EFFICIENT AND CONVENIENT SYNTHESIS OF ANGULAR FURANOCOUMARINS FROM HYDROXYCOUMARINS

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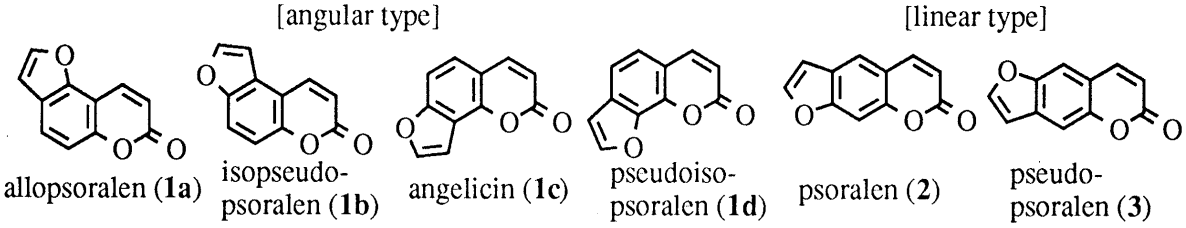
Angular furanocoumarins (**1**) were synthesized *via* sequential reactions of vinylation of halo-hydroxycoumarins (**5** or **6**) with chlorodimethylvinylsilane (**8**) and Pd catalyst, oxidation of $Tl(NO_3)_3$ in methanol, and treatment with acid.

KEY WORDS angular furanocoumarin; halo-hydroxycoumarin; vinylation; cross-coupling reaction

Furanocoumarins have a wide range of biological properties,[1] and have been applied in medicine for the treatment of skin diseases. Linear furanocoumarins (**2** and **3**), especially **2**, undergo [2+2] photocycloadditions to pyrimidine bases of DNA and RNA to form cross-linking di-adducts,[2] which occasionally cause undesirable carcinogenic and mutagenic effects.[3] Considerable efforts to diminish such side effects have been made, leading to the development of angular furanocoumains (**1**), which only permit monofunctional photobinding with DNA[4] and cannot cross-link with DNA because of their geometry.[5] Recently, we have reported effective and general synthesis of hydroxycoumarins (**4**) from salicylaldehydes and Wittig reagent in refluxing diethylaniline.[6] Subsequently, we planned to develop a convenient and general synthetic method of **1** from **4**. Synthesis of angular furanocoumarins (**1**) has been already achieved by i) Claisen rearrangement of allyloxycoumarin,[7a] ii) benzannulation reaction of carbene complexes with acetylene,[7b] iii) coupling of an acetylenic reagent with *o*-iodohydroxycoumarin,[7c] or iv) α-pyrone ring formation of *o*-formyl hydroxybenzofuran.[7d,e] However, these have some disadvantages, such as many steps, low yield, and/or lack of generality.



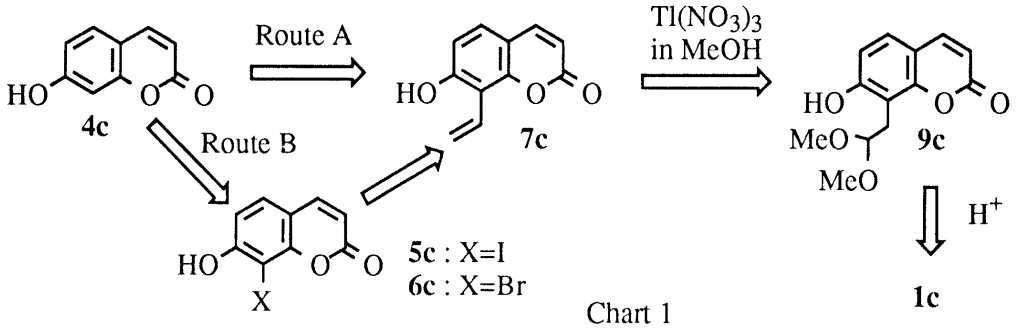


Chart 1

Our general strategy for the synthesis of angular furanocoumarin (**1**), using angelicin (**1c**) as a representative example, is shown in Chart 1: i) direct introduction of a vinyl group to an ortho position of a phenol group (Route A), or ii) indirect introduction of a vinyl group *via* *o*-halophenol (Route B), and then oxidation of the styrene moiety with $Tl(NO_3)_3$[8] followed by acid treatment to synthesize **1c**.

First, we applied the ortho vinylation method reported by Yamaguchi *et al.*[9] to hydroxycoumarin (**4**), resulting in the recovery of starting material in 56-88% yield and no desired product. Next, we planned to investigate Route B. Hiyama *et al.* have reported the cross-coupling of alkenylsilanes with aryl halides mediated by palladium catalyst and fluoride ion.[10] In order to apply this method, we first examined halogenation (iodination and bromination) of **4**. The results are summarized in Table 1. Subsequently, the cross-coupling reaction of iodo-coumarin (**5**) with vinyl reagent by Hiyama's

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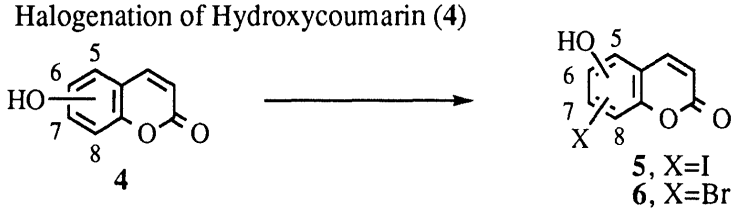
method [10a] was investigated. Reaction of **5c** with trimethylvinylsilane using $(\eta^3\text{-}C_3H_5PdCl)_2$ and nBu_4NF (TBAF) in the presence of a cocatalyst (triethylphosphite) gave no desired vinyl-hydroxycoumarin (**7c**).[11] Furthermore, Hiyama *et al.* have revealed that introduction of fluorine(s) to the silyl groups of alkenyl-silanes accelerated the coupling reaction with alkenyl iodides mediated by Pd catalyst and fluoride ion.[10b] Therefore, we attempted to apply chlorosilane, chlorodimethylvinylsilane (**8**), in place of fluorosilane to the synthesis of vinyl-hydroxycoumarin (**7**) from **5** or **6**, because **8** is commercially available and less toxic than vinyltin reagent. Then, vinylation of **5** and **6** using **8** and Pd reagent was investigated. The results are summarized in Table 2. As can be seen from Table 2, bromo compounds (**6**) are much less reactive than the corresponding iodo compounds (**5**) or unreactive even when using a stoichiometric amount of Pd reagent. However, 7-bromo-8-hydroxycoumarin (**6d**) provided the desired **7d** in a 62% yield (see Run 9 in Table 2).

Finally, oxidation of **7** with $Tl(NO_3)_3$ in methanol at room temperature followed by treatment with *p*-TsOH in xylene under reflux provided **1** in a good yield except for 6-hydroxy-5-vinylcoumarin (**7b**), as

Table 1. Halogenation of Hydroxycoumarin (**4**)

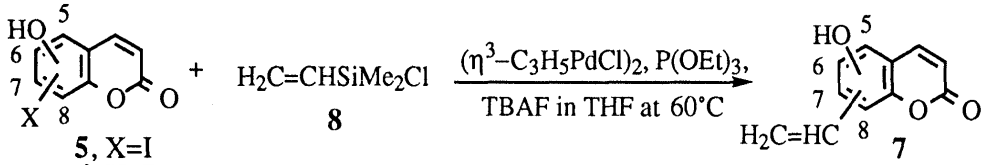


4 → **5**, X=I; **6**, X=Br

Starting material	Method*	Product and yield			
		5 or **6**		Other	
5-OH (**4a**)	A	5-OH, 6-I (**5a**)	59	5-OH, 6,8-di-I	5
	C	5-OH, 6-Br (**6a**)	77		
6-OH (**4b**)	B	6-OH, 5-I (**5b**)	90		
	D	6-OH, 5-Br (**6b**)	84		
7-OH (**4c**)	A	7-OH, 8-I (**5c**)	41		
	C	7-OH, 8-Br (**6c**)	72		
8-OH (**4d**)	A	8-OH, 7-I (**5d**)	24	8-OH, 5-I	33
	C	8-OH, 7-Br (**6d**)	65		

* Method A: I_2 and KI in 20% NH_4OH. Method B: benzyltrimethylammmonim dichloroiodate in CH_2Cl_2 and MeOH. Method C: Br_2 and *t*-$BuNH_2$ in toluene. Method D: *N*-bromosuccimide in dimethylformamide.

Table 2. Vinylation of Halo-hydroxycoumarin (**5** or **6**) with Chlorodimethylvinylsilane (**8**)



5, X=I; **6**, X=Br + $H_2C{=}CHSiMe_2Cl$ (**8**) → $(\eta^3\text{-}C_3H_5PdCl)_2$, $P(OEt)_3$, TBAF in THF at 60°C → **7**

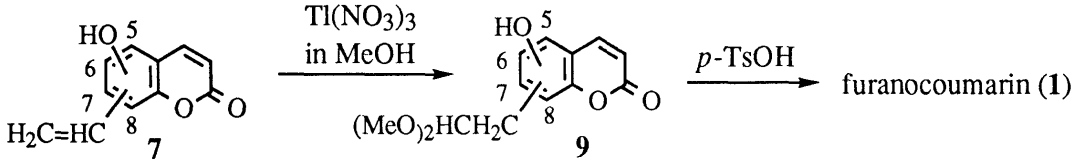
Run	Starting material	Pd (mol%)	Time	Product	Yield*	
1	5-OH, 6-I (**5a**)	20	30 min	5-OH, 6-vinyl (**7a**)	69	
2	5-OH, 6-Br (**6a**)	100	10 h			(87)
3	6-OH, 5-I (**5b**)	10	3 h	6-OH, 5-vinyl (**7b**)	76	
4	6-OH, 5-Br (**6b**)	100	10 h	(**7b**)	27	(38)
5	6-OMOM, 5-I	10	4 h	6-OMOM, 5-vinyl	80	
6	7-OH, 8-I (**5c**)	10	7 h	7-OH, 8-vinyl (**7c**)	66	(25)
7	7-OH, 8-Br (**6c**)	100	10 h			(95)
8	8-OH, 7-I (**5d**)	10	7 h	8-OH, 7-vinyl (**7d**)	52	
9	8-OH, 7-Br (**6d**)	100	1 h	(**7d**)	62	

* Isolated yield. The values in parentheses are yields of recovered starting material.

shown in Table 3. Surprisingly, **7b** gave an unexpected 6-methoxy-5-vinylcoumarin in a 24% yield along with the expected acetal (**9b**) in a 41% yeild. However, methoxymethyl (MOM) ether of **7b**, which was prepared by vinylation of MOM ether of **5b** (see Run 5 in Table 2), afforded the desired **1b** in a 55% total yield by successive treatment with $Tl(NO_3)_3$ followed by *p*-TsOH.

In conclusion, angular furanocoumarins (**1**) can be synthesized in 19-49% yield from the corresponding hydroxycoumarins (**4**) by following to Route B shown in Chart 1.

Table 3. Results of Conversion of Vinyl-Hydroxycoumarin (**7**) to Furanocoumarin (**1**) *via* Dimethylacetal (**9**)



Starting material	Product (**9**)	Yield	Product (**1**)	Yield
5-OH, 6-vinyl (**7a**)	5-OH, 6-$CH_2CH(OMe)_2$ (**9a**)	71	(**1a**)	84
6-OH, 5-vinyl (**7b**)	6-OH, 5-$CH_2CH(OMe)_2$ (**9b**)	41*		
6-OMOM, 5-vinyl	6-OMOM, 5-$CH_2CH(OMe)_2$	89	(**1b**)	84
7-OH, 8-vinyl (**7c**)	7-OH, 8-$CH_2CH(OMe)_2$ (**9c**)	83	(**1c**)	85
8-OH, 7-vinyl (**7d**)	8-OH, 7-$CH_2CH(OMe)_2$ (**9d**)	71	(**1d**)	89

* See text.

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11) This reaction afforded the Heck reaction product, 8-(2'-TMS-*trans*-vinyl)-7-hydroxycoumarin, in a 27% yield along with the recovery of 36% yield of **5c**.

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