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Beyond Benzoin Condensation: Trimerization of Aldehydes via Metal-Free Aerobic Oxidative Esterification of Aldehydes with Benzoin Products in the Presence of Cyanide

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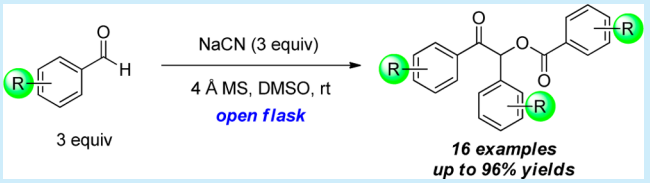
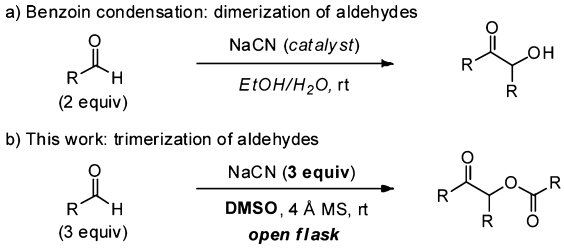
Supporting Information

ABSTRACT: An unusual trimerization of aldehydes in the presence of cyanide via metal-free aerobic oxidative esterification under ambient conditions is described. Various aromatic aldehydes provided the corresponding oxidative esterification products in good to excellent yields. Mechanistic studies suggested that this reaction would proceed via a two-step sequence: cyanide-catalyzed benzoin condensation of aldehydes and subsequent aerobic oxidative esterification of aldehydes with the resultant benzoin products. The usefulness of this protocol was further demonstrated by converting the resulting trimeric products into other biologically important compounds.



Since the cyanide-catalyzed benzoin condensation[1] is an important C−C bond formation reaction between aldehydes leading to the construction of synthetically useful α-hydroxyketones (Scheme 1a), this reaction has been extensively investigated by many research groups for decades. The mechanism of this reaction, initially proposed by Lapworth in 1903,[2] and affirmed by Schowen's group,[3] is now generally accepted by the chemical community.[4,5] In contrast, most of the mechanistic studies have focused on the elucidation of the role of cyanide as a nucleophilic catalyst and there have been few reports about the exact role of other reaction parameters.[5] For example, although the reaction rate for benzoin condensation was significantly enhanced in polar aprotic solvents, such as dimethyl sulfoxide (DMSO),[5,6] the exact role of DMSO in benzoin condensation has been poorly understood.[7]

Scheme 1. Dimerization of Aldehydes (Benzoin Condensation) and Trimerization of Aldehydes (This Work)



Here, we report the cyanide-mediated trimerization of aldehydes in polar aprotic solvents, such as DMSO and DMF, in an open flask under ambient conditions via metal-free aerobic oxidative esterification of aldehydes (Scheme 1b). This result was based on our recent findings of the unexpected formation of trimeric compounds of aldehydes under the oxidative cyclization conditions[8] previously used for the synthesis of benzofused azole compounds in the presence of NaCN. Mechanistic studies suggested that the trimeric products would be formed via the two-step sequence: the cyanide-catalyzed benzoin condensation of aldehydes and subsequent aerobic oxidative esterification of aldehydes with the resulting benzoin condensation products. Furthermore, the usefulness of this new transformation was demonstrated by converting the resulting trimeric compounds into other useful products, which might be difficult to be achieved directly from the benzoin condensation products in some cases.

Recently, we developed an efficient method for the synthesis of benzoxazoles under aerobic oxidative cyclization conditions without the assistance of any metal cocatalysts using cyanide as a nucleophilic catalyst by converting disfavored *5-endo-trig* cyclization of imines into favored *5-exo-tet* cyclization.[8] In the continued effort to develop environmentally benign protocols for the synthesis of biologically important heteroaromatic compounds,[8,9] we attempted to extend this nucleophile-catalyzed aerobic oxidation protocol to the synthesis of quinazolinones from anthranilamide and aldehydes.[10] When anthranilamide **2** and benzaldehyde **1a** were applied to the reaction conditions[8] previously used for the preparation of benzoxazoles, the expected quinazolinone **3** was not observed; instead, an unexpected compound was obtained as the major product. After careful structural analysis, the unexpected product was assigned to be benzoylated benzoin product **4a**, a trimeric compound of **1a** presumably via aerobic oxidative esterification (Scheme 2).[11]

With this rather unexpected result in hand, we were surprised to find that although several examples of oxidative esterification of aldehydes in the presence of cyanide were reported, most of the previous methods must be carried out in the presence of oxidants[12] and there have been few reports of aerobic oxidative esterification

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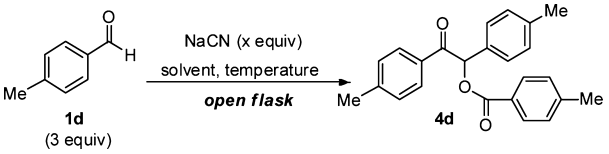
Scheme 2. Unexpected Formation of Compound 4a

in the presence of cyanide without any aid of cooxidant.[13] Even more surprisingly, although cyanide-catalyzed benzoin condensation had been extensively investigated for over a century,[1−4] this type of trimerization of aldehydes in the cyanide-catalyzed benzoin reaction has never been reported. Thus, we decided to investigate this unusual trimerization of an aldehyde through aerobic oxidative esterification in the presence of cyanide.[14−16]

Using *para*-tolualdehyde **1d** as a model compound, we first attempted to investigate the reaction parameters controlling this trimerization (Table 1). Initially, we suspected that

Table 1. Optimization of Reaction Conditions

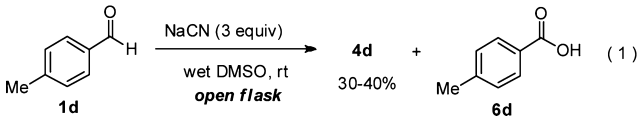


entry	solvent	NaCN (x equiv)	temp (°C)	time (h)	conversion[a]
1[b]	DMSO	3	100	4	100
2	DMSO	3	100	4	100 (30)[d]
3	DMF	3	100	6	100
4	EtOH	3	100	24	N.R.
5	H_2O	3	100	24	N.R.
6	dioxane	3	100	24	N.R.
7	toluene	3	100	24	N.R.
8[c]	DMSO	3	100	4	100 (51)[d]
9[c]	DMSO	3	70	8	100 (65)[d]
10[c]	DMSO	3	rt	24	100 (83)[d]
11[c]	DMSO	0.5	rt	24	– (19)[d]
12[c]	DMSO	1	rt	24	– (39)[d]
13[c]	DMSO	2	rt	24	– (62)[d]
14[c]	DMSO	4	rt	24	– (82)[d]

[a]Conversion was determined by ^{1}H NMR analysis of **1d** remained in the crude mixture. [b]With 3 equiv of **2**. [c]In the presence of 4 Å molecular sieves. [d]The value in parentheses was the isolated yield of **4d**.

anthranilamide **2** might play some role in this transformation. When the reaction was carried out in the absence of **2**, however, **1d** was still completely consumed, which led us to conclude that anthranilamide **2** had no effect on the formation of trimeric compound **4d** (entries 1 and 2). Then, the solvent effect on this transformation was examined (entries 2−7). Interestingly, the choice of solvent turned out to have a strong influence on the reactivity of this transformation. **1d** was completely consumed in DMSO and DMF (entries 2 and 3), whereas no reaction was observed in any other solvent (entries 4−7). Since the reaction proceeded slightly faster in DMSO than in DMF, DMSO was chosen as the solvent of choice for further investigation.

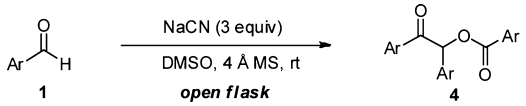
At that moment, however, we encountered a rather serious problem in reproducing the yield of trimeric compound **4d**. Although aldehyde **1d** was completely consumed, **4d** was obtained in moderate yield along with a significant amount of the corresponding carboxylic acid **6d** (eq 1).[17]



We suspected that **6d** might be formed through the hydrolysis of an intermediate for the oxidative esterification of **1d**. In order to avoid the unwanted hydrolysis, we carried out this reaction in the presence of molecular sieves (entry 8). Delightfully, the yield of **4d** was significantly increased in the presence of molecular sieves. Furthermore, lowering the reaction temperature had a beneficial effect on the suppression of the direct oxidation of aldehyde to the corresponding carboxylic acid (entries 8−10). To our surprise, this reaction proceeded even at rt to afford the desired product in 83% yield (entry 10). Next, we examined the amount of cyanide and found that it has a strong influence on this transformation (entries 10−14). The yield of **4d** increased with the amount of cyanide when a substoichiomeric amount of cyanide was used (entries 11 and 12), and it reached a plateau after 3 equiv of cyanide (entries 10 and 14). Thus, we decided to use 3 equiv of cyanide for further investigation.

Under these optimized conditions, the substrate scope of aldehydes for this transformation was investigated (Table 2).

Table 2. Substrate Scope



entry	products	Ar	time (h)	yield (%)[a]
1	**4a**	Ph	12	63
2	**4b**	4-(Me_2N)Ph	72	N.R.
3	**4c**	4-MeOPh	24	71
4[b]	**4d**	4-MePh	24	83
5[b]	**4e**	4-ClPh	12	45
6[b]	**4f**	4-BrPh	5	52
7[b]	**4g**	3-MeOPh	8	96
8[b]	**4h**	3,5-$(MeO)_2$Ph	8	87
9	**4i**	3-MePh	6	90
10	**4j**	3-ClPh	5	30
11[b]	**4k**	2-MeOPh	8	57
12	**4l**	2-MePh	6	67
13	**4m**	2-ClPh	5	53
14	**4n**	2-furyl	3	83
15	**4o**	2-thienyl	3	72
16	**4p**	2-naphthyl	15	71
17	**4q**	1-naphthyl	15	45
18[c]	**4d**	4-MePh	24	82

[a]Isolated yield of **4**. [b]In the presence of 100 mg of 4 Å molecular sieves. [c]On 30 mmol scale.

Various aromatic aldehydes could be applied to this protocol and afforded the desired trimeric products **4** in moderate to high yields. Interestingly, the electronic natures of the substituents on the aromatic ring system had a significant influence on the efficiency of this transformation. Aromatic aldehydes bearing a strong electron-donating amino group at the *para*-position did not undergo this transformation (entry 2), whereas moderate electron-rich aromatic aldehydes provided the desired products in good to high yields (entries 1 and 3−4). On the other hand, aldehydes carrying electron-withdrawing

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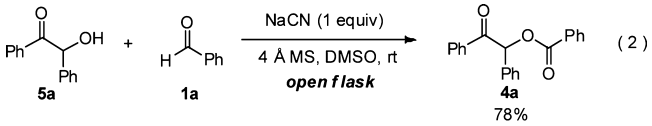
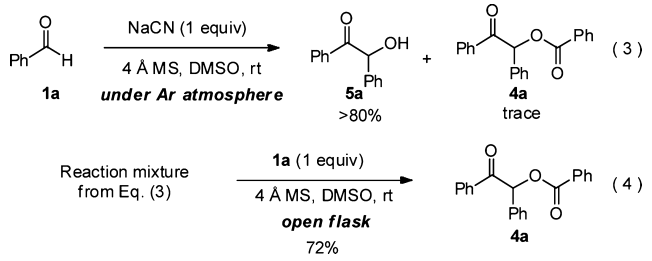
substituents generated the desired products in only moderate yields and a significant amount of the corresponding carboxylic acids were obtained via direct oxidation of aldehydes (entries 5 and 6). Substituents at the *meta*-positions of aldehydes displayed a similar trend in reactivity as ones with the *para*-substituents (entries 7−10). Electron-rich aldehydes afforded the desired products in high yields (entries 7−9), while an aldehyde bearing an electron-withdrawing substituent afforded the desired product in a low yield and a significant amount of the corresponding benzoic acid derivative was obtained (entry 10).[14] The steric bulk of aldehydes had a harmful effect on the formation of the desired products **4**. Aromatic aldehydes bearing a substituent at the *ortho*-position provided the desired products in only moderate yields regardless of the electronic natures of the substituents (entries 11−13). Heteroaromatic aldehydes and fused aromatic aldehydes, such as naphthyl aldehydes, could be applied to this protocol (entries 14−17). Furthermore, the protocol could be performed at a 30 mmol scale without sacrificing efficiency (entry 18).

With these rather unexpected results in hand, we performed several experiments to gain information about the reaction mechanism for this trimerization of aldehydes. Since the cyanide-catalyzed benzoin reaction is well-known,[1−4] we first suspected that a trimeric product **4** might be formed through the corresponding benzoin condensation product **5** as the key intermediate. When a 1:1 mixture of benzoin product **5a** and aldehyde **1a** was subjected to the standard reaction conditions, the corresponding trimer **4a** was obtained in a yield comparable to that from the aldehyde (eq 2).

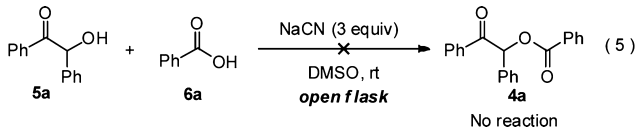


Then, we moved our attention to the oxidative esterification step. When the reaction was performed under an argon atmosphere, benzoin condensation product **5a** was obtained as the major product along with a trace amount of **4a** (eq 3).[18] Furthermore, when **1a** was added to the above reaction mixture and then the reaction mixture was exposed to air, however, the oxidative esterification again took place to afford **4a** in high yield (eq 4). These results strongly suggested that the



trimerization of an aldehyde would proceed through a benzoin condensation product of the aldehyde, followed by aerobic oxidative esterification of aldehyde with the resulting benzoin condensation product.

Next, we focused on the elucidation of an activated carboxylic acid derivative from aldehyde during aerobic oxidative esterification step. Since carboxylic acid was observed during the optimization of the reaction conditions, we first examined the possibility of the ester bond formation from the condensation between benzoin product **5a** and benzoic acid **6a** under standard conditions (eq 5). However, when **5a** and **6a**



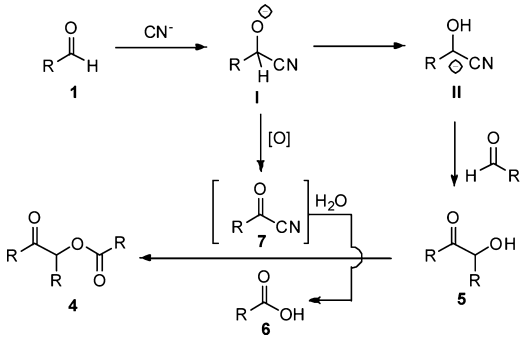
were subjected to the optimized conditions, no formation of **4a** was observed, which led us to rule out this possibility.

Based on this result, we assumed that **4** would be generated by the reaction of the benzoin product with an activated benzoic acid derivative in situ generated from aldehyde in the presence of cyanide under aerobic oxidation conditions. Since there have been a few reports of oxidative esterification in the presence of cyanide via benzoyl cyanide **7** as the key intermediate,[12] we assumed that this reaction might also proceed through benzoyl cyanide **7**. To test this possibility, we performed the reaction between benzoin product **5a** with benzoyl cyanide **7** (eq 6). To our delight, the reaction of

benzoin product **5a** with benzoyl cyanide **7** afforded the trimeric compound **4a** in high yield.

Based on these results, we proposed the trimerization of aldehydes (Scheme 3). Cyanohydrin intermediate **I**, initially formed by cyanide addition to aldehyde **1**, undergoes normal

Scheme 3. Proposed Reaction Mechanism



cyanide-catalyzed benzoin condensation to afford compound **5**. Under aerobic oxidation conditions, intermediate **I** could also undergo oxidation to yield benzoyl cyanide **7**. Subsequent reaction between **5** and **7** might lead to trimeric compound **4**.

The proposed reaction mechanism could explain several of the observed experimental results. Under an argon atmosphere, benzoin condensation product **5** was obtained as the major product along with a trace amount of trimeric products **4** (eq 3). Since it is impossible for aldehyde **1** to undergo aerobic oxidation to afford benzoyl cyanide **7** under such conditions, benzoin product **5** was obtained as the major product and no formation of **4** was observed. Furthermore, we also observed that the formation of benzoic acid **6** was observed under the standard conditions using wet organic solvents. Since water could compete with the benzoin product toward **7**, a significant amount of **6** was observed in wet DMSO. However, molecular

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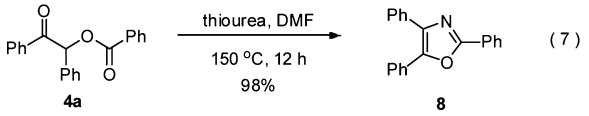
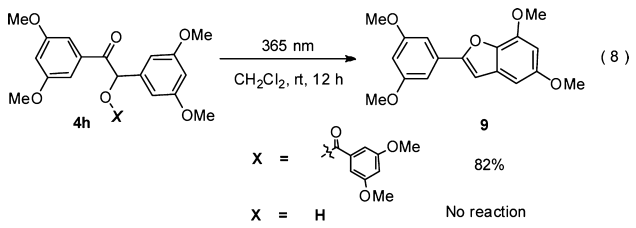
sieves efficiently remove water from the reaction mixture, which suppresses the formation of benzoic acid **6**.

With these results in hand, we further demonstrated the usefulness of this protocol by converting the resulting trimeric products into other useful compounds. When **4a** was treated with thiourea in DMF under an elevated temperature, the corresponding oxazole **8** was obtained in excellent yield (eq 7).[19]



Furthermore, when **4h** was irradiated (365 nm) under ambient conditions, the resulting benzofuran **9** was obtained in high yields (eq 8).[20] However, when the corresponding



benzoin product was subjected to the same reaction conditions, no desired benzofuran product **9** was observed.

In conclusion, we have described an unusual trimerization of aldehydes in the presence of cyanide in an open flask in the absence of any metal catalysts and co-oxidants. Various aromatic aldehydes provided the trimeric compounds in good to excellent yields. Mechanistic studies suggested that the trimers of aldehydes would be formed via the cyanide-catalyzed benzoin reaction, followed by aerobic oxidative esterification between the resulting benzoin products and aldehydes in the presence of cyanide. The usefulness of this protocol was further demonstrated in the direct transformation of the resulting products into other biologically useful compounds.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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