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

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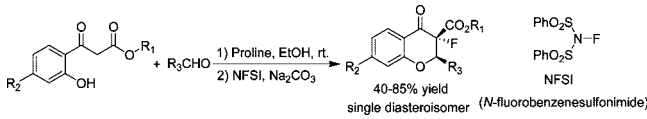
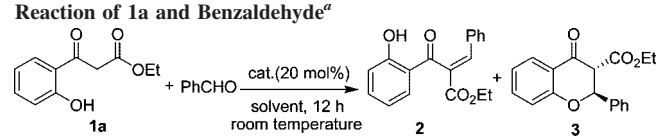


A series of fluorinated flavanones were synthesized in moderate to good yields with excellent diastereoselectivities under mild reaction conditions via a one-pot tandem procedure involving a proline-catalyzed Knoevenagel condensation, a Michael addition, and an electrophilic fluorination by NFSI.

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-4*H*-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 potential utility in biological and pharmaceutical studies, and the development of tandem procedures would well serve this purpose.

TABLE 1. Effect of Catalysts and Additives on the Knoevenagel Reaction of 1a and Benzaldehyde[a]



			yield (%)[b]	
entry	catalyst	solvent	**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_2Cl_2	trace	trace
7	L-proline	toluene	trace	trace
8	L-proline	THF	82	8
9	L-proline	CH_3CN	59	trace
10	L-proline	H_2O	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 CH_3COOH was added as additive.

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

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

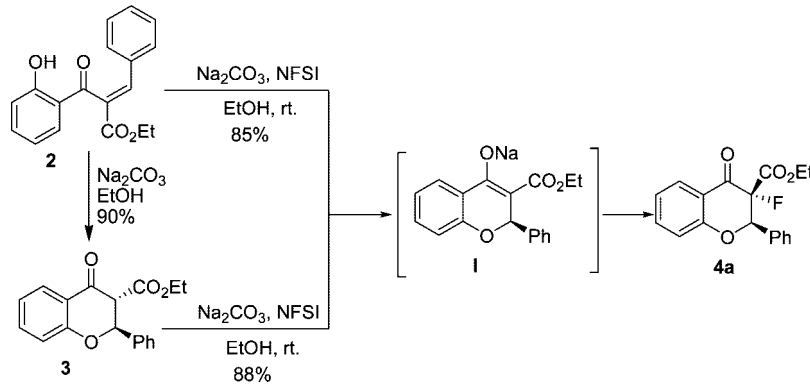
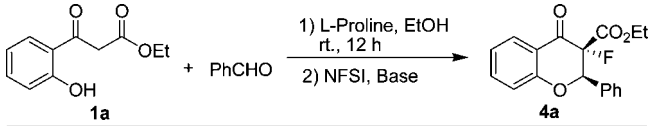


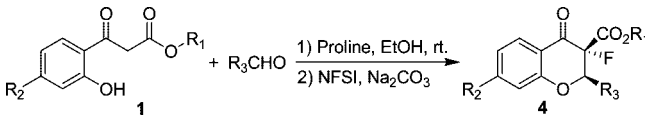
TABLE 2. Effect of Bases on the One-Pot Synthesis of Monofluorinated Flavanone Derivative 4a[a]



entry	base	yield (%)[b]
1	none	*c*
2	K_2CO_3	63
3	KOH	48
4	Li_2CO_3	47
5	NaOH	50
6	Na_2CO_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_6H_5	**4a**: 77
2	**1a**	Et	H	*p*-F-C_6H_4	**4b**: 50
3	**1a**	Et	H	*p*-Cl-C_6H_4	**4c**: 52
4	**1a**	Et	H	*p*-Br-C_6H_4	**4d**: 79
5	**1a**	Et	H	*p*-Me-C_6H_4	**4e**: 63
6	**1a**	Et	H	*p*-Ph-C_6H_4	**4f**: 81
7	**1a**	Et	H	*p*-MeO-C_6H_4	**4g**: 74
8	**1a**	Et	H	*p*-BnO-C_6H_4	**4h**: 57
9	**1a**	Et	H	*p*-NO_2-C_6H_4	**4i**: 64
10	**1a**	Et	H	*o*−Br-C_6H_4	**4j**: 74
11	**1a**	Et	H	*m*−Br-C_6H_4	**4k**: 73
12	**1a**	Et	H	3-BnO-4-MeO-C_6H_3	**4l**: 57
13	**1a**	Et	H	furan-2-yl	**4m**: 85
14	**1a**	Et	H	pentyl	**4n**: 67
15	**1b**	*t*-Bu	H	*p*-Me-C_6H_4	**4o**: 40
16	**1b**	*t*-Bu	H	*p*-Br-C_6H_4	**4p**: 58
17	**1b**	*t*-Bu	H	*p*-MeO-C_6H_4	**4q**: 50
18	**1c**	*t*-Bu	Me	*p*-Me-C_6H_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 ^{1}H 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 Na_2CO_3 (Table 2, entry 6). Moreover, no desired fluorinated product **4a** was obtained in the absence of bases (Table 2, entry

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(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 diastereosectivity 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-2*H*-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 CH_2Cl_2 (3 × 2 mL). The combined organic phases were washed with brine (5 mL) and dried over anhydrous Na_2SO_4. 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; ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{19}F NMR (282 MHz, $CDCl_3$) δ −175.48 (d, J = 8.5 Hz, 1F); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{18}H_{15}FO_4$: 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; ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{19}F NMR (282 MHz, $CDCl_3$) δ −111.65 (m, 1F), −174.66 (d, J = 8.1 Hz, 1F); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{18}H_{14}F_2O_4$: C, 65.06; H, 4.25. Found: C, 64.97; H, 4.46.

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Supporting Information Available: Experimental procedures, copies of ^{1}H NMR, ^{19}F NMR, and ^{13}C 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.

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