4*H*-1,2-Benzoxazines with Electron-Withdrawing Substituents on the Benzene Ring: Synthesis and Application as Potent Intermediates for Oxygen-Functionalized Aromatic Compounds

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Although 4*H*-1,2-benzoxazine is one of the fundamental structures of the oxazine group, its chemical nature has not been well studied simply because of the lack of the general synthetic methods for 4*H*-1,2-benzoxazines. Some derivatives of 4*H*-1,2-benzoxazine were synthesized for the first time by means of a Friedel–Crafts type reaction of nitroalkenes with benzene in the presence of a superacid such as trifluoromethanesulfonic acid (TFSA).[1a–d] However, the method has limitations for synthesizing 4*H*-1,2-benzoxazine derivatives bearing substituents on the benzene ring, because biaryl compounds are obtained as major products in the intermolecular reaction with substituted benzenes and nitroalkenes.[1d] Other reports have also described synthesis of derivatives of 4*H*-1,2-benzoxazines, but the yields were low, and the methods lack generality, since only limited starting materials can be employed and the structures of the products are too complicated for easy further modification.[1e–k] Thus, a general synthetic method of 4*H*-1,2-benzoxazines has not been established, and the potential of this heterocycle in organic synthesis and functional molecular sciences, such as materials and pharmaceutical sciences, remains unknown.[1l]

Herein, we present the acid-catalyzed cyclization reaction of 1-nitro-2-arylethane derivatives as a general method to obtain the corresponding 4*H*-1,2-benzoxazines. We also show that this type of heterocycle can be a potent intermediate to oxygen-functionalized aromatic compounds, which represent basic architecture for functionalized materials such as medicines.

We first examined the acid-catalyzed cyclization reaction of 2-nitro-3-phenylpropane **1** as a model substrate. No cyclization reaction of **1** took place in the presence of acids such as TFA or TFSA. We found, however, that the sodium salt **2** gave 3-methyl-4*H*-1,2-benzoxazine **3** in 27% yield in the presence of TFA (Scheme 1). These results suggest that an *aci*-nitro species or *O*-protonated *aci*-nitro species participates in the cyclization reaction.[1c] Thus, we studied the reaction of methyl 2-nitro-3-phenylpropionate **4a**, in which the ester group facilitates enolization to the *aci*-nitro species.[2] When methyl 2-nitro-3-phenylpropionate **4a** was added to 10 equiv of TFSA with CHCl$_3$ as a cosolvent and the mixture was heated at 50 °C for 30 min, 3-methoxycarbonyl-4*H*-1,2-benzoxazine **5a** was obtained in 85% yield. Without the use of the cosolvent, the yield of **5a** was decreased (<58%). The reaction did not proceed at all in TFA even when it was carried out for 2 days under reflux. This result indicates that the reaction requires extremely high acidity, which probably catalyzes both enolization of **4a** to the *aci*-nitro form and the cyclization process. This is consistent with the fact that α-ethoxycarbonylnitromethane is enolized to the *aci*-nitro form in TFSA, while such enolization does not occur in a weaker acid such as TFA.[2] The reaction also proceeded in the presence of an

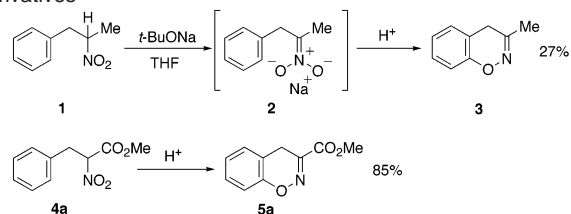**Scheme 1.** Acid-Catalyzed Cyclization of 1-Nitro-2-Phenylethane Derivatives

Table 1. Cyclization of Methyl 3-Aryl-2-Nitropropionates to Substituted 4*H*-1,2-Benzoxizines

entry[a]	reactant (**4**)	product (**5**)	yield (%)
1	**4a**	**5a**	85
2	**4b**	**5b**	93
3	**4c**	**5c**	88
4	**4d**	**5d** + **5d'**	total 78 (**5d:5d'**=89:11)
5	**4e**	**5e**	38
6[b]	**4f**	**5f**	85
7[b]	**4g**	**5g**	98
8	**4h**	**5h**	88
9[b]	**4i**	**5i**	59
10	**4j**	**5j**	81
11	**4k**	**5k**	16
12	**4l**	**5l** + **6**	trace 55

[a] Typical reaction conditions: a solution of the substrate (1.0 mmol) in 10 mL of CHCl$_3$ was added to 10 equiv amount of TFSA (0.89 mL) at 0 °C. The mixture was heated at 50 °C for 30 min. [b] 50 equiv of TFSA was used.

excess amount of a Lewis acid such as TiCl$_4$, but the yield was moderate (45%).

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Then, similar reactions of methyl 3-aryl-2-nitropropionates (**4b**–**4l**) with various substituents on the benzene ring were investigated (Table 1). To our surprise, the reactions proceeded smoothly to give the corresponding 4*H*-1,2-benzoxazines in moderate to good yields even when the substituent on the benzene ring was an electron-withdrawing group such as a halogen **4b**–**4e**, ester **4f**, amide **4g**, trifluoromethyl **4h**, cyano **4i**, or nitro group **4j**. In contrast, the reaction of substrates with an electron-donating group on the benzene ring resulted in low yields of the 4*H*-1,2-benzoxazines. In the case of **4k** (methyl), the yield of **5k** was only 16%. In particular, the reaction of **4l** (methoxy) gave the spiro compound **6** as a major product together with a trace amount of the corresponding 4*H*-1,2-benzoxazine **5l**.[1f]

Next, the potential to generate oxygen-functionalized aromatic compounds via the 4*H*-1,2-benzoxazines obtained here was examined (Scheme 2). It was reported that 3-alkyl analogues of 4*H*-1,2-benzoxazine such as **3** can undergo thermal formation of *o*-benzoquinone methide **7a**,[4] which is a useful reactive intermediate in organic synthesis.[1c,5–7] Gentle heating of a solution of **5a** in toluene in the presence of styrene gave a chroman derivative **8a** in 56% yield. This product was formed by the Diels–Alder reaction of the in-situ formed **7a** with styrene. Similar reactions proceeded in good yields (77–93%) when we used **5b** (*p*-Cl), **5f** (*p*-CO$_2$Me), **5g** (*p*-CON(*i*-Pr)$_2$), or **5i** (*p*-CN). These results support the generation of *o*-benzoquinone methides bearing a halogen **7b**, ester **7f**, amide **7g**, or cyano group **7i** on the benzene ring, which have not been reported before. These aromatic substituents can easily be further transformed in various ways so that the synthetic value of *o*-benzoquinone methide would be greatly extended by this approach.

Scheme 2. Transformation to Oxygen-Functionalized Aromatic Compounds via 4*H*-1,2-Benzoxiazines
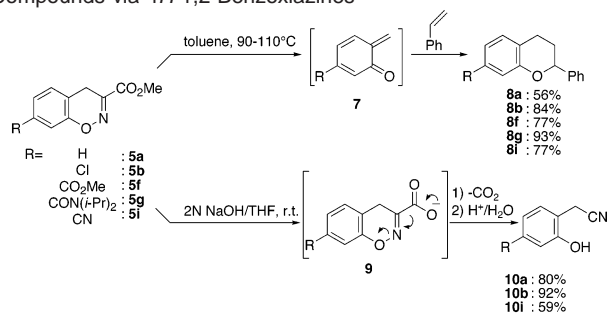
Furthermore, basic hydrolysis of **5a** in aqueous sodium hydroxide in THF gave (2-hydroxyphenyl)acetonitrile **10a** in 80% yield. This product is assumed to be formed through decarboxylative *N*–*O* bond cleavage of the resulting carboxylate ion **9**. We confirmed that other derivatives, **5b** and **5i**, gave the corresponding phenols, **10b** and **10i**, respectively, under the same reaction conditions. This is a new synthetic route to multisubstituted phenols.

In conclusion, we have established a general synthetic method of 4*H*-1,2-benzoxazine derivatives with various substituents, especially electron-withdrawing groups, on the benzene ring from arylnitroalkanes. The compounds obtained by this method provide a new scaffold for medicinal chemistry. We have also preliminarily established the potential intermediacy of the 4*H*-1,2-benzoxazines for synthesizing *o*-benzoquinone methides and phenols. These transformations can be regarded as an intramolecular transfer of an oxygen atom of the nitro group of **2** to the benzene ring through the 4*H*-1,2-benzoxazines **3**. Further studies on the reaction mechanisms and other possible applications of 4*H*-1,2-benzoxazines in organic synthesis and pharmaceutical sciences are under way.

Supporting Information Available: Experimental procedures and characterizations (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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