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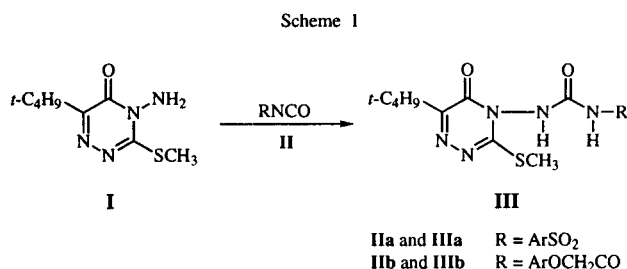
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The reaction of benzoyl isothiocyanates and methoxycarbonyl isothiocyanate with 4-amino-4,5-dihydro-3-(methylthio)-1,2,4-triazin-5-ones in acetonitrile gave several substituted 4*H*-1,3,4-thiadiazolo[2,3-*c*]-1,2,4-triazin-4-ones **VIa-h** instead of the expected thioureas. In addition, benzoyl isothiocyanate reacted with 4-amino-3-(methylthio)-5-(trifluoromethyl)-4*H*-1,2,4-triazole to give the benzoyl thiourea **IX** and with 4-amino-3-mercapto-5-(trifluoromethyl)-4*H*-1,2,4-triazole to give the bicyclic compound *N*-[3-(trifluoromethyl)-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazol-6-yl]benzamide **IX**.

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A few years ago, it was reported [1,2] that 4-amino-6-*tert*-butyl-3-(methylthio)-1,2,4-triazin-5(4*H*)-one **I** reacts with sulfonyl isocyanates **IIa** and with phenoxyacetyl isocyanates **IIb** to give *N*-arenesulfonyl-*N'*-[1,2,4-triazin-5(4*H*)-on-4-yl]ureas **IIIa** and *N*-phenoxyacetyl-*N'*-[1,2,4-triazin-5(4*H*)-on-4-yl]ureas **IIIb** as outlined in Scheme 1.



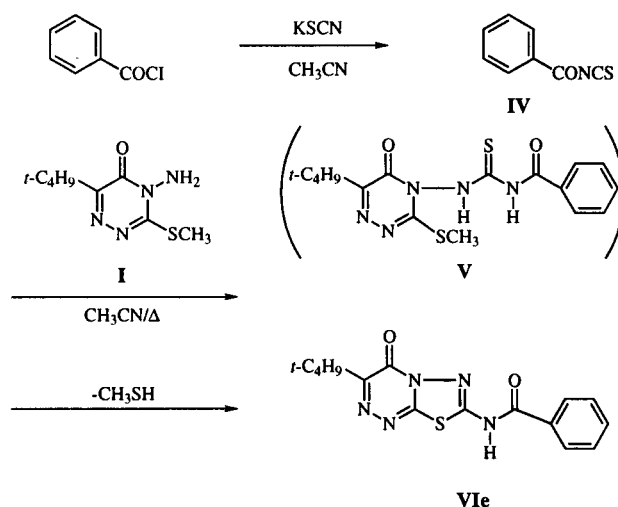
Our interest in the reactions of 4-aminotriazin-5(4*H*)-ones prompted us to investigate the reaction of 4-amino-6-*tert*-butyl-3-(methylthio)-1,2,4-triazin-5(4*H*)-one **I** with benzoyl isothiocyanates **IV**. We expected that *N*-benzoyl-*N'*-[1,2,4-triazin-5(4*H*)-on-4-yl]thioureas **V** would result from the reaction. Surprisingly, the aforementioned reaction (**I** + **IV** in acetonitrile at reflux) gave only *N*-[3-*tert*-butyl-4-oxo-4*H*-1,3,4-thiadiazolo[2,3-*c*]-1,2,4-triazin-7-yl]benzamides **VI** as outlined in Scheme 2.

During the course of the reaction, we were able to detect only compounds **I**, **IV** and **VI** by thin layer chromatography. Presumably compound **V** was rapidly converted to the final product **VI**.

Similarly, other benzoyl isothiocyanates and methoxycarbonyl isothiocyanate reacted to give the substituted 4*H*-1,3,4-thiadiazolo[2,3-*c*]-1,2,4-triazin-4-ones listed in Table 1.

A few years ago, Molina, Alajarin and Benzal [3] prepared several 7-arylamino-3-methyl-4*H*-1,3,4-thiadiazolo[2,3-*c*]-1,2,4-triazin-4-ones by heating a solution of 4-amino-6-methyl-3-thioxo-1,2,4-triazin-5-(4*H*)-one **VII** and the aryl isothiocyanates in dimethylformamide for 48

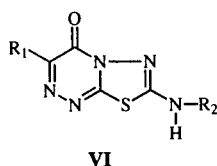
Scheme 2



hours at 100°. When benzoyl isothiocyanate was used in lieu of the aryl isothiocyanate, 7-benzamido-3-methyl-4*H*-1,3,4-thiadiazolo[2,3-*c*]-1,2,4-triazin-4-one **VI**d was obtained (Scheme 3). Our synthesis provides an alternate method for the preparation of 7-benzamido-3-substituted 4*H*-1,3,4-thiadiazolo[2,3-*c*]-1,2,4-triazin-4-ones **VI** under mild conditions from readily available starting materials.

The formation of 7-benzamido-3-methyl-4*H*-1,3,4-thiadiazolo[2,3-*c*]-1,2,4-triazin-4-one **VI**d by Molina's method (elimination of hydrogen sulfide) and by our method (elimination of methyl mercaptan) from the intermediate benzoyl thioureas led us to believe that 4-amino-3-(methylthio)-5-(trifluoromethyl)-4*H*-1,2,4-triazole **VIII**, a compound that has a methylthio group adjacent to an amino group, would react with benzoyl isothiocyanate to give a benzoylthiourea which would readily lose methyl mercaptan to give the bicyclic *N*-[3-(trifluoromethyl)-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazol-6-yl]benzamide **IX**. At ambient temperature, no product could be

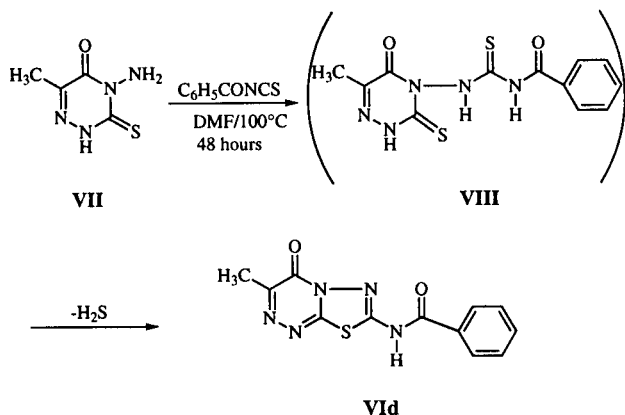
Table 1



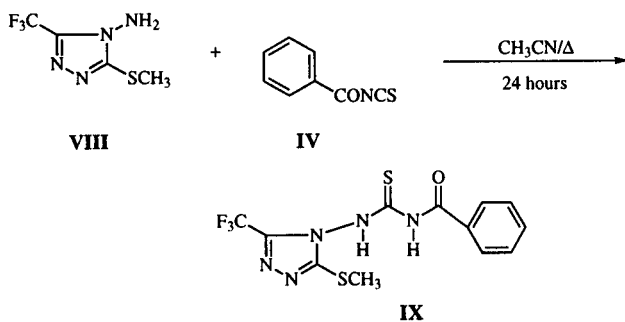
Compound	R ₁	R ₂	Crystallization solvent	Yield (%)	mp (°C)
VIa	<i>tert</i> -butyl	carbomethoxy	CH ₃ CN	25	232-234
VIb	phenyl	carbomethoxy	DMF	36	244-246
VIc	<i>tert</i> -butyl	4-bromobenzoyl	THF	46	278-281
VI d	methyl	benzoyl	DMF	84	>290
VIe	<i>tert</i> -butyl	benzoyl	CH ₃ CN	37	237-239
VI f	<i>tert</i> -butyl	3-(trifluoromethyl)benzoyl	CH ₃ CN	58	178-180
VI g	<i>tert</i> -butyl	2-nitrobenzoyl	CH ₃ CN	27	243-245
VI h	<i>tert</i> -butyl	4- <i>tert</i> -butylbenzoyl	CH ₃ CN	39	267-269
VI i	cyclohexyl	benzoyl	DMF	67	>265
VI j	<i>tert</i> -butyl	4-methoxybenzoyl	THF	76	294-296

detected after four hours. Surprisingly, upon heating the reaction mixture at reflux for twenty-four hours we obtained only 1-benzoyl-3-[3-(methylthio)-5-(trifluoromethyl)-4*H*-1,2,4-triazol-4-yl]thiourea **IX** (Scheme 4), with no evidence of a bicyclic product.

Scheme 3

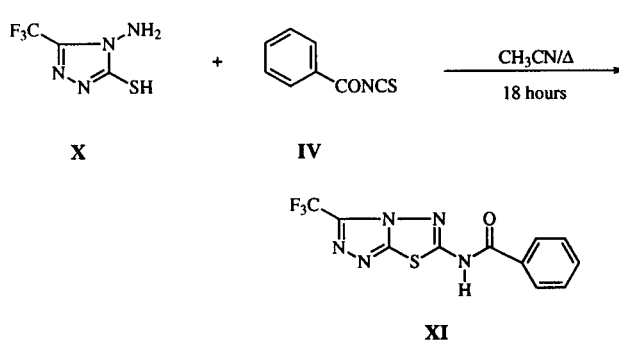


Scheme 4



In contrast, benzoyl isothiocyanates reacted with 4-amino-3-mercapto-5-(trifluoromethyl)-4*H*-1,2,4-triazole **X** to give the bicyclic *N*-[3-(trifluoromethyl)-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazol-6-yl]benzamides when the reactants were heated under reflux for 18 hours (Scheme 5).

Scheme 5



EXPERIMENTAL

Melting points were determined with a Thomas Hoover capillary melting point apparatus and are reported uncorrected. The ¹H nmr spectra were recorded using a Varian Unity Plus 300 or Varian VXR 400. Chemical shift values are reported in parts per million on the δ scale. The nmr spin multiplicities are indicated by the symbols: s (singlet), d (doublet), t (triplet), q (quartet) and m (multiplet). Elemental analyses were performed by Quantitative Technologies Inc., Whitehouse, New Jersey, U.S.A. The benzoyl isothiocyanate used in this investigation was purchased from Aldrich Chemical Company. In general, the substituted benzoyl isothiocyanates and the methoxycarbonyl isothio-

cyanate were prepared *in situ* by reaction of the substituted benzoyl chloride or methyl chloroformate with potassium or ammonium thiocyanate in acetonitrile [4]. The 6-substituted-4-amino-3-(methylthio)-1,2,4-triazin-5(4*H*)-ones are known compounds and were prepared by the literature method [5]. The 4-amino-3-mercapto-5-(trifluoromethyl)-4*H*-1,2,4-triazole was prepared by the reaction of thiocarbonylhydrazide with trifluoroacetic acid [6].

General Procedures for the Preparation of Substituted 4*H*-1,3,4-Thiadiazolo[2,3-*c*]-1,2,4-triazin-4-ones VIa-j.

In a nitrogen atmosphere, the benzoyl chloride or methyl chloroformate (0.011 mole) was added over two minutes to a stirred solution of 1.1 g (0.011 mole) of potassium thiocyanate in 50 ml of acetonitrile. The reaction mixture was heated under reflux for 10 minutes and then cooled to about 30°. A 6-substituted 4-amino-4,5-dihydro-3-(methylthio)-1,2,4-triazin-5-one (0.010 mole) was added in one portion, and the reaction mixture was heated under reflux for 4 hours. Water (25 ml) was added to the cooled reaction mixture and the product was removed by filtration and crystallized from a suitable solvent. Only VII was prepared by heating the commercially available benzoyl isothiocyanate with 4-amino-6-cyclohexyl-3-(methylthio)-1,2,4-triazin-5(4*H*)-one. Data for the compounds prepared are listed in Tables 1 and 2.

Table 2

Compound	Formula			¹ H NMR (DMSO- <i>d</i> ₆) δ, J (Hz)
	Anal.	Calcd.	(Found)	
	C	H	N	
VIa	C ₁₀ H ₁₃ N ₅ O ₃ S			1.39 (s, 9H), 3.83
	42.40	4.62	24.72	(s, 3H), 13.05
	(42.33)	4.44	24.73)	(br s, 1H)
VIb	C ₁₂ H ₉ N ₅ O ₃ S			3.85 (s, 3H),
	47.52	2.99	23.09	7.49-7.52 (m, 3H),
	(47.74)	2.96	23.13)	8.12-8.16 (m, 2H),
VIc	C ₁₅ H ₁₄ BrN ₅ O ₂ S•H ₂ O			13.15 (br s, 1H)
	42.26	3.78	16.43	1.42 (s, 9H), 7.83
	(42.58)	3.62	16.47)	(d, J = 8.6 Hz, 2H),
VIId	C ₁₂ H ₉ N ₅ O ₂ S			8.07 (d, J = 8.6 Hz, 2H)
	50.17	3.16	24.38	2.44 (s, 3H),
	(49.82)	3.07	24.02)	7.58-8.16 (m, 5H),
VIe	C ₁₅ H ₁₅ N ₅ O ₂ S			13.75 (br s, 1H)
	54.70	4.59	21.26	1.43 (s, 9H),
	(54.99)	4.49	21.08)	7.58-8.17 (m, 5H),
VIIf	C ₁₆ H ₁₄ F ₃ N ₅ O ₂ S			13.80 (br s, 1H)
	48.36	3.55	17.62	1.43 (s, 9H), 7.86
	(48.13)	3.45	17.47)	(t, J = 7.9 Hz, 1H),
VIg	C ₁₅ H ₁₄ N ₆ O ₄ S			8.09 (d, J = 7.9 Hz, 1H),
	48.12	3.77	22.45	8.41 (d, J =
	(48.10)	3.61	22.45)	7.9 Hz, 1H), 8.55
VIh	C ₁₉ H ₂₃ N ₅ O ₂ S•H ₂ O			(s, 1H)
	56.56	6.24	17.36	1.42 (s, 9H),
	(56.42)	6.06	17.30)	7.84-7.99 (m, 3H),

continued

Table 2 continued

Compound	Formula			¹ H NMR (DMSO- <i>d</i> ₆) δ, J (Hz)
	Anal.	Calcd.	(Found)	
	C	H	N	
VII	C ₁₇ H ₁₇ N ₅ O ₂ S			1.24-1.93 (m, 10H),
	57.45	4.82	19.70	3.1 (m, 1H),
	(57.70)	4.80	19.84)	7.58-8.17 (m, 5H,
VIJ	C ₁₆ H ₁₇ N ₅ O ₃ S			13.75 (br s, 1H)
	53.47	4.77	19.48	1.42 (s, 9H), 3.87 (s,
	(53.57)	4.67	19.20)	3H), 7.13 (d, J =

4-Amino-3-(methylthio)-5-(trifluoromethyl)-4*H*-1,2,4-triazole VIII.

In a nitrogen atmosphere, 4-amino-3-mercapto-5-(trifluoromethyl)-4*H*-1,2,4-triazole (2.0 g, 0.011 mole) was added to a stirred solution of sodium methoxide (0.6 g, 0.011 mole) in 75 ml of methanol. The resulting solution was cooled to 5°, methyl iodide (0.7 ml, 0.011 mole) was added dropwise, and the reaction mixture was stirred at ambient temperature for 4 hours. The methanol was removed under vacuum, warm ethyl acetate (75 ml) was added to the residue, and the ethyl acetate solution of the product was filtered to remove a small amount of a solid. Evaporation of the ethyl acetate under vacuum gave the crude product, which was purified by column chromatography on silica gel eluting with ethyl acetate/hexane (1:1), yield 1.65 g (77%), mp 99-100°; ¹H nmr (DMSO-*d*₆): 2.75 (s, 3H), 4.79 (s, 2H).

Anal. Calcd. for C₄H₅N₄S: C, 24.24; H, 2.54; N, 28.27. Found: C, 24.41; H, 2.32; N, 28.33.

1-Benzoyl-3-[3-(methylthio)-5-(trifluoromethyl)-4*H*-1,2,4-triazol-4-yl]thiourea IX.

In a nitrogen atmosphere, benzoyl isothiocyanate (0.5 ml, 0.0033 mole) was added to a solution of 4-amino-3-(methylthio)-5-(trifluoromethyl)-4*H*-1,2,4-triazole (0.7 g, 0.0035 mole) in 30 ml of acetonitrile. The reaction mixture was stirred and heated under reflux for 24 hours, cooled to ambient temperature and the acetonitrile was removed under vacuum to give the crude product. The product was purified by column chromatography on silica gel eluting with ethyl acetate/hexane (1:2) and then with ethyl acetate/hexane (1:1) to give an oil, [R_f 0.61, silica gel, ethyl acetate/hexane (1:1)]. The oil solidified and was crystallized from 1-chlorobutane, yield 0.91 g (72%), mp 124-127°; ¹H nmr (DMSO-*d*₆): 2.79 (s, 3H), 7.56-7.94 (m, 5H), 9.35 (s, 1H), 12.75 (br s, 1H).

Anal. Calcd. for C₁₂H₁₀F₃N₅OS₂: C, 39.58; H, 2.79; N, 19.38. Found: C, 39.80; H, 2.44; N, 19.21.

N-[3-(Trifluoromethyl)-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazol-6-yl]-benzamide XI.

In a nitrogen atmosphere, benzoyl isothiocyanate (0.75 ml, 0.005 mole) was added to a solution of 4-amino-3-mercapto-5-(trifluoromethyl)-4*H*-1,2,4-triazole (1.0 g, 0.005 mole) in 20 ml of acetonitrile. The resulting solution was stirred and heated under reflux for 18 hours (a solid formed during the course of the reaction). The reaction mixture was cooled to 5° and the solid was removed by filtration. The crude product was crystall-

lized from tetrahydrofuran containing a few drops of dimethyl formamide, yield 0.7 g (41%), mp >260°; ¹H nmr (DMSO-d₆): 7.58-8.15 (m, 5H).

Anal. Calcd. for C₁₁H₆F₃N₅OS: C, 42.17; H, 1.93; N, 22.36. Found: C, 42.55; H, 2.08; N, 22.29.

The following compounds were prepared by the above method from 4-amino-3-mercapto-5-(trifluoromethyl)-4*H*-1,2,4-triazole **X** and the appropriate benzoyl isothiocyanate. The benzoyl isothiocyanates used to prepare **XIa** and **XIb** were prepared by the literature method [4] and purified by column chromatography [silica gel, ethyl acetate/hexane (1:10)].

3-(Trifluoromethyl)-*N*-[3-(trifluoromethyl)-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazol-6-yl]benzamide **XIa**.

This compound was prepared from 3-(trifluoromethyl)benzoyl isothiocyanate and **X**, yield 41%, mp >260°, ¹H nmr (DMSO-d₆): 7.85 (t, *J* = 7.9 Hz, 1H), 8.09 (d, 7.9 Hz, 1H), 8.39 (d, 7.9 Hz, 1H), 8.53 (s, 1H).

Anal. Calcd. for C₁₂H₅F₆N₅OS: C, 37.80; H, 1.32; N, 18.37. Found: C, 38.21; H, 1.44; N, 18.29.

4-Methoxy-*N*-[3-(trifluoromethyl)-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazol-6-yl]benzamide **XIb**.

This compound was prepared from 4-methoxybenzoyl isothiocyanate and **X**, yield 39%, mp >260°; ¹H nmr (DMSO-d₆): 3.87 (s, 3H), 7.13 (d, 9.0 Hz, 2H), 8.15 (d, 9.0 Hz, 2H), 13.44 (br s, 1H).

Anal. Calcd. for C₁₂H₈F₃N₅O₂S: C, 41.98; H, 2.35; N, 20.40. Found: C, 42.28; H, 2.25; N, 20.10.

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