ChemComm
Chemical Communications

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View Article Online
DOI: 10.1039/C9CC09213G

COMMUNICATION

Synthesis of Aryl-Substituted 2-Methoxyphenol Derivatives from Maltol-Derived Oxidopyrylium Cycloadducts through an Acid-Mediated Ring Contraction Cascade

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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Oxidopyrylium cycloadducts derived from maltol and aryl acetylenes undergo acid-mediated rearrangements to generate aryl-substituted 2-methoxyphenol (guaiacol) derivatives. Specifically, the cycloadducts react with boron trichloride to form 2-methoxy-5-arylphenol molecules, and with methane sulfonate to form 2-methoxy-4-aryl-6-methylphenol molecules.

2-methoxyphenol (or guaiacol) is a naturally occurring benzene derivative found in both the parent form,[1] and also embedded in countless natural products and biologically active synthetic constructs.[2] Among them are various aryl-substituted guaiacol derivatives that have demonstrated a variety of different biological activities, particularly against cancer cells (**Figure 1**).[3] Thus, new approaches towards aryl-substituted guaiacol derivatives would be valuable in both medicinal chemistry and total synthesis efforts. The present manuscript describes our discovery that oxidopyrylium cycloadducts derived from maltol and aryl acetylenes react with boron trichloride and methane sulfonic acid to generate aryl-substituted guaiacol derivatives.

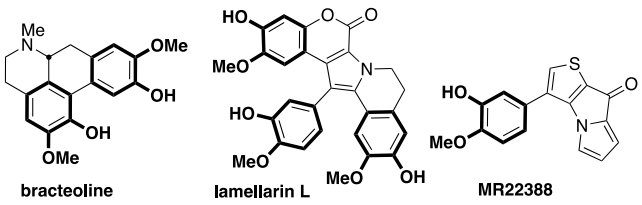
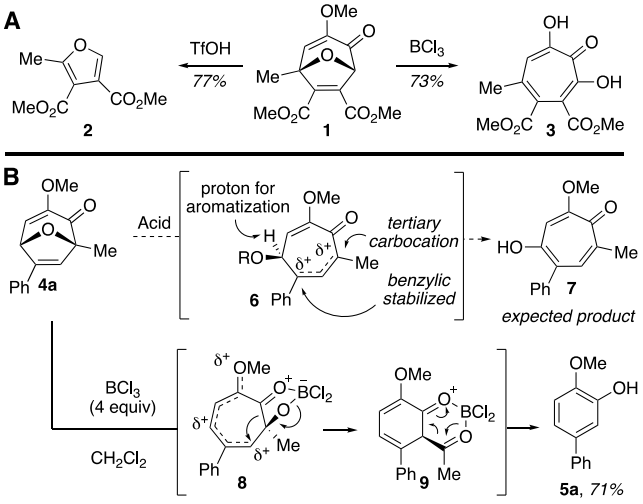


Figure 1. Examples of anti-cancer natural products and synthetic constructs possessing guaiacol-aryl appendages.

This discovery emerged from our lab's ongoing interest in developing and exploiting intermolecular 3-hydroxy-4-pyrone-based cycloadditions.[4] To date, our lab has found particular interest in both boron trichloride[5] and sulfonic acid-mediated rearrangements[6] of allomaltol-derived oxidopyrylium cycloadducts. In some instances, the choice of acid can have a dramatic difference on product outcome, highlighted by the rearrangement of dimethyl acetylene dicarboxylate cycloadducts **1** to either furan **2** or 7-hydroxytropolones **3** (**Scheme 1A**).[5,6] We have recently presented studies detailing oxidopyrylium cycloadditions with maltol-derived oxidopyrylium ylides,[7] and became interested in exploring acid-mediated ring-opening reactions on these cycloadducts. Our hypothesis was that the alternative positioning of the methyl group might lead to an alternative ring-opening to form 4-hydroxytropolones (*ie* **7**, **Scheme 1B**).[8] Instead, when phenylacetylene-derived cycloadduct **4a** was treated to boron trichloride, the known molecule 2-methoxy-5 phenylphenol **5a**[9] was generated in 71% yield.



Scheme 1. Acid-mediated reactions of oxidopyrylium-alkyne cycloadducts. (A) Example of previously established acid-mediated ring-openings of an allomaltol-derived cycloadduct **1** to furan **2** or 7-hydroxytropolone **3**. (B). Anticipated outcome for acid-mediated ring-opening of maltol-derived cycloadduct (**4a** → **7**), and observed guaiacol product **5a**.

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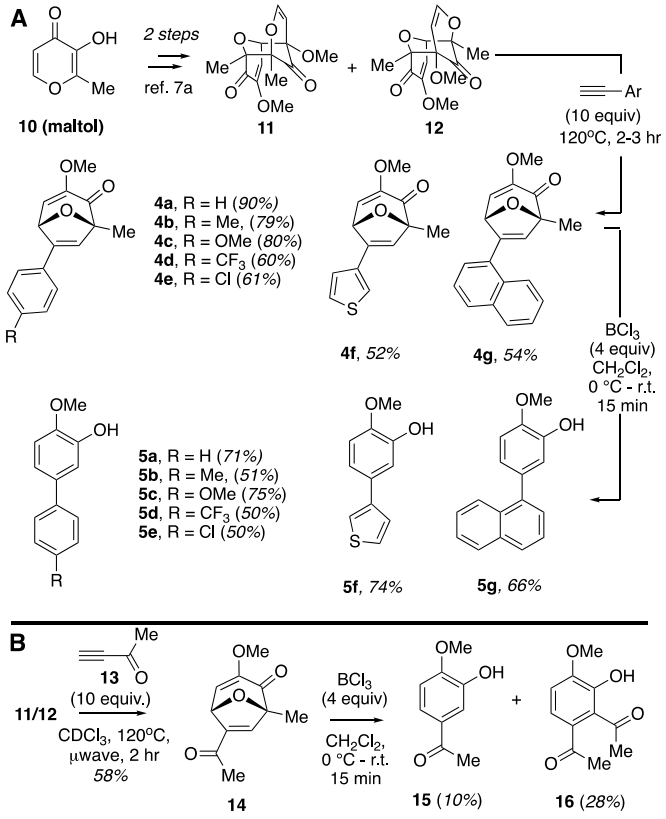
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

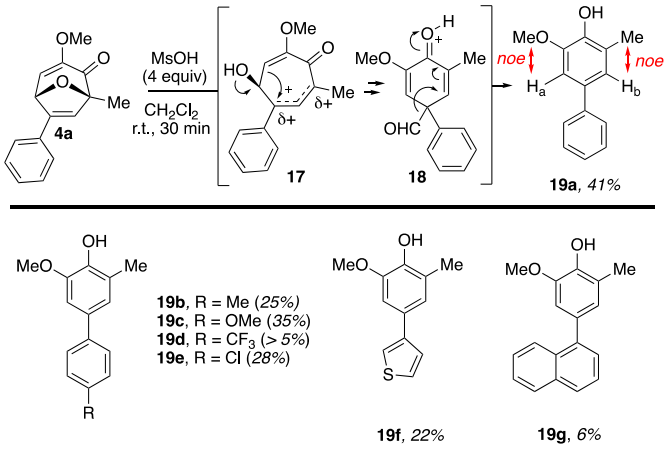
Our current hypothesis is that the ring-opening takes place toward rather than away from the methyl group, resulting in the secondary carbocation (**8**, **Scheme 1B**). Once the ring-opening takes place, the molecule can undergo a ring-contraction (**8** → **9**) and then aromatize via a reverse-Friedel-Crafts acylation.[10] It is unclear if the acylium ion is formed, as when the reaction was monitored in $CDCl_3$, we only observed acetyl chloride, and no acetophenone was observed when the reaction was performed with benzene as co-solvent. Thus, it is possible that the chloride ion assists in the deacylation. While the regioselectivity of the ring-opening was not anticipated, particularly in light of the high carbocation stabilization on account of the phenyl group (*ie,* **6**), we speculated that this could be explained electronically based upon a combination of the carbonyl destabilizing the cation of the anticipated regioisomeric ring-opening intermediate (**6**), as well as resonance stabilization of the presumed carbocation through the α-methoxyenone (**8**, **Scheme 1**).



Scheme 2. Substrate scope for oxidopyrylium cycloaddition route to guaiacol derivatives. Synthesis of (A) aryl acetylene-derived and (B) 3-butyn-2-one-derived cycloadducts, and products resulting after reaction with boron trichloride.

Given both the high yields and value of the 2-methoxyphenol, we felt this unanticipated reaction was worth exploring further. Our first task was to optimize the cycloaddition, as we had previously carried out the reaction to characterize new molecules for mechanistic purposes, and achieved only 16% yield.[7] After optimization, we found that by performing the cycloaddition using purified maltol-derived dimers (**11** and **12**) and phenylacetylene as the solvent at 120°C in a microwave, this yield could be increased to *90%* (**11/12** → **4a, Scheme 2**). We also carried out the cycloaddition with six alternative arylacetylenes and achieved yields ranging from *52-80%* (**11/12** → **4b-e**, **Scheme 2A**). Gratifyingly, these cycloadducts, which included electron-poor, rich, sterically demanding, and heteroaromatic, were all capable of proceeding to the corresponding 2-methoxyphenol derivatives (**4a-g** → **5a-g**), in yields ranging from *50-75%*. We also carried out the cycloaddition with methyl-ketone derivative **14** (**Scheme 2B**). In this instance, the reaction yield was low and further complicated by the production of two ring-contraction products, **15** and **16**, the latter of which would arise through tautomerization-based rearomatization rather than deacylation. It is possible that the methyl ketone in this instance serves as an internal base to facilitate the tautomerization, leading to substantial production of **16**.

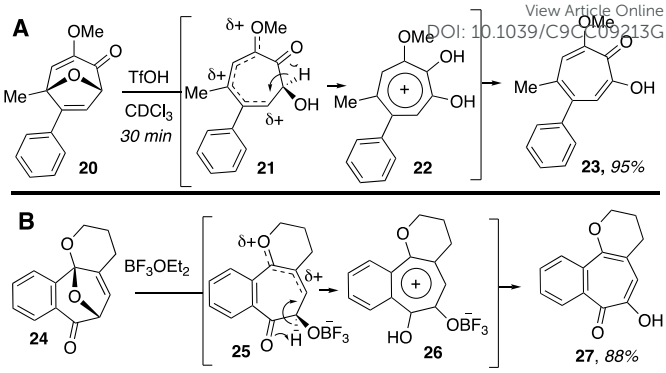
During the course of these studies, we also found that sulfonic acids were capable of promoting formation to alternative 2-methoxyphenol derivatives, **19a-g** (**Scheme 3**). In this instance, methane sulfonic acid provided the highest yields, which were only *41%* in the best case. Slightly lower yields were observed with triflic acid, and comparable yields were obtained when boron trifluoride diethyl etherate was used (result not shown). Consistent with the proximity of the appendage to the resultant carbocation, the reaction did not work with the more electronically poor aromatic acetylene derivative **4d** or methyl ketone-derived bicycle **14** (result not shown). In addition, the more sterically-charged napthyl-derived bicycle **4g** was also low yielding, which could be on account of the steric nature of the tertiary carbon atom that results from the ring-contraction (see **18**). We believe this transformation proceeds through a mechanistically analogous, albeit regioisomerically different, ring-opening/ring-contraction/retro-Friedel Crafts cascade process, to that previously proposed with boron trichloride.



Scheme 3. Ring-contraction of oxidopyrylium cycloadducts mediated by methane sulfonic acid, along with mechanistic hypothesis.

The combination of these results provide interesting insight related to acid-mediated oxabicycle ring-openings and

rearrangements more generally that are worth discussing. Firstly, given the alternative regioisomeric opening of methane sulfonic acid suggests that boron trichloride-mediated ring-opening may be more likely driven by coordination rather than carbocation stabilization, although reversibility of the ring-opening may also be at play, and the difference could be driven by downstream preferences. Either way, these results provide precedence for chemical control over the regioselectivity of the ring-opening of oxidopyrylium cycloadducts. Furthermore, in one of our early studies we reported that regioisomeric cycloadduct **20** reacts with triflic acid very cleanly to form tropolone **23** (**Scheme 4A**).[6] Given both the electronic similarities between proposed intermediates **21** and **8**, as well as the presence of an even weaker conjugate base than was used in the formation **19a**, there must be some structural preference for **21** to undergo the elimination. One possibility is that it proceeds through an internal acid-base process facilitated by the proximity of the carbonyl (similar to proposal for formation of **16**), which could result in the clean formation of product. Similar high yields were observed by Friedrichsen in his seminal studies on ring-openings of oxidopyrylium cycloadducts (**Scheme 4B**).[11] Mechanistic studies are warranted to gauge these differences in an effort to predict and control the product formation in acid-mediated ring-opening reactions of oxidopyrylium cycloadducts.



Scheme 4. Acid-mediated rearrangments of oxidopyrylium cycloadducts to tropolones. (A) Triflic acid-mediated ring-opening of cycloadducts **16**, which is an isomer of **4a**.[6] (B) Boron trifluoride-mediated ring-openings of benzo-fused oxidopyrylium cycloadducts **24**.[11]

Conclusions

In conclusion, oxidopyrylium cycloadducts derived from maltol and aryl acetylenes can undergo an acid-promoted ring-contraction/aromatization cascade process to form aryl-substituted guaiacol derivatives. Given the broad interest in developing oxidopyrylium cycloaddition reaction[12] and using this reaction in complex target synthesis,[13] these studies represent a new utility for oxidopyrylium cycloadducts that could find usage in natural product synthesis and medicinal chemistry-based pursuits. They furthermore provide valuable information on the propensity of oxidopyrylium cycloadducts to undergo acid-mediated rearrangements.

Conflicts of interest

There are no conflicts to declare.

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