Tetrahedron Letters 52 (2011) 6952–6956

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

A versatile combined *N*-heterocyclic carbene and base-catalyzed multiple cascade approach for the synthesis of functionalized benzofuran-3-(2*H*)-ones

Johannes F. Franz, Patrick J.W. Fuchs, Kirsten Zeitler *

Institut für Organische Chemie, Universität Regensburg, Universitätsstrasse 31, D-93053 Regensburg, Germany

ARTICLE INFO

Article history:
Received 20 September 2011
Revised 11 October 2011
Accepted 14 October 2011
Available online 20 October 2011

Keywords:
Benzofuranones
N-Heterocyclic carbene catalysis
Cascade catalysis
Retro-Michael reaction
Rearrangements
Hydroacylation

ABSTRACT

Functionalized 2,2-disubstituted benzofuran-3-(2*H*)-ones have been synthesized from simple aldehyde building blocks in a combined NHC- and base-catalyzed one-pot cascade reaction in moderate to excellent yields. This modular approach comprises a NHC-catalyzed hydroacylation/Stetter reaction sequence followed by a retro-Michael, 1,3-H shift and oxa-Michael cascade rearrangement promoted by strong bases.

Catalytic, multistep one-pot reactions, in addition to tandem, domino, and cascade transformations, i.e., multicatalytic sequences,[1] have attracted considerably increased levels of interest during the last few years.[2] This is not just due to the obvious advantages with respect to the avoidance of typical cost-increasing intermittent isolation and purification steps as well as the omitting of waste-producing and time-consuming manual operations. Compared to the traditional 'one-step, one-pot' approach, multicatalytic single-flask strategies can circumvent serious detrimental drawbacks associated with iterative synthesis. Hence, they represent an attractive more step- and atom-economical synthetic strategy.[3]

Admittedly, here critical issues, such as reliability and compatibility (e.g., unwanted interaction of different catalysts) can bedevil such processes. But the growing number of organocatalytic transformations[4] coupled with their increased tolerance to air and moisture (relative to many transition-metal ion-based systems) has recently started to offer new perspectives for the development of simple and efficient single-flask sequences.[5] While organocatalysts are commonly remarkably robust, substrate selective and condition tolerant, the highly versatile 'dual' character of NHCs[6] has limited their frequent use in cascade and domino reactions. In recent years a few notable such applications have been reported. These include both multiple step sequences promoted by NHCs[7] and reactions involving carbenes employed in concert with other catalysts.[8,9] Some of these transformations have been proven to operate via concurrent activation of the reaction partners; others benefit from improved yield and selectivity only if simultaneous addition of both catalysts is attempted. Only recently, Scheidt could demonstrate that the combination of early transition metal Lewis acids with NHC organocatalysis results in a complete change of the reaction course to provide access to hitherto inaccessible products.[10] Rovis and co-workers proved the beneficial effects of co-operative Brønsted acid H-bonding catalysis in certain NHC-catalyzed transformations.[11] However, whereas most NHC processes rely on the presence of a base to generate the catalytically active free carbene from their corresponding heterazolium precatalysts,[12] examples of cascade catalysis involving NHCs in combination with alternative base-catalyzed steps are very rare.[9f,h,i]

Following on from our ongoing interest in the application of alkyne building blocks in NHC catalysis,[13] the recently disclosed work on carbene-catalyzed alkene hydroacylation[14] inspired us to investigate the possible extension of this chemistry to propargylic substrates.

Our initial goal was to use the expected α-methylene ketone product **5** (Scheme 1) as an active intermediate in further organocatalytic one-pot transformations for the cascade assembly of interesting heterocyclic target structures. While this work was in progress Glorius and co-workers reported the selective generation of chromanones via a hydroacylation–Stetter reaction cascade sequence.[15] However, under our (more basic) conditions the reaction always yielded a mixture of products (i.e., **3** and **4**, Scheme 1).

* Corresponding author. Fax: +49 941 943 4121.
E-mail address: kirsten.zeitler@chemie.uni-regensburg.de (K. Zeitler).

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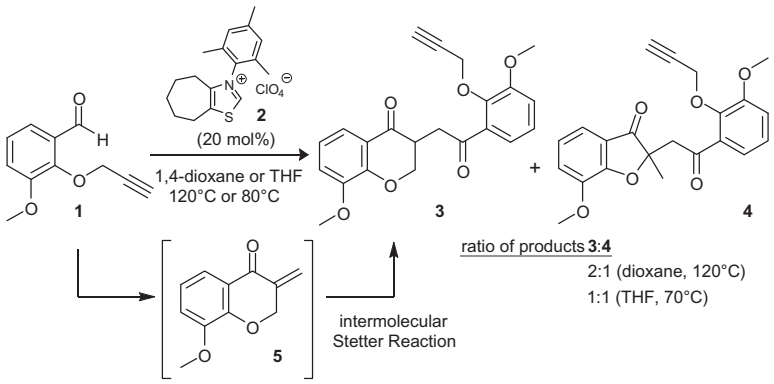
doi:10.1016/j.tetlet.2011.10.078



Scheme 1. Initial results of the hydroacylation attempts of propargylated salicylaldehydes.

Careful analysis revealed that in addition to the presence of the known 1,4-diketo chromanone **3**,[15a] as a second major product (of very similar polarity and identical mass) 2,2-disubstituted benzofuran-3(2*H*)-one **4** was formed—especially upon prolonged reaction times. These structures were unambiguously confirmed by X-ray structure analysis[16] (see Fig. 1).

The broad range of biological activities[17] of the benzofuranone *motif* containing a quaternary stereocenter at C2, which forms a key subunit of several natural products such as griseofulvin or photinides,[18] has led to the development of a number of methods to access these structures (also including NHC-catalyzed intramolecular approaches pioneered by Rovis and She, Scheme 2).[19] Despite, most of the existing methodologies require quite advanced synthetic precursors of considerable synthetic complexity. The elegant multi-catalytic Michael–Stetter approach devised by Rovis[9f]

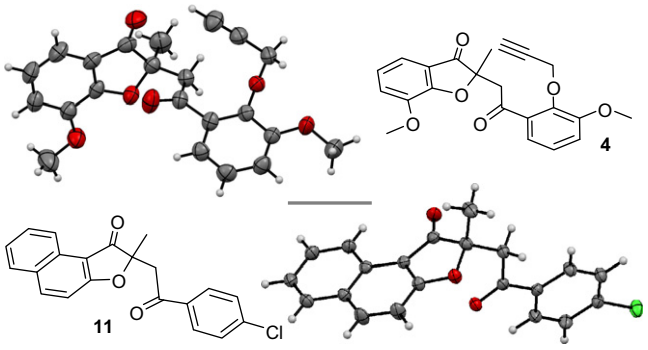


Figure 1. X-ray structure of symmetrical and 'crossed' benzofuranones **4** and **11**.

(which provides 2-alkylcarboxylate substituted benzofuranones) can be considered a rare exception.

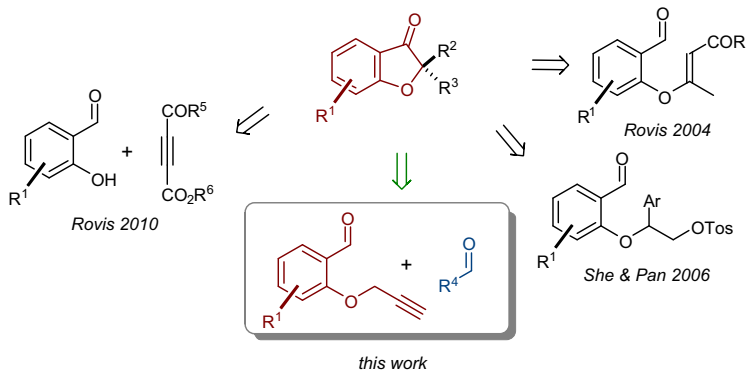
Hence, we were encouraged to attempt to exploit the serendipitous formation of the benzofuran-3(2*H*)-one unit in the reactions outlined in Scheme 1 toward the development of a general, novel protocol for the preparation of these highly attractive synthetic targets. A very recent similar report by Biju and Glorius[20] prompted us now to disclose our own results in this area.[21]

The predominance of **4** after extended reaction times led us to speculate that **3** was being converted into **4** via an initial retro-Michael reaction, followed by a base-catalyzed 1,3-H shift,[22] and a subsequent 5-*exo*-trig oxa-Michael ring closure (Scheme 3).

If this hypothesis is correct, it potentially allows developing a process of expanded scope and utility through the use of distinct coupling partners, such as easily accessible propargylated salicylaldehydes, in conjunction with either aromatic or aliphatic aldehyde partners, in an atom-economic one-pot, five-step sequence involving NHC-catalyzed hydroacylation, a subsequent intermolecular Stetter reaction, followed by a base-promoted retro-Michael reaction and a 1,3-H shift, completed by a 5-*exo*-trig oxa-Michael ring closure (for a detailed mechanistic proposal *vide infra*—Scheme 5).

As we anticipated a base-catalyzed isomerization/rearrangement of the NHC catalysis-derived 1,4-diketo intermediate[15a] we first examined the use of several bases of variable strength (see Table 1) with the aim to gain further insight into the pK_{aH}[23] dependency of this process.

Weak to medium bases (entries 1–5) only produce traces of the desired benzofuranone. In contrast, stronger bases such as DBU (entries 6–8) and guanidines (entries 9 and 10) proved to be suitable to trigger the initial retro-Michael[24] ring-opening (phenoxide elimination) by deprotonation. Potassium *tert*-butoxide resulted in decomposition of the substrate. Relatively low loadings of either



Scheme 2. Overview on NHC-catalyzed approaches toward disubstituted benzofuran-3(2*H*)ones.