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Synthesis of isomeric trifluoromethyl pyrazoles and isoxazoles

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Abstract

Three regioisomeric trifluoromethyl pyrazoles and four regioisomeric trifluoromethyl isoxazoles were completely selectively synthesized from three trifluoromethyl enones or acroleins (**1**, **2** and **3**) and phenylhydrazine, azide or hydroxylamine. © 1997 Elsevier Science S.A.

Keywords: Azide; Hydroxylamine; Phenylhydrazine; Trifluoromethyl phenyl isoxazoles; Trifluoromethyl phenyl pyrazoles

1. Introduction

Because trifluoromethyl-substituted heterocycles often show biological activity [1,2], much current research is focused on the development of methods for the regioselective synthesis of such compounds [3]. Trifluoromethyl-substituted five-membered heterocycles have received considerable attention [4]; studies on the synthesis of trifluoromethyl-substituted pyrazoles and isoxazoles have been reported [5–17], but often a mixture of two regioisomers is obtained.

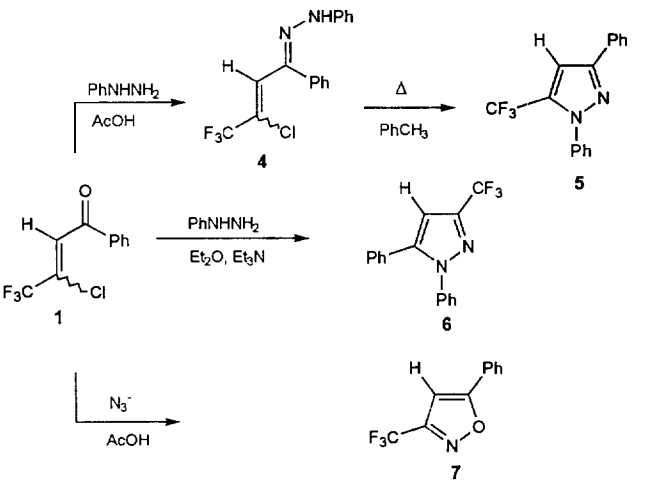
We report here a completely regioselective synthesis of several trifluoromethyl pyrazoles and isoxazoles from β-chloro unsaturated carbonyl compounds.

2. Results and discussion

2.1. Trifluoromethyl pyrazoles

β-Chloro β-trifluoromethyl enone **1** (Scheme 1) or acrolein **2** (Scheme 2) with phenyl hydrazine affords, in acidic medium, the corresponding hydrazone **4** or **8**.

These hydrazones are easily transformed to the corresponding pyrazole **5** or **9**. In basic medium, phenylhydrazine and **1** give the isomeric pyrazole **6**. In acidic medium, the β-chloro trifluoromethyl ketone **3** (Scheme 3) gives a mixture of the two pyrazoles **5** and **6** (yield, 72%; **5** : **6** = 73 : 27). The latter result can be explained by the lower basicity of this ketone, which decreases the electrophilic assistance in acidic medium [18]. Compounds **5** and **6** were previously described as a mixture obtained from the corresponding β-diketone and phenylhydrazine [19].



Scheme 1.

2.2. Trifluoromethyl isoxazoles

The azide anion gives a vinylic substitution with a β-chloro conjugated ketone or aldehyde [20,21]; pyrolysis of the vinylazide leads to the formation of an isoxazole. When the β-chloro trifluoromethyl compounds **1**, **2** and **3** were reacted with sodium azide in acetic acid medium, the corresponding trifluoromethyl isoxazoles **7**, **10** and **13** were obtained directly as pure compounds. **13** was previously obtained as a minor compound in a cycloaddition reaction [22] and from 4,4,4-trifluoro-1-phenyl-1,3-butane dione [23].

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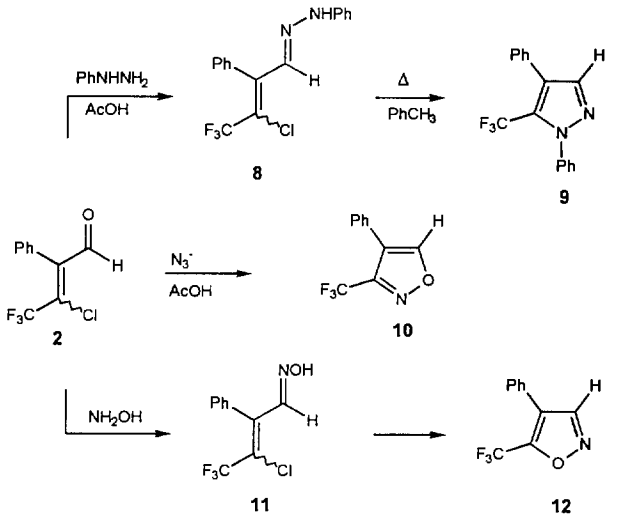
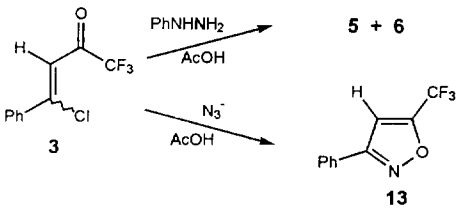


Scheme 2.



Scheme 3.

3. Conclusions

Using a Vilsmeier reagent and a trifluoromethyl ketone, it is easy to prepare starting material, such as **1**, **2** or **3** [24], from which it is possible to synthesize selectively different isomeric trifluoromethyl pyrazoles or isoxazoles.

4. Experimental section

Nuclear magnetic resonance (NMR) spectra were recorded in $CDCl_3$, unless otherwise noted, at 200 MHz (^1H), 56.4 MHz (^{19}F) and 75.47 MHz (^{13}C). Tetramethylsilane (TMS) was used as an internal standard for ^1H and ^{13}C NMR and $CFCl_3$ for ^{19}F NMR. Chemical shifts are reported in parts per million. Infrared (IR) spectra were recorded on a Perkin–Elmer 297. Mass spectra were recorded using a Nermag R10–10^5 instrument operated at 70 eV. Melting points are uncorrected. Merck 60 (0.063–0.200 mm) and Merck 60H silica gels and EGA-Chemie basic alumina gel were used for column chromatography. All reactions involving air-sensitive materials were conducted under a nitrogen atmosphere.

Compounds **1**, **2** and **3** have been described previously [24].

For the preparation of phenylhydrazones **4** and **8**, **1** or **2** (2 mmol), phenylhydrazine (2.5 mmol) and acetic acid (3 ml) were stirred for several hours at room temperature, followed by classical work-up and chromatography. A mixture of the two isomers (*Z*,*E*) was obtained.

Compound **4** (yield, 55%). IR: 3310, 1625–1530, 1180–1130 cm^{-1}. ^{19}F NMR: −69.3 (s) major: 80%; −69.4 (s) minor: 20%. ^1H NMR: 7.4 (m, 11H), 8.0 (1H, NH). MS (*m*/*z*): 326 (M^+ + 2, 19%), 324 (M^+, 55%).

Compound **8** (yield, 48%). IR: 3325, 1600, 1550, 1180–1130 cm^{-1}. ^{19}F NMR: −58.2 (s) major: 57%; −59.1 minor: 43%. ^1H NMR: 7 (m, 10H), 7.6 (s, 1H), 7.8 (1H). MS (*m*/*z*): 326 (M^+ + 2, 21%), 324 (M^+, 61%).

For the preparation of pyrazole **5** or **9**, hydrazone **4** or **8** (1 mmol), toluene (8 ml) and pyridine (1.5 mmol) were stirred for 3 h at reflux, followed by classical work-up and chromatography.

1,3-Diphenyl-5-trifluoromethyl pyrazole **5** (yield, 87%). IR: 1675, 1600–1560, 1170–1130 cm^{-1}. ^{19}F NMR: −58.3 (s). ^1H NMR: 7.1 (s, 1H), 7.4 (m, 3H), 7.6 (m, 5H, NPh), 7.8 (dt, 2H, ^3J = 6.9, ^4J = 1.7). ^{13}C NMR: 106.1 (q, *C*H, $^3J_{CF}$ = 2.4), 119.8 (q, *C*F_3, $^1J_{CF}$ = 269.1), 125–128 (m, 7*C*H), 128.9 (q, *C*-CF_3, $^2J_{CF}$ = 39.0), 129.2 (m, 3CH), 131.7 (s), 139.2 (s), 151.6 (s, C=N). MS (*m*/*z*): 288 (M^+, 100).

1,4-Diphenyl-5-trifluoromethyl pyrazole **9** (yield, 59%). IR: 1600, 1565, 1175–1130 cm^{-1}. ^{19}F NMR: −54.6 (s). ^1H NMR: 7.4 (s, 5H), 7.5 (s, 5H), 7.7 (s, 1H). MS (*m*/*z*): 288 (M^+, 100).

For the preparation of 1,5-diphenyl-3-trifluoromethyl pyrazole **6** (yield, 65%), **1** (0.2 g, 1 mmol) and ethylether (8 ml) were refluxed for 20 h, followed by classical work-up and chromatography (SiO_2). Melting point (m.p.): 79 °C. IR: 1620–1560, 1160–1130 cm^{-1}. ^{19}F NMR: −62.6 (s). ^1H NMR: 6.7 (s, 1H), 7.3 (m, 10H). ^{13}C NMR: 105.6 (q, CH, $^3J_{CF}$ = 2.0), 121.4 (q, CF_3, $^1J_{CF}$ = 268.9), 125.5 (s, 2CH), 128–129 (m, 8CH), 129.2 (s, Cq), 139.2 (s, Cq), 143.2 (q, CF_3–*C*=N, ^2J = 38), 144.6 (s, C5).

For the preparation of 3-chloro-4,4,4-trifluoro-2-phenyl-but-2-enal oxime (**11**), **2** (1.0 g, 4 mmol), hydroxylamine hydrochloride (0.84 g, 12.1 mmol) and ethanol (15 ml) were stirred for 20 min at reflux. Filtration and crystallization in petroleum ether yielded 0.6 g (55%) of **11** (m.p., 144 °C).

Compound **11*Z***. ^{19}F NMR: −60.2 (s). ^1H NMR: 7.1 (m, 2H), 7.3 (m, 3H), 8.4 (s, 1H), 8.6 (s, 1H).

Compound **11*E***. ^{19}F NMR: −58.9 (s). ^1H NMR: 7.1 (m, 2H), 7.3 (m, 3H), 8.3 (q, 1H, $^5J_{HF}$ = 1.6), 8.5 (s, 1H).

Analysis for $C_{10}H_7ClF_3NO$: calculated: C, 48.10%; H, 2.80%; N, 5.61%; Cl, 14.23%; found: C, 48.06%; H, 2.74%; N, 5.27%; Cl, 14.67%.

For the preparation of isoxazoles **7**, **10** and **13**, the following general procedure was used: 2 mmol of the corresponding β-chlorocarbonyl compound and 20 ml of acetic acid were added to 10 mmol of sodium azide and 8 ml of water; the solution was stirred for several hours, followed by classical work-up and chromatography.

3-Trifluoromethyl-5-phenyl-isoxazole **7**, obtained from **1** (2.9 mmol). Yield, 0.47 g (76%). IR: 1610, 1575, 1190–1120 cm^{-1}. ^{19}F NMR: −63.8 (s). ^1H NMR: 6.7 (s, 1H), 7.6 (m, 5H). MS (*m*/*z*): 213 (100 M^+).

3-Trifluoromethyl-4-phenyl-isoxazole **10**, obtained from **2** (2.1 mmol). Yield, 0.37 g (84%). IR: 1600, 1580, 1200–

1130 cm^{-1}. ^{19}F NMR: 63.3 (s). ^{1}H NMR: 7.5 (m, 5H), 8.1 (s, 1H). ^{13}C NMR: 116.5 (q, CF_3, $^{1}J=270.7$), 125.9 (s), 129.0 (s), 129.2 (s), 129.3 (s), 135.5 (s), 142.2 (s), 151.0 (q, $^{2}J_{CF}=44.2$).

5-Trifluoromethyl-3-phenyl-isoxazole **13**, obtained from **3** (1.8 mmol). Yield, 0.19 g (50%). M.p., 80 °C. IR: 1630, 1580, 1440, 1190–1160 cm^{-1}. ^{19}F NMR: −65.0 (s). ^{1}H NMR: 6.9 (s, 1H), 7.5 (m, 5H). ^{13}C NMR: 103.5 (q, $^{3}J_{CF}=2.0$), 118.0 (q, $^{1}J_{CF}=270.2$), 127.0 (s), 127.5 (s), 131.0 (s), 159.3 (q, $^{2}J_{CF}=45.5$), 162.7 (s). MS (*m/z*): 213 (58 M^+), 77 (100).

For the preparation of 5-trifluoromethyl-4-phenyl-isoxazole **12**, pyridine (0.07 ml, 0.9 mmol), oxime **11** (0.2 g, 0.8 mmol) and toluene (8 ml) were stirred under reflux for 5 h. Hydrolysis, classical work-up and chromatography (petroleum ether–ether, 95 : 5) yielded 0.09 g (45%) of **12**. IR: 1635–1580, 1390, 1190–1140 cm^{-1}. ^{19}F NMR: −61.7 (s). ^{1}H NMR: 7.4 (s, 5H), 8.5 (s, 1H). MS (*m/z*): 213 (100 M^+).

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