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Insight into the Mechanism of the Pechmann Condensation Reaction Using NMR

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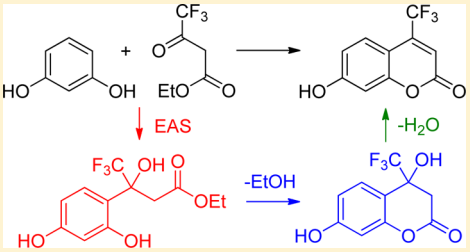
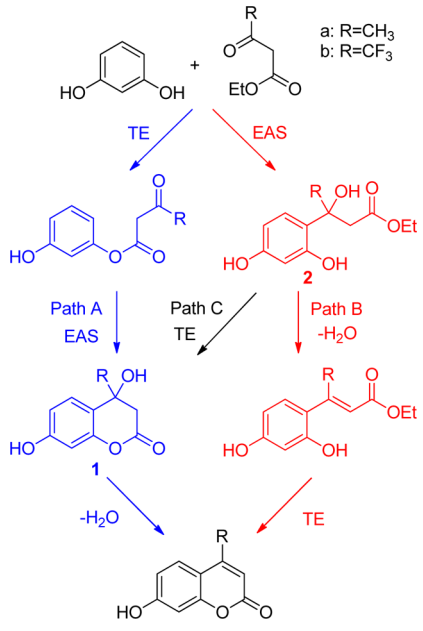
Supporting Information

ABSTRACT: The mechanism of the Pechmann condensation is still controversial despite the technological and biochemical importance of coumarins. Here, we present NMR evidence for a mechanism featuring the sequence of initial electrophilic aromatic substitution followed by trans-esterification and a final dehydration. This mechanism has been convincingly defined and supported by the temporal evolution of two key intermediates which could be purified and identified.



The Pechmann condensation reaction,[1] which allows the synthesis of coumarins by reaction of phenols with β-keto esters, has received significant attention as a synthetically useful strategy in organic synthesis. The Pechmann reaction is a one-pot reaction that is believed to proceed through three steps; electrophilic aromatic substitution (EAS), transesterification (TE, −EtOH), and dehydration ($-H_2O$), but the order of the steps is unknown (Scheme 1).[2] While many scientists have proposed mechanisms for this reaction, starting with resorcinol and ethyl acetoacetate (Scheme 1, R = CH_3), no one has been able to support their mechanism with identification of intermediates.[3−5]

Scheme 1. Possible Mechanisms for the Pechmann Condensation Reaction



Tyagi et al.[6] used GC to monitor the reaction of 7-substituted 4-methylcoumarins for conversion and selectivity. However, they did not report detecting any intermediates, only byproducts that were formed at higher reaction time and temperature. In 2010, Calvino-Casilda et al.[7] used Raman spectroscopy to monitor the reaction of resorcinol and ethyl acetoacetate in real time. They were unable to observe any intermediates. Daru and Stirling[3] performed a theoretical study on the Pechmann reaction of 7-hydroxy-4-methylcoumarin and determined that all three paths are relatively equivalent and therefore possible.

The Pechmann reaction is most commonly used to combine activated phenols with ethyl acetoacetate to form 4-methylcoumarin derivatives. When ethyl 4,4,4-trifluoroacetoacetate is used as the β-keto ester to form 7-hydroxy-4-(trifluoromethyl)coumarin (HFC), the reaction tends to be sluggish, either the yield is low,[8] or the reaction requires a higher catalyst load.[9] Previously, in trying to understand the lower yield of the trifluoromethyl derivatives, a possible intermediate, 4,7-dihydroxy-4-(trifluoromethyl)chroman-2-one **1b** (Figure 1), was isolated. It was determined that if the reaction was heated to a higher temperature (>80 °C), this compound **1b** was not isolated.[10] Preliminary studies on the viability of using ^{19}F and ^{1}H NMR to monitor this reaction are described below.

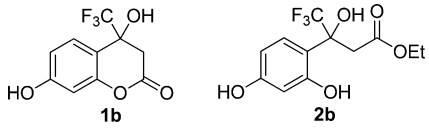


Figure 1. Intermediates isolated in the synthesis of 7-hydroxy-4-(trifluoromethyl)coumarin.

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The reaction of ethyl 4,4,4-trifluoroacetoacetate and resorcinol with iodine catalyst in toluene can be monitored by ^{19}F NMR. At the start of the reaction there are two main peaks (−75.8 and −79.9 ppm) and a few minor peaks in the ^{19}F NMR spectra coming from tautomerization of ethyl 4,4,4-trifluoroacetoacetate (Figure 2A).[11,12] As the reaction proceeds,

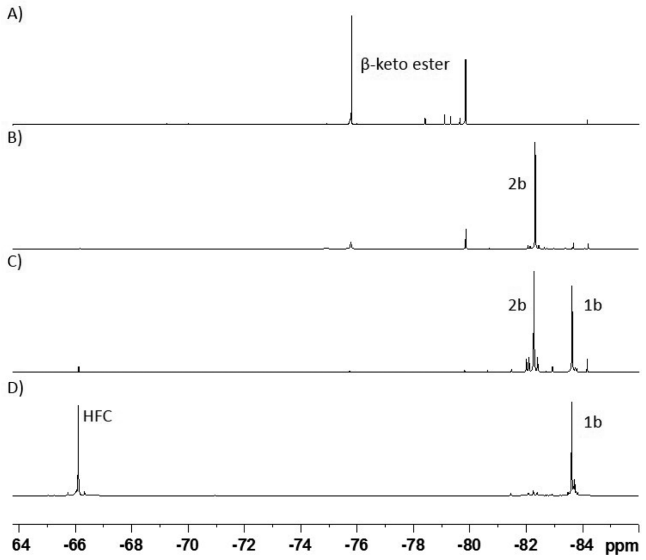

Figure 2. ^{19}F NMR spectra from the synthesis of HFC at (A) start of the reaction, (B) 2 h, 70 °C, (C) 5 h, 90 °C, and (D) overnight, 90 °C.

the *β*-keto ester peaks are significantly reduced. Initially, a peak at −82.3 ppm appears (Figure 2B). When the temperature is increased above 80 °C, a second peak appears at −83.7 ppm, resulting from compound **1b** (Figure 2C). After the reaction is heated overnight, the peak at −82.3 ppm decreases dramatically and the product (HFC) peak at −66.2 ppm is a major peak (Figure 2D).

Observation of this new peak at −82.3 ppm in the ^{19}F NMR spectra of the reaction led us to investigate the structure of this compound. Through monitoring the reaction over time at various temperatures we were able to tailor the reaction conditions to enhance the production of this new compound (Table 1). Running the reaction between 50 and 80 °C yielded this new compound as the major component. This compound is heat labile therefore identification depended heavily on NMR

Table 1. Optimization Conditions for 2b

		yield[a] (%)		
time (h)	*T* (°C)	**2b**	**1b**	**HFC**
1	50	1	0	0
2	50	8	0	0
1	60	38	0	0
2	60	80	3	0
3	60	87	4	0
1	70	81	4	0
2	70	86	8	0
3	70	80	18	0
1	80	82	7	1
2	80	82	11	1
3	80	81	17	1

[a]Determined by ^{19}F NMR.

experiments (^{1}H, ^{13}C and 2D (HSQC and HMBC) to determine the structure of compound **2b** (Figure 1).

Characterization of compound **2b** by ^{1}H−^{13}C HSQC revealed the single carbon-13 signal at δ_C 38.4 ppm correlated to the diastereotopic methylene protons at δ_H 2.90 and 3.68 ppm. The ethyl ester signals at δ_H 1.04 and 3.93 ppm corresponded to carbon signals δ_C 13.8 and 59.6 ppm, respectively. The aromatic protons at δ_H 6.22, 6.23, and 7.24 ppm corresponded to carbon signals δ_C 106.2, 102.9, and 130.1 ppm, respectively. The three hydroxyl peaks at δ_H 6.69, 9.33, and 9.69 ppm did not correlate to any carbon peaks, as expected.

Monitoring the reaction by ^{19}F NMR limits this method to only fluorinated compounds. The reaction can also be monitored by ^{1}H NMR due to a number of distinct resonances displayed by each component in solution. At the start of the reaction there are a grouping of quartets at 4.0−4.2 ppm from the tautomerization of ethyl 4,4,4-trifluoroacetoacetate. As compound **2b** forms, a pair of doublets are observed at 2.9 and 3.5 ppm arising from the diastereotopic methylene protons and a quartet at 3.9 ppm from the ethyl ester. Compound **1b** has a pair of doublets at 3.1 and 3.3 ppm, arising from its diastereotopic methylene protons. As compound **2b** is converted to compound **1b**, ethanol is produced, which can be observed by a quartet around 3.4 ppm. All peaks are well resolved and therefore can be integrated to measure conversion. The solvent peaks from toluene do not interfere with any of these peaks but water can interfere with one of the doublets from compound **1b.**

In the range of 9−11 ppm, the aromatic hydroxyl peaks can be used to monitor the progress of the reaction. Resorcinol has a single hydroxyl peak at 9.1 ppm. Compound **2b** has two phenolic peaks at 9.3 and 9.7 ppm. Compound **1b** has a single aromatic hydroxyl around 10.1 ppm. HFC has a phenolic peak around 11 ppm. Caution should be used in this range because the peaks arise from acidic protons where the peak position and width is highly concentration dependent.

Building upon the success of monitoring the synthesis of HFC starting with ethyl 4,4,4-trifluoroacetoacetate, we attempted to apply this method to the synthesis of 7-hydroxy-4-methylcoumarin with ethyl acetoacetate. The reaction with ethyl acetoacetate proceeds quicker and with less catalyst.[9] Even at lower temperatures, approaching the solubility limit of resorcinol, well-defined intermediates were not observed. Our results are consistent with previous experimental literature.[7,6] The theoretical study done with ethyl acetoacetate by Daru and Stirling[3] shows that in the Gibbs free energy profile the intermediates are not very stable and not separated from the next step by a large energy barrier and , therefore, less likely to be observable.

The observation and isolation of compounds **2b** and **1b** imply that the synthesis of HFC by the Pechmann condensation reaction proceeds through an electrophilic aromatic substitution reaction followed by transesterification ending in dehydration (path C). To determine if this path applies to all coumarins synthesized by the Pechmann condensation reaction, the synthesis of a wide variety of coumarins will be monitored. It is possible that the strong electron-withdrawing effects of the CF_3 group may force the reaction to take a specific mechanistic path. A large number of catalysts have been shown to be effective for this reaction, and different types of catalyst may proceed through a different

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mechanistic path. Therefore, the role of all types of catalysts used for the Pechmann reaction will be further investigated.

NMR is increasingly being used in process development as a way to provide in situ analysis and real time data on the progress of a reaction and identify undesired byproducts.[13] Our experiment adds to the literature on NMR reaction monitoring by observing the formation and disappearance of intermediates to determine the mechanism of the reaction.[14] Monitoring a reaction by NMR also helps to identify reaction conditions that yield each intermediate and can be used for kinetic studies.[15]

EXPERIMENTAL SECTION

The procedure has been modified from previous literature.[10] Iodine (317 mg, 1.25 mmol, 25 mol %) was added into a mixture of resorcinol (550 mg, 5 mmol), ethyl 4,4,4-trifluoroacetoacetate (880 μL, 6 mmol), and trifluorotoluene (60 μL, 0.5 mmol) in toluene (1 mL). The reaction was heated and stirred. A 50 μL sample was removed at designated time periods and diluted with 600 μL of DMSO-d_6, and NMR spectra were acquired. Upon completion, the reaction mixture was cooled to room temperature, diluted with 10 mL of ethyl acetate, and washed with 10 mL of distilled water. The combined organic layers were dried over anhydrous sodium sulfate and the solvent removed under vacuum. Purification was performed via column chromatography (hexane/ethyl acetate, 8:2). ^{1}H, ^{13}C{^{1}H}, ^{19}F, ^{1}H−^{13}C HSQC, and ^{1}H−^{13}C HMBC NMR spectra were obtained for both intermediates.

Ethyl 3-(2,4-Dihydroxyphenyl)-4,4,4-trifluoro-3-hydroxybutanoate (2b). The reaction was heated at 60 °C and stirred for 3 h: clear oil (0.94 g, 63%); R_f = 0.33 (hexane/EtOAc, 1:1); IR (film) ν 3360, 2988, 1713, 1627, 1603, 1167 cm^{-1}; ^{1}H NMR (500 MHz, DMSO) δ 1.04 (t, J = 7.10 Hz, 3H, CH_3), 2.90 (d, J = 15.9 Hz, 1H), 3.68 (d, J = 15.9 Hz, 1H), 3.93 (q, J_1 = 7.10 Hz, J_2 = 2.10 Hz, 2H, CH_2), 6.23 (m, 2H), 6.69 (s, 1H, OH), 7.24 (d, 1H, J = 9.2 Hz), 9.33 (s, 1H, OH), 9.69 (s, 1H, OH); ^{13}C{^{1}H} NMR (125 MHz, DMSO) δ 13.8, 38.4, 59.6, 74.7 (q, J = 28.6 Hz), 102.9, 106.2, 112.3, 125.6 (q, J = 28.6 Hz), 130.1, 156.1, 158.3, 168.5; ^{19}F NMR (DMSO) δ −82.3 ppm. The sample was thermally unstable for MS.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01802.

^{1}H, ^{13}C, ^{19}F, HSQC, and HMBC NMR spectra of compound **2b** (PDF)

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Notes

The authors declare no competing financial interest.

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