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REGIOSELECTIVE SYNTHESIS OF TRIFLUOROMETHYL GROUP SUBSTITUTED PYRAZOLE DERIVATIVES FROM 1-ARYL-3,4,4,4-TETRAFLUORO-2-BUTEN-1-ONES

Keisuke Sano and Shoji Hara*

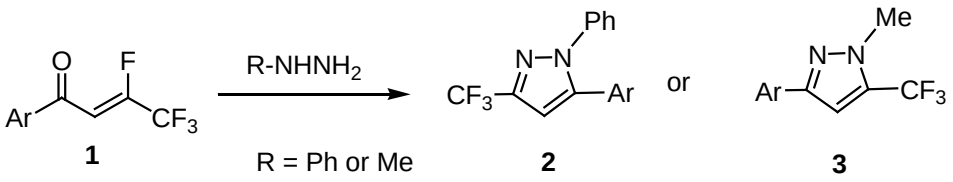
Graduate School of Engineering, Hokkaido University, Sapporo 060-8628, Japan
E-mail: shara@eng.hokudai.ac.jp

Abstract – Trifluoromethyl group substituted pyrazole derivatives were prepared from hydrazines and 1-aryl-3,4,4,4-tetrafluoro-2-buten-1-ones obtained by the deoxyfluorination of β-diketones. The reaction proceeded regioselectively and 5-aryl-3-trifluoromethyl-1-phenyl-1*H*-pyrazole was obtained from phenylhydrazine. On the other hand, when methylhydrazine was used, 3-aryl-5-trifluoromethyl-1-methyl-1*H*-pyrazole was selectively formed.

INTRODUCTION

Pyrazoles with a trifluoromethyl substituent are of considerable interest because they are present in pharmacologically and agrochemically important compounds.[1] A pyrazole ring was generally prepared from β-diketones with hydrazines.[2] However, when unsymmetrical β-diketones such as 1-aryl-4,4,4-trifluoro-1,3-butanones were used, a mixture of regioisomers were formed and it was difficult to obtain the desired regioisomer selectively.[3] Recently, we reported the regioselective synthesis of 1-aryl-3,4,4,4-tetrafluoro-2-buten-1-ones (**1**) by the deoxyfluorination reaction of 1-aryl-4,4,4-trifluoro-1,3-butanones with *N*,*N*-diethyl-α,α-difluoro-(*m*-methylbenzylamine) (DFMBA).[4] In this paper, we report the regioselective synthesis of a trifluoromethyl group substituted pyrazole derivative (**2** or **3**) by the reaction of 1-aryl-3,4,4,4-tetrafluoro-2-buten-1-ones (**1**) with *mono*-substituted hydrazines (Scheme 1).[5]

Dedicated to Professor Akira Suzuki on the occasion of his 80th birthday.

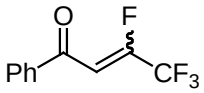
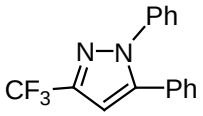
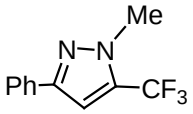
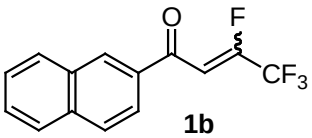
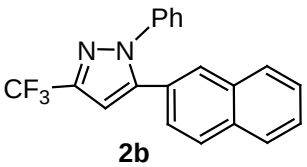
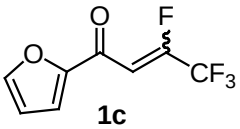
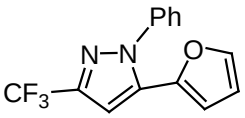
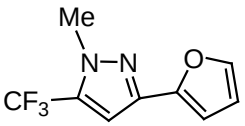
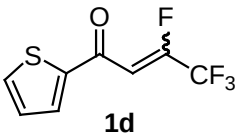
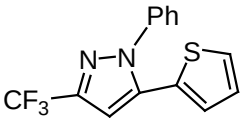


Scheme 1

RESULTS AND DISCUSSION

The reaction of 3,4,4,4-tetrafluoro-1-phenyl-2-buten-1-one (**1a**) with phenylhydrazine was performed in ether under reflux for 24 h and 3-trifluoromethyl-1,5-diphenyl-1*H*-pyrazole (**2a**) was obtained in 88% yield (Entry 1 in Table 1). Interestingly, its regioisomer, 5-trifluoromethyl-1,3-diphenyl-1*H*-pyrazole, was not formed at all. On the other hand, when methylhydrazine was used, 5-trifluoromethyl-1-methyl-3-phenyl-1*H*-pyrazole (**3a**) was obtained in 95% yield and its regioisomer, 3-trifluoromethyl-1-methyl-5-phenyl-1*H*-pyrazole, was not formed (Entry 2). The selectivity is not dependent on the type of aryl group in **1**, and 5-aryl-3-trifluoromethyl-1-phenyl-1*H*-pyrazole (**2a-d**) was formed selectively from phenylhydrazine (Entries 1, 3, 4, and 6). On the other hand, from methylhydrazine, 3-aryl-5-trifluoromethyl-1-methyl-1*H*-pyrazole (**3a,c**) was selectively obtained (Entries 2 and 5). Recently, the regioselective synthesis of 1-aryl-3-trifluoromethyl-1*H*-pyrazoles **2** by the reaction of 1-aryl-4,4,4-trifluoro-1,3-butanones with phenylhydrazines was reported.[6] However, the selective synthesis of 3-aryl-5-trifluoromethyl-1-methyl-1*H*-pyrazole **3** from 1-aryl-4,4,4-trifluoro-1,3-butanones and methylhydrazine has not yet been performed. Therefore, our method is useful for the selective synthesis of various pyrazole derivatives with trifluoromethyl substituent.

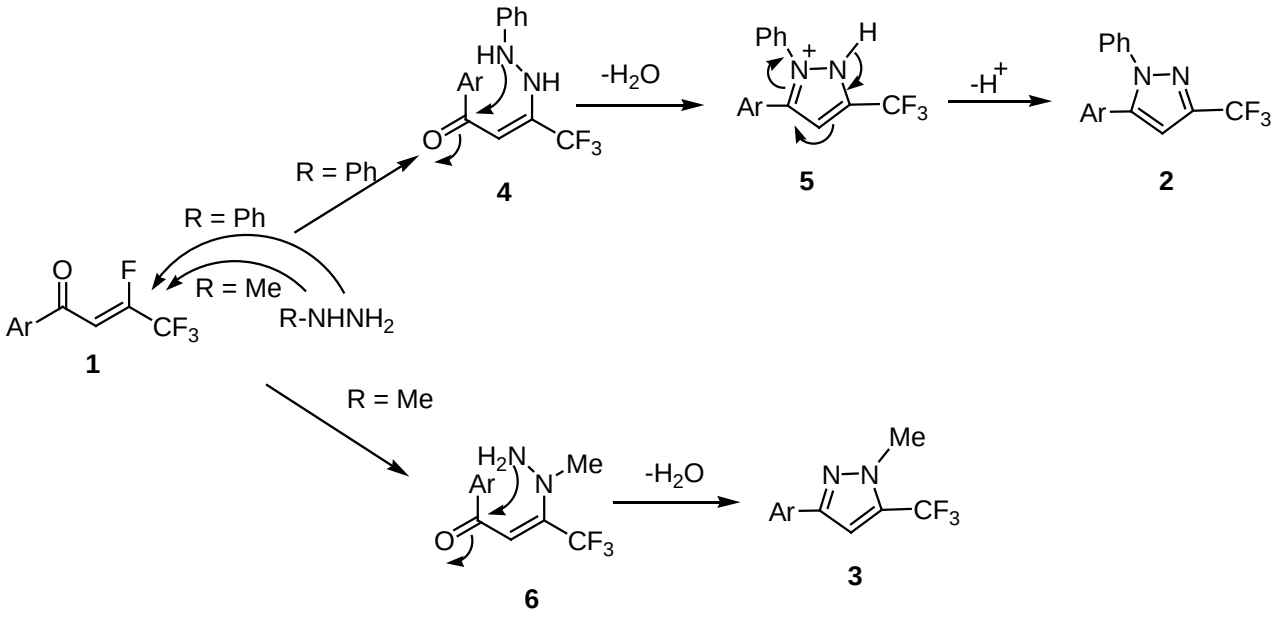
Table 1. Synthesis of trifluoromethylpyrazoles[a]

Entry	Substrate[b]	Hydrazine, R	Time (h)	Product	Yield(%)[c]
1	 **1a**	Ph	24	 **2a**	88
2	**1a**	Me	12	 **3a**	95
3	 **1b**	Ph	24	 **2b**	94
4	 **1c**	Ph	24	 **2c**	89
5	**1c**	Me	12	 **3c**	86
6	 **1d**	Ph	24	 **2d**	90

a. The reaction was carried out in ether under reflux. b. A mixture of stereoisomers was used.
c. Isolation yield based on **1**.

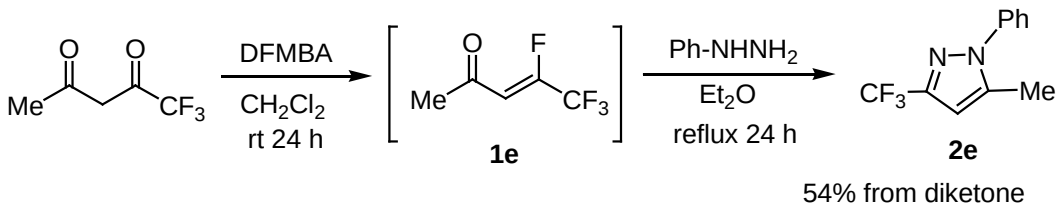
This high selectivity can be explained by the difference between the reactivity of phenylhydrazine and that of methylhydrazine. In phenylhydrazine, -NH_2 is more nucleophilic than –NHPh due to the electron-withdrawing effect of the Ph group[6c] and –NH_2 attacks the C3 carbon of **1** to yield the intermediate **4**.[7] The subsequent addition of –NHPh to the carbonyl group yields a cyclic imminium salt **5** that changes to the pyrazole **2**. On the other hand, in the reaction with methylhydrazine, –NHMe is more reactive than –NH_2 due to the electron-donating effect of the methyl group and –NHMe attacks the C3 carbon of **1** to yield an intermediate **6**.[6c] The subsequent cyclization proceeds by the attack of –NH_2 on the carbonyl group to give the pyrazole **3**, selectively. As the formation of **4** or **6** by the 1,4-addition reaction of the hydrazines to **1** is irreversible, the regioselectivity of the reaction is determined at the

initial step, attack of nitrogen to C3, and largely influenced by the nucleophilicity of the nitrogen on the hydrazines. On the other hand, in the reaction with β-diketones, the initial addition of the nitrogen to the carbonyl group is reversible and the regioselectivity is determined at the dehydration step.[2,3,6c] Therefore, the regioselectivity in the reaction with β-diketones is not so influenced by the nucleophilicity of the nitrogen on the hydrazines as in the reaction with **1** and a similar selectivity was not observed (Scheme 2).



Scheme 2

For the synthesis of 3-trifluoromethyl-5-methyl-1-phenyl-1*H*-pyrazole (**2e**), a volatile 4,5,5,5-tetrafluoro-3-penten-2-one (**1e**) is required. Therefore, we synthesized **2e** from β-diketone without isolating **1e**. The reaction of 1,1,1-trifluoropentane-2,4-dione with DFMBA was carried out at room temperature for 24 h. From the ^{19}F NMR analysis of the crude mixture, deoxyfluorination was found to occur at the C2 position selectively and 4,5,5,5-tetrafluoro-3-penten-2-one (**1e**) was formed in 70% yield. Crude **1e** was used for the reaction with phenylhydrazine, and **2e** was selectively formed in 54% yield from the diketone (Scheme 3).



Scheme 3

Celecoxib, 4-[5-(4-methylphenyl)-3-trifluoromethyl-1*H*-pyrazol-1-yl]benzenesulphonamide, is widely used as an anti-inflammatory drug for the treatment of osteoarthritis, rheumatoid arthritis, and acute pain.[8] Using our method, we prepared Celecoxib from 4,4,4-trifluorobutane-1-(*p*-tolyl)-1,3-dione.[9] The deoxyfluorination of the diketone with DFMBA was performed in CH_2Cl_2 at 20 °C for 24 h to produce 3,4,4,4-tetrafluoro-1-(*p*-tolyl)-2-buten-1-one (**1f**) in 91% yield as a mixture of stereoisomers. The reaction of **1f** with *p*-aminosulfonylphenylhydrazine hydrochloride was performed in a mixture of DMF and H_2O (4:1) at 40 °C for 12 h to give Celecoxib in 80% yield and the formation of its regioisomer was not observed (Scheme 4).

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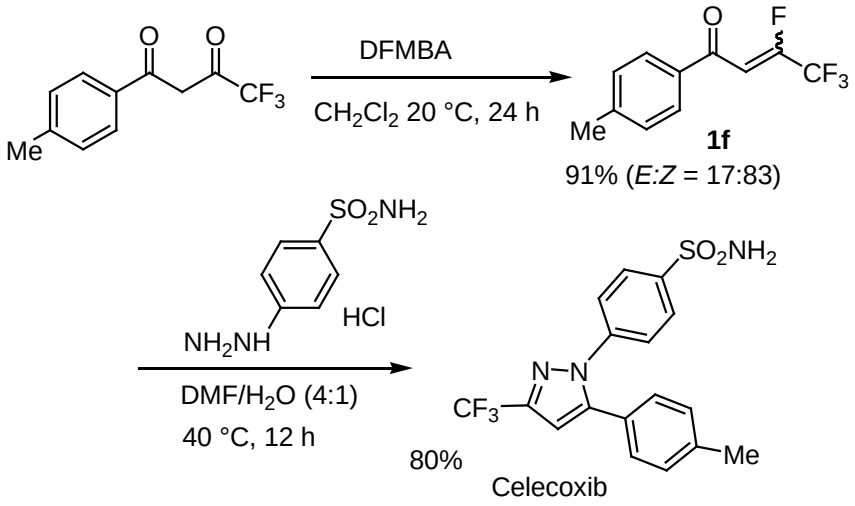

Scheme 4

EXPERIMENTAL

4.1. General

The melting points were measured with a Yanagimoto micro melting-point apparatus. The IR spectra were recorded using a JASCO FT/IR-410. The ^{1}H NMR (400 MHz) spectra, ^{19}F NMR (376 MHz) spectra, and ^{13}C NMR (100 MHz) were recorded in $CDCl_3$ on a JEOL JNM-A400II FT NMR and the chemical shift, δ, is referred to TMS (^{1}H, ^{13}C) and $CFCl_3$ (^{19}F), respectively. The EI-high-resolution mass spectra were measured on a JEOL JMS-700TZ. Methylhydrazine, phenylhydrazine, 4-hydrazinobenzenesulfonamide hydrochloride, and diketones were purchased from Tokyo Kasei Kogyo Co., Ltd. 4,4,4-Trifluoro-1-(*p*-tolyl)-butane-1,3-dione was prepared according to a literature.[9] 1-Aryl-3,4,4,4-tetrafluoro-2-buten-1-ones **1a**, **1b**, **1c**, and **1d** were prepared from the corresponding diketones by the reported method.[4] DFMBA was donated from Mitubishi Gas Chemical Company Inc.

Preparation of 1-Aryl-3,4,4,4-tetrafluoro-2-buten-1-one[4] (1)

A mixture of 1-aryl-4,4,4-trifluorobutane-1,3-dione (1 mmol), DFMBA (426 mg, 2 mmol), and CH_2Cl_2 (1

mL) in a reaction vessel made of Teflon™ FEP with a tight screw cap was stirred at 20 °C for 24 h. The mixture was poured into water, neutralized with sat. aq. $NaHCO_3$, and extracted with Et_2O (20 mL x 3). The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. Purification by column chromatography (silica gel/hexane-Et_2O) gave **1**.

Preparation of 5-Aryl-3-trifluoromethyl-1-phenyl-1*H*-pyrazole (2)

To **1** (0.48 mmol) in Et_2O (8 mL) was added at rt phenylhydrazine (64 mg, 0.59 mmol) and the mixture was stirred under reflux for 24 h. Solid material was removed by filtration and the filtrate was concentrated under reduced pressure. Purification by column chromatography (silica gel/hexane-Et_2O) gave **2**.

Preparation of 3-aryl-5-trifluoromethyl-1-methyl-1*H*-pyrazole (3)

To **1** (0.48 mmol) in Et_2O (8 mL) was added at rt methylhydrazine (50 mg, 1.08 mmol) and the mixture was stirred under reflux for 12 h. Solid material was removed by filtration and the filtrate was concentrated under reduced pressure. Purification by column chromatography (silica gel/hexane-Et_2O) gave **3**.

3-Trifluoromethyl-1,5-diphenyl-1*H*-pyrazole (2a)

a pale yellow solid; mp 87–88 °C (lit.,[10] 87–88 °C): IR (KBr): 1496, 1236, 1122 cm^{-1}. ^1H NMR δ 7.37–7.21 (m, 10H), 6.76 (s, 1H). ^{13}C NMR δ 144.6, 143.1 (q, *J* = 38.1 Hz), 139.1, 129.1, 129.0 (2C), 129.0, 128.8 (2C), 128.7 (2C), 128.4, 125.4 (2C), 121.3 (q, *J* = 268.9 Hz), 105.5 (q, *J* = 1.9 Hz). ^{19}F NMR δ –62.82 (s, 3F) {lit.,[11] –62.6 (s)}.

5-Trifluoromethyl-1-methyl-3-phenyl-1*H*-pyrazole (3a)

clear oil: IR (neat): 1441, 1275, 1204, 1126 cm^{-1}. ^1H NMR δ 7.78–7.76 (m, 2H), 7.43–7.32 (m, 3H), 6.89 (s, 1H), 4.04 (s, 3H). ^{13}C NMR δ 150.3, 133.1 (q, *J* = 39.1 Hz), 132.0, 128.8 (2C), 128.3, 125.5 (2C), 120.0 (q, *J* = 268.3 Hz), 104.5 (q, *J* = 2.7 Hz), 38.1 (q, *J* = 1.9 Hz). ^{19}F NMR δ –61.10 (s, 3F) {lit.,[6c] –60.9 (s)}.

3-Trifluoromethyl-5-(2-naphtyl)-1-phenyl-1*H*-pyrazole (2b)

highly viscous liquid: IR (neat): 1599, 1486, 1124 cm^{-1}. ^1H NMR δ 7.84–7.74 (m, 4H), 7.55–7.49 (m, 2H), 7.43–7.35 (m, 5H), 7.22–7.20 (m, 1H), 6.87 (s, 1H). ^{13}C NMR δ 144.6, 143.2 (q, *J* = 38.6 Hz), 139.2, 132.9, 132.9, 129.1 (2C), 128.4, 128.3 (2C), 128.1, 127.7, 127.0, 126.7, 126.4, 125.7, 125.3 (2C), 121.3 (q, *J* = 268.9 Hz), 105.8 (q, *J* = 1.9 Hz). ^{19}F NMR δ –62.79 (s, 3F) {lit.,[10] –62.3 (s)}.

3-Trifluoromethyl-5-(fur-2-yl)-1-phenyl-1*H*-pyrazole (2c)

clear liquid; IR (neat): 1496, 1247, 1134 cm^{-1}. ^1H NMR δ 7.51–7.42 (m, 6H), 6.91 (s, 1H), 6.35–6.34 (m, 1H), 5.96 (d, *J* = 2.5 Hz, 1H). ^{13}C NMR δ 143.2, 143.2 (q, *J* = 38.2 Hz), 143.0, 139.3, 136.1, 129.5, 129.3 (2C), 126.0 (2C), 121.1 (q, *J* = 268.9 Hz), 111.4, 109.8, 103.7 (q, *J* = 2.4 Hz). ^{19}F NMR δ –62.95

(s, 3F) {lit.,[10] –62.5 (s)}.

5-Trifluoromethyl-3-(fur-2-yl)-1-methyl-1*H*-pyrazole (3c)

clear liquid; IR (neat): 1274, 1126 cm^{-1}. ^1H NMR δ 7.46 (s, 1H), 6.82 (s, 1H), 6.68 (d, *J* = 3.6 Hz, 1H), 6.47 (dd, *J* = 3.2, 1.8 Hz, 1H), 4.02 (s, 3H). ^{13}C NMR δ 147.3, 142.8, 142.2, 132.8 (q, *J* = 39.1 Hz), 119.7 (q, *J* = 269.0 Hz), 111.3, 106.4, 104.2 (q, *J* = 1.9 Hz), 38.0 (q, *J* = 1.9 Hz). ^{19}F NMR δ –61.26 (s, 3F) {lit.,[6c] –61.1 (s, 3F)}.

3-Trifluoromethyl-1-phenyl-5-(thien-2-yl)-1*H*-pyrazole (2d)

yellow solid; mp 65-66 °C (lit.,[10] 82–83 °C): IR (KBr): 1469, 1251, 1129 cm^{-1}. ^1H NMR δ 7.46–7.39 (m, 5H), 7.33–7.32 (m, 1H), 6.96 (dd, *J* = 5.0, 3.7 Hz, 1H), 6.87–6.86 (m, 1H), 6.81 (s, 1H). ^{13}C NMR δ 143.0 (q, *J* = 38.1 Hz), 138.8, 138.7, 129.5, 129.2, 129.2 (2C), 128.0, 127.5, 127.4, 126.3 (2C), 121.1 (q, *J* = 269.0 Hz), 105.2 (q, *J* = 1.9 Hz). ^{19}F NMR δ –62.94 (s, 3F)

3-Trifluoromethyl-5-methyl-1-phenyl-1*H*-pyrazole (2e)

A mixture of 1,1,1-trifluoropentane-2,4-dione (74 mg, 0.48 mmol), DFMBA (212 mg, 1 mmol) and CH_2Cl_2 (2 mL) in a reaction vessel made of Teflon™ FEP with a tight screw cap was stirred at rt for 24 h. Then, the mixture was poured into sat. aq. $NaHCO_3$ (20 mL) and extracted with Et_2O (10 mL). The ethereal solution of 4,5,5,5-tetrafluoro-3-penten-2-one was transferred into a reaction vessel and phenylhydrazine (45.5 mg, 0.42 mmol) was added. The mixture was stirred under reflux for 24 h. The solid material was removed by filtration and filtrate was concentrated under reduced pressure. Purification by column chromatography (silica gel/hexane-Et_2O) gave **2e** (59 mg) in 54% overall yield from 1,1,1-trifluoropentane-2,4-dione. clear oil: IR (neat): 1489, 1384, 1240, 1140 cm^{-1}. ^1H NMR δ 7.53–7.43 (m, 5H), 6.46 (s, 1H), 2.35 (s, 3H). ^{13}C NMR δ 142.6 (q, *J* = 37.6 Hz), 140.7, 138.8, 129.2 (2C), 128.7, 125.2 (2C), 121.4 (q, *J* = 268.9 Hz), 104.8 (q, *J* = 1.9 Hz), 12.2. ^{19}F NMR δ –62.85 (s, 3F) {lit.,[10] –62.5 (s)}.

Synthesis of Celecoxib

3,4,4,4-Tetrafluoro-1-(*p*-tolyl)-2-buten-1-one (1f)

A mixture of 1,1,1-trifluoro-4-(*p*-tolyl)pentane-2,4-dione (232 mg, 1.01 mmol), DFMBA (425 mg, 1.99 mmol) and CH_2Cl_2 (2 mL) in a reaction vessel made of Teflon™ FEP with a tight screw cap was stirred at 30 °C for 24 h. Then, the mixture was poured into sat. aq. $NaHCO_3$ (20 mL) and extracted with Et_2O (20 mL x 3). The combined organic layer was dried over $MgSO_4$ and the volatile part was removed under reduced pressure. Purification by column chromatography (silica gel/hexane-Et_2O) gave **1f** (196 mg) in 84% yield as a mixture of stereoisomers (*E:Z* = 13:77, only *Z* isomer is isolable as a pure form). clear oil: (*Z*)-isomer: IR (neat): 2929, 1707, 1608, 1208 cm^{-1}. ^1H NMR δ 7.82 (d, *J* = 8.2 Hz, 2H), 7.32 (d, *J* = 7.9 Hz, 2H), 6.90 (d, *J* = 31.6 Hz, 1H, =CH), 2.45 (s, 3H). ^{13}C NMR δ 185.9, 150.7 (dq, *J* = 282.0, 39.4 Hz),

145.6, 133.7, 129.6 (2C), 128.8 (2C), 117.8 (dq, *J* = 40.3, 273.1 Hz), 107.9-107.8 (m), 21.6. ^{19}F NMR δ –73.75 (d, *J* = 9.8, 3F), –118.28 (dq, *J* = 31.4, 9.8 Hz, 1F). HRMS(EI): calcd for $C_{11}H_8OF_4$; 232.0511. Found; 232.0514.

Celecoxib

To **1f** (a mixture of the stereoisomers was used, 114 mg, 0.49 mmol) in a 4:1 mixture of DMF and H_2O (5 mL) was added 4-hydrazinobenzenesulfonamide hydrochloride (133 mg, 0.60 mmol) and the mixture was stirred at 40 °C for 12 h. After cooling to rt, H_2O (40 mL) was added to the mixture. The mixture was extracted with Et_2O (40 mL x 3), and the organic layer was washed with H_2O (40 mL x 3), and brine (40 mL). The organic layer was dried over $MgSO_4$, concentrated under reduced pressure. Purification by column chromatography (silica gel/hexane-Et_2O) gave Celecoxib (150 mg) in 80% yield; a white crystal; mp 154–156 °C (lit.,[8a] 157–159 °C): IR (KBr): 3267, 1164 cm^{-1}. ^{1}H NMR δ 7.91 (d, *J* = 8.4 Hz, 2H), 7.48 (d, *J* = 8.4 Hz, 2H), 7.18 (d, *J* = 8.4 Hz, 2H), 7.11 (d, *J* = 8.0 Hz, 2H), 6.75 (s, 1H), 4.85 (s, 2H), 2.39 (s, 3H). ^{13}C NMR δ 145.2, 144.1 (q, *J* = 38.7 Hz), 142.5, 141.2, 139.8, 129.7 (2C), 128.7 (2C), 127.5 (2C), 125.6, 125.5 (2C), 121.0 (q, *J* = 269.0 Hz), 106.3 (q, *J* = 1.9 Hz), 21.3. ^{19}F NMR δ –63.03 (s, 3F)

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