Ring-fluorinated pyrazoles

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Abstract

2-Fluoro-1,3-diketones react with phenylhydrazine to yield ring-fluorinated pyrazoles in high yield. An isoxazole is produced when 2-fluoro-1,3-diphenyl-1,3-propandione is treated with hydroxylamine hydrochloride.

Introduction

An increasing number of agrochemicals and pharmaceuticals contain fluorine atoms [1], and the need for new routes for introducing fluorine selectively into a variety of substrates continues to grow. Among the fluorine-containing compounds, pyrazoles and isoxazoles fluorinated on the heterocyclic ring represent classes essentially unexplored. Kvasyuk and coworkers [2] reported in 1983 the direct fluorination of 3-carbomethoxypyrazole to 4-fluoro-3-carbomethoxypyrazole but in only 20% conversion. Reaction of hydrazine with α-fluoro-β-keto esters was observed by Ishikawa [3] to give fluorinated hydroxypyrazoles but the reaction failed with phenylhydrazine. The study was confined to keto esters and hence to hydroxypyrazoles. The polyfluoroaromatic β-diketone $(C_6F_5CO)_2CHF$ was found by Osadchii and Barkhash [4] to undergo cyclization to a pyrazole with hydrazine, but to form a pyrone with phenylhydrazine. Reports dealing with trifluoromethylated pyrazoles [5] and isoxazoles [5, 6] and with difluoroalkylpyrazoles [7] have appeared recently but these compounds do not have fluorine directly on the heterocyclic ring. Since a general synthesis of 2-fluoro-1,3-diketones has recently become available from work in our laboratory [8], and since 1,3-diketones have been used as starting materials for heterocyclic synthesis [9], we examined the possibility of employing these new fluorinated diketones as building blocks for synthesizing fluoropyrazoles and isoxazoles.

Experimental

General

Melting points were determined on a Meltemp apparatus and are reported uncorrected. Proton nuclear magnetic resonance, ^{13}C nuclear magnetic res-

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onance and fluorine nuclear magnetic resonance, infrared and mass spectra were obtained using the following instruments, respectively: General Electric 300 MHz NMR spectrometer, General Electric 300 MHz NMR spectrometer, Varian FM-390 NMR spectrometer, Perkin-Elmer 1430 IR spectrometer, Hewlett Packard 5985 GC/MS and Jeol HX 1100 HF high-resolution mass spectrometers. Gas chromatography (GC) was performed on a Hewlett Packard 5890 gas chromatograph with a fused silica capillary column and helium as the carrier gas. Thin-layer chromatography (TLC) was undertaken on Baker Flex silica gel IB-F coated plates. Visualization was accomplished with 254 nm (UV) light. All column chromatography was performed with Aldrich 70–270 mesh silica gel using a hexane/ethyl acetate mixture as the eluent system. Combustion analyses were performed by Atlantic Microlab, Inc., Atlanta, GA, USA.

Starting materials

The following chemicals were available from Aldrich Chemical Company: dibenzoylmethane, bis(trimethylsilyl)acetamide (BSA), phenylhydrazine, 2,4-pentanedione and 4,4,4-trifluoro-1-phenyl-1,3-butanedione. 1-(4-nitrophenyl)-1,3-butanedione was provided by Dr S. T. Purrington, North Carolina State University. Fluorine, 5% diluted in nitrogen, was obtained from Air Products and Chemicals Company. Sodium fluoride (used as a scrubber) and potassium iodide (used in fluorination traps to destroy excess fluorine) were obtained from Fisher Scientific Company. Freon-11 was purchased from the Fluka Chemical Company. All solvents were dried and distilled prior to use.

Preparation of silyl enol ethers (Scheme 1)

Silyl enol ethers were prepared from 1,3-diketones by the method of Chu and Huckin [10], except that bis(trimethylsilyl)acetamide (BSA) was used instead of bis(trimethylsilyl)formamide. Since the silylated products hydrolyze so readily they were fluorinated immediately.

Fluorinations

The silyl enol ethers were fluorinated in the manner previously described [8]. Data are recorded in Table 1.

*4-Fluoro-1,3,5-triphenylpyrazole (**2a**)*

To 1.20 g (0.00490 mol) of compound (**1a**) in 10 ml absolute ethanol was added 0.00540 mol phenylhydrazine. After 10 min, 2 ml concentrated sulfuric acid was added dropwise and the mixture was stirred at room temperature for 16 h. Recrystallization from hexanes yielded 1.06 g (83%) of yellowish-brown crystals, m.p., 141–142 °C. Additional data are collected in Table 2.

*4-Fluoro-3,5-dimethyl-1-phenylpyrazole (**2b**)*

To 0.600 g (0.00560 mol) of compound (**1c**) in 10 ml absolute ethanol was added 0.00570 mol phenylhydrazine. After 10 min, 1 ml concentrated

sulfuric acid was added dropwise and the mixture was stirred at room temperature for 36 h. Fractional distillation yielded 0.900 g (85%) of a reddish liquid, b.p., 98–100 °C/10 mmHg. Additional data are collected in Table 2.

*4-Fluoro-5-methyl-3-(4-nitrophenyl)-1-phenylpyrazole (**2c**)*

To 0.190 g (0.000850 mol) of compound (**1b**) in 10 ml absolute ethanol was added 0.00085 mol phenylhydrazine. After 10 min, 1 ml concentrated sulfuric acid was added dropwise and the mixture was stirred at room temperature for 44 h. A yellowish-brown solid, 0.201 g (79%) was obtained which decomposed at 240 °C. Additional data are collected in Table 2.

*4-Fluoro-3-trifluoromethyl-1,5-diphenylpyrazole (**2d**)*

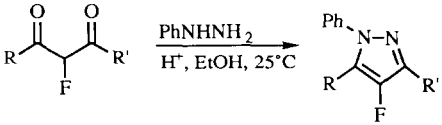
To 0.580 g (0.00250 mol) of compound (**1d**) in 10 ml absolute ethanol was added 0.00250 mol phenylhydrazine and 1 ml concentrated sulfuric acid. The mixture was stirred for 70 h, then refluxed for 2 h. 0.550 g (72%) of a yellowish-brown solid was obtained, 263 °C (dec.). Additional data are collected in Table 2.

*4-Fluoro-3,5-diphenylisoxazole (**3**)*

To 0.926 g (0.00410 mol) of compound (**1a**) in 10 ml absolute EtOH was added 0.00590 mol hydroxylamine hydrochloride. After 5 min, 2 ml concentrated sulfuric acid was added dropwise and the mixture was stirred at room temperature for 20 h. Chromatography and recrystallization from hexanes yielded 0.304 g (33%) of brownish crystals, m.p., 67–69 °C. ^{1}H NMR: δ 7–7.5 (m, 5H); 8–8.1 (m, 5H) ppm. ^{19}F NMR: δ −173 (s) ppm. IR (CCl_4) (cm^{-1}): 3060 (C=C−H); 1610 (C=N); 1200 (C−F). Mass spectral data (*m/e*): calcd: 239.07872; found: 239.07845.

Results and discussion

The 2-fluoro-1,3-diketones described in Table 1 were treated with phenylhydrazine as shown in eqn. (1). Results are summarized in Table 2.



(1)

(1)(a–d) **(2)(a–d)**

(**a**) R = R′ = Ph
(**b**) R = R′ = Me
(**c**) R = Me; R′ = *p*-nitrophenyl
(**d**) R = Ph; R′ = CF_3

Reaction of phenylhydrazine with compound (**1d**) can give rise to regioisomers but only one product was obtained according to the NMR spectrum (Table 2). Observations of the fragment Ph−C≡$\overset{+}{N}$−Ph in the mass

TABLE 1

2-Fluoro-1,3-diketones

Compound	Yield[b] (%)	Molecular ion	B.p. (°C/Torr) [m.p., °C]	NMR spectral data[a]		IR (C=O)
				^{19}F (δ ppm)	^{1}H (δ ppm)	(cm^{-1})
1a	74	242	[73–75]	−187 d J_{FH}=52 Hz	6.37 (d, 1H, J_{FH}=52.0 Hz); 7.4–7.6 (m, 5H); 8.1–8.2 (m, 5H)	1680
1b	62	118	50/10	−190d J_{FH}=51 Hz	2.0–2.1 (s, 6H); 5.8 (d, 1H, J_{HF}=51.3 Hz)	1670
1c	84	225	[103–104]	−190 d J_{FH}=51 Hz	2.4 (s, 3H); 5.5 (d, 1H), J_{HF}=51.1); 7.0–8.4 (m, 4H)	1520
1d	60	234	[72–74]	−81 s; −196 d J_{FH}=50 Hz	5.6 (d, 1H, J_{HF}=50.0 Hz); 7.4–8.1 (m, 5H)	1525

[a] ^{19}F chemical shifts are in parts per million downfield relative to $FCCl_3$ as external reference. ^{1}H chemical shifts are in parts per million downfield relative to $Si(CH_3)_4$ as internal standard. $CDCl_3$ was the solvent in all cases.
[b] From silyl enol ethers, see Scheme 1.

TABLE 2

Pyrazole formation

Compound	Yield[c] (%)	NMR spectral data[a]		High-resolution MS (*m/e*)	
		^{19}F (δ ppm)	^{1}H (δ ppm)	Calcd.	Found
2a	83	−173 s	7.2–7.5 (m, 10H); 8.0–8.2 (m, 5H)	[b]	
2b	85	−178 s	2.25 (s, 3H); 2.35 (s, 3H); 7.2–7.7 (m, 5H)	190.0906	190.0906
2c	79	−175 s	2.4 (s, 3H); 7.2–7.5 (m, 5H); 7.6–8.2 (m, 4H)	297.0914	297.0915
2d	72	−173 (s, 1F); −80 (s, 3F)	6.8–8.0 m	306.0780	306.0780

[a] See footnote a, Table 1.
[b] Combustion analyses: Calcd. for $C_{21}H_{15}FN_2$: C, 80.25; H, 4.78; N, 8.92%. Found: C, 80.17; H, 4.85; N, 8.90%.
[c] Based on eqn. (1).

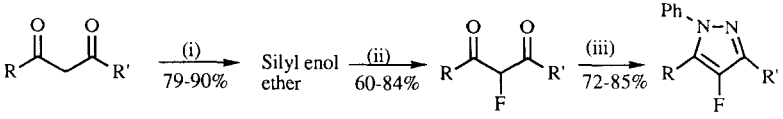
spectrum of the pyrazole from **1d** indicates **2d** is the isomer obtained. This regiochemistry is that expected if the more nucleophilic β-nitrogen of phenylhydrazine attacks the more electrophilic carbonyl, i.e. the one adjacent to the trifluoromethyl group. The pyrazole from **1c** is assigned **2c** on similar grounds.

The observations summarized in Table 2, coupled with those collected in Scheme 1, demonstrate that the sequence in Scheme 1 constitutes a practical route to fluorinated pyrazoles.

A range of substituents can be used [see eqn. (1)] and the yields are moderate to high. Formation of **2d** shows that the method can lead to pyrazoles which are fluorinated and trifluoromethylated.

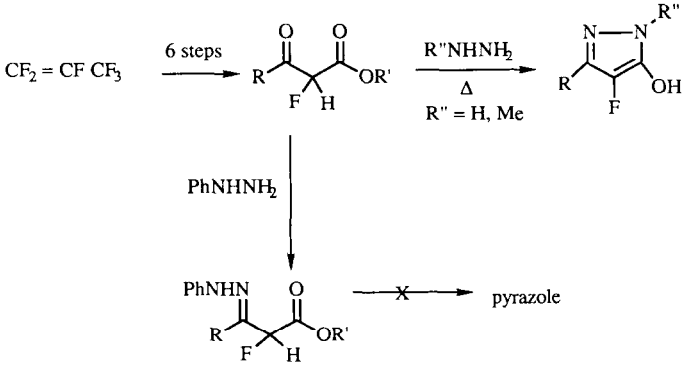
In an earlier study [3], hydroxypyrazoles were obtained by Ishikawa from α-fluoro-β-keto esters and hydrazines, but the synthetic scope of this reaction is limited to hydrazine and methylhydrazine. Attempted cyclizations with phenylhydrazine failed [3], probably due to the decreased reactivity of the ester moiety (Scheme 2). In addition, Ishikawa's route to the intermediate 2-fluoroketo esters involves starting with perfluoropropene or trifluoroethene [3], resulting in a lengthy series which is inefficient with respect to the use of fluorine. Since fluoroketo esters, the Ishikawa precursors to fluoro-hydroxypyrazoles, now can be prepared by direct fluorination [8], a more practical, economical synthesis of hydroxypyrazoles can be delineated, as outlined in Scheme 3.

The sequence in Scheme 1 can be modified to prepare ring-fluorinated isoxazoles. Reaction of **1a** with hydroxylamine hydrochloride in ethanol gave isoxazole (**3**) in 33% unoptimized yield [eqn. (2)].

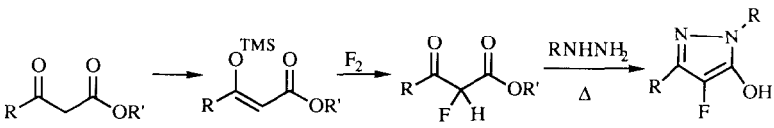


Reagents: (i) bis(trimethylsilyl)acetamide: (ii) 5% F_2/N_2; (iii) phenylhydrazine

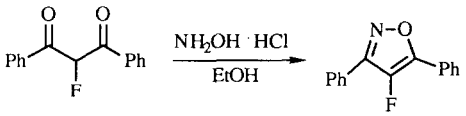
Scheme 1.



Scheme 2.



Scheme 3.



(2)

(1a) (3)

Compound (3) shows a singlet in the ^{19}F NMR spectrum at -173 ppm; multiplets in the ^{1}H NMR spectrum at 7.0–7.5 and 8.0–8.1 ppm, and a consistent high-resolution mass spectrum (see Experimental). Ring-fluorinated isoxazoles have not been reported previously to our knowledge although several groups have mentioned trifluoromethylated derivatives [5, 6].

In conclusion, 2-fluoro-1,3-diketones can be used with phenylhydrazine and hydroxylamine to produce selectively fluorinated pyrazoles and isoxazoles in a practical manner. If trifluoromethyl groups are incorporated into the 2-fluoro-1,3-diketones, then fluorinated, trifluoromethylated products can be obtained as well.

Acknowledgement

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