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Regioselective cyclization of *m*-acylaryl 1,1-dimethylpropargyl ethers giving 5-acyl-2,2-dimethyl-2*H*-chromenes

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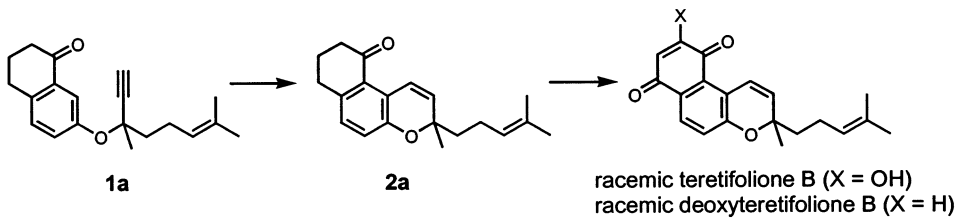
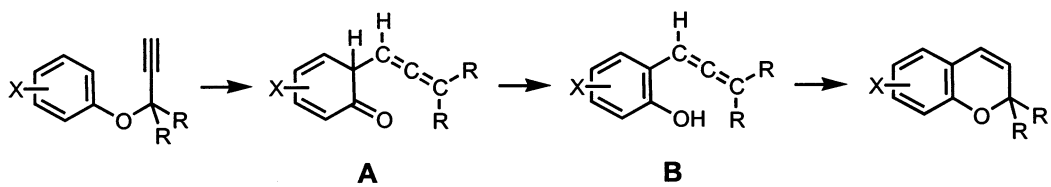
Abstract—Thermal cyclization of some *m*-acylaryl 1,1-dimethylpropargyl ethers (**1a–f**) effected regioselective *ortho*cyclization giving the corresponding 5-acyl-2,2-dimethyl-2*H*-chromenes (**2a–f**)

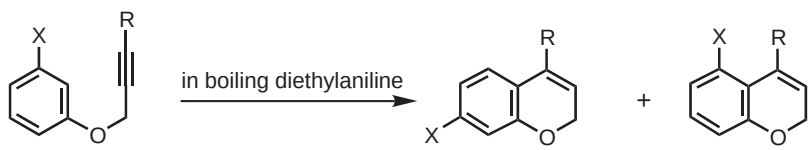
Our recent interest has been focused on the synthesis of natural 2,2-dimethyl-2*H*-chromenes.[1] As a key compound for natural teretifolione B and deoxyteretifolione B, as shown in Scheme 1, 3-methyl-3-(4-methyl-3-pentenyl)-8,9-dihydro-10(7*H*)-benzo[*f*]chromenone (**2a**) was prepared by several methods,[2] and the thermal cyclization of 7-(1-ethynyl-1,5-dimethyl-4-hexenyl)oxy-3,4-dihydro-1(2*H*)-naphthalenone (**1a**) was the most effective method. The regioselective cyclizations of some *m*-acylphenyl 1,1-dimethylpropargyl ethers giving the corresponding 5-acyl-2,2-dimethyl-2*H*-chromenes are described in this paper.



Scheme 1.



Scheme 2.



Scheme 3.

Keywords: chromenes; cyclization; regioselection.

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Thermal cyclization of a phenyl propargyl ether is an effective procedure for preparing the corresponding 2*H*-chromene.[3] It is effectively carried out by refluxing in *N*,*N*-diethylaniline, and the mechanism is explained as shown in Scheme 2; the substrate is first converted to an *ortho*-rearranged allene A via [3,3]sigmatropic rearrangement, and A is readily re-aromatized to give an allenic phenol B, which consecutively effects the cyclization giving the corresponding 2*H*-chromene.

The substituent effects have already been described in earlier papers.[3] Methyl substituent (R = Me) at the propargyl side chain stabilizes the allene intermediate B (or A), and the yields of 2,2-dimethyl-2*H*-chromenes are usually higher than those of non-substituted 2*H*-chromenes.

In cyclizations of *m*-substituted phenyl propargyl ethers, as shown in Scheme 3, two directions of cyclization are possible; *ortho*-cyclization gives 5-substituted 2*H*-chromenes and *para*-cyclization gives 7-substituted 2*H*-chromenes. Cyclizations of some *m*-substituted phenyl propargyl ethers were already studied; most of them showed non-regioselective cyclization giving both chromenes in approximately 50:50 ratio; *m*-methoxy (X = OMe) shows the ortho/para ratio 49/51 in 24.4% (15 h),[3b] *m*-chloro (X = Cl) shows 25/75 in 64% (14 h),[3b] *m*-acetoxy (X = OAc) shows 57/43 in 51% (15 h),[3b] and *m*-methyl (X = Me) shows 47/53 in 89% (15 h).[3b] A few of them showed regioselective cyclization; 7-coumarinyl or 2-naphthyl propargyl ether shows *ortho*-selective cyclization, and *m*-methoxyphenyl 1,1-dimethylpropargyl ether shows *para*-selective cyclization. The *ortho*-selectivity in 7-coumarinyl or 2-naphthyl propargyl ether was explained by the character of the aromatic C=C bond (having higher bond order), and the *para*-selectivity in *m*-methoxyphenyl 1,1-dimethylpropargyl ether was explained by the steric hindrance.

According to the improved procedure,[4] propargyl ether **1b** was effectively prepared from 7-hydroxy-3,4-dihydro-1(2*H*)-naphthalenone (**4a**) and 3-methylbut-1-yn-3-ol by stirring with trifluoroacetic anhydride in the presence of copper(II) chloride. Then, **1b** was heated in *N*,*N*-dimethylaniline at 160°C for 1 h for the cyclization. The thermal cyclization gave the desired angular chromene **2b** in 90% yield, and gave only 5% of the linear isomer, 2,2-dimethyl-7,8-dihydro-2*H*,6*H*-benzo[*g*]chromen-9-one (**3b**). Then, 7-(1-ethynyl-1,5-dimethyl-4-hexenyl)oxy-3,4-dihydro-1(2*H*)-naphthalenone (**1a**) was similarly prepared from **4a** and 3,7-dimethyloct-6-en-1-yn-3-ol in 55% yield, and the cyclization of **1a** selectively gave 3-methyl-3-(4-methyl-3-pentenyl)-8,9-dihydro-10(7*H*)-benzo[*f*]chromenone (**2a**) in 86% yield, and the corresponding linear isomer **3a** was not observed.

An earlier paper described that the electron-withdrawing group (X = Ac) on the aromatic ring deactivates the thermal cyclization.[3e] However, the cyclizations of **1a** and **1b**, in spite of having an electron-withdrawing carbonyl group, show both good yields and high *ortho*-selectivity. To clarify the effectivity and regioselectivity in the cyclization, the thermal cyclizations of some other *m*-acylaryl 1,1-dimethylpropargyl ethers (**1c**–**f**) were similarly studied. 6-(1,1-Dimethyl-2-propynyl)oxy-1-indanone **1c**, having a different ring size, *m*-acetyl **1d** and *m*-formyl **1e**, having non-fixed carbonyl conformations by free-rotation, and **1f**, having a fixed carbonyl conformation by hydrogen-bonding, were subjected to the cyclization, and the results are summarized in Table 1.

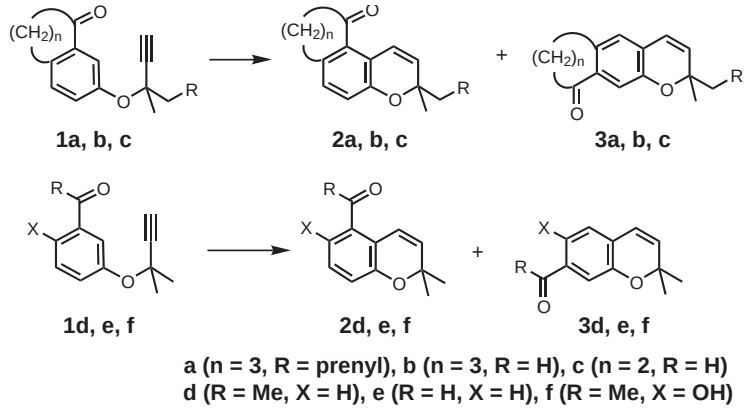
An earlier paper showed that thermal cyclizations of some *m*-substituted phenyl propargyl ethers, having no substituent at the propargyl part, require long reaction time (15 h) and most of the yields are low (<10–64%) except the substrate having *m*-methyl substituent (89%).[3c] Another paper showed that *m*-methoxyphenyl and 7-coumarinyl 1,1-dimethylpropargyl ethers require reaction time of 8 h and 2 h, respectively, and both yields are high (80–95%).[3d]

But, in our data shown in Table 1 and Scheme 4, the cyclization of **1a**–**c** and **1f** was completed after 1 h, and it shows high regioselective *ortho*-cyclization. The cyclizations of **1d** and **1e** require longer reaction time, 4 h and 7.5 h, respectively, and show lower *ortho*-selectivity.

These observations led us to a new different conclusion; *m*-acyl groups may serve to activate the cyclization and

Table 1. Thermal cyclizations of some *m*-acylaryl 1,1-dimethylpropagyl ethers **1**

Entry	Substrate propargyl ether **1**	Cyclization time	Cyclized products		Recovery
			2 (Yield: %)	**3** (Yield: %)	**1** (Yield: %)
1	**1a**	1 h	**2a** (86%)	–	–
2	**1b**	1 h	**2b** (90%)	**3b** (5%)	–
3	**1c**	1 h	**2c** (87%)	–	–
3	**1d**	1 h	**2d** (28%)	**3d** (5%)	**1d** (47%)
4	**1d**	4 h	**2d** (66%)	**3d** (20%)	–
5	**1e**	1 h	**2e** (39%)	**3e** (10%)	**1e** (8%)
6	**1e**	7.5 h	**2e** (56%)	**3e** (14%)	–
7	**1f**	1 h	**2f** (83%)	–	–



Scheme 4.

1,1-dimethyl substituents serve to stabilize the allene intermediate.

This conclusion was quite different from that of Anderson's, that is, an electron-withdrawing group may deactivate the thermal cyclization. Anderson's opinion might be based on the low yield of the *m*-acetylpheny derivative. However, in our revised opinion, it should be due to the instability of the allenic intermediate, not to the deactivation.[5] The low yield of the *m*-diethylaminophenyl derivative, shown in Anderson's report, should be due to the deactivation and this may support our conclusion.[6] The conclusion is "the inductive effects of the *m*-acyl groups activate the thermal cyclization." The high efficiency in the cyclizations of **1a–c** and **1f** might be explained by the co-planarity of the carbonyl, and the lower efficiency in **1d** and **1e** might be explained by the free-rotation of the carbonyl. The *ortho*-selectivity in the thermal cyclization of (*m*-acylaryl)phenyl propargyl ethers also may be explained by the stronger inductive effect of the carbonyl group on the ortho position.

References

1. Yamaguchi, S.; Shouji, N.; Kuroda, K. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 305.
2. Condensation of 8-formyl-7-hydroxy-3,4-dihydro-1(2*H*)-naphthalenone with methyl 3-methyl-2-butenoate gave **2b** in 5% yield. Cyclization of 4-(2,2-dimethyl-2*H*-chromen-6-yl)butanoic acid with trifluoroacetic anhydride gave **2b** (19%: minor) and **3b** (78%: major). The details will be reported soon.
3. (a) Iwai, I.; Ide, J. *Chem. Pharm. Bull.* **1962**, *10*, 926; (b) Iwai, I.; Ide, J. *Chem. Phar. Bull.* **1963**, *11*, 1042; (c) Hlubucek, J.; Ritchie, E.; Taylor, W. C. *Tetrahedron Lett.* **1969**, 1369; (d) Hlubucek, J.; Ritchie, E.; Taylor, W. C. *Aust. J. Chem.* **1971**, *24*, 2347; (e) Anderson, W. K.; Lavoie, E. J.; Whitkop, P. G. *J. Org. Chem.* **1974**, *39*, 881.
4. Some aryl 1,1-dimethylpropargyl ethers were previously prepared from the corresponding phenols and 3-bromo-3-methyl-1-butyne, but the yields were not so good. Recently a new revised procedure, treating phenols and 2-methyl-3-butyn-2-ol with trifluoroacetic anhydride-copper(II) chloride, was reported by Godfrey, Jr., J. D.; Mueller, R. H.; Sedergran, T. C.; Soundarajan, N.; Colandrea, V. J. *Tetrahedron Lett.* **1994**, *35*, 6405.
5. The low yield in *m*-Ac might be due not to the deactivation but to the unstabilizing effect of non-methyl substituent in the allenic intermediate.
6. The substituent of *m*-NEt_2 showed selective *ortho*-cyclization but only in low yield. The *m*-diethylamino group, being a powerful electron-donating group, might deactivate the cyclization and, furthermore, 7-diethylamino substituent enhances the electron-density in the chromene double bond. The decomposition of the *para*-cyclized product may apparently enhance the *ortho*-cyclization ratio.