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Syntheses of 1,2,3-functionalized naphthols and phenols by decarboxylative cycloaddition/aromatization reactions of α-oxygenated lactones with allenoates or electron-deficient alkynes

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Base-mediated reactions between hydroxypyrones or isochroman-3,4-diones and allenoates or butynoates allow for the direct synthesis of various 1,2,3-substituted phenols and naphthols under mild conditions. These transformations are proposed to proceed first *via* a [4 + 2]-cycloaddition of the starting materials, followed by an immediate decarboxylation/re-aromatization process.

Introduction

Phenols and naphthols are amongst the most important aromatic scaffolds, frequently occurring in different (biologically) relevant natural and synthetic compounds.[1] A variety of different properties and features are associated with these arenols, such as antioxidant, anticancer and antimalarial activities[2] as well as their potential use as dyes and fluorescent agents.[3] Thus, it comes as no surprise that the development of synthesis routes to access such highly functionalized arenols has emerged as an important task. Numerous strategies have been developed, each with their specific advantages and limitations.[4,5] Notably, the synthesis of phenols and naphthols with a 1,2,3-substitution pattern (see Fig. 1 for selected examples) may sometimes pose challenges.[5] Previous strategies for constructing highly substituted phenols and naphthols have relied on mechanistically distinct approaches (Scheme 1). For example, in 2020 Beaudry's group demonstrated that hydroxypyrones participate in Lewis-acid-promoted formal [4 + 2] cycloadditions with nitroalkenes under high temperature conditions, leading to the formation of phenolic products after rearomatization (Scheme 1A).[6]

Conceptually alternatively, oxabenzonorbornadienes can undergo Brønsted acid-mediated ring-opening rearrangements to furnish naphthol derivatives bearing synthetically useful substitution patterns, as demonstrated by Sarpong's group (Scheme 1B).[7] Very recently, cobalt-catalyzed photochemical dehydrogenative couplings have also been successfully introduced to access various naphthols from *o*-hydroxyaryl precursors under mild conditions, thus providing a complementary oxidative route to these structures (Scheme 1C).[8]

Isochroman-3,4-diones **1** and hydroxypyrones **2** are readily available compounds that have recently been shown to undergo Diels–Alder type cycloadditions under basic conditions.[9,10] We therefore wondered whether a protocol could be devised for the direct synthesis of α-naphthols **3** or phenols **4** from **1** and **2** (Scheme 1D). Our idea was to use either allenoates **5** or propynoates **6** as dienophiles. The [4 + 2]-cycloaddition between the diene-precursor **1** or diene **2** and dienophiles **5** or **6** was expected to provide bicyclic Diels–Alder products **A** and/or **B**. It was anticipated that intermediate **B** would then easily undergo aromatization by means of a retro-[4 + 2]-reaction with extrusion of CO_2, thus providing a straightforward route towards the highly functionalized arenols **3** or **4**.

Results & discussion

We started our investigations by optimizing the reaction between the parent isochroman-3,4-dione **1a** (which is known to form the necessary diene species *in situ*[10]) and ethyl allenoate **5a** (Table 1, entries 1–11, provides a condensed overview of the most significant results;[11] it should be emphasized that

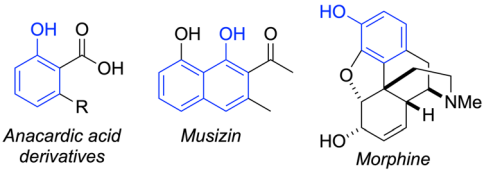

Fig. 1 Representative bioactive 1,2,3-substituted phenols or naphthols.

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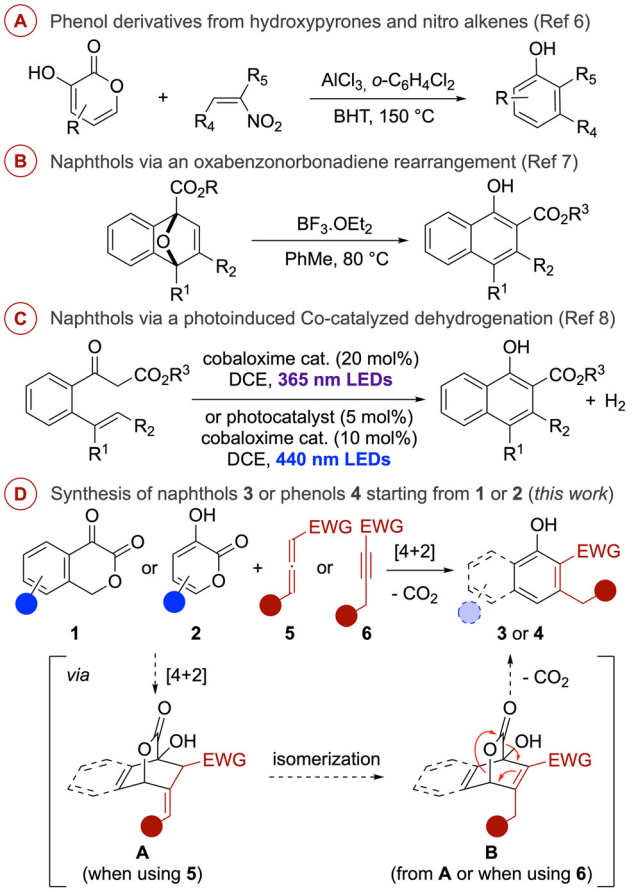


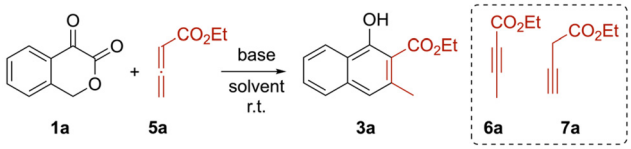
Scheme 1 Recently reported strategies to access 1,2,3-substituted phenols or naphthols (A–C) and the strategy described herein employing isochroman-3,4-diones **1** or hydroxypyrones **2** (D).

throughout all our investigations, we exclusively observed the expected products, with the EWG-group of the dienophile being *ortho* to the newly formed OH-group). Initial experiments using 2 eq. of Et_3N as a base in DCE (1,2-dichloroethane) showed that using an excess of isochroman-3,4-dione **1a** is beneficial, as compared to experiments using an excess of allenoate **5a** (entries 1 and 2). Furthermore, DCE clearly outperformed other solvents such as dichloromethane (DCM), acetonitrile (AcN), methyl *t*-butylether (MTBE), and toluene (entries 3–7). Other bases, such as diisopropylethylamine (DIPEA) or Cs_2CO_3 showed inferior performance as compared to Et_3N (entries 8–10).

In general, most of the lower yielding experiments were accompanied by the formation of significant amounts of unidentified side products. Gratifyingly, an increased reaction time of 20 h in DCE in combination with 3 eq. of Et_3N allowed us to access product **3a** in >80% isolated yield (entry 10). Finally, we again tested different stoichiometric ratios of **1a** and **5a**, underscoring the need for a 2-fold excess of **1a** (entries 10–12).

With reliable conditions for the synthesis of **3a** using allenoate **5a** in hand, we next investigated the suitability of the

Table 1 Optimization of the synthesis of naphthol **3a**[a]



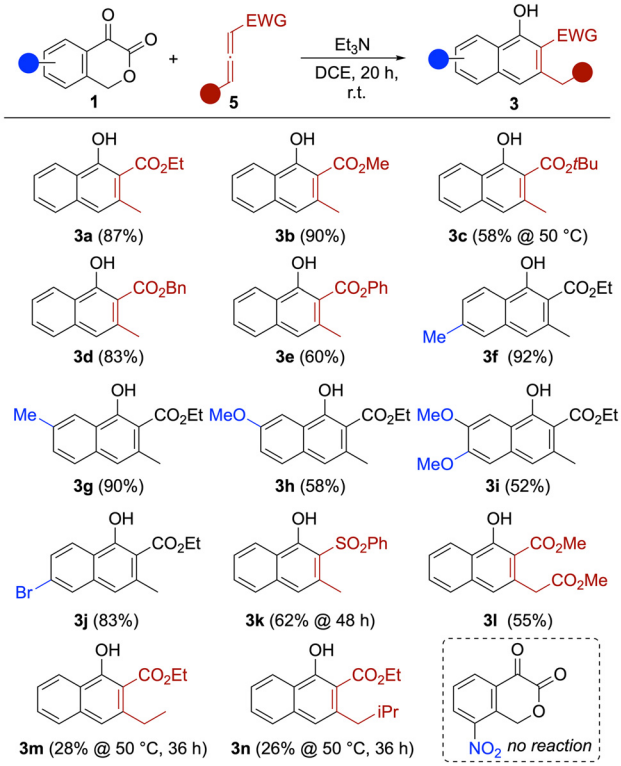
Entry	**1a : 5a**	Solvent	Base	*t* [h]	**3a**[b] [%]
1	1 : 2	DCE	Et_3N (2×)	6	39
2	2 : 1	DCE	Et_3N (2×)	4	48
3	2 : 1	DCE	Et_3N (2×)	12	74
4	2 : 1	DCM	Et_3N (2×)	12	34
5	2 : 1	AcN	Et_3N (2×)	12	39
6	2 : 1	Toluene	Et_3N (2×)	48	16
7	2 : 1	MTBE	Et_3N (2×)	48	12
8	2 : 1	DCE	DIPEA (2×)	12	43
9	2 : 1	DCE	Cs_2CO_3 (3×)	15	40
10	2 : 1	DCE	Et_3N (3×)	20	87 (80)[c]
11	1.5 : 1	DCE	Et_3N (3×)	20	63
12	1 : 1	DCE	Et_3N (3×)	20	42
With 6a:	**1a : 6a**	**Solvent**	**Base**	***t* [h]**	**3a [%]**[b]
13	2 : 1	DCE (50 °C)	Et_3N (3×)	24	37
With 7a:	**1a : 7a**	**Solvent**	**Base**	***t* [h]**	**3a [%]**[b]
14	2 : 1	DCE	Et_3N (3×)	24	82

[a] All reactions were run using 0.1 mmol of the limiting reagent in the given solvent (0.2 M) unless otherwise stated.[11] [b] Isolated yields. [c] 1 mmol scale.

isomeric butynoates **6a** and **7a** for this naphthol-forming reaction. While but-2-ynoate **6a** reacted significantly more slowly and less cleanly as compared to allenoate **5a** (entry 13), but-3-ynoate **7a** performed more or less identically (entry 14; this result comes as no surprise keeping in mind the well-established base-mediated isomerization of but-3-ynoates **7** to allenoates **5**).[12]

Next, we investigated the generality of these base-mediated decarboxylative naphthol-forming protocols by testing a variety of differently functionalized allenoates **5** and alkynoates **6** for the reaction with diones **1** (Scheme 2). Using various allenoates **5** first, we in general found different ester functionalities to be well-tolerated, except for the use of *t*-butyl esters (compare products **3a–3e**). The reduced reactivity of the *t*-butyl ester can be explained by its higher steric bulk and its stronger electron-donating effect, thus making the dienophile less reactive.

Variations of the dione partner were also possible, provided the introduced groups were not overly electron-withdrawing, as demonstrated by products **3g–j**; in contrast, the presence of a NO_2-group really made the dione too unactivated to undergo the [4 + 2]-cycloaddition. Gratifyingly, the use of a sulfone-containing allene[13] was well-tolerated (**3k**). On the other hand, the use of γ-substituted allenoates **5** showed that functional groups at this position strongly influence the overall performance. While the presence of an additional ester group still allowed for a reasonable yield (**3l**), the presence of electron-donating alkyl groups significantly reduced the reactivity of the dienophile, necessitating prolonged reaction times and higher temperatures to achieve at least low yields of products

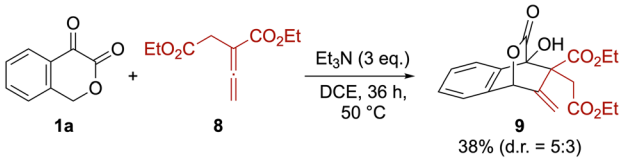


Scheme 2 Syntheses of naphthols **3** with allenoates **5**.

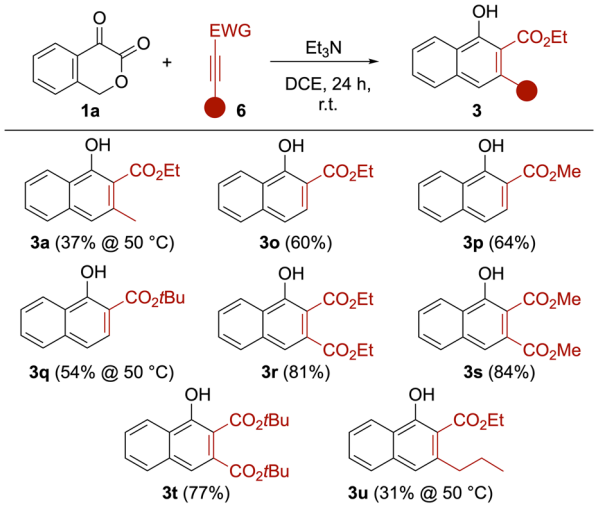
3m and **3n**. Out of curiosity, we also tested the α-branched allenoate **8**, which should be incapable of undergoing the decarboxylative aromatization step required for the formation of naphthols **3** (Scheme 3). Interestingly, we were hereby able to isolate the primary cycloaddition product **9**, albeit in a rather low yield, as a mixture of diastereomers, which supports our mechanistic hypothesis illustrated in Scheme 1D.

Next, we also employed different alkynoates **6** in the reaction with **1a** (Scheme 4). While the parent but-2-ynoate **6a** (compare with entry 13, Table 1) gave product **3a** in low yield only at elevated temperatures, propynoates were found to be significantly more reactive (products **3o–q**). Diester-based alkynes were also well-tolerated at room temperature (**3r–t**), whereas the synthesis of the hexynoate-derived product **3u** again required a higher temperature and the product was obtained only in low yield.

Having established the syntheses of naphthols **3** starting from diones **1**, we next turned our attention towards analogous cycloadditions of pyrones **2** with allenoates **5** (as stated above,

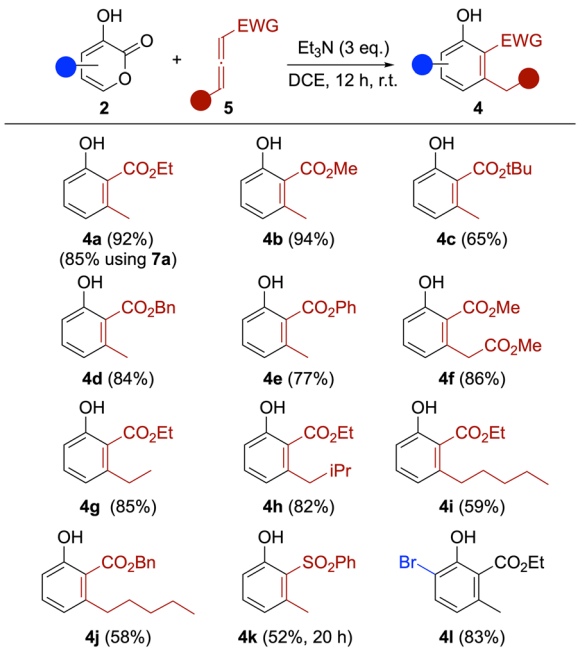


Scheme 3 Syntheses of the bridged adduct **9** with allenoate **8**.

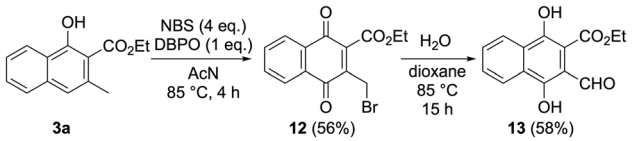


Scheme 4 Syntheses of naphthols **3** with alkynoates **6**.

decarboxylative cycloadditions of **2** are known, even though these often require rather harsh reaction conditions).[6] As outlined in Scheme 5, the formation of phenols **4** starting from **2** and **5** proceeded comparably, or even more efficiently, than our naphthol synthesis. Different esters, even *t*-butyl-based ones, all gave the corresponding 1,2,3-substituted phenols **4a–e** in high yields within 12 h reaction time. γ-Substituted allenoates were also better tolerated in this system (see products **4f–j** and compare with the results obtained for **3l–n**, Scheme 2). Although the sulfone-containing phenol **4k** was obtained in slightly lower yield, the *o*-Br-substituted product **4l** could be accessed in high yield under the standard conditions.



Scheme 5 Syntheses of phenols **4** with allenoates **5**.



3a 12 (56%) 13 (58%)

Scheme 6 Follow-up manipulations.

Finally, we evaluated the suitability of naphthol **3a** for several follow-up transformations. In addition to standard ester saponifications,[11] which afforded the API intermediate 6-methylsalicylic acid **10** (also an intermediate in the synthesis of anacardic acids)[2c] and 1-hydroxy-3-methyl-2-naphthoic acid **11** (for further information, see the SI), we also investigated radical side-chain brominations. Interestingly, using *N*-bromosuccinimide (NBS) and dibenzoyl peroxide (DBPO) led to the formation of the brominated 1,4-naphthoquinone **12** (for an example of the synthesis of analogous naphthoquinones[14]). This compound could finally be hydrolyzed, leading to the highly functionalized naphthalene derivative **13** (Scheme 6).

Conclusion

We have developed a straightforward protocol for the synthesis of various 1,2,3-substituted naphthols **3** and phenols **4** by reacting either isochroman-3,4-diones **1** or hydroxypyrones **1** with electron-deficient allenes **5** or butynoates **6** under basic conditions. In this reaction, compounds **1** and **2** serve as diene partners that can be engaged in [4 + 2]-cycloadditions with dienophiles **5** or **6**. This process initially results in the formation of bridged primary cycloaddition products, which then undergo immediate decarboxylation, a process driven by re-aromatization, resulting in the direct formation of the valuable arenols **3** and **4**.

Author contributions

M. S. M., A. M. and M. W. conceived the idea and wrote the manuscript. M. S. M. performed the experiments and analysed the data. M. S. M., A. M. and M. W. discussed the results and commented on the manuscript. All authors have given approval to the final version of the manuscript.

Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this article have been included as part of the supplementary information (SI). Supplementary information with detailed experimental procedures and analytical details is available. See DOI: **https://doi.org/10.1039/d5qo01582k**.

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