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An Oxidopyrylium Cyclization/Ring-Opening Route to Polysubstituted α -Hydroxytropolones

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Abstract

α -Hydroxytropolones are a class of molecules with therapeutic potential against several human diseases. However, structure-activity relationship studies on these molecules have been limited due to a scarcity of efficient synthetic methods to access them. It is demonstrated herein that α -hydroxytropolones can be generated through a BCl_3 -mediated ring-opening/aromatization/demethylation process on 8-oxabicyclo[3.2.1]octenes. Used in conjunction with an improved method based on established oxidopyrylium dipolar cycloadditions, several polysubstituted α -hydroxytropolones can be accessed in 3 steps from readily available α -hydroxy- γ -pyrones.

α -Hydroxytropolones are a class of molecules with a broad range of biological activity against several diseases, from HIV¹ and malaria² to bipolar disorder and hypertension (Figure 1).³ This activity is often attributed to bimetallic enzyme inhibition,^{1c,3} but in many instances is not known. To date, α -hydroxytropolones have not found utility clinically due in part to their toxicity.⁴ Thus, directed structure-activity relationship (SAR) studies are needed to increase selectivity as well as potency. Current synthetic methods unfortunately have limitations, particularly as it relates to the introduction of polysubstitution,⁵ and SAR studies to date have opted to focus instead on natural hydroxytropolones or synthetic modifications of them.⁶ SAR studies will benefit from new routes that address these limitations. Herein we report a short and divergent route to polysubstituted α -hydroxytropolones.

The key steps in our route are an oxidopyrylium dipolar cycloaddition and subsequent ring-expansion (Scheme 1). Ring expansions of oxidopyrylium-generated 8-oxabicyclo[3.2.1]octanes have been used previously in tropolone synthesis, and provided ample precedence for this approach.⁷ Adapting this strategy toward α -hydroxytropolone synthesis requires an α -hydroxy- γ -pyrone-based oxidopyrylium cyclization developed by the Wender and Mascareñas labs,⁸ and modified for intermolecular cyclizations through N,N-dimethylaniline activation of triflate salt **3** (Scheme 2, eq. 1).^{9a} We focused our efforts

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Supporting Information Available Full experimental data and characterization for all new compounds are available free of charge and can be found via the internet at <http://pubs.acs.org>.

on this intermolecular cycloaddition process with SAR studies in mind because it allows for late-stage diversification with readily available alkynes.

At the onset of our studies, only a single example of this intermolecular oxidopyrylium cyclization with an alkyne was known, and it was with the highly dipolarophilic dimethyl acetylenedicarboxylate (DMAD, eq. 1).^{9a} After a brief survey of other alkynes, we found that the method as described suffered a few key disadvantages including sluggish reaction times and low yields. Fortunately, two key observations were made during these studies.

The first discovery was that compound **7**, a known oxidopyrylium dimer whose formation had been previously optimized against,^{9a} formed instantly upon addition of base. Despite this, oxidopyrylium cyclization products formed over time, suggesting reversibility of the dimerization. Assuming that heat would speed the interconversion as well as the cyclization, we isolated dimer **7**, and heated it in the presence of DMAD. It was found that at 100 °C in the microwave, bicyclooctene **5a** was formed in only 5 minutes (Scheme 2, eq. 2).

Our second discovery was the formation of salt **9**, presumably through demethylation of ylide **8** (Scheme 2, eq. 3), as was evidenced by a signature ¹H NMR pattern of the γ position of the pyrone at 6.25 ppm and of the 9 methyl protons of the trimethylammonium counterion at 3.78 ppm. Heating salt **9** in the presence of DMAD did not lead to product within 5 minutes, and longer reaction times led to complex mixtures. After surveying several bases, the use of the bulkier N,N-diisopropylaniline was found to dramatically suppress demethylation.

With these observations in mind, all reactions were carried out in the presence of N,N-diisopropylaniline to eliminate demethylation, and with microwave irradiation to shorten reaction times. Indeed, both yields and times were improved dramatically when compared to our attempts with previously described conditions (Scheme 3, conditions A vs. conditions B). For example, the known coupling of **3a** with DMAD increased in yield from 74% to 89%, and the reaction was done in only 5 minutes compared to 17 hours. Coupling of **3a** with ethyl propiolate or 3-butyne-2-one using conditions A yielded 44% of **5d** or **5e**. Newly developed condition B increased these yields dramatically to 88% and 97% respectively. The internal alkyne, ethyl but-2-ynoate, is both more sterically congested and electronically rich, and would not react at all using condition A. Gratifyingly, compound **5g** could be generated in 32% yield within an hour using condition B. Phenylacetylene, which yields **5h** in 35% yield after one week when condition A is used provides the same molecule in 57% yield in a half hour when condition B is used. The regioselectivity in this instance suggests that the phenyl group is serving as electron accepting group rather than electron-donating. Indeed, the electronically poor 4-nitrophenylacetylene can also be used, generating **5i** with slightly improved yields.

The reaction also works with alternative oxidopyrylium species, as we have demonstrated by synthesizing chloro **5b** and methoxy **5c** congeners.¹⁰ The chloro substrate is particularly valuable, as it provides a versatile synthon for further functionalization. In these instances longer reaction times were needed, and the yields were lower. This trend is currently being investigated, although our current hypothesis is that the electron withdrawing nature of the groups may destabilize the partial positive charge on the adjacent oxocarbenium carbon resulting in lower concentrations of the oxidopyrylium ylide in solution.

One of the current limitations to this method as it stands now is the amount of alkyne needed. Our optimizations, which had been carried out with phenylacetylene, suggested that 20 equivalents maximized yields. However, when the reaction was run neat, we were able to use 5 equivalents and obtain a 42% yield. Given the low costs associated with most alkynes,

and our desire not to limit ourselves to liquid alkynes, 20 equivalents were used. However, 1-phenylprop-2-yn-1-one represented a solid alkyne in which 20 equivalents was cost prohibitive. In this instance 5 equivalents of alkyne led to **5f** in excellent yields in only 10 minutes. Moreover, 70% of the unreacted alkyne was recovered providing a net alkyne consumption of only 2.2 equivalents.

We next moved toward the desired ring-expansion. In an attempt to perform ring opening and demethylation in a single pot, boron trihalides were tested. We began with BBr₃, which after 20 minutes led to a complex mixture of compounds from which 33% isolated yield of α -methoxytropolone **10a** was obtained (Scheme 4). Attempts at optimizing the conditions with BBr₃ were not fruitful. Gratifyingly, however, switching to an excess of BCl₃ led cleanly to hydroxytropolone **6a**, which was confirmed by X-ray crystallographic analysis.

The ring-expansion is successful with most substrates, although a significant substrate scope trend was observed with respect to formation of α -methoxytropolone vs. α -hydroxytropolone (Scheme 5, **6a–i** vs. **10a–i**). With all DMAD-derived oxabicyclo[3.2.1]octenes, selective formation of the hydroxytropolone was observed upon treatment with BCl₃ (**6a–6c**), although higher equivalents were necessary for **6b**. Methyl ketone **5e** also converted selectively to hydroxytropolone **6e**. The ethyl propiolate derived bicycle **5d** also led selectively to hydroxytropolone **6d**, but with slightly more methoxytropolone (7:1 ratio). In this case, the mass recovery was significantly lower, which we suspect may be due to hydrolysis of a more exposed ester upon aqueous workup. Surprisingly, phenyl ketone containing bicycle **5f** led to a 1:1 ratio of the two tropolones (**6f** and **10f**).

An even more dramatic change in reactivity was seen with compound **5g**, which possesses an added electron-donating methyl group at R³. In this instance, clean conversion to methoxytropolone **10g** takes place, and no hydroxytropolone is observed at all. Phenyl substrate **5h** led to a complex and inseparable mixture of products (result not shown). The nitroaryl-containing bicycle **5i**, however, led to a mixture of methoxytropolone and hydroxytropolone in a 1:1 ratio. In most cases in which mixtures arose, the major compounds could be isolated using reverse-phase chromatography. Alternatively, the reaction mixture can be homogenized to solely hydroxytropolone by heating in HBr in acetic acid.⁵ This method was particularly useful for nitroaryl tropolone **6i**, which was unstable to chromatographic conditions (Scheme 6).

The simplest explanation on the onset to the α -methoxytropolone vs. α -hydroxytropolone observation was that some substrates were more prone to demethylation by BCl₃ than others, and that methoxytropolones were in fact intermediates toward hydroxytropolones. However, if this were the case, longer reaction times would be expected to lead to more hydroxytropolone, which was not observed. In addition, subjecting **10a** to BCl₃ did not lead to demethylation.

Our current hypothesis is that when R³ is an electron donating group, such as the methyl group in **6g**, the ring opening is favored due to the increased stabilization of the allylic cation, and the reaction proceeds smoothly to α -methoxytropolones (**11** → **10a–i**, Scheme 7). When R³ is instead an electron-withdrawing group, such as the ethyl esters in **5a–c**, ring-opening is disfavored due to cation destabilization. Instead, demethylation drives the ring-expansion, and hydroxytropolones are formed (**13** → **6a–i**, Scheme 7).

In instances where R³ is a proton, variability exists. For example, when R² is a methyl ketone or ester, selectivity for hydroxytropolone formation exists. These groups may destabilize the carbocation through inductive withdrawing, favoring hydroxytropolone

formation (**6d** and **6e**). While the phenyl ketone of substrate **5f** may also have similar inductive withdrawing capabilities, it may also participate in a through-space cation- π interaction, stabilizing the carbocation of **11**.¹¹ These competing factors could explain the lower selectivity in this instance. Nitroaryl derivative **5i** has less inductive withdrawing than the carbonyls, leading again to a 1:1 ratio.

In conclusion, we have demonstrated that polysubstituted α -hydroxytropolones can be generated readily through the use of oxidopyrylium cyclizations followed by BCl_3 -mediated ring expansions. This route will benefit SAR studies devoted to α -hydroxytropolone therapeutic development.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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β -Thujaplicinol
(anti-HIV)

Puberulic acid
(anti-malarial)

Puberulonic acid
(inositol monophosphatase inhibitor)

Figure 1.
Examples of bioactive natural α -hydroxytropolones

Scheme 1.
General route toward polysubstituted α -hydroxytropolones from commercially available kojic acid

Scheme 2.

Established oxidopyrylium cyclization and relevant observations used for reaction optimization

Scheme 3.

Substrate studies for oxidopyrylium cyclization

^a **Condition A**: 2 equiv of N,N-dimethylaniline, CH₂Cl₂, rt.

Condition B: 1.2 equiv of N,N-diisopropylaniline, CHCl₃, 100 °C, μ wave. Unless otherwise indicated, 20 equiv of alkyne were used.

^b 5 equiv of alkyne were used. ^c Reaction run without solvent.

Scheme 4.

Select results comparing BBr_3 and BCl_3 along with crystal structure of α -hydroxytropolone **6a**

Scheme 5.

Ring-expansion substrate scope

^a Reactions were run with 7 equiv of BCl_3 unless otherwise noted. Reaction yields are reported following aqueous workup with ratios of **6a-i** to **10a-i** being calculated by ^1H NMR integration.

^b 15 equiv of BCl_3 were used.

Scheme 6.

Example of homogenizing α -methoxy and α -hydroxytropolone mixture by HBr/AcOH demethylation

Scheme 7.
Proposed mechanism