Reaction of 2,5-Bis(trifluoromethyl)-1,3,4-oxadiazole with Primary Amines. Synthesis of 4-Substituted-3,5-bis(trifluoromethyl)-4*H*-1,2,4-triazoles

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Reaction of 3,5-bis(trifluoromethyl)-1,3,4-oxadiazole (**1a**) with primary amines under a variety of conditions conveniently produced 4-substituted-3,5-bis(trifluoromethyl)-4*H*-1,2,4-triazoles **4a** in 26-85% yield. Alkyl amines reacted with **1a** in methanol at -42° to provide hydrogen-bonded monoadduct-methanol complexes **5a**, as determined by X-ray. The reaction of **1a** with sterically hindered or strongly electron deficient anilines required high temperatures in the absence of solvent.

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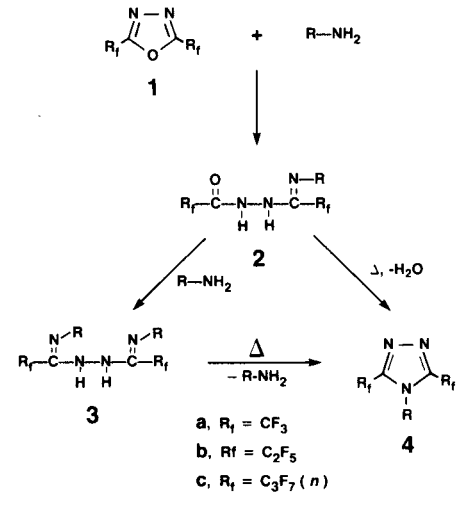
Introduction.

In searching for a general procedure for the synthesis of 4-substituted-3,5-bis(trifluoromethyl)-4*H*-1,2,4-triazoles, we found a report by Brown and Cheng [2] that 2,5-bis(trifluoromethyl)-1,3,4-oxadiazoles **1a-c** reacted with ammonia and methylamine to produce the corresponding 1-(perfluoroalkylimidoyl)-2-(perfluoroacyl)hydrazines **2a-c** (R = H) or 1,2-bis(*N*-alkylperfluoroalkylimidoyl)hydrazines **3a-c** (R = CH_3), respectively. The authors suggested that this reaction occurs by attack of the nucleophilic amine on the electron deficient oxadiazole ring carbon to afford the monoadducts **2a-c**, as shown in Scheme I. Although the monoadducts **2a-c** (R = H) were stable in ammonia, **2a-c** (R = CH_3) underwent further reaction with the more nucleophilic methylamine to provide only the bisadducts **3a-c** (R = CH_3). Subsequently, adducts **2a-c** (R = H) and **3a-c** (R = CH_3) were thermally converted to the corresponding 4-substituted-3,5-bis(perfluoroalkyl)-4*H*-1,2,4-triazoles **4a-c** (R = H or CH_3).

In the belief that the reaction of **1a** with primary amines might be a general, direct, and efficient synthetic route to 4-substituted-3,5-bis(trifluoromethyl)-4*H*-1,2,4-triazoles, we investigated the scope and limitations of this reaction. We now wish to report the results of our study.

Scheme I



Results and Discussion.

Alkyl amines.

In an attempt to moderate the reaction of alkyl amines with **1a** so that the monoadduct **2a** might be isolated, the reaction was carried out in methanol at -42° (acetonitrile/dry ice bath) in the presence of excess **1a**. Surprisingly, the reaction of **1a** (2 equivalents) in methanol at -42° with condensed methylamine (1 equivalent) did not produce the monoadduct **2a** (R = CH_3), nor did it produce the bisadduct **3a** (R = CH_3). The product which was isolated in 78% yield was determined by elemental analysis and proton nuclear magnetic resonance (^{1}H nmr) spectroscopy to be a monoadduct with an incorporated molecule of methanol. Since it was known (*vida infra*) that methanol reacts with **1a** in the presence of base or at high temperatures, and that the methanol was retained in the sample even after 24 hours at high vacuum (0.01 torr), it was conceivable that the product isolated might contain a covalently bound methanol molecule. An X-ray crystal structure determination, however, proved that the product isolated was simply the hydrogen-bonded monoadduct-methanol complex **5a** (R = CH_3). The ORTEP representation of **5a** is shown in Figure 1.

Monoadduct-methanol complex formation seems to be general for all alkylamines. Table I shows the few examples for which isolation was attempted. The complexes **5a** (R = CH_3, C_2H_5, and $CH(CH_3)C_2H_5$) were converted to the corresponding triazoles **4a** (R = CH_3, C_2H_5, and $CH(CH_3)C_2H_5$) by stirring in methanol at reflux. However, isolation of **5a** prior to cyclization proved to be unnecessary for the preparation of 4-alkyl triazoles **4a**. In fact, acceptable yields of 4-alkyl triazoles were isolated without the use of excess **1a** or the use of methanol as solvent to

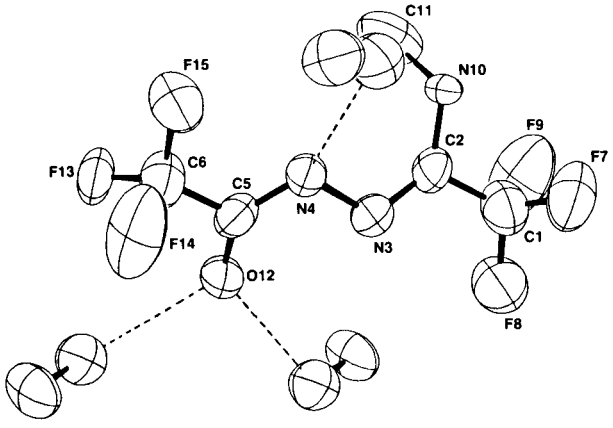
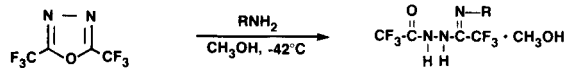


Figure 1. X-Ray Crystal Structure of **5a**.

moderate the reaction. Examples of 4-alkyl-3,5-bis(trifluoromethyl)-4*H*-1,2,4-triazoles prepared are listed in Table I and detailed reaction conditions are given in the experimental section. The yields given in Table I are not optimized.

Scheme II



The reaction of **1a** with hydrazine in methanol at -42° produced **2a** (R = NH_2) in 76% yield. Due to the addition of aqueous acid in the workup procedure, the monoadduct-methanol complex **5a** (R = NH_2) was not isolated. The monoadduct **2a** (R = NH_2) was converted to **4a** (R = NH_2) in 85% by stirring in acetic acid at reflux. The details of this reaction as well as the structure proof for **4a** (R = NH_2) have been reported elsewhere [3].

Table I

Preparation of 3,5-Bis(trifluoromethyl)-4-alkyl-4*H*-1,2,4-triazoles **4a** from **1a**

R	Method	**5a** (%)	Reaction Time (hours)	**4a** (%)
CH_3	A	78	12	54
C_2H_5	A	90	17	56
$C_3H_7(n)$	[a]	[b]	12	83
$CH(CH_3)_2$	[a]	[b]	12	70
$CH_2CH=CH_2$	[a]	[b]	0.5	26
$C_4H_9(n)$	[a]	[b]	12	40
$CH(CH_3)C_2H_5$	A	95	12	39
C_6H_{11}(cyclo)	[a]	[b]	1	52
$CH_2C_6H_4$(4-Cl)	B	[b]	18	72
NH_2	[a]	76 [c]	2	85

[a] See experimental section for details. [b] Isolation of complex **5a** was not attempted. [c] Product isolated was actually **2a** [3].

Table II

Preparation of 3,5-Bis(trifluoromethyl)-4-aryl-4*H*-1,2,4-triazoles **4a** from **1a**

R	Method	Reaction Temp (°C)	Reaction Time (hours)	**4a** (%)
C_6H_4(4-OCH_3)	B	25	17	76
C_6H_4(3-OCH_3)	B	25	18	52
C_6H_4(2-OCH_3)	B	25	65	65
C_6H_4(4-CH_3)	B	25	19	40
C_6H_4(3-CH_3)	B	25	120	74
C_6H_4(2-CH_3)	B	25	45	61
C_6H_5	C	65	24	66
C_6H_4(4-CF_3)	D	120	14	29
C_6H_4(3-CF_3)	C	65	110	73
C_6H_4(2-CF_3)	D	125	72	34
C_6H_4(4-F)	B	25	24	67
C_6H_4(3-F)	C	65	29	37
C_6H_4(4-Cl)	C	65	22	32
C_6H_3(2,4-Cl)	D	140	24	54
C_6H_3(3,4-Cl)	C	65	69	50
C_6H_2(2,4,5-Cl)	D	140	48	46
C_6H_3(2,6-CH_3)	D	150	72	75
C_6H_3(2,6-C_2H_5)	D	150	72	37
C_6H_3(3,5-CF_3)	C	65	137	39
C_6H_4(4-NH_2)	D	140	48	58 [a]

[a] Bistriazole isolated.

Aromatic amines.

The reaction of **1a** with aromatic amines, *i.e.*, substituted anilines, in methanol at reflux proceeded smoothly and generally provided 4-aryl-3,5-bis(trifluoromethyl)-4*H*-1,2,4-triazoles **4a** (R = aryl) in moderate to good yields (Table II). However, if the aromatic amine had a strong electron withdrawing substituent (*e.g.*, CF_3) in either the 2- or 4-position or if it had several moderate electron withdrawing substituents (*e.g.*, Cl), 4-aryl triazoles **4a** (R = aryl) were not produced in methanol at reflux. The reaction also proved to be sensitive to steric hindrance. For example, if substituents were in both the 2-and 6-positions, whether they were electron withdrawing or electron releasing, the reaction in methanol at reflux failed to produce triazoles. Examination of models revealed that in order for 3,5-bis(trifluoromethyl)-4-(2',6'-disubstitutedphenyl)-4*H*-1,2,4-triazoles to be produced, the aromatic ring must rotate out of the plane of the triazole ring so that the two trifluoromethyl groups at the 3,5-positions do not sterically interfere with the two substituents in the 2,6-positions of the aromatic ring..

Assuming that these difficulties could be surmounted by higher reaction temperatures, **1a**, 2-trifluoromethylaniline, and methanol were sealed in a glass ampoule and

heated to 115°. After 24 hours the 2-trifluoromethylaniline was recovered unchanged, however, **1a** had reacted with methanol to give unknown products which were not investigated. Repeating the reaction in the absence of solvent provided **4a** [R = $C_6H_4(2\text{-}CF_3)$] in 34% yield after recrystallization. Moreover, neat reaction conditions generally proved useful for the synthesis of 4-substituted-3,5-bis(trifluoromethyl)-4*H*-1,2,4-triazoles from sterically hindered 2,6-disubstituted anilines or anilines which contained multiple electron withdrawing groups.

Conclusion.

Primary alkyl amines reacted with excess **1a** in methanol at -42° to provide hydrogen-bonded monoadduct-methanol complexes **5a** (R = CH_3, C_2H_5, and $CH(CH_3)C_2H_5$). The structure of **5a** (R = CH_3) was confirmed by an X-ray crystal structure determination. The complexes **5a** were subsequently converted to the corresponding 3,5-bis(trifluoromethyl)triazoles **4a** (R = CH_3, C_2H_5, and $CH(CH_3)C_2H_5$) by stirring in methanol at reflux. 4-Alkyl-3,5-bis(trifluoromethyl)-4*H*-1,2,4-triazoles could also be prepared by the low temperature reaction of **1a** with excess primary alkyl amines in the absence of solvent. In general, the reaction of **1a** with aromatic amines in methanol at reflux provided triazoles **4a** (R = aryl) in moderate to good yields. For anilines which were strongly electron deficient or sterically hindered, it was necessary to perform the reaction without solvent in a sealed tube at high temperatures.

EXPERIMENTAL

General.

Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. Boiling points, taken from distillations, are likewise uncorrected. Proton nuclear magnetic resonance (^{1}H nmr) spectra were taken on a Varian T-60 or EM-360L spectrometer and chemical shifts are reported in δ (ppm) downfield from an internal tetramethylsilane (TMS) reference unless otherwise stated. Fluorine nuclear magnetic resonance (^{19}F nmr) spectra were taken on a Varian EM-360L spectrometer and chemical shifts are reported in δ (ppm) downfield from an external trifluoroacetic acid (TFA) reference unless otherwise stated. The X-ray structure was solved on a Syntex P21 diffractometer by Dr. Huey-Sheng Shieh of Monsanto Corporate Research Laboratories. High pressure liquid chromatographies (hplc) were performed on a Waters Associates Prep 500A Chromatograph using silica gel column. Elemental analyses were performed by Galbraith Laboratories, Inc. of Knoxville, Tennessee.

Materials.

All solvents and starting materials from commercial sources were used without further purification.

General Procedure A. Preparation of Monoadduct-methanol Complexes **5a**.

A solution of 41.2 g (200 mmoles) of **1a** in 100 ml of methanol was cooled -42° (acetonitrile/dry ice slush bath) and 100 mmoles of the alkyl amine was added neat over 5 minutes causing a noticeable exotherm. The reaction was allowed to warm to 0° and stirred for 1 hour. Concentration *in vacuo* produced a solid which was further dried on a high vacuum line (0.01 mm) to ensure removal of all unreacted **1a**.

General Procedure B. Preparation of 4-Substituted-3,5-bis(trifluoromethyl)-4*H*-1,2,4-triazoles **4a**.

A solution of 100 mmoles of **1a** in 30 ml of methanol was cooled to 0° and treated dropwise with 100 mmoles of the primary amine in 24 ml of methanol. After the addition was complete, the reaction was allowed to warm to ambient temperature and stir until complete; progress of the reaction was monitored by ^{19}F nmr. Cooling the reaction mixture or concentration *in vacuo* provided the crude material which was purified as specified for each example.

General Procedure C. Preparation of 4-Aryl-3,5-bis(trifluoromethyl)-4*H*-1,2,4-triazoles **4a**.

A solution of 100 mmoles of **1a** and 100 mmoles of the substituted aniline in 55 ml of methanol was stirred at reflux until the reaction was complete as determined by ^{19}F nmr. Cooling the concentrated reaction mixture provided the crude material which was purified as specified for each example.

General Procedure D. Preparation of Sterically Hindered 4-Aryl-3,5-bis(trifluoromethyl)-4*H*-1,2,4-triazoles **4a**.

A thick-walled glass ampule (rated to withstand 25 atmospheres) containing 100 mmoles of **1a** and 100 mmoles of the substituted aniline was cooled in liquid nitrogen and sealed under high vacuum. The ampule was heated in an oil bath at 120-150° (**caution**: use a safety shield) for 2-3 days and then cooled to 0°. Filtration gave the crude product which was purified as specified for each example.

2,5-Bis(trifluoromethyl)-1,3,4-oxidazole (**1a**).

A solution of 500 g (3.5 moles) of ethyl trifluoroacetate in 4000 ml of absolute ethanol was cooled to -10° and treated dropwise over 45 minutes with 124 g (3.7 moles) of anhydrous hydrazine (95%). The reaction was allowed to warm to ambient temperature overnight and then concentrated *in vacuo*. The residue was dissolved in 500 ml of trifluoroacetic acid and treated dropwise with 1.2 kg (5.6 moles) of trifluoroacetic anhydride over 2 hours. The cloudy solution was heated to reflux and allowed to cool slowly. Filtration gave 772 g (98%) of colorless 1,2-bis(trifluoroacetyl)hydrazine which was thoroughly mixed with 2 kg of phosphorus pentoxide and placed in a reaction vessel which was equipped with a distillation head. The mixture was covered with an additional 1.5 kg of phosphorus pentoxide and under static nitrogen, the flask was slowly heated to 300°. The crude product was collected and redistilled from calcium hydride to give 613 g (86%) of colorless **1a**, bp 65° (lit [4] bp 65°); ^{19}F nmr (neat): δ 10.4 (s).

Anal. Calcd. for $C_4F_6N_2O$: C, 23.32; F, 55.32; N, 13.60. Found: C, 23.17; F, 55.14; N, 13.57.

N^2-(α-Hydrazonotrifluoromethyl)trifluoroacetylhydrazide (**2a**) (R = NH_2).

Following the procedure published elsewhere [3], 25.0 g (121 mmoles) of **1a** was reacted with 25 g (750 mmoles) of anhydrous hydrazine in 125 ml of methanol at -42° to give 21.1 g (76%) of colorless **2a** (R = NH_2), mp 127-128° dec; ^{19}F nmr (DMSO-d_6): δ 3.3 (s, anti $COCF_3$), 4.3 (s, syn $COCF_3$), 10.0 (s, anti $NCCF_3$), 12.4 (s, syn $NCCF_3$).

Anal. Calcd. for $C_4H_4F_6N_4O$: C, 20.18; H, 1.69; F, 47.88; N, 23.53. Found: C, 20.04; H, 1.75; F, 47.78; N, 23.44.

3,5-Bis(trifluoromethyl)-4-methyl-4*H*-1,2,4-triazole (**4a**) (R = CH_3).

A 13.8 g (51.3 mmoles) sample of **5a** (R = CH_3) was stirred in methanol at reflux for 12 hours. Distillation gave 6.1 g (54%) of colorless **4a** (R = CH_3), bp 196-199° (lit [2] bp 199-200°); ^{19}F nmr (DMSO-d_6): δ 13.6 (s).

3,5-Bis(trifluoromethyl)-4-ethyl-4*H*-1,2,4-triazole (**4a**) (R = C_2H_5).

A 37.9 g (134 mmoles) sample of **5a** (R = C_2H_5) was stirred in methanol at reflux for 17 hours. Vacuum distillation gave 17.6 g (56%) of colorless **4a** (R = C_2H_5), bp 104-107° (94 mm); ^{1}H nmr (DMSO-d_6): δ 1.45 (t, J = 7 Hz, 3H, NCH_2CH_3, 4.38 (q, J = 7 Hz, 2H, NCH_2CH_3); ^{19}F nmr

(DMSO-d_6): δ 15.8 (s).

Anal. Calcd. for $C_6H_5F_6N_3$: C, 30.91; H, 2.16; F, 48.90; N, 18.02. Found: C, 30.98; H, 2.22; F, 48.78; N, 18.06.

3,5-Bis(trifluoromethyl)-4-propyl-4*H*-1,2,4-triazole (**4a**) [R = $C_3H_7(n)$].

A 20.6 g (100 mmoles) sample of **1a** was added dropwise to 40 ml of *n*-propylamine at -78°. The reaction was stirred at -78° for 2 hours, warmed to ambient temperature, and concentrated *in vacuo*. The residue was dissolved in 100 ml of methanol and stirred at reflux for 12 hours. Concentration *in vacuo* provided the crude product which was purified by vacuum distillation to give 15.4 g (83%) of colorless **4a** [R = $C_3H_7(n)$], bp 135-137° (93 mm); ^{1}H nmr (DMSO-d_6): δ 1.06 (t, J = 7 Hz, 3H, $NCH_2CH_2CH_3$), 1.58-2.28 (m, 2H, $NCH_2CH_2CH_3$), 4.06-4.48 (m, 2H, $NCH_2CH_2CH_3$); ^{19}F nmr (DMSO-d_6): δ 15.6 (s).

Anal. Calcd. for $C_7H_7F_6N_3$: C, 34.02; H, 2.85; F, 46.13; N, 17.00. Found: C, 33.98; H, 2.97; F, 45.68; N, 16.75.

3,5-Bis(trifluoromethyl)-4-(2'-methylethyl)-4*H*-1,2,4-triazole (**4a**) (R = $CH(CH_3)_2$).

A 20.6 g (100 mmoles) sample of **1a** was added dropwise to 50 ml of isopropylamine at -30°. The reaction was stirred at -30° for 1 hour, warmed to ambient temperature, and concentrated *in vacuo*. The residue was dissolved in 100 ml of methanol and stirred at reflux for 12 hours. Cooling the reaction mixture to -78° gave 17.2 g (70%) of colorless **4a** (R = $CH(CH_3)_2$), mp 35-38°; ^{1}H nmr (DMSO-d_6): δ 1.63 (d, J = 7 Hz, 6H, $CH(CH_3)_2$), 4.57-5.33 (m, 1H, $CH(CH_3)_2$); ^{19}F nmr (DMSO-d_6): δ 18.2 (s).

Anal. Calcd. for $C_7H_7F_6N_3$: C, 34.02; H, 2.85; F, 46.13; N, 17.00. Found: C, 33.97; H, 2.85; F, 46.04; N, 16.93.

3,5-Bis(trifluoromethyl)-4-(2'-propenyl)-4*H*-1,2,4-triazole (**4a**) (R = $CH_2CH=CH_2$).

Following procedure A, the crude product **5a** (R = $CH_2CH=CH_2$) did not solidify so it was redissolved in 100 ml of methanol and stirred at reflux for 30 minutes. The reaction mixture was concentrated, vacuum distilled, and then purified by hplc using 3% ethyl acetate in cyclohexane to give 6.3 g (25%) of colorless **4a** (R = $CH_2CH=CH_2$), bp 116° (53 mm); ^{1}H nmr (neat): δ 4.86-6.37 (m, $NCH_2CH=CH_2$); ^{19}F nmr (neat): δ 14.1 (s).

Anal. Calcd. for $C_7H_5F_6N_3$: C, 34.30; H, 2.06; F, 46.50; N, 17.14. Found: C, 34.37; H, 2.13; F, 46.43; N, 17.22.

3,5-Bis(trifluoromethyl)-4-butyl-4*H*-1,2,4-triazole (**4a**) [R = $C_4H_9(n)$].

A 20.6 g (100 mmoles) sample of **1a** was added dropwise to 25 ml of *n*-butylamine at -30°. After 30 minutes, the reaction was stirred at reflux for 12 hours. Concentration *in vacuo* provided the crude material which was purified by vacuum distillation to give 10.8 g (40%) of colorless **4a** [R = $C_4H_9(n)$], bp 145-152° (96 mm); ^{1}H nmr (neat): δ 0.72-2.25 (m, 7H, $NCH_2(CH_2)_2CH_3$), 4.22-4.63 (m, 2H, NCH_2); ^{19}F nmr (neat) δ 14.4 (s).

Anal. Calcd. for $C_8H_9F_6N_3$: C, 36.79; H, 3.47; F, 43.65; N, 16.09. Found: C, 36.92; H, 3.60; F, 43.70; N, 15.92.

3,5-Bis(trifluoromethyl)-4-(1'-methylpropyl)-4*H*-1,2,4-triazole (**4a**) (R = $CH(CH_3)C_2H_5$).

A 23.5 g (75.7 mmoles) sample of **5a** (R = $CH(CH_3)C_2H_5$) was dissolved in methanol and stirred at reflux for 12 hours. The reaction was concentrated to provide the crude product which was purified by vacuum distillation to give 7.6 g (39%) of pale yellow **4a** (R = $CH(CH_3)C_2H_5$): bp 116-124° (53 mm); ^{1}H nmr (DMSO-d_6): δ 0.78 (t, J = 7 Hz, 3H, $NCH(CH_3)CH_2CH_3$), 1.48-2.27 (m, 5H, $NCH(CH_3)CH_2CH_3$), 4.42-4.88 (m, 1H, $NCH(CH_3)CH_2CH_3$); ^{19}F nmr (DMSO-d_6): δ 17.8 (s).

Anal. Calcd. for $C_8H_9F_6N_3$: C, 36.79; H, 3.47; F, 43.65; N, 16.09. Found: C, 36.66; H, 3.60; F, 43.34; N, 16.17.

3,5-Bis(trifluoromethyl)-4-cyclohexyl-4*H*-1,2,4-triazole (**4a**) [R = C_6H_{13}(cyclo)].

A large exotherm was observed when 23.6 g (115 mmoles) of **1a** was added quickly to 60 ml of cyclohexylamine. The reaction was stirred at ambient temperature and subsequently heated to reflux for 1 hour. Concentration *in vacuo* gave the crude product which was recrystallized from toluene to give 17.2 g (52%) of colorless **4a** [R = C_6H_{13}(cyclo)], mp 61.5-63.0°; ^{1}H nmr (DMSO-d_6): δ 0.95-2.38 (m, 10H, CH_2), 4.05-4.68 (m, 1H, CHN); ^{19}F nmr (DMSO-d_6): δ 18.4 (s).

Anal. Calcd. for $C_{20}H_{11}F_6N_3$: C, 41.82; H, 3.86; F, 39.69; N, 14.63. Found: C, 41.89; H, 3.86; F, 39.52; N, 14.62.

3,5-Bis(trifluoromethyl)-4-(4'-chlorophenylmethyl)-4*H*-1,2,4-triazole (**4a**) [R = $CH_2C_6H_4$(4-Cl)].

Cooling the reaction mixture to -20° provided the crude product which was sublimed at 100° (3 mm) to give 23.7 g (72%) of colorless **4a** [R = $CH_2C_6H_4$(4-Cl)], mp 107-110°; ^{1}H nmr (DMSO-d_6): δ 5.60 (s, 2H, NCH_2), 7.05-7.33 (m, 2H, ArH), 7.33-7.62 (m, 2H, ArH); ^{19}F nmr (DMSO-d_6): δ 17.5 (s).

Anal. Calcd. for $C_{11}H_6ClF_6N_3$: C, 40.08; H, 1.83; F, 34.58; N, 12.75. Found: C, 40.09; H, 1.84; F, 34.46; N, 12.75.

3,5-Bis(trifluoromethyl)-4-amino-4*H*-1,2,4-triazole (**4a**) (R = NH_2).

Following the procedure which was published elsewhere [3], 5.0 g (21.0 mmoles) of **2a** (R = NH_2) was converted to 3.94 g (85%) of colorless **4a** (R = NH_2), mp 76-77°; ^{19}F nmr (DMSO-d_6): δ 15.6 (s).

Anal. Calcd. for $C_4H_2F_6N_4$: C, 21.83; H, 0.92; F, 51.79; N, 25.46. Found: C, 21.81; H, 0.93; F, 51.86; N, 25.48.

3,5-Bis(trifluoromethyl)-4-(4'-methoxyphenyl)-4*H*-1,2,4-triazole (**4a**) [R = C_6H_4(4-OCH_3)].

Cooling the reaction mixture provided the crude product which was sublimed at 60° (1.5 mm) and subsequently recrystallized from methanol to give 23.5 g (76%) of colorless **4a** [R = C_6H_4(4-OCH_3), mp 55.5-57.5°; ^{1}H nmr (DMSO-d_6): δ 3.9 (s, 3H, OCH_3), 6.98-7.37 (m, 2H, ArH), 7.53-7.90 (m, 2H, ArH); ^{19}F nmr (DMSO-d_6): δ 17.5 (s).

Anal. Calcd. for $C_{11}H_7F_6N_3O$: C, 42.46; H, 2.27; F, 36.63; N, 13.50. Found: C, 42.43; H, 2.27; F, 36.74; N, 13.51.

3,5-Bis(trifluoromethyl)-4-(3'-methoxyphenyl)-4*H*-1,2,4-triazole (**4a**) [R = C_6H_4(3-OCH_3)].

Cooling the reaction mixture gave 16.2 g (52%) of buff colored **4a** [R = C_6H_4(3-OCH_3)], mp 86-89°; ^{1}H nmr (DMSO-d_6): δ 3.83 (s, 3H, OCH_3), 7.15-7.77 (m, 4H, ArH); ^{19}F nmr (DMSO-d_6): δ 14.4 (s).

Anal. Calcd. for $C_{11}H_7F_6N_3O$: C, 42.47; H, 2.27; F, 36.63; N, 13.50. Found: C, 42.44; H, 2.26; F, 36.68; N, 13.53.

3,5-Bis(trifluoromethyl)-4-(2'-methoxyphenyl)-4*H*-1,2,4-triazole (**4a**) [R = C_6H_4(2-OCH_3)].

Cooling the reaction mixture gave 17.9 g (61%) of colorless **4a** [R = C_6H_4(2-OCH_3)], mp 78.5-81.0°; ^{1}H nmr (DMSO-d_6): δ 3.80 (s, 3H, OCH_3), 7.03-7.97 (m, 4H, ArH); ^{19}F nmr (DMSO-d_6): δ 16.2 (s).

Anal. Calcd. for $C_{11}H_7F_6N_3O$: C, 42.46; H, 2.27; F, 36.63; N, 13.50. Found: C, 42.31; H, 2.30; F, 36.79; N, 13.50.

3,5-Bis(trifluoromethyl)-4-(4'-methylphenyl)-4*H*-1,2,4-triazole (**4a**) [R = C_6H_4(4-CH_3)].

Cooling the reaction mixture gave 11.7 g (40%) of colorless **4a** [R = C_6H_4(4-CH_3)], mp 68.5-71.0°; ^{1}H nmr (DMSO-d_6): δ 2.4 (s, 3H, CH_3), 7.27-7.52 (m, 2H, ArH), 7.52-7.78 (m, 2H, ArH); ^{19}F nmr (DMSO-d_6): δ 18.2 (s).

Anal. Calcd. for $C_{11}H_7F_6N_3$: C, 44.76; H, 2.39; F, 38.62; N, 14.23. Found: C, 44.76; H, 2.16; F, 38.91; N, 14.27.

3,5-Bis(trifluoromethyl)-4-(3'-methylphenyl)-4*H*-1,2,4-triazole (**4a**) [R = C_6H_4(3-CH_3)].

Cooling the reaction mixture gave 21.8 g (74%) of colorless **4a** [R = C_6H_4(3-CH_3)], mp 87.0-89.5°; ^{1}H nmr (DMSO-d_6): δ 2.40 (s, 3H, CH_3), 7.50 (s, 4H, ArH); ^{19}F nmr (DMSO-d_6): δ 17.6 (s).

Anal. Calcd. for $C_{11}H_7F_6N_3$: C, 44.79; H, 2.39; F, 38.62; N, 14.23. Found: C, 44.82; N, 2.42; F, 38.75; N, 14.24.

3,5-Bis(trifluoromethyl)-4-(2'-methylphenyl)-4*H*-1,2,4-triazole (**4a**) [R = C_6H_4(2-CH_3)].

Cooling the reaction mixture gave 17.9 g (61%) of colorless **4a** [R = C_6H_4(2-CH_3)], mp 92-94°; ^{1}H nmr (DMSO-d_6): δ 2.10 (s, CH, CH_3), 6.93-7.93 (m, 4H, ArH); ^{19}F nmr (DMSO-d_6): δ 16.5 (s).

Anal. Calcd. for $C_{11}H_7F_6N_3$: C, 44.76; H, 2.39; F, 38.62; N, 14.23. Found: C, 44.69; H, 2.52; F, 38.50; N, 14.11.

3,5-Bis(trifluoromethyl)-4-phenyl-4*H*-1,2,4-triazole (**4a**) (R = C_6H_5).

Cooling the reaction mixture provided the crude product which was recrystallized from methanol to give 18.7 g (66%) of colorless **4a** (R = C_6H_5); mp 79-82°; ^{1}H (DMSO-d_6): δ 7.47-8.00 (m, 5H, ArH); ^{19}F nmr (DMSO-d_6): δ 17.0 (s).

Anal. Calcd. for $C_{10}H_5F_6N_3$: C, 42.72; H, 1.79; F, 40.54; N, 14.94. Found: C, 42.81; H, 1.79; F, 40.66; N, 14.89.

3,5-Bis(trifluoromethyl)-4-(4′-trifluoromethylphenyl)-4*H*-1,2,4-triazole (**4a**) [R = C_6H_4(4-CF_3)].

Cooling the reaction mixture provided the crude product which was recrystallized from methanol and subsequently sublimed at 120° (0.05 mm) to give 10.0 g (29%) of colorless **4a** [R = C_6H_4(4-CF_3)], mp 76-78°; ^{1}H nmr (DMSO-d_6): δ 8.13 (s, ArH); ^{19}F nmr (DMSO-d_6): δ 16.8 (s, 3F, $ArCF_3$), 17.7 (s, 6F, $NCCF_3$).

Anal. Calcd. for $C_{11}H_4F_9N_3$: C, 37.84; H, 1.15; F, 48.97; N, 12.03. Found: C, 37.91; H, 1.18; F, 49.08; N, 12.02.

3,5-Bis(trifluoromethyl)-4-(3′-trifluoromethylphenyl)-4*H*-1,2,4-triazole (**4a**) [R = C_6H_4(3-CF_3)].

Cooling the reaction mixture gave 25.6 g (73%) of colorless **4a** [R = C_6H_4(3-CF_3)], mp 96.5-98°; ^{1}H nmr (DMSO-d_6): δ 7.75-8.58 (m, ArH); ^{19}F nmr (DMSO-d_6): δ 16.4 (s, 3F, ArF), 17.3 (s, 6F, $NCCF_3$).

Anal. Calcd. for $C_{11}H_4F_9N_3$: C, 37.84; H, 1.15; F, 48.97; N, 12.03. Found: C, 37.70; H, 1.18; F, 48.85; N, 12.10.

3,5-Bis(trifluoromethyl)-4-(2′-trifluoromethylphenyl)-4*H*-1,2,4-triazole (**4a**) [R = C_6H_4(2-CF_3)].

Cooling the reaction mixture provided the crude product which was recrystallized from methanol to give 6.2 g (34%) colorless **4a** [R = C_6H_4(2-CF_3)]; mp 85-86°; ^{1}H nmr (DMSO-d_6): δ 7.95-8.20 (m, ArH); ^{19}F nmr (DMSO-d_6): δ 17.2-17.6 (q, 6F, $NCCF_3$), 18.9-19.5 (m, 3F, $ArCF_3$).

Anal. Calcd. for $C_{11}H_4F_9N_3$: C, 37.84; H, 1.15; F, 48.97; N, 12.04. Found: C, 37.75; H, 1.14; F, 49.04; N, 12.01.

3,5-Bis(trifluoromethyl)-4-(4′-fluorophenyl)-4*H*-1,2,4-triazole (**4a**) [R = C_6H_4(4-F)].

Cooling the reaction mixture gave 19.9 g (67%) of colorless **4a** [R = C_6H_4(4-F)], mp 101-103°; ^{1}H nmr (DMSO-d_6): δ 7.27-8.08 (m, ArH); ^{19}F nmr (DMSO-d_6): δ (+) 29.9- (+) 30.7 (m, 1F, ArF), 17.1 (s, 6F $NCCF_3$).

Anal. Calcd. for $C_{10}H_4F_7N_3$: C, 40.15; H, 1.35; F, 44.46; N, 14.05. Found: C, 40.18; H, 1.37; F, 44.39; N, 14.03.

3,5-Bis(trifluoromethyl)-4-(3′-fluorophenyl)-4*H*-1,2,4-triazole (**4a**) [R = C_6H_4(3-F)].

Cooling the reaction mixture gave 11.1 g (37%) of colorless **4a** [R = C_6H_4(3-F)]; mp 79.5-81.0°; ^{1}H nmr (DMSO-d_6): δ 7.27-8.08 (m, ArH); ^{19}F nmr (DMSO-d_6): δ (+) 30.8- (+) 31.6 (m, 1F, ArF), 17.2 (s, 6F, $NCCF_3$).

Anal. Calcd. for $C_{10}H_4F_7N_3$: C, 40.15; H, 1.35; F, 44.46; N, 14.05. Found: C, 40.14; H, 1.50; F, 44.29; N, 14.18.

3,5-Bis(trifluoromethyl)-4-(4′-chlorophenyl)-4*H*-1,2,4-triazole (**4a**) [R = C_6H_4(4-Cl)].

Cooling the concentrated reaction mixture provided the crude product which was sublimed at 60° (0.1 mm) and subsequently recrystallized from methanol to give 10.0 g (32%) of colorless **4a** [R = C_6H_4(4-Cl)], mp 79-82°; ^{1}H nmr (DMSO-d_6): δ 7.62-8.08 (m, ArH); ^{19}F nmr (DMSO-d_6): δ 17.5 (s).

Anal. Calcd. for $C_{10}H_4ClF_6N_3$: C, 38.06; H, 1.28; Cl, 11.23; F, 36.12; N, 13.31. Found: C, 38.04; H, 1.34; Cl, 11.30; F, 36.22; N, 13.23.

3,5-Bis(trifluoromethyl)-4-(2′,4′-dichlorophenyl)-4*H*-1,2,4-triazole (**4a**) [R = C_6H_3(2,4-Cl)].

Cooling the reaction mixture provided the crude product which was recrystallized from methanol and subsequently sublimed at 68° (0.01 mm) to give 9.5 g (54%) of colorless **4a** [R = C_6H_3(2,4-Cl)]: mp 93-95°; ^{1}H nmr (DMSO-d_6): δ 7.77-8.23 (m, ArH); ^{19}F nmr (DMSO-d_6): δ 16.4 (s).

Anal. Calcd. for $C_{10}H_3Cl_2F_6N_3$: C, 34.31; H, 0.86; Cl, 20.26; F, 32.57; N, 12.00. Found: C, 34.27; H, 0.87; Cl, 20.29; F, 32.41; N, 12.01.

3,5-Bis(trifluoromethyl-4-(3′,4′-dichlorophenyl)-4*H*-1,2,4-triazole (**4a**) [R = C_6H_3(3,4-Cl)].

Cooling the reaction mixture provided the crude product which was sublimed at 65° (0.1 mm) to give 17.1 g (50%) of colorless **4a** [R = C_6H_3(3,4-Cl)]; mp 84-86°; ^{1}H nmr (DMSO-d_6): δ 8.00 (s, 2H, ArH), 8.40 (s, 1H, ArH); ^{19}F nmr (DMSO-d_6): δ 17.5 (s).

Anal. Calcd. for $C_{10}H_3Cl_2F_6N_3$: C, 34.31; H, 0.86; F, 32.57; N, 12.00. Found: C, 34.30; H, 0.86; F, 32.44; N, 11.99.

3,5-Bis(trifluoromethyl)-4-(2′,4′,5′-trichlorophenyl)-4*H*-1,2,4-triazole (**4a**) [R = C_6H_2(2,4,5-Cl)].

Cooling the reaction mixture provided the crude product which was sublimed at 60° (0.01 mm) and subsequently recrystallized from methanol to give 9.0 g (46%) of colorless **4a** [R = C_6H_2(2,4,5-Cl)]: mp 142-144°; ^{1}H nmr (DMSO-d_6): δ 8.38 (s, 1H, ArH), 8.55 (s, 1H, ArH); ^{19}F nmr (DMSO-d_6): δ 16.6 (s).

Anal. Calcd. for $C_{10}H_2Cl_3F_6N_3$: C, 31.24; H, 0.52; Cl, 27.66; F, 29.65; N, 10.93. Found: C, 31.18; H, 0.61; Cl, 27.59; F, 29.81; N, 10.89.

3,5-Bis(trifluoromethyl)-4-(2′,6′-dimethylphenyl)-4*H*-1,2,4-triazole (**4a**) [R = C_6H_3(2,6-CH_3)].

Cooling the reaction mixture provided the crude product which was recrystallized from methanol and subsequently sublimed at 60° (0.01 mm) to give 11.2 g (75%) of colorless **4a** [R = C_6H_3(2,6-CH_3)], mp 121-122°; ^{1}H nmr (deuteriochloroform): δ 2.05 (s, 6H, CH_3), 7.05-7.40 (m, 3H, ArH); ^{19}F nmr (deuteriochloroform): δ 14.8 (s).

Anal. Calcd. for $C_{12}H_9F_6N_3$: C, 46.61; H, 2.93; F, 36.86; N, 13.59. Found: C, 46.52; H, 2.92; F, 36.68; N, 13.67.

3,5-Bis(trifluoromethyl)-4-(2′,6′-diethylphenyl)-4*H*-1,2,4-triazole (**4a**) [R = C_6H_3(2,6-C_2H_5)].

Cooling the reaction mixture provided the crude product which was recrystallized from methanol and subsequently sublimed at ambient temperature (0.01 mm) to give 12.0 g (37%) of colorless **4a** [R = C_6H_3(2,6-C_2H_5)]; mp 89-90°; ^{1}H nmr (deuteriochloroform): δ 1.25 (t, J = 7 Hz, 6H, CH_2CH_3), 2.25 (q, J = 7 Hz, 4H, CH_2CH_3), 7.25-7.80 (m, 3H, ArH); ^{19}F nmr (deuteriochloroform): δ 15.7 (s).

Anal. Calcd. for $C_{14}H_{13}F_6N_3$: C, 49.85; H, 3.89; F, 33.80; N, 12.46. Found: C, 49.99; H, 3.95; F, 33.99; N, 12.46.

3,5-Bis(trifluoromethyl)-4-[3′,5′-bis(trifluoromethyl)phenyl]-4*H*-1,2,4-triazole (**4a**) [R = C_6H_3(3,5-CF_3)].

Cooling the reaction mixture provided the crude product which was recrystallized from methanol to give 16.4 g (39%) of colorless **4a** [R = C_6H_3(3,5-CF_3)], mp 118-120°; ^{1}H nmr (DMSO-d_6): δ 8.90 (s, 2H, *o*-ArH), 8.50 (s, 1H, *p*-ArH); ^{19}F nmr (DMSO-d_6): δ 15.9 (s, 6F, $ArCF_3$), 17.2 (s, 6F, $NCCF_3$).

Anal. Calcd. for $C_{12}H_3F_{12}N_3$: C, 34.55; H, 0.72; F, 54.65; N, 10.07. Found: C, 34.42; H, 0.78; F, 54.78; N, 10.14.

4,4′-(1,4-Phenylene)bis[3,5-bis(trifluoromethyl)]-4*H*-1,2,4-triazole (**4a**) (Bisadduct).

The bistriazole was obtained from 21.1 g (102 mmoles) of **1a** and 5.4 g (50 mmoles) of 4-phenylenediamine. The crude product was recrystallized from methanol and subsequently from acetone to give 14.0 g (58%) of colorless bistriazole, mp 230-233°; ^{1}H nmr (DMSO-d_6): δ 7.80 (s, ArH); ^{19}F nmr (DMSO-d_6): δ 15.7 (s).

Anal. Calcd. for $C_{14}H_4F_{12}N_6$: C, 34.73; H, 0.83; F, 47.09; N, 17.36. Found: C, 34.62; H, 0.84; F, 46.97; N, 17.48.

1-(*N*-Methyltrifluoroacetimidoyl)-2-(trifluoroacetyl)hydrazine, Complex with Methanol (**5a**) (R = CH_3).

Following procedure A, 20.9 g (78%) of colorless **5a** (R = CH_3) was isolated, mp 101-102° dec; ^1H nmr (DMSO-d_6): δ 2.40 (s, 3H, NCH_3), 3.80 (s, 1H, OH), 4.20 (s, 3H, OCH_3), 8.20 (s, 2H, NH); ^{19}F nmr (DMSO-d_6): δ 6.0 (s, $COCF_3$), 8.9 (s, $NCCF_3$).

Anal. Calcd. for $C_6H_9F_6N_3O_2$: C, 26.77; H, 3.37; F, 42.35; N, 15.61. Found: C, 26.62; H, 3.17; F, 42.69; N, 15.31.

1-(*N*-Ethyltrifluoroacetimidoyl)-2-(trifluoroacetyl)hydrazine, Complex with Methanol (**5a**) (R = C_2H_5).

Following procedure A, 25.5 g (90%) of colorless **5a** (R = C_2H_5) was isolated, mp 83-88° dec; ^1H nmr (DMSO-d_6): δ 1.15 (t, J = 7 Hz, 3H, NCH_2CH_3), 2.81 (q, J = 7 Hz, 2H, NCH_2CH_3), 3.75 (s, 2.4H, $CHOH$), 4.10 (s, 0.6H, CH_3OH), 8.10 (s, 3H, NHNH and CH_3OH); ^{19}F nmr (DMSO-d_6): δ 6.4 (s, 2.4F, anti $NCCF_3$), 6.9 (s, 0.6F, syn $NCCF_3$), 9.2 (s, 2.4F, anti $COCF_3$), 12.5 (s, 0.6F, syn $COCF_3$).

Anal. Calcd. for $C_7H_{11}F_6N_3O_2$: C, 29.69; H, 3.92; F, 40.26; N, 14.84. Found: C, 29.51; H, 3.87; F, 40.26; N, 14.76.

1-[*N*-(1'-Methylpropyl)trifluoroacetimidoyl]-2-(trifluoroacetyl)hydrazine, Complex with Methanol (**5a**) (R = $CH(CH_3)C_2H_5$).

Following procedure A, 29.5 g (95%) of colorless **5a** (R = $CH(CH_3)C_2H_5$) was isolated, mp 70-74° dec; ^1H nmr (DMSO-d_6): δ 0.57-1.83 (m, 8H, $NCH(CH_3)CH_2CH_3$), 2.63-3.20 (m, 1H, NCH), 3.65 (s, 0.6H, CH_3OH), 4.00 (s, 2.4H, CH_3OH), 8.27 (s, 3H, NHNH and CH_3OH); ^{19}F nmr (DMSO-d_6): δ 6.1 (s, 0.6F, anti $NCCF_3$), 6.6 (s, 2.4F, syn $NCCF_3$), 7.5 (s, 0.6F, anti $COCF_3$), 12.2 (s, 2.4F, syn $COCF_3$).

Anal. Calcd. for $C_9H_{15}F_6N_3O_2$: C, 34.73; H, 4.86; F, 36.63; N, 13.50. Found: C, 34.72; H, 4.76; F, 36.45; N, 13.45.

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