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Acid-promoted rearrangement of 2-aryl-2,3-epoxy acylates: construction of chiral benzylic quaternary carbon centers

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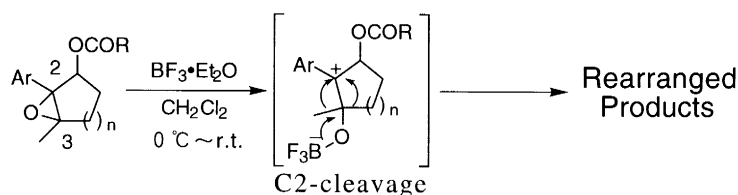
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Abstract

The reactions of 2-aryl-2,3-epoxy acylates with $\text{BF}_3 \cdot \text{Et}_2\text{O}$ were examined in detail. *Trans*-2-aryl-2,3-epoxy acylates afforded the rearranged products in good yields via the C2-carbocation intermediates. The reaction was used for constructing the optically active benzylic quaternary carbon center. © 2000 Elsevier Science Ltd. All rights reserved.

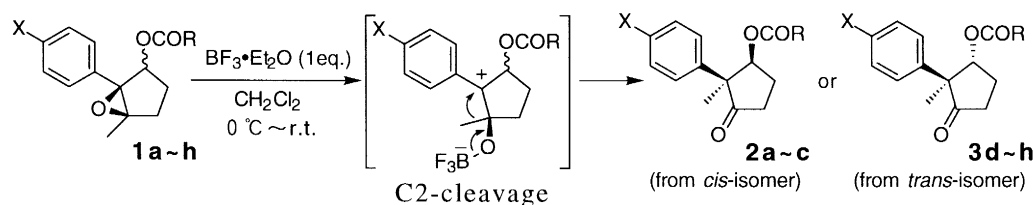
Recently, we disclosed the Lewis acid-promoted rearrangement of 2,3-epoxy acylates.¹ In these cases, acylates work as electron-withdrawing groups and the 2,3-epoxy acylates rearrange via C3-cleavage of the oxirane ring. On the other hand, in our synthesis of fredericamycin A, we found that the rearrangement reactions of the tetrahydrobenz[e]indan systems proceeded via C2-cleavage of the oxirane ring.² The phenyl group is known as a cation-stabilizing group, and phenyl epoxides also rearranged via the benzylic cation intermediates.³ We wondered if a benzo-fused system like fredericamycin A was a special case or the 2,3-epoxy acylates with a C2-aryl substituent rearranged via the C2-cleavage of oxirane. In other words, which is more stable, the C2- versus the C3-carbocation during the rearrangement of the 2,3-epoxy acylates with a C2-aryl substituent? We now present evidence that the cyclic 2-aryl-2,3-epoxy acylates rearrange via the C2-cleavage of oxirane (Scheme 1).



Scheme 1.

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We first investigated the five-membered epoxy acylates (Scheme 2, Table 1). Every reaction occurred via the C2-cleavage of the oxirane ring. The *cis*-epoxy acylates **1a–1c** rearranged in low yields along with reasonable side products, orthoesters by neighboring group participation from pivalate **1a** and benzoate **1b** and the enone via hydride rearrangement and dehydration from *p*-nitrobenzoate **1c** (Entries 1–3). The *trans*-epoxy acylates **1d–1f** afforded high yields of the corresponding rearrangement products **3d–3f** (Entries 4–6).⁴ The rearranged products **3** from the *trans*-epoxy acylates are different from the products **2** of the *cis*-epoxy acylates. This means that the rearrangements proceeded in a stereospecific manner. Among the used acyloxy groups, the *p*-nitrobenzoyloxy group is the best based on the reaction time and the chemical yield (Entry 6). The effect of the substituent on the aromatic ring was next studied. The 4-methoxyphenyl group accelerated the rearrangement and a very high yield of the product **3g** via C2-cleavage was obtained for a short reaction time (Entry 7).

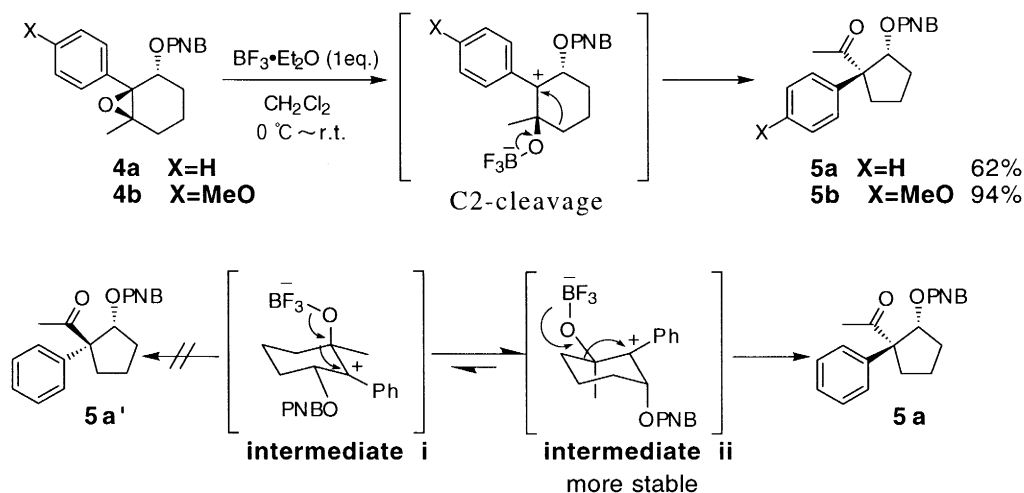


Scheme 2.
Table 1

Entry	RCO	X	Time	2	3	Byproduct
1	1a : <i>cis</i> -Piv	H	3.5hr	2a : 25%	–	48%
2	1b : <i>cis</i> -Bz	∕	5hr	2b : 27%	–	43%
3	1c : <i>cis</i> -PNB	∕	2hr	2c : 50%	–	31%
4	1d : <i>trans</i> -Piv	∕	2day	–	3d : 84%	–
5	1e : <i>trans</i> -Bz	∕	3day	–	3e : 67%	–
6	1f : <i>trans</i> -PNB	∕	3hr	–	3f : 90%	–
7	1g : ∕	MeO	15min	–	3g : 97%	–
8	1h : ∕	AcO	3hr	–	3h : 96%	–

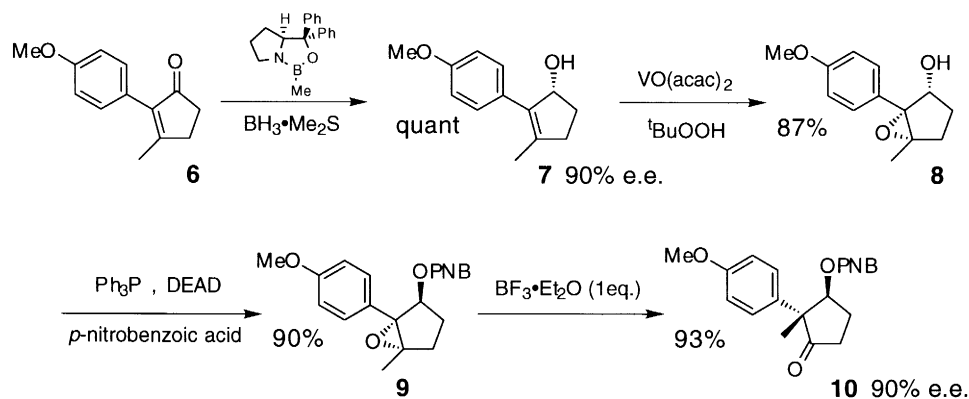
Rearrangement via C2-cleavage of the oxirane ring was also observed in the six-membered ring. 2-Phenyl *trans*-epoxy *p*-nitrobenzoate **4a** afforded the ring-contracted five-membered product **5a** via C2-cleavage of the oxirane ring followed by ring-methylene rearrangement. The structure of the product was unambiguously determined by X-ray analysis. The configuration of the quaternary carbon center proved to be opposite to the product predicted by the concerted rearrangement. Quite recently, Neef et al. reported that it is very difficult to predict the configuration of the quaternary carbon center produced

by the rearrangement via the benzylic cation intermediates, because the benzylic group prolongs the lifetime of the cation and the rearrangement proceeds in a non-concerted way.⁵ However, we rationalized that our result must be due to the more stable conformation of the cation intermediate **ii** rather than to the intermediate **i** because of the long lifetime of the cation. In fact, the PM3 calculation shows that intermediate **ii** is 3.2 kcal/mol more stable than intermediate **i**. The same rearrangement was observed in the reaction of 2-(4-methoxyphenyl)*trans*-epoxy *p*-nitrobenzoate **4b** to give **5b** in good yield (Scheme 3).



Scheme 3.

We next determined that our method was applicable to the construction of optically active benzylic quaternary carbon centers. Optically active epoxy *p*-nitrobenzoate **9** was prepared by the asymmetric reduction of the corresponding enone **6** by Corey's method,^{6,7} epoxidation with *t*-BuOOH/ $\text{VO}(\text{acac})_2$,⁸ then the Mitsunobu reaction with *p*-nitrobenzoic acid.⁹ Treatment of the epoxy *p*-nitrobenzoate **9** with $\text{BF}_3 \cdot \text{Et}_2\text{O}$ afforded the optically active product with the same enantiomeric excess value as the starting epoxy alcohol **7**¹⁰ (Scheme 4).



Scheme 4.

In conclusion, we found that the C2-carbocations are more stable than the C3 ones in the 2-aryl-2,3-epoxy acylate systems and rearrangement proceeds via C2-cleavage of the oxirane with stereospecificity and succeed in the construction of the optically active benzylic quaternary carbon center. Since many

natural products contain a chiral benzylic quaternary carbon center, this method would be a useful tool for constructing them.

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