

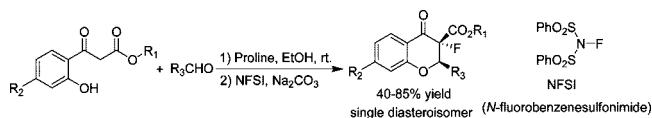
Facile Stereoselective Synthesis of Fluorinated Flavanone Derivatives via a One-Pot Tandem Reaction

Haifeng Cui, Peng Li, Zhuo Chai, Changwu Zheng,
Gang Zhao,* and Shizheng Zhu*

Laboratory of Modern Synthetic Organic Chemistry and Key
Laboratory of Organofluorine Chemistry, Shanghai Institute of
Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin
Lu, Shanghai 200032, People's Republic of China

zhaog@mail.sioc.ac.cn

Received October 23, 2008



A series of fluorinated flavanones were synthesized in moderate to good yields with excellent diastereoselectivities under mild reaction conditions via a one-pot tandem procedure involving a proline-catalyzed Knoevenagel condensation, a Michael addition, and an electrophilic fluorination by NFSI.

Flavanones represent an important structural motif occurring in many natural products with a variety of biological activities such as antitumor and anti-inflammatory properties.¹ Therefore, a large number of methods have been developed for the synthesis of flavanones and their derivatives.² On the other hand, the introduction of the fluorine atom is often adopted as a measure to usher in great changes in the physicochemical and biological properties of the protio molecules;³ however, to the best of our knowledge, only one fluoro-containing flavanone has been reported to be synthesized from its direct protio compound 2,3-dihydro-4H-1-benzopyranone in the literature.⁴ As a result, it is desirable to devise novel methods to allow easy access to fluoro-containing flavanones in view of their great

TABLE 1. Effect of Catalysts and Additives on the Knoevenagel Reaction of **1a** and Benzaldehyde^a

entry	catalyst	solvent	yield (%) ^b	
			2	3
1	L-proline	EtOH	90	trace
2 ^c	L-proline	EtOH	trace	90
3	pyrrolidine	EtOH	trace	87
4	piperidine	EtOH	trace	83
5 ^d	piperidine	EtOH	trace	85
6	L-proline	CH ₂ Cl ₂	trace	trace
7	L-proline	toluene	trace	trace
8	L-proline	THF	82	8
9	L-proline	CH ₃ CN	59	trace
10	L-proline	H ₂ O	trace	trace

^a **1a**/benzaldehyde = 1:1 in 1.5 mL of solvents. ^b Isolated yield after flash chromatography. ^c 60 mg of MS 4 Å was used as additive. ^d 20 mol % of CH₃COOH was added as additive.

potential utility in biological and pharmaceutical studies, and the development of tandem procedures would well serve this purpose.

Recently, Ma has reported the synthesis of fluorinated indanones via a triple cascade Knoevenagel condensation/Nazarov cyclization/electrophilic fluorination reaction of aromatic β -ketoesters and aldehydes.⁵ However, stoichiometric Lewis acids were required in this system to effect the reaction. On the other hand, Scheidt has reported the organocatalyzed enantioselective synthesis of flavanones via the use of alkylidene β -ketoesters **2a** (preformed via Knoevenagel condensation), which was presumed to be able to enhance the reactivity of the conjugate acceptor and favor the flavanone products over the acyclic chalcones.⁶ Moreover, a number of electrophilic fluorinating agents with a N–F structure have been employed to introduce the fluorine atom into organic molecules,⁷ and the electrophilic fluorination reaction of β -ketoesters with these fluorinating reagents is also well-documented.⁸ On the basis of these studies and as a part of our continued interests in the synthesis of fluorinated heterocyclic compounds,⁹ we reasoned

(5) (a) Cui, H.-F.; Dong, K.-Y.; Zhang, G.-W.; Wang, L.; Ma, J.-A. *Chem. Commun.* **2007**, 2284–2286. (b) Nie, J.; Zhu, H. W.; Cui, H.-F.; Hua, M.-Q.; Ma, J.-A. *Org. Lett.* **2007**, 9, 3053–3056.

(6) Biddle, M. M.; Lin, M.; Scheidt, K. A. *J. Am. Chem. Soc.* **2007**, 129, 3830–3831.

(7) For excellent reviews, see: (a) Wilkinson, J. A. *Chem. Rev.* **1992**, 92, 505–519. (b) Rozen, S. *Acc. Chem. Res.* **1996**, 29, 243–248. (c) Lal, G. S.; Pez, G. P.; Syvret, R. G. *Chem. Rev.* **1996**, 96, 1737–1755. (d) Rozen, S. *Chem. Rev.* **1996**, 96, 1717–1736. (e) Taylor, S. D.; Kotoris, C. C.; Hum, G. *Tetrahedron* **1999**, 55, 12431–12477. (f) Ma, J.-A.; Cahard, D. *Chem. Rev.* **2004**, 104, 6119–6146. (g) Ma, J.-A.; Cahard, D. *J. Fluorine Chem.* **2007**, 128, 975–996.

(8) (a) Barnette, W. E. *J. Am. Chem. Soc.* **1984**, 106, 452–454. (b) Umemoto, T.; Fukami, S.; Tomizawa, G.; Harasawa, K.; Kawada, K.; Tomita, K. *J. Am. Chem. Soc.* **1990**, 112, 8563–8575. (c) Takeuchi, Y.; Suzuki, T.; Satoh, A.; Shiragami, T.; Shibata, N. *J. Org. Chem.* **1999**, 64, 5708–5711. (d) Hintermann, L.; Togni, A. *Angew. Chem., Int. Ed.* **2000**, 39, 4359–4362. (e) Hamashima, Y.; Yagi, K.; Takano, H.; Tamas, L.; Sodeoka, M. *J. Am. Chem. Soc.* **2002**, 124, 14530–14531. (f) Ma, J.-A.; Cahard, D. *Tetrahedron: Asymmetry* **2004**, 15, 1007–1011. (g) Shibata, N.; Ishimura, T.; Nagai, T.; Kohno, J.; Toru, T. *Synlett* **2004**, 1703–1706. (h) Ma, J.-A.; Cahard, D. *J. Fluorine Chem.* **2004**, 125, 1357–1361. (i) Hamashima, Y.; Sodeoka, M. *Synlett* **2006**, 1467–1478.

* Corresponding author. Fax: 0086-21-64166128.

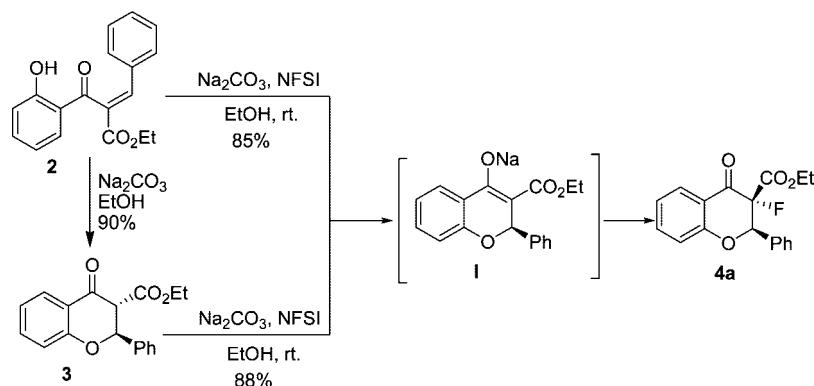
(1) (a) Harborne, J. B., Ed. *The Flavonoids: Advances in Research Since 1980*; Chapman and Hall: New York, 1988. (b) Harborne, J. B.; Williams, C. A. *Nat. Prod. Rep.* **1995**, 12, 639–657. (c) Chang, L. C.; Kinghorn, A. D. In *Bioactive Compounds from Natural Sources: Isolation Characterisation and Biological Properties*; Tringali, C., Ed.; Taylor & Francis Ltd.: London, UK, 2001; Chapter 5. (d) *Flavonoids: Chemistry, Biochemistry and Applications*; Andersen, Ø. M., Markham, K. R., Eds.; Taylor & Francis Ltd.: London, UK, 2006.

(2) (a) Kabbe, H. J.; Widdig, A. *Angew. Chem., Int. Ed.* **1982**, 21, 247–256. (b) Ramadas, S.; Krupadanam, G. L. D. *Tetrahedron: Asymmetry* **2004**, 15, 3381–3391. (c) Brown, M. K.; Degrado, S. J.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2005**, 44, 5306–5310. (d) Hodgetts, K. J. *Tetrahedron* **2005**, 61, 6860–6870.

(3) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, 37, 320–330.

(4) Stavber, S.; Jereb, M.; Zupan, M. *Synthesis* **2002**, 2609–2615.

SCHEME 1. Electrophilic Fluorination of 2 or 3 To Form 4a

TABLE 2. Effect of Bases on the One-Pot Synthesis of Monofluorinated Flavanone Derivative 4a^a

entry	base	yield (%) ^b
1	none	^c
2	K ₂ CO ₃	63
3	KOH	48
4	Li ₂ CO ₃	47
5	NaOH	50
6	Na ₂ CO ₃	77

^a **1a**/benzaldehyde/NFSI = 3:3:4 in 1.5 mL of EtOH. ^b Isolated yield after flash chromatography. ^c 60 mg of MS 4 Å was used as additive.

TABLE 3. Scope of the One-Pot Reaction To Synthesize Fluorinated Flavanone Derivatives^a

entry	substrate	R ₁	R ₂	R ₃	yield of 4/% ^b
1	1a	Et	H	C ₆ H ₅	4a : 77
2	1a	Et	H	<i>p</i> -F-C ₆ H ₄	4b : 50
3	1a	Et	H	<i>p</i> -Cl-C ₆ H ₄	4c : 52
4	1a	Et	H	<i>p</i> -Br-C ₆ H ₄	4d : 79
5	1a	Et	H	<i>p</i> -Me-C ₆ H ₄	4e : 63
6	1a	Et	H	<i>p</i> -Ph-C ₆ H ₄	4f : 81
7	1a	Et	H	<i>p</i> -MeO-C ₆ H ₄	4g : 74
8	1a	Et	H	<i>p</i> -BnO-C ₆ H ₄	4h : 57
9	1a	Et	H	<i>p</i> -NO ₂ -C ₆ H ₄	4i : 64
10	1a	Et	H	<i>o</i> -Br-C ₆ H ₄	4j : 74
11	1a	Et	H	<i>m</i> -Br-C ₆ H ₄	4k : 73
12	1a	Et	H	3-BnO-4-MeO-C ₆ H ₃	4l : 57
13	1a	Et	H	furan-2-yl	4m : 85
14	1a	Et	H	pentyl	4n : 67
15	1b	<i>t</i> -Bu	H	<i>p</i> -Me-C ₆ H ₄	4o : 40
16	1b	<i>t</i> -Bu	H	<i>p</i> -Br-C ₆ H ₄	4p : 58
17	1b	<i>t</i> -Bu	H	<i>p</i> -MeO-C ₆ H ₄	4q : 50
18	1c	<i>t</i> -Bu	Me	<i>p</i> -Me-C ₆ H ₄	4r : 61

^a **1a**/benzaldehyde/NFSI = 3:3:4 in 1.5 mL of EtOH. ^b Isolated yield after flash chromatography.

that fluorinated flavanones may also be accessible through a Knoevenagel condensation/Michael addition/electrophilic fluorination sequence directly from β-ketoesters **1** and aldehydes. Herein, we report our results with this strategy.

Initially, the Knoevenagel condensation reaction of **1a** and benzaldehyde was investigated. Delightfully, it was found that

a catalytic amount of L-proline was enough to catalyze the reaction to give the desired product alkylidene β-ketoesters **2** in 90% yield (Table 1, entry 1) under very mild reaction conditions. Surprisingly, when the reaction was performed in the presence of molecular sieves 4 Å (MS 4 Å) or with piperidine or pyrrolidine as the catalyst, only the trans cyclized product **3** (the configuration of **3** was determined by ¹H NMR) was obtained (Table 1, entry 2). Subsequent screening of several other solvents revealed that EtOH was the solvent of choice (Table 1, entries 6–10). Notably, only a single diastereoisomer of **4a** was observed in both cases and its structure was confirmed by X-ray crystallographic analysis.¹⁰ Moreover, it was found in our subsequent investigation that compound **2** could be easily converted to **3** under basic conditions and both compounds could undergo facile electrophilic fluorination reaction to provide the desired monofluoro-flavanone **4a** in comparable yields and the same excellent diastereoselectivity in the presence of inorganic bases (Scheme 1); however, the product **4a** is racemic. Therefore, it is safe to say that the transformation of **2** to **4a** proceeded through **3** as an intermediate under the reaction conditions (Scheme 1), which may then form a reactive enolate **I** in the presence of bases, and the sterically hindered phenyl group would drive the electrophilic fluorinating agent NFSI to attack from the opposite plane accounting for the excellent diastereoselectivity observed in this process. Encouraged by these results, it was assumed that the Knoevenagel condensation, cyclization, and electrophilic fluorination may be done in one pot to deliver the desired monofluorinated product. The conditions of entry 1 (Table 1), namely, 20 mol % L-proline as the catalyst and EtOH as the solvent, were chosen for subsequent studies for the simplicity of the reaction system.

Next, we examined the one-pot synthesis of the monofluoro flavanone **4a** directly from β-ketoester **1a** and benzaldehyde using NFSI as the fluorinating reagent. After completion of the proline-catalyzed Knoevenagel condensation of **1a** and benzaldehyde (monitored by TLC), bases and NFSI were then added to the reaction system (Table 2). The screening of a series of inorganic bases revealed a pronounced influence on the overall yield for the different bases used and the best yield was obtained with Na₂CO₃ (Table 2, entry 6). Moreover, no desired fluorinated product **4a** was obtained in the absence of bases (Table 2, entry

(9) (a) Pang, W.; Zhu, S.; Jiang, H.; Zhu, S. *J. Fluorine Chem.* **2007**, *128*, 1379–1384. (b) Li, D.-M.; Song, L.-P.; Li, X.-F.; Xing, C.-H.; Peng, W.-M.; Zhu, S.-Z. *Eur. J. Org. Chem.* **2007**, 3520–3525. (c) Song, S.; Song, L.-P.; Dai, B.; Yi, H.; Jin, G.; Zhu, S.; Shao, M. *Tetrahedron* **2008**, *64*, 5728–5735. (d) Li, P.; Chai, Z.; Zhao, G.; Zhu, S.-Z. *Synlett* **2008**, 2547–2551.

(10) See the Supporting Information for the ORTEP structure of **4a**.

1) and in all the cases examined; the desired product **4a** was invariably obtained as a single diastereoisomer.

Subsequently, a selected spectrum of aldehydes were examined to test the scope of this tandem procedure (Table 3). Diastereoisomerically pure *trans*-monofluorinated flavanones **4a–l** were obtained in moderate to good yields for all the substituted benzaldehydes examined, irrespective of the electronic nature or positions of the substituents on the phenyl ring (Table 3, entries 1–12). Notably, heterocyclic furan-2-carbaldehyde and aliphatic aldehyde hexanal also proved to be a suitable substrate for this transformation, giving the corresponding products **4m** and **4n** in 85% and 67% yields, respectively (Table 3, entries 13 and 14). On the other hand, when β -ketoester **1b** bearing a more sterically demanding *tert*-butyl group on the ester moiety was subjected to similar reaction conditions as its ethyl counterpart **1a**, the same excellent diastereoselectivity could also be obtained with the desired products **4o–r**, albeit with a decrease in the yields (Table 3, entries 15–18).

In conclusion, we have developed a novel one-pot tandem procedure for the synthesis of a series of monofluorinated flavanones derivatives. This method is featured with mild reaction conditions, simple operation, and a good substrate scope. Efforts on the asymmetric synthesis of these compounds are underway in our laboratories.

Experimental Section

General Procedure for the One-Pot Tandem Reaction To Synthesize Fluorinated Flavanone Derivatives. *trans*-Ethyl 3-Fluoro-4-oxo-2-phenyl-3,4-dihydro-2H-chromene-3-carboxylate, **4a** (Table 3, entry 1). To a solution of **1a** (69 mg, 0.3 mmol) and benzaldehyde (32 mg, 0.3 mmol) in ethanol (1.5 mL) was added L-proline (7 mg, 20 mol %) at room temperature and the mixture was stirred for 12 h. Then sodium carbonate (37 mg, 0.4 mmol) and NFSI (110 mg, 0.4 mmol) were added sequentially to the reaction mixture. Upon completion of the reaction (monitored by TLC), the solvent was removed in vacuum and the residue was mixed with 2 mL of water, then extracted with CH₂Cl₂ (3 $\times$ 2 mL). The combined organic phases were washed with brine (5 mL) and dried over anhydrous Na₂SO₄. Filtration and concentration of

the filtrate gave the crude product, which was purified by column chromatography on silica gel (hexane/ethyl acetate 10:1) to provide the desired product **4a** (80 mg, 77% yield) as a white solid: mp 128–129 °C; ¹H NMR (300 MHz, CDCl₃) δ 8.01 (d, *J* = 7.9 Hz, 1H), 7.63 (t, *J* = 8.5 Hz, 1H), 7.52 (d, *J* = 3.0 Hz, 2H), 7.44–7.42 (m, 3H), 7.17 (t, *J* = 8.5 Hz, 2H), 5.54 (d, *J* = 7.8 Hz, 1H), 4.11–4.03 (m, 2H), 1.03 (t, *J* = 7.1 Hz, 3H); ¹⁹F NMR (282 MHz, CDCl₃) δ –175.48 (d, *J* = 8.5 Hz, 1F); ¹³C NMR (100 MHz, CDCl₃) δ 185.0 (d, *J* = 16.6 Hz), 163.6 (d, *J* = 26.1 Hz), 161.2, 137.2, 133.2, 129.6, 128.5, 128.0, 126.9, 122.7, 119.5, 118.2, 91.6 (d, *J* = 203.5 Hz), 81.7 (d, *J* = 27.6 Hz), 62.5, 13.7; IR (KBr) ν 1766, 1733, 1704, 1607, 1475, 1465, 1307, 1226 cm^{–1}; EI-MS (*m/z*) 314 (M⁺, 11%), 120 (100), 92 (18), 121 (11), 194 (10), 241 (10), 165 (7), 101 (6). Anal. Calcd for C₁₈H₁₅FO₄: C, 68.78; H, 4.81. Found: C, 68.46; H, 5.09.

trans-Ethyl 3-Fluoro-2-(4-fluorophenyl)-4-oxochroman-3-carboxylate, **4b** (Table 3, entry 2). **4b** was prepared according to the general procedure as a white solid (50 mg, 50% yield): mp 110–111 °C; ¹H NMR (300 MHz, CDCl₃) δ 7.90 (d, *J* = 7.6 Hz, 1H), 7.53 (t, *J* = 7.1 Hz, 1H), 7.42 (d, *J* = 5.6 Hz, 2H), 7.10–7.00 (m, 4H), 5.43 (d, *J* = 8.2 Hz, 1H), 4.03–3.92 (m, 2H), 0.95 (t, *J* = 6.8 Hz, 3H); ¹⁹F NMR (282 MHz, CDCl₃) δ –111.65 (m, 1F), –174.66 (d, *J* = 8.1 Hz, 1F); ¹³C NMR (100 MHz, CDCl₃) δ 184.7 (d, *J* = 17.0 Hz), 163.3 (d, *J* = 246.9 Hz), 163.4 (d, *J* = 25.7 Hz), 161.0, 137.2, 129.0 (d, *J* = 2.6 Hz), 128.7 (d, *J* = 8.4 Hz), 127.9, 122.7, 119.4, 118.0, 115.4 (d, *J* = 21.9 Hz), 91.5 (d, *J* = 201.0 Hz), 81.9 (d, *J* = 27.9 Hz), 62.5, 13.7; IR (KBr) ν 2924, 1766, 1737, 1705, 1607, 1581, 1512, 1475, 1465, 1375 cm^{–1}; EI-MS (*m/z*) 332 (M⁺, 24%), 120 (100), 92 (21), 259 (17), 212 (13), 121 (12), 268 (8), 183 (8). Anal. Calcd for C₁₈H₁₄F₂O₄: C, 65.06; H, 4.25. Found: C, 64.97; H, 4.46.

Acknowledgment. The generous financial support from the National Natural Science Foundation of China, QT Program, Shanghai Natural Science Council, and Excellent Young Scholars Foundation of NNSF is gratefully acknowledged.

Supporting Information Available: Experimental procedures, copies of ¹H NMR, ¹⁹F NMR, and ¹³C NMR spectra, characterization data for all the new compounds, and a CIF file and X-ray crystal structure data for **4a**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

JO8023818