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NHC-Catalyzed Oxidative Cyclization Reactions of 2-Alkynylbenzaldehydes under Aerobic Conditions: Synthesis of O-Heterocycles

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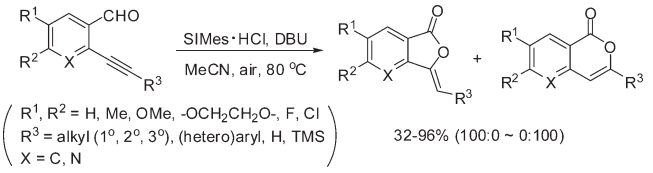
ABSTRACT



An NHC-catalyzed, regio- and stereoselective oxidative cyclization of *o*-alkynylbenzaldehydes bearing an unactivated alkyne moiety as an internal electrophile has been developed to afford phthalides and isocoumarins. A single organocatalytic system enabled two sequential C−O bond formations to take place in an atom economical manner via highly efficient dual activation. Molecular oxygen in air could be utilized as a source of an oxygen atom for the oxidation of aldehydes to the corresponding benzoic acids under our newly developed reagent system.

Since its seminal discovery in 1943,[1] N-heterocyclic carbenes (NHCs) have become an important and powerful class of organocatalysts with widespread applications in a variety of synthetic transformations.[2] Among which, NHC-catalyzed oxidative esterification[3] of aldehydes in the presence of alcohol represents a mild and efficient transformation and a powerful variant of the classical esterification reactions. This process circumvents the use of stoichiometric or often excessive amounts of carboxylic acid activating/coupling reagents, avoids the necessity of protecting group manipulations, and alleviates the generation of unwanted byproducts.[4] In general, NHC-catalyzed oxidative esterification of aldehydes can be achieved either through an internal redox reaction of α-functionalized aldehydes[5] or in the presence of an external oxidant in the case of unfunctionalized aldehydes.[6] Recently, several examples of NHC-catalyzed oxidative lactonizations of hydroxy aldehydes have also been reported.[7] To the best of our knowledge, however, syntheses of phthalides and isocoumarins have not yet been exploited in

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(5) For selected examples, see: (a) Reynolds, N. T.; de Alaniz, J. R.; Rovis, T. *J. Am. Chem. Soc.* **2004**, *126*, 9518. (b) Chow, K. Y.-K.; Bode, J. W. *J. Am. Chem. Soc.* **2004**, *126*, 8126. (c) Chan, A.; Scheidt, K. A. *Org. Lett.* **2005**, *7*, 905. (d) Sohn, S. S.; Bode, J. W. *Angew. Chem., Int. Ed.* **2006**, *45*, 6021. (e) Zeitler, K. *Org. Lett.* **2006**, *8*, 637.

(6) For selected recent examples, see: (a) De Sarkar, S.; Studer, A. *Org. Lett.* **2010**, *12*, 1992. (b) De Sarkar, S.; Grimme, S.; Studer, A. *J. Am. Chem. Soc.* **2010**, *132*, 1190. (c) Maki, B. E.; Scheidt, K. A. *Org. Lett.* **2008**, *10*, 4331. (d) Guin, J.; De Sarkar, S.; Grimme, S.; Studer, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 8727.

(7) For selected recent examples, see: (a) Rose, C. A.; Zeitler, K. *Org. Lett.* **2010**, *12*, 4552. (b) Zeitler, K.; Rose, C. A. *J. Org. Chem.* **2009**, *74*, 1759.

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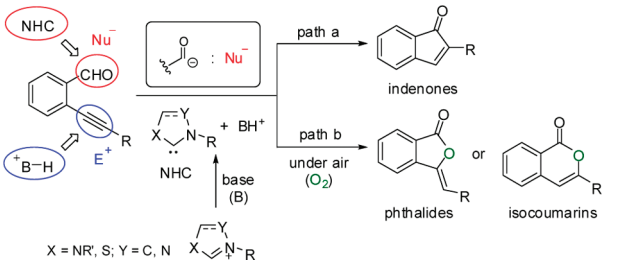
Scheme 1. NHC-Catalyzed Cyclization Reaction: Dual Activation of Two Functionalities



the context of NHC catalysis.[8] Phthalides[9] and isocoumarins[10] are important classes of naturally occurring lactones that have been found to exhibit a wide range of biological indications and to be versatile building blocks for the synthesis of bioactive compounds.[11] Consequently, a number of synthetic strategies have been developed for their constructions, generally involving 5-*exo* or 6-*endo* cyclizations of either preformed[12] or in situ generated[13] *o*-alkynylbenzoic acids through electrophilic activation of the alkyne moiety. Here, we disclose the discovery of a highly effective, NHC-catalyzed oxidative cyclization of *o*-alkynylbenzaldehydes that enabled the easy preparation of a diverse array of phthalides and isocoumarins (Scheme 1, path b). This is the first example of an *NHC-catalyzed oxidative lactonization of aldehydes under aerobic conditions involving an unactivated alkyne as an internal electrophile*.[14,15] In sharp contrast to the related oxidative esterification processes,[5–7] the present system exploits the *molecular oxygen in air as the source of an oxygen atom instead of alcohols*.[16,17] From a practical perspective, this newly developed method offers a user-friendly entry to a variety of lactones through oxidation of aldehydes under atmospheric oxygen, thereby obviating any precautionary measures to rigorously exclude air and moisture from the reaction mixture.

Before proceeding with the discussions, a few cursory words of mechanistic considerations would be appropriate at this juncture which provided the basis for our discovery. In this context, generation of the NHC species through deprotonation of the heterazolium salt followed by its reaction with the aldehyde moiety renders an acyl anion intermediate with its nucleophilicity toward internal (e.g., alkyne) or external (e.g., molecular oxygen) electrophiles. Meanwhile, the so-obtained conjugate acid (BH^+) resulting from deprotonation of the heterazolium salt could serve as a π-activator toward the alkyne moiety.[12d,f,13a] Since both processes are well-documented, we envisaged a reaction involving catalytic dual activation[18] of a bifunctional substrate containing both aldehyde and alkyne functionalities at appropriate positions, to furnish a cyclized product. Indeed, along these lines of thoughts, the following sections describe the results of our investigations and realization of our hypothesis.

We began our studies on the proposed cyclization reaction using **1a** as the test substrate. We initially anticipated that **1a** would undergo an intramolecular hydroacylation reaction involving the addition of the Breslow intermediate to the proximal alkyne moiety (activated by BH^+) to afford the corresponding indenone product (Scheme 1, path a). Much to our surprise, instead of the expected 2-phenylindenone, phthalide **2a** was obtained exclusively (for details, see Supporting Information). Undaunted by this unexpected result, we set out to examine the reaction parameters in order to further optimize this serendipitous transformation. Among the variety of heterazolium salts examined, 1,3-bis(2,4,6-trimethylphenyl)imidazolinium chloride (**A**) proved most superior for this reaction. DBU was revealed as the most effective base among all the inorganic and organic bases examined, while MeCN was the solvent of choice at high concentrations (0.2 M). Lastly, control experiments employing only either **A** or DBU gave no conversions.

With the optimized reaction conditions in hand, we set out to explore the substrate scope of this newly developed process, and the results are summarized in Table 1. Both terminal and internal alkynes were well tolerated for this reaction, and the regiochemical

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(14) During our investigations, Glorius and co-workers reported an example of NHC-catalyzed intramolecular cyclization of benzaldehydes bearing an unactivated alkyne moiety; see: Biju, A. T.; Wurz, N. E.; Glorius, F. *J. Am. Chem. Soc.* **2010**, *132*, 5970. However, this reported reaction differs significantly from our work described herein in terms of reactivity under the conditions described, the product obtained, and the mechanistic pathway involved. The same group reported NHC-catalyzed hydroacylation of unactivated alkenes and arynes; see: (a) Hirano, K.; Biju, A. T.; Piel, I.; Glorius, F. *J. Am. Chem. Soc.* **2009**, *131*, 14190. (b) Biju, A. T.; Glorius, F. *Angew. Chem., Int. Ed.* **2010**, *49*, 9761.

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(16) For examples of NHC-catalyzed reactions involving esterification through a similar mechanism under aerobic conditions, see: (a) Liu, Y.-K.; Li, R.; Yue, L.; Li, B.-J.; Chen, Y.-C.; Wu, Y.; Ding, L.-S. *Org. Lett.* **2006**, *8*, 1521. (b) Lin, L.; Li, Y.; Du, W.; Deng, W.-P. *Tetrahedron Lett.* **2010**, *51*, 3571.

(17) For an example using CO_2 as an oxidant for NHC-catalyzed oxidation of aldehydes, see: (a) Gu, L.; Zhang, Y. *J. Am. Chem. Soc.* **2010**, *132*, 914. (b) Nair, V.; Varghese, V.; Paul, R. R.; Jose, A.; Sinu, C. R.; Menon, R. S. *Org. Lett.* **2010**, *12*, 2653.

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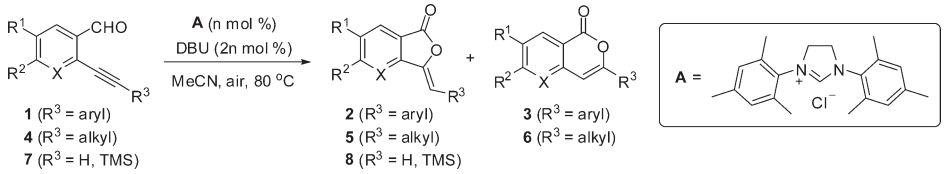
Table 1. NHC-Catalyzed Oxidative Cyclization Reaction of 2-Alkynylbenzaldehydes



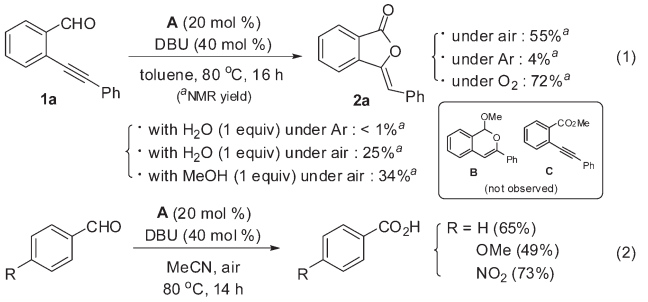
entry	substrate	R^1	R^2	R^3	X	*n* (mol %)	time (h)	product	yield (%)[a]
1	**1a**	H	H	Ph	CH	10	5.5	**2a/3a**	84 (95:5)
2	**1b**	H	Me	Ph	CH	10	24	**2b/3b**	67 (94:6)
3	**1c**	OMe	H	Ph	CH	20	5	**2c/3c**	91 (96:4)
4	**1d**	OMe	OMe	Ph	CH	20	24	**2d/3d**	74 (97:3)
5	**1e**	$-OCH_2O-$		Ph	CH	10	22	**2e/3e**	56 (96:4)
6	**1f**	F	H	Ph	CH	15	2	**2f/3f**	80 (93:7)
7	**1g**	Cl	H	Ph	CH	20	2.5	**2g/3g**	71 (94:6)
8	**1h**	H	H	Ph	N	10	5	**2h/3h**	74 (55:45)[b]
9	**1i**	OMe	H	4-$MeOC_6H_4$	CH	10	24	**2i/3i**	74 (92:8)
10	**1j**	OMe	H	4-MeC_6H_4	CH	20	14	**2j/3j**	62 (>99:1)
11	**1k**	OMe	H	4-ClC_6H_4	CH	20	14	**2k/3k**	60 (>99:1)
12	**1l**	OMe	H	4-$NO_2C_6H_4$	CH	20	10	**2l/3l**	–
13	**1m**	OMe	H	2-BrC_6H_4	CH	20	24	**2m/3m**	40 (>99:1)
14	**1n**	OMe	H	2-naphthyl	CH	10	6	**2n/3n**	64 (>99:1)
15	**1o**	OMe	H	2-pyridyl	CH	20	6	**2o/3o**	60 (78:22)[b]
16	**4a**	H	H	*n*Bu	CH	15	24	**5a/6a**	61 (16:84)
17	**4b**	H	Me	*n*Bu	CH	15	12	**5b/6b**	70 (17:83)
18	**4c**	OMe	H	*n*Bu	CH	10	12	**5c/6c**	80 (28:72)
19	**4d**	F	H	*n*Bu	CH	10	8	**5d/6d**	96 (35:65)[b]
20	**4e**	Cl	H	*n*Bu	CH	10	11	**5e/6e**	80 (39:61)[b]
21	**4f**	H	H	*n*Bu	N	10	24	**6f**	74
22	**4g**	OMe	H	CH_2OH	CH	20	24	**5g/6g**	32 (>99:1)
23	**4h**	OMe	H	CH_2OTHP	CH	20	4	**5h/6h**	68 (96:4)
24	**4i**	OMe	H	CH_2OAc	CH	20	17	**5i/6i**	75 (>99:1)
25	**4j**	OMe	H	CH_2OBn	CH	10	6	**5j/6j**	58 (94:6)
26	**4k**	H	H	*c*Pr	CH	20	8	**5k/6k**	77 (78:22)
27	**4l**	OMe	H	*c*Pr	CH	15	6	**5l/6l**	74 (80:20)
28	**4m**	OMe	H	*t*Bu	CH	20	24	**5m/6m**	42 (61:39)
29	**7a**	H	H	H	CH	20	12	**8a**	61
30	**7b**	OMe	H	H	CH	10	4	**8b**	67
31	**7c**	H	H	TMS	CH	20	7	**8c/8a**	47 (13:87)[b–c]
32	**7d**	OMe	H	TMS	CH	20	7	**8d/8b**	62 (24:76)[b–c]

[a] Isolated yields. Value in parentheses indicates the ratio of two inseparable isomers which was determined by ^1H NMR. [b] Two isomers could be separated. [c] The ratio of silylated to desilylated phthalide products is given.

outcome of this process showed strong substituent dependence at the alkyne terminus. In general, phthalides were obtained predominantly via 5-*exo*-*dig* cyclizations, with the exception of *n*-butyl substituted alkynes (**4a**–**f**).[19] In the case of propargyl alcohol derivatives (**4g**–**j**), formation of phthalides **5** were strongly favored inconsequential of the presence or nature of the protecting group, although the free hydroxyl group afforded a much inferior yield of product **5g**. Aryl-substituted alkynes (R^3 = aryl) bearing either electron-donating or moderately electron-withdrawing groups at the *para* position were well tolerated, apart from *para*-NO_2 substituted substrate **1l**. Steric hindrance appeared to hamper the reaction as seen for alkyne substrates bearing *t*-Bu (**4m**), 2-BrC_6H_4 (**1m**), and TMS (**7c**) substituents. TMS-substituted alkynes (**7c**–**d**) led to chromatographically separable mixtures of silylated and desilylated phthalides **8**, where the latter compound was formed predominantly.

Subsequently, we also investigated the effects of substituents (R^1, R^2) residing on the aromatic moiety of 2-alkynylbenzaldehydes (entries 2–7 and 17–20). Electron-donating and -withdrawing substituents *para* to the alkyne moiety (R^1) had no significant effect on the reactivity. However, electron-donating substituents *para* to the aldehyde moiety (R^2) retarded the reaction considerably, presumably as a consequence of the reduced electrophilicity of the aldehyde carbon toward reaction with the NHC catalyst (entries 2 and 4–5). Halogen substituents (Cl, F) were also well tolerated in this reaction. Lastly, heteroaromatic motifs such as pyridine could be also incorporated either in the form of a 2-alkynyl substituted pyridyl aldehyde (**1h**, **4f**) or

as a substituent at the alkyne terminus (**1o**). It is noteworthy that, in all cases, (*Z*)-isomers of phthalides were obtained stereoselectively.



To gain further mechanistic insights into this reaction, a series of control experiments were rationally designed and performed (eqs 1−2). The first set of experiments was conducted in order to determine the source of the "O" atom in this unique oxidative cyclization reaction (eq 1). Reaction of **1a** under an argon atmosphere while leaving other experimental parameters unaltered resulted in a drastically decreased conversion, while replacing air with an atmosphere of O_2 (balloon) markedly improved the yield of **2a**. On the other hand, the introduction of water or MeOH under either argon or aerobic conditions had a detrimental effect on the reactivity, leading to a significantly lower yield of **2a** along with mostly recovered **1a**. Interestingly, in the presence of MeOH, acetal **B** (or the corresponding isobenzofuran) resulting from the domino nucleophilic addition−cyclization reaction[20] or methyl ester **C** from the corresponding NHC-catalyzed oxidative esterification[6] could neither be isolated nor detected. The absence of methyl ester **C** also suggests that an active acyl imidazolinium ion intermediate was not generated during the reaction. These preliminary findings indicate that oxygen plays an essential role as the source of the "O" atom in this transformation and water is not responsible for the product formation.

Next, we examined the oxidation of a series of benzaldehydes in the absence of the alkyne moiety under our standard reaction conditions (eq 2). In stark contrast to the relevant reports where in all cases the source of the "O" atom originates from either water or CO_2[21] and only electron-deficient benzaldehydes could be oxidized to the corresponding benzoic acids under aerobic NHC catalysis,[21b] oxidation of electron-rich and -deficient benzaldehydes took place smoothly under our newly developed reaction conditions. This result also implicates that 2-alkynylbenzoic acids could be generated from an NHC-catalyzed preoxidation of alkynylbenzaldehyde under aerobic conditions, which could be a plausible intermediate in our oxidative cyclization reaction.

Based on our experimental findings and by analogy with the mechanism proposed for the related NHC-catalyzed reactions under aerobic conditions,[16] a plausible mechanism for this oxidative cyclization reaction is conceived as follows: The Breslow intermediate formed by an initial nucleophilic addition of an in situ generated NHC species to the aldehyde functionality is incorporated with electrophilic O_2, followed by the intramolecular nucleophilic attack of the anionic oxygen of the resulting intermediate to the alkyne moiety (activated by DBU−H^+).[12d,f,13a,20b] An alternative mechanism involving the intramolecular cyclization of *o*-alkynylbenzaldehydes through a concerted or stepwise pathway prior to oxidation with O_2 could also be proposed (for details, see Supporting Information).

In summary, we have developed an NHC-catalyzed oxidative cyclization of *o*-alkynylbenzaldehydes bearing an unactivated alkyne moiety as an internal electrophile to afford a range of O-heterocycles. The duality of a carefully selected base (DBU) renders its ability to generate the active NHC catalytic species and, concomitantly, to activate the alkyne moiety through its conjugate acid. As a result, a single organocatalytic system enabled two sequential C−O bond formations to take place in an atom economical manner. For the first time, molecular oxygen in air could be utilized as a source of an oxygen atom for the oxidation of various benzaldehydes to the corresponding benzoic acids under our newly developed reagent system. This NHC-catalyzed, direct oxidation of aldehydes using atmospheric oxygen as the oxidant may open up new horizons to sustainable and eco-friendly oxidation processes and expand the scope of NHC-catalyzed umpolung reactions. Further investigations along this direction and application of NHC catalysis in the synthesis of heterocycles are currently underway in our laboratory.

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Supporting Information Available. Full experimental details and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

(20) For selected examples of a base-promoted domino nucleophilic addition−cyclization reaction of 2-alkynylbenzaldehydes with alcohols, see: (a) Dell'Acqua, M.; Facoetti, D.; Abbiati, G.; Rossi, E. *Synthesis* **2010**, 2367. (b) Cikotiene, I.; Morkunas, M.; Motiejaitis, D.; Rudys, S.; Brulstus, A. *Synlett* **2008**, 1693. (c) Chandra, A.; Singh, B.; Khanna, R. S.; Singh, R. M. *J. Org. Chem.* **2009**, *74*, 5664.

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