A Convenient and Versatile Synthesis of 4-Trifluoromethyl-substituted Pyrazoles

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Trifluoromethyl-substituted pyrazoles were synthesized *via* 1,3-dipolar cycloaddition from sydnones **2a-j** and 1-aryl-3,3,3-trifluoro-propynes **5a-f**. The regioselectivity of the reaction and the spectroscopic characteristics of the products are discussed.

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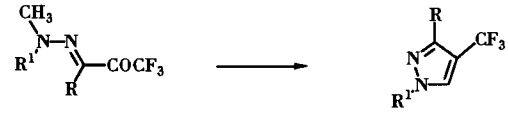
Introduction.

Fluorinated organic molecules receive increasing interest owing to their outstanding biological activity [1,2]. A number of fluorinated heterocyclic compounds have been prepared so far [3]. It is well known that 1,3-dipolar cycloaddition reactions of double or triple bond systems with a large number of 1,3-dipoles give rise to several expected heterocyclic rings [4]. Fluorinated dipolarophiles [5,6] as well as fluorinated dipoles [7-11] have been in turn employed in the synthesis of fluorinated heterocyclic compounds.

We and other authors have thus used reactions between fluorinated alkynes or alkenes and dipoles such as azides [12], nitrile oxides [13,14], diazomethane [15,16] and trifluoromethyldiazomethane [17] with the aim to obtain new fluorine-containing heterocyclic compounds [18]. Trifluoromethyl substituted pyrazoles are compounds possessing high biological activity as herbicides [19], fungicides [20], insecticides [21], analgesics, antipyretics, antiinflammatories [22] and hyperglycemic agents [23].

The majority of the compounds belonging to these classes synthesized up to now, bear the trifluoromethyl group in the 3- and 5-position of the pyrazole ring. These compounds can be prepared according to the typical procedures depicted in Scheme 1 [24-26]. These reactions however do not allow one to obtain 4-trifluoromethyl substituted pyrazoles. The latter compounds have been synthesized by means of few methods that suffer from several disadvantages. In fact, they involve the use of expensive perfluorinated olefins [27,28] or acetylenes [29], phosphorus-containing [30] and oxygen-containing [31] polycyclic compounds and lead only to polyfluorinated pyrazoles. Other procedures employ hazardous reagents such as diazoalkanes [32], or involve the transformation of a carboxylic acid group into a trifluoromethyl group with sulfur tetrafluoride in liquid hydrogen fluoride as the solvent [33]. All the procedures cited hardly ever are clear, give a sufficient degree of regioselectivity and are versatile. Even the recent method [34,35] involving the cyclization of *C*-trifluoroacetylated aldehyde alkyl methyl hydrazones is limited to obtaining 3-substituted-4-trifluoromethyl pyrazoles bearing only alkyl groups in 1-position and no substituent in 5-position, as outlined in Scheme 2.

Scheme 2



We now report a practical and flexible methodology for the construction of pyrazoles bearing a trifluoromethyl group in the 4-position employing sydnones and appropriately substituted trifluoromethyl alkynes.

Discussion.

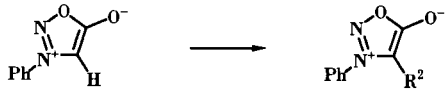
Various mesoionic compounds represent useful dipole systems, not yet widely employed as compared with the previously mentioned ones, which undergo 1,3-dipolar cycloadditions with different dipolarophiles. Among the congerie of mesoionic compounds sydnones are the best

Scheme 1

studied and thoroughly known. Sydnones can be readily prepared by cyclodehydration of *N*-substituted-*N*-nitroso-amino acids **1** with acetic acid anhydride. The resulting compounds contain a mesoionic aromatic system which can only be depicted with polar resonance structures [36,37].

Scheme 3

1 **2a-h**



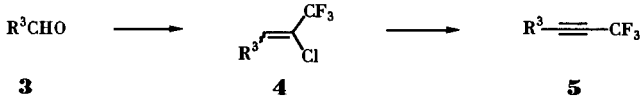
2a **2i-j**

1,2	R^1	R^2
a	C_6H_5	H
b	4-ClC_6H_4	H
c	4-$CH_3OC_6H_4$	H
d	$C_6H_5CH_2$	H
e	$(CH_3)_3C$	H
f	CH_3	H
g	C_6H_5	CH_3
h	C_6H_5	4-ClC_6H_4
i	C_6H_5	Br
j	C_6H_5	CH_3S

It is well known that sydnones readily undergo 1,3-dipolar cycloaddition reactions with acetylenes to give pyrazoles [38-40]. Continuing our studies on the reactivity of trifluoromethylalkynes with 1,3-dipoles, we have now investigated the cycloaddition reaction with sydnones.

1-Aryl-3,3,3-trifluoropropynes **5** are readily prepared in two steps from the corresponding aldehydes **3** *via* the known alkene intermediates **4** [12,13], Scheme 4. Except in the case of the nitro-substituted compound **5b** the dehydrochlorination of alkenes **4** can be achieved using sodium or potassium hydroxide in commercial dimethyl sulfoxide

Scheme 4



3 **4** **5**

3,4,5	R^3
a	4-$CH_3OC_6H_4$
b	4-$NO_2C_6H_4$
c	4-ClC_6H_4
d	2-ClC_6H_4
e	4-$CH_3SC_6H_4$
f	4-$CH_3SO_2C_6H_4$

at room temperature [12]. This method appears to be better than those previously reported [13,41]. In the case of alkyl derivatives **3** the method is unsuccessful. In fact when R^3 is a tertiary alkyl group the aldehydes do not react at all, while when R^3 is a secondary alkyl group the dehydrochlorination of alkenes **4** leads to the corresponding allenes. Finally if R^3 is a primary alkyl group, during the dehydrochlorination step a migration of the triple bond away from the trifluoromethyl group occurs [42].

Sydnones **2a-f** undergo smooth cycloaddition with 1-aryl-3,3,3-trifluoromethylpropynes **5** in high yield and with elevated regioselectivity to give pyrazoles **6** together with small quantities of **7**. Lower regioselectivity is obtained employing 4-substituted sydnones **2g-j**, Table 1. The reaction is performed by heating equimolar amounts of the two reactants in a high boiling aromatic solvent or in ethylene glycol for several hours, checking the progress of the reaction by glc and tlc analyses. This reaction involves a 1,3-dipolar cycloaddition of the sydnones to the corresponding alkynes followed by carbon dioxide evolution and aromatization, Scheme 5.

Table 1

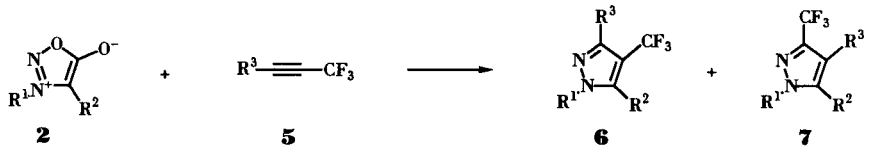
Yields and Regioselectivity of the Reaction of **2** + **5** to Give **6** + **7**

Products	Yield [a] (%)	Ratio [b] 6/7
6a/7a	56	93/7
6b/7b	93	93/7
6c/7c	90	93/7
6d/7d [c]	92	94/6
6e/7e	86	92/8
6f/7f	75	93/7
6g/7g	90	93/7
6h/7h	84	93/7
6i/7i	65	91/9
6j/7j	58	93/7
6k/7k	92	92/8
6l/7l	75	84/16
6m/7m	57	60/40
6n/7n [c]	43	71/29
6o/7o [c]	62	43/57

[a] Yield of isolated pure products **6** + **7** after chromatography. [b] The ratios of **6**:**7** were estimated by gc and ^{19}F nmr analyses of the crude reaction mixtures. [c] Inseparable mixtures were obtained.

The principle advantages of using sydnones are the great variety of substituents available for R^1 and R^2, the possibility of modifying the substituents in the 4-position of sydnones by known reactions and the capability of sydnones, owing to their aromatic character, to give electrophilic substitution in the 4-position with a great number of common electrophiles [36,43]. This great flexibility in the type of substituents in the sydnone ring will be reflected in the corresponding substitution of the resulting pyrazole.

Scheme 5



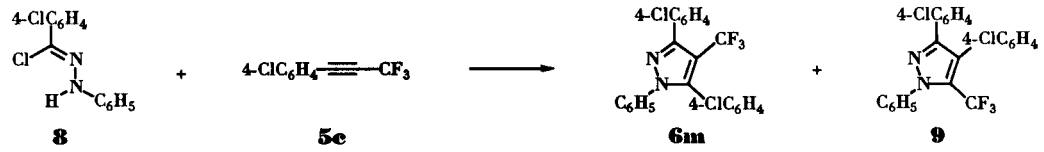
2 **5** **6** **7**

6,7	R^1	R^2	R^3
a	C_6H_5	H	4-$CH_3OC_6H_4$
b	C_6H_5	H	4-$NO_2C_6H_4$
c	C_6H_5	H	4-$CH_3SC_6H_4$
d	C_6H_5	H	2-ClC_6H_4
e	C_6H_5	H	4-$CH_3SO_2C_6H_4$
f	C_6H_5	H	4-ClC_6H_4
g	4-ClC_6H_4	H	4-ClC_6H_4
h	4-$CH_3OC_6H_4$	H	4-ClC_6H_4
i	$C_6H_5CH_2$	H	4-ClC_6H_4
j	$(CH_3)_3C$	H	4-ClC_6H_4
k	CH_3	H	4-ClC_6H_4
l	C_6H_5	CH_3	4-ClC_6H_4
m	C_6H_5	4-ClC_6H_4	4-ClC_6H_4
n	C_6H_5	Br	4-ClC_6H_4
o	C_6H_5	CH_3S	

The results summarized in Table 1 show that the prevailing orientation is that which places the trifluoromethyl group in the 4-position of the resulting pyrazole ring. Our previous results pointed out that also the cycloadditions of nitrile oxides [13] and azides [12] with aryltrifluoromethylacetylenes lead to regioisomeric mixtures where the cycloadducts having the trifluoromethyl substituent in the 4-position greatly predominate. A similar behaviour was observed by Huisgen [38] in the reaction of *N*-phenylsydnone with methyl 3-phenylpropynoate which leads exclusively to the formation of 4-methoxycarbonyl-1,3-diphenylpyrazole. Whilst the reaction of *N*-phenylsydnone with 1-fluoro-3,3,3-trifluoropropyne gave a 1:2 mixture of 3-fluoro-1-phenyl-4-trifluoromethylpyrazole and 4-fluoro-1-phenyl-3-trifluoromethylpyrazole [44]. The observed regioselectivity could be explained on the basis of Houk's model for HOMO-LUMO interactions between the reacting species [45-47]. The presence of the electron-deficient withdrawing group CF_3 lowers the HOMO and the LUMO energy of dipolarophiles so that the reaction becomes HOMO-dipole-LUMO-dipolarophile controlled. The preferred regioisomeric transition state will be the one in which the nitrogen atom (larger atomic orbital coefficient in the HOMO of the sydnone) interacts with the carbon atom bearing the aryl group (larger atomic orbital coefficient in the LUMO of the dipolarophile) and the carbon atom of the sydnone interacts with the carbon atom bearing the CF_3 group of the dipolarophiles. A more recent work [48] reports a charge distribution and coefficient values (in the ground state), of the atoms of the sydnone involved in the reactions, different from those assumed above. These authors consider that during a concerted approach of the two reactants (lying in parallel planes) a partial overlap of the terminal atoms occurs on the way to the transition state. This implies a stretching of the O1-N2 and the C4-C5 bonds of sydnone already in the transition state. An inversion of the frontier orbital coefficients is expected increasing the O1-N2 and the C4-C5 bond lengths. Therefore, assuming that the position of the transition state is close to the product, the inversion of the coefficients leads to a description of the preferred interactions similar to the one formerly given.

As can be inferred from Table 1, the regioselectivity is not affected by the substituents in the aryl moiety of the dipolarophiles **6,7a-f**, as well as modifying the nature of the substituent R^1 in the sydnone ring, **6,7g-k**. Instead, a remarkable effect is obtained when the 4-position of the sydnone is substituted, **6,7l-o**. Lower regioselectivity is displayed employing sydnones with electron-releasing groups in the 4-position. In particular with the 4-CH_3S derivative **2j** the regioselectivity is very low and reversed, **6,7o**. Attempts to perform the cycloaddition with 4-NO_2 and 4-CH_3SO_2 substituted sydnones have failed. The presence of an electron-withdrawing group lowers the HOMO energy of the dipole, thus increasing the gap to the alkyne LUMO, and the thermal decomposition of the sydnone reasonably becomes the preferred process. Except in the case of sydnone **2i** [49] change in the reaction solvent from xylene to ethylene glycol does not affect the reaction time, the yield and the regioselectivity. Working in the presence

Scheme 6



of BHT, no improvement of the yield was achieved.

The ^{19}F nmr spectra allow us to assign the structure of the regioisomers **6** and **7**. In agreement with the previously reported data for trifluoromethylpyrazoles [44] the trifluoromethyl group of **6** resonates at lower fields (4-6 ppm) than the trifluoromethyl group of **7**.

The mass spectra of these compounds do not allow us, in general, to distinguish between **6** and **7**. In both the regioisomeric series the M^+ peak is present and often represents the base peak. In the other cases the $[R^1]^+$ is the base peak. These spectra seem to be highly influenced by the type and the position of the substituents so that no schematic generalization can be made. However we may observe that in compounds **7** there is ofter present the $[M^+-CF_3]$ and $[M^+-CF_3CN]$ peaks. Instead, compounds **6** sometimes show the $[R_3CN]^+$ peak. A clear distinction can be made in the two regioisomeric series in which R^3 is 4-chlorophenyl, **6,7f-o**. In fact, compounds **6** show the $[4-ClC_6H_4]^+$ peak arising directly from the M^+ peak or by the loss of CN from the $[4-ClC_6H_4CN]^+$ peak. In compounds **7** the loss of CF_3CN from the M^+ peak gives rise to the $[R^1N-CH=C-(4-ClC_6H_4)]^+$ peak which loses R^1 to give $[4-ClC_6H_4-C=CHN]^+$ that finally loses HCN and gives the $[4-ClC_6H_4C]^+$ peak.

We have also found that nitrileimines react with trifluoromethylalkynes to give 4-trifluoromethylpyrazoles in high yields with almost complete regioselectivity. 3,5-Bis(4-chlorophenyl)-1-phenyl-4-trifluoromethylpyrazole (**6m**) was obtained in 87% yield by cycloaddition of the nitrileimine derived from *N*-phenyl-4-chlorobenzhydrazidoyl chloride (**8**) with the alkyne **5c** accompanied by 2% of 3,4-bis(4-chlorophenyl)-1-phenyl-5-trifluoromethylpyrazole (**9**) (Scheme 6).

A complete study of this topic, as well as a systematic investigation concerning the use of mesoionic compounds as dipoles in 1,3-dipolar cycloaddition with trifluoromethylalkynes, is in progress in our laboratories.

EXPERIMENTAL

Analytical tlc plates and silica gel (230-400 mesh) were purchased from Merck. Melting points were determined using a Buchi SMP-20 apparatus and are reported uncorrected. The gc analyses were carried out on a Carlo Erba HRGC 5300 chromatograph. Microanalyses were obtained using a Hewlett-Packard 185 element analyser. Mass spectra were obtained using a Finnigan MAT INCOS 50 spectrometer with an electron impact source at 70 eV. The ir spectra were obtained using a Perkin-Elmer 1420 spectrophotometer. The ^1H nmr and ^{19}F nmr spectra were obtained using a Bruker AC 200 spectrometer, with deuteriochloroform as the solvent and TMS or trichlorofluoromethane respectively as the internal standards. All reagents were of commercial quality. Anhydrous solvents were dried on molecular sieves. Alkynes **4a-d** [12,13], sydnones **2a-i** [37], sydnone **2j** [50] and *N*-phenyl-4-chlorobenzhydrazidoyl chloride (**8**) [51] were prepared as described previously.

1-(4-Methylthiophenyl)-2-chloro-3,3,3-trifluoropropene (**4e**).

To a stirred suspension of zinc dust (5.9 g, 0.09 g-atom) in anhydrous *N,N*-dimethylformamide (10 ml), under a nitrogen atmosphere, a solution of 1,1,1-trichloro-2,2,2-trifluoroethane (18.5 g, 0.10 mole) in *N,N*-dimethylformamide (15 ml) was slowly added dropwise. After the exothermic reaction began, the internal temperature was kept within 50° by external cooling. The reaction mixture was stirred at 50° for 2 hours, then a solution of 4-methylthiobenzaldehyde (10 g, 0.065 mole) in dimethylformamide (25 ml) was added dropwise and the reaction mixture was allowed to react at 50-55° overnight. Acetic anhydride (6.8 ml, 0.073 mole) and zinc dust (4.8 g, 0.29 g-atom) were added and the mixture was stirred at 50° for 4 hours, then diluted with water, acidified with dilute hydrochloric acid and extracted with methylene chloride. The organic phase was washed with water, dried with sodium sulfate and evaporated. The crude product was purified by chromatography on silica-gel (100 g), with *n*-hexane as the eluant to give a 10:1 mixture of (*Z*)- and (*E*)-isomers **4e** (11.5 g, 69% yield); ^{19}F nmr: δ -68.62 ((*Z*)-isomer), -61.54 ((*E*)-isomer); ^1H nmr: δ 7.66 (d, 2H, aryl protons), 7.26 (d, 2H, aryl protons), 7.22 (s, CH (*Z*)-isomer), 7.20 (s, CH (*E*)-isomer), 2.50 (s, CH_3S (*Z*)-isomer), 2.48 (s, CH_3S (*E*)-isomer).

Anal. Calcd. for $C_{10}H_8ClF_3S$: C, 47.53; H, 3.19; Cl, 14.03; F, 22.56; S, 12.69. Found: C, 47.38; H, 3.26; F, 22.42.

1-(4-Methylthiophenyl)-3,3,3-trifluoro-1-propyne (**5e**).

To a stirred solution of **4e** (11 g, 0.043 mole) in dimethyl sulfoxide (15 ml) was added finely powdered 85% potassium hydroxide (3.1 g, 0.05 mole). The mixture was stirred at room temperature overnight, then diluted with water (100 ml) and extracted with ethyl ether. The organic phase was washed with water and dried with sodium sulfate. The solvent was evaporated and the crude mixture was purified *via* silica gel chromatography (*n*-hexane) to give **5e** (8.5 g, 91% yield), mp 49.5°; ir: 2240 (C≡C), 1150 (CF_3) cm^{-1}; ^{19}F nmr: δ -50.10; ^1H nmr: δ 7.43 (d, 2H, J = 8.5 Hz, aryl protons), 7.19 (d, 2H, J = 8.5 Hz, aryl protons), 2.48 (s, 3H, CH_3S).

Anal. Calcd. for $C_{10}H_7F_3S$: C, 55.55; H, 3.26; F, 26.36; S, 14.83. Found: C, 55.28; H, 3.31; F, 26.24.

1-(4-Methylsulfonylphenyl)-3,3,3-trifluoro-1-propyne (**5f**).

1-(4-Methylthiophenyl)-2-chloro-3,3,3-trifluoropropene (**4e**) (2.17 g, 10 mmoles) was dissolved in methanol (10 ml) and sodium

tungstate dihydrate (0.05 g, 0.15 mmole) dissolved in water (0.5 ml) was added. The solution was heated to 60° and 33% hydrogen peroxide (2.7 ml, 29 mmoles) was slowly added dropwise. Heating and stirring were continued for 1.5 hours, then the mixture was diluted with water (100 ml) and extracted with methylene chloride. The organic phase was dried with sodium sulfate and evaporated to give **5f** (2.40 g, 96% yield), mp 129-130°; ir: 2250 (C≡C), 1150 (CF_3) cm^{-1}; ^{19}F nmr: δ -50.96; ^1H nmr: δ 7.98 (d, 2H, J = 8.4 Hz, aryl protons), 7.75 (d, 2H, J = 8.4 Hz, aryl protons), 3.06 (s, 3H, CH_3SO_2).

Anal. Calcd. for $C_{10}H_7F_3O_2S$: C, 48.39; H, 2.84; F, 22.96; S, 12.92. Found: C, 48.21; H, 2.93; F, 22.85.

Synthesis of Pyrazoles **6** and **7**. General Procedure [52].

Sydnone **2** (4 mmoles) and aryl trifluoromethylpropyne **5** (4 mmoles) were dissolved in xylene (7 ml) and heated at 120-125° for 48-72 hours. The solvent was evaporated and the crude mixture separated by silica gel chromatography.

3-(4-Methoxyphenyl)-1-phenyl-4-trifluoromethylpyrazole (**6a**).

This compound was obtained from **2a** and **5a** and had mp 90-91°; ir: 1620, 1560 (C=C, C=N), 1125 (CF_3) cm^{-1}; ^{19}F nmr: δ -55.75; ^1H nmr: δ 8.22 (s, 1H, 5-H), 7.77-6.96 (m, 9H, aryl protons), 3.86 (s, 3H, CH_3O); ms: (m/z) 318 (M^+, 98), 303 (M^+-CH_3, 18), 215 (M^+-C_6H_5CN, 3), 200 (M^+-CH_3-C_6H_5CN, 7), 104 ($C_6H_5NCH^+$, 25), 77 (100).

Anal. Calcd. for $C_{17}H_{13}F_3N_2O$: C, 64.15; H, 4.12; F, 17.91; N, 8.80. Found: C, 64.22; H, 4.21; F, 17.88; N, 8.70.

4-(4-Methoxyphenyl)-1-phenyl-3-trifluoromethylpyrazole (**7a**).

This compound was obtained as the minor product from **2a** and **5a** and characterized from the crude reaction mixture; ^{19}F nmr: δ -60.15; ms: (m/z) 318 (M^+, 70), 303 (M^+-CH_3, 18), 78 (100), 77 (45).

3-(4-Nitrophenyl)-1-phenyl-4-trifluoromethylpyrazole (**6b**).

This compound was obtained from **2a** and **5b** and had mp 119-120°; ir: 1605, 1560 (C=C, C=N), 1345 (NO_2), 1125 (CF_3) cm^{-1}; ^{19}F nmr: δ -55.64; ^1H nmr: δ 8.30 (s, 1H, 5-H), 8.34-7.41 (m, 9H, aryl protons); ms: (m/z) 333 (M^+, 100), 303 (M^+-NO, 8), 287 (M^+-NO_2, 8), 184 (M^+-NO_2-C_6H_5CN, 11), 104 ($C_6H_5NCH^+$, 18), 77 (100).

Anal. Calcd. for $C_{16}H_{10}F_3N_3O_2$: C, 57.66; H, 3.02; F, 17.10; N, 12.61. Found: C, 57.81; H, 3.07; F, 17.01; N, 12.49.

4-(4-Nitrophenyl)-1-phenyl-3-trifluoromethylpyrazole (**7b**).

This compound was obtained as the minor product from **2a** and **5b** and characterized from the crude reaction mixture; ^{19}F nmr: δ -59.93; ms: (m/z) 333 (M^+, 88), 303 (M^+-NO, 12), 104 ($C_6H_5NCH^+$, 10), 77 (100).

3-(4-Methylthiophenyl)-1-phenyl-4-trifluoromethylpyrazole (**6c**).

This compound was obtained from **2a** and **5e** and had mp 98-99°; ir: 1610, 1575 (C=C, C=N), 1120 (CF_3) cm^{-1}; ^{19}F nmr: δ -55.71; ^1H nmr: δ 8.24 (s, 1H, 5-H), 7.76-7.30 (m, 9H, aryl protons), 2.52 (s, 3H, methylthio); ms: (m/z) 334 (M^+, 100), 319 (M^+-CH_3, 19), 149 ($CH_3SC_6H_4CN^+$, 4), 108 ($C_6H_5S^+$, 4), 104 ($C_6H_5NCH^+$, 11), 77 (41).

Anal. Calcd. for $C_{17}H_{13}F_3N_2S$: C, 61.07; H, 3.92; F, 17.05; N, 8.38; S, 9.59. Found: C, 61.09; H, 3.95; F, 16.94; N, 8.32.

4-(4-Methylthiophenyl)-1-phenyl-3-trifluoromethylpyrazole (**7c**).

This compound was obtained as the minor product from **2a** and **5e** and characterized from the crude reaction mixture; ^{19}F nmr: δ -60.03; ms: (m/z) 334 (M^+, 100), 319 (M^+-CH_3, 29), 104 ($C_6H_5NCH^+$, 3), 77 (29).

3-(2-Chlorophenyl)-1-phenyl-4-trifluoromethylpyrazole (**6d**).

This compound was obtained as the main product from **2a** and **5d** and characterized after chromatography from the inseparable oily mixture; ^{19}F nmr: δ -56.68; ms: (m/z) 322 (M^+, 96), 287 (M^+-Cl, 14), 184 (M^+-Cl-C_6H_5CN, 7), 137 ($ClC_6H_5CN^+$, 6), 111 ($ClC_6H_5^+$, 16), 104 ($C_6H_5NCH^+$, 29), 77 (100).

4-(2-Chlorophenyl)-1-phenyl-3-trifluoromethylpyrazole (**7d**).

This compound was obtained as the minor product from **2a** and **5d** and characterized after chromatography from the inseparable oily mixture; ^{19}F nmr: δ -60.66; ms: (m/z) 322 (M^+, 60), 123 ($ClC_6H_5C^+$, 8), 104 ($C_6H_5NCH^+$, 16), 77 (100).

3-(4-Methylsulfonylphenyl)-1-phenyl-4-trifluoromethylpyrazole (**6e**).

This compound was obtained from **2a** and **5f** and had mp 169-171°; ir: 1605, 1560 (C=C, C=N), 1305 (SO_2), 1140 (CF_3) cm^{-1}; ^{19}F nmr: δ -55.60; ^1H nmr: δ 8.30 (s, 1H, 5-H), 8.02-7.40 (m, 9H, aryl protons), 3.10 (s, 3H, CH_3SO_2); ms: (m/z) 366 (M^+, 76), 351 (M^+-CH_3, 3), 303 (M^+-$SOCH_3$, 19), 287 (M^+-SO_2CH_3, 71), 184 (M^+-SO_2CH_3-C_6H_5CN, 13), 104 ($C_6H_5NCH^+$, 22), 77 (100).

Anal. Calcd. for $C_{17}H_{13}F_3N_2O_2S$: C, 55.73; H, 3.58; F, 15.56; N, 7.65; S, 8.75. Found: C, 55.94; H, 3.69; F, 15.64; N, 7.77.

4-(4-Methylsulfonylphenyl)-1-phenyl-3-trifluoromethylpyrazole (**7e**).

This compound was obtained as the minor product from **2a** and **5f** and characterized from the crude reaction mixture; ^{19}F nmr: δ -59.90; ms: (m/z) 366 (M^+, 95), 351 (M^+-CH_3, 2), 303 (M^+-$SOCH_3$, 31), 287 (M^+-SO_2CH_3, 44), 104 ($C_6H_5NCH^+$, 11), 77 (100).

3-(4-Chlorophenyl)-1-phenyl-4-trifluoromethylpyrazole (**6f**) [53].

This compound was obtained from **2a** and **5c** and had mp 76°; ir: 1610, 1560 (C=C, C=N), 1120 (CF_3) cm^{-1}; ^{19}F nmr: δ -55.70; ^1H nmr: δ 8.25 (s, 1H, 5-H), 7.78-7.35 (m, 9H, aryl protons); ms: (m/z) 322 (M^+, 58), 184 (M^+-Cl-C_6H_5CN, 5), 137 ($ClC_6H_5CN^+$, 6), 111 ($ClC_6H_5^+$, 32), 104 ($C_6H_5NCH^+$, 61), 77 (100).

Anal. Calcd. for $C_{16}H_{10}ClF_3N_2$: C, 59.55; H, 3.12; Cl, 10.99; F, 17.66; N, 8.68. Found: C, 59.81; H, 3.21; F, 17.74; N, 8.49.

4-(4-Chlorophenyl)-1-phenyl-3-trifluoromethylpyrazole (**7f**).

This compound was obtained as the minor product from **2a** and **5c** and characterized from the crude reaction mixture; ^{19}F nmr: δ -60.02; ms: (m/z) 322 (M^+, 100), 253 (M^+-CF_3, 4), 150 ($ClC_6H_4C=CHN^+$, 7), 123 ($ClC_6H_5C^+$, 7), 104 ($C_6H_5NCH^+$, 5), 77 (67).

1,3-Bis(4-chlorophenyl)-4-trifluoromethylpyrazole (**6g**).

This compound was obtained from **2b** and **5c** and had mp 114-115°; ir: 1610, 1555 (C=C, C=N), 1130 (CF_3) cm^{-1}; ^{19}F nmr: δ -55.84; ^1H nmr: δ 8.21 (s, 1H, 5-H), 7.76-7.39 (m, 8H, aryl protons); ms: (m/z) 356 (M^+, 93), 321 (M^+-Cl, 3), 286 (M^+-2Cl, 6), 219 (M^+-ClC_6H_4CN, 6), 138 ($ClC_6H_4NCH^+$, 43), 111 ($ClC_6H_4^+$, 100).

Anal. Calcd. for $C_{16}H_9Cl_2F_3N_2$: C, 53.81; H, 2.54; Cl, 19.85; F, 15.96; N, 7.84. Found: C, 54.00; H, 2.57; F, 16.16; N, 7.91.

1,4-Bis(4-chlorophenyl)-3-trifluoromethylpyrazole (**7g**).

This compound was obtained as the minor product from **2b** and **5c** and characterized from the crude reaction mixture; ^{19}F nmr: δ -60.16; ms: (m/z) 356 (M^+, 100), 287 (M^+-CF_3, 3), 261 (M^+-CF_3CN, 3), 252 (M^+-CF_3-Cl, 21), 138 ($ClC_6H_4NCH^+$, 10), 123 ($ClC_6H_4C^+$, 14), 111 ($ClC_6H_4^+$, 41).

3-(4-Chlorophenyl)-1-(4-methoxyphenyl)-4-trifluoromethylpyrazole (**6h**).

This compound was obtained from **2c** and **5c** and had mp 53-54°; ir: 1590, 1535 (C=C, C=N), 1115 (CF_3) cm^{-1}; ^{19}F nmr: δ -55.48; ^1H nmr: δ 8.13 (s, 1H, 5-H), 7.75-6.94 (m, 8H, aryl protons), 3.84 (s, 3H, CH_3O); ms: (m/z) 352 (M^+, 100), 337 (M^+-CH_3, 21), 134 ($CH_3OC_6H_4NCH^+$, 7), 111 ($ClC_6H_4^+$, 39), 107 ($CH_3O-C_6H_4^+$, 32), 92 ($C_6H_4O^+$, 13).

Anal. Calcd. for $C_{17}H_{12}ClF_3N_2O$: C, 57.89; H, 3.43; Cl, 10.05; F, 16.16; N, 7.94. Found: C, 57.91; H, 3.53; F, 15.98; N, 8.09.

4-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3-trifluoromethylpyrazole (**7h**).

This compound was obtained as the minor product from **2c** and **5c** and characterized from the crude reaction mixture; ^{19}F nmr: δ -59.78; ms: (m/z) 352 (M^+, 100), 337 (M^+-CH_3, 20), 283 (M^+-CF_3, 3), 227 (M^+-CF_3CN, 3), 134 ($CH_3OC_6H_4NCH^+$, 4), 123 ($ClC_6H_4C^+$, 6), 107 ($CH_3OC_6H_4^+$, 5), 92 ($C_6H_4O^+$, 12).

1-Benzyl-3-(4-chlorophenyl)-4-trifluoromethylpyrazole (**6i**).

This compound was obtained from **2d** and **5c** and had mp 43-45°; ir: 1585, 1555 (C=C, C=N), 1110 (CF_3) cm^{-1}; ^{19}F nmr: δ -55.33; ^1H nmr: δ 7.70 (s, 1H, 5-H), 7.67-7.30 (m, 9H, aryl protons), 5.35 (s, 2H, CH_2Ph); ms: (m/z) 336 (M^+, 54), 335 (M^+-H, 49), 111 ($ClC_6H_4^+$, 3), 91 ($C_6H_5CH_2^+$, 100).

Anal. Calcd. for $C_{17}H_{12}ClF_3N_2$: C, 60.64; H, 3.59; Cl, 10.53; F, 16.93; N, 8.32. Found: C, 60.60; H, 3.59; F, 17.11; N, 8.28.

1-Benzyl-4-(4-chlorophenyl)-3-trifluoromethylpyrazole (**7i**).

This compound was obtained as the minor product from **2d** and **5c** and characterized from the crude reaction mixture; ^{19}F nmr: δ -59.73; ms: (m/z) 336 (M^+, 39), 335 (M^+-H, 19), 267 (M^+-H-CF_3, 7), 150 ($ClC_6H_4C=CHN^+$, 2), 123 ($ClC_6H_4C^+$, 2), 91 ($C_6H_5-CH_2^+$, 100).

1-*tert*-Butyl-3-(4-chlorophenyl)-4-trifluoromethylpyrazole (**6j**).

This compound was obtained from **2e** and **5c** and had mp 61-63°; ir: 1580, 1555 (C=C, C=N), 1120 (CF_3) cm^{-1}; ^{19}F nmr: δ -54.99; ^1H nmr: δ 7.82 (s, 1H, 5-H), 7.66 (d, 2H, J = 8.5 Hz, aryl protons), 7.38 (d, 2H, J = 8.5 Hz, aryl protons), 1.63 (s, 9H, *tert*-butyl); ms: (m/z) 302 (M^+, 25), 287 (M^+-CH_3, 4), 246 ($M^+-C_4H_8$, 100), 137 ($ClC_6H_4CN^+$, 2), 111 ($ClC_6H_4^+$, 6), 57 ($C_4H_9^+$, 31).

Anal. Calcd. for $C_{14}H_{14}ClF_3N_2$: C, 55.55; H, 4.66; Cl, 11.71; F, 18.83; N, 9.25. Found: C, 55.67; H, 4.74; F, 18.88; N, 9.41.

1-*tert*-Butyl-4-(4-chlorophenyl)-3-trifluoromethylpyrazole (**7j**).

This compound was obtained as the minor product from **2e** and **5c** and characterized from the crude reaction mixture; ^{19}F nmr: δ -59.39; ms: (m/z) 302 (M^+, 19), 287 (M^+-CH_3, 4), 246 ($M^+-C_4H_8$, 100), 207 (M^+-CF_3CN, 2), 123 ($ClC_6H_4C^+$, 4), 57 ($C_4H_9^+$, 20).

3-(4-Chlorophenyl)-1-methyl-4-trifluoromethylpyrazole (**6k**).

This compound was obtained from **2f** and **5c** and had mp 40-41°; ir: 1605, 1560 (C=C, C=N), 1120 (CF_3) cm^{-1}; ^{19}F nmr: δ -55.21; ^1H nmr: δ 7.70 (s, 1H, 5-H), 7.64 (d, 2H, J = 8.5 Hz, aryl protons), 7.39 (d, 2H, J = 8.5 Hz, aryl protons), 3.93 (s, 3H, CH_3); ms: (m/z) 260 (M^+, 100), 259 (M^+-H, 15), 219 (M^+-CH_3CN, 6), 137 ($ClC_6H_4CN^+$, 4), 111 ($ClC_6H_4^+$, 18), 42 (CH_3NCH^+, 84).

Anal. Calcd. for $C_{11}H_8ClF_3N_2$: C, 50.69; H, 3.09; Cl, 13.60; F, 21.87; N, 10.75. Found: C, 50.80; H, 3.15; F, 21.97; N, 10.59.

4-(4-Chlorophenyl)-1-methyl-3-trifluoromethylpyrazole (**7k**).

This compound was obtained as the minor product from **2f** and **5c** and characterized from the crude reaction mixture; ^{19}F nmr: δ -59.67; ms: (m/z) 260 (M^+, 100), 191 (M^+-CF_3, 2), 165 (M^+-CF_3CN, 2), 123 ($ClC_6H_4C^+$, 7), 42 (CH_3NCH^+, 30).

3-(4-Chlorophenyl)-5-methyl-1-phenyl-4-trifluoromethylpyrazole (**6l**).

This compound was obtained from **2g** and **5c** and had mp 61-63°; ir: 1605, 1560 (C=C, C=N), 1100 (CF_3) cm^{-1}; ^{19}F nmr: δ -55.83; ^1H nmr: δ 7.63-7.36 (m, 9H, aryl protons), 2.44 (s, 3H, CH_3); ms: (m/z) 336 (M^+, 70), 335 (M^+-H, 17), 301 (M^+-Cl, 4), 118 ($C_6H_5NCCH_3^+$, 25), 111 ($ClC_6H_4^+$, 13), 77 (100).

Anal. Calcd. for $C_{17}H_{12}ClF_3N_2$: C, 60.64; H, 3.59; Cl, 10.53; F, 16.92; N, 8.32. Found: C, 60.72; H, 3.68; F, 16.75; N, 8.41.

4-(4-Chlorophenyl)-5-methyl-1-phenyl-3-trifluoromethylpyrazole (**7l**).

This compound was obtained as the minor product from **2g** and **5c** and characterized from the crude reaction mixture; ^{19}F nmr: δ -60.04; ms: (m/z) 336 (M^+, 86), 335 (M^+-H, 33), 301 (M^+-Cl, 3), 123 ($ClC_6H_4C^+$, 5), 118 ($C_6H_5NCCH_3^+$, 17), 77 (100).

3,5-Bis(4-chlorophenyl)-1-phenyl-4-trifluoromethylpyrazole (**6m**).

This compound was obtained from **2h** and **5c** and had mp 135-136°; ir: 1605 (C=C, C=N), 1110 (CF_3) cm^{-1}; ^{19}F nmr: δ -52.51; ^1H nmr: δ 7.70-7.20 (m, 13H, aryl protons); ms: (m/z) 432 (M^+, 65), 214 ($ClC_6H_4-C=N-C_6H_5^+$, 11), 111 ($ClC_6H_4^+$, 7), 91 ($C_6H_5N^+$, 15), 77 (100).

Anal. Calcd. for $C_{22}H_{13}Cl_2F_3N_2$: C, 60.99; H, 3.02; Cl, 16.37; F, 13.15; N, 6.47. Found: C, 60.84; H, 3.06; F, 13.06; N, 6.36.

4,5-Bis(4-chlorophenyl)-1-phenyl-3-trifluoromethylpyrazole (**7m**).

This compound was obtained from **2h** and **5c** and had mp 148-149°; ir: 1600 (C=C, C=N), 1130 (CF_3) cm^{-1}; ^{19}F nmr: δ -59.89; ^1H nmr: δ 7.45-6.69 (m, 13H, aryl protons); ms: (m/z) 432 (M^+, 79), 123 ($ClC_6H_4C^+$, 3), 77 (100).

Anal. Calcd. for $C_{22}H_{13}Cl_2F_3N_2$: C, 60.99; H, 3.02; Cl, 16.37; F, 13.15; N, 6.47. Found: C, 61.09; H, 2.98; F, 13.07; N, 6.40.

5-Bromo-3-(4-chlorophenyl)-1-phenyl-4-trifluoromethylpyrazole (**6n**).

This compound was obtained as the main product from **2i** and **5c**, employing ethylene glycol as the solvent, and characterized after chromatography from the inseparable solid mixture. Attempt to perform the reaction in xylene gave only tarry materials and unreacted **5c**; ^{19}F nmr: δ -55.10; ms: (m/z) 400 (M^+, 16), 321 (M^+-Br, 10), 184 ($M^+-Cl-C_6H_5CN$, 5), 111 ($ClC_6H_4^+$, 13), 77 (100).

5-Bromo-4-(4-chlorophenyl)-1-phenyl-3-trifluoromethylpyrazole (**7n**).

This compound was obtained as the minor product from **2i** and **5c** and characterized after chromatography from the inseparable solid mixture; ^{19}F nmr: δ -60.70; ms: (m/z) 400 (M^+, 34), 321 (M^+-Br, 4), 252 ($M^+-Cl-CF_3$, 14), 123 ($ClC_6H_4C^+$, 38), 77 (100).

3-(4-Chlorophenyl)-5-methylthio-1-phenyl-4-trifluoromethylpyrazole (**6o**).

This compound was obtained as the minor product from **2j** and **5c** and characterized after chromatography from the inseparable oily mixture; ^{19}F nmr: δ -54.49; ms: (m/z) 368 (M^+, 65), 353 (M^+-CH_3, 3), 333 (M^+-Cl, 4), 321 (M^+-CH_3S, 4), 137 ($ClC_6H_4CN^+$, 4), 111 ($ClC_6H_4^+$, 13), 77 (100).

4-(4-Chlorophenyl)-5-methylthio-1-phenyl-3-trifluoromethylpyrazole (**7o**).

This compound was obtained as the main product from **2j** and **5c** and characterized after chromatography from the inseparable oily mixture; ^{19}F nmr: δ -60.21; ms: (m/z) 368 (M^+, 100), 353 (M^+-CH_3, 3), 333 (M^+-Cl, 5), 123 ($ClC_6H_4C^+$, 18), 77 (90).

Reaction of 1-(4-Chlorophenyl)-3,3,3-trifluoro-1-propyne (**5c**) with *N*-Phenyl-4-chlorobenzhydrazidoyl Chloride (**8**).

Compound **8** (2.17 g, 4.4 mmoles), **5c** (0.82 g, 4 mmoles) and triethylamine (1.12 ml, 8 mmoles) were dissolved in chloroform (7 ml) and heated to reflux for 16 hours. After dilution with chloroform the solution was treated with 3% hydrochloric acid, washed with water and dried with sodium sulfate. The solvent was evaporated and the product was purified by silica gel chromatography (*n*-hexane/ethyl acetate 9:1). The product 3,5-bis(4-chlorophenyl)-1-phenyl-4-trifluoromethylpyrazole (**6m**) was obtained in 87% yield. The regioisomer 3,4-bis(4-chlorophenyl)-1-phenyl-5-trifluoromethylpyrazole (**9**) was obtained as the minor product and characterized from the crude reaction mixture; ^{19}F nmr: δ -54.88; ms: (m/z) 432 (M^+, 16), 228 ($ClC_6H_4-C=N-N-C_6H_5^+$, 7), 123 ($ClC_6H_4C^+$, 41), 111 ($ClC_6H_4^+$, 11), 77 (100).

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[53] This reaction was also performed in ethylene glycol as the solvent and gave the same result.