_3$ (627.5)	50.56 (50.60)	3.20 (3.24)	18.15 (18.16)	10.36 (10.38)
4g	65	170	$C_{25}H_{17}N_9S_2ClO_3F_3$ (646.5)	46.30 (46.33)	2.60 (2.62)	19.40 (19.45)	9.85 (9.88)
4h	64	182	$C_{25}H_{18}N_8S_2ClOF_3$ (605.5)	49.76 (49.79)	2.95 (2.98)	18.55 (18.58)	10.60 (10.62)
4i	70	174	$C_{22}H_{18}N_8S_2ClOF_3$ (565.5)	46.55 (46.50)	3.15 (3.17)	19.75 (19.70)	11.27 (11.29)

Table II Spectral data of compounds **4a–i**

Compound	IR (KBr) ν_{max} (cm^{-1})	^1H NMR ($CDCl_3$) δ (ppm)
4a	3120 (>NH, br); 3050 (>NHCSNH<); 1380 ($-OCH_3$); 1115 (thioureido CS)	8.9 (s, 2H, >NH), 6.5–6.9 (m, 10H, aromatic), 4.8 (s, 2H, >NHCSNH<), 3.7 (s, 3H, $-OCH_3$).
4b	3130 (>NH, br); 3040 (>NHCSNH<); 1380 ($-OCH_3$); 1120 (thioureido CS)	9.0 (s, 2H, >NH), 6.6–6.9 (m, 10H, aromatic), 4.7 (s, 2H, >NHCSNH<), 3.8 (s, 3H, $-OCH_3$).
4c	3120 (>NH, br); 3060 (>NHCSNH<); 1370 ($-OCH_3$); 1130 (thioureido CS)	8.9 (s, 2H, >NH), 6.7–7.00 (m, 10H, aromatic), 5.0 (s, 2H, >NHCSNH<), 3.9 (s, 3H, $-OCH_3$).
4d	3140 (>NH, br); 3070 (>NHCSNH<); 1380 ($-OCH_3$); 1140 (thioureido CS)	9.1 (s, 2H, >NH), 6.7–7.0 (m, 10H, aromatic), 5.0 (s, 2H, >NHCSNH<), 3.6 (s, 3H, $-OCH_3$).
4e	3120 (>NH, br); 3040 (>NHCSNH<); 1370 ($-OCH_3$); 1120 (thioureido CS)	8.8 (s, 2H, >NH), 6.4–6.8 (m, 10H, aromatic), 4.7 (s, 2H, >NHCSNH<), 3.6 (s, 3H, $-OCH_3$), 3.4 (s, 3H, $-OCH_3$).
4f	3130 (>NH, br); 3050 (>NHCSNH<); 1360 ($-OCH_3$); 1130 (thioureido CS)	9.0 (s, 2H, >NH), 6.5–6.8 (m, 10H, aromatic), 4.8 (s, 2H, >NHCSNH<), 3.7 (s, 3H, $-OCH_3$), 1.8 (s, 3H, $-CH_3$).
4g	3140 (>NH, br); 3070 (>NHCSNH<); 1380 ($-OCH_3$); 1140 (thioureido CS)	9.1 (s, 2H, >NH), 6.7–7.1 (m, 10H, aromatic), 5.1 (s, 2H, >NHCSNH<), 3.8 (s, 3H, $-OCH_3$).
4h	3140 (>NH, br); 3060 (>NHCSNH<); 1360 ($-OCH_3$); 1130 (thioureido CS)	8.9 (s, 2H, >NH), 6.5–6.9 (m, 11H, aromatic), 4.7 (s, 2H, >NHCSNH<), 3.8 (s, 3H, $-OCH_3$).
4i	3130 (>NH, br); 3070 (>NHCSNH<); 1370 ($-OCH_3$); 1140 (thioureido CS)	9.0 (s, 2H, >NH), 6.6–7.1 (m, 10H, aromatic), 5.0 (s, 2H, >NHCSNH<), 3.5 (s, 3H, $-OCH_3$), 4.6 (s, 2H, $=CH_2$), 4.0 (d, 2H, $-CH_2-$), 1.7 (t, 1H, $-CH=$)

solid was filtered, dried, and recrystallized from ethanol. Mp 172°C, yield (62%); IR (KBr) ν_{max}; 3120 (>NH, br), 3050 (>NHCSNH<), 1380 ($-OCH_3$), 1115 "(thioureido CS)", ^1H NMR ($CDCl_3$): 8.9 (s, 2H, >NH), 6.5–6.9 (m, 10H, aromatic), 4.8 (s, 2H, >NHCSNH<), 3.7 (s, 3H, $-OCH_3$), ^{19}F NMR: (−5) to (−10) ($\geq C-F$), 30–40 ($\geq C-F$), MS: 620.5 (m/z). Found C, 48.31, H, 2.71, N, 18.00, S, 10.29, $C_{25}H_{16}N_8ClF_4OS_2$ requires C, 48.34, H, 2.73 N, 18.04, S, 10.31%.

Compounds **4b–i** were prepared similarly. Their physical and analytical data are recorded in Table I, and spectral data are recorded in Table II.

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