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Synthesis of 7-Alkoxy-4-trifluoromethylcoumarins via the Pechmann Condensation Reaction Using Catalytic Iodine

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Abstract

Coumarin derivatives are common compounds used widely in the scientific community, ranging from pharmaceutical to commercial applications. 7-Alkoxy-4-trifluoromethylcoumarins are used in fluorometric enzyme assays and to make laser dyes. Due to the fact that these coumarin derivatives are relatively expensive to purchase and are found in small quantities, it is advantageous to synthesize these compounds both cost effectively and in larger quantities. This paper reports the synthesis of several 7-alkoxy-4-trifluoromethylcoumarins via the Pechmann condensation reaction using molecular iodine as a catalyst. 7-Hydroxy-4-trifluoromethylcoumarin, 7-methoxy-4-trifluoromethylcoumarin, 7-ethoxy-4-trifluoromethylcoumarin, and 7-benzyloxy-4-trifluoromethylcoumarin have been successfully synthesized (71%, 37%, 41%, 24%, respectively). All coumarin derivatives were purified through flash chromatography and confirmed by NMR spectroscopy.

Keywords: Coumarin, Pechmann Condensation

1. Background

Coumarins have found widespread use in biochemical and commercial applications, such as fragrances, cosmetics, pharmaceuticals, agrochemicals and dyes. When coumarins contain an electron-withdrawing group, such as trifluoromethyl, at the 4-position and an electron donating group, such as alkoxy, at the 7-position (Figure 1) they are highly fluorescent. The fluorescence properties of 7-alkoxy-4-trifluoromethylcoumarins are useful for enzymatic fluorometric assays[1] and to make laser dyes[2]. These coumarins are expensive to purchase, with as little as 5 mg costing over $400 from Sigma Aldrich, and are only sold by a few companies. Therefore, there is a need to develop a high yielding, cost effective, method for synthesizing these coumarins in larger quantities from inexpensive commercially available starting materials. The hydroxy derivative, 7-hydroxy-4-trifluoromethylcoumarin (HFC), can be made efficiently and effectively from inexpensive starting materials via the Pechmann condensation reaction. This poses the question, can 7-alkoxy-4-trifluoromethylcoumarins be made in this same manner?

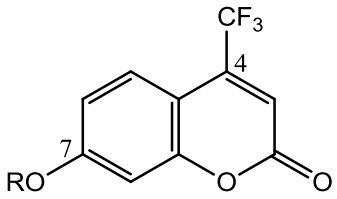


Figure 1. 7-Alkoxy-4-trifluoromethylcoumarin

The Pechmann condensation reaction is a one-step reaction which combines a phenol with a β-keto ester in the presence of a catalyst to yield the desired coumarin derivative. The original reaction used sulfuric acid to synthesize coumarin derivatives[3]. Since then, a wide variety of reagents have been shown to affect the Pechmann reaction. Here, it is reported that iodine can be used as a catalyst, minimizing the harsh conditions of sulfuric acid, to synthesize 7-alkoxy-4-trifluoromethylcoumarin derivatives (Scheme 1).

2. Materials and Methods

2.1 Materials and Instrumentation

Resorcinol, ethyl 4,4,4-trifluoroacetoacetate, ethyl acetate, and methanol were purchased from Acros Organics (Morris Plains, NJ). Resublimed iodine, hexane, toluene, and anhydrous sodium sulfate were purchased from Fischer Scientific Company (Fair Lawn, NJ). Ethanol and dichloromethane were purchased from Pharmco-AAPER (Brookfield, CT). Silica gel and TLC plates were purchased from Sorbent Technologies (Norcross, GA). 3-Methoxyphenol was purchased from Sigma Aldrich (St. Louis, MO) and 3-ethoxyphenol was purchased from Alfa Aesar (Ward Hill, MA). 3-Benzyloxyphenol was purchased from Tokyo Chemical Industry (Portland, OR) and dimethyl sulfoxide-d6 was purchased from Cambridge Isotope Laboratories, Inc. (Andover, MA).

Bruker Avance III 500 MHz spectrometer was used to record ^{1}H and ^{13}C NMR spectra in deuterated solvents. ^{1}H NMR data is reported as chemical shift (δ, ppm), multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), integration, and coupling constant (Hz), while ^{13}C is reported as chemical shift (δ, ppm). AVATAR 370 FT-IR Spectrometer was used to record infrared spectra and are reported in frequency of absorption. Hewlett Packard 5972 Series II was used to record mass spectroscopy. Thin layer chromatography (TLC) was completed using glass silica gel plates (0.25 nm, 230-400 mesh) infused with a fluorescent indicator 254 nm. Column chromatography was performed using silica gel (60Å, 40-63 μm, 230x400 mesh). Melting points were recorded with Thomas Hoover capillary melting point apparatus.

2.2 Experimental Procedure

The procedure has been modified from previous literature[4]. Iodine (25 mol%) was added into a mixture of 3-alkoxyphenol (5 mmol) and ethyl 4,4,4-trifluoroacetoacetate (6 mmol) in toluene (1 mL). The reaction was heated at 80°C and stirred for a period of 24 hours and monitored by TLC. 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 of the product was performed via flash chromatography (silica gel, hexane:ethyl acetate = 95:5 to 80:20).

7-Hydroxy-4-trifluoromethylcoumarin (HFC, 2a)[4]: white crystals (0.82 g, yield = 71%, m.p. = 173-174°C). R_f = 0.46 (dichloromethane:methanol = 20:1); NMR spectral data previously reported. ^{13}C-NMR: δ 103.1, 105.2, 112.0, 114.0, 122.9, 126.2, 140.3, 155.9, 158.9, 162.2.

7-Methoxy-4-trifluoromethylcoumarin (MFC, 2b)[5]: white solid (0.46 g, yield = 37%, m.p. = 70.8-72.1°C). R_f = 0.39 (hexane:ethyl acetate = 90:10); ^{1}H NMR spectral data previously reported. ^{13}C-NMR: δ 56.2, 101.7, 106.4, 113.2, 113.3, 122.8, 125.8, 139.6, 155.9, 158.7, 163.1; FTIR: cm^{-1} 1142, 1199, 1282, 1413, 1614, 1727, 3094.

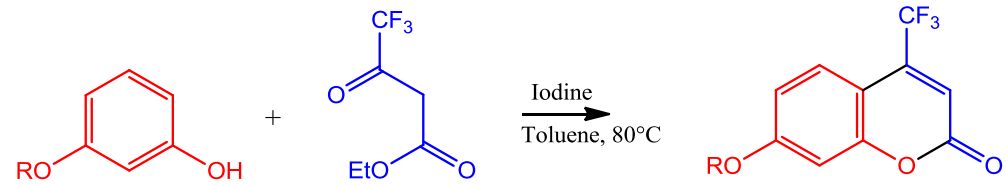
7-Ethoxy-4-trifluoromethylcoumarin (EFC, 2c): white solid (0.53 g, yield = 41%, m.p. = 63.4-64.7°C). *Rf* = 0.44 (hexane:ethyl acetate = 90:10); ^{1}H-NMR: δ 1.37 (t, $^{3}J_{2',1'}$ = 7.0 Hz, 1H), 4.18 (q, $^{3}J_{1',2'}$ = 7.0 Hz, 1H), 6.86 (s, 1H), 7.06 (dd, $^{3}J_{6,5}$ = 9.0 Hz, $^{4}J_{6,8}$ = 2.6 Hz, 1H), 7.14 (d, $^{4}J_{8,6}$ = 2.5 Hz, 1H), 7.62 (dq, $^{3}J_{5,6}$ = 9.0 Hz, $^{5}J_{5,8+3}$ = 2.0 Hz, 1H); ^{13}C-NMR: δ 14.4, 64.3, 102.0, 106.2, 113.0, 113.6, 118.4, 125.8, 139.6, 155.9, 158.5, 162.4; FTIR: cm^{-1} 1131, 1193, 1278, 1453, 1615, 1745, 3088.

7-Benzyloxy-4-trifluoromethylcoumarin (BFC, 2d): white solid (0.38 g, yield = 24%). *Rf* = 0.51 (hexane:ethyl acetate = 90:10); ^{1}H-NMR: δ 5.28 (s, 1H), 6.87 (s, 1H), 7.15 (dd, $^{3}J_{6,5}$ = 9.0 Hz, $^{4}J_{6,8}$ = 2.6 Hz, 1H), 7.25 (dd, $^{4}J_{8,6}$ = 2.6, 1H), 7.37 (t, $^{3}J_{4',3'}$ = 7.3 Hz, 1H), 7.43 (t, $^{3}J_{3',2'+4'}$ = 7.0 Hz, 2H), 7.49 (d, $^{3}J_{2',3'}$ = 7.0 Hz, 2H), 7.64 (dq, $^{3}J_{5,6}$ = 9.0 Hz, $^{5}J_{5,CF_3}$ = 2.0 Hz, 1H); ^{13}C-NMR: δ 70.2, 102.5, 106.6, 113.1, 113.9, 121.7, 125.8, 127.8, 128.0, 128.4, 136.1, 139.7, 156.0, 158.5, 162.3; FTIR: cm^{-1} 1137, 1201, 1277, 1407, 1613, 1747, 3034, 3093.

2,6-Diiodo-3-methoxyphenol (3b): yellow oil. *Rf* = 0.75 (hexane:ethyl acetate = 1:2); ^{1}H-NMR: δ 3.79 (s, 3H), 6.39 (d, $^{3}J_{4,5}$ = 8.6 Hz, 1H), 7.65 (d, $^{3}J_{4,5}$ = 8.6 Hz, 1H), 9.37 (s, 1H); ^{13}C-NMR: δ 56.7, 76.2, 79.3, 106.0, 138.5, 156.1, 159.4.

3. Results

According to literature procedure, HFC (2a) can be synthesized in 99% yield using the Pechmann condensation reaction by treating resorcinol (1a) with ethyl 4,4,4-trifluoroacetoacetate in toluene in the presence of 50 mol% iodine at 80°C for 3-12h (Scheme 1)[4]. In this reaction, only 25 mol% of iodine was used due to the molecular weight of iodine (I) being mistakenly used in calculation, causing the use of half the amount of iodine catalyst as compared to the literature. The literature reaction was monitored by TLC and purified by column chromatography, with information on the solvent systems excluded. Therefore, an initial study was done to determine the appropriate solvent system and purification conditions for both TLC and column chromatography. Various ratios of dichloromethane:methanol solvent were used ranging from (99:1-20:1). This solvent produced red/orange crystals indicative of an impure product. This system was then replaced with hexane:ethyl acetate with a ratio of 90:10. This column chromatography solvent system was able to produce a white solid, suggestive of a pure product, further confirmed by NMR. A second study varied the synthesis time of the reaction. The time was first increased to three days because no further product formation was seen after 12 hours and starting material was still present. The reaction time study concluded that no further product was produced after 24 hours, as there was no presence of the starting material and no further formation of the product spot through TLC. The highest percentage yield of 71% as well as white crystals were achieved after a 24 hour reaction through purification with the hexane:ethyl acetate solvent.



1 ethyl 4,4,4-trifluoroacetoacetate **2**

a: R= H (Resorcinol)
b: R= CH_3 (3-methoxyphenol)
c: R= CH_2CH_3 (3-ethoxyphenol)
d: R= Bz (3-benzyloxyphenol)

a: R= H (HFC)
b: R= CH_3 (MFC)
c: R= CH_2CH_3 (EFC)
d: R= Bz (BFC)

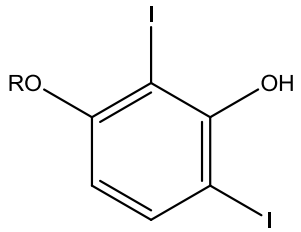
Scheme 1. General Reaction Scheme for the Pechmann Condensation Reaction of 7-Alkoxy-4-trifluoromethylcoumarins

The reaction conditions established in the HFC study were applied for the synthesis of 7-methoxy-4-trifluoromethylcoumarin (MFC), 7-ethoxy-4-trifluoromethylcoumarin (EFC), and 7-benzyloxy-4-trifluoromethylcoumarin (BFC) (Scheme 1). For the synthesis of MFC, a pure product was obtained with a yield of 37% (Table 1). Previously, MFC has only been synthesized using trifluoroacetic acid as the catalyst[5]. The synthesis of EFC produced a pure white solid with a yield of 41% (Table 1). The synthesis of EFC has not been reported in the literature before. The synthesis of BFC produced a pure white solid with a yield of 24% (Table 1). This is the first synthesis of BFC using the Pechmann condensation reaction. The only reported synthesis of BFC was by a Williamson etherification of HFC with a yield of 22%[6].

Table 1. Summary Of Synthesis Results Of 7-Alkoxy-4-Trifluoromethylcoumarin Derivatives

Product	Yield	Literature Yield for Pechmann
HFC	71%	99%[4]
MFC	37%	63% *CF_3COOH catalyst[5]
EFC	41%	no data
BFC	24%	no data

A diiodo side product has been isolated and obtained for all 7-alkoxy-4-trifluoromethylcoumarin derivatives as well as for HFC (Figure 2). This byproduct is a result of the iodine embedding itself onto the 3-alkoxyphenol starting material. The structure of this compound has been confirmed through NMR spectroscopy, with the iodides located ortho to the hydroxide. Because of this, we are unable to obtain a higher yield for our desired coumarin derivatives as the iodine is reacting with the limiting reagent. When using column chromatography, the diiodo side product is the first compound to elude from the column on the TLC plate, followed by the desired coumarin derivative.



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a: R= H
b: R= CH_3
c: R= CH_2CH_3
d: R= Bz

Figure 2. Diiodo Phenol Side Product

Figure 3 shows a carbon/proton 2D NMR displaying both the HSQC and HMBC correlations of HFC. According to NMR analysis, the carbon located at 162 ppm (C7) does not couple to the peak at 6.8 ppm (C3) as the peak at 159 ppm (C2) does because it is located fewer bonds away from C3 than C7 is from this carbon. C7 does however couple to the peak at 7.6 ppm (C5) while C2 does not. C2 and C7 were incorrectly assigned in literature to have values of 162 and 159 ppm, respectively[7]. However, as seen in figure 3, the assignments for these two carbons have been adjusted with C2 having a value of 159 ppm and C7 162 ppm.

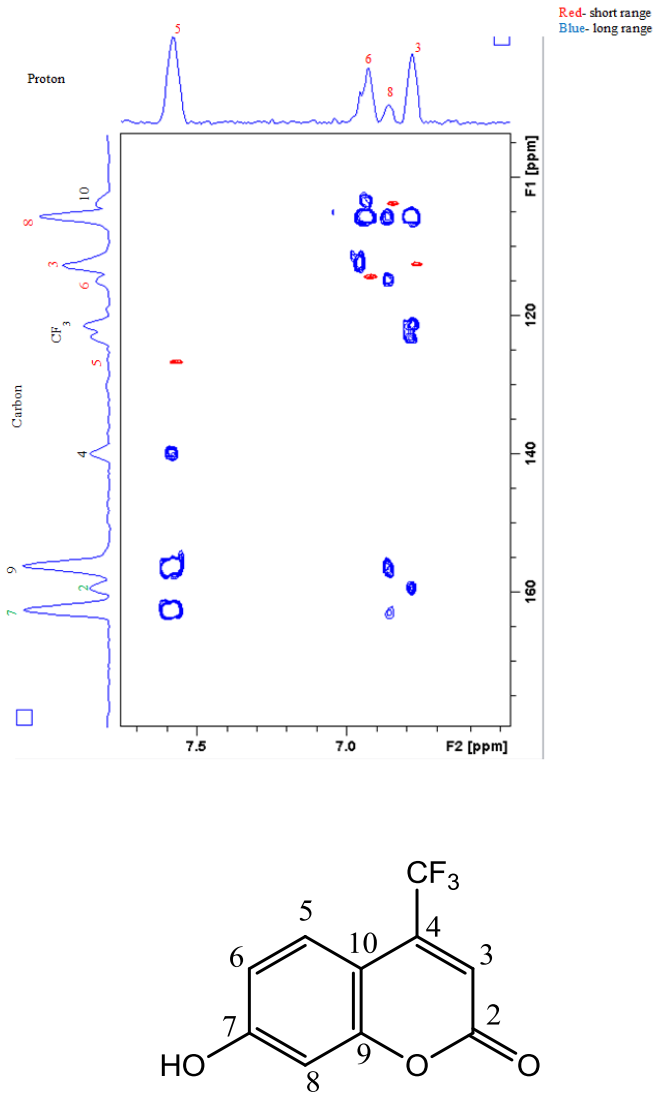

Figure 3. 2D NMR Displaying Both The HSQC and HMBC Correlations of HFC.

4. Conclusion

MFC has been successfully synthesized for the first time using iodine as the catalyst with a yield of 37%. EFC and BFC have been synthesized with a yield of 41% and 24%, respectively. The use of iodine as a catalyst is useful because it eliminated the harsh environment that sulfuric acid requires. However, due to the production of diiodo phenol side products, it is not ideal to use this catalyst to obtain the highest yield possible. It may be useful to attempt a slow addition of the iodine catalyst over a large period of time to potentially reduce the amount of side product that is being produced, and thus obtain a larger yield of the desired coumarin derivative.

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6. References

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