SYNTHESIS OF 3-SUBSTITUTED ISOCOUMARINS AND RELATED NATURAL PRODUCTS

Shunsaku OHTA,* Yasuhiro KAMATA, Takayo INAGAKI, Yukari MASUDA, Satoshi YAMAMOTO, Masayuki YAMASHITA, and Ikuo KAWASAKI

Kyoto Pharmaceutical University, 5 Nakauchi-cho, Misasagi, Yamashina-ku, Kyoto 607, Japan

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.

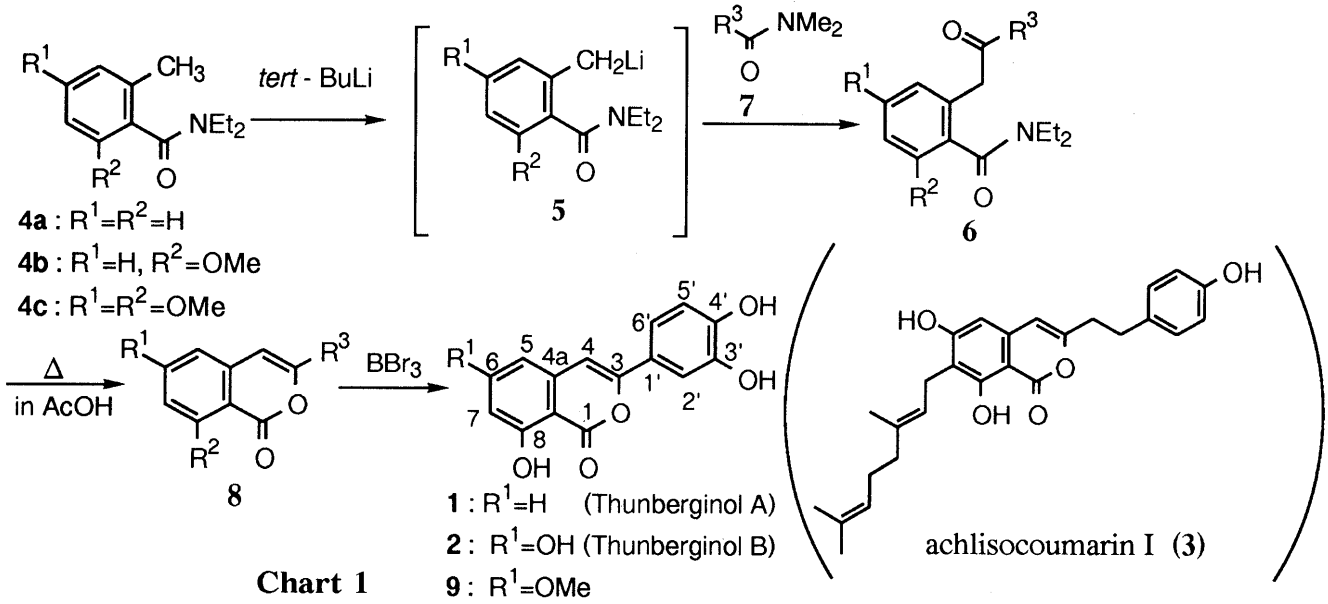
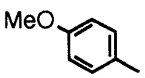
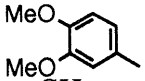
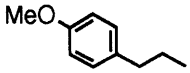
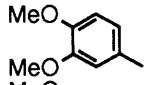
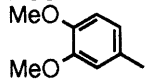
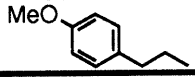


Chart 1

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	R^3	Isolated yield (%)	Isolated yield (%)	mp (°C)
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** : CH_3-	**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).

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

Entry	Additive	Solvent	Temp. (°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	*t*-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**.

Under the same conditions as 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 BBr_3 (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 BBr_3-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.

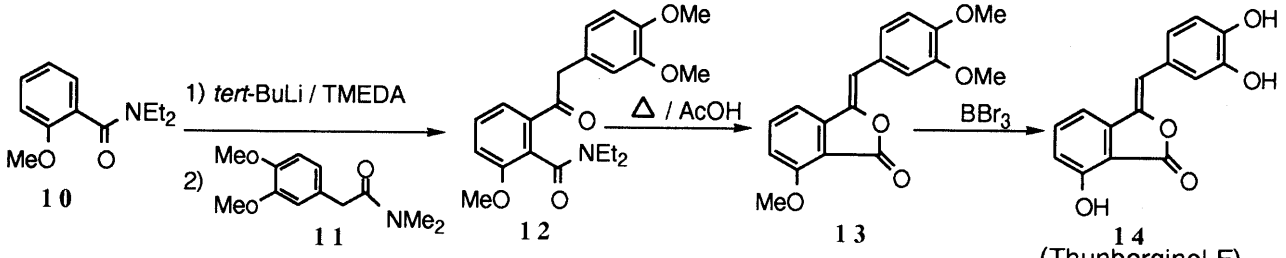


Chart 2

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

1) F. M. Hauser and V. M. Baghdanov, *J. Org. Chem.*, **53**, 4676 (1988); J. K. Kendall, T. H. Fisher, H. P. Schultz, and T. P. Schultz, *J. Org. Chem.*, **54**, 4218 (1989) and references cited therein.
2) M. Yoshikawa, E. Uchida, N. Chatani, N. Murakami, and J. Yamahara, *Chem. Pharm. Bull.*, **40**, 3121 (1992).
3) M. Mizuno, S. Yoshida, M. Iinuma, T. Tanaka, F. A. Lang, and K. Goto, *Chem. Pharm. Bull.*, **38**, 2075 (1990).
4) a) M. Watanabe, M. Sahara, M. Kubo, S. Furukawa, R. J. Billedeau, and V. Snieckus, *J. Org. Chem.*, **49**, 742 (1984); b) V. Snieckus, *Chem. Rev.*, **90**, 879 (1990); c) R. D. Clark, *Heterocycles*, **23**, 825 (1985); d) R. D. Clark and Jahangir, *J. Org. Chem.*, **52**, 5378 (1987) and **53**, 2378 (1988).
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 ^{1}H-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).
11) C. K. Bradsher and T. G. Wallis, *J. Org. Chem.*, **43**, 3817 (1978).
12) R. B. Tirodkar and R. N. Usgaonkar, *J. Indian Chem. Soc.*, **46**, 935 (1969).
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, ^{1}H-NMR and HRMS) of the new compounds in this communication were obtained.

(Received March 13, 1993)