CESIUM FLUORIDE-MEDIATED CLAISEN REARRANGEMENT OF ARYL PROPARGYL ETHER AND ITS APPLICATION TO THE SYNTHESIS OF CHELERYTHRINE

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In the presence of cesium fluoride, the Claisen rearrangement of aryl propargyl ethers selectively provided 2-methylbenzofurans, which was successively treated with osmium tetroxide, periodic acid and 5% sodium hydroxide to give salicylaldehydes in good yields. The method was used to synthesize chelerythrine (**2**) *via* the common intermediate (**8**) prepared by the two routes as shown in Chart 3.

KEYWORDS benzo[c]phenanthridine alkaloid synthesis; chelerythrine; antileukaemic activity; Claisen rearrangement; cesium fluoride; aryl propargyl ether; benzofuran

In previous papers,[1] we reported the generally applicable synthesis method for the fully aromatized, phenolic and non-phenolic nitidine (**1**) type of benzo[c]phenanthridine alkaloids, which have attracted attention because of their antileukaemic properties.[2] However, the Bischler-Napieralski reaction[1a] of the aromatic amide (**3**) produced exclusively nitidine (**1**) through the expected cyclization of formyl group to the *para* position of the C_3-methoxy group and produced no chelerythrine (**2**), as shown in Chart 1. Therefore, we planned to develop a widely applicable method for the synthesis of chelerythrine type of alkaloids, which have four successive substituents on a benzene ring. We designed a way to utilize a Claisen rearrangement of the aryl propargyl ether (**A**) appropriately substituted for the synthesis of chelerythrine (**2**), since the Claisen rearrangement of the ether (**A**), followed by oxidative cleavage is anticipated to be useful for a regioselective introduction of carbon unit at the *ortho* position to phenol, as shown in Chart 2. In 1962, Iwai and Ide reported that a thermal Claisen rearrangement of β-naphthyl propargyl ether (**4**) in diethylaniline under reflux for 0.5 h gave exclusively benzopyran (**5**) in 40% yield.[3] Claisen rearrangement of a primary ether (**A**, R=H) other than **4** generally gives a poorer yield than that of a tertiary ether (**A**, R=Me).[4] Since a primary propargyl ether can be prepared easily in high yield, an examination of the mechanism for Claisen rearrangement proposed by Schmid *et al.*[5] was made to obtain a clue for improving the yield of the Claisen rearrangement of the primary ether (**A**, R=H). According to this mechanism, it appeared that the enolization step of α-allenylketone (**B**) would be a rate determining one, and addition of cesium fluoride (CsF) as a soft base would accelerate the enolization and easily cause a Claisen rearrangement to give rise to benzopyran (**E**). On the basis of this assumption, the Claisen rearrangement of **4** in the presence of CsF was investigated. Unexpectedly, heating of **4** in diethylaniline at 215°C for 1 h gave selectively 2-methylbenzofuran (**6**), in contrast to Iwais' results [3] (a thermal Claisen rearrangement without CsF). So the Claisen rearrangement of **4** under reaction conditions was investigated using various molar equivalents of CsF or other additives. The results are listed in Table 1, showing that CsF is essential and

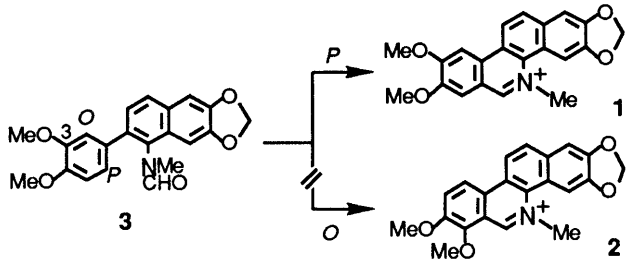


Chart 1

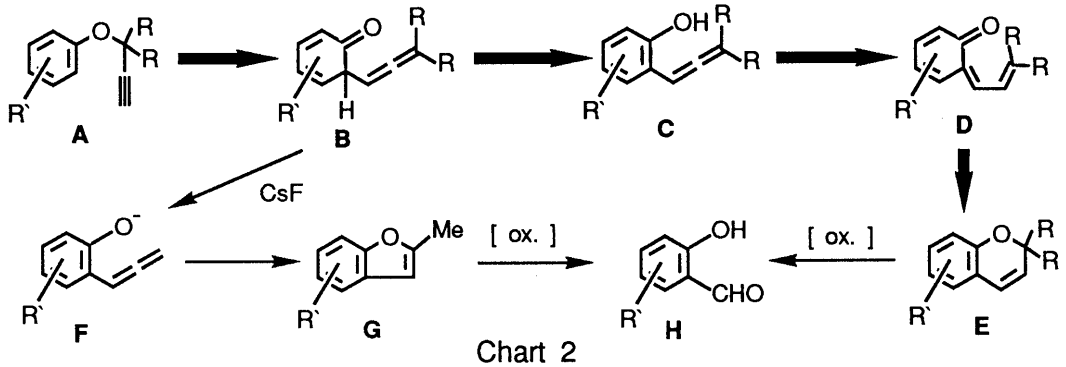
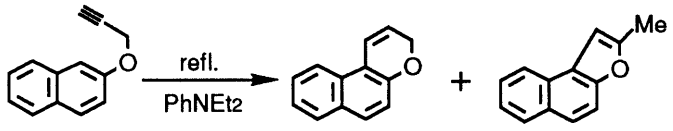


Chart 2

Table I. The Effects of Additives on Claisen Rearrangement of **4**



Additive (mol eq)	Yield (%) 5/6	Additive (mol eq)	Yield (%) 5/6
CsF (0.01)	25.4/59.6	KF (26.3)	84.0/—
(0.1)	6.8/86.9	RbF (14.6)	97.3/—
(1.4)	4.3/84.6	CaF_2 (19.4)	85.7/—
(10.0)	2.2/85.7	BaF_2 (8.7)	86.8/—
CsCl (9.1)	88.8/—		

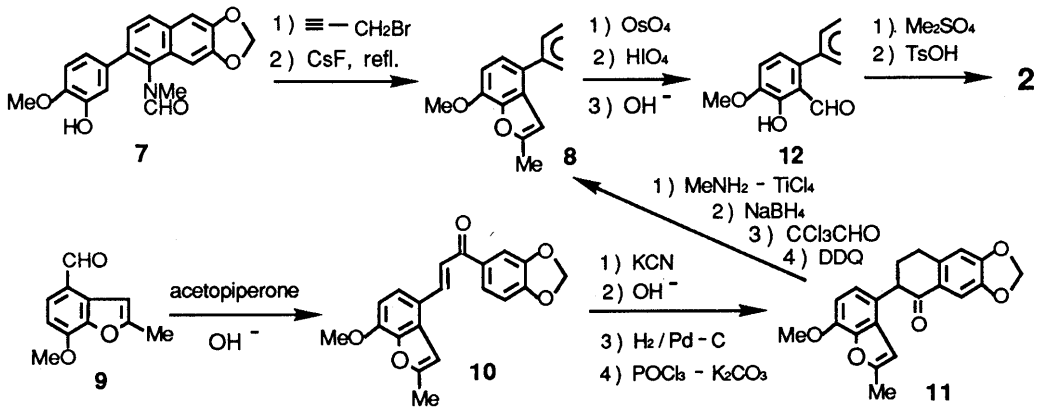


Chart 3

even a catalytic amount of CsF is enough to form benzofuran (**6**).[6] This can be reasonably explained assuming that the enolate anion (**F**) generated by abstraction of α-hydrogen atom in the α–allenylketone (**B**) with CsF makes a nucleophilic attack on the central carbon atom of the allenyl group.[7] Subsequently, by taking advantage of the Claisen rearrangement of the aryl propargyl ether, we attempted to synthesize chelerythrine (**2**).

Propargylation of phenol (**7**),[8] followed by a CsF-mediated Claisen rearrangement in diethylaniline at 215°C afforded exclusively benzofuran (**8**) in 56.9% yield.[9] On the other hand, the key intermediate (**8**) was prepared by another route of applying our method developed for the synthesis of nitidine.[1a] Thus, aldehyde (**9**) was prepared *via* propargylation of isovanilline, acetalization with ethyl orthoformate, CsF-mediated Claisen rearrangement, and acid treatment in 55.5% yield. The Claisen-Schmidt reaction of **9** with acetopiperone produced chalcone (**10**), which was successively subjected to hydrocyanation with potassium cyanide, alkaline hydrolysis, hydrogenolysis on Pd-C and basic intramolecular acylation[1c] to provide tetralone (**11**) in 50.8% yield from **9**. Reductive alkylation[1a] of **11**, followed by formylation[1a] with freshly distilled chloral and dehydrogenation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) gave the key intermediate (**8**) mentioned above in 70.5% yield from **11**. Successive treatment of **8** with a stoichiometric amount of osmium tetroxide in pyridine, periodic acid, and aqueous 5% sodium hydroxide gave salicylaldehyde (**12**), which was methylated with dimethylsulfate and subsequently treated with *p*-toluenesulfonic acid in xylene under reflux to yield chelerythrine (**2**)[10, 11] in 22.9% yield.

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REFERENCES AND NOTES

1) a) H.Ishii, Y.Ichikawa, E.Kawanabe, M.Ishikawa, T.Ishikawa, K.Kuretani, M.Inomata, and A.Hoshi, *Chem. Pharm. Bull.*, **33**, 4139 (1985); b) H.Ishii, I.-S.Chen, and T.Ishikawa, *J. Chem. Soc., Perkin Trans. 1,* **1987**, 671; c) H.Ishii, I.-S.Chen, S.Ueki, T.Masuda, K.Morita, and T.Ishikawa, *J. Chem. Soc., Perkin Trans.1,* **1987**, 2415.
2) M.Suffness and G.A.Cordell, "The Alkaloids," Vol. **25**, ed. by A.Brossi, Academic Press, Inc., New York, 1985, p1.
3) I.Iwai and J.Ide, *Chem. Pharm. Bull.,* **10,** 926 (1962).
4) M.Harfenist and E.Thom, *J. Org. Chem.*, **37**, 841 (1972).
5) J.Zsindely and H.Schmid, *Helv. Chim. Acta,* **51**, 1510 (1968).
6) However, a relatively large amount (1.4 mol eq) of CsF was required for reliable results. In this regard, the CsF-mediated Claisen rearrangement of the propargyl ethers of vanillin diethyl acetal, isocreosole, and isoscopoletin also afforded the corresponding respective benzofurans in good yields, whereas the thermal Claisen rearrangement of the propargyl ethers mentioned above afforded the corresponding benzopyrans. These facts indicate the generality of the new reaction. These details will be reported in separate papers.
7) R.Gaertner, *J. Am. Chem. Soc.*, **73**, 4400 (1951).
8) H.Ishii, I.-S.Chen, S.Ueki, M.Akaike, and T.Ishikawa, *Chem. Pharm. Bull.*, **35**,.2717 (1987).
9) Thermal Claisen rearrangement of propargyl ether of **7** in diethylaniline afforded a benzopyran derivative only in 17.9% yield.
10) H.Ishii, T.Ishikawa, and J.Haginiwa, *Yakugaku Zasshi*, **97**, 890 (1977).
11) For synthesis, see. a) A.S.Bailey and C.R.Worthing, *J. Chem. Soc.,* **1956**, 4535; b) M.Onda, K.Yonezawa, and K.Abe, *Chem. Pharm. Bull.*, **19**, 31 (1971); c) J.Šmidrkal, *Collect. Czech. Chem. Commun.*, **49**, 1412 (1984); d) M.Hanaoka, T.Motonishi, and C.Mukai, *J. Chem. Soc., Perkin Trans. 1,* **1986**, 2253; e) S.V. Kessar, Y.P.Gupta, P.Balakrishnan, K.K.Sawal, T.Mohammad, and M.Dutt, *J. Org. Chem.*, **53**, 1708 (1988).

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