A facile synthesis of fluoroalkylpyrazoles

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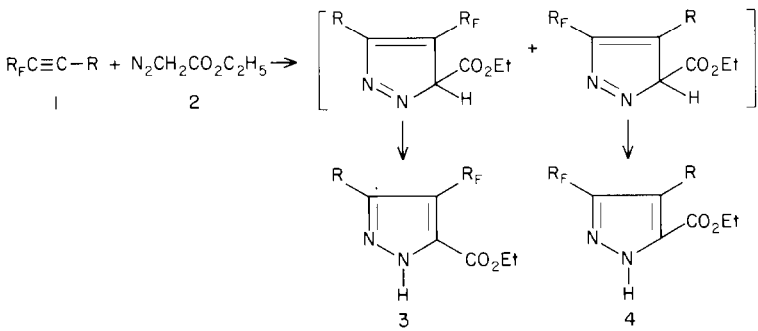
Abstract

Fluorinated pyrazoles have been conveniently synthesized via 1,3-dipolar cycloaddition of ethyl diazoacetate with fluorine-containing acetylenes of the type $R_FC{\equiv}CR$, where R_F = polyfluoroalkyl and R = CN or CO_2CH_3.

Introduction

Several pyrazoles have been shown to possess useful biological properties and can be used as bacteriostats, bactericides, insecticides, fungicides, sedatives, anticarcinogens and psychopharmacological agents [1]. A number of heterocyclic compounds bearing a fluorine atom are also known to be effective pharmaceutically and agrochemically [2]. Hence methods for the synthesis of pyrazoles with fluorine-containing groups have attracted much interest. One such method is based on the use of a building block with a fluorine-containing substituent.

Fluorinated alkynes have been found to be good dipolarophiles as exemplified by the reaction of aromatic nitrile oxides and methyl perfluoro-2-alkynoates [3]. 1,3-Dipolar cycloaddition is a useful method for the synthesis of heterocyclic compounds of biological interest [4]. We describe here a convenient route to perfluoroalkyl pyrazoles in excellent yield using fluorine-containing acetylenes as dipolarophiles.



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Results and discussion

Treatment of ethyl diazoacetate (**2**) in diethyl ether with the fluorinated acetylenes **1** gave the pyrazoles **3** and **4**, which were easily separated chromatographically (see Table 1). The chemical shift of the perfluoroalkyl group in the 4-position of the pyroazole ring is downfield and that of the 3-substituted perfluoroalkyl groups in the pyrazole ring is upfield [5].

Interestingly, reaction of the cyanoacetylenes with ethyl diazoacetate takes place only at the C—C triple bonds, giving the pyrazoles **3f**, **4f**, **3g** and **4g**. All these compounds are new, and their structures have been ascertained by MS, IR and NMR spectra and by microanalysis.

Experimental

All melting points and boiling points are reported uncorrected. The infrared spectra of liquid products were determined as films while the solid products were determined as KBr disks on a Shimadzu IR-440 spectrometer. NMR spectra (chemical shifts in ppm from TMS for ^{1}H NMR and from external TFA for ^{19}F NMR, positive for upfield shifts) were obtained on a Varian EM-360 spectrometer at 60 MHz. Mass spectra were recorded on a Finnigan GC–MS 4021 mass spectrometer.

The fluorine-containing acetylenes were obtained by literature methods [6, 7].

General procedure for the preparation of 3 and 4

To a solution of 1 (2 mmol) in absolute diethyl ether (2 ml) was added dropwise **2** (2 mmol) at 0 °C. The mixture was stirred at 0 °C for 15 min, then warmed to room temperature and stirred for a further 6 h. After removal of the solvent, the residue was separated by chromatography on silica gel eluting with a petroleum ether (b.p., 30–60 °C)/ethyl acetate (9:1) mixture to give **3**, and then **4**.

TABLE 1

Preparation of fluoroalkylpyrazoles

Compound	R	R_F	Yield (%)[a]	3:4[b]
3a+4a	CO_2CH_3	CF_3	88	84:16
3b+4b	CO_2CH_3	n-C_3F_7	94	67:33
3c+4c	CO_2CH_3	$ClCF_2$	96	68:32
3d+4d	CO_2CH_3	$Cl(CF_2)_3$	88	71:29
3e+4e	CO_2CH_3	n-$C_3F_7OCFCF_3$	94	77:23
3f+4f	CN	n-C_3F_7	94	75:25
3g+4g	CN	$Cl(CF_2)_3$	98	90:10

[a]Yields of isolated mixtures.
[b]Ratios of isolated products.

Compound **3a**: b.p., 180 °C/1 mmHg. IR(film) cm^{-1}: 1240 (s); 1740 (s). ^1H NMR (CCl_4) δ: 1.14 (t, 3H, $J=7$ Hz); 3.30 (s, 3H); 4.17 (q, 2H, $J=7$ Hz); 12.71 (br., 1H) ppm. ^{19}F NMR (CCl_4) δ: -22.2 (s) ppm. MS *m/e*: 266 (M^+); 235($M^+ - OCH_3$); 221($M^+ - OC_2H_5$). Analysis: Calcd. for $C_9H_9F_3N_2O_4$: C, 40.61; H, 3.41; N, 10.52%. Found: C, 40.16; H, 3.59; N, 10.42%.

Compound **4a**: m.p., 54 °C. IR (KBr) cm^{-1}: 1235 (s); 1740 (s). ^1H NMR (CCl_4) δ: 1.14 (t, 3H, $J=7$ Hz); 3.30 (s, 3H); 4.17 (q, 2H, $J=7$ Hz); 12.71 (br., 1H) ppm. ^{19}F NMR (CCl_4) δ: -15.3 (s) ppm. MS *m/e*: 266(M^+); 235 ($M^+ - OCH_3$); 221 ($M^+ - OC_2H_5$). Analysis: Calcd. for $C_9H_9F_3N_2O_4$: C, 40.61; H, 3.41; N, 10.52%. Found: C, 40.14; H, 3.71; N, 10.38%.

Compound **3b**: b.p., 186 °C/1 mmHg. IR(film) cm^{-1}: 1230 (s); 1730 (s). ^1H NMR (CCl_4) δ: 1.10 (t, 3H, $J=7$ Hz); 3.65 (s, 3H); 4.13 (q, 2H, $J=7$ Hz); 11.85 (br., 1H) ppm. ^{19}F NMR (CCl_4) δ: 3.90 (t, 3F, $J=10$ Hz); 24.7 (q, 2F, $J=10$ Hz); 47.3 (br., s, 2F) ppm. MS *m/e*: 366 (M^+); 335 ($M^+ - OCH_3$); 321 ($M^+ - OC_2H_5$). Analysis: Calcd. for $C_{11}H_9F_7N_2O_4$: C, 36.08; H, 2.46; N, 7.65%. Found: C, 36.10; H, 2.56; N, 7.88%.

Compound **4b**: m.p., 68 °C. IR (KBr) cm^{-1}: 1240 (s); 1730 (s). ^1H NMR (CCl_4) δ: 1.19 (t, 3H, $J=7$ Hz); 3.71 (s, 3H); 4.21 (q, 2H, $J=7$ Hz); 12.13 (br., 1H) ppm. ^{19}F NMR (CCl_4) δ: 3.91 (t, 3F, $J=10$ Hz); 32.7 (q, 2F, $J=10$ Hz); 49.7 (br., s, 2F) ppm. MS *m/e*: 366 (M^+); 335 ($M^+ - OCH_3$); 321 ($M^+ - OC_2H_5$). Analysis: Calcd. for $C_{11}H_9F_7N_2O_4$: C, 36.08; H, 2.46; N, 7.65%. Found: C, 36.33; H, 2.72; N, 7.66%.

Compound **3c**: m.p., 43 °C. IR (KBr) cm^{-1}: 1230 (s); 1730 (s). ^1H NMR (CCl_4) δ: 1.17 (t, 3H, $J=7$ Hz); 3.73 (s, 3H); 4.20 (q, 2H, $J=7$ Hz); 12.83 (br., s, 1H) ppm. ^{19}F NMR (CCl_4) δ: -35.2 ppm. MS *m/e*: 282 (M^+); 251 ($M^+ - OCH_3$); 237 ($M^+ - OC_2H_5$). Analysis: Calcd. for $C_9H_9ClF_2N_2O_4$: C, 38.24; H, 3.21; N, 9.91%. Found: C, 37.76; H, 3.06; N, 9.46%.

Compound **4c**: m.p., 58 °C. IR (KBr) cm^{-1}: 1200 (s); 1720 (s). ^1H NMR (CCl_4) δ: 1.17 (t, 3H, $J=7$ Hz); 3.73 (s, 3H); 4.20 (q, 2H, $J=7$ Hz); 12.15 (br., s, 1H) ppm. ^{19}F NMR (CCl_4) δ: -29.7 ppm. MS *m/e*: 282 (M^+); 251 ($M^+ - OCH_3$): 237 ($M^+ - OC_2H_5$); 247 ($M^+ - Cl$). Analysis: Calcd. for $C_9H_9ClF_2N_2O_4$: C, 38.24; H, 3.21; N, 9.91%. Found: C, 37.82; H, 3.02; N, 9.55%.

Compound **3d**: b.p., 144 °C/ 1 mmHg. IR (film) cm^{-1}: 1230 (s); 1730 (s). ^1H NMR (CCl_4) δ: 1.22 (t, 3H, $J=7$ Hz); 3.78 (s, 3H); 4.30 (q, 2H, $J=7$ Hz); 12.90 (br., 1H) ppm. ^{19}F NMR (CCl_4) δ: -9.0 (t, 2F, $J=16$ Hz); 23.5 (t, 2F, $J=16$ Hz); 41.5 (br., s, 2F) ppm. MS *m/e*: 382 (M^+); 351 ($M^+ - OCH_3$); 337 ($M^+ - OC_2H_5$). Analysis: Calcd. for $C_{11}H_9ClF_6N_2O_4$: C, 34.53; H, 2.37; N; 7.32%. Found: C, 34.49; H, 2.17; N, 7.71%.

Compound **4d**: m.p., 46 °C. IR (KBr) cm^{-1}: 1240 (s); 1740 (s). ^1H NMR (CCl_4) δ: 1.22 (t, 3H, $J=7$ Hz); 3.78 (s, 3H); 4.25 (q, 2H, $J=7$ Hz); 12.72 (br., 1H) ppm. ^{19}F NMR (CCl_4) δ: -8.8 (t, 2F, $J=16$ Hz); 31.67 (t, 2F, $J=16$ Hz); 44.5 (br., s, 2F) ppm. MS *m/e*: 382 (M^+); 351 ($M^+ - OCH_3$); 337 ($M^+ - OC_2H_5$). Analysis: Calcd. for $C_{11}H_9ClF_6N_2O_4$: C, 34.53; H, 2.37; N, 7.32%. Found: C, 34.53; H, 2.09; N, 7.20%.

Compound **3e**: b.p., 128 °C/1 mmHg. IR (film) cm^{-1}: 1230 (s); 1740 (s). ^1H NMR (CCl_4) δ: 1.17 (t, 3H, $J=7$ Hz); 3.37 (s, 3H); 4.22 (q, 2H, $J=7$ Hz); 12.17 (br., 1H) ppm. ^{19}F NMR (CCl_4) δ: 2.5–8.2 (m, 8F); 39.7 (m, 1F); 53.2 (br., 2F) ppm. MS *m/e*: 482 (M^+); 451 ($M^+ - OCH_3$); 437 ($M^+ - OC_2H_5$); 297 ($M^+ - OC_3F_7$). Analysis: Calcd. for $C_{13}H_9F_{11}N_2O_5$: C, 32.38; H, 1.88; N, 5.81%. Found: C, 32.29; H, 1.99; N, 6.08%.

Compound **4e**: b.p., 148 °C/1 mmHg. IR (film) cm^{-1}: 1230 (s); 1740 (s). ^1H NMR (CCl_4) δ: 1.18 (t, 3H, $J=7$ Hz); 3.37 (s, 3H); 4.25 (q, 2H, $J=7$ Hz); 12.20 (br., 1H) ppm. ^{19}F NMR (CCl_4) δ: 3.0–8.3 (m, 8F); 51.2 (m, 1F); 53.7 (br., 2F) ppm. MS *m/e*: 482 (M^+); 451 ($M^+ - OCH_3$); 437 ($M^+ - OC_2H_5$); 297 ($M^+ - OC_3F_7$). Analysis: Calcd. for $C_{13}H_9F_{11}N_2O_5$: C, 32.38; H, 1.88; N, 5.81%. Found: C, 32.33; H, 1.96; N, 6.01%.

Compound **3f**: m.p., 71 °C. IR (KBr) cm^{-1}: 1220 (s); 1710 (s); 2250 (w) (C≡N str.). ^1H NMR (CCl_4) δ: 1.30 (t, 3H, $J=7$ Hz); 4.34 (q, 2H, $J=7$ Hz); 12.13 (br., 1H) ppm. ^{19}F NMR (CCl_4) δ: 2.7 (t, 3F, $J=10$ Hz); 27.3 (q, 2F, $J=10$ Hz); 47.8 (br., s, 2F) ppm. MS *m/e*: 333 (M^+); 288 ($M^+ - OC_2H_5$); 214 ($M^+ - C_2F_5$). Analysis: Calcd. for $C_{10}H_6F_7N_3O_2$: C, 36.05; H, 1.82; N, 12.61%. Found: C, 35.93; H, 1.46; N, 12.45%.

Compound **4f**: m.p., 59 °C. IR (KBr) cm^{-1}: 1230 (s); 1730 (s); 2280 (w) (C≡N str.). ^1H NMR (CCl_4) δ: 1.30 (t, 3H, $J=7$ Hz); 4.34 (q, 2H, $J=7$ Hz); 12.00 (br., 1H) ppm. ^{19}F NMR (CCl_4) δ: 2.7 (t, 3F, $J=10$ Hz); 33.7 (q, 2F, $J=10$ Hz); 49.0 (br., s, 2F) ppm. MS *m/e*: 333 (M^+); 288 ($M^+ - OC_2H_5$); 214 ($M^+ - C_2F_5$). Analysis: Calcd. for $C_{10}H_6F_7N_3O_2$: C, 36.05; H, 1.82; N, 12.61%. Found: C, 36.00; H, 1.40; N, 12.48%.

Compound **3g**: m.p., 43 °C. IR (KBr) cm^{-1}: 1190 (s); 1730 (s); 2280 (w) (C≡N str.). ^1H NMR (CCl_4) δ: 1.33 (t, 3H, $J=7$ Hz); 4.43 (q, 2H, $J=7$ Hz); 12.43 (br., 1H) ppm. ^{19}F NMR (CCl_4) δ: −9.8 (t, 2F, $J=14$ Hz); 26.5 (t, 2F, $J=14$ Hz); 42.3 (br., s, 2F) ppm. MS *m/e*: 349 (M^+); 304 ($M^+ - OC_2H_5$); 214 ($M^+ - ClCF_2CF_2$). Analysis: Calcd. for $C_{10}H_6ClF_6N_3O_2$: C, 34.35; H, 1.73; N, 12.02%. Found: C, 34.34; H, 1.43; N, 12.13%.

Compound **4g**: m.p., 54 °C. IR (Kbr) cm^{-1}: 1210 (s); 1710 (s); 2200 (w) (C≡N str.). ^1H NMR (CCl_4) δ: 1.33 (t, 3H, $J=7$ Hz); 4.43 (q, 2H, $J=7$ Hz); 12.40 (br., 1H) ppm. ^{19}F NMR (CCl_4) δ: −9.8 (t, 2F, $J=12$ Hz); 32.7 (t, 2F, $J=12$ Hz); 43.8 (br., s, 2F) ppm. MS *m/e*: 349 (M^+); 304 ($M^+ - OC_2H_5$); 214 ($M^+ - ClCF_2CF_2$). Analysis: Calcd. for $C_{10}H_6ClF_6N_3O_2$: C, 34.35; H, 1.73; N, 12.02%. Found: C, 34.06; H, 1.41; N, 12.30%.

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