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Efficient Synthesis of Benzofuranones: N-Heterocyclic Carbene (NHC)/Base-Catalyzed Hydroacylation—Stetter—Rearrangement Cascade

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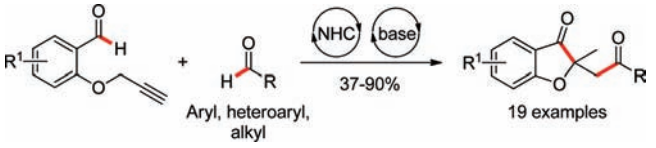
ABSTRACT



A N-heterocyclic carbene/base-catalyzed cascade reaction leading to the formation of functionalized benzofuranones is reported. The reaction proceeds via an intramolecular hydroacylation of unactivated alkynes followed by an intermolecular Stetter reaction and a base-catalyzed chromanone to benzofuranone rearrangement.

Benzofuran-3(2*H*)-ones are attractive synthetic targets, primarily due to the range of antifungal, antipsychotic, and anticancer properties associated with them.[1] The 2,2-disubstituted benzofuranone core is found in various natural products including griseofulvin (antifungal agent) and Sch 202596 (Alzheimer's disease) (Figure 1).[2] Consequently, a number of methods for the synthesis of benzofuranones containing a quaternary stereocenter at C2 have been developed.[3,4] N-Heterocyclic carbene (NHC)-catalyzed approaches toward the synthesis of 2,2-disubstituted benzofuranones have been uncovered by the research group of Rovis and She.[4,5] Although many of the known strategies for benzofuranone synthesis provide the products in good yield, multiple steps are required for the substrate synthesis. To address this problem, Rovis and co-workers recently developed an elegant and highly enantioselective NHC-catalyzed benzofuranone synthesis using commercially available starting materials via a multicatalytic cascade reaction.[6]

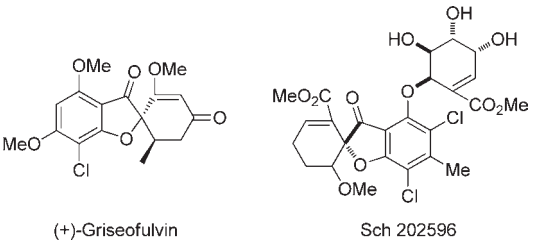


Figure 1. Selected biologically active benzofuranones.

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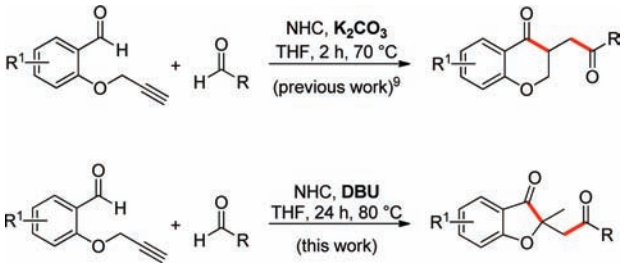
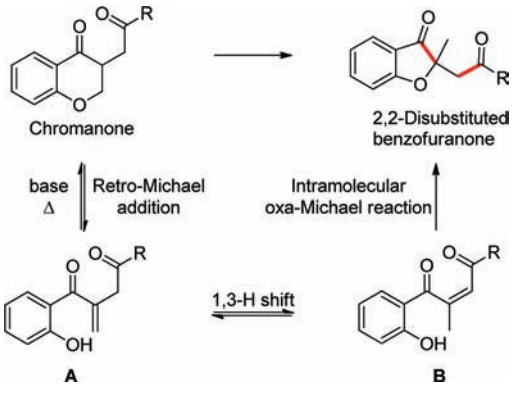
During the course of our endeavor on NHC-organocatalysis,[7] we recently disclosed an NHC-catalyzed unique cascade reaction involving the hydroacylation[8] of unactivated alkynes followed by an intermolecular Stetter reaction leading to the formation of chromanones with a valuable 1,4-diketone moiety.[9] The chromanone formation took place in spite of various selectivity issues including the undesired benzoin and Stetter pathways, and the key to success was the right choice of NHC and base. It was surmised that when the reaction is carried out using a relatively strong base, the initially formed chromanone will be poised for a retro-Michael reaction leading to phenol **A**, which upon a 1,3-H shift to **B** followed by an intramolecular oxa-Michael reaction leads to the formation of 2,2-disubstituted benzofuranones (Scheme 1).[10] Herein, we report a unique cascade reaction comprising an NHC-catalyzed hydroacylation followed by an intermolecular Stetter reaction and a subsequent base-catalyzed chromanone to benzofuranone rearrangement (Scheme 2).[11,12]

Our present study commenced with the NHC/base-catalyzed reaction of 2-propargyloxy 1-naphthaldehyde

Scheme 1. Cascade Catalysis Using NHC



Scheme 2. Proposed Mechanism of Base-Catalyzed Rearrangement of Chromanones to Benzofuranones



(**1a**) with 4-chlorobenzaldehyde (**2a**) leading to the formation of chromanone **3a** and benzofuranone **4a**. After a series of experiments, we found that treatment of **1a** and **2a** with the carbene generated by the deprotonation of the thiazolium salt **5**[13] with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) resulted in the exclusive formation of the benzofuranone **4a** in 94% yield (based on ^{1}H NMR spectroscopy, Table 1, entry 1). Notably, in contrast to this NHC, other common NHCs derived from precursors **6**–**9** are less effective (entries 2–5). The role of the base was found to be crucial for the chromanone–benzofuranone rearrangement, and other bases including K_2CO_3, KO*t*-Bu, Et_3N, and 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) furnished the benzofuranone in reduced yields (entries 6–9). Solvents other than THF resulted in inferior selectivity and hence are not beneficial (entries 10 and 11). Additionally, 5 and 10 mol % loadings of **5** and DBU, respectively, reduced the yield of **4a** as it affected the rearrangement step (entry 12). Gratifyingly, reducing the loading of **5** to 5 mol % and increasing the DBU amount to 20 mol % maintained the reactivity and afforded the desired benzofuranone in 90% isolated yield (entry 13).

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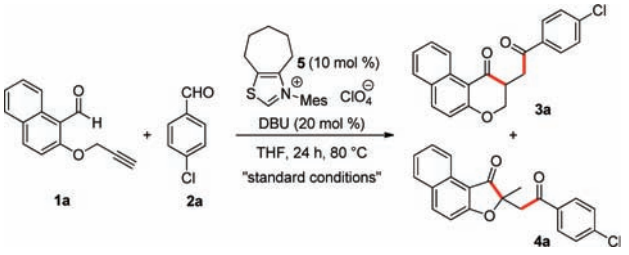
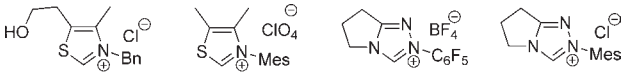
Table 1. Optimization of the Reaction Conditions[a]



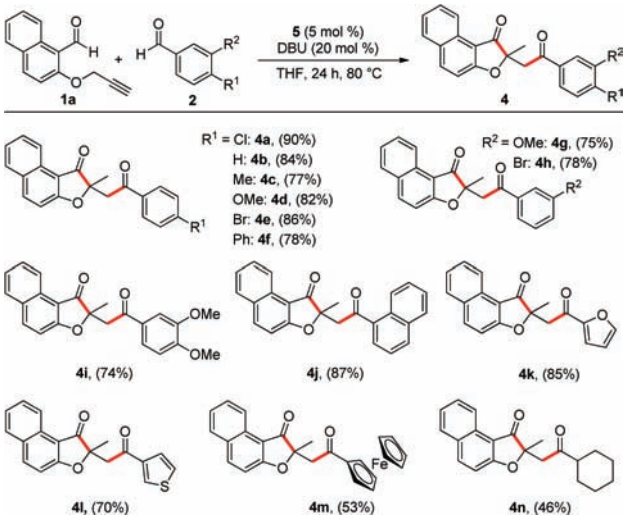
entry	variation of the standard conditions[a]	**3a**, yield (%)[b]	**4a**, yield (%)[b]
1	None	<1	94
2	**6** instead of **5**	6	5
3	**7** instead of **5**	<1	60
4	**8** instead of **5**	6	6
5	**9** instead of **5**	<1	20
6	K_2CO_3 instead of DBU	66	32
7	KO*t*-Bu instead of DBU	27	24
8	Et_3N instead of DBU	60	<1
9	TBD instead of DBU	82	6
10	1,4-dioxane instead of THF	74	24
11	DME instead of THF	16	82
12	(5 mol %) **5** and DBU (10 mol %)	20	78
13	**(5 mol %) 5 and DBU (20 mol %)**	**<1**	**93 (90)**[c]

[a] Standard conditions: **1a** (0.25 mmol), **2a** (0.25 mmol), NHC·HX (10 mol %), DBU (20 mol %), THF (0.5 mL), 80 °C, and 24 h. [b] The yields were determined by ^{1}H NMR analysis of crude products using CH_2Br_2 as the internal standard. [c] Isolated yield in parentheses.



With these optimized reaction conditions in hand, we then examined the scope of this unique NHC/base-catalyzed hydroacylation−Stetter−rearrangement cascade (Scheme 3). The parent system worked well, and a variety of substituents at the 4-position of the ring are well tolerated leading to the formation of functionalized benzofuranones in 77−90% yields (**4a**−**4f**). Moreover, 3-substituted aldehydes and a disubstituted aldehyde resulted in a smooth conversion to the product (**4g**−**4i**). The parent naphthyl system worked well affording the product in 87% yield (**4j**). Moreover, this novel cascade reaction is not limited to aromatic aldehydes. Gratifyingly, heterocyclic aldehydes also worked well leading to the formation of the desired products (**4k**, **4l**) in good to excellent yields. Furthermore, challenging aldehydes like ferrocene carboxaldehyde[14] and aliphatic aldehyde[15,16] also furnished moderate to good yields of the desired products, further expanding the scope of this NHC/base-catalyzed reaction (**4m**, **4n**).

Scheme 3. NHC/Base-Catalyzed Cascade Reaction: Variation of the Aldehyde Moiety[a]



[a] General conditions: **1a** (1.0 mmol), **2** (1.0 mmol), **5** (5 mol %), DBU (20 mol %), THF (2.0 mL), 80 °C, and 24 h.

In view of these interesting results, we further investigated the scope of the reaction using various differently substituted 2-propargyloxy benzaldehydes (Scheme 4). The unsubstituted parent system (2-propargyloxy benzaldehyde)[17] provided the product in a moderate yield (**4o**); however, electron-donating groups at the benzene ring improved the yield[18] (**4p**, **4q**). Additionally, a disubstituted as well as halogen substituted substrate[16] also afforded the corresponding product in good to moderate yields (**4r**, **4s**).

Mechanistically, the reaction proceeds via the formation of a nucleophilic Breslow intermediate[19] by the addition of carbene generated from **5** to **1** followed by its intramolecular nucleophilic addition to an unactivated triple bond resulting in the formation of the intermediate enone, which undergoes an intermolecular Stetter reaction with the Breslow intermediate generated from the aldehyde **2** leading to the formation of the chromanone. Under basic conditions, the chromanone undergoes a unique rearrangement furnishing the benzofuranones (Scheme 2).

(14) When ferrocene carboxaldehyde is employed as a coupling partner, 19% of corresponding chromanone was also isolated.

(15) 26% of the corresponding chromanone was isolated with the desired product when cyclohexanecarbaldehyde is used as the coupling partner.

(16) Simple aliphatic aldehydes like octanal resulted in complex reaction mixtures.

(17) Substrates **1o** and **1s** gave only a complex reaction mixture under the reaction conditions. Therefore, using a slightly modified procedure involving the separation of the crude chromanone product by simple filtration gave moderate to acceptable yields. For further details, see the Supporting Information.

(18) Under the optimized conditions, substrate **1q** gave only 40% of the desired product. However, a slight modification of the conditions improved the yield to 67%. For details, see the Supporting Information.

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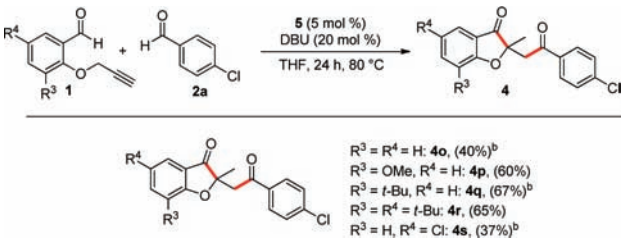
Scheme 4. Variation of 2-Propargyloxy Aldehyde Moiety[a]



[a] General conditions: **1** (1.0 mmol), **2a** (1.0 mmol), **5** (5 mol %), DBU (20 mol %), THF (2.0 mL), 80 °C, and 24 h. [b] Chromanone is generated in first step using (5 mol %) **5** and (10 mol %) K_2CO_3 in THF at 70 °C for 2 h. The addition of DBU (20 mol %) furnishes the furanone at 80 °C for 22 h in THF (for more details see the Supporting Information).

In conclusion, we have uncovered an efficient synthesis of 2,2-disubstituted benzofuranones through a multicatalytic process using the combination of NHC and a base. The present transition-metal-free catalysis involves an intramolecular hydroacylation of unactivated alkynes followed by an intermolecular Stetter reaction and a subsequent base-catalyzed rearrangement. Further studies on the use of NHCs in cascade catalysis should be rewarding.

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Supporting Information Available. Experimental procedures and full spectroscopic data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.