

SYNTHESIS OF 3-SUBSTITUTED ISOCOUMARINS AND RELATED NATURAL PRODUCTS

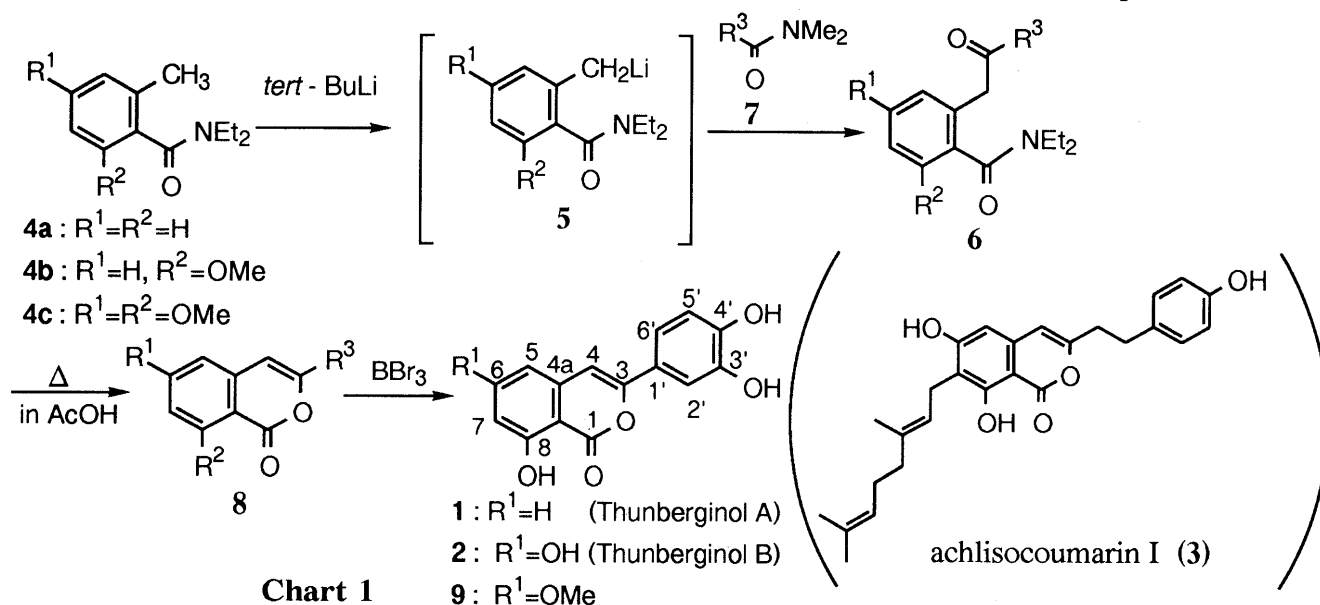
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Several *N,N*-diethyl-2-acylmethylbenzamides (**6**) were prepared from *N,N*-diethyl-2-toluamides (**4**), and the ketoamides (**6**) were easily cyclized to the corresponding 3-substituted isocoumarins (**8**) by heating in acetic acid or xylene. This simple procedure was applied to the synthesis of thunberginol A (**1**), thunberginol B (**2**), thunberginol F (**14**), and a key-intermediate (**8j**) for achlisocoumarin I (**3**).

KEYWORDS isocoumarin; lithiation; cyclization; total synthesis; thunberginol; achlisocoumarin I


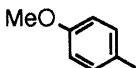
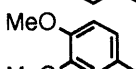
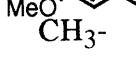

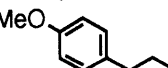
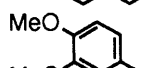
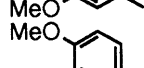
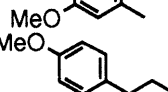
Natural products having a 3-substituted isocoumarin skeleton have been rare, and few methods for construction of the skeleton have been developed.¹⁾ Recently, several biologically interesting 3-substituted isocoumarins were isolated --- for example, thunberginol A (**1**) and thunberginol B (**2**) from *Hydrangeamacrophylla* SERINGE var. *thunbergii* MAKINO by Yoshikawa *et al.*,²⁾ and achlisocoumarin I (**3**) from *Achlys triphylla* by Mizuno *et al.*³⁾ This communication deals with a short-step construction of the 3-substituted isocoumarin skeleton and its application to the total synthesis of these natural products.



We planned application of the benzylic metalation methodology reported by Snieckus *et al.* to synthesis of *N,N*-diethyl-2-phenacylbenzamide (**6a**).⁴⁾ Thus the amide (**4a**) was lithiated with LDA, and

then the lithio intermediate (**5a**) was acylated with *N,N*-dimethylbenzamide (**7a**), but yield of the amide (**6a**) was not satisfactory.⁵⁾ So we examined the lithiation condition for **4a** with various lithiating agents such as LDA, *sec*- and *tert*-BuLi by use of the amide (**7a**) as an electrophile. The best yield of the δ -ketoamide (**6a**) was obtained when **4a** was treated with *tert*-BuLi at -70°C , and the generality of these reaction conditions was proved as shown in Table I.

TABLE I. Synthesis of δ -Ketoamides (**6**) and Isocoumarins (**8**)

Entry	Toluamide (4)		Acyl source (7)	δ -Ketoamide (6)	Isocoumarin (8)	
	R ¹	R ²			Isolated yield (%)	Isolated yield (%)
1	4a :	H H	7a :		6a : 60.2	8a : 91.0 88.2-89.1 (lit. 87-88) ¹⁰⁾
2	4a :	H H	7b :		6b : 82.1	8b : 91.0 114.1-115.1 (lit. 119-121) ¹¹⁾
3	4a :	H H	7c :		6c : 82.2	8c : 97.9 119.6-120.8 (lit. 116) ¹¹⁾
4	4a :	H H	7d :		6d : 80.6	8d : 87.0 70.9-71.3 (lit. 71-72) ¹²⁾
5	4a :	H H	7e :	CH ₃ (CH ₂) ₅ -	6e : 73.3	8e : 99.4 oil (bp ₃ 146)
6	4a :	H H	7f :		6f : 66.0	8f : 76.4 93.8-94.2
7	4a :	H H	7g :		6g : 82.0	8g : 96.1 87.3-88.4
8	4b ¹³⁾ :	H OMe	7c :		6h : 72.6	8h : 81.3 152.8-154.4
9	4c ¹³⁾ :	OMe OMe	7c :		6i : 67.5	8i : 99.0 155.9-157.2
10	4c ¹³⁾ :	OMe OMe	7g :		6j : 93.4	8j : 90.7 146.6-147.1

We found unexpectedly that the phenacylbenzamide (**6a**) was cyclized to 3-phenylisocoumarin (**8a**) by heating. Cyclization conditions for **6a** were examined, and the best cyclization occurred when the substrate (**6a**) was only refluxed in acetic acid or xylene for several hours (Table II).

Under the same conditions as

TABLE II. Cyclization of δ -Ketoamide (**6a**)

Entry	Additive	Solvent	Temp. ($^\circ\text{C}$)	Time (h)	Yield (%) ^{a)}
1	-	AcOH	50	6	21.6
2	-	AcOH	100	3	88.3
3	-	AcOH	Reflux	3	91.0
4	10% HCl ^{b)}	THF ^{b)}	50	6	12.6
5	<i>t</i> -BuOLi ^{c)}	THF	r.t.	12	N.R. ^{d)}
6	-	Toluene	100	3	25.2
7	-	Xylene	Reflux	2	86.4

a) Isolated yield after purification by PTLC.

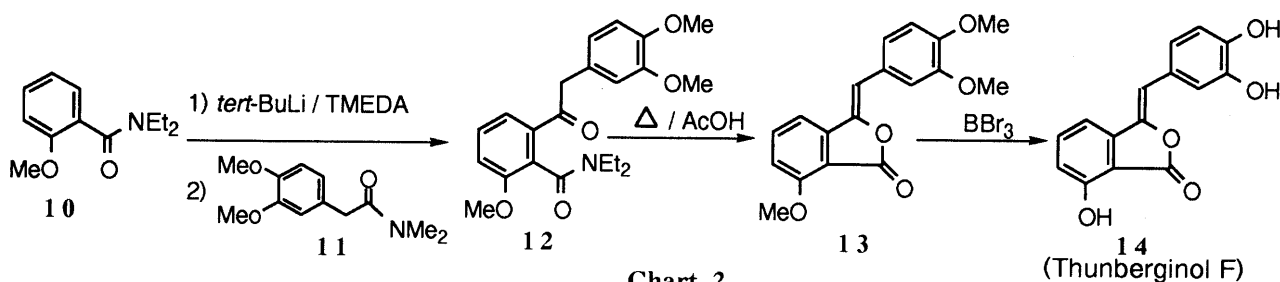
b) 10% HCl / THF : 1 / 1. c) 1 eq. d) Recovery of **6a**.

entry 3 in Table II, various amides (**6b** - **6j**) were cyclized to the corresponding isocoumarins (**8b** - **8j**) in high yields (Table I). The ease of this cyclization may be explained by the thermodynamic stability of the isocoumarin nucleus based on its pseudoaromaticity.

Demethylation of the compounds (**8h** and **8i**) was proceeded by treatment with BBr₃ (6 - 8 eq.).⁶⁾ In the case of **8h**, deprotection successfully proceeded under the mild conditions to give thunberginol A (**1**), but in the case of **8i**, under the same conditions as used in **8h** the 6-methoxy group survived to give **9**, probably because of the electron-withdrawing effect of the lactone-carbonyl group and the absence of a BBr₃-chelating neighboring group.⁷⁾ Complete demethylation of the 6-methoxy group in **9** was achieved

by treatment with an excess of BBr_3 in refluxing 1,1,2,2-tetrachloroethane. Structures of the synthetic products (1 and 2) were confirmed by comparisons of their spectral data with those of the natural thunberginol A and B.²⁾

Next we planned synthesis of thunberginol F (14), which is one of the (*Z*)-3-benzylidenephthalides and is also an antiallergic and antimicrobial constituent of the same plant as thunberginol A and B.^{2,8)} The benzamide (10) was acylated by phenylacetamide (11) via the Snieckus' *ortho*-lithiation to give the γ -ketoamide (12) in 10.8% yield.^{4b,9)} The γ -ketoamide (12) was easily converted to thunberginol F (14) in good yield in the above-mentioned manner.



The isocoumarin (8j) is a synthetic precursor positioned just two steps before achlisocoumarin I (3), and the conversion of 8j to 3 is now in progress.

Thus we developed a new access to the 3-substituted isocoumarin derivatives and its application to several natural products.¹⁴⁾

REFERENCES AND NOTES

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- 5) Only one example for acylation of 4 with ester appeared in the ref. 4a, but the yield was less than 60%. In ref. 4a, incomplete lithiation of 4 can be estimated from the facts that yields of the reported reaction are generally low. For example: 30 - 65% (c.f. ref. 4a). Although in ref. 4a Snieckus used *sec*-BuLi/TMEDA as benzylic lithiating agent, we recommend the combination of *tert*-BuLi/TMEDA.
- 6) a) R. A. Hill, R. H. Carter, and J. Staunton, *J. Chem. Soc., Perkin Trans. 1*, **1981**, 2570; b) T. Furuta, Y. Fukuyama, and Y. Asakawa, *Phytochemistry*, **25**, 517 (1986).
- 7) The presence of the 6-methoxy group in 9 was presumed on the bases of the success in the conversion of 8h to 1 and ¹H-NMR of 9.
- 8) Simple benzylidenephthalide can be obtained by Perkin-type reaction using phthalic anhydride, phenylacetic acid and sodium acetate [R. Weiss, *Org. Synth., Coll. Vol. II*, 61 (1943)]. But the substituted benzylidenephthalides such as 13 may be not easily obtained by this reaction.
- 9) The low yield may be due to anion exchange at the benzyl position of 11 by the *o*-lithiated 10.
- 10) R. C. Larock, S. Varaprath, H. H. Lau, and C. A. Fellows, *J. Am. Chem. Soc.*, **106**, 5274 (1984).
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- 13) Toluamides (4b and 4c) were prepared by methylation of the corresponding benzamides via the Snieckus' *ortho*-lithiation methodology (ref. 4b).
- 14) Satisfactory elemental microanalyses and spectral data (IR, ¹H-NMR and HRMS) of the new compounds in this communication were obtained.

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