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Synthesis of 7-alkoxy-4-trifluoromethylcoumarins via the von Pechmann reaction catalyzed by molecular iodine

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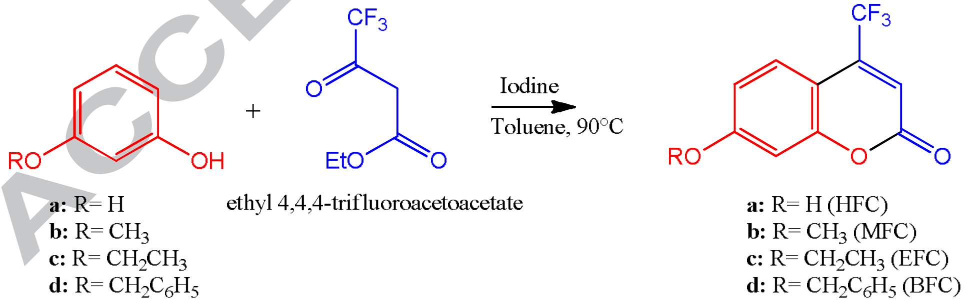
Abstract:

The synthesis of a series of 7-alkoxy-4-trifluoromethylcoumarins via the von Pechmann reaction catalyzed by molecular iodine is described. The reaction protocol is simple, inexpensive and leads to the formation of the corresponding coumarin derivatives in good yield and high purity. A key intermediate as well as several iodo byproducts were isolated.



Keywords:

4-trifluoromethylcoumarin, von Pechmann condensation, molecular iodine, fluorescent

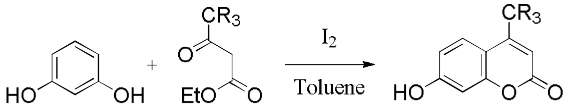
Introductions:

Coumarins, a class of bicyclic lactones, have a wide variety of uses. Some coumarin derivatives are biologically active,[1] such as the anticoagulant warfarin. Other coumarins, such as umbelliferone, fluoresce, which makes them useful as laser dyes.[2] When a coumarin contains an electron-withdrawing group, such as trifluoromethyl, at the 4-position and electron-donating group, such as alkoxy or hydroxyl, at the 7-position, the fluorescence is strengthened dramatically. Thus 7-alkoxy-4-trifluoromethylcoumarins (AFC) have good fluorescence properties and are used as fluorescent dyes.[3] These AFCs are currently used by pharmaceutical companies as synthetic substrates in fluorometric high-throughput screening assays for cytochrome P450s.[4] The synthesis and characterization of some of these compounds have never been reported in the literature and are the subject of this paper.

Various methods can be used to synthesize 4-substituted coumarin derivatives with the von Pechmann reaction[5] being the most common and versatile. This method involves the condensation of a phenol with a β-ketoester in the presence of a condensing agent. The original reaction used harsh conditions with concentrated sulfuric acid as the catalyst and solvent[5]. A wide variety of condensing agents have been developed for the Pechmann reaction but only a few of these catalysts have been used to synthesize 4-trifluoromethyl coumarins. Brønsted-Lowry acids (ex. CF_3CO_2H),[6] Lewis acids (AgOTf,[7] $Bi(NO_3)_3$,[3,8] I_2[7,9], $Mg(NTf_2)_2$,[10] $ZnCl_2$[11]), and solid acid catalysts (ex. Amberlyst-15),[12] have been used successfully to synthesize 7-hydroxy-4-trifluoromethylcoumarins (HFC). However, most of these catalysts have not been used in the synthesis of the alkoxy derivatives, AFCs. Molecular iodine has been shown to catalyze the synthesis of HFC in 99% yield.[7] This paper reports the use of molecular iodine as a catalyst for the synthesis of AFCs.

Results and discussions

Previous work by Wu et al[7] showed that molecular iodine could be used as a catalyst in the Pechmann condensation of resorcinol and β-keto esters (Scheme 1). Their conditions were optimized using ethyl acetoacetate (R = H) yet they reported that if ethyl 4,4,4-trifluoromethylacetoacetate (R = F) was used the catalyst load had to be increased to 50 mol%. They did not report any further optimization. Since we wanted to synthesize a series of 7-alkoxy-4-trifluoromethylcoumarins, optimizing the reaction conditions for resorcinol and ethyl 4,4,4-trifluoromethylacetoacetate was necessary (Table 1).



Scheme 1. Synthesis of coumarins using molecular iodine

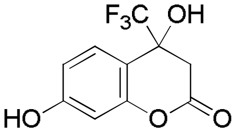
Table 1. Optimization of reaction conditions for synthesis of 7-hydroxy-4-trifluoromethylcoumarin (HFC)[a]

Entry	Temperature (°C)	Solvent	volume (mL)	Catalyst amount (mol%)	Yield[b] (%)
1	80	Toluene	1	50	50
2	90	Toluene	1	50	59
3	100	Toluene	1	50	71
4	90	Toluene	1	25	89
5	90	Toluene	1	15	86
6	90	Toluene	1	5	44
7	100	Toluene	5	50	41
8	90	nitrobenzene	1	25	50
9	reflux	THF	1	25	11
10	90	none		25	52

[a] All reactions were performed with resorcinol (5 mmol), and ethyl 4,4,4-trifluoroacetoacetate (6 mmol).

[b] Isolated yield.

Wu et al reported that 7-hydroxy-4-alkylcoumarins can be synthesized from resorcinol and β-ketoesters with molecular iodine in toluene at 80 °C in 3-12 h.[7] In our lab, the reaction did not go to completion in 3-12 hours based on the presence of resorcinol by TLC. If the reaction was allowed to run overnight, resorcinol was no longer visible by TLC but there were many new spots. The isolated yield of HFC was low (50 %) at 80 °C (entry 1). The other components of the reaction were isolated and it was determined that an intermediate was present (**1**, Figure 1). If the temperature was increased to 90 °C the yield increased (entry 2) and the amount of intermediate decreased. When the temperature was increased to 100 °C the reaction went to completion (entry 3).



1

Figure 1. Intermediate isolated from reactions performed at lower temperature.

Previous researchers have tried to monitor the synthesis of coumarins by the Pechmann condensation but were unable to detect the presence of intermediates.[13] This is the first report of an isolated intermediate in the Pechmann reaction. The Pechmann condensation reaction involves three steps: transesterification, electrophilic aromatic substitution and dehydration. The isolated intermediate is formed from only undergoing the transesterification and electrophilic aromatic substitution (EAS). All previous mechanistic studies have been done on the synthesis of 7-hydroxy-4-methylcoumarin,[14] where this work focused on the trifluoromethyl derivative. This strong electron withdrawing group appears to play an important role in the ability to isolate an intermediate and will be studied further.

In the process of isolating and identifying byproducts we also determined that both the starting phenol and product becomes iodinated (Figure 2). The most common iodo byproducts were 4-hydroxy-2-iodophenol (**2**), 3-hydroxy-2,6-diiodophenol (**3**), and 7-hydroxy-6-iodo-4-trifluoromethyl coumarin (**4**). These byproducts are formed due to the mild Lewis acidity of the catalyst iodine and its ability to function as an electrophile in EAS. The position of the iodine implies that the hydroxyl group is preferentially directing the iodine ortho.

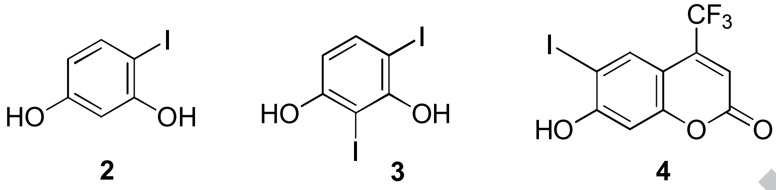


Figure 2. Most common iodinated byproducts.

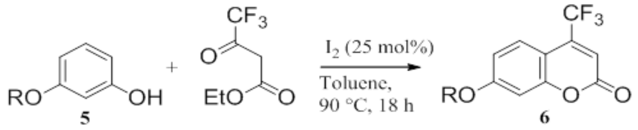
Due to the presence of iodinated byproducts, the amount of catalyst required for the reaction was studied. When the catalyst load was reduced to 25 and 15 mol% the amount of iodinated byproducts was reduced and the yield improved to 89 and 86% (entry 4 and 5, respectively). If the catalyst load was further reduced to 5 mol% the yield dropped off to 44% (entry 6).

The role of the solvent was the studied. The original report did not state the volume of solvent used, therefore we assessed the solvent amount. It was found that increasing the amount of solvent from 1 to 5 mL dramatically reduced the yield from 71 to 41 % (entry 3 and 7, respectively). Different observations have been reported in the literature with respect to solvent polarity. Most commonly non-polar solvents favor the Pechmann reaction while polar solvents cause cleavage.[15] When more polar solvents were used, nitrobenzene and THF, the yield decreased to 50 and 11%, respectively (entry 8 and 9, respectively). We believe the yield in THF was so small because the boiling point of THF is low. Many Pechmann reactions give high yields in solvent-free conditions,[10,13,15,16] however this was not the case with iodine as the catalyst. In solvent-free conditions, with 1.2 eq. of the β-ketoester the yield was only 52% (entry 10). Often in solvent-free conditions the β-ketoester is increased to 2 eq. We found that increasing the amount of β-ketoester slightly improved the yield to 61% but it also caused a dimer to form. Therefore it appears that non-polar toluene is the best solvent.

Using the optimized conditions with molecular iodine in toluene at 90 °C, we report the synthesis of 7-methoxy-4-trifluoromethylcoumarin (2b), 7-ethoxy-4-trifluoromethylcoumarin (2c), and 7-benzyloxy-4-trifluoromethylcoumarin (2d) in 42-82% yield (Table 2). These coumarins are made from inexpensive, commercially available starting materials. Reactions were monitored by TLC and products were purified by column chromatography.

Table 2

Reaction of phenols **5** with ethyl 4,4,4-trifluoroacetoacetate catalyzed by molecular iodine.[a]



Entry	R	Phenol **5**	Coumarin **6**	Yield[b] (%)
a	H	resorcinol	HFC	89
b	CH_3	3-methoxyphenol	MFC	82
c	CH_2CH_3	3-ethoxyphenol	EFC	65
d	$CH_2C_6H_5$	3-benzyloxyphenol	BFC	42

[a] All reactions were performed with **1** (5 mmol), ethyl 4,4,4-trifluoroacetoacetate (6 mmol) and 25 mol % molecular iodine (1.25 mmol) in toluene (1 mL) at 90 °C for 18 h.

[b] Isolated yield.

All the products were characterized by ^{1}H, ^{13}C and 2D NMR analysis. All coumarin derivatives were identified by comparison of their physical and spectral data with the literature[3,7,10,17,18] or commercial samples. The HMBC spectra for HFC shows that the carbon peak at 159 ppm correlates to the ^{1}H peak at 6.76 ppm (3CH) while the carbon peak at 162 ppm correlates to the ^{1}H peak at 7.56 (5CH), 10.96 (OH) and 6.84 ppm (8CH). Therefore the ^{13}C peak at 159 ppm should be assigned to C2 and the peak at 162 should be assigned to C7. These assignments were switched in comparison to Wang's assignments.[10]

Conclusions

In summary, molecular iodine was shown to be a suitable catalyst for the synthesis of several 7-alkoxy-4-trifluoromethyl coumarins from a phenol and ethyl 4,4,4-trifluoro-acetoacetate. This study demonstrated that if the reaction is not heated to 90 °C the hydrated intermediate is still present. This study also showed that the iodine catalyst substitutes ortho to the phenol causing unwanted byproducts.

Acknowledgements

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Supplemental data

Supplemental data associated with this article can be found in the online version. The data includes spectroscopic data for the most important compounds described.

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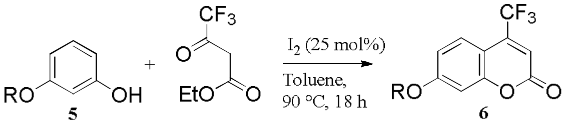

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