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N-Heterocyclic carbene catalyzed intramolecular crossed aldehyde–ketone benzoin condensation in the chalcone of *o*-phthalaldehyde: a facile synthesis of naphthalenones

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ABSTRACT

The intramolecular crossed aldehyde–ketone benzoin condensation in the chalcone of *o*-phthalaldehyde (OPA) catalyzed by *N*-heterocyclic carbene (NHCs) generated in situ from readily available imidazolium and thiazolium salts is described. In this reaction, bicyclic α-hydroxyl ketones (naphthalenone type tertiary alcohol) were selectively produced in good yields (75–94%) in shorter reaction times (20 min) through nucleophilic addition of acyl anion generated by umpolung in OPA–chalcone (regio controlled).

Umpolung (polarity inversion) in carbonyl compounds catalyzed by organo *N*-heterocyclic carbene catalysts (NHCs) is a versatile transformation to process traditional C–C bond formation via unconventional reaction path both in nature and laboratory chemistry.[1] The transformation of α-keto acids to the corresponding carbonyl anions by an NHC derived from thiamine (vitamin B_1) is one of the best example for this concept, which inspired the related chemical processes.[2] Depending on the nature of aldehyde, either acyl anion or homoenolate anion synthones were found to form via the addition of NHC during these catalytic cycles.

Benzoin condensation is a kind of umpolung process, which can be achieved by generating an acyl anion equivalent from an aldehyde moiety of a molecule which adds to a second aldehyde moiety of another molecule (intermolecular) or keto/aldehyde moiety in the same molecule (intramolecular).[1a,3] Liebig in 1832 first discovered the intermolecular benzoin condensation catalyzed by cyanide salts.[4] Cyanide ion can serve four distinct roles, namely, (i) high nucleophilic activity, (ii) facilitating the proton transfer, (iii) ability to stabilize the negative charge in active aldehyde intermediate, and (iv) ability to depart finally. Later, Breslow in 1958 first recognized that the NHCs could also serve all these roles similar to that of cyanide ion in benzoin condensation,[5] and NHCs are better nucleophiles and leaving groups than cyanide. Nevertheless, the discovery of stable carbenes[6] by Arduengo in 1991 provided the access to develop a variety of NHC catalysts[7] for benzoin condensation.

As compared to the investigations on intermolecular benzoin condensation,[1a,2b,8] intramolecular benzoin condensation reactions, while known, only represent a small portion of the literature.[9] Nevertheless the contributions by Enders and Suzuki are much interesting.[10] This is due to the rarity of suitable dicarbonyls for the intramolecular reaction to take place. Among these reactions, aldehyde–ketone cross benzoin condensation appears to be worth studying. We planned to investigate the intramolecular crossed benzoin condensation in some pre-synthesized chalcones (aldehyde–ketone) (**1a–j**) of *o*-phthaladehyde (OPA) using an organo-NHC catalyst. The formation of C–C bond in this reaction will lead to carbocylization via umpolung mechanism to produce naphthalenone type metabolites. Previously, hydroxylative dearomatization and oxygenation of phenols and naphthaols were used to obtain these targets.[11] Earlier, we have reported the application of OPA as a good starting material in the synthesis of quinazolines and Schiff base ligands and their biological and catalytic studies.[12] Regarding other reports on OPA–chalcone, selective reduction of enone and imine of OPA–chalcone to carbocycles and heterocycles using organoiodotin hydride has been reported.[13]

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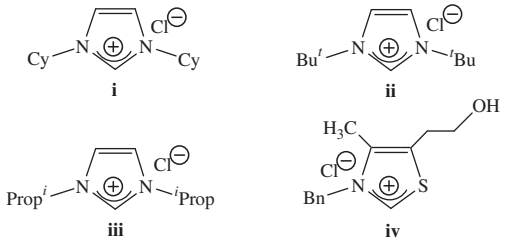


Figure 1. NHC precursors investigated in the present work.

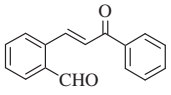
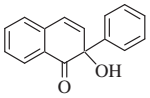
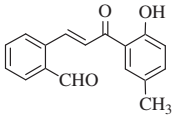
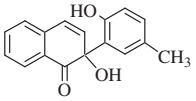
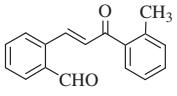
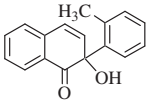
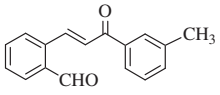
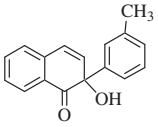
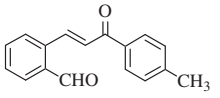
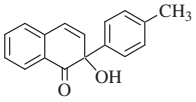
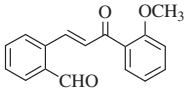
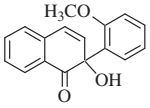
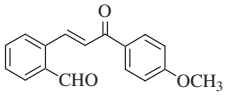
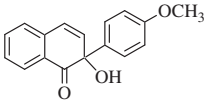
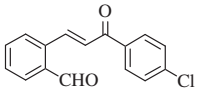
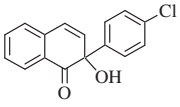
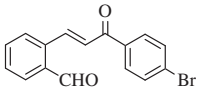
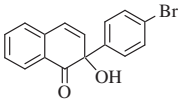
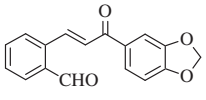
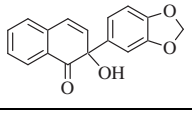
In the present work we describe the application of OPA–chalcone as a substrate to study the intramolecular crossed aldehyde–ketone benzoin condensation. In general, the condensation reaction between simple mono aryl-aldehydes and acetopheneone gives a common chalcone, that is, α,β,-unsaturated ketones. However, the present task needs an additional aldehyde functionality on chalcone to initiate the cyclization process. In this respect, the condensation reaction of OPA and various acetophenones in alkaline medium has provided the desired chalcones (**1a–j**).

Table 1
Optimization of reaction conditions for intramolecular benzoin condensation of OPA–chalcone (**1a**)

1a **2a**

Entry	NHC precursor	Reaction time (min)	GC yield (%)
1	i	20	90
2	ii	20	92
3	iii	25	85
4	iv	30	83

Table 2
Organo-NHC catalyzed intramolecular benzoin condensation of OPA–chalcones (**1a–j**)[a]

Entry	OPA–Chalcone (**1a–j**)	Naphthalenone (**2a–j**)	Reaction time (min) (yield, %)[b]
1			20 (92)
2			20 (94)
3			22 (84)
4			180 (34)[c]
5			18 (90)
6			20 (85)
7			20 (85)
8			22 (76)
9			22 (75)
10			20 (80)

[a] All products were characterized by IR, $^{1}H/^{13}C$ NMR and mass spectral analysis.
[b] Determined by GC.
[c] Et_3N as a base.

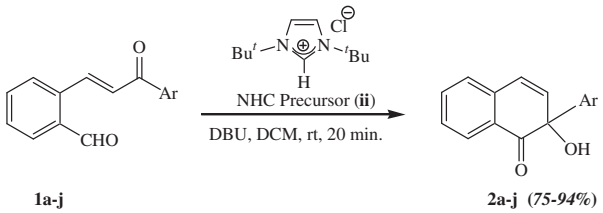
At first, we investigated the intramolecular crossed benzoin condensation in the chalcone **1a** using four different readily available azolium salts (imidazolium/thiazolium) as NHC catalyst precursors (**i–iv**, Fig. 1) to optimize the reaction conditions and to investigate the role of NHC ligand on the rate of the reaction. The details of the reactant and product yields are shown in Table 1. A base 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was used to generate NHC catalysts in situ in DCM at room temperature via the deprotonation of C_2-proton of azolium salts. The three imidazolium salts (**i–iii**) were synthesized according to the procedure described by Arduengo,[14] whereas the thiazolium salt (**iv**) is commercially available.

In order to suppress the side reactions such as possible base-catalyzed aldol reaction of **1a** by DBU, NHC catalyst was generated in situ before the addition of **1a** in DCM. The in situ generated NHC was then allowed to react with **1a**. Upon careful observation, we have noticed that the benzoin condensation reaction was accomplished smoothly within 20 min turning the reaction solution to a wine red color under simple stirring at room temperature as determined by TLC. It is noticeable that there was no reaction without organo-NHC catalyst. All the four NHCs generated in situ from azolium salts efficiently catalyzed the benzoin condensation and provided opportunity to afford selectively the naphthalenone (bicyclic tertiary alcohol) product (**2a**) in reasonably good yields (83–92% GC, Table 1).[15] Further, no intermolecular benzoin condensed product was observed in the above work. Besides, when Et_3N was used as a base, very less yield of **2a** (Table 2, entry 4) was noted, indicating the influence of the base.

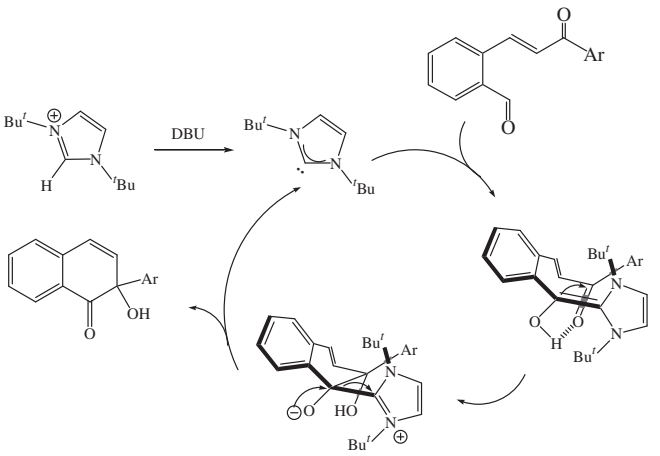
The formation of product **2a** was determined by IR, mass, ^1H and ^{13}C NMR spectroscopic data. For instance, the disappearance of aldehydic proton of chalcone and the appearance of new hydroxyl proton in ^1H NMR spectral analysis supports the formation of condensed product (**2a**). Despite the fact that the aldehyde–ketone crossed benzoin condensation is unfavorable compared with conventional aldehyde–aldehyde benzoin condensation the target compound **2a** is a bicyclic tertiary alcohol having a quaternary stereo centre.

After the above effort, the intramolecular crossed benzoin protocol was extended to study other OPA–chalcones (**1b–j**) (Scheme 1). The investigations were carried out by using only the imidazolium salt (**ii**) as NHC precursor. Similar to the reaction of **1a**, the proposed reactions of **1b–j** were also accomplished smoothly and produced selectively the desired bicyclic tertiary alcohols (naphthalenones **2b–j**) in good yields (GC, 75–94%, Table 2), which are further analyzed and confirmed by IR, mass, and NMR spectroscopies.

Based on the above results obtained, a possible umpolung mechanism involved in the intramolecular benzoin condensation of abovementioned chalcone is proposed and is depicted in Scheme 2. The NHC generated in situ will attack the aldehyde functionality of chalcone via nucleophilic addition and form initially a homoenolate. The hydrogen bond formed now between enol hydrogen and carbonyl oxygen of keto-group of homoenolate intermediate before the nucleophilic attack of the ketone will facilitate the formation of a six-membered cyclic transition state,[1a,9b–d] which leads to form the final products, that is, 2-hydroxy-2-aryl-2*H*-naphthalen-1-ones.



Scheme 1. Organo-NHC catalyzed intramolecular crossed aldehyde–ketone benzoin condensation reaction.



Scheme 2. A plausible mechanism for the formation of naphthalenones.

In summary, we have developed a facile one-pot synthetic route to obtain naphthalenone based bicyclic tertiary alcohols in good yields from OPA–chalcone via intramolecular aldehyde–ketone crossed benzoin condensation reaction catalyzed by NHC-promoted umpolung mechanism. The use of Ag(I)–NHCs as precursors to provide free NHC catalyst to study the benzoin condensation is under progress.

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Supplementary data

Supplementary data (experimental procedures and spectroscopic characterization) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.05.070.

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15. In a typical procedure, a chalcone of OPA (**1a**) (0.236 g, 1 mmol) was added to NHC precursor (**ii**) (0.0216 g, 0.1 mmol, 10 mol %) in dry DCM (5 ml) in the presence of base DBU (0.0152 g, 0.1 mmol, 10 mol %) under nitrogen atmosphere. The reaction was accomplished smoothly within 20 min turning the reaction solution to a wine red color under simple stirring at room temperature. The reaction was quenched with saturated aqueous NH_4Cl. The product was extracted with DCM (2×20 ml). The combined organic layers were dried (anhydrous Na_2SO_4) and evaporated under reduced pressure to afford a crude product which was subjected to chromatography (silica gel, 60–120 mesh, eluent; *n*-hexane/EtOAc gradient) to afford pure 2-hydroxy-2-phenyl-2*H*-naphthalen-1-one (**2a**) as a light brown solid mp 91–92 °C (0.217 g, 92%). IR (KBr, cm^{-1}): 3426, 3020, 1690, 1600, 1025, 756 and 695. ^1H NMR (200 MHz, $CDCl_3$): δ 4.52 (s, 1H), 6.12 (d, 1H), 6.82 (d, 1H), 7.12–7.18 (m, 5H, Ar–H), 7.45–7.56 (m, 4H, Ar–H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 88.21, 126.52, 126.80, 127.22, 127.54, 127.94, 128.30, 129.25, 130.44, 132.63, 134.32, 135.60, 135.81, 176.42; MS (EI, 70 eV): *m*/*z* (%) 259 $[M+Na]^+$. EA calcd for $C_{16}H_{12}O_2$: (236.08): calcd C 81.34, H 5.12; found C 81.33, H 5.10.