Regioselective Synthesis of Trifluoromethylated Pyrazoles by Selective Protection of Trifluoromethyl-β-diketones

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Received October 20, 1989

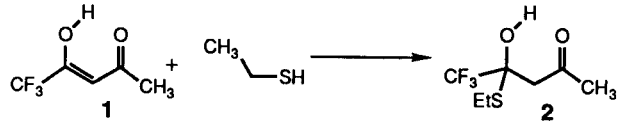
1,1,1-Trifluoropentane-2,4-dione was selectively protected by treatment with pyrrolidine to give **6**. The reaction of **6** with arylhydrazines gave **5** exclusively. The structural assignment for **5** was confirmed by quenching the dianion of **8** with ethyl trifluoroacetate.

J. Heterocyclic Chem., **27**, 919 (1990).

N-Arylpyrazoles, especially those containing fluorine, are of considerable interest in the Agrochemical field as exemplified by the large number of recent disclosures in the patent literature [1]. Several new methods for their synthesis have appeared [2], however, most offer little improvement over the classic hydrazine-β-diketone route to unsymetrical pyrazoles where isomeric mixtures would be expected [3]. We required a method for regioselectively preparing 5-trifluoromethylpyrazoles. This report presents our strategy toward this goal using arylhydrazines and trifluoromethyl-β-diketones.

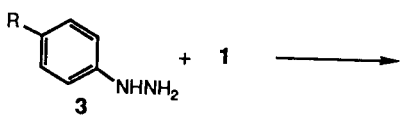
Trifluoromethyl-β-diketones exist substantially in the enol form [4]. They react with nucleophiles, presumably through the enol form, to give tetrahedral adducts [5]. For example, the reaction of ethanethiol with 1,1,1-trifluoromethylpentane-2,4-dione (**1**) was reported to result in a 25% conversion to **2** (Scheme I) [6]. We thought that this methodology could be used to develop an *in situ* blocking procedure which would allow reversal of the normal direction of nucleophilic attack on trifluoromethyl-β-diketones.

Scheme I

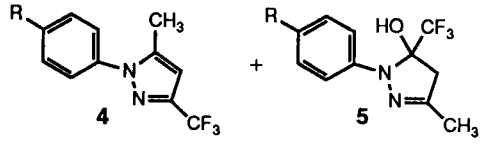


Normally, arylhydrazines **3** react with **1** to form 1-aryl-3-trifluoromethyl-5-substituted-pyrazoles **4** as the major product along with minor amounts of the hydroxypyrazoline **5** (Scheme II) [7]. The introduction of fluorine enhances the reactivity of the adjacent carbonyl group toward the phenylhydrazine [7a,8]. For example, the addition of phenylhydrazine (**3a**) to **1** at −25° gave a 5:1 mixture of **4a** and **5a**.

Scheme II

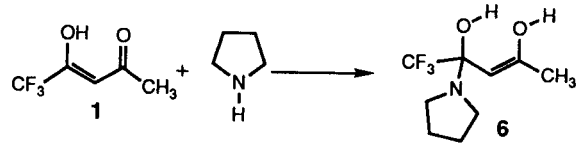


a. R=H
b. R=Cl



When pyrrolidine was allowed to react with **1** at 0°, a new product **6** was formed (Scheme III) which was identified using ^1H, ^{13}C, and ^{19}F nmr spectra. The presence of two exchangable protons (deuterium oxide) at 8.95 ppm in the ^1H nmr, a methine carbon at 98.8 ppm in the ^{13}C nmr, and one signal at −74.6 ppm in the ^{19}F nmr suggested that **6** exists in the enol form. Compound **6** is stable for several weeks if kept at −10° but slowly decomposes over several days if left at room temperature.

Scheme III

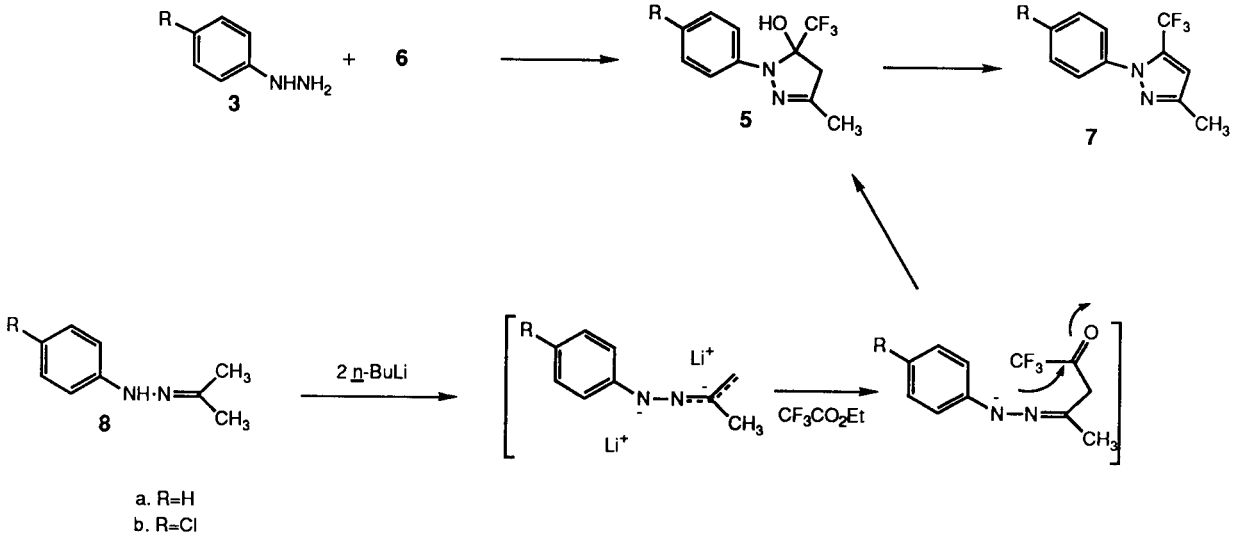


Addition of phenylhydrazine to **6** at room temperature, afforded the hydroxypyrazoline **5a** in 59% yield with no detectable presence of **4a** (Scheme IV). The reaction also works equally well when **3** is added to **6** generated *in situ* at −25°. Compound **5a** exhibits a characteristic AB quartet at 3.09 ppm in the ^1H nmr as well as a ^{19}F nmr signal at −78.6 ppm [2a]. Dehydration of **5a** to **7a** was readily accomplished in 95% yield by treatment with hydrochloric acid in dichloromethane at room temperature.

To confirm the structural assignment, **5** was prepared unambiguously by treating the acetone phenylhydrazone **8** with 2 equivalents of *n*-butyl lithium followed by quenching with ethyl trifluoroacetate [9]. The spectral and physical properties of **5a** and **5b** prepared in this way, were identical to those from the pyrrolidine route.

In conclusion, we have demonstrated that by the use of pyrrolidine as a transient carbonyl blocking group, one can completely reverse the regiochemistry of arylhydrazine addition to trifluoromethyl-β-diketones.

Scheme IV



a. R=H
b. R=Cl

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. ^1H (300 MHz) and ^{13}C (75.5 MHz) nmr spectra were recorded in deuteriochloroform on a General Electric QE300. Chemical shifts are expressed in parts per million downfield from internal tetramethylsilane. The ^{19}F (282 MHz) nmr spectra were recorded in deuteriochloroform on a Nicolet NT300. Chemical shifts are expressed in parts per million upfield from internal fluorotrichloromethane. Elemental analyses were performed at FMC Corporation, Analytical Services Department. Chromatography was done using EM silica gel 60 (0.040-0.063 mm) according to the procedure of Still *et al.* [10].

Reaction of **3** with **1**. Synthesis of 5-Methyl-1-phenyl-3-trifluoromethylpyrazole (**4a**).

A solution of 1.3 ml (13.2 mmoles) of phenylhydrazine dissolved in 5 ml of tetrahydrofuran was added dropwise over 10 minutes to a mixture of 1.6 ml (13.2 mmoles) of 1,1,1-trifluoro-2,4-pentanedione (**1**), 2 g of 3A molecular sieve, and 20 ml of tetrahydrofuran maintained at −25° under argon. The mixture was allowed to warm to room temperature and stirred for 16 hours. The mixture was filtered through celite then concentrated to an amber oil which partially solidified. Petroleum ether was added, 50 ml (35-60°), and the solid was filtered to give 0.5 g (17%) of **5a**, mp 125-127°. Concentration of the filtrate gave 2.4 g (82%) of **4a**, bp 97° (0.6 torr).

Compound **4a** had ^1H nmr: δ 2.32 (s, 3 H), 6.44 (s, 1 H), 7.44 (m, 5H); ^{19}F nmr: δ −62.6.

Anal. Calcd. for $C_{11}H_9F_3N_2$: C, 58.41; H, 4.01; N, 12.38. Found: C, 58.17; H, 3.72; N, 12.35.

Compound **5a** had ^1H nmr: δ 2.01 (s, 3 H), 3.09 (q, 2 H), 7.30 (m, 5 H); ^{19}F nmr: δ −78.6.

Anal. Calcd. for $C_{11}H_{11}F_3N_2O$: C, 54.10; H, 4.54; N, 11.47. Found: C, 54.35; H, 4.48; N, 11.28.

Synthesis of 1-(4-Chlorophenyl)-5-methyl-3-trifluoromethylpyrazole (**4b**).

A solution of 1.3 g (9.1 mmoles) of 4-chlorophenylhydrazine in tetrahydrofuran was added to 1.1 ml (9.1 mmoles) of **1** as above to give, after chromatography (3:7, ethyl acetate/heptane), 1.7 g 72%) of **4b**, R_f = 0.5, bp 113° (0.6 torr), and 0.42 g (18%) of **5b**, R_f = 0.2, mp 104-105°.

Compound **4b** had ^1H nmr: δ 2.33 (s, 3 H), 6.45 (s, 1 H), 7.42 (m, 4 H); ^{19}F nmr: δ −62.6.

Anal. Calcd. for $C_{11}H_8ClF_3N_2$: C, 50.69; H, 3.09; N, 10.75. Found: C, 50.76; H, 2.88; N, 10.48.

Compound **5b** had ^1H nmr: δ 2.03 (s, 3 H), 3.12 (q, 2 H), 7.26 (m, 4 H); ^{19}F nmr: δ −78.6.

Anal. Calcd. for $C_{11}H_{10}ClF_3N_2O$: C, 47.41; H, 3.61; N, 10.05. Found: C, 47.59; H, 3.43; N, 10.20.

Synthesis of **6**.

To 3 ml (24 mmoles) of **1** dissolved in 40 ml of petroleum ether at 0° was added slowly 2 ml (24 mmoles) of pyrrolidine. The resulting solid was collected to afford 5 g (90%) of a white solid, mp 85-87°; ^1H nmr: δ 1.80 (m, 4 H), 1.95 (s, 3 H), 3.19 (m, 4 H), 5.43 (s, 1 H), 8.95 (bs, 2 H); ^{19}F nmr: δ −74.6 (**1** at −75.7); ^{13}C nmr: δ 24.0, 45.0 (pyrrolidine), 29.7 (C-5), 92.8 (C-3), 119.4 (C-1, q, J_{CF} = 289 Hz), 167.7 (C-2, q, J_{CF} = 29 Hz), 195.6 (C-4).

Reaction of **3** with **6**. Synthesis of 5-hydroxy-3-methyl-1-phenyl-5-trifluoromethylpyrazoline (**5a**).

A solution of 1.9 g (8.4 mmoles) of **6**, 0.83 ml (8.4 mmoles) of **3a**, and 10 ml of tetrahydrofuran was stirred at room temperature for 3 hours, concentrated, then chromatographed with 4:1 heptane/ethyl acetate to afford 1.2 g (59%) of a white solid identical to **5a** above.

Reaction of **3** with **6** (generated *in situ*). Synthesis of 3-methyl-1-phenyl-5-trifluoromethylpyrazole (**7a**).

A solution of 1.1 ml (13 mmoles) of pyrrolidine in 5 ml of tetrahydrofuran was added to a mixture of 1.58 ml (13 mmoles) of **1**, 2 g of 3A molecular sieve, and 15 ml of THF at −25° under argon. After 30 minutes, a solution of 1.28 ml (13 mmoles) of phenylhydrazine in 5 ml of tetrahydrofuran was added dropwise. The resulting mixture was stirred at −25° for 30 minutes, warmed to room temperature, and stirred for 16 hours. After filtration, the

reaction mixture was concentrated to an oil then chromatographed (3:7, ethyl acetate/heptane) to afford 1.53 g (48%) of **5a**.

To a solution of 2.26 g (9.3 mmoles) of **5a** in 50 ml of dichloromethane was added 4 drops of concentrated hydrochloric acid. After 30 minutes stirring at room temperature, 25 ml of saturated aqueous sodium bicarbonate was added. The organic layer was dried over magnesium sulfate and concentrated to afforded 2.02 g (95%) of **7a**, bp 67° (0.65 torr); ^{1}H nmr: δ 2.35 (s, 3 H), 6.59 (s, 1 H), 7.45 (m, 5 H); ^{19}F nmr: δ −58.0.

Anal. Calcd. for $C_{11}H_9F_3N_2$: C, 58.41; N, 4.01; N, 12.38. Found: C, 58.59; H, 3.93; N, 12.61.

Synthesis of 1-(4-Chlorophenyl)-3-methyl-5-trifluoromethylpyrazole (**7b**).

In the same manner as for **7a**, 0.94 ml (11.2 mmoles) of pyrrolidine, 1.36 ml (11.2 mmoles) of **1**, 1 g of 3A molecular sieve, and 1.6 g (11.2 mmoles) of **3b** afforded, after chromatography (3:7, ethyl acetate/heptane) 1.22 g (40%) of **5b**.

A solution of 1.5 g (5.4 mmoles) of **5b** in 30 ml of dichloromethane was treated with 4 drops of concentrated hydrochloric acid. Workup as for **7a** afforded 1.38 g (98%) of **7b**, mp 49-51°; ^{1}H nmr: δ 2.34 (s, 3 H), 6.59 (s, 1 H), 7.41 (m, 4 H); ^{19}F nmr: δ −58.0.

Anal. Calcd. for $C_{11}H_8ClF_3N_2$: C, 50.69; H, 3.09; N, 10.75. Found: C, 50.68; H, 3.07; N, 10.88.

Synthesis of 5-Hydroxy-3-methyl-1-phenyl-5-trifluoromethylpyrazoline (**5a**). Acetone Hydrazone Route.

To a solution of 2.95 g (20 mmoles) of acetone phenylhydrazone, prepared from acetone and phenylhydrazine, in 50 ml of tetrahydrofuran at −25° under argon, was added 16 ml (40 mmoles) of 2.5 *M* *n*-butyllithium. After the addition, the mixture was stirred at −25° for 1 hour, then a solution of 2.4 ml (20 mmoles) of ethyl trifluoroacetate in 5 ml of tetrahydrofuran was added. The mixture was warmed to room temperature, stirred for 16 hours, then poured into 50 ml of 1 *M* ammonium chloride and 100 ml of ethyl ether. The ether layer was washed with brine, dried over magnesium sulfate, and concentrated to a solid which was chromatographed (3:7, ethyl acetate/heptane) to afford 2.9 g (64%) of **5a**.

Synthesis of 1-(4-Chlorophenyl)-5-hydroxy-3-methyl-5-trifluoromethylpyrazoline (**5b**). Acetone Hydrazone Route.

A solution of 2.65 g (14.5 mmoles) of acetone 4-chlorophenylhydrazone, prepared from acetone and 4-chlorophenylhydrazine, in 50 ml of tetrahydrofuran under argon was stirred at −25° as 11.6 ml (29 mmoles) of 2.5 *M* *n*-butyllithium was added dropwise. After the addition, the amber solution was stirred at −30° for 1 hour, then a solution of 2.1 g (14.5 mmoles) of ethyl trifluoroacetate in 5 ml of tetrahydrofuran was added. The mixture was allowed to warm to room temperature, stirred for 16 hours, then poured into 50 ml of 1 *M* ammonium chloride and 100 ml of ethyl ether. The ether layer was washed with brine, dried over magnesium sulfate, then concentrated to afford 2.7 g (67%) of **5b**.

Acknowledgement.

We acknowledge Dr. R. W. Creekmore for his assistance with the nmr experiments and Dr. K. R. Wilson for his support and encouragement.

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