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A Facile Synthesis Of Fluorinated 4-Hydroxycoumarins

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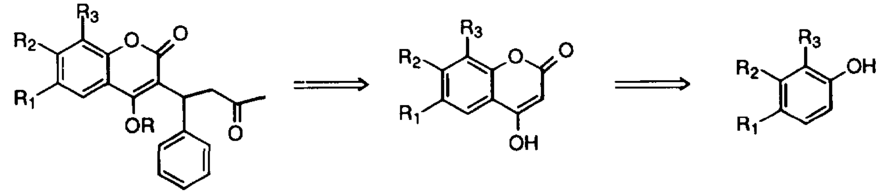
Summary: Fluorinated 4-hydroxycoumarins were prepared from readily available fluorinated phenols *via* a $AlCl_3$ catalyzed Friedel-Crafts ring closure and followed by sequential one pot decarboxylation and deacetylation with 90% H_2SO_4.

4-Hydroxycoumarins possess a wide range of biological activities, predominantly anticoagulant[2] and HIV protease inhibition.[3,4] Coumadin® (sodium warfarin, **1**, R=Na)[5] is the most widely prescribed anti-thrombotic in North America.[6] The major metabolites of S-warfarin are S-6-hydroxyl and S-7-hydroxyl warfarin, which are derived by 2C9 P450 isoenzyme.[7] The 2C9 isoenzyme is also critical for the metabolism of many other common drugs, thus one of the problems associated with warfarin is drug-drug interactions. We propose that fluorinated warfarin analogs might be able to overcome this problem since fluorine has been well known to block the metabolism site for organic molecules *in vivo*, while maintaining the biological activity. Surprisingly, little study has been reported on preparation of these fluorinated coumarins. We report here a practical and robust process for synthesis of this important class of compounds.



1: R=H, Warfarin
R=Na, Sodium Wafarin

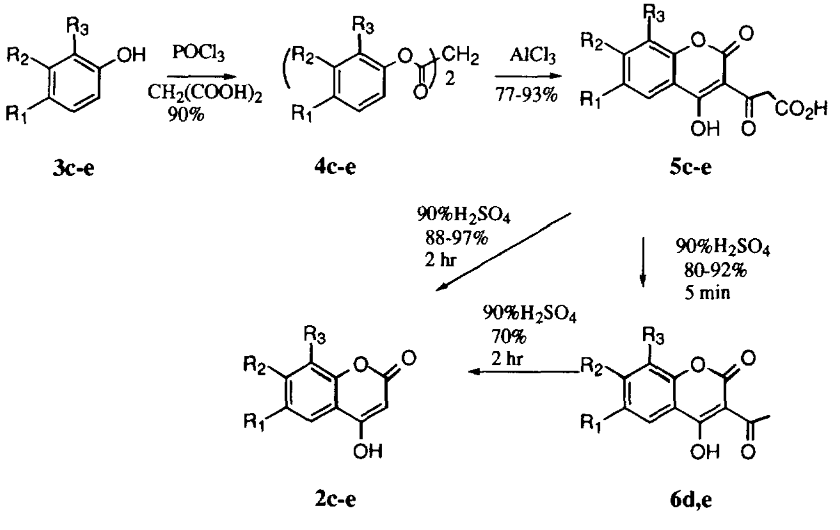
2a: $R_1=R_2=R_3=H$
2b: $R_1=H, R_2=F, R_3=H$
2c: $R_1=F, R_2=R_3=H$
2d: $R_1=F, R_2=H, R_3=F$
2e: $R_1=R_2=R_3=F$

3a-e

4-hydroxycoumarin is normally synthesized from a condensation of phenol **3a** with malonic acid in the presence of $ZnCl_2$ and phosphorous oxychloride[8]. Syntheses involving *o*-hydroxyacetophenone condensing with diethyl carbonate[9] or other carbonyl equivalents[10,11] to produce coumarins have also been well studied. The $ZnCl_2$ procedure has been used successfully to prepare 7-fluorowarfarin.[12] The same procedure for the synthesis of 6-fluoro, 6,8-difluoro and 6,7,8-trifluorowarfarin analogs failed in our lab due to the stronger electron withdrawing effect caused by fluorine substitution. Danek reported[12] that 6-fluorocoumarin was obtained in 20% yield by treating **4b** with neat $AlCl_3$ followed by a tedious steam-distillation. When we attempted to repeat this result, **5b** was isolated as the only product after treatment of **4b** with neat $AlCl_3$ followed an aqueous work-up. Apparently the Friedel-Crafts ring closure went well to give the desired 6-fluorocoumarin, but the newly formed 4 position of coumarin was much more reactive than *othro*-position of phenol malonate, thus it immediately reacted with another molecular of malonate to give **5** upon aqueous work-up. After careful analysis of structure **5**, we foundd that 90% H_2SO_4 can remove the extra 4 substitution cleanly *via* a facile decarboxylation and deacetylation, thus furnishing the synthesis of a series of fluorinated 4-hydroxycoumarins. Each step of this process provides a single product and no column chromatography is needed. This novel synthesis of substituted coumarins might be extended to other coumarins possessing electron withdrawing group(s) on the phenyl ring.

The malonates **4c-e** were prepared from commercially available phenols in good yield according to the literature procedure.[12] Treatment of **4c-e** with neat $AlCl_3$ for 10-15 min. at 180°C gave **5c-e** as a sole product. We were able to remove the side chain cleanly by simply heating **5c-e** in 90% H_2SO_4 for 2 hr to give the desired fluorinated 4-hydroxyl coumarins **2c-e** as the sole product. This reaction goes through **6** as a intermediate which then can be further deacetylated to **2**. The decarboxylation is a very fast reaction. Indeed, when we quenched the reaction within 5 min after heating at 160°C, **6** was isolated as the only product (Scheme 1).

Scheme 1



The structure of **5** was confirmed by spectroscopic analysis. It exists predominately in the enone form according to ^{1}H-NMR. It was subsequently methylated with (trimethylsilyl)diazomethane to give **8** (Scheme 2). **5e** cyclized spontaneously to **7** in methanol.

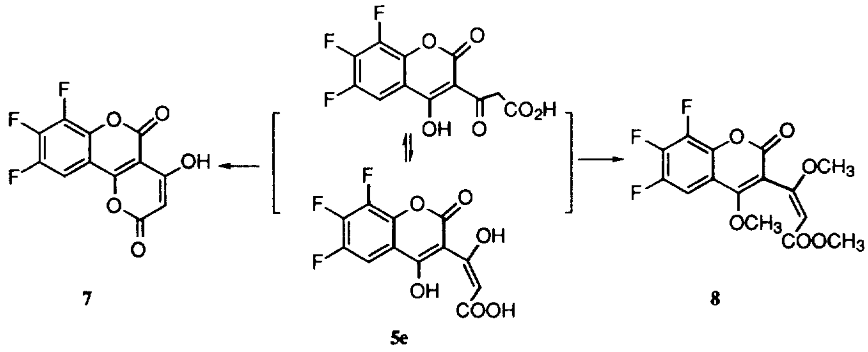
Table 1. Lewis Acids Catalyzed Coumarin Formation with Malonate

entry	substrates	Products	conditions*	yields (%)
1	**3b**	**2b**	A	54
2	**3c**	**2c**	A	0.7
3	**4c**	**5c**	B	77
4	**4d**	**5d**	B	85
5	**4e**	**5e**	B	86(93)
6	**5c**	**2c**	C	97
7	**5d**	**2d**	C	88(92)
8	**5e**	**2e**	C	95
9	**6e**	**2e**	C	70
10	**5d**	**6d**	D	92
11	**5e**	**6e**	D	84

*Reaction conditions: A). $ZnCl_2/POCl_3$, 60°C, 36hr. B). $AlCl_3$, 180°C, 10min. C). 90%H_2SO_4, 180°C, 2hr. D). 90%H_2SO_4 180°C, 5min.. All yields are not optimized.

7 was one of the products accompanying **2** and **6**, in Danek's work,[12] presumably due to the incomplete decomposition of **5** caused by steam distillation. Deacetylations have been carried out in both basic[13,14] and acidic conditions.[15,16] Since the coumarin ring is not very stable to strong base[17], we decided to proceed with this transformation under acidic conditions, which went very smoothly in high yield. It is possible that the 4-hydroxyl group might facilitate the deacelylation. This simple deacetylation procedure provides a tool that an acetyl group can be used as a protecting group when derivatizing the coumarin ring system.

Scheme 2



These fluorinated 4-hydroxycoumarins have been converted to a series of fluorinated warfarin analogs *via* a Michael addition with 4-phenyl-3-buten-2-one. The details of synthesis and biological studies of these compounds will be published in a separate article.

Typical Experimental procedure

To a round-bottomed flask, fitted with a thermometer, is charged fluorinated phenol (0.15 mol), malonic acid(7.84g, 75mmol) and phosphorous oxychloride(13.4g, 87momol). The reaction mixture is heated at 110°C for one hour and then at 120°C for another one hour. The clear upper layer of the reaction mass is separated and poured on ice. The solid is filtered and dried. The solid and anhydrous aluminum chloride (9.2g, 69mmol) are mixed and melted at 140°C and then the reaction mixture is heated at 180°C for 10 min with stirring. After cooling, the reaction mixture is poured into 100ml of ice-cooled 10%HCl. The solid is filtered and washed with methylene chloride and water. The solid is dried and then mixed in a solution of conc. H_2SO_4 (20g) and water (2g). The mixture is heated on a 160°C oil bath for 2 hours. After cooling, 150ml of ice-water is added and the mixture is extracted with ethyl acetate three times (3X100ml). The organic layer is washed with saturated sodium chloride and dried over anhydrous sodium sulfate. The solvent is removed under vacuum to give the fluorinated coumarin.

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(17) We have observed some ring opening products when coumarins were treated with strong base or primary amine.

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