Synthesis of triaryl-4-trifluoromethylpyrazoles via 1,3-dipolar cycloaddition

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Abstract

Triaryl-substituted trifluoromethylpyrazoles may be synthesized from nitrileimines, formed *in situ* from the corresponding α-halohydrazones, and various substituted 1-aryl-3,3,3-trifluoro-1-propynes. The spectroscopic characteristics of the products and the regioselectivity of the reaction are discussed.

Introduction

Over the past few years, great efforts have been directed towards the synthesis of fluorinated organic compounds, see, for example, refs. 1–7. A large number of fluoroalkyl-substituted heterocyclic compounds have been synthesized via 1,3-dipolar cycloaddition reactions. Fluorinated dipoles, or alternatively fluorinated dipolarophiles, can be used for this purpose, for example refs. 8–22.

It is known that nitrileimines $R-C^{+}=N-N^{-}-R'$ react with alkynes to give pyrazoles [23]. Continuing our research with the aim of obtaining enhanced biological activity through the introduction of a fluorine-containing moiety into target molecules, we have now investigated the reaction between aryltrifluoromethyl alkynes and nitrileimines.

In a previous paper we reported the preparation of new 4-trifluoromethylpyrazoles employing sydnones [15]. We now report the synthesis of complementary molecules using conveniently substituted nitrileimines, prepared *in situ* from the corresponding α-halohydrazones in the presence of triethylamine as an acid acceptor.

Experimental

General techniques

Analytical TLC plates and silica gel (230–400 mesh) were purchased from Merck. Melting points were determined using a Büchi SMP-20 apparatus and are reported uncorrected. GC analyses were carried out on a Carlo-Erba HRGC 5300 chromatograph. Microanalyses were obtained using a Perkin-Elmer 2400 CHN element analyzer. Mass spectra were obtained using a Finnigan MAT INCOS 50 spectrometer with an electron impact source at 70 eV. IR spectra were obtained using a Perkin-Elmer 1420 spectrophotometer. ^{19}F NMR spectra were obtained using a Bruker AC 200 spectrometer at 188.3 MHz, with $CDCl_3$ as the solvent and $CFCl_3$ as the internal standard. All reagents were of commercial quality. Anhydrous solvents were dried on molecular sieves.

Alkynes **1a–f** [15–17] and α-halohydrazones **2a–h** [23] were prepared as described previously.

Synthesis of pyrazoles 3 and 4. General procedure

Alkyne **1** (4 mmol), halohydrazone **2** (4.4 mmol) and triethylamine (1.12 ml, 8 mmol) were dissolved in chloroform (7 ml) and heated to reflux for the time length indicated in Table 1. After dilution with chloroform, the solution was treated with 3% hydrochloric acid, washed with water and dried with sodium sulphate. The solvent was evaporated under reduced pressure and the crude product purified by silica gel chromatography (n-hexane/EtOAc), followed by crystallization to afford pure regioisomers **3**. Compounds **4** have been characterized by examination of the crude reaction mixtures. Analytical data for the compounds obtained are as follows:

3a: m.p. 154–155 °C (n-hexane/EtOAc 7:1). ^{19}F NMR δ: −52.51 ppm. IR (Nujol) (cm^{-1}): 1600 (w); 1115 (s). Mass spectrum *m/z* (%): 398 (M^{+}, 52); 363 ($M^{+}-Cl$, 3); 214 ($ClC_6H_4-C=N-C_6H_5^{+}$, 15); 77 (100); 69 (3). Analysis: Found (Calc.): C, 66.47 (66.26): H, 3.61 (3.54): F, 14.12 (14.29); N, 7.14 (7.02)%.

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TABLE 1. Yields and regioselectivity in the reaction 1+2 to give 3+4

Product	Yield of 3[a] (%)	Reaction time (h)	Ratio of 3/4[b,c]
3a/4a	84	12	97:3
3b/4b	87	16	98:2
3c/4c	80	16	97:3
3d/4d	89	16	96:4
3e/4e	73	24	97:3
3f/4f	87	16	98:2
3g/4g	85	16	96:4
3h/4h	72	12	97:3
3i/4i	86	16	96:4
3j/4j	42	30	99:1
3k/4k	22	24	98:2
3l/4l	81	16	97:3
3m/4m	10	24	96:4

[a]Yield of isolated pure products 3.
[b]Compounds of type 4 were not isolated.
[c]The ratios of 3/4 were estimated by GC methods (capillary column SIM-DIST CB, i.d. = 0.32 mm, length 10 m; temperature program 80–320 °C) and ^{19}F NMR spectral analyses.

4a: ^{19}F NMR δ: −54.80 ppm. Mass spectrum *m/z* (%): 398 (M^+, 55); 363 (M^+-Cl, 5); 226 ($C_6H_5-C=N-C-C_6H_4Cl^+$, 5); 123 ($ClC_6H_4C^+$, 28); 77 (100); 69 (2).

3b: m.p. 135–136 °C (n-hexane/EtOAc 5:1). ^{19}F NMR δ: −52.51 ppm. IR (Nujol) (cm^{-1}): 1605 (w); 1110 (s). Mass spectrum *m/z* (%): 432 (M^+, 39); 397 (M^+-Cl, 2); 214 ($ClC_6H_4-C=N-C_6H_5^+$, 14); 111 ($ClC_6H_4^+$, 12); 91 ($C_6H_5N^+$, 15); 77 (100). Analysis: Found (Calc.): C, 61.21 (60.99); H, 3.08 (3.02); F, 12.89 (13.15); N, 6.38 (6.47)%.

4b: ^{19}F NMR δ: −54.88 ppm. Mass spectrum *m/z* (%): 432 (M^+, 23); 149 ($ClC_6H_4CNC^+$, 7); 123 ($ClC_6H_4C^+$, 42); 111 ($ClC_6H_4^+$, 10); 91 (6); 77 (100).

3c: m.p. 100–101 °C (n-hexane). ^{19}F NMR δ: −52.41 ppm. IR (Nujol) (cm^{-1}): 1620 (m); 1105 (s). Mass spectrum *m/z* (%): 428 (M^+, 100); 413 (M^+-CH_3, 7); 210 ($CH_3OC_6H_4-C=N-C_6H_5^+$, 6); 111 ($ClC_6H_4^+$, 9); 91 ($C_6H_5N^+$, 9); 77 (35). Analysis: Found (Calc.): C, 64.44 (64.42); H, 3.86 (3.76); F, 13.40 (13.29); N, 6.38 (6.53)%.

4c: ^{19}F NMR δ: −54.78 ppm. Mass spectrum *m/z* (%): 428 (M^+, 100); 413 (M^+-CH_3, 10); 256 ($ClC_6H_4CNCC_6H_4OCH_3^+$, 2); 119 ($CH_3OC_6H_4C^+$, 3); 77 (10).

3d: m.p. 165–166 °C (n-hexane/EtOAc 5:1). ^{19}F NMR δ: −52.41 ppm. IR (Nujol) (cm^{-1}): 1605 (w); 1100 (s). Mass spectrum *m/z* (%): 443 (M^+, 100); 413 (M^+-NO, 3); 396 (M^+-HNO_2, 17); 225 ($NO_2C_6H_4-C=N-C_6H_5^+$, 2); 111 ($ClC_6H_4^+$, 4); 91 ($C_6H_5N^+$, 2); 77 (9). Analysis: Found (Calc.): C, 59.41 (59.54); H, 3.03 (2.95); F, 12.70 (12.84); N, 9.55 (9.47)%.

4d: ^{19}F NMR δ: −54.75 ppm. Mass spectrum *m/z* (%): 443 (M^+, 100); 425 (M^+-HF, 6); 413 (M^+-NO, 3); 396 (4); 225 ($ClC_6H_4CNCC_6H_4^+$, 2); 111 (2); 77 (13).

3e: m.p. 138–139 °C (n-hexane/EtOAc 5:1). ^{19}F NMR δ: −52.46 ppm. IR (Nujol) (cm^{-1}): 1610 (m); 1100 (s). Mass spectrum *m/z* (%): 444 (M^+, 100); 429 (M^+-CH_3, 7); 397 (M^+-SCH_3, 4); 226 ($CH_3SC_6H_4C=N-C_6H_5^+$, 2); 111 ($ClC_6H_4^+$, 3); 91 ($C_6H_5N^+$, 5); 77 (16). Analysis: Found (Calc.): C, 62.11 (62.09); H, 3.70 (3.63); F, 12.61 (12.81); N, 6.26 (6.30)%.

4e: ^{19}F NMR δ: −54.87 ppm. Mass spectrum *m/z* (%): 444 (M^+, 100); 429 (M^+-CH_3, 9); 397 (M^+-SCH_3, 3); 272 ($ClC_6H_4CNCC_6H_4SCH_3^+$, 3); 135 ($CH_3SC_6H_4C^+$, 14); 120 ($SC_6H_4C^+$, 10); 111 (8); 91 (4); 77 (89).

3f: m.p. 223–224 °C (n-hexane/EtOAc 6:4). ^{19}F NMR δ: −52.34 ppm. IR (Nujol) (cm^{-1}): 1605 (m); 1125 (s). Mass spectrum *m/z* (%): 476 (M^+, 100); 413 (M^+-CH_3SO, 2); 397 ($M^+-CH_3SO_2$, 11); 258 ($CH_3SO_2C_6H_4C=NC_6H_5^+$, 2); 179 ($C_6H_4C=N-C_6H_5^+$, 3); 111 (3); 91 (2); 77 (8). Analysis: Found (Calc.): C, 58.18 (57.93); H, 3.48 (3.38); F, 11.84 (11.95); N, 5.72 (5.87)%.

4f: ^{19}F NMR δ: −54.72 ppm. Mass spectrum *m/z* (%): 476 (M^+, 100); 413 (M^+-CH_3SO, 5); 397 ($M^+-CH_3SO_2$, 8); 362 ($M^+-CH_3SO_2-Cl$, 8); 190 ($C_6H_4CNCC_6H_4^+$, 3); 77 (11).

3g: m.p. 75–76 °C (n-hexane). ^{19}F NMR δ: −53.92 ppm. IR (Nujol) (cm^{-1}): 1605 (w); 1115 (s). Mass spectrum *m/z* (%): 432 (M^+, 100); 397 (M^+-Cl, 92); 214 ($ClC_6H_4-C=N-C_6H_5^+$, 11); 111 ($ClC_6H_4^+$, 8); 91 ($C_6H_5N^+$, 6); 77 (44). Analysis: Found (Calc.): C, 61.08 (60.99); H, 3.08 (3.02); F, 13.13 (13.15); N, 6.31 (6.47)%.

4g: ^{19}F NMR δ: −56.37 ppm. Mass spectrum *m/z* (%): 432 (M^+, 100); 397 (M^+-Cl, 19); 123 ($ClC_6H_4C^+$, 9); 111 ($ClC_6H_4^+$, 2); 77 (17).

3h: m.p. 89–90 °C (n-hexane). ^{19}F NMR δ: −54.10 ppm. IR (Nujol) (cm^{-1}): 1610 (m); 1105 (s). Mass spectrum *m/z* (%): 432 (M^+, 42); 397 (M^+-Cl, 12); 214 ($ClC_6H_4-C=N-C_6H_5^+$, 20); 111 ($ClC_6H_4^+$, 12); 91 ($C_6H_5N^+$, 14); 77 (100). Analysis: Found (Calc.): C, 61.25 (60.99); H, 3.07 (3.02); F, 13.15 (13.15); N, 6.41 (6.47)%.

4h: ^{19}F NMR δ: −54.63 ppm. Mass spectrum *m/z* (%): 432 (M^+, 35); 397 (M^+-Cl, 25); 149 ($ClC_6H_4CNC^+$, 6); 123 ($ClC_6H_4C^+$, 44); 77 (100).

3i: m.p. 149–150 °C (n-hexane/EtOAc 5:1). ^{19}F NMR δ: −52.54 ppm. IR (Nujol) (cm^{-1}): 1620 (m); 1110 (s). Mass spectrum *m/z* (%); 428 (M^+, 100); 413 (M^+-CH_3, 10); 214 ($ClC_6H_4C=NC_6H_5^+$, 11); 111 ($ClC_6H_4^+$, 2); 91 ($C_6H_5N^+$, 2); 77 (20). Analysis: Found (Calc.): C, 64.38 (64.42); H, 3.70 (3.76); F, 13.39 (13.29); N, 6.39 (6.53)%.

4i: ^{19}F NMR δ: −54.81 ppm. Mass spectrum *m/z* (%): 428 (M^+, 100); 413 (M^+-CH_3, 8); 256 ($ClC_6H_4CNCC_6H_4OCH_3^+$, 2); 123 ($ClC_6H_4C^+$, 7); 77 (30).

3j: m.p. 158–159 °C (n-hexane/EtOAc 5:1). ^{19}F NMR δ: −52.45 ppm. IR (Nujol) (cm^{-1}): 1615 (m); 1115 (s). Mass spectrum *m/z* (%): 443 (M^+, 100); 413 (M^+-NO, 3); 396 (M^+-HNO_2, 12); 214 ($ClC_6H_4-C=N-C_6H_5^+$, 4); 111 ($ClC_6H_4^+$, 2); 91 ($C_6H_5N^+$, 2); 77 (20). Analysis: Found (Calc.): C, 59.55 (59.54); H, 2.99 (2.95); F, 12.67 (12.84); N, 9.38 (9.47)%.

4j: ^{19}F NMR δ: −54.99 ppm. Mass spectrum *m/z* (%): 443 (M^+, 100); 413 (M^+-NO, 24); 396 (M^+-HNO_2, 5); 225 ($ClC_6H_4CNCC_6H_4^+$, 2); 123 ($ClC_6H_4C^+$, 2); 91 (2); 77 (25).

3k: m.p. 138–139 °C (n-hexane/EtOAc 5:1). ^{19}F NMR δ: −52.56 ppm. IR (Nujol) (cm^{-1}): 1610 (m); 1100 (s). Mass spectrum *m/z* (%): 432 (M^+, 72); 397 (M^+-Cl, 21); 248 ($ClC_6H_4-C=N-C_6H_4Cl^+$, 37); 125 ($ClC_6H_4N^+$, 17); 111 ($ClC_6H_4^+$, 100); 77 (57). Analysis: Found (Calc.): C, 61.07 (60.99); H, 3.04 (3.02); F, 13.02 (13.15); N, 6.40 (6.47)%.

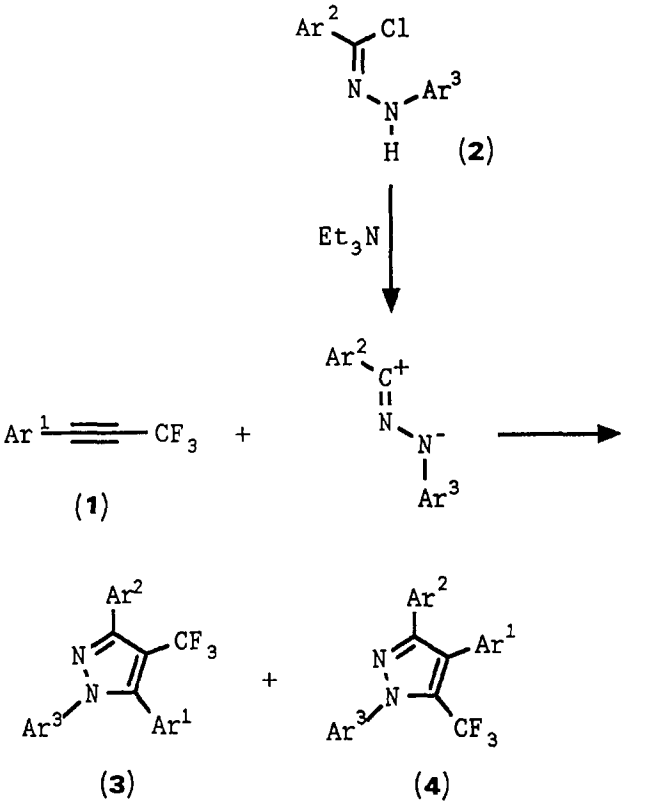
4k: ^{19}F NMR δ: −56.61 ppm. Mass spectrum *m/z* (%): 432 (M^+, 100); 397 (M^+-Cl, 14); 226 ($ClC_6H_4CNCC_6H_4Cl^+$, 7); 123 ($ClC_6H_4C^+$, 84); 111 ($ClC_6H_4^+$, 49); 77 (25).

3l: m.p. 104–105 °C (n-hexane). ^{19}F NMR δ: −52.40 ppm. IR (Nujol) (cm^{-1}): 1610 (w); 1105 (s). Mass spectrum *m/z* (%): 428 (M^+, 100); 413 (M^+-CH_3, 7); 244 ($ClC_6H_4C=NC_6H_4OCH_3^+$, 3); 121 ($CH_3OC_6H_4N^+$, 2); 111 ($ClC_6H_4^+$, 2); 107 ($CH_3OC_6H_4^+$, 2); 92 ($C_6H_4O^+$, 5); 77 (17). Analysis: Found (Calc.): C, 64.61 (64.42); H, 3.82 (3.76); F, 13.42 (13.29); N, 6.49 (6.53)%.

4l: ^{19}F NMR δ: −55.05 ppm. Mass spectrum *m/z* (%): 428 (M^+, 100); 413 (M^+-CH_3, 4); 226 ($C_6H_5CNCC_6H_4Cl^+$, 2); 123 ($ClC_6H_4C^+$, 4); 92 (4); 77 (15).

3m: m.p. 132–133 °C (n-hexane). ^{19}F NMR δ: −52.72 ppm. IR (Nujol) (cm^{-1}): 1605 (m); 1110 (s). Mass spectrum *m/z* (%): 443 (M^+, 100); 413 (M^+-NO, 3); 396 (M^+-HNO_2, 21); 259 ($ClC_6H_4-C=N-C_6H_4NO_2^+$, 6); 90 ($C_6H_4N^+$, 9); 77 (24); 76 (21). Analysis: Found (Calc.): C, 59.62 (59.54); H, 2.99 (2.95); F, 12.66 (12.84); N, 9.47 (9.47)%.

4m: ^{19}F NMR δ: −54.25 ppm. Mass spectrum *m/z* (%): 443 (M^+, 100); 408 (M^+-Cl, 8); 396 (M^+-HNO_2, 10); 190 ($C_6H_4CNCC_6H_4^+$, 11); 123 ($ClC_6H_4C^+$, 12); 90 (14); 77 (15); 75 (18).



1	Ar^1	2	Ar^2	Ar^3
a	$4\text{-}ClC_6H_4$	a	C_6H_5	C_6H_5
b	$4\text{-}CH_3OC_6H_4$	b	$4\text{-}ClC_6H_4$	C_6H_5
c	$4\text{-}NO_2C_6H_4$	c	$2\text{-}ClC_6H_4$	C_6H_5
d	$4\text{-}CH_3SC_6H_4$	d	$4\text{-}CH_3OC_6H_4$	C_6H_5
e	$4\text{-}CH_3SO_2C_6H_4$	e	$4\text{-}NO_2C_6H_4$	C_6H_5
f	$2\text{-}ClC_6H_4$	f	C_6H_5	$2\text{-}ClC_6H_4$
		g	C_6H_5	$4\text{-}CH_3OC_6H_4$
		h	C_6H_5	$4\text{-}NO_2C_6H_4$

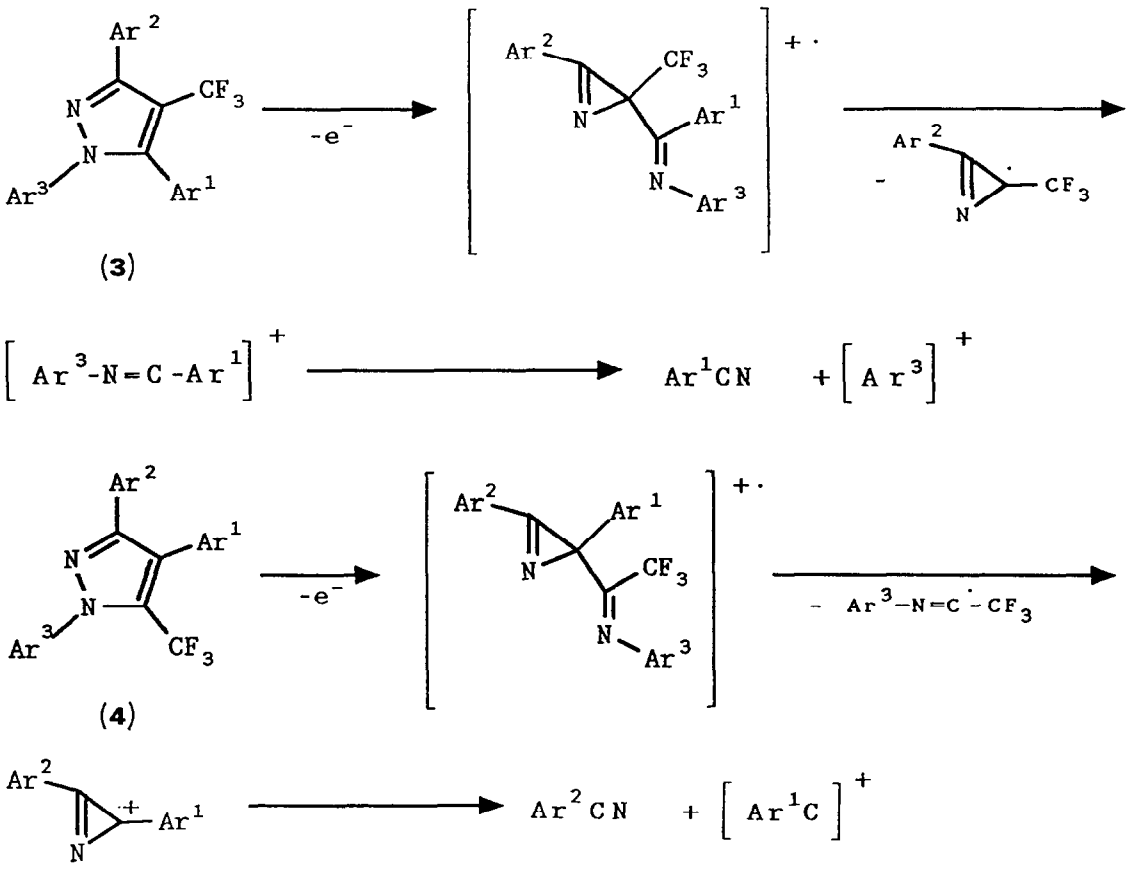
3, 4	Ar^1	Ar^2	Ar^3
a	$4\text{-}ClC_6H_4$	C_6H_5	C_6H_5
b	$4\text{-}ClC_6H_4$	$4\text{-}ClC_6H_4$	C_6H_5
c	$4\text{-}CH_3OC_6H_4$	$4\text{-}ClC_6H_4$	C_6H_5
d	$4\text{-}NO_2C_6H_4$	$4\text{-}ClC_6H_4$	C_6H_5
e	$4\text{-}CH_3SC_6H_4$	$4\text{-}ClC_6H_4$	C_6H_5
f	$4\text{-}CH_3SO_2C_6H_4$	$4\text{-}ClC_6H_4$	C_6H_5
g	$2\text{-}ClC_6H_4$	$4\text{-}ClC_6H_4$	C_6H_5
h	$4\text{-}ClC_6H_4$	$2\text{-}ClC_6H_4$	C_6H_5
i	$4\text{-}ClC_6H_4$	$4\text{-}CH_3OC_6H_4$	C_6H_5
j	$4\text{-}ClC_6H_4$	$4\text{-}NO_2C_6H_4$	C_6H_5
k	$4\text{-}ClC_6H_4$	C_6H_5	$2\text{-}ClC_6H_4$
l	$4\text{-}ClC_6H_4$	C_6H_5	$4\text{-}CH_3OC_6H_4$
m	$4\text{-}ClC_6H_4$	C_6H_5	$4\text{-}NO_2C_6H_4$

Scheme 1.

Results and discussion

The known alkynes **1** are prepared in two steps from the corresponding aldehydes [15–17]. Nitrileimines, obtained from their precursor α-halohydrazones **2**, readily react with 1-aryl-3,3,3-trifluoropropynes **1** to give 4-trifluoromethyl-substituted pyrazoles **3**, together with small quantities of the 5-trifluoromethyl regioisomers **4** (Table 1).

The reaction is performed by heating equimolar amounts of the two reactants in chloroform solution



Scheme 2.

in the presence of triethylamine according to Scheme 1.

The results summarized in Table 1 show that aryl-trifluoromethyl alkynes undergo 1,3-dipolar cycloaddition with nitrileimines with high regioselectivity. The prevailing orientation is the one which places the trifluoromethyl group in the 4-position of the resulting pyrazole. As already pointed out, similar results were achieved, but with decreasing regioselectivity, employing nitrileoxides, sydnones and azides [15–17].

Similar behaviour was observed by Huisgen *et al.* in the reaction between diphenylnitrileimine and methyl 3-phenylpropynoate or methyl 2-butynoate, which leads to the formation of 4- and 5-methoxycarbonyl-substituted pyrazoles in the ratios of 96:4 and 77:23, respectively [24].

According to Houk's model, the regioselectivity obtained in these cycloaddition reactions can be explained in terms of HOMO–LUMO interactions between the reacting species [25, 26]. The presence of the electron-withdrawing group CF_3 lowers the HOMO and LUMO energy of the dipolarophile so that the reaction is 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 nitrileimine) interacts with the carbon atom bearing the aryl group (larger atomic coefficient in the LUMO of the dipolarophile), and the carbon atom of the nitrileimine interacts with the carbon atom bearing the CF_3 group of the dipolarophile.

The regioselectivity observed may also be explained by considering the Coulombic or dipole–dipole interactions in the perturbation equation [27]. In this case the favoured interaction will be the one between the nitrogen atom of the nitrileimines $Ar^2-C^+=N-N^--Ar^3$ and the carbon atom bearing the Ar^1 group of the polarized alkynes $Ar^1-C^{\delta+}\equiv C^{\delta-}CF_3$.

As can be argued from Table 1, the regioselectivity is not affected by varying the nature of substituent Ar^1 in the alkyne as well as modifying the substituents Ar^2 and Ar^3 in the nitrileimine.

Poor yields were obtained in the presence of the electron-withdrawing group NO_2 in the aryl moieties Ar^2 or Ar^3 of the nitrileimine (**3j** and **3m**). This result is reasonable in view of the lowering of the dipole HOMO energy so that the gap to the alkyne LUMO is increased. Hence, beside the desired reaction pathway, other side-transformations may take place. Moreover,

an attempted reaction of **1a** with methyl chloroglyoxalate phenylhydrazone gave only a small conversion to the desired product.

Steric hindrance seems to have a relevant effect, as shown by the fact that when Ar^3 is 2-ClPh (**3k**) the yield is lowered. The compounds described here can also be prepared via sydnone cycloaddition, but this results in lower yields and an absence of regioselectivity.

In conclusion, this method provides a useful route to aryl-substituted pyrazoles bearing a 4-CF_3 group.

Spectra

^{19}F NMR spectra

The ^{19}F NMR spectra enable the structures of the regioisomers **3** and **4** to be allocated. In agreement with the previously reported data for trifluoromethylpyrazoles, the trifluoromethyl group of **3** resonates at lower fields (2–3 ppm) than the trifluoromethyl group of **4** [28].

Mass spectra

The mass spectra allow further differentiation of the two regioisomers. For both **3** and **4**, the M^+ peak is often the base peak. Compounds **3** give the $[Ar^3-N=C-Ar^1]^+$ peak which subsequently loses the nitrile Ar^1CN and gives the $[Ar^3]^+$ peak. This fragmentation pathway seems to be characteristic for compounds **3** and passes through the more stable iminium ion.

In contrast, compounds **4** lose the $Ar^3-N=C-CF_3$ radical with the formation of the more stable azirinium ion, which loses the nitrile Ar^2CN and gives the $[Ar^3C]^+$ peak.

The processes involved in the fragmentation of these compounds are outlined in Scheme 2.

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