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

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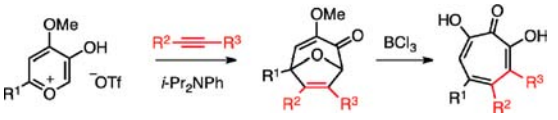
ABSTRACT



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 three 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 HIV[1] and malaria[2] 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.

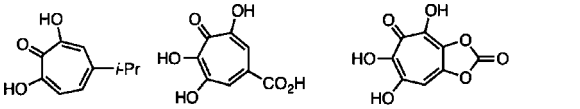


Figure 1. Examples of bioactive natural α-hydroxytropolones.

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

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(1) For lead examples relevant to HIV, see: (a) Budihas, S. R.; Gorshkova, I.; Gaidamakov, S.; Wamiru, A.; Bona, M. K.; Parniak, M. A.; Crouch, R. J.; McMahon, J. B.; Beutler, J. A.; Le Grice, S. F. J. *Nucleic Acids Res.* **2005**, *33*, 1249. (b) Semenova, E. A.; Johnson, A. A.; Marchand, C.; Davis, D. A.; Yarchoan, R.; Pommier, Y. *Mol. Pharmacol.* **2006**, *69*, 1454. (c) Himmel, D. M.; Maegley, K A.; Pauly, T. A.; Bauman, J. D.; Das, K.; Dharia, C.; Clark, A. D., Jr.; Ryan, K.; Hickey, M. J.; Love, R. A.; Hughes, S. H.; Bergqvist, S.; Arnold, E. *Structure* **2009**, *17*, 1625.

(2) For lead examples relevant to malaria, see: (a) Omura, S.; Kasuhiko, O.; Iwatsuki, M.; Shiomi, K.; Masuma, R. *Jpn. Kokai Tokkyo Koho*, 2011084534 A 20110428, **2011**. (b) Iwatsuki, M.; Takada, S.; Mori, M.; Ishiyama, A.; Namatame, M.; Otoguro, K.; Nishihara-Tsukashima, A.; Nonaka, K.; Masuma, R.; Otoguro, O.; Shiomi, K.; Omura, S. *J. Antibiot.* **2011**, *64*, 183.

(3) Piettre, S. R.; Ganzhorn, A.; Hoflack, J.; Islam, K.; Hornsperger, J.-M. *J. Am. Chem. Soc.* **1997**, *119*, 3201.

(4) Nakagawa, Y.; Tayama, K. *Chem.-Biol. Interact.* **1998**, *116*, 45.

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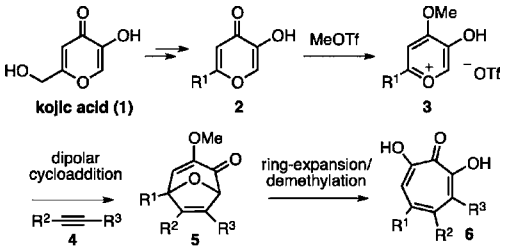
synthesis and provided ample precedence for this approach.[7] Adapting this strategy toward α-hydroxytropolone synthesis requires an α-hydroxy-γ-pyrone-based oxidopyrylium cyclization developed by the Wender and Mascareñas laboratories,[8] and modified for intermolecular cyclizations through *N*,*N*-dimethylaniline activation of triflate salt **3** (Scheme 2, eq 1).[9a] We focused our efforts on this intermolecular cycloaddition process with SAR studies in mind because it allows for late-stage diversification with readily available alkynes.

Scheme 1. General Route toward Polysubstituted α-Hydroxytropolones from Commercially Available Kojic Acid

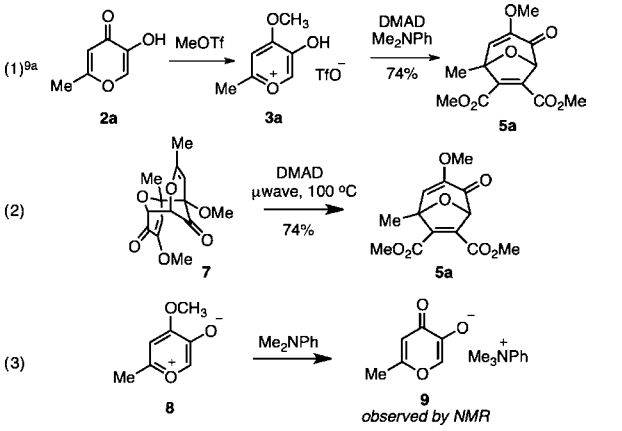


At the onset of our studies, only a single example of this intermolecular oxidopyrylium cyclization with an alkyne was known, and it was with the highly dipolarophilic dimethyl acetylenedicarboxylate (DMAD, eq 1).[9a] After a brief survey of other alkynes, we found that the method as described suffered 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 a 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 min (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 ^{1}H 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 min, 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.

Scheme 2. Established Oxidopyrylium Cyclization and Relevant Observations Used for Reaction Optimization



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 completed in only 5 min compared to 17 h. Coupling of **3a** with ethyl propiolate or 3-butyn-2-one using conditions A yielded 44% of **5d** or **5e**. Newly developed conditions B increased these yields dramatically to 88% and 97% respectively. The internal alkyne, ethyl but-2-ynoate, is both more sterically conjested and electronically rich and would not react at all using conditions A. Gratifyingly, compound **5g** could be generated in 32% yield within 1 h using conditions B. Phenylacetylene, which yields **5h** in 35% yield after one week when conditions A are used, provides the same molecule in 57% yield in 0.5 h when conditions B are used. The regioselectivity in this instance suggests that the phenyl

(5) (a) Banwell, M. G.; Collis, M. P.; Crisp, G. T.; Lambert, J. T.; Reum, M. E.; Scoble, J. A. *J. Chem. Soc., Chem. Commun.* **1989**, *10*, 616. (b) Zinser, H.; Sonja, H.; Foehlisch, B. *Eur. J. Org. Chem.* **2004**, *6*, 1344.

(6) For recent examples, see: (a) Didierjean, J.; Isel, C.; Querré, F.; Mouscadet, J.-F.; Aubertin, A.-M.; Valnot, J.-V.; Piettre, S. R.; Marquest, R. *Antimicrob. Agents Chemother.* **2005**, *49*, 4884. (b) Chung, S.; Himmel, D. M.; Jiang, J.-K.; Wojtak, K.; Bauman, J. D.; Rausch, J. W.; Wilson, J. A.; Beutler, J. A.; Thomas, C. J.; Arnold, E.; Le Grice, S. F. J. *J. Med. Chem.* **2011**, *54*, 4462.

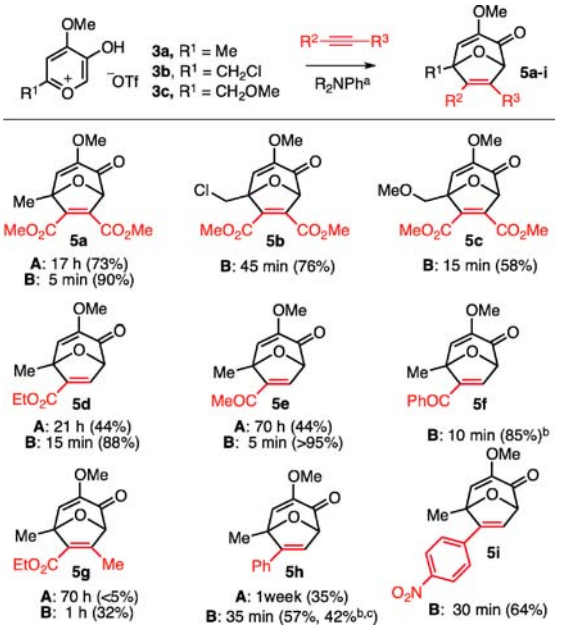
(7) (a) Baldwin, J. E.; Mayweg, A. V. W.; Neuman, K.; Prichard, G. J. *Org. Lett.* **1999**, *1*, 1933. (b) Adlington, R. M.; Baldwin, J. E.; Mayweg, A. V. W.; Pritchard, G. J. *Org. Lett.* **2002**, *4*, 3009. (c) Baldwin, J. E.; Mayweg, A. V. W.; Pritchard, G. J.; Adlington, R. M. *Tetrahedron Lett.* **2003**, *44*, 4543. (d) Graening, T.; Bette, V.; Neudorfl, J.; Lex, J.; Schmalz, H.-G. *Org. Lett.* **2005**, *7*, 4317.

(8) (a) Wender, P. A.; McDonald, F. E. *J. Am. Chem. Soc.* **1990**, *112*, 4956. (b) Rumbo, A.; Mouriño, A.; Castedo, L.; Mascareñas, J. L. *J. Org. Chem.* **1996**, *61*, 6114. (c) Mascareñas, J. L.; Pérez, I.; Rumbo, A.; Castedo, L. *Synlett*. **1997**, 81. (d) Rodríguez, J. R.; Rumbo, A.; Castedo, L.; Mascareñas, J. L. *J. Org. Chem.* **1999**, *64*, 4560. (e) Wender, P. A.; D'Angelo, N.; Elitzin, V. I.; Ernst, M.; Jackson-Ugueto, E. E.; Kowalski, J. A.; McKendry, S.; Rehfeuter, M.; Sun, R.; Voigtlaender, D. *Org. Lett.* **2007**, *9*, 1829. For some recent reviews covering oxidopyrylium cycloadditions, see: (f) *Advances in Cycloaddition*; Harmata, M., Ed.; Jai Press: Stamford, CT, 1999; Vol. 6. (g) Singh, V.; Krishna, U. M.; Vikrant; Trivedi, G. K. *Tetrahedron* **2008**, *64*, 3405. (h) Pellissier, H. *Adv. Synth. Catal.* **2011**, *353*, 189.

(9) (a) Wender, P. A.; Mascareñas, J. L. *Tetrahedron Lett.* **1992**, *33*, 2115. (b) For related work, see: Wender, P. A.; Mascareñas, J. L. *J. Org. Chem.* **1991**, *56*, 6267.

group is serving as an electron-accepting group rather than one that is electron-donating. Indeed, the electronically poor 4-nitrophenylacetylene can also be used, generating **5i** with slightly improved yields.

Scheme 3. Substrate Studies for Oxidopyrylium Cyclization



[a] **Conditions A**: 2 equiv of *N*,*N*-dimethylaniline, CH_2Cl_2, rt. **Conditions B**: 1.2 equiv of *N*,*N*-diisopropylaniline, $CHCl_3$, 100 °C, microwave. Unless otherwise indicated, 20 equiv of alkyne were used. [b] 5 equiv of alkyne were used. [c] Reaction run without solvent.

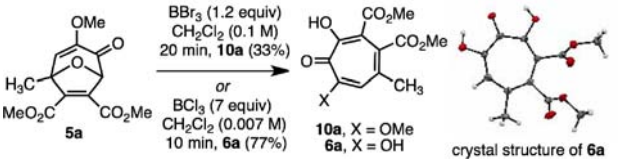
The reaction also works with alternative oxidopyrylium species, as we have demonstrated by synthesizing chloro **5b** and methoxy **5c** congeners.[10] The chloro substrate is particularly valuable, as it provides a versatile synthon for further functionalization. In these instances longer reaction times 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 equiv maximized yields. However, when the reaction was run neat, we were able to use 5 equiv and obtain a 42% yield. Given the low costs associated with most alkynes and our desire not to limit ourselves to liquid alkynes, 20 equiv were used. However, 1-phenylprop-2-yn-1-one represented a solid alkyne in which 20 equiv were cost prohibitive. In this instance 5 equiv of alkyne led to **5f** in excellent yields in only 10 min. Moreover, 70% of the unreacted alkyne was recovered providing a net alkyne consumption of only 2.2 equiv.

(10) For details on the synthesis of salts **3b** and **3c**, see the Supporting Information.

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 BBr_3, which after 20 min led to a complex mixture of compounds from which a 33% isolated yield of α-methoxytropolone **10a** was obtained (Scheme 4). Attempts at optimizing the conditions with BBr_3 were not fruitful. Gratifyingly, however, switching to an excess of BCl_3 led cleanly to hydroxytropolone **6a**, which was confirmed by X-ray crystallographic analysis.

Scheme 4. Select Results Comparing BBr_3 and BCl_3 along with Crystal Structure of α-Hydroxytropolone **6a**

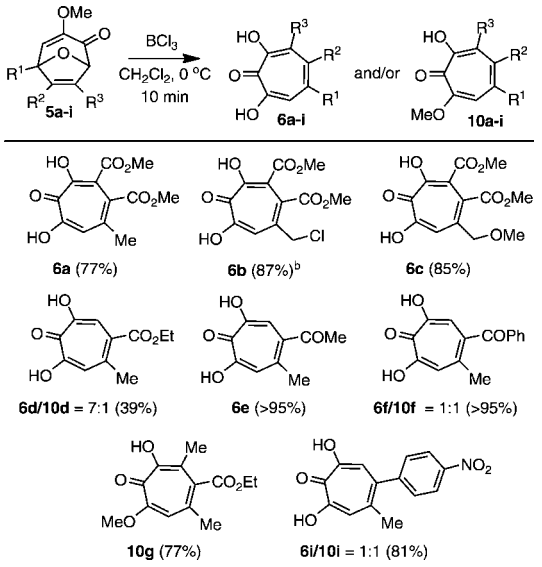


The ring expansion is successful with most substrates, although a significant substrate scope trend was observed with respect to formation of α-methoxytropolone vs α-hydroxytropolone (Scheme 5, **6a**–**i** vs **10a**–**i**). With all DMAD-derived oxabicyclo[3.2.1]octenes, selective formation of the hydroxytropolone was observed upon treatment with BCl_3 (**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 R^3. 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 reversed-phase chromatography. Alternatively, the reaction mixture can be homogenized to solely hydroxytropolone by heating in HBr and in acetic acid.[5] This method was particularly useful for nitroaryl tropolone **6i**, which was unstable to chromatographic conditions (Scheme 6).

The simplest explanation for the onset to the α-methoxytropolone vs α-hydroxytropolone observation was that some substrates were more prone to demethylation by BCl_3 than others, and that methoxytropolones were in fact intermediates toward hydroxytropolones. However, if this were

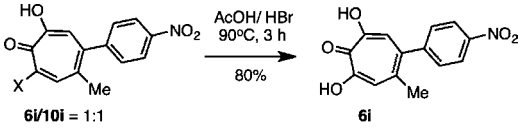
Scheme 5. Ring-Expansion Substrate Scope[a]



[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 ^{1}H NMR integration. [b] 15 equiv of BCl_3 were used.

the case, longer reaction times would be expected to lead to more hydroxytropolone, which was not observed. In addition, subjecting **10a** to BCl_3 did not lead to demethylation.

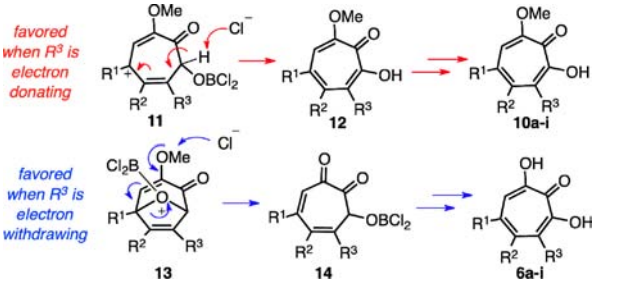
Scheme 6. Example of Homogenizing α-Methoxy and α-Hydroxytropolone Mixture by HBr/AcOH Demethylation



Our current hypothesis is that when R^3 is an electron-donating group, such as the methyl group in **5g**, 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 R^3 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).

(11) For lead reference, see: Dougherty, D. A. *Science* **1996**, *271*, 163.

Scheme 7. Proposed Mechanism



In instances where R^3 is a proton, variability exists. For example, when R^2 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 then 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.

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Note Added after ASAP Publication. Scheme 5 contained an error in version published ASAP November 20, 2012; the correct version reposted November 21, 2012.

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

The authors declare no competing financial interest.