# Synthesis of 1-Aryl-3,3,3-trifluoro-1-propynes and 3,5-Diaryl-4-trifluoromethylisoxazoles

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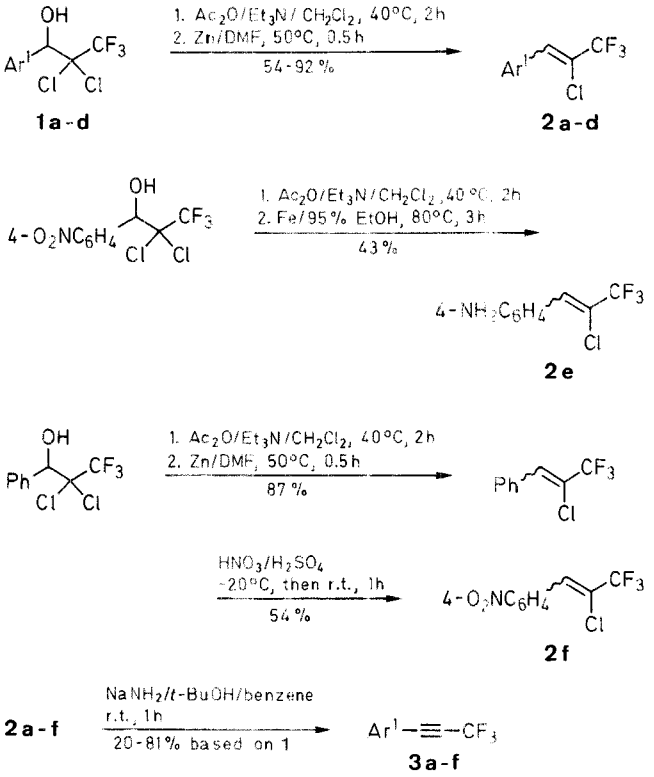
Diaryl-substituted trifluoromethylisoxazoles **5a–i**, **6a–c**, and **6e–i** are synthesized from aromatic nitrile oxides and various substituted 1-aryl-3,3,3-trifluoro-1-propynes.

Heterocyclic compounds bearing a fluorine atom or a trifluoromethyl group are of potential interest as intermediates for pharmaceuticals or agrochemicals, but have received fairly limited attention.[1] It is also well known that 1,3-dipolar cycloaddition reactions provide a convenient route to many heterocyclic structures.[2–6] Alcohols **1**, easily available by reaction of 1,1,1-trichloro-2,2,2-trifluoroethane with aldehydes,[7] have been employed by us as intermediates for agrochemicals.[8]

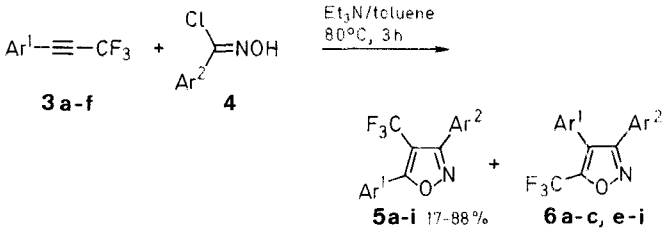
Here we describe the synthesis of 1-aryl-3,3,3-trifluoro-1-propynes **3** via the known alcohols **1** and an investigation relative to the behavior of **3** as dipolarophiles in 1,3-dipolar cycloaddition reactions. In the present paper we describe the synthesis of trifluoromethylisoxazoles starting from various alkynes and nitrile oxides. The preparation of fluorinated dipolarophiles is shown in Scheme **A**[9] (Table 1).




| 1, 2, 3 | $Ar^1$ |
|---|---|
| a | $4\text{-}ClC_6H_4$ |
| b | $2\text{-}ClC_6H_4$ |
| c | 3-pyridyl |
| d | $4\text{-}MeOC_6H_4$ |
| e | $4\text{-}H_2NC_6H_4$ |
| f | $4\text{-}O_2NC_6H_4$ |

Scheme **A**

The nitrile oxides have been formed *in situ*,[10] from the corresponding hydroximic acid chlorides[11] in the presence of triethylamine as acid acceptor, so that they would add to the dipolarophile immediately according to Scheme **B**.




| 5, 6 | $Ar^1$ | $Ar^2$ |
|---|---|---|
| **a** | 2-$ClC_6H_4$ | 4-$ClC_6H_4$ |
| **b** | 4-$ClC_6H_4$ | 4-$ClC_6H_4$ |
| **c** | 3-pyridyl | 4-$ClC_6H_4$ |
| **d** | 4-$MeOC_6H_4$ | 4-$ClC_6H_4$ |
| **e** | 4-$O_2NC_6H_4$ | 2,6-$Cl_2C_6H_3$ |
| **f** | 4-$ClC_6H_4$ | 2,6-$Cl_2C_6H_3$ |
| **g** | 4-$MeOC_6H_4$ | 2,6-$Cl_2C_6H_3$ |
| **h** | 2-$ClC_6H_4$ | 2,6-$Cl_2C_6H_3$ |
| **i** | 4-$H_2NC_6H_4$ | 2,6-$Cl_2C_6H_3$ |

Scheme **B**

We have found that 1-aryl-3,3,3-trifluoro-1-propynes **3** react with aryl nitrile oxides **4** readily, while it is well known that 1-phenyl-1-propyne does not react at all.[12]

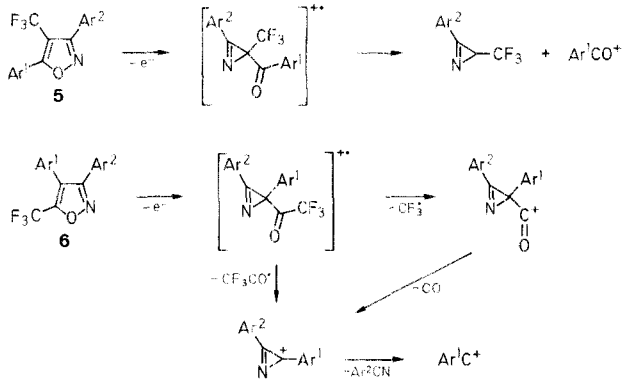
The cycloadditions **(3 + 4)** described here proceed with good regioselectivity to afford **5** together with small amounts (1–7%) of **6** (Table 2). It should be noted that the presence of an electron-releasing group in the aryl moiety of dipolarophiles raises the selectivity, while steric effects seem to have a little relevance in determining the selectivity of these reactions as can be inferred from Table 2.

The regioselectivity observed in these cycloaddition reactions can be explained on the basis of the model proposed by Houk for HOMO-LUMO interactions between the reacting species.[13–15] 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 that one in which the oxygen atom (larger atomic orbital coefficient in the HOMO of nitrile oxide) interacts with the carbon atom bearing the aryl group (larger atomic orbital coefficient in the LUMO of dipolarophiles) and the carbon atom of nitrile oxide interacts with the carbon atom bearing the $CF_3$ group of the dipolarophile. This leads to unequal extent of bond formation in the transition state.

The regioselectivity obtained may, perhaps more properly, be explained considering the Coulombic or dipole-dipole interactions in the perturbation equation.[16] In this case the favored transition state is that which implies interaction between the oxygen atom of nitrile oxides $Ar^2-C{\equiv}N^+-O^-$ and the carbon atom bearing the aryl group of the polarized alkynes $Ar^1-C^{\delta+}{\equiv}C^{\delta-}-CF_3$. A quite similar behavior was observed by Huisgen[17] in the reaction between benzonitrile oxide and methyl 3-phenylpropynoate or methyl 2-butynoate, which lead to the formation of 4- and 5-methoxycarbonyl-substituted isoxazoles in 98.8:1.2 and 98.7:1.3 ratio, respectively.

The mass spectra of these compounds have been investigated. Isoxazoles **5** and **6** do not show any fragment arising from retro-1,3-dipolar cycloaddition, therefore no rearrangements altering the molecular framework are taking place. Mass spectra may thus be used to allocate the structure of the regioisomers **5** and **6**.[18,19] The mass spectra of **5a–i** include, besides the $M^+$ peak, $[Ar^1CO]^+$ as the base peak. The fragmentations involved lead to the formation of the most stable oxonium ion. Instead, compounds **6a, b** and **6f–i** show, besides the $M^+$ peak, the $[M^+ - CF_3]$ and $[M^+ - CF_3CO]$ peaks with the formation of the most stable azirinium ion, which loses the nitrile $Ar^2CN$ and gives $[Ar^1C]^+$ as the base peak.

The mass spectra of compound **6c** and **6e** in which the aryl moiety contains an electron-withdrawing group do not show the $[Ar^1C]^+$ peak. In this case the $[M^+ - CF_3]$ is the base peak. The $M^+$ and $[M^+ - CF_3CO]$ peaks are also observed in significative percentage. The processes involved in the fragmentation of these compounds are summarized in Scheme **C**.




Scheme **C**

The $^{19}F$-NMR spectra allow further differentiation between **5** and **6**. In agreement with the previously reported values of perfluoroalkylated isoxazoles,[20] the trifluoromethyl group of **5** resonates at lower fields ($\delta$ = 5–8) than the trifluoromethyl group of **6**.

**Table 1.** Compounds **3** Prepared

| Product | Yield[a] (%) | mp (°C)[b] (solvent) or bp (°C/mbar) | Molecular Formula[c] or Lit. Data | IR $\nu$ (cm$^{-1}$) |
|---|---|---|---|---|
| **3a** | 81 | 67/20 | 65 °C/7 mbar[21] | 2250, 1170[d] |
| **3b** | 57 | 73/20 | $C_9H_4ClF_3$ (204.6) | 2260, 1150[d] |
| **3c** | 40 | 48–50 (toluene) | $C_8H_4F_3N$ (171.1) | 2260, 1170[e] |
| **3d** | 76 | 87/20 | 172 °C[22] | 2250, 1150[e] |
| **3e**[f] | 20 | 60–61 (toluene) | $C_9H_6F_3N$ (185.1) | 3200, 3300, 2240, 1140[e] |
| **3f**[g] | 45 | 71–72 (toluene) | 72–73 °C[21] | 2250, 1155[e] |

[a] Yield of isolated pure product **3** based on **1**.
[b] Uncorrected.
[c] Satisfactory microanalyses obtained: C ±0.21, H ±0.14, F ±0.28.
[d] Liquid film.
[e] Nujol.
[f] Compound **3e** is prepared from **1** ($Ar^1$ = 4-$O_2NC_6H_4$).
[g] Compound **3f** is prepared from **1** ($Ar^1$ = Ph).

**Table 2.** Yields and Regioselectivity of the Reaction **3** + **4** → **5** + **6**

| Product | Yield of **5**[a] (%) | Ratio[b,c] **5/6** |
|---|---|---|
| **5a/6a** | 40 | 93 : 7 |
| **5b/6b** | 45 | 97 : 3 |
| **5c/6c** | 59 | 97 : 3 |
| **5d** | 17 | 100 |
| **5e/6e** | 74 | 93 : 7 |
| **5f/6f** | 88 | 95 : 5 |
| **5g/6g** | 81 | 99 : 1 |
| **5h/6h** | 84 | 96 : 4 |
| **5i/6i** | 45 | 99 : 1 |

[a] Yield of isolated pure products **5** after crystallization.
[b] Compounds **6** have not been isolated.
[c] The ratios **5** : **6** were estimated by GC (OV 1, 3%, 2 m, temperature program 100 → 280 °C) and $^{19}$F-NMR analyses.

All reagents were of commercial quality. Anhydrous solvents were dried on molecular sieves. Analytical TLC plates and silica gel (230–400 mesh) were purchased from Merck. Melting points were taken using a Büchi SMP-20 apparatus and are uncorrected. GC analyses were obtained using Carlo Erba Strumentazione 4200 chromatograph. Microanalyses were obtained using a Hewlett-Packard 185 element analyser. Mass spectra were obtained using a Varian Mat 1125 spectrometer with 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 WH-90 spectrometer.

**1-Aryl-2-chloro-3,3,3-trifluoropropenes 2a–d; General Procedure:**
To a stirred solution of **1a–d** (50 mmol) in $CH_2Cl_2$ (100 mL), $NEt_3$ (60 mmol) and $Ac_2O$ (60 mmol) are added. The mixture is stirred at 40 °C for 2 h, washed with 1 N NaOH (30 mL) and then with 1 N HCl (30 mL). The organic layer is dried with $Na_2SO_4$, and the solvent is evaporated under reduced pressure. To a stirred solution of this crude product in anhydrous DMF (100 mL) under nitrogen atmosphere, Zn powder (60 mmol) is added portionwise keeping the temperature below 50 °C. The mixture is stirred at 50 °C for a further 30 min, then poured into $H_2O$ (500 mL) and extracted with $Et_2O$ (2 × 100 mL). The combined ethereal extracts are dried with $Na_2SO_4$, and the solvent is removed under reduced pressure to give **2a–d**.

**Table 3.** Trifluoromethylisoxazoles **5** and **6**

| Product | mp (°C) (EtOAc/*n*-hexane) | Molecular Formula[a] | IR (Nujol) $\nu$ (cm$^{-1}$) | $^{19}$F-NMR ($CDCl_3$/$CFCl_3$) $\delta$ | MS (70 eV) *m/z* (%) |
|---|---|---|---|---|---|
| **5a** | 102 | $C_{16}H_8Cl_2F_3NO$ (358.1) | 1635 (s), 1125 (s) | −55.8 (s) | 357 ($M^+$, 19); 139 ($C_6H_4ClCO^+$, 100); 111 ($C_6H_4Cl^+$, 61) |
| **6a** | | $C_{16}H_8Cl_2F_3NO$ (358.1) | | −63.1 (s) | 357 ($M^+$, 20); 322 ($M^+ - Cl$, 56); 288 ($M^+ - CF_3$, 17); 260 ($M^+ - CF_3CO$, 15); 137 ($C_6H_4ClCN^+$, 9); 123 ($C_7H_4Cl^+$, 100); 111 ($C_6H_4Cl^+$, 16) |
| **5b** | 122 | $C_{16}H_8Cl_2F_3NO$ (358.1) | 1635 (s), 1140 (s) | −53.8 (s) | 357 ($M^+$, 24); 139 ($C_6H_4ClCO^+$, 100); 111 ($C_6H_4Cl^+$, 62) |
| **6b** | | $C_{16}H_8Cl_2F_3NO$ (358.1) | | −61.9 (s) | 357 ($M^+$, 32); 288 ($M^+ - CF_3$, 43); 260 ($M^+ - CF_3CO$, 28); 137 ($C_6H_4ClCN^+$, 11); 123 ($C_7H_4Cl^+$, 100); 111 ($C_6H_4Cl^+$, 12) |
| **5c** | 108 | $C_{15}H_8ClF_3N_2O$ (324.7) | 1625 (s), 1170 (s) | −54.2 (s) | 324 ($M^+$, 43); 289 ($M^+ - Cl$, 4); 246 ($M^+ - C_5H_4N$, 3); 137 ($C_6H_4ClCN^+$, 15); 111 ($C_6H_4Cl^+$, 18); 106 ($C_5H_4NCO^+$, 100); 78 ($C_5H_4N^+$, 95) |
| **6c** | | $C_{15}H_8ClF_3N_2O$ (324.7) | | −61.8 (s) | 324 ($M^+$, 84); 255 ($M^+ - CF_3$, 100); 227 ($M^+ - CF_3CO$, 96); 137 ($C_6H_4ClCN^+$, 19); 111 ($C_6H_4Cl^+$, 52) |
| **5d** | 92 | $C_{17}H_{11}ClF_3NO_2$ (353.7) | 1615 (s), 1130 (s) | −54.0 (s) | 353 ($M^+$, 73); 246 ($M^+ - C_6H_4OCH_3$, 2); 135 ($CH_3OC_6H_4CO^+$, 100); 111 ($C_6H_4Cl^+$, 15); 107 ($C_6H_4OCH_3^+$, 30) |
| **5e** | 148 | $C_{16}H_7Cl_2F_3N_2O_3$ (403.1) | 1620 (s), 1160 (s) | −56.4 (s) | 402 ($M^+$, 65); 367 ($M^+ - Cl$, 8); 280 ($M^+ - C_6H_4NO_2$, 7); 150 ($NO_2C_6H_4CO^+$, 100); 145 ($C_6H_3Cl_2^+$, 12); 104 ($C_6H_4CO^+$, 97) |
| **6e** | | $C_{16}H_7Cl_2F_3N_2O_3$ (403.1) | | −62.1 (s) | 402 ($M^+$, 42); 333 ($M^+ - CF_3$, 100); 305 ($M^+ - CF_3CO$, 85); 145 ($C_6H_3Cl_2^+$, 37) |
| **5f** | 115 | $C_{16}H_7Cl_3F_3NO$ (392.6) | 1615 (s), 1140 (s) | −53.0 (s) | 391 ($M^+$, 8); 171 ($C_6H_3Cl_2CN^+$, 12); 139 ($C_6H_4ClCO^+$, 100); 111 ($C_6H_4Cl^+$, 25) |
| **6f** | | $C_{16}H_7Cl_3F_3NO$ (392.6) | | −57.9 (s) | 391 ($M^+$, 11); 322 ($M^+ - CF_3$, 14); 294 ($M^+ - CF_3CO$, 10); 123 ($C_7H_4Cl^+$, 100) |
| **5g** | 112 | $C_{17}H_{10}Cl_2F_3NO_2$ (388.2) | 1620 (s), 1130 (s) | −56.5 (s) | 387 ($M^+$, 81); 280 ($M^+ - C_6H_4OCH_3$, 2); 145 ($C_6H_3Cl_2^+$, 9); 135 ($CH_3OC_6H_4CO^+$, 100); 107 ($CH_3OC_6H_4^+$, 32) |
| **6g** | | $C_{17}H_{10}Cl_2F_3NO_2$ (388.2) | | −61.7 (s) | 387 ($M^+$, 31); 318 ($M^+ - CF_3$, 7); 290 ($M^+ - CF_3CO$, 19); 216 ($M^+ - C_6H_3Cl_2$, 6); 145 ($C_6H_3Cl_2^+$, 27); 119 ($CH_3OC_7H_4^+$, 100) |
| **5h** | 128 | $C_{16}H_7Cl_3F_3NO$ (392.6) | 1635 (s), 1145 (s) | −58.2 (s) | 391 ($M^+$, 21); 280 ($M^+ - C_6H_4Cl$, 2); 139 ($C_6H_4ClCO^+$, 100); 111 ($C_6H_4Cl^+$, 58) |
| **6h** | | $C_{16}H_7Cl_3F_3NO$ (392.6) | | −63.5 (s) | 391 ($M^+$, 8); 356 ($M^+ - Cl$, 43); 322 ($M^+ - CF_3$, 10); 294 ($M^+ - CF_3CO$, 9); 123 ($C_7H_4Cl^+$, 100) |
| **5i** | 143 | $C_{16}H_9Cl_2F_3N_2O$ (373.2) | 1615 (s), 1130 (s) | −56.3 (s) | 372 ($M^+$, 22); 145 ($C_6H_3Cl_2^+$, 3); 120 ($NH_2C_6H_4CO^+$, 100); 92 ($C_6H_4NH_2^+$, 23) |
| **6i** | | $C_{16}H_9Cl_2F_3N_2O$ (373.2) | | −61.5 (s) | 372 ($M^+$, 38); 303 ($M^+ - CF_3$, 11); 275 ($M^+ - CF_3CO$, 32); 104 ($NH_2C_7H_4^+$, 100) |

[a] Satisfactory microanalyses obtained: C ± 0.35, H ± 0.14, F ± 0.52.

**1-(4-Aminophenyl)-2-chloro-3,3,3-trifluoropropene (2e):**[8]
To a stirred solution of 2,2-dichloro-3,3,3-trifluoro-1-(4-nitrophenyl)-1-propanol (15.2 g, 50 mmol) in $CH_2Cl_2$ (100 mL), $NEt_3$ (6.07 g, 60 mmol) and $Ac_2O$ (6.1 g, 60 mmol) are added. The mixture is stirred at 40 °C for 2 h, washed with 1 N NaOH (30 mL) and then with 1 N HCl (30 mL). The organic layer is dried with $Na_2SO_4$, and the solvent is evaporated under reduced pressure. To a stirred solution of this crude product in 95% EtOH (100 mL) iron powder (14 g, 250 mmol) is added portionwise keeping the temperature below 25 °C. The mixture is stirred at 80 °C for 3 h, filtered, and the solvent is evaporated under reduced pressure. The crude product is purified by chromatography on silica gel (*n*-hexane/$Et_2O$, 8:2) to give **2e** as a yellowish solid; yield: 4.8 g (43%); mp 45–47 °C.

**2-Chloro-3,3,3-trifluoro-1-(4-nitrophenyl)propene (2f):**[8]
2-Chloro-3,3,3-trifluoro-1-phenylpropene is prepared according to the method previously described for **2a–d**; yield: 87%; colorless oil; bp 162 °C.

To a stirred solution of 65% $HNO_3$ (16.38 g, 260 mmol) in 96% $H_2SO_4$ (40.18 g, 410 mmol) maintained below −20 °C, 2-chloro-3,3,3-trifluoro-1-phenylpropene (17 g, 82 mmol) is slowly added. The mixture is stirred at r.t. for 1 h, then poured into ice-cold $H_2O$ (250 mL) and extracted with $Et_2O$ (3 × 50 mL). The organic layer is separated, washed with $H_2O$ (50 mL), and dried with $Na_2SO_4$. The solvent is evaporated under reduced pressure, and the crude product is purified by chromatography on silica gel (*n*-hexane) to give **2f** as a pale yellow solid; yield: 11.2 g (54%); mp 64–65 °C.

**1-Aryl-3,3,3-trifluoro-1-propynes 3a–f; General Procedure:**
To a stirred suspension of $NaNH_2$ (25 mmol as a 50% dispersion in toluene) in anhydrous benzene (16 mL), under an inert atmosphere, a solution of **2a–f** (20 mmol) and *t*-BuOH (25 mmol) in anhydrous benzene (8 mL) is slowly added. The mixture is stirred at r.t. for 1 h, then quenched by addition of aqueous 26% $NH_4Cl$ (50 mL) and extracted with $Et_2O$ (50 mL). The organic phase is separated, washed with $H_2O$ (50 mL) and dried with $Na_2SO_4$. The solvent is evaporated under reduced pressure, and the crude product is purified by chromatography on silica gel (*n*-hexane) to give **3a–f** (Table 1).

**3,5-Diaryl-4-trifluoromethylisoxazoles 5a–i and Regioisomeric 3,4-Diaryl-5-trifluoromethylisoxazoles 6a–c, e–i; General Procedure:**
$NEt_3$ (0.98 g, 9.7 mmol) in toluene (5 mL) is added to a stirred solution of **3a–f** (4.85 mmol) and **4** (4.85 mmol) in toluene (15 mL) over 1 h. The mixture is stirred at 80 °C for 3 h, poured into ice-cold, 0.5 N HCl (30 mL), and extracted with $Et_2O$ (25 mL). The organic layer is separated, washed with brine (30 mL), and dried ($Na_2SO_4$). The solvent is evaporated, and the resulting solid is triturated with *n*-hexane (30 mL) and collected by filtration to give **5a–i, 6a–c,** and **6e–i** (Tables 2 and 3). Crystallization (EtOAc/*n*-hexane, 1:2) affords pure regioisomers **5a–i**.

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