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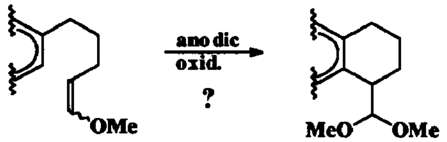
INTRAMOLECULAR ANODIC OLEFIN COUPLING REACTIONS: INITIAL STUDIES CONCERNING THE USE OF ELECTRON-RICH ARYL RINGS

Kevin D. Moeller* and Dallas G. New
Department of Chemistry, Washington University, St. Louis, MO 63130

Abstract: Intramolecular anodic olefin coupling reactions involving electron-rich aryl rings were examined and shown to afford fused bicyclic products. When alkoxysubstituted phenyl rings were used, the reactions benefited from the use of either controlled potential electrolysis conditions or a vinyl sulfide initiating group. Coupling reactions involving heteroatomic aryl rings also led to good yields of cyclized product.

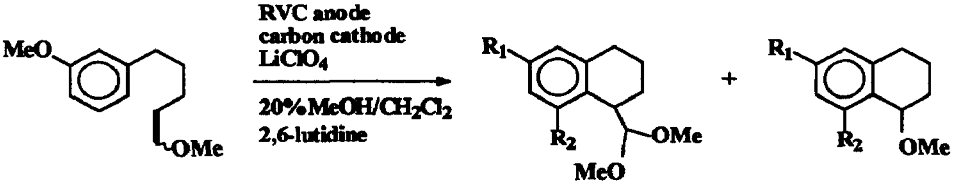
The intramolecular coupling of electron rich olefins at anode surfaces can provide a novel method for the construction of carbon-carbon bonds.[1] To date, these reactions have been intitiated by the oxidation of enol ethers and terminated the use of with simple alkyl olefins, styrenes, enol ethers, allylsilanes, and vinylsilanes. Our interest in extending these reactions to the synthesis of fused polycyclic ring skeletons led us to ask whether aromatic rings could serve as participants in these reactions.



Surprisingly, cyclization reactions of this type have not been reported, even though aromatic rings have played critical roles in earlier anodic coupling reactions. For example, intramolecular coupling reactions of aromatic rings have been used to synthesize a variety of biphenyl ring skeletons,[2] and intramolecular coupling reactions of 4-substituted phenols and olefins have been used to synthesize spirocyclic ring skeletons.[3] In addition, intermolecular coupling reactions between phenols and electron-rich styrene derivatives have been reported.[4] Based on the success of these studies, it seemed likely that coupling reactions between aromatic rings and electron-rich olefins would prove useful for the construction of fused ring skeletons. We report herein the first coupling reactions of this type.

Initially, substrate 1 was selected for study (Scheme 1).[5] The 3-methoxy phenyl ring was chosen as the terminating group in order to bias the system toward formation of a fused bicyclic skeleton, even though the choice of the electron-rich aryl ring did raise concerns about overoxidation. As a starting point, the oxidation was performed using conditions identical to those employed in a number of earlier anodic olefin coupling reactions. To this end, the oxidation of 1 was carried out in an undivided cell using a reticulated vitreous carbon (RVC) anode, a carbon rod cathode, a 0.4 M $LiClO_4$ in 20% $MeOH/CH_2Cl_2$ electrolyte solution, 2,6-lutidine as a proton scavanger, and a constant current of 11 mA. After 2.0 F/mole had been passed, a 57% isolated yield of fused bicyclic products was obtained along with a 22% yield of recovered starting material. Overoxidation did prove to be a problem. The cyclized product obtained was a mixture of two

Scheme 1



1

2a. R_1=OMe, R_2=H
b. R_1=H, R_2=OMe

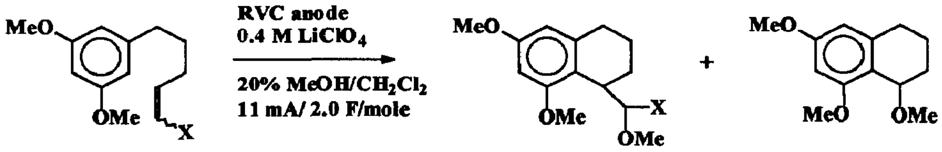
3a. R_1=OMe, R_2=H
b. R_1=H, R_2=OMe

Conditions	Yield	Product 2	:	Product 3
Const. Current 11mA/ 2.0 F/mole	57% (22% rec. S.M.)	2.7 (2a/2b=2)	:	1 (3a/3b=2.8)
Controlled potential 1.10 V/ 1.6 F/mole	57% (21% rec. S.M.)	16 (2a/2b=1.6)	:	1 (3a/3b=1.5)

primary products, **2a** and **2b**, formed from cyclization para and ortho to the aryl methoxy group and two secondary products, **3a** and **3b**. The ratio of the desired products **2a** and **2b** to **3a** and **3b** was 2.7:1.[6] Products **3a** and **3b** could be envisioned as arising from oxidation of **2a** and **2b** to form a radical cation followed by elimination of the dimethoxymethyl group and loss of a second electron to form the methyl *p*-quinone methide and methyl *o*-quinone methide oxonium ions. Trapping with methanol and loss of a proton would then afford **3a** and **3b**. While a constant current electrolysis had difficulty differentiating between oxidation of the starting material and the product, the oxidation potentials measured for the products ($E_{p/2}$ for **2a** = +1.53 V vs. Ag/AgCl; $E_{p/2}$ for **2b** = +1.61 V vs. Ag/AgCl)[7] and the starting material ($E_{p/2}$ *ca.* +1.35 V vs. Ag/AgCl)[7] suggested that a controlled potential electrolysis might serve to reduce the amount of product oxidation observed. In this experiment, a Ag/AgCl reference electrode was added to the reaction and substrate **1** electrolyzed at a controlled potential of 1.10 V. After 1.6 F/mole had been passed, a 57% isolated yield of cyclized products was obtained along with a 21% yield of recovered starting material. The ratio of desired product to overoxidized material was approximately 16 to 1.[6]

Although very successful, the controlled potential electrolysis of **1** had pushed the technique to its limits. In order to get a useful selectivity, the potenitial had been dropped to 1.10 V. At this potential, only a small amount of current could be passed. The reaction was slow and very difficult to push to completion. It was not clear that this solution would work when the cyclization reactions involved still more electron-rich aryl rings. For example, when substrate **4a** was oxidized using constant current conditions a one to one ratio of desired product **5a** to overoxidized product **6a** was obtained (Scheme 2). Very little if any selectivity existed for oxidation of the starting material. In this case, an even lower potential would be needed for a successful controlled potential electrolysis. It appeared that a better solution would be to increase the selectivity for oxidation of the substrate. For this reason, the vinyl sulfide substrate **4b** was synthesized. The

Scheme 2



4a. X=OMe (25% rec.)
4b. X=SMe

5a. 31%
5b. 72%

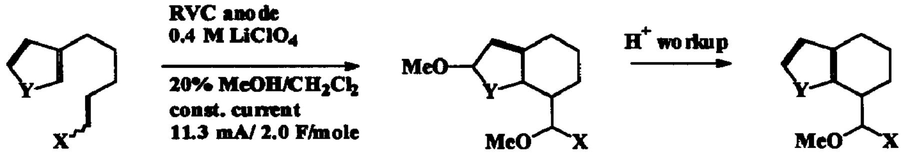
6a. 33%
–

oxidation potential of the vinyl sulfide ($E_{p/2}$ = +0.90 V vs. Ag/AgCl)[7] moiety was approximately 0.5 V lower than that of an enol ether.[8] The preparative oxidation of **4b** using constant current conditions led to a 72% isolated yield of cyclized product **5b**. None of the overoxidized material was obtained. Clearly, the oxidations could be controlled by manipulating the nature of the intitiating group.

The use of a vinyl sulfide did not improve the cyclization reaction using the 3-methoxyphenyl ring as the terminator. In this case, the use of a vinyl sulfide initiator led to only a 38% yield of products **2a** and **2b**, even though none of the overoxidized material was obtained. Evidently, the use of the vinyl sulfide initiating group required a very good nucleophile as a terminating moiety.

The suggestion that the cyclization reactions worked best with very nucleophillic aryl rings led to questions regarding the feasibility of using furan and pyrrole rings as participants in the anodic oxidation reactions. For this reason, substrates **7a**, **7b**, and **10a** were synthesized and oxidized (Scheme 3).

Scheme 3



7a. Y=O, X=SMe

7b. Y=O, X=OMe

10. Y=Npivaloyl, X=SMe

8

9a. Y=O, 54% (X=SMe)
17% (X=OMe)

9b. Y=O, 75% (X=OMe)

11. Y=NR, 66% (X=SMe)

Both the furan and pyrrole ring proved to be excellent participants in the reactions. When **7a** was oxidized using constant current conditions a mixture of the desired cyclized products **9a** and intermediate **8** was obtained. Modification of the electrolysis workup to include acidification of the reaction medium with TsOH led to the elimination of methanol from **8** and isolation of **9a** as the only cyclized products. From this procedure a combined 71% yield of cyclized product was obtained. Since the initially formed product **8** could not undergo a second oxidation reaction, there was no risk of overoxidation and the use of the vinyl sulfide was not required. Anodic oxidation of the enol ether substrate **7b** led to the formation of a 75% isolated yield of the cyclized product **9b** after the acidic workup. The oxidation of **7a** and **7b** were virtually identical. Finally, the anodic oxidation of **10** led to a 66% isolated yield of the bicyclic product **11**.

In summary, anodic coupling reactions involving electron-rich aryl rings can be used to synthesize fused bicyclic ring skeletons. Reactions involving the use of simple alkoxy substituted phenyl rings were plagued by overoxidation of the product. These problems were overcome with the use of either a controlled potential electrolysis or a vinyl sulfide initiating group. Cyclizations involving furan and pyrrole rings led to good yields of the bicyclic products. Studies aimed at exploring the effect of different aryl ring substituent patterns on the cyclizations, the size of the ring that can be formed, the compatibility of the reactions with the formation of quaternary carbons, and the overall synthetic utility of these reactions are currently underway.

Sample Procedure: In a typical experiment, an oven dried 100 mL round bottom flask (24/40 joint) was charged with 0.203 g (1.22 mmol) of **7b**, 9.8 mL of methanol and 39.0 mL of CH_2Cl_2. To this solution was added 0.655 g (6.11 mmol) of 2,6-lutidine and 2.077 g of lithium perchlorate. The reaction was degassed by sonocation for 30 min, and then the round bottom flask fitted with a two hole rubber stopper having a carbon rod attached to a piece of reticulated vitreous carbon occupying one hole and a simple carbon rod occupying the second. A needle was forced through the stopper as a nitrogen inlet. The carbon rod attached to the reticulated vitreous carbon was used as the anode and the second carbon rod used as the cathode. The reaction was electrolyzed at a constant current of 11.3 mA until 2.0 F/mole had been passed. When complete, 1.160 g (6.11 mmol) of TsOH was added and the reaction stirred at room temperature for 12 h. The reaction was poured into a separatory funnel along with 30 mL ether and 30 mL water, the layers separated, and the aqueous layer extracted with ether. The combined organic layers were then washed with water and brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was chromatographed through silica gel using a gradient elution from hexane to 20% ether/hexane to afford 0.179g (75%) of the bicyclic furan compound **9b**. The spectral data for **9b** were as follows: ^1H NMR (300 MHz/$CDCl_3$) δ 7.29 (d, J = 0.9 Hz, 1H), 6.19 (d, J = 0.9 Hz, 1H), 4.46 (d, J = 3 Hz, 1H), 3.43 (s, 3H), 3.36 (s, 3H), 3.07-3.01 (m, 1H), 2.48-2.34 (m, 2H), 1.89-1.77 (m, 3H), 1.72-1.60 (m, 1H); ^{13}C NMR (75 MHz/ $CDCl_3$) δ 149.4, 144.1, 118.9, 110.3, 106.0, 54.6, 54.3, 37.3, 24.2, 22.2, 21.2; IR (neat/ NaCl) 2933, 2854, 2832, 1505, 1457, 1447, 1374, 1303, 1236, 1217, 1181, 1159, 1122, 1106, 1077, 1054, 976, 954, 892 cm^{-1}; LRMS (PCI) *m/e* (rel. intensity) 165 (M-CH_3O, 95), 75 (100); HRMS (EI) *m/e* calcd for $C_{11}H_{16}O_3$ 196.1099, found 196.1080. Anal. Calcd. for $C_{11}H_{16}O_3$: C, 67.31; H, 8.22. found: C, 67.14; H, 8.20.

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4. Gates, B. D.; Dalidowicz, P.; Tebben, A.; Wang, S.; Swenton, J. S. *J. Org. Chem.* **1992**, *57*, 2135.
5. All new compounds were characterized by ^1H NMR, ^{13}C NMR, IR, LRMS, and HRMS. The synthesis of the substrates will be reported at a later date.
6. This ratio was determined by NMR integration of the acetal methine protons of the desired products vs. the benzylic methine protons of the overoxidized products.
7. $E_{p/2}$ values were obtained by cyclic voltammetry using a BAS 100B electrochemical analyzer, a platinum anode, a Ag/AgCl reference electrode (purchased from BAS), a sweep rate of 25 mV/sec, and a 0.1 N $LiClO_4$ in CH_3CN electrolyte solution. The quality of the reference electrode was checked and the potentials measured calibrated with the use of a simple methoxy enol ether.[8] The potentials for **1**, **2a**, **2b**, the vinyl sulfide, and the enol ether standard were run on the same day so that any drift of the reference electrode would be minimized.
8. In our hands, simple enol ethers consistently give rise to $E_{p/2}$ values of +1.40 V vs. Ag/AgCl when measured using a platinum anode, a Ag/AgCl reference electrode, a sweep rate of 25 mV/sec, and a 0.1 N $LiClO_4$ in CH_3CN electrolyte solution. For examples see reference 1b.

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