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Cyclodehydration and Baker-Venkataraman Rearrangement Methodologies for the Preparation of Fluorinated 4*H*-Chromones

Chloe Fernandes, Sang H. Park, Joseph Sloop*, Karla Wilmott

School of Science and Technology, Georgia Gwinnett College, 1000 University Center Lane, Lawrenceville, G.A. 30043, USA

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ABSTRACT

Trifluoromethylated and ring-fluorinated 4*H*-chromones have been prepared via cyclodehydration and *via* the baker-venkataraman rearrangement. The cyclodehydration of 4,4,4-trifluoro-1-(1-naphthol-2-yl)-1,3-butanedione was performed under a variety of base promoted and acid catalyzed processes enroute to 2-trifluoromethyl-*β*-naphthochromone. Using microwave irradiative, sonication and conventional processes, selected *o*-hydroxyaromatic ketones underwent single-pot, based promoted baker-venkataraman rearrangements with trifluoroacetic anhydride to give trifluoromethylated 4*H*-chromones in yields ranging from 50-82%. Microwave irradiation conditions allowed for yields ranging from 50-80%, which compare favorably to yields achieved *via* conventional methods (60-82%) as well as reducing reaction times by 55% compared to conventional refluxing conditions.

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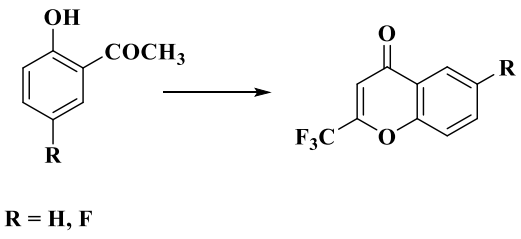
Graphical Abstract



R = H, F

*Corresponding author: E-mail: jsloop@ggc.edu, School of Science and Technology, Georgia Gwinnett College, 1000 University Center Lane, Lawrenceville, GA 30043, USA, Tel: Tel: +16784855021; Fax: +16784075938

Introduction

The preparation of heterocyclic molecules which have medicinal and industrial value are of continued interest to the pharmaceutical communities [1-9]. For example, the 4*H*-chromenone (chromone) moieties have broad applications as pharmaceuticals that possess anticancer, anti-HIV, anti-inflammatory, antioxidant and antibacterial properties [10-19].

Claisen-type condensations of ketones have been investigated for many years whereby functionalized di- and triketones are prepared *via* treatment of ketones and an ester with a strong base. Fluorinated analogs are routinely synthesized by using R_fCO_2R, $R_fCO_2COR_f$ and R_fCOX as the source of fluorine [20-27]. Ortho-hydroxyaromatic 1,3-diketones, which are precursors to 4*H*-chromones, can be cyclized under catalysis by transition metals, Lewis acids as well as Brønsted-Lowry acids and bases [7, 11-18]. Trifluoromethylated chromones may be conveniently prepared by the condensation of *o*-hydroxyaromatic ketones and trifluoroacetic anhydride *via* the baker-venkataraman (B-V) rearrangement [13].

The importance of greener synthetic methods such as solvent-free processes, aqueous reactions, microwave-mediated processes and ultrasonic irradiation prompted a broader assessment of cyclocondensation-dehydration reactions in these ketones [26]. The primary goal of this work was to compare the efficacy of several preparative routes to fluorinated examples of 4*H*-chromones from naphtholic and phenolic scaffolds. The principal novelty of this work rests on the use and comparison of green synthesis methods such as microwave and ultrasonic irradiation versus conventional reaction processes. The ketone starting materials in this study are shown in Figure 1.

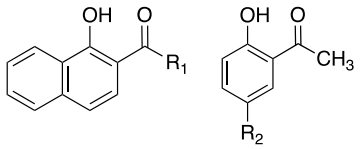


Figure 1. Ketones investigated

Experimental

Chemicals

All reagents and solvents were obtained from the aldrich chemical company, eastman kodak, or fisher chemical company and were used as purchased. Starting materials **2-4** are commercially available and were used without further purification. Compound **1** was prepared in accord with literature methods [22, 23].

Instrumentation

Melting points were obtained on an SRS digimelt MPA160 melting point apparatus and are uncorrected. NMR data were collected in $CDCl_3$ with TMS as an internal standard using a varian VXR-400 spectrometer with a broad band probe operating at 400.0 MHz for ^{1}H, 376.2 MHz for ^{19}F (C_6F_6 as an internal standard) and 100.3 MHz for ^{13}C, and/or an Anasazi-90 spectrometer operating at 90.51 MHz for ^{1}H, 84.8 MHz for ^{19}F ($CFCl_3$ as an external standard) and 22.7 MHz for ^{13}C. Gas chromatographic and mass spectral data were collected on a Shimadzu QP 20105 GC-MS instrument. IR data were collected on a thermo scientific nicolet iS5 FT-IR spectrometer (iD5 ATR) with resolutions of 2 cm^{-1}. Microwave reactions were carried out using a CEM discover microwave system with thermostatically controlled temperatures, in capped 10 mL vials. Sonication mediated reactions were carried out using a Branson 1800 ultrasonic system operating at 40 Hz with thermostatically controlled temperatures, in 50 mL round bottom flasks. Temperature control for conventional reactions was provided by a J-Kem 210 temperature controller. Radial chromatography was performed on a chromatotron using 4 mm gypsum/silica gel plates (analtech) with a gradient elution of 10-30% ethyl acetate in hexane. Flash chromatography was performed using a 2" diameter glass column loaded with 60 mesh silica gel (sigma-aldrich) using a gradient elution of 10-30% ethyl acetate in hexane.

Methods and procedures for the cyclization of 4,4,4-trifluoro-1-(1-naphthol-2-yl)-1,3-butanedione (1)

Methods A & B: A 25 mL round bottom flask equipped with a magnetic stirrer is charged with **1** (0.25 g, 0.89 mmol) and 10 mL CH_3CN. To this solution is added pyridine (Pyr) (0.072 mL, 0.89 mmol; method A) or triethylamine (TEA) (0.124 mL, 0.89 mmol; method B) and stirred for 24 h. The solvent is removed under reduced pressure, and the residue taken up in 5 mL EtOAc. The resulting solution is neutralized with 1M HCl and washed twice with distilled water (2x5 mL). The organic layer was dried over Na_2SO_4, the solvent removed under reduced pressure and the residue dried in vacuo. Chromone **1a** was not isolated from either method.

Methods C & D: Reaction vessel and quantities of reagents used were identical to methods A & B. Method C: Pyr; method D: TEA. The reaction mixture was refluxed at 80 °C for 3 h. After cooling to room temperature, the workups for these methods were identical to methods A & B. Purification of the crude product by flash chromatography gradient elution of 10-30% ethyl acetate in hexane afforded 2-trifluoromethyl-*β*-naphthochromone (**1a**). Yield: method C: 79% (0.185 g); method D: 13% (0.030 g). Colorless crystals, mp 124-126 °C (lit. [13] mp 126.4–127.0 °C). FT-IR (ATR) 1674 cm^{-1} (C=O); ^{1}H NMR (400 MHz) δ 9.89 (1H, d, J = 9 Hz); 8.18 (1H, d; J = 8 Hz); 7.91 (1H, dd, J = 7; 1 Hz); 7.78 (1H, m); 7.69 (1H,

m); 7.58 (1H, d, J = 9 Hz); 6.91 (1H, s); ^{13}C NMR (100 MHz) δ 178.2; 156.8; 149.6 (q, $^{2}J_{C\text{-}F}$ = 38 Hz); 136.5; 131.0; 129.6; 129.1; 128.3; 127.4; 126.7; 118.4 (q, $^{1}J_{C\text{-}F}$ = 276 Hz); 117.0; 113.7; 113.3; ^{19}F NMR (376 MHz) δ -70.5 (s, 3F); MS: m/z 264 (100%, M+), 236 (53%, M-CO+).

Note: For methods E-H, physical constant and spectral data obtained for **1a** were consistent with that described in paragraph 2.3.2.

Method E: A 50 mL round bottom flask equipped with a magnetic stirrer is charged with **1** (0.25 g, 0.89 mmol) and 10 mL CH_3CN. To this solution is added Pyr (0.072 mL, 0.89 mmol), the reaction flask placed into a sonicator, a reflux condenser attached and the reaction mixture heated at 69 °C (max temperature of water bath) for 3 h. After cooling to room temperature, the workup for this method was identical to methods A & B. Purification of the crude product by flash chromatography using a gradient elution of 10-30% ethyl acetate in hexane afforded **1a** in 41% yield (0.095 g).

Methods F & G: A 10 mL microwave reaction vial equipped with a magnetic stirrer is charged with **1** (0.10 g, 0.35 mmol) and 4 mL CH_3CN. To this solution is added Pyr (0.030 mL, 0.38 mmol, method F) or TEA (0.050 mL, 0.36 mmol, method G). The reaction mixture is placed into the microwave reactor and irradiated for 40 min at 80 °C, at which time a 0.1 mL aliquot was removed for analysis. Following another 40 min μwave cycle at 80 °C, the reaction mixture was allowed to cool, transferred to a 25 mL round bottom flask, the solvent removed under reduced pressure and the residue taken up in 3 mL EtOAc. The resulting solution is washed in rapid succession with 1M HCl (1x3 mL) and distilled water (2x3 mL). The organic layer was passed through a Na_2SO_4-filled pasteur filter-tip pipet, the solvent removed under reduced pressure and the residue dried in vacuo. Purification of the crude product by radial chromatography using a gradient elution of 10-30% ethyl acetate in hexane afforded **1a** in the following yields: method F: 82% (0.192 g); method G: 12% (0.028 g).

Method H: A 25 mL round bottom flask equipped with a magnetic stirrer is charged with **1** (0.25 g, 0.89 mmol) and polyphosphoric acid (PPA) (5.0 mL) and heated at 80 °C for 3 h. After cooling, the reaction mixture was neutralized with saturated $NaHCO_3$, filtered through celite, extracted with EtOAc (3x5 mL) and washed with distilled water (2x10 mL). The organic layer was dried over Na_2SO_4, the solvent removed under reduced pressure and the residue dried in vacuo. Purification of the crude products by radial chromatography using a gradient elution of 10-30% ethyl acetate in hexane afforded **1a** in 33% yield (0.077 g).

Preparation of trifluoromethylated chromones 1a, 3a and 4a [13]

Method I: A 10 mL microwave reaction vial equipped with a magnetic stirrer is charged with the ketone (0.35 mmol) and trifluoroacetic anhydride (TFAA) (0.49 mL, 0.70 mmol). To this stirred solution is added Pyr (0.030 mL, 0.38 mmol). The reaction mixture is placed into the microwave reactor and

irradiated for 40 min at 80 °C, at which time a 0.1 mL aliquot was removed for analysis. Following another 40 min μwave cycle at 80 °C, the reaction mixture was allowed to cool to room temperature, neutralized with 1M HCl, extracted with EtOAc (2x5 mL) and washed twice with distilled water (2x5 mL). The organic layer was passed through a Na_2SO_4-filled pasteur filter-tip pipet, the solvent removed under reduced pressure and the residue dried in vacuo. The desired chromone was purified by radial chromatography using a gradient elution of 10-30% ethyl acetate in hexane.

2-trifluoromethyl-*β*-naphthochromone (1a), yield: 50% (0.041 g)

2-trifluoromethylchromone (**3a**). Colorless crystals, mp: 94.0–95.9 °C (lit. [13] mp: 95–97 °C); yield: 80% (0.060 g); FT-IR (ATR) 1674 cm^{-1} (C=O); ^{1}H NMR (90.5 MHz): δ 8.19 (1H, m), 7.75 (1H, m), 7.53 (1H, d, J = 8 Hz), 7.46 (1H, m), 6.70 (1H, s); ^{13}C NMR (22.7 MHz) δ 176.5; 155.1; 152.0 (q, $^2J_{C-F}$ = 38 Hz); 134.7; 126.2; 125.9; 124.0; 118.8 (q, $^1J_{C-F}$ = 273 Hz, CF_3); 118.2; 110.5; ^{19}F NMR (84.8 MHz): δ -70.4 (3F, s); MS: m/z 214 (100%, M+), 186 (55%, M-CO+).

6-Fluoro-2-trifluoromethylchromone (**4a**). Colorless crystals, mp: 75.1-77.0 °C (lit. [13] mp 76.5 °C); Yield: 60% (0.049 g); FT-IR (ATR): 1676 cm^{-1} (C=O); ^{1}H NMR (90.5 MHz): δ 7.75 (1H, dd, J = 8; 3 Hz); 7.49 (1H, dd, J = 9; 4 Hz); 7.42 (1H, m); 6.64 (1H, s); ^{13}C NMR (22.7 MHz) δ 176.2; 159.8 (d, $^1J_{C-F}$ = 250 Hz); 152.4 (q, $^2J_{C-F}$ = 38 Hz); 151.0; 125.0; 123.3; 120.1; 118.2 (q, $^1J_{C-F}$ = 272 Hz); 112.1; 109.4; ^{19}F NMR (84.8 MHz): δ -115.2 (1F, m); -71.0 (3F, s); MS: m/z 232 (100%, M+), 214 (50%, M-CO+).

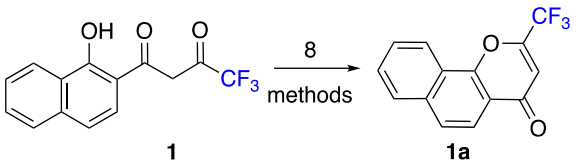
Method J: Procedure conducted as in method I with the addition of 1.6 mL CH_3CN as reaction solvent. Workup and purification conducted according to method F provided chromone products in the following yields: **1a**: 60% (0.049 g); **3a**: 82% (0.061 g); **4a**: 65% (0.053 g).

Method K: A 10 mL round bottom flask equipped with a magnetic stirrer was charged with **1**, **3** or **4** (0.89 mmol) and TFAA (1.25 mL, 1.8 mmol). To this solution was added Pyr (0.072 mL, 0.89 mmol) and heated at 80 °C for 3 h. Workup and purification conducted according to method I provided chromone products in the following yields: **1a**: 61% (0.143 g); **3a**: 80% (0.152 g); **4a**: 64% (0.132 g).

Results and discussion

Cyclodehydration of 4,4,4-trifluoro-1-(1-naphthol-2-yl)-1,3-butanedione (1)

This part of the investigation focused on determining the most efficacious method for the base- and acid-promoted cyclodehydration of diketone **1** enroute to 2-trifluoromethyl-*δ*-naphthochromone. The mild bases pyridine and triethylamine were selected due to their known non-nucleophilicity. Polyphosphoric Acid (PPA), known for its dehydration ability in solvent-free processes, was also chosen for the study. See Scheme 1.



Method	Process	% Yield (1a)
A	**C**[a]	0[e]
B	**C**	0[e]
C	**C**	79
D	**C**	13
E	**S**[b]	41
F	**M**[c]	[56][f] (82)[g]
G	**M**	[8][f] (12)[g]
H	**C/SFR**[d]	33

[a] Conventional, [b] Sonication, [c] Microwave, [d] Solvent-Free Reaction, [e] Intermediate product observed in ^{19}F NMR, [f] [ ]= yield of **1a** after 1x40 minute μwave cycle, [g] ( )= yield of **1a** after 2x40 minute μwave cycles

Scheme 1. 2-trifluoromethyl-β-naphthochromone formation *via* cyclodehydration

The conventional base-promoted processes A and B were conducted to assess whether cyclodehydration could be effected at room temperature. As indicated, no chromone product was formed after 3 hr. However, ^{19}F NMR conducted on a solution of the residue obtained from method A showed two -CF_3 signals peaks in a 1:1.3 ratio. The signal at -71.6 ppm corresponds to the enol form of **1** [23, 28-29], while the signal at -86.5 ppm (present in the larger proportion), is likely attributable to the structure (**1-Int-I**) depicted in Figure 2 [25]. Method B showed an enol:**1-Int-I** ratio of 1:0.7.

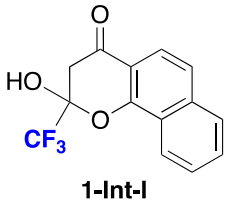


Figure 2. 2-hydroxy-2-trifluoromethyl-β-naphthochromanone pre-dehydration intermediate

Whereas, while the refluxing conditions of conventional methods C and D were necessary to provide **1a**, the data show that TEA was only 1/5 as effective as pyridine in promoting the cyclodehydration. As expected, the lower temperature used in the sonication method (E) led to a more modest yield of **1a** than method C. The microwave processes F and G again highlighted the efficacy of pyridine over TEA for cyclodehydration. The yields were comparable to those obtained for the refluxing conventional reactions. Additionally, the overall reaction time was reduced by 55%.

Based on spectroscopic data which is consistent with the observed formation of the intermediate shown in Figure 2, a plausible mechanism for the base promoted formation of 2-trifluoromethyl-*β*-naphthochromone is proposed and presented in Figure 3 [30].

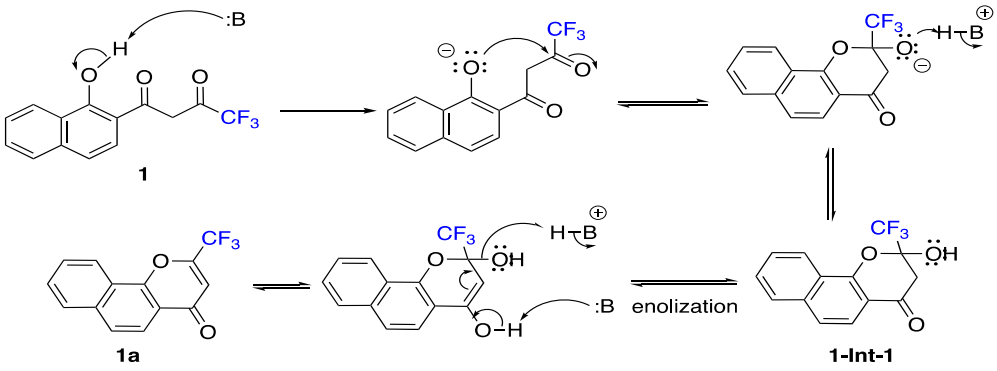
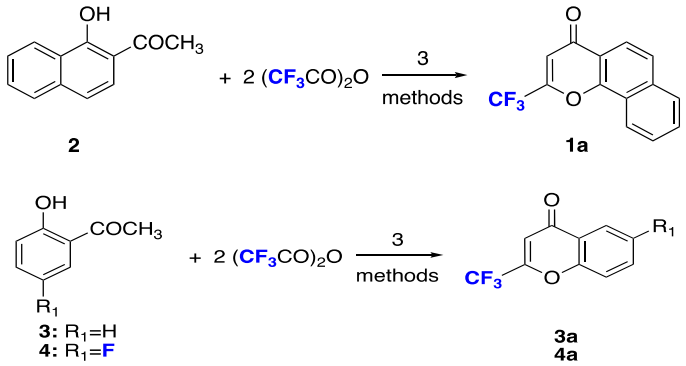


Figure 3. Mechanism for the formation of *β*-naphthochromone **1a**

Finally, the PPA-mediated method H provided **1a** in lower yields than the pyridine-promoted methods C, E and F. It is not clear at this point why the PPA-catalyzed cyclodehydration was not as effective as the pyridine promoted methods.

Baker–venkataraman (B-V) rearrangements-routes to functionalized chromones

Based on the efficacy of pyridine as well as the demonstrated need for elevated temperatures to effect the cyclodehydration of **1**, we undertook B-V rearrangements of *o*-hydroxyaromatic ketones **2**-**4** and trifluoroacetic anhydride (TFAA) using pyridine (Pyr) at 80 °C to prepare the trifluoromethylated chromones. A combination of solvent-free processes and microwave irradiation were employed to minimize reaction time, limit waste stream production and maximize atom economy. Scheme 2 shows the scope of the reactions studied and Table 2 provides a comparison of yields obtained for methods I-K.



Scheme 2. Trifluoromethylated chromone formation

Table 1. Trifluoromethylated chromone yields

Ketone	Method	Process	Product	Yield[a,b]
2	I	M/SFR	**1a**	[35][c] (50)[d]
	J	M		[45][c] (60)[d]
	K	C/SFR		61
3	I	M/SFR	**3a**	[46][c] (80)[d]
	J	M		[45][c] (82)[d]
	K	C/SFR		80
4	I	M/SFR	**4a**	[41][c] (60)[d]
	J	M		[42][c] (65)[d]
	K	C/SFR		64

[a] Yields determined by GC/MS. [b] CF_3 incorporation determined by ^{19}F NMR, [c] [ ]= yield after 1x40 min μwave cycle. [d] ( )= yield after 2x40 min μwave cycles

Method I, the microwave-mediated, solvent-free method investigated, proved effective in producing the trifluoromethyl chromones in yields comparable to both the microwave-mediated method J and conventional method K. The slightly lower yield of chromone **1a** may likely be due, at least in part, to the diminished solubility of starting solid ketone 2 in the PYR-TFAA solution compared to the liquid ketone 3 and solid ketone 4. Method J, which contained CH_3CN as solvent, enhanced the yield of **1a** by 20%, but provided smaller improvements in the yields of **3a** (2.5%) and **4a** (8.3%).

The solvent-free, conventional refluxing method K produced the desired chromones in yields similar to those obtained from methods I and J. During the preparation of **4a**, an aliquot from the reaction solution was analyzed by ^{19}F NMR at 80 minutes. Figure 4 shows the ^{19}F signals that identify the intermediate species as well as the final product [23-28]. The 4-Int-II intermediate is similar in structure to that of the intermediate discussed in section 3.1 (Figure 2).

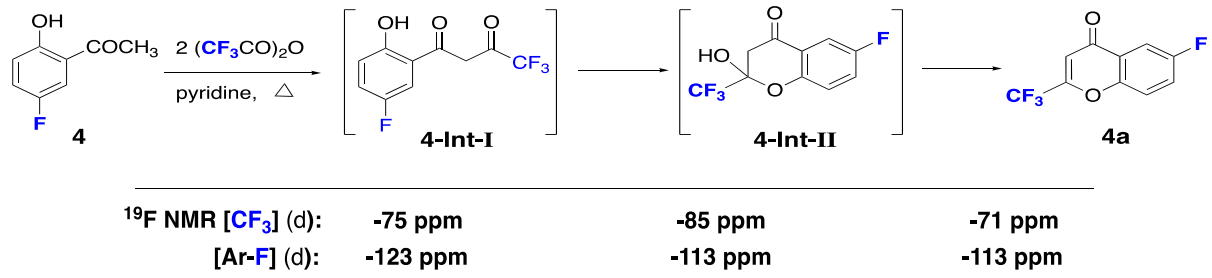


Figure 4. Monitoring chromone 4a formation by ^{19}F NMR

In view of this spectroscopic evidence, a mechanism that is consistent with the formation of these intermediate products and which leads to the formation of **4a** is proposed and presented in Figure 5 [28-30].

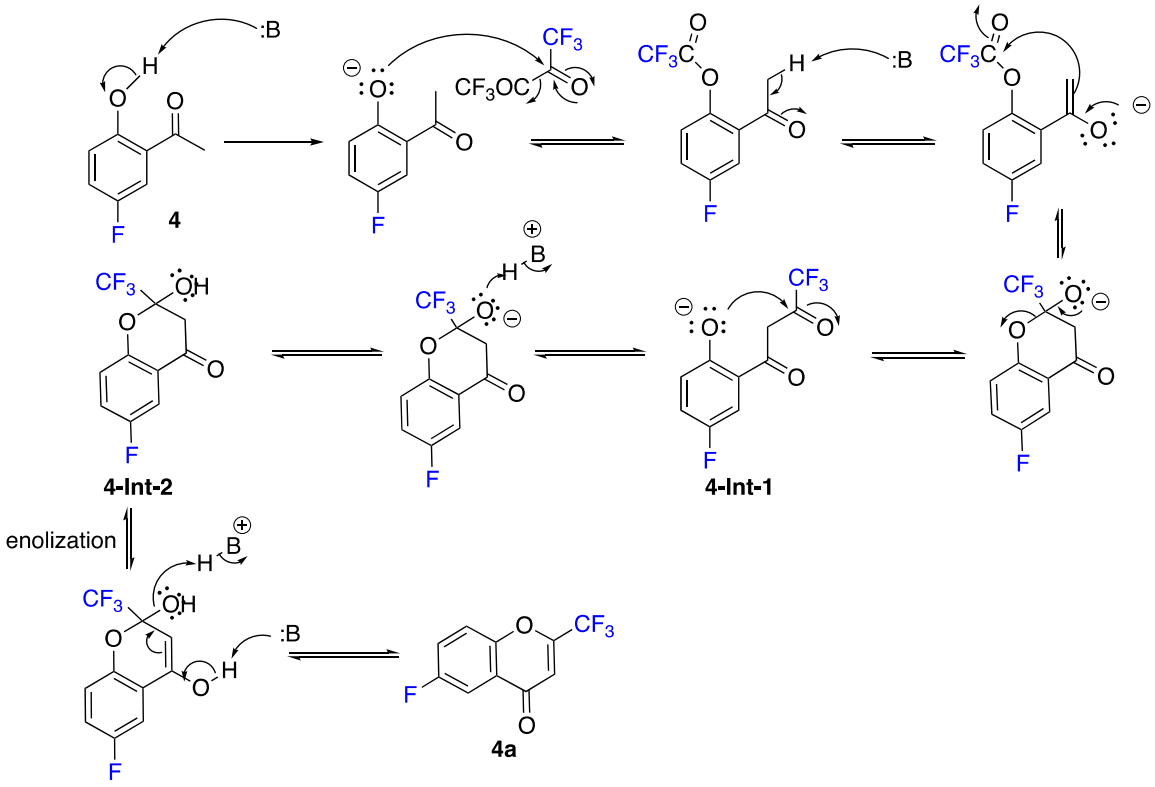


Figure 5. Mechanism for the formation of chromone **4a**

Future work may include a kinetic study on this rearrangement to experimentally establish the stepwise pathway proposed for this baker-venkataraman rearrangement as well as ascertain the effect of fluorine on the rate of cyclization and dehydration.

Conclusions

This methodological study has shown that both trifluoromethylated and ring-fluorinated, trifluoromethylated 4*H*-chromones can be prepared efficiently by either cyclodehydration of *o*-hydroxyaromatic 1,3-diketones or *via* a baker-venkataraman rearrangement of *o*-hydroxyacetophenones. The environmentally responsible, solvent-free, microwave mediated processes we have described in this work enable preparation of chromone products in yields comparable to those of the conventional reactions. These green processes limit waste stream production by minimizing solvent usage and reducing energy expenditure.

Principal findings of this work include:

- Pyridine is 5 times more effective than TEA and more than 2.5 times as effective as PPA in the promotion of 4*H*-chromone formation.

- Yields of fluorinated 4*H*-chromones *via* pyridine-promoted, microwave irradiative methods range from 50-82%, comparing favorably to yields achieved by conventional methods (60-80%).
- Microwave processes shorten reaction times by 55%, thus reducing energy expenditure over conventional processes.

Acknowledgments

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