Synthesis of Trifluoromethyltriazoles from Trifluoroacetohydrazonoyl Bromide [1]

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N-Phenyltrifluoroacetohydrazonoyl bromide (**1**) reacted with potassium isothiocyanate and isocyanate to give 5-imino-4-phenyl-2-trifluoromethyl-$\triangle^2$-1,3,4-thiadiazoline and 1-phenyl-3-trifluoromethyl-$\triangle^2$-1,2,4-triazolin-5-one, respectively. On treatment with several types of cumulative double bonds such as alkyl isothiocyanate, isocyanate, and carbodiimide, **1** afforded regioselectively the corresponding trifluoromethylthiadiazoline, -oxadiazoline, and -triazoline, respectively. These cycloadducts were assumed to form through the stepwise path involving the addition of **1** toward the cumulative double bond followed by the intramolecular cyclization. Concerning cyanamides, the corresponding triazoles were obtained and the reactions with pyridines afforded the triazolopyridinium bromides. The reactivity of the latter was found to depend on the substituents on the pyridine nucleus.

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The introduction of a trifluoromethyl group into heterocyclic ring systems has received current interest from the viewpoint of pharmacological activity [2]. On the other hand, hydrazonoyl halides have offered a versatile tool in synthesis of azoles such as pyrazoles and triazoles [3]. So far, we have demonstrated the successful pathway for the synthesis of trifluoromethylpyrazoles by the cycloadditions of (trifluoromethyl)nitrilimines, derived *in situ* from trifluoroacetohydrazonoyl halides in the presence of base, toward the carbon-carbon multiple bonds of olefins and acetylenes [4]. As a development of this study, we wish to describe in the present paper the synthesis of trifluoromethyltriazole derivatives from the reactions of *N*-phenyltrifluoroacetohydrazonoyl bromide (**1**) or *N*-phenyl-*C*-(trifluoromethyl)nitrilimine (**2**) with various dipolarophiles having the carbon-nitrogen multiple bonds.

The bromide **1** was first subjected to the reaction with dipolarophiles involving cumulative double bonds. The bromide **1** was reacted with potassium isothiocyanate for three hours in refluxing methanol, to give 5-imino-4-phenyl-2-trifluoromethyl-$\triangle^2$-1,3,4-thiadiazoline (**3**) in a good yield (Table 1). The thiadiazoline **3** was converted into 4-phenyl-2-trifluoromethyl-$\triangle^2$-1,3,4-thiadiazolin-5-one (**5**) by nitrosation followed by thermal decomposition of the *N*-nitroso derivative **4** obtained [5]. The structure of **3** was confirmed on the basis of these chemical conversions and its spectral data, particularly the ir and ^{13}C nmr data supporting the existence of the 5-imino group (Table 2). With methyl isothiocyanate, the similar orientation of the cycloaddition was observed to afford the analogous *N*-methylthiadiazoline **6** in as low as 14% yield. The structure of **6** was similarly supported by its spectral data and

Scheme 1

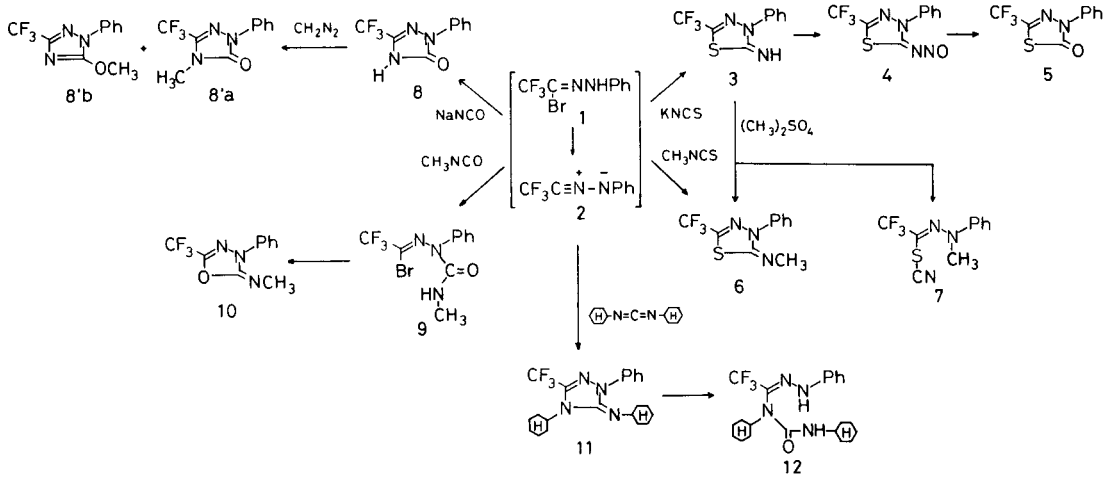


Table 1

Preparation of Trifluoromethylthiadiazolines, -triazolines, -triazolinones, -triazoles, -oxadiazolines, and -triazolopyridinium Bromides

Compounds	Yield (%)	Mp (°C) [Bp (°C/mm Hg)]	Formula	Analysis, % Found/(Calcd.) C	H	N
3	83	[115/4]	$C_9H_6F_3N_3S$	44.41 (44.08)	2.22 (2.47)	17.18 (17.14)
4	70	73-76	$C_9H_5F_3N_4OS$	39.68 (39.42)	1.79 (1.84)	20.59 (20.43)
5	80	oil	$C_9H_5F_3N_2OS$	43.79 (43.91)	1.96 (2.05)	11.45 (11.38)
6	14	oil	$C_{10}H_8F_3N_3S$	46.35 (46.33)	2.83 (3.11)	16.04 (16.21)
8	32	183-185 [a]				
9	22	107-109	$C_{10}H_5BrF_3N_3O$	36.98 (37.06)	2.52 (2.80)	12.72 (12.97)
10	62	oil	$C_{10}H_8F_3N_3O$	49.02 (49.39)	2.95 (3.32)	16.94 (17.28)
11	68	89-90	$C_{21}H_{27}F_3N_4$	63.89 (64.27)	7.10 (6.93)	14.30 (14.28)
12	48	175-177	$C_{21}H_{29}F_3N_4O\cdot1.5H_2O$	57.56 (57.65)	7.21 (7.37)	12.58 (12.81)
14	55	oil	$C_{11}H_{11}F_3N_4$	51.91 (51.56)	4.23 (4.33)	21.81 (21.87)
15	57	152-154	$C_{10}H_9F_3N_6$	44.49 (44.45)	3.23 (3.36)	30.90 (31.10)
16	49	144-146	$C_{14}H_{13}F_3N_6O_2$	47.35 (47.46)	3.46 (3.70)	23.59 (23.72)
17	63	225-227	$C_{12}H_7F_3N_6O_2$	44.63 (44.45)	2.10 (2.18)	25.53 (25.92)
18	68	342-343	$C_{13}H_9BrF_3N_3$	45.11 (45.37)	2.54 (2.64)	12.14 (12.21)
19	28	297-300	$C_{14}H_{11}BrF_3N_3$	47.08 (46.95)	2.82 (3.10)	11.77 (11.73)
20	74	209-210 dec	$C_{14}H_{13}BrF_3N_3$	47.16 (46.69)	3.37 (3.64)	11.54 (11.67)

[a] Lit [13] mp 185-186°.

also identified by methylation of **3** with dimethyl sulfate giving the same product **6** along with the ring-cleaved hydrazone **7**. The alternative cycloadduct across the carbon-nitrogen double bond could not be detected at all, in contrast to the concomitant formation of two regioisomers in the cycloaddition of *N*-phenylbenzonitrilimine derived from 2,5-diphenyltetrazole [6]. With sodium isocyanate, the cycloaddition took place on the carbon-nitrogen double bond to give 1-phenyl-3-trifluoromethyl-$\triangle^2$-1,2,4-triazolin-5-one (**8**). Its structure was established by the fact that, on treatment with diazomethane, **8** afforded a mixture of *O*- and *N*-methylated derivatives **8'a** and **8'b** [7]. In the case with methyl isocyanate, unexpectedly, the linear intermediate **9** could be isolated, which cyclized under more drastic conditions, affording 5-methylimino-4-phenyl-2-trifluoromethyl-$\triangle^2$-1,3,4-oxadiazoline (**10**), accompanied by no isomeric cycloadduct across the carbon-nitrogen double bond. It should be noted that 5-imino-1,3,4-oxadiazolines were exclusively formed in the direct cyclization of *N*-phenylbenzohydrazonoyl chloride with aryl isocyanates without isolation of the corresponding linear intermediates, as reported by Huisgen and his coworkers [8]. The reaction with dicyclohexylcarbodiimide produced exclusively one cycloadduct, 4-cyclohexyl-5-cyclohexylimino-1-phenyl-3-trifluoromethyl-$\triangle^2$-1,2,4-triazoline (**11**), in a moderate yield. Its orientation was proved by the chemical transformation of **11** into the urea derivative **12** on treatment with aqueous hydrochloric acid. And the high regioselectivity of this cycloaddition is consistent with that of *N*-phenylbenzonitrilimine [9].

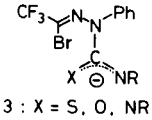
The cycloaddition of **1** toward cumulative double bonds may be rationalized by a stepwise path involving the addition of **1** followed by the intramolecular cyclization of the initially formed ambident anion **13**, as suggested in the case of methyl isocyanate.

Table 2

Spectral Data of Trifluoromethylthiadiazolines, -triazolines, -triazolinones, -triazoles, -oxadiazolines, and -triazolopyridinium Bromides

Compound	IR (cm^{-1})	^1H NMR (δ ppm)	^{13}C NMR (δ ppm)
3	3220 (NH), 1630, 1610 (C=N) 1195, 1135 (CF_3)	7.1-7.8 (arom and NH)	118.8 (CF_3, q, J = 268.9 Hz) 123.7, 127.9, 129.5, 138.0 (Ph) 136.0 (2-C, q, J = 46.1 Hz), 160.0 (5-C)
4	1140, 1120 (CF_3)	7.4-7.9 (arom)	
5	1720 (C=O), 1200, 1140 (CF_3)	7.2-7.9 (arom)	
6	1650 (C=N), 1175, 1140 (CF_3)	3.12 (s, 3H), 7.25-7.85 (arom, 5H)	44.5 (Me), 119.0 (CF_3, q, J = 270.7 Hz) 122.7, 127.0, 129.1, 138.8 (Ph) 135.5 (2-C, q, J = 46.4 Hz), 154.0 (5-C)
8	3100-2600 (NH), 1720 (C=O) 1150, 1140 (CF_3)	7.3-8.0 (arom and NH)	117.0 (CF_3, q, J = 270.0 Hz) 119.8, 126.9, 129.2, 136.5 (Ph) 136.6 (3-C, q, J = 44.0 Hz), 153.5 (5-C)
8'a	1730, 1720 (C=O) 1195, 1125 (CF_3)	3.50 (s, 3H), 7.25-7.95 (arom, 5H)	28.3 (Me), 117.4 (CF_3, q, J = 270.0 Hz) 119.1, 126.5, 129.1, 137.0 (Ph) 136.0 (3-C, q, J = 41.1 Hz), 151.5 (5-C)
8'b	1180, 1145 (CF_3)	4.25 (s, 3H), 7.4-7.8 (arom, 5H)	59.3 (Me), 119.0 (CF_3, q, J = 270.0 Hz) 121.6, 128.0, 129.3, 135.8 (Ph) 149.9 (3-C, q, J = 39.1 Hz), 159.2 (5-C)
9	3370 (NH), 1690 (C=O) 1612 (C=N), 1200, 1120 (CF_3)	2.95 (d, 3H), 6.3 (br s, 1H) 7.1-7.5 (arom, 5H)	
10	1735 (C=O), 1160, 1130 (CF_3)	3.15 (s, 3H), 7.15-7.95 (arom, 5H)	34.1 (Me), 116.0 (CF_3, q, J = 265.8 Hz) 118.1, 125.2, 129.1, 137.0 (Ph) 143.0 (2-C, q, J = 46.1 Hz), 144.0 (5-C)
11	1660 (C=N), 1190, 1130 (CF_3)	0.8-1.9 (m, 18H), 2.60 (m, 2H) 2.92 (m, 1H), 3.88 (m, 1H) 7.4 (arom, 5H)	24.3, 25.2, 26.0, 26.2, 28.4, 35.0, 52.9 56.6 (cyclohexy), 118.0 (CF_3, q, J = 270.9 Hz), 126.8, 128.3, 128.9, 140.4 (Ph) 137.9 (3-C, q, J = 39.1 Hz), 141.0 (5-C)
12	3400, 3300 (NH), 1620 (C=O) 1200, 1140 (CF_3)	1.0-2.2 (m, 22H), 5.8 (br s, 1H) 7.4-7.6 (arom, 5H), 11.0 (br s, 1H)	
14 [a]	1180, 1135 (CF_3)	2.83 (s, 6H), 7.4-7.6 (arom, 5H)	41.0 (Me), 119.3 (CF_3, q, J = 270.0 Hz) 124.5, 128.9, 129.5, 138.0 (Ph) 151.3 (3-C, q, J = 39.1 Hz), 159.3 (5-C)
15 [b]	3480, 3380, 3300, 3210 (NH_2) 1630, 1610 (C=N) 1180, 1120 (CF_3)	2.28 (s, 2H), 2.35 (s, 2H) 7.4-8.0 (arom, 5H)	
16 [c]	3100 (NH), 1755, 1705 (C=O) 1650 (C=N), 1180, 1130 (CF_3)	2.30 (s, 3H), 2.35 (s, 3H), 7.4-8.0 (arom, 5H), 11.3 (br s, 1H), 12.4 (br s, 1H)	25.3, 26.3 (Me), 119.0 (CF_3, q, J = 270.9 Hz) 123.8, 128.6, 129.0, 136.6 (Ph), 146.2 (C=N) 149.7 (3-C, q, J = 40.1 Hz), 154.4 (5-C) 169.2 171.8 (C=O)
17	3200 (NH), 1770 (C=O), 1650 (C=N), 1150 (CF_3)	7.3-8.0 (arom and NH)	
18	3000-2400, 1640 (C=N) 1190, 1140 (CF_3)	7.6-8.0 (arom, 5H), 8.0 (dd, 1H) 8.4-8.6 (m, 2H), 9.30 (d, 1H) [d]	
19	1190, 1140 (CF_3)	2.63 (s, 3H), 7.9 (arom, 5H) 8.5 (br s, 2H), 9.2 (br s, 1H) [d]	
20	3100-2700, 1610 (C=N) 1175, 1110 (CF_3)	2.80 (s, 3H), 7.3 (arom, 5H) 8.3-9.3 (A_2X_2, 4H) [d]	

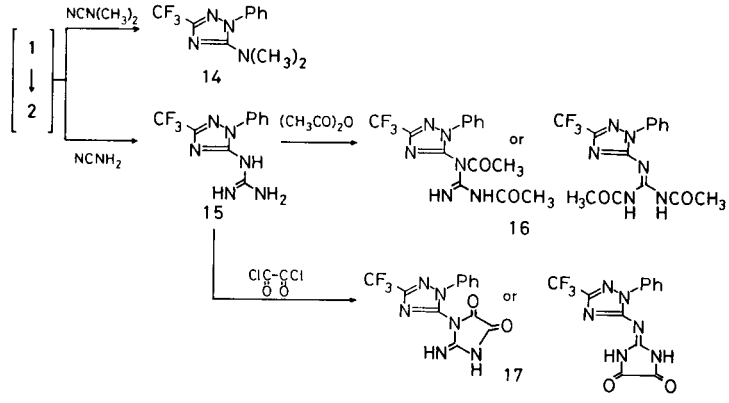
[a] uv (ethanol): λ max 255 nm (ϵ = 1.63 x 10^4). [b] uv (ethanol): λ max 272 nm (ϵ = 1.63 x 10^4). [c] uv (ethanol): λ max 288 nm (ϵ = 1.47 x 10^4). [d] Measured in DMSO-d_6.



13 : X = S, O, NR

The behavior of cyanamide and its derivatives was also investigated. Although **1** is unreactive toward common nitriles, dimethylcyanamide, an activated nitrile, gave the expected triazole, 5-dimethylamino-1-phenyl-3-trifluoromethyl-1,2,4-triazole (**14**), in a good yield. The structure of

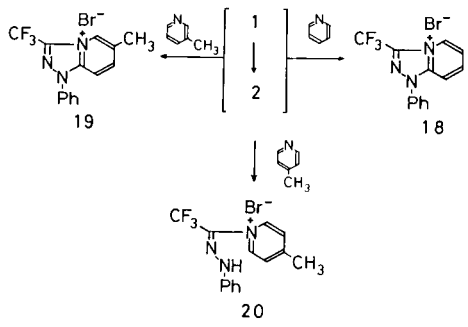
Scheme 2



14 was fully characterized from its spectral data, particularly ^{13}C nmr and uv spectra (Table 2) [10]. With cyanamide itself, two molecules of cyanamide participated in the reaction, resulting in the formation of the triazole **15** from which the diacyl derivatives **16** and **17** were easily produced. It has been reported that ordinary nitrilimines react with cyanamide to give 5-imino-$\triangle^2$-1,2,4-triazolines *via* the 1,3-addition products [11]. Therefore, the formation of **15** would be explained by the base catalyzed addition of the initially formed iminotriazoline with another molecule of cyanamide.

It has been also reported that nitrilimine cycloadds with pyridine and the resulting cycloadduct is subsequently oxidized to the corresponding bicyclic pyridinium salt [12]. The similar reaction was also observed in the case of **1** with pyridine to afford 1-phenyl-3-trifluoromethyltriazolo-[4,5-*a*]pyridinium bromide (**18**). However, picolines showed some difference in the reactivity. α-Picoline did not produce the expected salt, whereas β-picoline did the salt **19** in 28% yield without detecting its regioisomer. On the other hand, γ-picoline gave only the substituted salt **20**, which failed in subsequent cyclization. This could be ascribed to the γ-methyl group stabilizing the cationic property of the pyridinium ring. The similar cyclization was attempted with pyridines having electron-withdrawing group, resulting in recovery of **1** unchanged.

Scheme 3



In conclusion, the bromide **1** was found to provide the convenient route for the preparation of various trifluoromethyltriazole and -thiadiazole derivatives by the reactions with a variety of compounds having the carbon-nitrogen multiple bonds and the cumulative double bonds. And these reaction paths are thought to be initiated by several different mechanisms including the addition process followed by the intramolecular cyclization of the linear intermediates or the direct cycloaddition process, being dependent upon the dipolarophiles used.

EXPERIMENTAL

All melting points are uncorrected. The ir spectra were recorded on a JASCO A-100 spectrometer. Samples were run as potassium bromide pellets for solid or films for liquid. The nmr spectra were measured with JEOL JNM-PMX 60 and/or GX 270 spectrometers, using tetramethylsilane as an internal standard, the chemical shifts being given in δ ppm downfield. Samples were prepared by dissolving in deuteriochloroform unless otherwise noted. The uv spectra were observed with a Hitachi 340 spectrometer. The ms spectra were obtained on a Finnigan 4023 GC-MS DS spectrometer.

The bromide **1** was prepared by bromination of trifluoroacetaldehyde phenylhydrazone with *N*-bromosuccinimide, according to the methods reported in our previous papers [4].

Preparation of 5-Imino-4-phenyl-2-trifluoromethyl-$\triangle^2$-1,3,4-thiadiazoline (**3**).

A mixture of **1** (2.70 g, 10.1 mmoles) and potassium isothiocyanate (3.90 g, 40.2 mmoles) in 40 ml of methanol was refluxed for 3 hours. After evaporation of methanol, the mixture was extracted with toluene and the solvent was removed. The resulting oily matter was placed on a column (silica gel) and eluted with hexane-ethyl acetate (3:1) to give 2.06 g (83%) of **3** which was further purified by distillation.

Preparations of 5-Nitrosoimino-4-phenyl-2-trifluoromethyl-$\triangle^2$-1,3,4-thiadiazoline (**4**) and 4-Phenyl-2-trifluoromethyl-$\triangle^2$-1,3,4-thiadiazolin-5-one (**5**).

To a solution of 0.30 g (1.2 mmoles) of **3** in 10 ml of acetic acid was added 4 ml of saturated aqueous sodium nitrite. After stirring at room temperature for 30 minutes, the formed red solid was filtered off and recrystallized from hexane to give 0.23 g (70%) of **4**. Thus obtained 0.28 g (1.0 mmoles) of **4** was dissolved in 40 ml of xylene and the solution was refluxed for 30 minutes. The reaction mixture was allowed to stand at

room temperature overnight and, after removing the solvent, the mixture was chromatographed on silica gel using hexane-ethyl acetate (4:1) to give 0.20 g (80%) of **5** which was further purified by gas chromatography.

Preparations of 5-Methylimino-4-phenyl-2-trifluoromethyl-$\triangle^2$-1,3,4-thiadiazoline (**6**), 4-Cyclohexyl-5-cyclohexylimino-1-phenyl-3-trifluoromethyl-$\triangle^2$-1,2,4-triazoline (**11**), and 5-Dimethylamino-1-phenyl-3-trifluoromethyl-1,2,4-triazole (**14**). General Procedures.

Triethylamine (11.8 mmoles) was added dropwise to a solution of **1** (11.2 mmoles) and 56.2 mmoles of methyl isothiocyanate, dicyclohexylcarbodiimide, or dimethylcyanamide in 40 ml of toluene. After stirring at room temperature for 12 hours, the formed salt was filtered off and the filtrate was evaporated. The resulting mixture was chromatographed (silica gel), giving the corresponding products **6**, **11**, and **14** which were further purified by gas chromatography for **6** and **14** or by recrystallization for **11**, respectively.

Methylation of **3**.

A mixture of **3** (0.50 g, 2.0 mmoles), dimethyl sulfate (1.30 g, 10.3 mmoles), and 2.00 g of potassium carbonate in 50 ml of benzene was refluxed for 3 hours. After the solid was filtered off, the filtrate was evaporated. The resulting oily matter was chromatographed (silica gel, hexane-ethyl acetate, 3:1) to give 0.05 g (9%) of **6** and 0.25 g (47%) of *N*-methyl-*N*-phenyltrifluoroacetohydrazonoyl thiocyanate (**7**); ir: 2210 ($C\equiv N$), 1140 cm^{-1} (CF_3); ^1H nmr: δ 2.63 (q, J = 2 Hz, 3H) and 7.0-7.4 (arom, 5H); ms: (m/e) 260 $(M+1)^+$.

Preparation of 1-Phenyl-3-trifluoromethyl-$\triangle^2$-1,2,4-triazolin-5-one (**8**).

A mixture of **1** (3.00 g, 11.2 mmoles) and sodium isocyanate (2.90 g, 44.6 mmoles) in 40 ml of methanol was refluxed for 3 hours. The similar procedures to the above gave 0.83 g (32%) of **8** which was further purified by recrystallization from hexane-chloroform-ethyl acetate. Melting point and ir spectra are consistent with those reported in the literature [13].

Methylation of **8**.

An excess of an ethereal solution of diazomethane was added dropwise to a solution of **8** (0.26 g, 1.1 mmoles) in 20 ml of diethyl ether. After stirring at room temperature for 2 hours, the solvent was removed to leave a residue which was chromatographed (silica gel, chloroform), giving 0.06 g (22%) of 4-methyl-1-phenyl-3-trifluoromethyl-$\triangle^2$-1,2,4-triazolin-5-one (**8'a**) and 0.04 g (14%) of 5-methoxy-1-phenyl-3-trifluoromethyl-1,2,4-triazole (**8'b**).

Compound **8'a** had mp 72-73° (recrystallized from hexane).

Anal. Calcd. for $C_{10}H_8F_3N_3O$: C, 49.39; H, 3.32; N, 17.28. Found: C, 49.61; H, 3.13; N, 17.30.

Compound **8'b** was obtained as a colorless oil.

Anal. Calcd. for $C_{10}H_8F_3N_3O$: C, 49.39; H, 3.32; N, 17.28. Found: C, 49.62; H, 3.23; N, 17.27.

Their spectral data are summarized in Table 2.

Preparations of *N*-Methylcarbamoyl-*N*-phenyltrifluoroacetohydrazonoyl Bromide (**9**) and 5-Methylimino-4-phenyl-2-trifluoromethyl-$\triangle^2$-1,3,4-oxadiazoline (**10**).

In the similar manner to the procedures for the preparations of **6** from **1**, 22% of **9** was isolated and recrystallized from hexane-chloroform. To a solution of thus obtained 0.15 g (0.5 mmoles) of **9** in 10 ml of toluene was added 1.00 g of triethylamine and refluxed for 3 hours. Usual work-up yielded 0.07 g (62%) of **10** which was further purified by gas chromatography.

Hydrolysis of **11**.

A solution of 0.40 g (1.0 mmole) of **11** in 10 ml of concentrated hydrochloric acid and 40 ml of methanol was refluxed for 10 hours. After the solvent was removed, the residual solid was washed with water and diethyl ether and recrystallized from ethyl acetate to give 0.20 g (48%) of 1-cyclohexyl-1-(*N*-phenyltrifluoroacetohydrazonoyl)-2-cyclohexylurea (**12**).

Preparation of 5-Guanidino- or diaminomethyleneamino-1-phenyl-3-trifluoromethyl-1,2,4-triazole (**15**).

Triethylamine (1.60 g, 15.8 mmoles) was added to a solution of **1** (4.00 g, 15.0 mmoles) and cyanamide (1.90 g, 45.2 mmoles) in 80 ml of methanol. The mixture was stirred at room temperature for 12 hours and evaporated to give a residue which was chromatographed (silica gel, hexane-ethyl acetate, 1:1), yielding 2.30 g (57%) of **15**. Recrystallization from hexane-chloroform further produced the pure **15**.

Acetylation of **15**.

A mixture of **15** (0.50 g, 1.9 mmoles) in 12 ml of acetic anhydride was refluxed for 12 hours. After removing the solvent, the residual solid was recrystallized from hexane-chloroform to give 0.32 g (49%) of 5-(*N*,*N'*-diacetylguanidino or -diaminomethyleneamino)-1-phenyl-3-trifluoromethyl-1,2,4-triazole (**16**).

Oxalylation of **15**.

To a solution of **15** (0.63 g, 2.3 mmoles) and oxalyl chloride (0.30 g, 2.4 mmoles) in 40 ml of toluene was added dropwise triethylamine (0.47 g, 4.7 mmoles). After stirring at room temperature for 12 hours, excess diethyl ether was added to the reaction mixture. And the mixture was washed with water, dried over magnesium sulfate, and evaporated. The residue was chromatographed (silica gel, hexane-ethyl acetate, 1:1), yielding 0.48 g (63%) of 5-(*N*,*N'*-oxalylguanidino or -diaminomethyleneamino)-1-phenyl-3-trifluoromethyl-1,2,4-triazole (**17**) which was further recrystallized from hexane-ethanol-diethyl ether.

Preparations of 1-Phenyl-3-trifluoromethyltriazolo[4,5-*a*]pyridinium Bromide (**18**) and 6-Methyl-1-phenyl-3-trifluoromethyltriazolo[4,5-*a*]-pyridinium Bromide (**19**). General Procedures.

A mixture of **1** (7.5 mmoles) and 6 ml of pyridine or β-picoline in 100 ml of toluene was stirred at 80° for 100 hours. The formed solid was collected on a filter and recrystallized from hexane-isopropyl alcohol to give **18** or **19**, respectively.

Preparation of 4-Methyl-1-(*N*-phenyltrifluoroacetohydrazonoyl)pyridinium Bromide (**20**).

A mixture of **1** (2.00 g, 7.5 mmoles) and 6 ml of γ-picoline in 100 ml of toluene was stirred at 80° for 24 hours. Further stirring at the same temperature resulted in the decomposition of the formed solid. The collected solid was washed with toluene and methanol to give 2.00 g (74%) of **20**. Recrystallization could not be performed by its easy decomposition.

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