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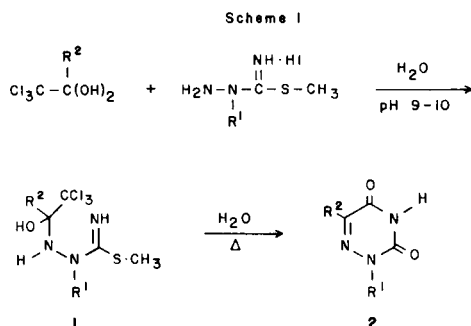
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Dedicated to Professor F. Korte on the
occasion of his 60th Birthday

The reaction of 1,1,1-trichloro-3,3,3-trifluoroacetone with *S*-methyl-2-arylisothiosemicarbazides affords an unusual synthesis of 1-aryl-3-trifluoromethyl-5-methylthio-1,2,4-triazoles from which 1-aryl-3-trifluoromethyl-1,2,4(4*H*)-triazole-5-ones are obtained on treatment with base.

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A synthesis of 1,2,4-triazine-3,5-dione ("6-azauracil"), **2a**, in which chloral hydrate methylisothiosemicarbazone, **1a**, was cyclized in refluxing water was described by Chang and Ulbricht [1]. The mechanism of the reaction was formulated as a series of eliminations of hydrogen chloride and water leading to a substituted asymmetrical triazine which could give rise to **2a** by hydrolysis (Scheme 1).



(**a**, R¹, R² = H; **b**, R¹ = aryl, R² = CF₃)

This method appeared applicable to the synthesis of di-substituted 6-azauracils of generalized structure **2b**. Although our attempt did not give 6-azauracils, we found an unusual synthesis of novel 1-aryl-3-trifluoromethyl-5-methylthio-1,2,4-triazoles from which 1-aryl-3-trifluoromethyl-1,2,4-triazole-5(4*H*)-ones are obtained on alkaline hydrolysis.

Results and Discussion.

The preparation of the starting materials, **10**, for the reaction with 1,1,1-trichloro-3,3,3-trifluoroacetone is outlined in Scheme 2.

The reaction of phenylhydrazine (in water) with cyanogen bromide (in ethanol) gave 1-phenylhydrazine-1-carbonitrile, **4a**, following the directions of Pellizzari [2]. 4-Tolylhydrazine, 4-fluorophenylhydrazine, and 4-chlorophenylhydrazine reacted analogously with cyanogen bromide in aqueous ethanol to give the respective 1-phenylhydrazine-1-carbonitriles, **4b**, **4c**, and **4d**, in fair to excellent yields (Table 1).

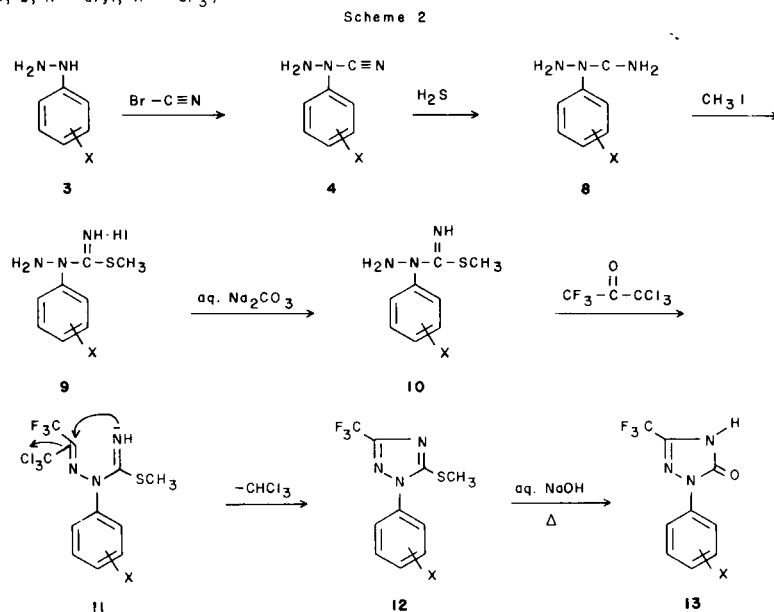


Table 1

1-Phenylhydrazine-1-carbonitriles, **4**, and 1-Phenylsemicarbazides, **5**

X	Compound	% Yield	Mp, °C	ν C≡N [a]	Compound	% Yield	Mp, °C
H	4a	20	83-86 [b]	2200	5a	[c]	171-172 [d]
4-CH ₃	4b	87	73-76	2210	—	—	—
4-F	4c	47	106-108	2210	—	—	—
4-Cl	4d	26	80-83	2220	—	—	—
2-F	4e	7	40-43	2220	5e	24	159-160
3-Cl	4f	8	79-80	2215	5f	4	150-152
3,4-Cl ₂	4g	6.5	116-118	2210	5g	[c]	—
2-Cl	—	—	—	—	5h	50	170-173
3-CF ₃	—	—	—	—	5i	25	140-142

[a] Infrared absorption (potassium bromide-pellet) in cm⁻¹. [b] Mp 89° (Ref [2]). [c] Not isolated. [d] Ref [3].

Table 2

2-Phenylthiosemicarbazides, **8**, and 2-Phenyl-3-methylisothiosemicarbazides, **10**

X	Compound	% Yield	Mp, °C	Compound	% Yield	Mp, °C
H	8a	60	149-151 [a]	10a	99	96-99 [b]
4-CH ₃	8b	88	116-118	—	—	—
4-F	8c	82	165-167	10c	71	113-115
4-Cl	8d	70	150-152	10d	89	105-108
2-F	8e	84	140-143	—	—	—
3-Cl	8f	97	142-144	10f	68	62-65
3,4-Cl ₂	8g	90	182-185	10g	93	125-128

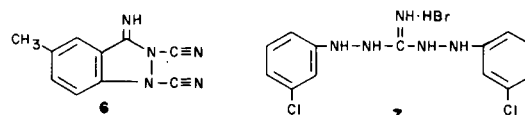
[a] Mp 153° (Ref [2]). [b] Hydroiodide, mp 176-179° dec.

The scope of the reaction of substituted phenylhydrazines with cyanogen bromide to give substituted phenylhydrazine-1-carbonitriles is limited. For example, *ortho*-substituents on phenyl which can cause steric crowding, and strongly electron withdrawing substituents in both the 3 (and 3,4)-positions gave largely reduced yields (6-8%) of substituted 1-phenylhydrazine-1-carbonitriles. The reactions of 2-chlorophenylhydrazine and 3-(trifluoromethyl)-phenylhydrazine with cyanogen bromide gave none of the desired carbonitriles. Instead, the reaction products from these hydrazines were the respective 1-phenylsemicarbazides, **5h** and **5i** (Table 1).

The formation of yet another side product was observed when 4-tolylhydrazine was allowed to react with cyanogen bromide. In addition to **4b** (87%), we isolated a small amount of the 3-indazoline imine, **6** (1%). The gross structure of **6** was readily established by analytical and spectral data, especially an intense M⁺ at m/z 197 with a compati-

ble fragmentation pattern, ν NH at ~3000 and ν C=N at 2260 and 2210 cm⁻¹.

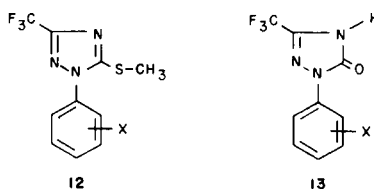
The reaction of 3-chlorophenylhydrazine with cyanogen bromide leading to **4f** (8%) and **5f** (4%) was accompanied by the formation of the hydrobromide of *N,N'*-bis(3-chloro-anilino)guanidine **7** (29%). The structure of **7** is based upon correct analytical and spectral data, especially an intense M⁺-HBr at m/z 307 under electron impact.



All 1-phenylhydrazine-1-carbonitriles, **4**, listed in Table 1 reacted readily with hydrogen sulfide in ethanol containing an excess of triethylamine to give 2-phenylthiosemicarbazides, **8**, in 60-97% yield (Table 2).

With the exception of 2-(4-tolyl)thiosemicarbazide, **8b**,

Table 3

1-Phenyl-3-trifluoromethyl-5-methylthio-1,2,4-triazoles, **12**, and 1-Phenyl-3-trifluoromethyl-1,2,4-triazoles-5(4*H*)-ones **13**

X	Compound	% Yield	Mp, °C	δ SCH ₃ [a]	M ⁺ [c]	Compound	% Yield	Mp, °C	ν C=O [b]	M ⁺ [c]
H	12	39	—	2.7	259	13a [d]	38	185-186	1720	—
4-F	12b	85	—	2.7	277	13b	11	161-164	1695	247
4-Cl	12c	60	63-65	2.75	—	13c [e]	83	181-183	1725	263
3-Cl	12d	43	66-67	2.7	293	13d [f]	92	171-173	1710	—
3,4-Cl ₂	12e	85	—	—	—	13e	33	187-189	1720	297

[a] The nmr positions for SCH₃ (s) in deuteriochloroform. [b] Infrared absorption (potassium bromide-pellet) in cm⁻¹. [c] Electron impact mass spectrum. [d] pKa 4.2 (50% aqueous methanol), 4.7 (50% aqueous DMF). [e] pKa 4.6 (50% aqueous methanol). [f] pKa (water).

and 2-(2-fluorophenyl)thiosemicarbazide, **8e**, the remaining **8** compounds listed in Table 2 underwent facile S-methylation with methyl iodide in methanol to give the hydriodides of 2-phenyl-3-methylisothiosemicarbazides, **9**, which on treatment with aqueous sodium carbonate gave the 2-phenyl-3-methylisothiosemicarbazides, **10**, in 68-93% yield (Table 2).

The attempted purification by silica chromatography of the reaction product obtained from **8b** and methyl iodide led to the recovery in 20% yield of **4b**. Since the work-up was accompanied by the appearance of methyl mercaptan and/or dimethyl disulfide odors, it is concluded that the free base, 4-tolyl-3-methylisothiosemicarbazide, is too unstable to be isolated. Reasons for the failure to isolate the S-methyl derivative of **8e** are not clear.

It was anticipated that the isothiosemicarbazides, **10**, would undergo condensation with 1,1,1-trichloro-3,3,3-trifluoroacetone and yield isolable isothiosemicarbazones, **11**. We have now found that this reaction proceeds exothermically in tetrahydrofuran, providing ready access to 1-aryl-3-trifluoromethyl-5-methylthio-1,2,4-triazoles, **12**, in 39-85% yields. We believe that the reaction involves the intermediate formation of **11** followed by elimination of chloroform as indicated to give the cyclized products, **12**.

The structures of the **12** compounds were established from analytical and spectral data. Infrared NH absorption was not apparent but CF₃ absorptions occurred near 1200 cm⁻¹. The nmr spectra showed the correct aromatic proton count near δ 7.5, and a sharp S-methyl chemical shift at δ 2.7. Those that have been investigated showed an M⁺ in their electron impact mass spectra (Table 3).

Treatment with aqueous methanol converts these methylthiotriazoles into 1-phenyl-3-trifluoromethyl-1,2,4-triaz-

ole-5(4*H*)-ones, **13**, in 11-92% yields (Table 3). The structural assignments of the **13** compounds are supported by analytical, nmr, infrared (ν NH ~2800 and ν C=O 1725-1695 cm⁻¹), and electron-impact mass spectral (M⁺) data.

Triazolones, **13**, are acidic. The pKa values for **13a**, **13c**, and **13d** fall within the range of 4.2 to 4.7. The strongly anionic properties of these compounds can be explained by the influence on basicity of the NH group of two adjacent electron-withdrawing groups, C=O and CF₃, which tend to reduce the basic character of the NH group.

EXPERIMENTAL

Representative methods of synthesis are described for **4b**, **6**, **8c**, **10c**, **12d**, and **13c**.

1-(4-Tolyl)hydrazine-1-carbonitrile, **4b**, and 5-Methylindazole-3-imine-1,2-dicarbonitrile, **6**.

To a stirred solution of 25.0 g (0.158 mole) of *p*-tolylhydrazine (Aldrich) and 6.3 g (0.158 mole) of sodium hydroxide in 550 ml of water and 500 ml of ethanol was added, within 5 minutes, a solution of 17.0 g (0.158 mole) of cyanogen bromide in 50 ml of ethanol. The mixture was stirred at ambient temperature for 20 hours. Most of the ethanol was removed by rotary evaporation. The resulting aqueous slurry was cooled in ice and filtered. The filter cake was dissolved in ether, dried (magnesium sulfate), filtered, and concentrated to a volume of 100 ml. Filtration at this point afforded 0.4 g (1%) of **6**, mp >300°; ir (potassium bromide): cm⁻¹ ~300° (NH, CH), 2260 and 2210 (C≡N), 1660 (C=N); ms: (70 eV) m/z 197 (M⁺), 171 (M⁺-CN), 130 (CH₃C₆H₃NCN⁺).

The ethanol filtrate was diluted with 75 ml of hexane, cooled and filtered to give 19.1 g (87%) of **4b** as a tan solid, mp 73-76°; ir (potassium bromide): cm⁻¹ 3360 (NH), 2210 (C≡N); ¹H nmr (deuteriochloroform): δ 1.3 (3, CH₃), 4.5 (2, NH₂), 7.1 (4, (CH)=).

2-(4-Fluorophenyl)thiosemicarbazide, **8c**.

Into a cooled (5°) solution of 26.0 g (0.172 mole) of **4c** in 400 ml of ethanol was introduced hydrogen sulfide to saturation, followed by the addition of 101.0 g (1.0 mole) of triethylamine. The solution was again saturat-

Table 4
Analytical Data of All Compounds Reported

Compound	Formula	Carbon		Hydrogen		Nitrogen	
		Calcd.	Found	Calcd.	Found	Calcd.	Found
4a	C ₇ H ₇ N ₃	63.2	63.2	5.3	5.3	31.6	31.2
4b	C ₆ H ₅ N ₃	65.3	65.3	6.1	6.1	28.6	28.6
4c	C ₇ H ₆ FN ₃	55.6	55.7	4.0	3.9	27.8	28.1
4d	C ₇ H ₆ ClN ₃	50.1	50.0	3.6	3.6	25.1	24.8
4e	C ₇ H ₆ FN ₃	55.6	55.5	4.0	4.0	27.8	27.9
4f	C ₇ H ₆ ClN ₃	50.1	50.0	3.6	3.5	25.1	25.3
4g	C ₇ H ₅ Cl ₂ N ₃ [a]	41.6	41.5	2.5	2.6	20.8	20.4
5e	C ₇ H ₆ FN ₃ O	49.7	49.6	4.7	4.6	24.9	25.4
5f	C ₇ H ₆ ClN ₃ O	45.3	45.1	4.3	4.2	22.6	22.4
5h	C ₇ H ₆ ClN ₃ O	45.3	45.4	4.3	4.3	22.6	22.6
5i	C ₆ H ₅ F ₃ N ₃ O	43.8	43.5	3.7	3.7	19.2	19.0
6	C ₁₀ H ₇ N ₅	60.9	60.7	3.6	3.6	35.5	35.7
7	C ₁₃ H ₁₄ BrCl ₂ N ₅	39.9	39.9	3.6	3.6	17.9	17.9
8a	C ₇ H ₉ N ₃ S	50.3	50.3	5.4	5.5	25.1	25.5
8b	C ₆ H ₁₁ N ₃ S	53.0	53.0	6.1	6.1	23.2	23.6
8c	C ₇ H ₈ FN ₃ S	45.4	45.2	4.3	4.3	22.7	22.7
8d	C ₇ H ₈ ClN ₃ S	41.7	41.8	4.0	3.9	20.8	20.8
8e	C ₇ H ₈ FN ₃ S	45.4	45.3	4.3	4.3	22.7	22.3
8f	C ₇ H ₈ ClN ₃ S [b]	41.7	41.8	4.0	4.0	20.8	20.8
8g	C ₇ H ₇ Cl ₂ N ₃ S [c]	35.6	35.5	3.0	3.0	17.8	17.6
9a	C ₈ H ₁₂ IN ₃ S [d]	31.1	30.8	3.9	3.6	13.6	13.2
9g	C ₈ H ₁₀ Cl ₂ IN ₃ S [e]	25.4	25.8	2.6	2.9	11.1	10.7
10a	C ₈ H ₁₁ N ₃ S	53.0	53.4	6.1	6.0	23.2	23.5
10c	C ₈ H ₁₀ FN ₃ S	48.2	48.0	5.0	5.0	21.1	21.5
10d	C ₈ H ₁₀ ClN ₃ S	44.5	44.5	4.6	4.6	19.5	20.0
10f	C ₈ H ₁₀ ClN ₃ S	44.5	45.0	4.6	4.5	19.5	19.1
10g	C ₈ H ₉ Cl ₂ N ₃ S	38.4	38.4	3.6	3.6	16.8	16.4
12a	C ₁₀ H ₉ F ₃ N ₃ S	46.3	46.6	3.1	3.2	16.2	16.0
12b	C ₁₀ H ₇ F ₄ N ₃ S	43.3	43.5	2.5	2.6	15.2	15.5
12c	C ₁₀ H ₇ ClF ₃ N ₃ S	40.9	41.1	2.4	2.5	14.3	14.2
12d	C ₁₀ H ₇ ClF ₃ N ₃ S	40.9	41.1	2.4	2.3	14.3	14.5
13a	C ₉ H ₆ F ₃ N ₃ O	47.2	47.2	2.6	2.7	18.3	18.3
13b	C ₉ H ₅ F ₄ N ₃ O	43.7	43.6	2.0	2.4	17.0	17.1
13c	C ₉ H ₅ ClF ₃ N ₃ O	41.0	41.4	1.9	2.0	15.9	15.6
13d	C ₉ H ₅ ClF ₃ N ₃ O	41.0	40.9	1.9	1.8	15.9	15.6
13e	C ₉ H ₄ Cl ₂ F ₃ N ₃ O	36.2	36.5	1.3	1.4	14.1	14.2

[a] Chlorine: Calcd. 35.1, Found 34.9. [b] Chlorine: Calcd. 17.6, Found 17.5. [c] Chlorine: Calcd. 30.1, Found: 29.6; Sulfur: Calcd. 13.6, Found 13.1. [d] Iodine: Calcd. 41.1, Found 40.9. [e] Chlorine: Calcd. 18.8, Found 18.6; Sulfur: Calcd. 8.5, Found 8.2; Iodine: Calcd. 33.6, Found 34.1.

ted with hydrogen sulfide and stored in an ice bath overnight. The reaction mixture was concentrated under rotary evaporation. The residue was triturated with hexane and filtered to give 26.0 g (82%) of colorless **8c**, mp 165-167°; ir (potassium bromide): cm⁻¹ 3500-3100 (NH); ¹H nmr (DMSO-d₆): δ 5.4 (2, NH₂), 7.75 (2, NH₂), ~7.2 (4, (CH=)₄).

2-(4-Fluorophenyl)-3-methylisothiosemicarbazide, **10c**.

To a stirred solution of 26.0 g (0.141 mole) of **8c** in 200 ml of methanol was added dropwise 21.3 g (0.15 mole) of methyl iodide. The reaction mixture was refluxed at 66° for 2 hours, concentrated under rotary evaporation and dissolved in 500 ml of water. The solution was decolorized with activated charcoal, filtered and cooled to 10° while aqueous sodium

carbonate was added to pH 9. The precipitate was removed by filtration and dried to give 20.0 g (71%) of colorless **10c**, mp 113-115°; ir (potassium bromide): cm⁻¹ 3350, 3270, and 3180 (NH); ¹H nmr (deuteriochloroform): δ 2.25 (3, CH₃), 4.5 (2, NH₂), 6.7 (1, NH), 6.9-7.4 (4, (CH=)₄).

Attempted Methylation of 2-(4-Tolyl)thiosemicarbazide, **8b**.

A solution of 16.0 g (0.088 mole) of **8b** in 160 ml of methanol was treated with 14.2 g (0.1 mole) of methyl iodide and refluxed for 6 hours. The solvent was removed under rotary evaporation. The residue was dissolved in 200 ml of water, made alkaline with aqueous sodium hydroxide and extracted with three 200 ml portions of ether. The combined extracts were purified by silica chromatography to give 1.0 g (6%) of colorless **4b**,

mp 73-76°; ir (potassium bromide): cm^{-1} 3370 (NH), 2220 (C≡N); ^1H nmr (deuteriochloroform): δ 2.3 (3, CH_3), 4.5 (2, NH_2), 7.1 (4, (CH=)₄).

In a second experiment, **4b** was obtained in 23% yield, mp 73-76° (mixed mp 73-76°).

1-(3-Chlorophenyl)-3-trifluoromethyl-5-methylthio-1,2,4-triazole, **12d**.

To a stirred solution of 3.5 g (0.016 mole) of **10f** in 100 ml of tetrahydrofuran was added 3.5 g (0.016 mole) of 1,1,1-trichloro-3,3,3-trifluoroacetone causing the temperature to rise from 20° to 34°. The mixture was refluxed for 3 hours and concentrated under rotary evaporation. The residual syrup, 6.3 g, was purified by silica chromatography (solvent mixture: 96% (by volume) hexane, 4% THF) to give 2.0 g (43%) of colorless **12d**, mp 66-67°; ir (potassium bromide): cm^{-1} ~1200 (CF_3), no apparent NH; ^1H nmr (deuteriochloroform): δ 2.7 (3, CH_3), ~7.5 (4, (CH=)₄); ms: (70 eV) m/z 293 (M^+).

1-(4-Chlorophenyl)-3-trifluoromethyl-1,2,4-triazole-5(4*H*)-one, **13c**.

A solution of 13.5 g (0.046 mole) of **12c** and 2.4 g (0.06 mole) of sodium

hydroxide in 225 ml of 66% aqueous methanol was refluxed for 24 hours. The cooled reaction mixture was diluted with 300 ml of ice water and acidified with hydrochloric acid. Filtration afforded 10.0 g (83%) of **13c** as a light yellow solid; mp 181-183°; p*K*_a (50% aqueous methanol) 4.6; ir (potassium bromide): cm^{-1} ~2800 (NH), 1725 (C=O); ^1H nmr (DMSO-d_6): δ indicates 4-chloro-position on phenyl; ms: (70 eV) m/z 263 (M^+), 244 ($\text{M}^+\text{-F}$), 220 ($\text{M}^+\text{-HNCO}$), 125 ($\text{C}_6\text{H}_4\text{ClN}^+$), 111 ($\text{C}_6\text{H}_5\text{Cl}^+$).

REFERENCES AND NOTES

- [1] P. K. Chang and T. L. V. Ulbricht, *J. Am. Chem. Soc.*, **80**, 976 (1978).
- [2] G. Pellizzari, *Gazz. Chim. Ital.*, **37**, 617; *ibid.*, **41**, 55 (1911).
- [3] E. Fischer, *Ann. Chem.*, **190**, 113 (1878); From "Beilstein", Vol **15**, 287.
- [4] The reaction of phenylhydrazine with cyanogen bromide has been reported [2] to give **4a** and **5a** in addition to the hydrobromides of *N,N'*-dianilinoguanidine and anilinophenylguanazole.