

EFFICIENT AND CONVENIENT SYNTHESIS OF ANGULAR FURANOCOUMARINS FROM HYDROXYCOUMARINS

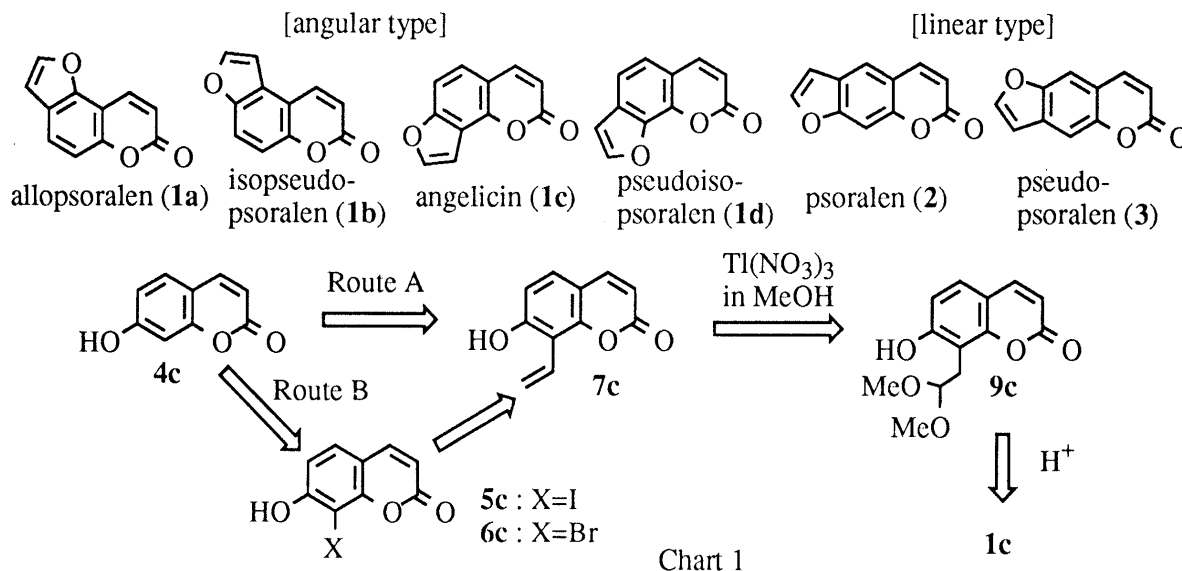
Takashi HARAYAMA * and Yoshitaka NISHITA

Faculty of Pharmaceutical Sciences, Okayama University, Tsushima-naka 1-1-1, Okayama 700, Japan

Angular furanocoumarins (**1**) were synthesized *via* sequential reactions of vinylation of halo-hydroxycoumarins (**5** or **6**) with chlorodimethylvinylsilane (**8**) and Pd catalyst, oxidation of $\text{Ti}(\text{NO}_3)_3$ 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 furanocoumarins (**1**), which only permit monofunctional photobinding with DNA⁴⁾ 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*-iodo-hydroxycoumarin,^{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.



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 $\text{Ti}(\text{NO}_3)_3$ ⁸⁾ followed by acid treatment to synthesize **1c**.

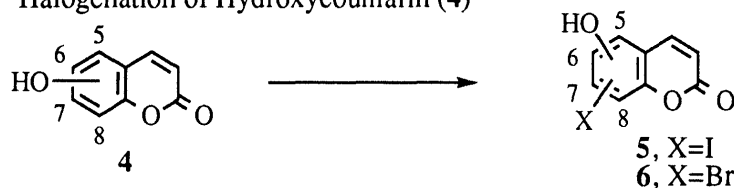
First, we applied the ortho vinylation method reported by Yamaguchi *et al.*⁹⁾ to hydroxycoumarin (**4**), resulting in the recovery of starting material in 56–88% yield and no desired product. Next, we planned to investigate Route B. Hiyama *et al.* have reported the cross-coupling of alkenylsilanes 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

* To whom correspondence should be addressed.

method ^{10a)} was investigated. Reaction of **5c** with trimethylvinylsilane using $(\eta^3\text{-C}_3\text{H}_5\text{PdCl})_2$ and $n\text{Bu}_4\text{NF}$ (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 $\text{Ti}(\text{NO}_3)_3$ 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

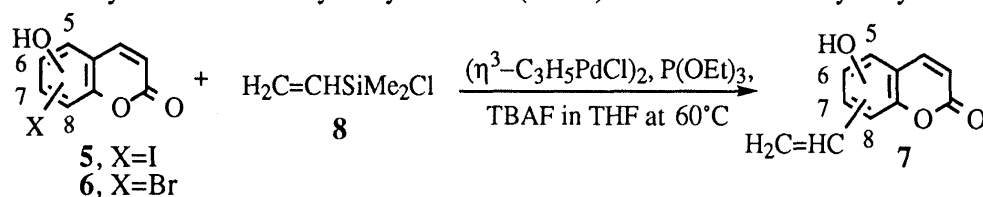
Table 1. Halogenation of Hydroxycoumarin (**4**)



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: benzyltrimethylammonium dichloriodate in CH_2Cl_2 and MeOH. Method C: Br_2 and *t*- BuNH_2 in toluene. Method D: *N*-bromosuccinimide in dimethylformamide.

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



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% yield. 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 $\text{Ti}(\text{NO}_3)_3$ 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- $\text{CH}_2\text{CH}(\text{OMe})_2$ (9a)	71	(1a)	84
6-OH, 5-vinyl (7b)	6-OH, 5- $\text{CH}_2\text{CH}(\text{OMe})_2$ (9b)	41*		
6-OMOM, 5-vinyl	6-OMOM, 5- $\text{CH}_2\text{CH}(\text{OMe})_2$	89	(1b)	84
7-OH, 8-vinyl (7c)	7-OH, 8- $\text{CH}_2\text{CH}(\text{OMe})_2$ (9c)	83	(1c)	85
8-OH, 7-vinyl (7d)	8-OH, 7- $\text{CH}_2\text{CH}(\text{OMe})_2$ (9d)	71	(1d)	89

* See text.

REFERENCES AND NOTES

- 1) a) Scott B. R., Pathak M. A., Mohn G. R., *Mut. Res.*, **39**, 29-74 (1976); b) Parrish J. A., Fitzpatrick T. B., Tanenbaum L., Pathak M. A., *N. Engl. Mutat Res.*, **291**, 1207-1211 (1974); c) Edelson R. L., *J. Photochem. Photobiol. B: Biol.*, **10**, 165-174 (1991); d) North J., Neyndorff H., Levy J. G., *ibid.*, **17**, 99-108 (1993); e) Zmudzka B. Z., Strickland A. G., Miller S. A., Valeri K., Dall'Acqua F., Beer J. Z., *Photochem. Photobiol.*, **58**, 226-232 (1993).
- 2) a) Kanne D., Straub K., Hearst J. E., Rapoport H., *J. Am. Chem. Soc.*, **104**, 6754-6764 (1982); b) Song P.-S., Tapley K. J. Jr., *Photochem. Photobiol.*, **12**, 131-171 (1984).
- 3) Ashwood-Smith M. J., Poulton G. A., Barker M., Mildenberger M., *Nature*, **285**, 407-409 (1980).
- 4) a) Blais J., Averbeck D., Moron J., Bisagni E., Vigny P., *Photochem. Photobiol.*, **45**, 465-572 (1987); b) Caelassre F., Baccichetti F., Guiotto A., Rodighiero P., Gia O., Capozzi A., Pastorini G., Bordin F., *J. Photochem. Photobiol. B: Biol.*, **5**, 25-39 (1990); c) Dall'Acqua, Caffieri S., Vedaldi D., Guiotto A., Rodighiero G., *ibid.*, **33**, 261-264 (1981).
- 5) a) Dall'Acqua F., Vedaldi D., Guiotto A., Rodighiero P., Carllassare F., Baccichetti F., Bordin F., *J. Med. Chem.*, **24**, 806-811 (1981); b) Dall'Acqua F., Vedaldi D., Bodin F., Baccichetti F., Carllassare F., Tamaro M., Rodighiero P., Pastorini G., Guiotto A., Recchia G., Cristofolini M., *ibid.*, **26**, 870-876 (1983); c) Guiotto A., Rodighiero P., Manzini P., Pastorini G., Bordin F., Baccichetti F., Carllassaro F., Vedaldi D., Dall'Acqua F., Tamaro F., Recchia G., Cristofolini M., *ibid.*, **27**, 959-967 (1984).
- 6) Harayama T., Katsuno K., Nishioka H., Fujii M., Nishita Y., Ishii H., Kaneko Y., *Heterocycles*, **39**, 613-622 (1994).
- 7) a) Aneja R., Mukerjee S.K., Seshadri T. R., *Tetrahedron*, **4**, 256-270 (1958); b) Wulff W. D., McCallum J. S., Kunng F. -A., *J. Am. Chem. Soc.*, **110**, 7419-7434 (1988); c) Zubia E., Luis F. R., Massanet G. M., Collado I. G., *Tetrahedron*, **48**, 4239-4246 (1992); d) Royer R., Rene L., Buisson J.-P., Demerseman P., *Eur. J. Med. Chem.*, **13**, 213-218 (1978); e) Lee Y. R., *Tetrahedron*, **51**, 3087-3094 (1995).
- 8) McKillop A., Hunt J. D., Kienzle F., Bigham E., Taylor E. C., *J. Am. Chem. Soc.*, **95**, 3635-3640 (1973).
- 9) Yamaguchi Y., Hayashi A., Hiramama M., *J. Am. Chem. Soc.*, **117**, 1151-1152 (1995).
- 10) a) Hatanaka Y., Hiyama T., *J. Org. Chem.*, **53**, 918-920 (1988); b) idem, *ibid.*, **54**, 268-270 (1989); c) idem, *Synlett*, **1991**, 845-853.
- 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**.

(Received August 26, 1996; accepted September 13, 1996)