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Remarkable Differences in Reactivity between Cyanide and N-Heterocyclic Carbenes in Ring-Closing Reactions of 4-(2-Formylphenoxy)but-2-Enoate Derivatives

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Cyanide and N-heterocyclic carbenes (NHCs) have been known to display similar reactivity as versatile organocatalysts in organic transformations.¹ Particularly, they can serve as nucleophilic catalysts toward the aldehyde to generate umpolung of the aldehyde, *i.e.*, conversion of an electrophilic reactivity of the aldehyde to a nucleophilic reactivity,² and a number of useful organic transformations including benzoin and Stetter reactions have been developed based on the umpolung reactivity of the aldehyde.¹ Despite the general acceptance of the similar reactivity of cyanide and NHCs in the generation of umpolung of the aldehyde, there have been few actual studies on the difference in reactivity between them.^{3,4} Herein, we describe the significant reactivity difference between cyanide and NHCs in the ring-closing reaction of 4-(2-formylphenoxy)but-2-enoate derivatives; NHCs afford dihydrochromones derivatives via the intramolecular Stetter reaction, while cyanide acts а base catalyst to provide as 2-vinylbenzofurans through aldol condensation reaction.

Since the intramolecular Stetter reaction of 4-(2-formylphenoxy)but-2-enoate derivatives **1** leading to dihydrochromones **2** is one of the most well-developed reactions utilizing the umpolung reactivity of the aldehyde with a NHC catalyst,⁵ we compared the reactivity between NHCs and cyanide in the Stetter reaction using methyl 4-(2-formylphenoxy)but-2-enoate (**1a**) as a model compound (Scheme 1).

As expected, when **1a** was treated with a catalytic amount of NHC catalyst derived from thiazolium salt in the presence of base, the corresponding dihydrochromone **2** was obtained in a quantitative yield in 22 h through the intramolecular Stetter reaction.⁶ On the other hand, the treatment of **1a** with a catalytic amount of cyanide provided no Stetter product **2** even though **1a** was completely consumed in 10 min at room temperature. In addition, the resulting mixture was warmed to 80 °C to afford the 2-vinylbenzofuran **3a** with 85% yield in 2 h.⁷

With this rather unexpected result in hand, we explored the generality of 4-(2-formylphenoxy)but-2-enoates 1 with a catalytic amount of cyanide (Table 1). The electronic nature of the substituents on the phenyl ring had little influence on the efficiency of this transformation and the desired benzofurans **3** were obtained in high yields regardless of the electronic nature of a substituent (entries 1–4). In addition, the position of a substituent on the phenyl ring was also found to exert little effect on the formation of the desired products **3** (entries 4–6). The steric bulk of the ester moiety was further investigated and found that the efficiency of this transformation was little affected by the size of alkoxy group in the ester moiety (entries 1 and 7). Furthermore, this protocol could be applicable to the preparation of benzofuran derivative bearing a simple ester moiety at the 2-position although this substrate displayed lower reactivity than its vinylogous analogues (entry 8) (Scheme 2).

With these rather unexpected results in hand, we performed several control experiments to understand the reaction mechanism for this transformation. When 1a was treated with 10 mol% of cyanide, 1a was completely consumed in 10 min and a mixture of aldol product A^8 were obtained in a quantitative yield (Eq. (1)). Then, the dehydration of the resulting mixture of the aldol adduct A was investigated. It was found that both cyanide and reaction temperature played a critical role in the dehydration leading to the desired benzofuran 3a. When the resulting mixture from Eq. (1) was directly subjected to the dehydration reaction at room temperature, only trace amount of 3a was obtained. However, the dehydration reaction occurred at 80°C to provide benzofuran **3a** in quantitative yield in 2 h (Eq. (2)). In addition, when the isolated aldol product A was subjected to the thermal dehydration conditions at



Scheme 1. Reactivity difference between NHCs and cyanide with ring-closing reaction of 1a.

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 Table 1. Substrate scope



^a 100 mol% of NaCN was used.

80 °C in the absence of cyanide, the formation of **3a** was not observed even after 24 h (Eq. (3)). However, upon addition of a catalytic amount of cyanide to the reaction mixture, the elimination reaction again proceeded to provide **3a** in a similar efficiency (Eq. (4)). Since cyanide acts as the active catalyst in cyclization and dehydration, **1a** could be directly converted to **3a** at 80 °C in a much shorter reaction time without any loss of efficiency (Eq. (5)).

Based on this result, we rationalized the reactivity difference between cyanide and NHCs toward the cyclization of compound 1. NHCs acts as a nucleophilic catalyst to the aldehyde in 1 to generate the Breslow intermediate I,⁹ which subsequently undergoes the Michael reaction leading to intermediate II. Hydrolysis of II would afford dihydrochromone 2 and NHC is regenerated as the catalyst. On the other hand, cyanide acts as a base catalyst rather than a nucleophilic catalyst. Thus, carbanion intermediate III, generated from 1 by a deprotonation at the vinylogous

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 α -position, undergoes addition to the aldehyde giving aldol adduct **A**.¹⁰ Subsequent cyanide-catalyzed thermal dehydration affords benzofuran **3** (Scheme 3).

Although cyanide and NHCs have been known to display similar reactivity in organic transformations as versatile organocatalysts,¹ this result strongly suggested that there should be considerable difference in the reactivity between cyanide and NHCs. Particularly, since the cyanide is more basic than the NHC catalyst,¹¹ they would display a considerable different reactivity toward the substrates carrying an acidic proton, such as compound **1**. These results would be in consistence with the fact that the cyanide-catalyzed benzoin condensation has been limited to the aromatic aldehydes,¹² which could possibly imply that cyanide could act as a base to deprotonate the α -proton of carbonyl group in the aliphatic



Scheme 3. Reactivity difference between NHC and cyanide in the cyclization of 1.

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aldehydes, although the importance of cyanide as the base catalyst has not been fully recognized.

In conclusion, we described a significant difference in reactivity between NHCs and cyanide toward 4-(2-formylphenoxy)but-2-enoates. NHCs act as a nucleophilic catalyst toward the aldehyde group to promote the expected intramolecular Stetter reaction, while cyanide could act as a base to generate the corresponding vinylogous enolate, which undergoes condensation with the aldehyde group. Particularly, the cyanide is more basic than the NHC catalyst, it displays a considerable different reactivity toward the substrates carrying acidic protons, such as compound 1. Further applications of the base reactivity of cyanide are currently underway in our laboratory and will be reported in due course.

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Supporting Information. Additional supporting information is available in the online version of this article.

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