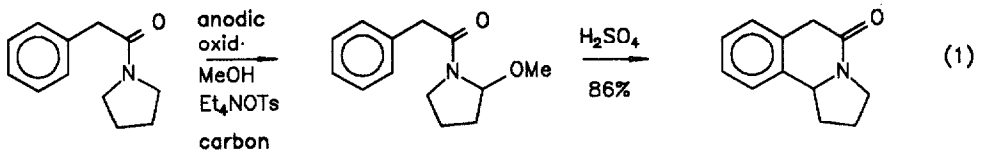
Tetrahedron Letters Vol.30,No.10,pp 1213-1216,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

ELECTROCHEMICAL AMIDE OXIDATIONS IN THE PRESENCE OF MONOMETHOXYLATED PHENYL RINGS. AN UNEXPECTED RELATIONSHIP BETWEEN THE CHEMOSELECTIVITY OF THE OXIDATION AND THE LOCATION OF THE METHOXY SUBSTITUENT

Kevin D. Moeller,* Sharif Tarazi, and Mohammad R. Marzabadi
Department of Chemistry, Washington University, St. Louis, Mo. 63130

ABSTRACT: The chemoselectivity of electrochemical amide oxidations in the presence of monomethoxylated phenyl rings was examined. Oxidation of (3-methoxyphenyl)acylpyrrolidine led to exclusive formation of the desired amide oxidation products, while oxidation of the 4-methoxyphenyl isomer led to exclusive formation of aromatic ring oxidation products.

In 1981 Shono and coworkers reported the anodic methoxylation of an amide in the presence of a phenyl ring (equation 1).[1] The resulting methoxylated amide was then cyclized with acid to generate a tricyclic alkaloid ring system.



86% (1)

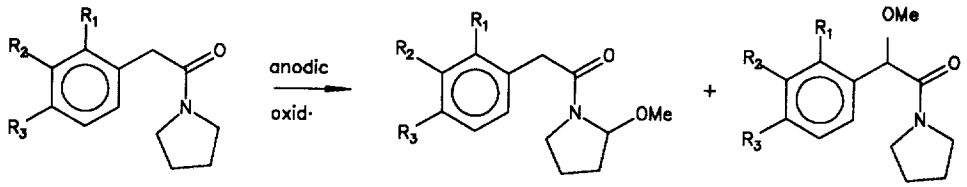
Yet in spite of the success of this reaction, and the potential for electrochemistry to provide a useful oxidative alternative for the generation of acyliminium ions, little has been done to extend these reactions to the construction of natural products.[2]

One of the chief barriers to using electrochemical amide oxidations in synthetic efforts involves the electron rich aromatic rings found in many natural products. Electron rich aromatic rings do not appear to be compatible with the anodic oxidation conditions needed to oxidize an amide.[3] For example, anisole is reported to have an oxidation potential of *ca.* + 1.76 v ($E_{1/2}$ vs. SCE),[4] while N-acylpyrrolidine is reported to have an oxidation potential of *ca.* + 1.88 v ($E_{1/2}$ vs. SCE).[5] These oxidation potentials would suggest that an amide can not be oxidized selectively in the presence of a monomethoxylated phenyl ring. However, in conjunction with a project aimed at extending the use of organic electrochemistry in synthesis, we have found that consideration of oxidation potentials alone is not satisfactory for predicting the chemoselectivity of these reactions (Scheme I).

Initially N-(3-methoxyphenyl)acylpyrrolidine (1a) was oxidized using a carbon anode in a 10% methanol/acetonitrile electrolyte solution containing 1 *M* tetraethylammonium tosylate. Constant current conditions were utilized. Surprisingly only the methoxylated products derived from amide oxidation were obtained in an 86% isolated yield (both isomers about the amide linkage were formed in a 1:1 ratio).[6] Analysis of the crude reaction mixture by 300 MHz ^{1}H NMR showed no evidence of aromatic ring oxidation. The methoxylated amide products (represented by 2a)

could be cyclized using titanium tetrachloride to afford a 2.9/1 mixture of para and ortho products in a combined 72% isolated yield. In contrast, the anodic oxidation of (4-methoxyphenyl)acylpyrrolidine (1b) led to formation of only the methoxylated product of aromatic ring oxidation in a 76% isolated yield. Analysis of the crude reaction mixture by 300 MHz ^1H NMR in this case indicated that no product from amide oxidation was formed. The product contanied a small amount of the overoxidized material (*ca.* 5%) having dimethoxy substitution at the benzylic carbon. Evidence that this compound was formed by overoxidation was provided by further oxidation of the monomethoxylated product 3b. It should be noted that *complete control* over the chemoselectivity of the oxidation can be gained through proper positioning of the methoxy substituent of the phenyl ring.

SCHEME I



1a· R_1=R_3=H, R_2=MeO	2a· 86%	3a· 0%
1b· R_1=R_2=H, R_3=MeO	2b· 0%	3b· 76%
1c· R_2=R_3=H, R_1=MeO	2c· 40%	3c· 5%

(17% S·M· was recovered)

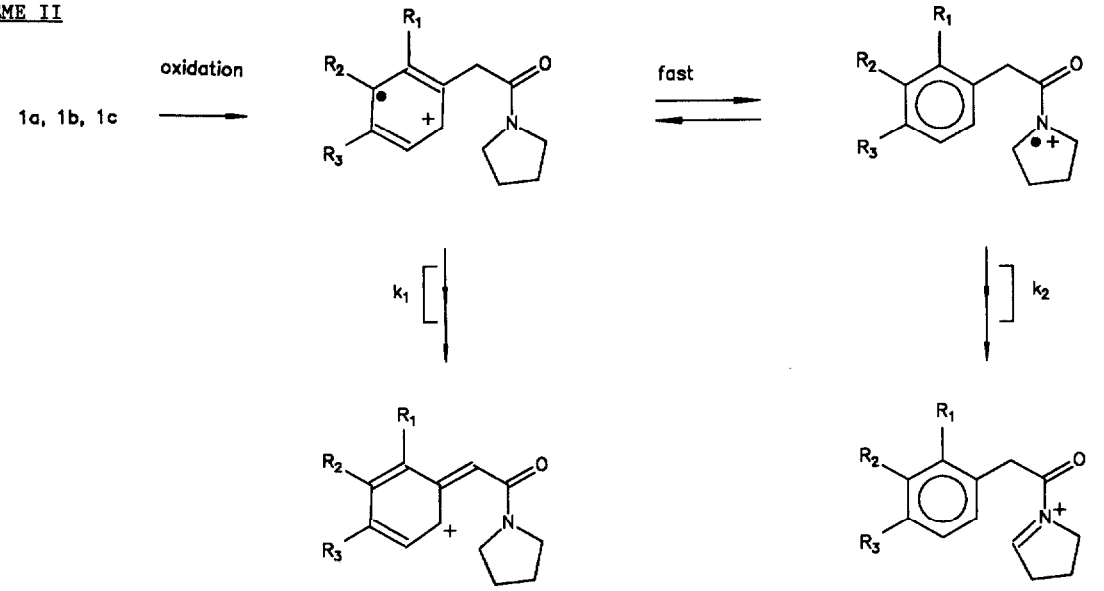
Finally, (2-methoxyphenyl)acylpyrrolidine (1c) was oxidized. This oxidation was not as selective as the earlier cases and led to a mixture of compounds. The major products arose from oxidation of the amide and were obtained in a 40% isolated yield (again both isomers about the amide linkage were found). These products were accompanied by formation of 5% of the aromatic ring oxidation product and 17% of the recovered starting material. In addition, a small amount of unidentified byproduct was obtained.

One possible mechanistic rationale for explaining these results is illustrated in Scheme II. This mechanism proposes a reversible intramolecular electron transfer between the radical cation of the aromatic ring and the amide. If the equilibrium process proposed is fast compared to the rates of k_1 and k_2, then product formation would be governed by the relative magnitudes of k_1 and k_2. For the oxidation of compound 1a the magnitude of k_1 would have to be small compared to the magnitude of k_2, since only amide oxidation products were obtained. It is tempting to suggest that due to the position of the methoxy substituent in 1a, the radical cation of the aromatic ring formed by oxidation is not ideally suited for assisting in elimination of the benzylic protons and formation of the aromatic ring oxidation product. On the other hand, the oxidation of compound 1b would lead to a radical cation which is better suited for elimination of a benzylic proton. This would lead to an increase in the magnitude of k_1 and hence an increase in formation of the product from aromatic ring oxidation relative to the oxidation of 1a.

Cyclic voltammetry data would appear to be consistent with the proposed equilibrium. The

oxidation wave obtained for 1a (using a Pt anode, 0.1*M* $LiClO_4$ in CH_3CN as solvent, and a Ag/AgCl reference electrode) showed an initial oxidation wave at $E_{1/2}$ = +2.06 and a second wave at $E_{1/2}$ = +2.25 V. This wave resembled the oxidation curve obtained for methyl (3-methoxyphenyl)acetate but not the wave obtained for either 4-pentenoylpyrrolidine or a 1:1 mix of 4-pentenoylpyrrolidine and methyl (3-methoxyphenyl)acetate. This suggests that oxidation of compound 1a occurs initially at the aromatic ring, even though only products of amide oxidation are observed in the preparative scale reactions. It is also interesting to note that the return reduction wave observed in the CV of 1a is different than the return reduction wave observed in the CV of methyl (3-methoxyphenyl)acetate.

SCHEME II



In summary, we have found that the chemoselectivity of electrochemical amide oxidations in the presence of monomethoxylated phenyl rings depends strongly on the position of the methoxy substituent. Anodic oxidation of 3-(methoxyphenyl)acylpyrrolidine led to exclusive formation of amide oxidation products in spite of the lower oxidation potential of the monomethoxyphenyl ring. Studies aimed at exploring the synthetic utility of this reaction, extending the reaction to more electron rich aromatic rings, and elucidating the mechanism of the oxidation are currently underway.

General Experimental: A two hole rubber stopper was fitted with a needle to be used as a nitrogen inlet and two carbon rod electrodes (6 mm in diameter). The stopper was placed an top of a vial which had been charged with 0.5 mL of methanol, 4.5 mL of acetonitrile, 1.5 g (5 mmol) of tetraethylammonium tosylate, and 89 mg (0.40 mmol) of (3-methoxyphenyl)acylpyrrolidine. The reaction was degassed by bubbling nitrogen through the system for five minutes and then electrolyzed with a constant current of 7.5 mA.[7] After 2.7 F of charge were passed the reaction was concentrated *in vacuo* and then immediately chromatographed through silica gel using 50% ether/dichloromethane as eluent to afford 85.6 mg (86%) of the purified product, 2a.[8] The product was obtained as an inseparable mixture of the two isomers about the amide linkage.

TLC R_f = 0.3 with 50% ether/dichloromethane (*p*-anisaldehyde stain); ^{1}H NMR (300 MHz) δ 7.23 (m, 1H), 6.90-6.74 (m, 3H), 5.48 (d, 1/2 H, J = 4.8 Hz, methine proton next to the methoxy group in one of the amide isomers), 5.01 (d, 1/2 H, J = 3.3, methine proton next to the methoxy group in one of the amide isomers), 3.80 (s, 3H), 3.73 and 3.65 (two s, 2H, benzylic methylene protons for the two isomers), 3.39 and 3.32 (two s, 3H, alkyl methoxy groups for the two isomers), 3.71-3.36 (series of multiplets totaling two H), 3.39 and 3.32 (two s, 3H, methoxy group on the pyrrolidine ring for the two isomers), 2.22 - 1.63 (m, 4H); IR (neat/NaCl) 2940, 2890, 2840, 1670-1640 (s), 1602, 1587, 1490, 1470-1400, 1100-1040 cm^{-1}; LRMS m/e (rel. intensity) 249 (M, 16), 250 (M+1, 3), 234 (M-Me, 56), 218 (M-MeO, 16), 217 (M-MeOH, 17), 148 (M-$C_5H_{10}NO$, 91), 128 (100), 86 (99), 69 (93); HRMS (EI) m/e: 249.1372 (calcd. for $C_{14}H_{19}NO_3$ = 249.1365).

Acknowledgments: We are pleased to acknowledge partial support of this work by BRSG 2 S07 RR07054-23 awarded by the Biomedical Research Support Grant Program, Division of Research Resources, National Institute of Health. We are also pleased to thank Washington University for "start-up" funds.

REFERENCES AND NOTES

1. Shono, T.; Matsumura, Y.; Tsubata, K. *J. Am. Chem. Soc.* **1981**, *103*, 1172.
2. To our knowledge there exists no other example of an intramolecular reaction using an electrochemically derived acyliminium ion and an aromatic nucleophile. There are a few examples of intramolecular reactions of this type using nonaromatic nucleophiles. a. Ban, Y.; Irie, K. *Heterocycles* **1981**, *15*, 201, b. Ban, Y.; Irie, K. *Heterocycles* **1982**, *18*, 255, c. Ban, Y.; Okita, M.; Wakamatsu, T. *Heterocycles* **1983**, *20*, 401, d. Shono, T.; Matsumura, Y.; Uchida, K.; Tagami, K. *Chem. Lett.* **1987**, 919, e. Mori, M.; Kagechika, K.; Tohjima, K.; Shibasaki, M. *Tetrahedron Lett.* **1988**, *29*, 1409.
3. Electrochemical oxidations of electron rich aromatic rings in the presence of amines are known to occur selectively in protic media. Miller, L.; Kerr, J. B.; Jempty, T. C. *J. Am. Chem. Soc.* **1979**, *101*, 7338.
4. Zweig, A.; Hodgson, W. G.; Jura, W. H. *J. Am. Chem. Soc.* **1964**, *86*, 4124.
5. Shono, T. *Tetrahedron* **1984**, *40*, 824.
6. All new compounds were characterized by 300 MHz ^{1}H NMR, IR, and HRMS. The spectral data of these compounds will be reported in due course.
7. The electrolysis were conducted using a model 630 coulometer, a model 410 potentiostatic controller, and a model 420A power supply purchased from The Electrosynthesis Company, Inc. Carbon rods were also purchased from The Electrosynthesis Company, Inc.
8. This electrolysis was also conducted using the identical conditions except for an increase in the amount of substrate to 244 mg (1.1 mmol). The reaction was electrolyzed at a constant current of 8.5 mA until 2.5 F of charge were passed. The reaction led to formation of 208 mg (76%) of the amide oxidation products, and recovery of 18 mg (7%) of the starting material.

(Received in USA 8 November 1988)