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 C₃-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 Iwai's results³⁾ (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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