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Formation of Fused Aromatic Architectures via an Oxidative Dearomatization - Radical Cyclization Rearomatization Approach

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Abstract

A new mild C-C bond forming cyclization approach of catechol derivatives is reported. This approach relies on an initial dearomatization step using lead (IV) acetate followed by a carefully controlled radical cyclization step, which under the reaction conditions also facilitates rearomatization. Triethylborane is the key to the success of this reaction as it enables the reaction to proceed at low temperatures and is also believed to aid rearomatization. The amount and ratio of triethylborane and reducing agent (tributyltinhydride) that is employed as well as the concentration the reaction is run at are all essential to the success of this new approach.

Keywords

Oxidative dearomatization; Radical cyclization; Rearomatization; Triethylborane; Catechol

Oxidative dearomatizations of phenolic substrates are useful transformations that generate highly reactive intermediates that can be leveraged forward productively in a variety of ways.ⁱ One of our research programs has been focused on investigating *in situ* generated quinone ketals, and applying them towards natural product targets. For example, in our recently completed total synthesis of vinigrolⁱⁱ we used such a dearomatization strategy to form an *ortho*-quinone ketal, which then underwent an intramolecular Diels-Alder reaction (IMDA) to form the bicyclic product shown. In this reaction two valuable C-C bonds (highlighted in red) were formed in an intramolecular fashion (Scheme 1). When surveying the literature of intramolecular C-C bond forming reactions onto *ortho*-quinone ketals it becomes apparent that IMDA reactions are the only C-C cyclization approach that has been employed, which is in contrast to its more stable and readily handled *para*-quinone cousin.ⁱⁱⁱ This is not entirely surprising as *ortho*-quinone ketals are prone to competing self dimerizations and are less stable to Lewis acids.

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Supplementary Material

Experimental procedures are provided as well as spectral data.

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In our pursuit of a different target (platensimycin), we attempted to address this lack of non-IMDA intramolecular C-C bond forming reactions onto *ortho*-quinone ketals by exploring the possibility of cyclizing carbon radicals (Scheme 2) onto a dearomatized core.^{iv} In our ambitious approach we were hoping to achieve both a 5-*exo-trig* and 6-*exo-trig* cyclizations to form two key quaternary centers of platensimycin in one step (see highlighted bonds in red). Unfortunately the 5-*exo-trig* cyclization did not succeed, which is why we abandoned this approach for a different strategy and thus never answered the question of whether radicals could be cyclized onto the *ortho*-quinone ketal core. The work detailed in this communication is focused on addressing this unanswered question.

For our investigations we chose to pursue simple substrates in order to be able to unambiguously assess the feasibility of this approach. Our substrates selection strategy and approach is outlined in Scheme 3. The first decision we needed to make was to decide whether we use an oxidant that incorporates an alkoxy or a carboxylate group (R in blue, **2**) in the dearomatization step. This is because the stability of the two is orthogonal for our desired outcome as dialkyl ketals are more stable towards Lewis acids than their carboxylate counterparts, but their diene component is more prone to Diels-Alder self-dimerization than the mixed carboxylate ketals.^v Although it has been long known that a bromide in the 4-position of the phenol is quite efficient at hindering self-dimerization of *ortho*-quinone ketals,^{vi} this would not be suitable for us as it would directly interfere with our second step (radical cyclization). For the radical cyclization step it was essential that the conditions used would allow the reaction to proceed at low temperatures and the radical activator to be not too Lewis acidic to inhibit a premature collapse of the newly formed ketal. It was our hope that the resulting optimized reaction conditions for the radical cyclization would also facilitate loss of ROH (form **4**), therefore resulting in a tandem radical cyclization – rearomatization to afford a fused phenol product (**5**).

For our optimization studies, we used a catechol functionalized with an ethylene iodide tether (**6**). Hypervalent iodide oxidations in the presence of methanol proceeded smoothly at low temperatures, however handling of the *ortho*-quinone ketal intermediate proved to be troublesome. Attempts at working under cold conditions to remove the methanol as well as using a polymer-supported oxidant,^{vii} then proceeding with radical cyclization yielded unsatisfactorily irreproducible yields. The diene component proved to be too reactive,^{viii} and it underwent self-dimerization during the removal of methanol and thus it did not provide us with the necessary window of reactivity to allow a radical cyclization to proceed in high yields. We therefore turned to exploring mixed carboxylate ketals, which we expected to be able to handle easier, but the radical cyclization step would require more demanding conditions as they are more sensitive to Lewis acids. Uneventfully these mixed carboxylate quinone ketals are made quantitatively without any purification upon treatment with lead (IV) acetate, and could even be stored in freezer with no self-dimerization or other decompositions. These products were then carried to the radical cyclization step to afford a new type of C-C bond forming reaction utilizing *ortho*-quinone ketals.

With a typical radical initiator such as AIBN not being suitable because of the thermal sensitivity of the dienes, we postulated that triethylborane,^{ix} which is capable of initiating radical reactions at low temperatures (as low as $-78\text{ }^{\circ}\text{C}$), might provide us with the

necessary window of reactivity to succeed. Our radical cyclization optimization studies (Table 1) for the mixed quinone ketal intermediate (**7**) quickly revealed that initiating the reaction at 0 °C was more optimal than at RT, whereas initiating the reaction at –78 °C yielded no product. Additionally, the amount of air used to initiate the formation of the radical was important, and it was found that saturating the reaction mixture with air gave the most satisfactory and reproducible results. The net concentration studies (accounting for the total solvent volume, including hexanes from the stock solution of triethylborane) proved that diluting the reaction was unfavorable (entry 1 vs. 2) while increasing the amount of tributyltinhydride (Bu₃SnH) resulted in improvements (entry 3 vs 2). Interestingly, although triethylborane mediated radical reactions are usually run under catalytic amounts of triethylborane, we found that it was critical for the success of this radical cyclization to use substantial amounts of triethylborane (entries 3-5), with three equivalents proving to be the most optimal amount (entry 5) resulting in 81% of the desired product being isolated. Alternative hydride sources (entries 6-7) were inferior to Bu₃SnH. The radical cyclization step was therefore possible without heating the reaction mixture due to triethylborane used as the reactive initiator.

With optimized radical cyclization conditions identified we turned our attention to exploring the substrate scope for this new methodology (Table 2). For our studies we chose three alkyl radical precursors (entries 1-3) and three aryl radical precursors (entries 4-6) evaluating both *5-exo-trig* (entries 1-2) and *6-exo-trig* (entries 4-6) cyclizations. As is evident from Table 2, the optimized reaction conditions worked without any incident on all of our substrates except one (entry 3). Unsurprisingly, *5-exo-trig* cyclizations (entries 1-2) gave better results than the *6-exo-trig* cyclizations (entries 3-6), with entry 2 giving the highest isolated yield (85%, or an average of 92%/step) and entry 6 giving the lowest isolated yield (45%, or an average of 67%/step). The relatively lower yield for the naphthalene derivative (entry 6) is unknown but could be due to the difference in stability of the *ortho*-quinone ketal intermediate and its reactivity as a radical acceptor compared to the other substrates. In the case of the propyl chain (entry 3), which failed to cyclize in a *6-exo* fashion unlike its more reactive aryl radical partners (entries 4-6), we only isolated products resulting from reduction of the iodide as well as reduction of the intermediate *ortho*-quinone ketal.^x We postulate that preferential reduction of the alkyl iodide preceded the reduction of the resulting *ortho*-quinone ketal. This could be attributed to the slower *6-exo-trig* cyclization relative to the aryl iodide counterparts (entries 4-6).

In summary, we report a new tethered approach for functionalization of catechol derivatives involving an initial oxidative dearomatization step followed by a low temperature radical cyclization using triethylborane as the initiator. The amount of initiator, reducing agent and reaction concentration are essential for the success of this reaction. This new approach provides access to various chromane and 2,3-dihydrobenzofuran products. Efforts are underway to use this concept to build more complex aromatic products in one step using radical trapping strategies as well as explore the formation of quaternary centers.

Representative experimental conditions

To a vial equipped with a stir bar, lead (IV) acetate (1.1 eq) and dichloromethane (DCM) were added and the mixture was stirred at -78°C before adding the phenol substrate (1.0 eq) dissolved in DCM via a syringe over 30 seconds. The reaction was stirred until TLC showed complete consumption of starting material (typically around 30 min) at which point the reaction mixture was diluted with EtOAc, poured over saturated NaHCO_3 and extracted twice with EtOAc. The organic fractions were combined, washed with saturated NaHCO_3 , brine then collected, dried with anhydrous Na_2SO_4 (**Note:** MgSO_4 should not be used as the intermediate ketal is sensitive), filtered, and concentrated *in vacuo* to give the quinone ketal product, which was then used without further purification, dissolved in toluene and the resulting solution cooled to 0°C and purged with N_2 for 10 min. Tributyltin hydride (2.0 eq) in toluene (0.10 mL) was at this point syringed in, followed by addition of triethylborane [1.0 M solution in hexanes] (3.0 eq). Upon completion of reagent addition the nitrogen feed was replaced with an air balloon (**Note:** The needle of air balloon should be submerged below the surface of the reaction mixture). The reaction mixture was stirred at 0°C for 10 minutes at which point the ice-bath was removed and stirring continued at room temperature for an additional hour before evaporating away the toluene and transferring the crude reaction mixture to silica gel chromatography.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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- x). 2-propoxyphenol type products were isolated as the major product.

Scheme 1.

Example of an Oxidative Dearomatization-IMDA reaction

Scheme 2.
Platensimycin Dearomatization Radical Cyclization Proposal

Scheme 3.
Dearomatization-Rearomatization Cyclization Proposal

Table 1

Proof of Concept – Radical Cyclization Optimization Studies

entry	BEt ₃	Hydride	concentration	yield
1	2.0 eq.	1.5 eq. Bu ₃ SnH	0.04 M	21 %
2	2.0 eq.	1.5 eq. Bu ₃ SnH	0.20 M	34 %
3	2.0 eq.	2.0 eq. Bu ₃ SnH	0.20 M	57 %
4	1.2 eq.	2.0 eq. Bu ₃ SnH	0.20 M	11 %
5	3.0 eq.	2.0 eq. Bu ₃ SnH	0.20 M	81 %
6	3.0 eq.	2.0 eq. Ph ₃ SnH	0.20 M	48%
7	3.0 eq.	2.0 eq. (TMS) ₃ SiH	0.20 M	16%

Table 2

Substrate Scope Studies

entry	starting material	product	yield
1			81%
2			85%
3	 R = H, C ₂ H ₅		0%
4			72%
5			64%
6			45%