solution turned red immediately. After the solution was stirred for 5 min at room temperature, hexane (10 mL) was added. The solution was washed with 10% aqueous NaCl (5 mL × 3), dried ($MgSO_4$), and concentrated to 5 mL under argon atmosphere. Hexane (30 mL) was added to the concentrate, and again this solution was concentrated to 5 mL under argon atmosphere. MPLC over SiO_2 (hexane) of the concentrate under argon atmosphere furnished **7** (79.2 mg, 91%) as a deep red oil.

7-Adamantylidene-1,3,5-cycloheptatriene (8).[18] The procedure was essentially similar to that described for **7**. From **5c**·ClO_4^- (215 mg, 0.662 mmol) in dry CH_2Cl_2 (2 mL) and triethylamine (73.3 mg, 0.724 mmol) was obtained **8** (136 mg, 92%) as a deep red oil. The spectral data are summarized in Table IV.

Reaction of the Heptafulvenes 7 and 8 with Tetracyanoethylene. To a stirred solution of **4c**·ClO_4^- (92.5 mg, 0.310 mmol) in dry CH_2Cl_2 (1 mL) was added triethylamine (62.4 mg, 0.617 mmol) at room temperature. The solution turned red. After stirring for 1 min at room temperature, a solution of tetracyanoethylene (79.0 mg, 0.617 mmol) in CH_2Cl_2 (11 mL) was added. The red color disappeared immediately. After stirring for 30 min, the solution was washed with 10% aqueous NaCl (10 mL × 3) and dried ($MgSO_4$). Evaporation of the solvent afforded a brown solid (132 mg). MPLC over SiO_2 (hexane–ether) and then recrystallization from hexane gave the [8 + 2] cycloaddition product **18** as a pale yellow powder (71.4 mg, 71% based on **4c**·ClO_4^-).

In the similar manner, the [8 + 2] cycloaddition product **19** was obtained from **5c**·ClO_4^- (111 mg, 0.342 mmol) in dry CH_2Cl_2 (1 mL), triethylamine (35 mg, 0.34 mmol), and tetracyanoethylene (86.2 mg, 0.673 mmol) in CH_2Cl_2 (12 mL) as a pale yellow powder (100 mg, 83% based on **5c**·ClO_4^-).

IR, ^1H NMR, and ^{13}C NMR spectra for **18** and **19** thus prepared were superimposable with those of the cycloaddition products obtained by trapping experiments of hetpafulvene intermediates (vide supra).

Hydrogenation of 7 and 8. A solution of **7** (279 mg, 1.41 mmol) in ethyl acetate (12 mL) was hydrogenated using 10% Pd/C catalyst (63 mg) under atmospheric pressure at room temperature for 20 h. Filtration of the reaction mixture followed by evaporation of the solvent afforded a colorless oil (245 mg). Distillation using Kugelrohr (145–160 °C/1.5 mmHg) gave **20** (226 mg, 78%): IR (CCl_4) 2930 s, 2860 s, 1460 m cm^{-1}; ^1H NMR (CCl_4) δ 0.7–2.2 (m, 26 H); ^{13}C NMR ($CDCl_3$) δ 20.7, 25.3, 26.2, 26.4, 26.7, 27.6, 28.5, 31.2, 32.6, 33.9 (CH_2), 25.1, 25.4, 29.2, 41.4, 43.2 (CH). Anal. Calcd for $C_{15}H_{26}$: C, 87.30; H, 12.70. Found: C, 87.56; H, 12.99.

Similarly, hydrogenation of **8** (229 mg, 1.02 mmol) with 10% Pd/C catalyst (47 mg) in ethyl acetate (9 mL) under atmospheric pressure at room temperature for 21 h followed by distillation using Kugelrohr (145–160 °C/2 mmHg) afforded **21** (235 mg, 99%) as a colorless oil: IR (CCl_4) 2925 s, 2860 s, 1470 m, 1455 m, cm^{-1}; ^1H NMR (CCl_4) δ 1.0–2.0 (m, 28 H); ^{13}C NMR ($CDCl_3$) δ 26.3, 29.0, 31.2, 32.0, 38.4, 39.6 (CH_2), 27.9, 28.2, 29.2, 37.5, 48.8 (CH). Anal. Calcd for $C_{17}H_{28}$: C, 87.86; H, 12.18. Found: C, 87.80; H, 12.18.

Acknowledgment. This work was supported by a Grant-in-Aid for Scientific Research on Priority Areas (No. 01648002) from the Ministry of Education, Science and Culture, Japan.

(18) A paper describes the ^{13}C NMR data for **8**, but it reports one extra signal [Adam, W.; Peters, E.-M.; Peters, K.; Rebollo, H.; Rosenthal, R. J.; Schnering, H. G. v. *Chem. Ber.* **1984**, *117*, 2393].

Anodic Amide Oxidations in the Presence of Electron-Rich Phenyl Rings: Evidence for an Intramolecular Electron-Transfer Mechanism

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The anodic oxidations of amides in the presence of mono-, di-, and trialkoxyphenyl rings were examined. Although literature reduction potentials suggest that these oxidations would lead to either selective aromatic ring oxidation or mixtures, the chemoselectivity of the reactions was found to be dependent on the substitution pattern of the phenyl ring. For example, the anodic oxidations of ((3-methoxyphenyl)acetyl)pyrrolidine, ((2-methoxyphenyl)acetyl)pyrrolidine, ((3-methoxy-4-(pivaloyloxy)phenyl)acetyl)pyrrolidine, and ((3,5-dimethoxy-4-(pivaloyloxy)phenyl)acetyl)pyrrolidine all led to selective methoxylation of the pyrrolidine ring. The anodic oxidations of ((4-methoxyphenyl)acetyl)pyrrolidine and ((3,4-dimethoxyphenyl)acetyl)pyrrolidine led to selective methoxylation of the benzylic carbon. Mechanistic studies indicate that both amide and aryl oxidation processes compete under the reaction conditions, but that intramolecular electron transfer leads to the selective formation of products. Evidence for this mechanism was obtained by examining the cyclic voltammogram of ((3-methoxyphenyl)-acetyl)pyrrolidine, competition studies, and the preparative electrolysis of ((4-methoxyphenyl)dimethyl-acetyl)pyrrolidine. The methoxylated amides were cyclized to form tricyclic amides using titanium tetrachloride.

The electrochemical oxidation of amides is among the most developed of electrochemical synthetic methods. It has been shown to be a versatile method for the preparation of *N*-(α-alkoxyalkyl)amides and hence *N*-acyliminium ions.[1] The potential power of these reactions lies in the oxidative alternative they can provide to the more common methods of *N*-acyliminium ion formation,[2] and the possibility they afford for developing a general annulation procedure for amines and amides.[3] However, a variety of questions still exist about the overall synthetic utility of these reactions. For example, although the anodic ox-

(1) For pioneering work, see: (a) Ross, S. D.; Finkelstein, M.; Peterson, C. *J. Am. Chem. Soc.* **1964**, *86*, 4139. Ross, S. D.; Finkelstein, M.; Peterson, C. *J. Org. Chem.* **1966**, *31*, 128. Ross, S. D.; Finkelstein, M.; Peterson, C. *J. Am. Chem. Soc.* **1966**, *88*, 4657. For reviews, see: (b) Shono, T. *Tetrahedron* **1984**, *40*, 11. (c) Shono, T.; Matsumura, Y.; Tsubata, K. In *Organic Synthesis*; Saucy, G., Ed.; John Wiley and Sons: New York, 1984; Vol. 63, p 206 and references therein.

(2) For reviews, see: (a) Zaugg, H. E. *Synthesis* **1984**, *85*, 181. (b) Speckamp, W. N.; Hiemstra, H. *Tetrahedron* **1985**, *41*, 4367. (c) Speckamp, W. N. *Recl. Trav. Chem. Pays-Bas* **1981**, *100*, 345.

(3) For a variety of examples, see: (a) Ban, Y.; Okita, M.; Wakamatsu, T.; Mori, M. *Heterocycles* **1980**, *14*, 1089. (b) Ban, Y.; Irie, K. *Heterocycles* **1981**, *15*, 201. (c) Ban, Y.; Irie, K. *Heterocycles* **1982**, *18*, 255. (d) Ban, Y.; Okita, M.; Wakamatsu, T. *Heterocycles* **1983**, *20*, 401. (e) Shono, T.; Matsumura, Y.; Uchida, K.; Tsubata, K.; Makino, A. *J. Org. Chem.* **1984**, *49*, 300. (f) Shono, T.; Matsumura, Y.; Uchida, K.; Tagami, K. *Chem. Lett.* **1987**, 919. (g) Mori, M.; Kagechika, K.; Tohjima, K.; Shibasaki, M. *Tetrahedron Lett.* **1988**, *29*, 1409.

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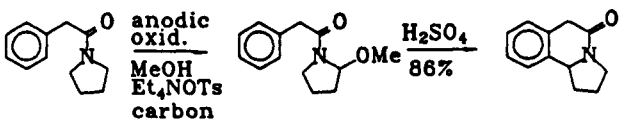
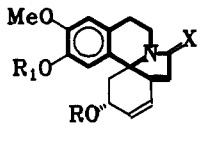
idation of an amide has been shown to be compatible with a phenyl substituent and can be utilized to generate tricyclic amide ring systems,[4] the reactions have not been

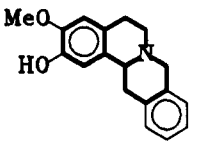


86%

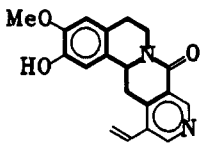
examined in order to determine their compatibility with the more electron-rich alkoxy aromatic rings found in natural products such as the erythrina alkaloids,[5] the protoberberine alkaloids,[6] and alangimaridine.[7]



Erythrina alkaloids



Protoberberine alkaloids

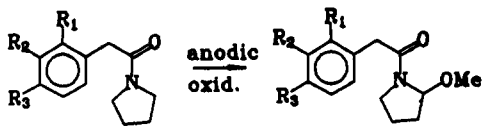


Alangimaridine

An examination of literature reduction potentials suggests that the anodic oxidation of an amide in the presence of an alkoxy aromatic ring would be problematic. For example, anisole has been reported to oxidize at a potential of +1.76 V ($E_{1/2}$ vs SCE),[8] while *N*-acetylpiperidine has been reported to oxidize at a potential of +1.88 V ($E_{1/2}$ vs SCE).[9] From these potentials it would appear that even the presence of a monomethoxyphenyl ring would interfere with the anodic oxidation of an amide.[10]

However, we recently discovered that the anodic oxidation of an amide could be accomplished in the presence of a monomethoxyphenyl ring, but that the selectivity of the reaction depended strongly upon the position of the methoxy substituent.[11] In these studies, it was found that the oxidation of ((3-methoxyphenyl)acetyl)pyrrolidine (**1a**) at a carbon anode in 1 N tetraethylammonium tosylate in 10% methanol–acetonitrile electrolyte solution led to exclusive formation of products derived from amide oxidation in an 86% isolated yield. On the other hand, anodic oxidation of ((4-methoxyphenyl)acetyl)pyrrolidine (**1b**) led to exclusive formation of products derived from aromatic ring oxidation in a 76% isolated yield (Scheme I). This product contained a small amount (about 5–10%) of the overoxidation product having dimethoxy substitution at the benzylic carbon. Oxidation of ((2-methoxyphenyl)-acetyl)pyrrolidine (**1c**) led to a mixture of products (45% yield plus 17% recovered starting material) with the product derived from amide oxidation predominating (8:1).

Scheme I. Amide Oxidations in the Presence of Monomethoxyphenyl Rings

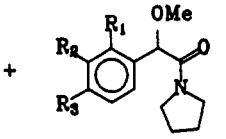


1a. R_1=R_3=H, R_2=OMe **2a. 86%**

1b. R_1=R_2=H, R_3=OMe **2b. 0%**

1c. R_2=R_3=H, R_1=OMe **2c. 40%**

(17% S.M. was recovered)

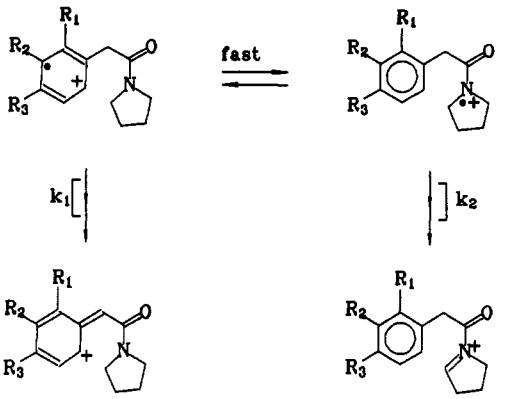


3a. 0%

3b. 76%

3c. 5%

Scheme II. Suggested Mechanism



One possibility for rationalizing the selectivity observed in these cases is outlined in Scheme II. The key to this explanation is the existence of a reversible electron transfer between the radical cation of the aromatic ring and the amide. If this equilibrium is fast compared to the rates of k_1 and k_2, then product formation would not depend upon which functional group oxidized first, but rather would depend on the relative magnitudes of k_1 and k_2 multiplied by the equilibrium constant.[12] In the oxidation of **1a**, the relative magnitude of $K_{eq}k_2$ would have to be much larger than k_1 since only amide oxidation products were observed. In the oxidation of **1b**, the opposite scenario would have to apply.

(4) Shono, T.; Matsumura, Y.; Tsubata, K. *J. Am. Chem. Soc.* **1981**, *103*, 1172.

(5) (a) For reviews on *Erythrina* alkaloids, see: Chawla, A. S.; Jackson, A. H. *Nat. Prod. Rep.* **1989**, *6*, 55; **1986**, *3*, 556; **1984**, *1*, 371. Dyke, S. F.; Quessy, S. N. In *The Alkaloids: Chemistry and Physiology*; Manske, R. H. F., Rodrigo, R. G. A., Eds.; Academic: New York, 1981; Vol. XVIII, Chapter 1.

(6) For a review, see: Bhakuni, D. S.; Jain, S. In *The Alkaloids: Chemistry and Physiology*; Brossi, A., Ed.; Academic: New York, 1986; Vol. 28, Chapter 2.

(7) Isolation: Pakrashi, S. C.; Achari, B.; Ali, E.; Ghosh Dastidar, P. P.; Sinha, R. R. *Tetrahedron Lett.* **1980**, *21*, 2667. Synthesis: (a) MacLean, D. B.; Jahangir; Holland, H. L. *Can. J. Chem.* **1986**, *64*, 1031. (b) MacLean, D. B.; Jahangir; Brook, M. A.; Holland, H. L. *J. Chem. Soc., Chem. Commun.* **1986**, 1608. (c) MacLean, D. B.; Janhangir; Brook, M. A.; Holland, H. L. *Can. J. Chem.* **1987**, *65*, 2362.

(8) Zweig, A.; Hodgson, W. G.; Jura, W. H. *J. Am. Chem. Soc.* **1964**, *86*, 4124.

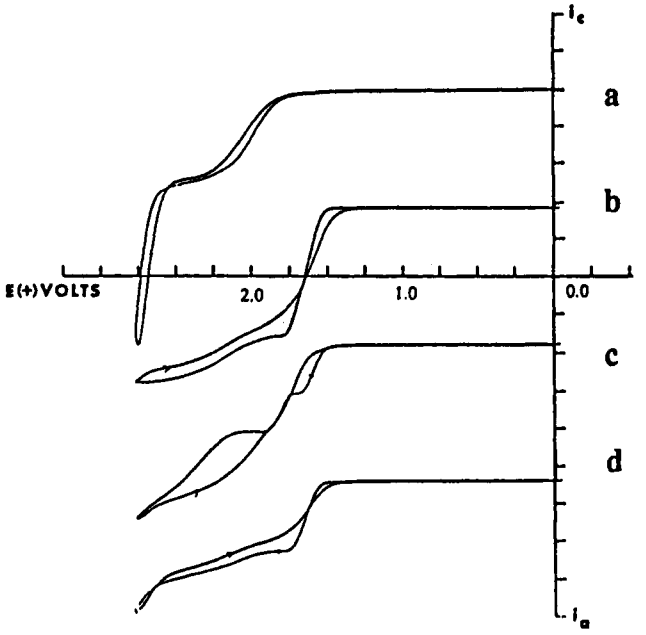
(9) See ref 1b, p 827.

(10) Electrochemical oxidations of electron-rich aromatic rings in the presence of amines are known to occur selectively in protic media. Miller, L. L.; Kerr, J. B.; Jempty, T. C. *J. Am. Chem. Soc.* **1979**, *101*, 7338.

(11) Moeller, K. D.; Tarazi, S.; Marzabadi, M. R. *Tetrahedron Lett.* **1989**, *30*, 1213.

(12) Zefirov, N. S. *Tetrahedron* **1977**, *33*, 2719.

Scheme III. Cyclic Voltammograms[a]

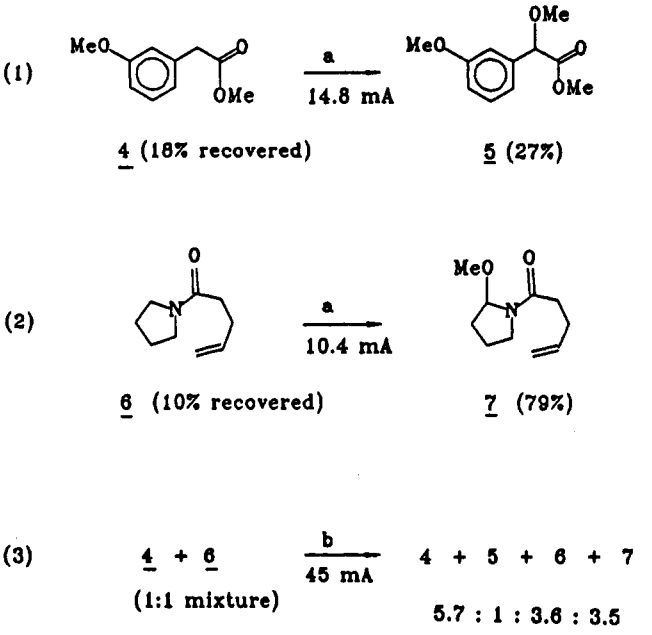


[a] (a) 4-Pentenoylpyrrolidine; (b) methyl (3-methoxyphenyl)-acetate; (c) compound **1a**; and (d) a 1:1 mixture of 4-pentenoylpyrrolidine and compound **1a**.

Evidence supporting this mechanism was derived in a number of ways. First, the cyclic voltammetry wave obtained for ((3-methoxyphenyl)acetyl)pyrrolidine was compared with the waves obtained for 4-pentenoylpyrrolidine, methyl (3-methoxyphenyl)acetate, and a 1:1 mixture of 4-pentenoylpyrrolidine and methyl (3-methoxyphenyl)-acetate (Scheme III). The oxidation waves for both the ((3-methoxyphenyl)acetyl)pyrrolidine and the methyl (3-methoxyphenyl)acetate had an $E_{1/2}$ of ca. +1.63 V while the wave for the 4-pentenoylpyrrolidine had an $E_{1/2}$ of +1.96 V (using a Pt anode, 1 N $LiClO_4$ in CH_3CN electrolyte solution, and a Ag/AgCl reference electrode.)[13] Under the cyclic voltammetry conditions, it appeared that when both the monomethoxylated phenyl ring and the amide were present *initial oxidation occurred at the aromatic ring* even for a case where preparative electrochemistry led to only the formation of amide oxidation products. In addition, there were substantial differences in the waves obtained for ((3-methoxyphenyl)acetyl)-pyrrolidine and for methyl (3-methoxyphenyl)acetate. This change in the wave indicated that the fates of the radical cation intermediates generated in the two cases were different and suggested an intramolecular interaction between the radical cation of the aromatic ring and the amide when both groups are present. This interaction was proven to be intramolecular by noting that the CV wave of a 1:1 mixture of methyl (3-methoxyphenyl)acetate and the 4-pentenoylpyrrolidine did not differ substantially from that derived from the pure methyl (3-methoxyphenyl)-acetate.

It is important to note that the cyclic voltammetry conditions used were chosen in order to maximize the reproducibility of the half wave potentials obtained and do not neccessarily reflect the conditions used for the preparative experiments. For example, preparative electrolysis using constant potential conditions indicated that both aryl and amide oxidations could compete to a greater extent than indicated by the cyclic voltammetry data (Scheme IV). To this end, the oxidations of methyl (3-methoxyphenyl)acetate (eq 1), 4-pentenoylpyrrolidine (eq 2), and a 1:1 mixture of methyl (3-methoxyphenyl)acetate and 4-pentenoylpyrrolidine (eq 3) were studied at a constant potential of +1.65 V vs a Ag/AgCl reference electrode. The reactions were run until 2 faradays (2 F) of charge had been passed. All other conditions were identical with the constant current reactions described earlier. As a benchmark, the oxidation of **1a** under these conditions led to the formation of a 43% isolated yield of **2a** along with 37% of recovered **1a**.[14] No products derived from benzylic methoxylation were observed in the crude reaction mixture by 300-MHz ^1H NMR. The oxidation of methyl (3-methoxyphenyl)acetate (**4**) under these conditions led to an initial current of 14.7 mA. Unfortunately, this oxidation led to only a 27% isolated yield of methoxylation at the benzylic position along with 18% of the recovered starting material. In this case, the product from benzylic methoxylation proved to be unstable. Oxidation of 4-pentenoylpyrrolidine (**6**) under these conditions led to an initial current of 10.4 mA and a 79% yield of methoxylated amide product. Ten percent of the starting material was recovered. Clearly, oxidation of the amide could compete

Scheme IV. Constant Potential Electrolysis Experiments: Evidence for Competitive Amide and Aryl Ring Oxidation[a]



[a] Conditions: (a) Constant potential electrolysis at +1.65 V vs Ag/AgCl until 2 F of charge had been passed, 1 N Et_4NOTs in 10% $MeOH/CH_3CN$, carbon rod anode, concentration of starting material = 0.49 M. (b) Conditions same as a, concentration of 4 = 0.49 M, concentration of 6 = 0.49 M, total of 1 F passed.

(13) These values differ from those reported earlier (ref 11) because of a problem discovered with the reference electrodes used. The reference electrodes, purchased from BAS, were found to drift substantially with time (in one case over +0.4 V in approximately 8 weeks). Although the reference electrode used in the earlier work was checked against a second electrode as suggested in the BAS catalogue, it was found that both of the electrodes purchased had drifted to an equal extent. The problem can be alleviated by standardizing the electrodes with the use of a reference compound of known potential prior to each use.

(14) The constant potential oxidation of **1a** was more efficient when run at a constant potential of +1.47 V vs Ag/AgCl. Under these conditions, the electrolysis of **1a** led to a 70% isolated yield of **2a** along with 23% recovered starting material. Although the lower potential conditions more accurately reflect the constant current conditions, they were inconveniently long. A 2 F reaction at +1.47 V required 7 h or longer depending on the substrate.

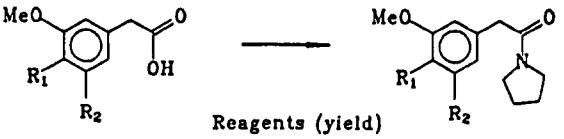
with oxidation of the 3-methoxyphenyl group under these conditions. In fact, the initial current flow measured for each oxidation indicated that the rate of amide oxidation did not differ greatly from the rate of methyl (3-methoxyphenyl)acetate oxidation.[15] A competition experiment between compounds **4** and **6** also indicated that oxidation of the two functional groups competed under the constant potential conditions. In this experiment, 55% of the amide was consumed while only 26% of the methyl (3-methoxyphenyl)acetate reacted (initial current flow = 45 mA). The formation of products from amide oxidation was favored in a 3.5:1 ratio over the formation of products from methyl (3-methoxyphenyl)acetate oxidation. It is not known whether the selectivity for amide oxidation in this experiment was due to selective oxidation of the amide group at the anode surface or the participation of a mechanism involving intermolecular mediation of the amide oxidation by the radical cation of methyl (3-methoxyphenyl)acetate.[16]

In contrast to the conclusions drawn from the cyclic voltammetry data, the evidence for competitive oxidation of the (3-methoxyphenyl)acetate and amide functional groups implied that both functional groups were oxidized during the electrolysis of compound **1a**. However, the *exclusive* formation of amide methoxylation products from **1a** suggested that both oxidation of the (3-methoxyphenyl)acetate moiety *and* oxidation of the amide led to amide methoxylation. Product formation did not depend upon the initial site of oxidation; a conclusion that is consistent with the mechanism outlined in Scheme II.

Further evidence for the potential participation of an electron-transfer mechanism was obtained by taking a closer look at the electrolysis of **1b**. A competition experiment between methyl (4-methoxyphenyl)acetate ($E_{1/2}$ = +1.61 V vs Ag/AgCl) and 4-pentenoylpyrrolidine indicated that the selectivity observed for **1b** was characteristic of the two functional groups even when they were not in the same molecule. In this experiment, electrolysis at a constant potential of +1.65 V led to mainly benzylic methoxylation products and only a small amount of amide oxidation product. The molar ratio of products derived from benzylic methoxylation (obtained as a 2.2:1 mixture of mono- and dimethoxylated compounds) to those from amide methoxylation was 14.5/1. Approximately 37% of the methyl (4-methoxyphenyl)acetate was recovered along with 77% of the 4-pentenoylpyrrolidine. As in the earlier case, the competitive formation of benzylic vs amide methoxylation products in this experiment combined with the *exclusive* formation of benzylic methoxylation product from the electrolysis of **1b** lends support for the mechanism outlined in Scheme II, particularly the possibility for initial amide oxidation leading to benzylic methoxylation in **1b**.

It is tempting to suggest that the difference between the 3-methoxyphenyl and 4-methoxyphenyl cases is a result of the relationship between the aryl ring radical cations generated and the benzylic protons. The radical cation obtained from oxidation of the 4-methoxyphenyl group would appear to overlap more strongly with the benzylic protons than would the radical cation obtained from oxidation of the 3-methoxyphenyl group. The increase in overlap would assist in the elimination of the benzylic protons and hence increase the rate of product formation

Scheme V. Synthesis of Amides 12a–c[a]

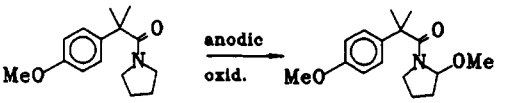


Reagents (yield)

9. R_1=OMe, R_2=H	a. (72%)	12a.
10. R_1=OH, R_2=H	b. (59%), c. (85%)	12b.
11. R_1=OMe, R_2=OMe	b. (86%), d,c. (56%)	12c.

[a] Reagents: (a) (i) $SOCl_2$; (ii) pyrrolidine. (b) (i) $(COCl)_2$, DMF, K_2CO_3; (ii) pyrrolidine. (c) Pivaloyl chloride, pyridine, DMAP. (d) TMSI.

from the 4-methoxyphenyl radical cation. In this scenario, the relative size of k_1 in Scheme II would increase for a 4-methoxyphenyl derivative and less opportunity would exist for the formation of amide oxidation products. This theory was tested by examining the anodic oxidation of compound **8**. In this experiment, compound **1b** was dialkylated (see the Experimental Section for details) in order to remove the possibility for elimination of a benzylic proton. This effectively forced k_1 in Scheme II to be zero.



8 — **50%**

(20% S.M. recovered)

Constant current oxidation of **8** ($E_{1/2}$ = +1.57 V vs Ag/AgCl) led to the formation of only amide oxidation products in a 50% isolated yield. Twenty percent of the starting material was recovered. No evidence for the formation of quinone-type products from aromatic ring oxidation was observed in the 300-MHz ^{1}H NMR spectrum of the crude reaction mixture. Hence, *in a case where it was known that aromatic ring oxidation occurred selectively, we were able to force the formation of amide oxidation products.*

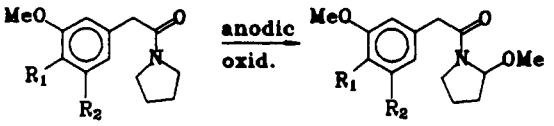
The anodic oxidations of amides **1a–c** suggested that the amide could be chemoselectively oxidized in the presence of a monomethoxylated phenyl ring as long as the methoxy group was not para to the benzylic position. However, it was not clear as to whether or not this relationship could be used in order to selectively oxidize an amide in the presence of the more electron-rich dialkoxy- and trialkoxyphenyl rings found in the natural products mentioned above. To this end, amides **12a–c** were synthesized as illustrated in Scheme V. One transformation in Scheme V deserves comment. Treatment of ((3,4,5-trimethoxyphenyl)acetyl)pyrrolidine (derived from **11**) with 2 equiv of trimethylsilyl iodide led to exclusive deprotection of the sterically most hindered methoxy group in 87% yield.[17] No evidence was obtained for loss of a second methoxy substituent. The use of 1 equiv of trimethylsilyl iodide led to no reaction. Evidently, the amide functionality efficiently ties up the first equivalent of trimethylsilyl iodide. (For comparison, the trimethoxylated acid **11** could be readily deprotected to afford 3,5-dimethoxy-4-hydroxyphenylacetic acid with just 1 equiv of the trimethylsilyl iodide.)

(15) Ross, S. D.; Finkelstein, M.; Rudd, E. J. *Anodic Oxidation*; Academic Press: New York, 1975; p 24.

(16) The increase in the initial current flow for the competition experiment supports a mechanism involving intermolecular mediation. Please see: *Organic Electrochemistry: An Introduction and A Guide*, 2nd ed.; Baizer, M. M., Lund, H., Eds.; M. Dekker: New York, 1983; pp 45 and 851.

(17) Eisenbraun, E. J.; Vickery, E. H.; Pahler, L. F. *J. Org. Chem.* 1979, *44*, 4444.

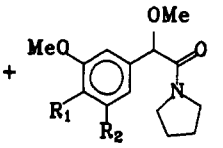
Scheme VI. Amide Oxidations in the Presence of Di- and Trialkoxyphenyl Rings



12a. R_1=OMe, R_2=H — 13a. 0%

12b. R_1=Opivaloyl, R_2=H — 13b. 82%

12c. R_1=Opivaloyl, R_2=OMe — 13c. 58%
(25% recovered s.m.)



14a. 66%

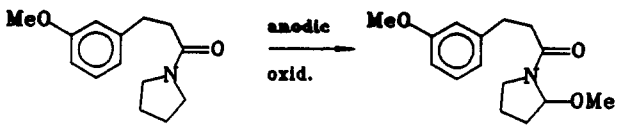
14b. 0%

14c. ?

Amides **12a–c** were oxidized at a constant current using a carbon anode, an undivided cell, and a 1 M Et_4NOTs in 10% methanol–acetonitrile electrolyte solution (Scheme VI). As expected amide **12a** led smoothly to the formation of products derived from aromatic ring oxidation (**14a**) in a 66% isolated yield. However, the oxidation of amide **12b** proved to be much more interesting. In this case, the para alkoxy substituent was protected with an ester in order to polarize the radical cation of the aromatic ring in a fashion similar to the 3-methoxyphenyl ring in **1a**. The ester was chosen because the addition of an ester substituent to a monomethoxylated phenyl ring had been shown to have little effect on the reduction potential of the ring.[18] It was rationalized that if the ester could be considered electronically neutral, then the oxidation of **12b** would be similar to the oxidation of **1a**. In practice, *anodic oxidation of **12b** led to the formation of an 82% isolated yield of the amide oxidation product.* No evidence for aromatic ring oxidation was observed in the 300-MHz ^1H NMR spectrum of the crude reaction mixture.

To our surprise, the selective oxidation of the amide could also be extended to the more electron-rich trialkoxy-substituted substrate **12c**. In this case, anodic oxidation led to the formation of a 58% isolated yield of amide oxidation products, along with 25% of the recovered starting material. Again no evidence for aromatic ring oxidation products was observed in the 300-MHz ^1H NMR spectrum of the crude reaction mixture.

Next, we turned our attention toward examining how a change in the length of the chain between the amide and the aromatic ring would affect the electron-transfer reaction. Initially these efforts focused on the synthesis of oxidation precursor **15**. Unfortunately, the anodic oxidation of **15** never led to high yields of products. In the best case, a 30% isolated yield of the methoxylated amide product **16** was obtained along with 23% of the recovered

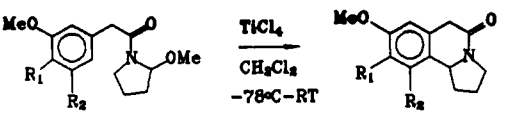


15 **16** (18–30%)

starting material. No other products were isolated from the reaction. Although the 300-MHz ^1H NMR spectrum of the crude reaction showed no evidence for aromatic ring oxidation, the poor mass balance obtained for the reaction renders meaningless any conclusions drawn about the reaction. A variety of conditions were utilized to try to improve the reaction. In all cases, variation of the solvent, electrolyte, anode material, and cell type (undivided vs divided) did not lead to an improvement in the outcome of the reaction. It was clear from these experiments that lengthening the chain between the amide and the phenyl ring by even one carbon led to a drastic decrease in the synthetic utility of the reactions.

In all of the oxidations we found that both the use of acetonitrile as a cosolvent and the use of a high concentration of tetraethylammonium salt were important for obtaining good yields. The use of pure methanol as solvent led to poor current efficiencies.[15] After 2.5 F in pure methanol the reactions were normally less then 50% complete. In contrast, after 2.5 F many of the reactions using 10% methanol–acetonitrile as solvent were complete, and the others were typically past the 70% completion mark. In general we found that continuing the electrolysis past 2.5 F did not lead to a substantial increase in the amount of product isolated but did decrease the amount of starting material recovered. The use of lower concentrations of electrolyte also dramatically affected the reaction. For the oxidation of ((3-methoxyphenyl)acetyl)-pyrrolidine the yield of methoxylated product fell to ca. 48% (11% recovered starting material) when the concentration of the electrolyte was reduced from 1.0 to 0.2 N in 10% methanol–acetonitrile. Strangely, there appeared to be no change in the "cleanliness" of the reaction by either TLC or ^1H NMR analysis. The reasons for the dropoff in yield are not readily apparent.

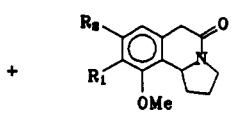
Finally, the methoxylated amides **2a**, **13b**, and **13c** were cyclized to finish the overall annulation procedure. All three compounds cleanly formed tricyclic products when treated with titanium tetrachloride in methylene chloride. Interestingly, compound **13b** led to the formation of only one tricyclic product, **17b**. No evidence for **18b** was found by 300-MHz ^1H NMR spectroscopy.



2a. R_1=R_2=H — 17a. R_1=R_2=H, 54%

13b. R_1=Opivaloyl, R_2=H — 17b. R_1=OH, R_2=H, 59%

13c. R_1=Opivaloyl, R_2=OMe — 17c. R_1=OH, R_2=OMe, 90%



18a. 19%

18b. 0%

(18) Eberson, L.; Nyberg, K. *J. Am. Chem. Soc.* **1966**, *88*, 1686.
(19) A similar observation has recently been reported: Hanzlik, R. P.; Hall, L. R.; Iwamoto, R. T. *J. Org. Chem.* **1989**, *54*, 2446.

In conclusion, we have found that the anodic oxidation of amides in the presence of electron-rich phenyl rings can lead to chemoselective methoxylation of the amide even though the initial oxidation occurs competitively at both the phenyl ring and the amide. The degree of selectivity observed is most likely due to an intramolecular electron-transfer mechanism that allows for equilibration of the initially derived intermediates. The reactions are selective for amide oxidation in the presence of di- and trialkoxyphenyl rings provided the phenyl ring is substituted with an electronically neutral ester group para to the alkyl chain connecting the phenyl ring and the amide. Studies aimed at further developing the amide oxidation as a general means for annulating rings onto amines are currently underway.

Experimental Section

Proton magnetic resonance spectra were recorded using either a Varian Gemini 300, Varian XL-300, or Varian XR-500 spectrometer. Carbon spectra were obtained on either the Varian Gemini 300 or the Varian XL-300 instrument at 75 MHz. Chemical shifts are reported as parts per million (ppm) downfield from tetramethylsilane (Me_4Si) in δ units, and coupling constants are given in cycles per second (hertz). Infrared spectra (IR) were obtained using either a Perkin-Elmer 283 B or a Mattson Polaris FT-IR spectrometer. Low-resolution mass spectral data were obtained on a HP 9500 GC/MS spectrometer. High-resolution mass spectral data were obtained using a VG ZAB-SE MS spectrometer with an 8 keV xenon FAB source. Carbon, hydrogen, and nitrogen analyses were obtained from Galbraith Laboratories Inc., Knoxville, TN. Melting points were obtained on a Thomas-Hoover capillary melting point apparatus and are uncorrected.

Gravity flow chromatography was accomplished by using E. Merck silica gel 60 (70–230 mesh). Reactions were monitored as a function of time by using TLC with E. Merck silica gel 60F-254 glass plates. The solvents used for chromatography were mixed by volume and are reported for each experiment. Capillary GC data were obtained using an HP Model 5890A instrument equipped with a HP 3396A integrator and a 20-m ULTRA II column.

Preparative electrolyses 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. Constant potential runs were done using a silver/silver chloride reference electrode purchased from BAS. Tetraethylammonium tosylate was purchased from Aldrich and stored in a vacuum desiccator (ca. 0.5 mmHg). Anhydrous methanol was purchased from Aldrich in Sure/Seal bottles and used without purification. Acetonitrile was freshly distilled from calcium hydride prior to use. Cyclic voltammetry data were obtained using a Model CV-1B voltammetry control unit, an RXY recorder, and a C-1B cell stand from BAS. All of the voltammograms were obtained using a platinum working electrode, a platinum wire auxiliary electrode, a silver/silver chloride reference electrode (purchased from BAS), and a 1 N lithium perchlorate in acetonitrile electrolyte solution.

3-Methoxyphenylacetic acid, 2-methoxyphenylacetic acid, 4-methoxyphenylacetic acid, and trimethylsilyl iodide were purchased from Aldrich and used without purification. Pivaloyl chloride, dimethyl formamide, and pyrrolidine were purchased from Aldrich and distilled prior to use. Oxalyl chloride (Aldrich) was freshly distilled prior to use.

All solvents used for synthesis were distilled before use. Methylene chloride and DMF were distilled from calcium hydride, while ether and tetrahydrofuran were distilled from benzophenone ketyl.

All reactions were run under an inert atmosphere of nitrogen unless otherwise specified.

The purity of all compounds was determined by either melting point, C, H, and N analyses, or proton and carbon NMR (>90–95%) data.

Synthesis of Amide Substrates. General Procedure for the Formation of Amides (Method A): ((4-Methoxyphenyl)acetyl)pyrrolidine (1b). Thionyl chloride (4.6 mL/63 mmol) was added dropwise to a round-bottom flask containing 4.24 g (25.5 mmol) of 4-methoxyphenylacetic acid. The reaction mixture was stirred until the evolution of gas was complete. The excess thionyl chloride was removed by vacuum, and then the remaining acid chloride was cannulated into a round-bottom flask containing 5.6 g (78.8 mmol) of pyrrolidine in 15 mL of toluene. The reaction mixture was stirred again until the evolution of gas was complete. When complete, the reaction mixture was washed two times with 10 mL of water, once with 10 mL of saturated sodium bicarbonate, and then a third time with 10 mL of water. The organic layer was concentrated in vacuo to afford white crystals. In the general case the reaction product was purified by either chromatography or recrystallization. In the present case, the product could be recrystallized from ethyl acetate and hexane to afford 4.11 g (75%) of the pure product: mp 55.6–56.7 °C; TLC R_f = 0.5 in 50% ether/methylene chloride (*p*-anisaldehyde stain): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20 (d, 2 H, J = 9 Hz), 6.85 (d, 2 H, J = 8.7 Hz), 3.79 (s, 3 H), 3.58 (s, 2 H), 3.48 (t, 2 H, J = 6.9 Hz), 3.42 (t, 2 H, J = 7.2 Hz), 1.95–1.78 (m, 4 H); IR (neat/NaCl) 3050, 2970, 2880, 2840, 1640, 1515, 1440, 1340, 1305, 1240, 1180, 1040 cm^{-1}; GCMS (35 eV) m/e (rel intensity) 220 (M^+ + 1, 1), 219 (M^+, 4), 148 (M^+ – pyrrolidine, 4), 121 (C_8H_9O, 28), 98 (100); HRMS (EI) m/e calcd for $C_{13}H_{17}NO_2$ 219.1259, found 219.1255.

((3-Methoxyphenyl)acetyl)pyrrolidine (1a). Method A: yield = 3.15 g (55%); TLC R_f = 0.3 with 50% ether/hexane (*p*-anisaldehyde stain); ^{1}H NMR (300 MHz/$CDCl_3$) δ 7.22 (t, 1 H, J = 7.8 Hz), 6.85 (m, 2 H), 6.79 (d, 1 H, J = 7.5 Hz), 3.79 (s, 3 H), 3.63 (s, 2 H), 3.48 (t, 2 H, J = 6.9 Hz), 3.42 (t, 2 H, J = 7.2 Hz), 1.95–1.81 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) 169.7, 159.9, 136.4, 129.6, 121.3, 114.4, 112.3, 54.9, 46.6, 45.7, 42.0, 25.7, 23.9; IR (neat/NaCl) 3060, 2980, 2880, 2840, 1620 br, 1490, 1440 br, 1340, 1320, 1290, 1260, 1230, 1190, 1160, 1050, 870, 770, 710, 690 cm^{-1}; MS (35 eV) m/e (rel intensity) 220 (M^+ + 1, 1), 219 (M^+, 8), 148 (M^+ – pyrrolidine, 4), 121 (C_8H_9O, 18), 98 (100); HRMS (EI) m/e calcd for $C_{13}H_{17}NO_2$ 219.1259, found 219.1264. Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39. Found: C, 70.64; H, 7.83; N, 6.41.

((2-Methoxyphenyl)acetyl)pyrrolidine (1c). Method A: yield = 3.30 g (62%); TLC R_f = 0.48 with 5% methanol/ether (*p*-anisaldehyde stain); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22 (m, 2 H), 6.913 (app t but couplings off, 1 H, J = 6.3 and 7.8 Hz), 6.86 (d, 1 H, J = 9.3 Hz), 3.81 (s, 3 H), 3.63 (s, 2 H), 3.50 (t, 2 H, J = 7.0 Hz), 3.44 (t, 2 H, J = 7.0 Hz), 1.94–1.82 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) 170.2, 157.2, 130.3, 128.0, 123.8, 120.6, 110.2, 55.2, 46.5, 45.6, 35.6, 25.0, 24.1; IR (neat/NaCl) 3080, 2980, 2860, 2840, 1640 br, 1600, 1580, 1500, 1440 br, 1340, 1325, 1300, 1250, 1190, 1170, 1110, 1050, 1030, 750 cm^{-1}; MS (35 eV) m/e (rel intensity) 220 (M^+ + 1, 4), 219 (M^+, 27), 201 ($M^+ - H_2O$, 1), 188 (M^+ – OMe, 6), 148 (M^+ – pyrrolidine, 6), 121 ($M^+ - C_5H_9NO$, 24), 98 (100); HRMS (EI) m/e calcd for $C_{13}H_{17}NO_2$ 219.1259, found 219.1257.

((4-Methoxyphenyl)dimethylacetyl)pyrrolidine (8). To a −78 °C solution of 2.87 g (25.5 mmol) of potassium *tert*-butoxide in 7.5 mL of tetrahydrofuran was added a solution of 1.87 g (8.5 mmol) of ((4-methoxyphenyl)acetyl)pyrrolidine. The reaction was stirred for 30 min, and then 4.54 g (32 mmol) of methyl iodide was added. The reaction was stirred at −78 °C for 1 h and then allowed to warm to room temperature. When no starting material remained by TLC the reaction mixture was washed three times with water. The combined water layers were then extracted with ether. The combined organic layers were then concentrated and the product precipitated to afford 1.046 g (53% yield) of the crude solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22 (d, 2 H, J = 8.7 Hz), 6.85 (d, 2 H, J = 8.7 Hz), 3.79 (s, 3 H), 3.69 (q, 1 H, J = 7.0 Hz), 3.58–3.37 (m, 3 H), 3.20 (m, 1 H), 1.91–1.73 (m, 4 H), 1.42 (d, 3 H, J = 6.9 Hz). This crude product was carried on to the next step.

To a −78 °C solution of 0.73 g (7.2 mmol) of diisopropylamine in 5 mL of tetrahydrofuran was added 2.8 mL (7.0 mmol) of a 2.5 N *n*-butyllithium in hexane solution. The reaction was stirred for 30 min, and then a solution of 0.85 g (3.6 mmol) of the ((4-methoxyphenyl)methylacetyl)pyrrolidine made above in 5 mL of tetrahydrofuran was added. After an additional 30 min, 1.53 g (10.8 mmol) of methyl iodide was added. The reaction was allowed to warm to room temperature and stirred overnight. The

reaction was quenched with water and the layers separated. The organic layer was washed with water three times, and then the combined aqueous layers were extracted with ether. The combined organic layers were dried over $MgSO_4$ and then concentrated in vacuo. Silica gel chromatography using 50% ether/hexane as eluant led to the isolation of 0.50 g (60%) of the purified product: mp 56.0–58.0 °C; TLC R_f = 0.2 with 50% ether/hexane (*p*-anisaldehyde stain); ^1H NMR (300 MHz, $CDCl_3$) δ 7.16 (d, 2 H, J = 8.8 Hz), 6.86 (d, 2 H, J = 8.8 Hz), 3.81 (s, 3 H), 3.51 (t, 2 H, J_{av} = 7.0 Hz), 2.75 (t, 2 H, J = 6.5 Hz), 1.68 (app q, 2 H, J = 7.1 Hz), 1.60 (app q, 2 H, J = 6.2 Hz), 1.52 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) 175.4, 158.1, 138.2, 126.5, 113.9, 55.0, 47.2, 46.8, 46.3, 27.2, 26.3, 22.9; IR (neat/NaCl) 3059, 2971, 2933, 2877, 2836, 1626, 1581, 1512, 1465, 1405, 1378, 1363, 1298, 1251, 1182, 1164, 1112, 1101, 1034, 832, 771 cm^{-1}; MS (35 eV) m/e (rel intensity) 247 (M^+, 2), 232 ($M^+ - CH_3$, 2), 150 (15), 149 ($M^+ - C_5H_9NO$, 100), 148 (9), 121 (25), 98 (21); HRMS (EI) m/e calcd for $C_{15}H_{21}NO_2$ 247.1572, found 247.1597.

((3,4-Dimethoxyphenyl)acetyl)pyrrolidine (12a). Method A: yield = 8.68 g (72%); mp 49.7–51 °C; TLC R_f = 0.34 using 50% ether/dichloromethane (*p*-anisaldehyde stain); ^1H NMR (300 MHz, $CDCl_3$) δ 6.87 (s, 1 H), 6.80 (s, 2 H), 3.88 (s, 3 H), 3.86 (s, 3 H), 3.59 (s, 2 H), 3.49 (s, 2 H, J = 6.4 Hz), 3.43 (t, 2 H, J_{av} = 6.7 Hz), 1.92 (p, 2 H, J_{av} = 6.4 Hz), 1.84 (p, 2 H, J_{av} = 6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.5, 148.9, 147.7, 127.3, 120.9, 112.0, 111.1, 55.9, 46.8, 45.9, 41.8, 26.2, 24.4; IR (neat/NaCl) 3060, 2953, 2876, 2835, 1639, 1590, 1516, 1449, 1341, 1262, 1237, 1028, 951, 915, 867, 791, 766, 696, 622 cm^{-1}; MS (solid probe, 35 eV) m/e (rel intensity) 250 (M^+ + 1, 2), 249 (M^+, 9), 178 ($M^+ - C_4H_9N$, 2), 151 ($M^+ - C_5H_8NO$, 46), 98 (C_5H_8NO, 100), 70 (C_4H_8N, 8); HRMS (EI) m/e calcd for $C_{14}H_{19}NO_3$ 249.1365, found 249.1388.

General Procedure for the Formation of Amides (Method B): ((4-Hydroxy-3-methoxyphenyl)acetyl)pyrrolidine. To a room temperature solution of 3.0 g (16.5 mmol) of homovaniliic acid, 3.5 g (33 mmol) of sodium carbonate, and 2.51 g (19.8 mmol) of oxalyl chloride in 82 mL of toluene was added 0.24 g (3.3 mmol) of *N,N*-dimethylformamide. The reaction mixture was stirred until the bubbling stopped, and then the mixture was cannulated into a room temperature solution of 5.86 g (82.3 mmol) of pyrrolidine in 82 mL of toluene. The reaction mixture was stirred at room temperature and monitored by TLC for loss of the starting material. When complete the reaction mixture was diluted with water and ether, the layers were separated, and the aqueous layer was extracted three times with both ether and dichloromethane. The organic layers were then dried over $MgSO_4$ and concentrated in vacuo. In the general case the product could be purified by either chromatography or recrystallization. In the present case the product was purified by recrystallization from dichloromethane/hexane solution to afford 2.07 g (54%) of the purified solid: mp 116.6–117.3 °C; TLC R_f = 0.37 using 10% methanol/ether (*p*-anisaldehyde stain); ^1H NMR (300 MHz, $CDCl_3$) δ 6.89 (d, 1 H, J = 2.0 Hz), 6.85 (d, 1 H, J = 8.0 Hz), 6.72 (dd, 1 H, J = 8.0 Hz, J = 2.1 Hz), 5.62 (s, 1 H, OH), 3.88 (s, 3 H), 3.58 (s, 2 H), 3.49 (t, 2 H, J_{av} = 6.9 Hz), 3.44 (t, 2 H, J_{av} = 6.9 Hz), 1.97–1.79 (m, 4 H); IR (neat/NaCl) 3500 br, 3162, 3152, 2983, 2879, 1611, 1589, 1523, 1469, 1436, 1387, 1340, 1283, 1257, 1220, 1153, 1128, 1034, 802, 784 cm^{-1}; MS (70 eV) m/e (rel intensity) 235 (M^+, 5), 164 ($M^+ - C_5H_{11}$, 1), 137 ($M^+ - C_5H_8NO$, 28), 122 (137 - Me, 8), 98 (C_5H_8NO, 100), 70 (11), 55 (60). Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.48, H, 7.35; N, 5.71.

((3-Methoxy-4-(pivaloyloxy)phenyl)acetyl)pyrrolidine (12b). To a room temperature solution of 0.25 g (1.05 mmol) of ((4-hydroxy-3-methoxyphenyl)acetyl)pyrrolidine, 0.25 g (3.15 mmol) of pyridine, and 25.6 mg (0.21 mmol) of (dimethylamino)pyridine in 2.1 mL of dichloromethane was added 0.38 g (3.15 mmol) of pivaloyl chloride. The reaction mixture was stirred until no starting material was evident by TLC. The reaction mixture was then washed with water. The aqueous layer was extracted with dichloromethane, and then the combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The crude product was chromatographed through silica gel using 50% ether/dichloromethane as eluant to afford 0.35 g (ca. 100%) of the pure ester: mp 64.4–65.8 °C; TLC R_f = 0.2 using 50% ether/dichloromethane (*p*-anisaldehyde stain); ^1H NMR (300 MHz, $CDCl_3$) δ 6.97 (d, 1 H, J = 1.8 Hz), 6.95 (d, 1 H, J = 7.9 Hz), 6.83 (dd, 1 H, J = 1.9, 8.1 Hz), 3.79 (s, 3 H), 3.62 (s, 2 H), 3.50 (t, 2 H, J_{av} = 6.8 Hz), 3.44 (t, 2 H, J_{av} = 6.6 Hz), 1.98–1.80 (m, 4 H), 1.35 (s, 9 H); IR (neat/NaCl) 3052, 2973, 2938, 2875, 1754, 1642, 1633, 1605, 1511, 1480, 1451, 1445, 1434, 1397, 1270, 1202, 1150, 1116, 1035 cm^{-1}; MS (70 eV) m/e (rel intensity) 235 (M^+ + 1 - C_5H_9O, 1), 137 (235 - C_5H_8NO, 12), 122 (137 - Me, 3), 113 (4), 111 (9), 98 (C_5H_8NO, 100), 70 (17); HRMS (EI-FAB) m/e calcd for $C_{18}H_{26}NO_4$ (M + 1) 320.1862, found 320.1825.

4-Pentenoylpyrrolidine (6). Method B: yield = 69%; TLC R_f = 0.20 using ether (*p*-anisaldehyde stain); ^1H NMR (300 MHz, $CDCl_3$) δ 5.88 (ddt, 1 H, J_d = 17.0, 10.3, J_t = 6.3 Hz), 5.07 (dq, 1 H, J_d = 17.2, J_q = 1.6 Hz), 4.99 (dm, 1 H, J_d = ca. 10 Hz), 3.47 (t, 2 H, J = 7.0 Hz), 3.42 (t, 2 H, J = 6.7 Hz), 2.38 (m, 4 H), 1.91 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0, 137.8, 115.0, 46.3, 45.3, 33.7, 28.6, 25.8, 24.1; IR (neat/NaCl) 3076, 2971, 2950, 2874, 1657, 1445, 1341, 1323, 1252, 1227, 1193, 914, 730 cm^{-1}; GCMS (PCI) m/e (rel intensity) 154 (M^+ + 1, 100), 153 (M^+, 5), 152 (M^+ 1, 10), 98 (13), 70 (7), 57 (12), 55 (16); HRMS (EI) m/e calcd for $C_9H_{15}NO$ 153.1153, found 153.1145.

((3,4,5-Trimethoxyphenyl)acetyl)pyrrolidine. Method B: yield = 2.40 g (86%); mp 63–64 °C; TLC R_f = 0.3 using 5% methanol/ether (*p*-anisaldehyde stain); ^1H NMR (300 MHz, $CDCl_3$) δ 6.51 (s, 2 H), 3.85 (s, 6 H), 3.83 (s, 3 H), 3.59 (s, 2 H), 3.50 (t, 2 H, J = 6.9 Hz), 3.46 (t, 2 H, J = 6.9 Hz), 1.95 (m, 2 H), 1.86 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) 169.0, 152.9, 136.5, 130.4, 105.8, 60.7, 56.0, 46.8, 45.9, 42.3, 26.1, 24.3; IR (neat/NaCl) 2999, 2965, 2940, 2884, 2830, 1626, 1588, 1507, 1447, 1423, 1336, 1328, 1248, 1233, 1153, 1121, 1006, 972, 793, 771, 635, 607, 530 cm^{-1}; MS (70 eV) m/e (rel intensity) 279 (M^+, 12), 264 ($M^+ - CH_3$, 1), 182 ($M^+ - C_5H_9NO$, 17), 181 ($M^+ - C_5H_{10}NO$, 47), 148 (4), 136 (2), 98 (C_5H_8NO, 100), 70 (10), 56 (22), 55(36); HRMS (EI) m/e calcd for $C_{15}H_{21}NO_4$ 279.1470, found 279.1470.

((3,5-Dimethoxy-4-hydroxyphenyl)acetyl)pyrrolidine. To a room temperature solution of 0.143 g (0.51 mmol) of ((3,4,5-trimethoxyphenyl)acetyl)pyrrolidine in 0.51 mL of dichloromethane was added 0.204 g (1.02 mmol) of trimethylsilyl iodide. The reaction mixture was stirred until all of the starting material was gone by TLC. The reaction mixture was then diluted with methanol and brine. The resulting mixture was extracted with ether until no more product was being removed as judged by TLC. The combined organic layers were then dried over $MgSO_4$ and concentrated. The crude product was chromatographed through silica gel using 10% methanol/ether as the eluant to afford 118 mg (87%) of the purified product. (Upon scaleup the reaction led to formation of 2.25 g (ca. 98%) of slightly impure material. This product was carried on to the next step without further purification.) TLC R_f = 0.3 using 10% methanol/ether (*p*-anisaldehyde stain); ^1H NMR (300 MHz, $CDCl_3$) δ 6.53 (s, 2 H), 5.31 (br s, 1 H), 3.86 (s, 6 H), 3.58 (s, 2 H), 3.49 (t, 2 H J_{av} = 6.8 Hz), 3.44 (t, 2 H, J_{av} = 6.7 Hz), 1.93 (app p, 2 H, J_{av} = 6.3 Hz), 1.84 (app p, 2 H, J_{av} = 6.8 Hz); IR (neat/NaCl) 3480–3170 br, 3056, 2951, 1877, 2839, 1616, 1516, 1456, 1331, 1245, 1216, 1114 cm^{-1}; MS (35 eV) m/e (rel intensity) 266 (M^+ + 1, 1), 265 (M^+, 7), 194 ($M^+ - C_4H_9N$, 2), 167 ($M^+ - C_5H_8NO$, 32), 98 (C_5H_8NO, 100), 70 (14).

((3,5-Dimethoxy-4-(pivaloyloxy)phenyl)acetyl)pyrrolidine (12c). To a room temperature solution of 97 mg (0.37 mmol) of alcohol, 5 mg (0.04 mmol) of (dimethylamino)pyridine, and 74 mg (0.73 mmol) of triethylamine in 0.73 mL of dichloromethane was added 88 mg (0.73 mmol) of pivaloyl chloride. The reaction mixture was stirred at room temperature and monitored by TLC. When no more starting material was evident by TLC, the reaction mixture was diluted with dichloromethane and water, the layers were separated, and the aqueous layer was extracted with dichloromethane. The combined organic layers were then dried over $MgSO_4$ and concentrated in vacuo. The crude product was chromatographed through silica gel using 10% methanol/ether as eluant to afford 98 mg (77%) of the pure ester. The scaleup of this reaction mentioned in the previous step produced 1.7 g of the desired product (57% from the ((3,4,5-trimethoxyphenyl)acetyl)pyrrolidine): mp 78.7–79.8 °C; TLC R_f = 0.4 using 10% methanol/ether (*p*-anisaldehyde stain); ^1H NMR (300 MHz, $CDCl_3$) δ 6.55 (s, 2 H), 3.78 (s, 6 H), 3.61 (s, 2 H), 3.49 (t, 2 H, J_{av} = 6.7 Hz), 3.42 (t, 2 H, J_{av} = 6.7 Hz), 1.92 (app p, 2 H, J_{av} = 6.7 Hz), 1.84 (app p, 2 H, J_{av} = 6.7 Hz), 1.37 (s, 9 H); IR (neat/NaCl) 3057, 2975, 2878, 2839, 1750, 1640, 1602, 1509, 1466, 1426, 1420, 1335, 1209, 1198, 1189, 1178, 1168, 1152, 1125, 1118,

1032, 973, 801, 782, 636 cm^{-1}; MS (70 eV) m/e (rel intensity) 350 (M^+ + 1, 1), 349 (M^+, 3), 266 ($M^+ - C_5H_9O$, 2), 265 ($M^+ - C_5H_{10}O$, 13), 194 (265 - pyrrolidine, 2), 167 (20), 111 (7), 98 (C_5H_8NO, 100); HRMS (EI) m/e calcd for $C_{19}H_{27}NO_5$ 349.1889, found 3 49.1890.

(3-(3-Methoxyphenyl)propanoyl)pyrrolidine (15). Made from 3-(3-methoxyphenyl)propanoic acid[20] using method B: yield = 0.401 g (86%); TLC R_f = 0.2 using 50% ether/dichloromethane (*p*-anisaldehyde stain); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21 (t, 1 H, J = 7.8 Hz), 6.85–6.72 (m, 3 H), 3.80 (s, 3 H), 3.47 (t, 2 H, J = 6.7 Hz), 3.30 (t, 2 H, J = 6 Hz), 2.97 (t, 2 H, J = 8 Hz), 2.56 (t, 2 H, J = 8 Hz), 1.9–1.8 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) 171.0, 159.9, 143.4, 129.5, 120.9, 114.2, 111.4, 55.0, 46.4, 45.5, 36.5, 31.0, 25.8, 24.1; IR (neat/NaCl) 2950, 2900, 1639, 1489, 1438, 1343, 1262, 1152, 1044 cm^{-1}; MS (70 eV) m/e (rel intensity) 233 (M^+, 47), 135 ($M^+ - C_5H_8NO$, 33), 112 ($M^+ - C_6H_{10}NO$, 37), 112 ($C_6H_{10}NO$, 100), 98 (C_5H_8NO, 25), 91 (30), 78 (13), 72 (14); HRMS (EI) m/e calcd for $C_{14}H_{19}NO_2$ 233.1416, found 233.1445.

Anodic Oxidation Reactions. General Procedure for Constant Current Electrolysis: Synthesis of 2-Methoxy-*N*-((3-methoxyphenyl)acetyl)pyrrolidine (2a). 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 on top of a vial that 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)acetyl)pyrrolidine (**1a**). The reaction mixture was degassed by bubbling nitrogen through the system for 5 min and then electrolyzed with a constant current of 7.5 mA. After 2.7 F of charge was passed the reaction was concentrated in vacuo and then immediately chromatographed through silica gel using 50% ether/dichloromethane as eluant to afford 85.6 mg (86%) of the purified product. The product was obtained as an inseparable mixture of the two isomers about the amide linkage. The electrolysis was also conducted using identical conditions except for an increase in the amount of substrate to 244 mg (1.1 mmol). The reaction mixture was electrolyzed at a constant current of 8.5 mA until 2.5 F of charge was 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. The spectral data of the methoxylated amides were as follows: TLC R_f = 0.3 using 50% ether/dichloromethane (*p*-anisaldehyde stain); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23 (m, 1 H), 6.90–6.74 (m, 3 H), 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 Hz, methine proton next to the methoxy group in one of the amide isomers), 3.80 (s, 3 H), 3.73 and 3.65 (2 s, 2 H, benzylic methylene signals for the two isomers), 3.71–3.36 (series of multiplets totaling 2 H) 3.39 and 3.32 (2 s, 3 H, methoxy group on the pyrrolidine ring for the two isomers), 2.22–1.63 (m, 4 H, pyrrolidine protons); ^{13}C NMR (75 MHz, $CDCl_3$) 171.3, 159.7, 136.0, 129.4, 121.3, 114.4, 112.2, 88.4, 56.2, 54.0, 46.0, 41.0, 30.9, 22.4; IR (neat/NaCl) 2940, 2890, 2840, 1670–1640 s, 1602, 1587, 1490, 1470–1400, 1100–1040 cm^{-1}; MS (35 eV) m/e (rel intensity) 250 (M^+ + 1, 3), 249 (M^+, 16), 234 (M^+ - Me, 56), 218 (M^+ - MeO, 16), 217 (M^+ - MeOH, 17), 148 ($M^+ - C_4H_{10}NO$, 91), 128 (100), 86 (99), 69 (93); HRMS (EI) m/e calcd for $C_{14}H_{19}NO_3$ 249.1365, found 249.1372. Anal. Calcd for $C_{14}H_{19}NO_3$: C, 67.45; H, 7.68; N, 5.61. Found: C, 67.50; H, 8.00; N, 5.58.

(Methoxy(4-methoxyphenyl)acetyl)pyrrolidine (3b). ((4-Methoxyphenyl)acetyl)pyrrolidine (96 mg, 0.44 mmol) was electrolyzed with a constant current of 8.0 mA until 2.07 F of charge had been passed. The reaction led to the formation of 83 mg (76%) of **3b**. The material was contaminated with about 5–10% of dimethoxylated material at the benzylic position: TLC R_f = 0.3 using 50% ether/dichloromethane (*p*-anisaldehyde stain); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (d, 2 H, J = 8.7 Hz), 6.89 (d, 2 H, J = 8.7 Hz), 4.80 (s, 1 H), 3.80 (s, 3 H), 3.60–3.40 (m, 3 H), 3.39 (s, 3 H), 3.24 (m, 1 H), 1.80 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.1, 159.9, 129.1, 128.2, 114.0, 82.7, 56.9, 55.1, 46.1, 45.6, 26.0, 23.4; IR (neat/NaCl) 3040, 3000, 2960, 2940, 2880, 1650, 1610, 1585, 1510, 1445 br, 1340, 1310, 1280, 1240, 1200, 1180, 1100, 1040, 820 cm^{-1}; MS (35 eV) m/e (rel intensity) 249 (M^+, 1), 248 (M^+ - 1, 1), 218 ($M^+ - CH_3OH$, 1), 151 ($C_9H_{11}O_2$, 100); HRMS (EI) m/e calcd for $C_{14}H_{19}O_3$ 249.1365, found 249.1350.

2-Methoxy-*N*-((2-methoxyphenyl)acetyl)pyrrolidine (2c) and (Methoxy(2-methoxyphenyl)acetyl)pyrrolidine (3c). ((2-Methoxyphenyl)acetyl)pyrrolidine (**1c**) (96 mg, 0.44 mmol) was electrolyzed at a constant current of 8.5 mA until 2 F of charge had been passed. The electrolysis led to the formation of 44 mg (40%) of **2c**, ca. 5.4 mg (ca. 5%) of **3c**, and 16 mg (17%) of recovered starting material. The spectral data for **2c** were as follows: TLC R_f = 0.57 using 50% ether/dichloromethane (*p*-anisaldehyde stain); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24 (m, 2 H), 6.93 (m, 1 H), 6.86 (d, 1 H, J = 7.5 Hz), 5.50 (d, $^1/_2$ H, J = 5.0 Hz, methine proton α to OMe for one amide rotomer), 5.12 (d, $^1/_2$ H, J = 5.4 Hz, methine proton a to OMe for one amide rotomer), 3.93 (A of AB, $^1/_2$ H, J = 15.9 Hz, benzylic methylene proton for one amide rotomer), 3.82 and 3.81 (2 s, 3 H), 3.65 (s, 1 H, benzylic methylene protons for one amide rotomer), 3.57 (B of AB, $^1/_2$ H, J = 15.9, benzylic methylene proton for one amide rotomer), 3.49–3.44 (m, total 2 H), 3.39 and 3.33 (2 s, 3 H), 2.25–1.85 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.4, 171.9, 157.8, 157.6, 131.1, 128.7, 128.6, 124.4, 124.1, 121.2, 121.1, 110.7, 89.2, 87.5, 56.8, 55.6, 54.3, 46.4, 45.8, 36.3, 35.4, 31.8, 31.3, 23.1, 21.2; IR (neat/NaCl) 3000, 2940, 2900, 2840, 1660, 1605 br, 1580, 1500, 1470, 1440, 1410, 1240, 1200, 1180, 1160, 1115, 1050, 1070, 1050, 1030, 940, 920 cm^{-1}; MS (35 eV) m/e (rel intensity) 250 (M^+ + 1, 1), 249 (M^+, 3), 234 ($M^+ - CH_3$, 1), 218 ($M^+ - CH_3O$, 5), 217 ($M^+ - CH_3OH$, 11), 148 ($M^+ - C_5H_{11}NO$, 57), 128 (100), 122 (87); HRMS (EI) m/e calcd for $C_{14}H_{19}NO$ 249.1365, found 249.1371. The spectral data for **3c** were as follows: TLC R_f = 0.39 using 50% ether/dichloromethane (*p*-anisaldehyde stain); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (dd, 1 H, J = 7.8 and 2 Hz), 7.30 (m, 1 H), 6.98 (m, 1 H), 6.9 (d, 1 H, J = 7.5 Hz), 5.35 (s, 1 H), 3.87 (s, 3 H), 3.63–3.40 (m, 3 H, methylene protons α to nitrogen), 3.39 (s, 3 H, methyl ether protons), 3.12 (m, 1 H, methylene proton α to nitrogen), 1.92–1.75 (m, 4 H); IR (neat/NaCl) 3050, 2960, 2850, 1670, 1605, 1590, 1470, 1445, 1415, 1200, 1180, 1160, 1110, 1080, 1070, 1050, 1030 cm^{-1}; MS (35 eV) m/e (rel intensity) 249 (M^+, 1), 217 ($M^+ - CH_3OH$, 1), 151 ($C_9H_{11}O_2$, 34), 148 ($M^+ - C_5H_{11}NO$, 15), 98 (100); HRMS (EI) m/e calcd for $C_{14}H_{19}NO_3$ 249.1365, found 249.1385.

2-Methoxy-*N*-((4-methoxyphenyl)dimethylacetyl)-pyrrolidine. ((4-Methoxyphenyl)dimethylacetyl)pyrrolidine (**8**) (200 mg, 0.8 mmol) was electrolyzed at a constant current of 8.5 mA until 2.3 F of charge had been passed. The electrolysis led to the formation of 112 mg (50%) of the methoxylated product and 40 mg (20%) of recovered starting material. The spectral data for the product were as follows: TLC R_f = 0.7 using 5% methanol/ether (*p*-anisaldehyde stain); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.16 (d, 2 H, J = 8.8 Hz), 6.87 (d, 2 H, J = 8.9 Hz), 5.58 (br d, 1 H, J = 3.8 Hz), 3.81 (s, 3 H), 3.42 (s, 3 H), 3.00–2.73 (m, 2 H), 1.58 and 1.50 (2 s, 6 H), 1.90–1.45 (br m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) 176.89, 158.1, 137.4, 126.3, 113.9, 88.8, 56.0, 54.9, 46.5, 45.6, 29.9, 27.9, 26.3, 22.9; IR (neat/NaCl) 3063, 2967, 2937, 2835, 1641, 1511, 1464, 1393, 1361, 1295, 1252, 1183, 1154, 1081, 1034, 832 cm^{-1}; MS (35 eV) m/e (rel intensity) 277 (M^+, 2), 245 ($M^+ - CH_3OH$, 3), 183 (3), 150 (46), 149 ($M^+ - C_6H_{10}NO_2$, 100), 148 (25), 134 (6), 121 (49); HRMS (EI) m/e calcd for $C_{16}H_{23}NO_3$ 277.1678, found 277.1670. Anal. Calcd for $C_{16}H_{23}NO_3$: C, 69.29; H, 8.36; N, 5.05. Found: C, 68.83; H, 8.26; N, 5.20.

((3,4-Dimethoxyphenyl)methoxyacetyl)pyrrolidine (14a). ((3,4-Dimethoxyphenyl)acetyl)pyrrolidine (**12a**) (122 mg/0.48 mmol) was electrolyzed at a constant current of 15.2 mA until 3.8 F of charge was passed. The electrolysis led to the formation of 91.1 mg (66%) of the product methoxylated at the benzylic position (**14a**): TLC R_f = 0.27 using 50% ether/dichloromethane (*p*-anisaldehyde stain); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.04 (d, 1 H, J = 1.7 Hz), 6.96 (dd, 1 H, J = 8.3 and 1.7 Hz), 6.83 (d, 1 H, J = 8.1 Hz), 4.79 (s, 1 H), 3.89 (s, 3 H), 3.65–3.25 (br m, 4 H), 2.00–1.70 (m, 4 H); IR (neat/NaCl) 3067, 2951, 2878, 2834, 1651, 1591, 1515, 1441, 1339, 1260, 1234, 1192, 1154, 1142, 1102, 1027, 978, 915, 871, 806, 761, 718, 687, 667 cm^{-1}; MS (35 eV) m/e (rel intensity) 279 (M^+, 2), 249 ($M^+ - CH_2O$, 2), 211 (6), 182 (22), 181 ($M^+ - C_5H_9NO$, 100), 166 (24), 165 (17), 151 (22); HRMS (EI) m/e calcd for $C_{15}H_{21}NO_4$ 279.1470, found 279.1435. Anal. Calcd for $C_{15}H_{21}NO_4$: C, 64.88; H, 7.58; N, 5.01. Found: C, 63.88; H, 7.35; N, 4.61.

2-Methoxy-*N*-((3-methoxy-4-(pivaloyloxy)phenyl)-

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acetyl)pyrrolidine (13b). ((3-Methoxy-4-(pivaloyloxy)-phenyl)acetyl)pyrrolidine (**12b**) (0.251 g/0.79 mmol) was electrolyzed at a constant current of 10.5 mA until 2 F of charge had been passed. The electrolysis led to the formation of 0.225 g (82%) of the methoxylated amide: TLC R_f = 0.4 using 50% ether/dichloromethane (*p*-anisaldehyde stain); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.01–6.80 (m, 3 H), 5.47 (d, $^1/_2$ H, J = 4.8 Hz, methine proton α to OCH_3 for one of the amide rotomers), 5.01 (d, $^1/_2$ H, J = 4.5 Hz, methine proton α to OCH_3 for one of the amide rotomers), 3.80 and 3.79 (2 s, 3 H, methyl ethers on the aryl ring for both amide rotomers), 3.74 and 3.65 (2 s, 2 H, benzylic methylene for both amide rotomers), 3.75 and 3.30 (2 m, 2 H), 3.39 and 3.32 (2 s, 3 H), 2.20–1.62 (m, 4 H), 1.36 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.2, 171.4, 171.0, 151.5, 151.4, 139.3, 133.7, 133.1, 122.8, 122.6, 121.4, 121.3, 113.3, 113.2, 88.7, 87.3, 56.6, 55.8, 53.8, 46.2, 45.8, 42.0, 40.9, 38.9, 31.2, 30.6, 26.0, 22.7, 20.8; IR (neat/NaCl) 3052, 2973, 2938, 2874, 1754, 1642, 1632, 1604, 1511, 1480, 1451, 1433, 1397, 1367, 1340, 1321, 1270, 1202, 1149, 1115, 1034, 891, 733 cm^{-1}; MS (PCI) m/e (rel intensity) 349 (M^+, 1), 318 (M^+ – MeO, 100), 233 (318 – C_5H_9O, 20), 232 (100); MS (70 eV) 318 (M^+ – MeO, 1), 317 (M^+ – MeOH, 33), 233 (318 – C_5H_9O, 7), 164 (33), 137 (36), 92 (22), 69 (99), 57 (100); HRMS (EI) m/e calcd for $C_{19}H_{27}NO_5$ 349.1889, found 349.1900.

2-Methoxy-*N*-((3,5-dimethoxy-4-(pivaloyloxy)phenyl)-acetyl)pyrrolidine (13c). ((3,5-Dimethoxy-4-(pivaloyloxy)-phenyl)acetyl)pyrrolidine (**13c**) (0.318 g, 0.91 mmol) was electrolyzed at a constant current of 10.5 mA until 2 F of charge had been passed. The electrolysis led to the formation of 0.20 g (58%) of the isolated methoxylated product along with 0.082 g (26%) of recovered starting material. The spectral data for the product were: TLC R_f = 0.25 using 70% ether/dichloromethane (*p*-anisaldehyde stain); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.55 and 6.53 (2 s, 2 H), 5.48 (d, $^1/_2$ H, J = 4.8 Hz, methine proton α to the OCH_3 in one amide rotomer), 5.01 (d, $^1/_2$ H, J = 4.5 Hz, methine proton α to the OCH_3 in one amide rotomer), 3.78 (s, 6 H), 3.72 (d, 1 H, J = 2.3 Hz, benzylic methylene protons for one amide rotomer), 3.64 (s, 1 H, benzylic methylene protons for one amide rotomer), 3.72–3.35 (v br m, 2 H), 3.40 and 3.32 (2 s, 3 H), 2.23–1.65 (br m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.8, 171.4, 170.0, 152.5, 152.4, 133.1, 132.5, 128.1, 105.9, 105.8, 88.6, 87.3, 56.5, 56.1, 53.8, 46.2, 45.8, 42.6, 41.7, 38.9, 31.2, 30.5, 27.0, 22.7, 20.8; IR (neat/NaCl) 3057, 2972, 2938, 2882, 2840, 1754, 1655, 1604, 1508, 1462, 1424, 1404, 1365, 1340, 1279, 1245, 1205, 1127, 1085, 936, 816, 759, 734, 613 cm^{-1}; MS (35 eV) m/e (rel intensity) 379 (M^+, 1), 348 (M^+ – OMe, 1), 347 (M^+ – MeOH, 3), 263 (10), 197 (13), 195 (6), 194 (45), 167 (23), 128 (18), 86 (18), 85 (23), 69 (80); HRMS (EI) m/e calcd for $C_{20}H_{29}NO_6$ 379.1995, found 379.1960. Analysis data was obtained after cyclization because the methoxylated amide decomposed with time.

2-Methoxy-*N*-(3-(3-methoxyphenyl)propanoyl)pyrrolidine (16). In the best case the electrolysis was carried out using 0.030 g (0.11 mmol) of (3-(3-methoxyphenyl)propanoyl)pyrrolidine (**15**) and constant current conditions (7.5 mA/3.5 F). The electrolysis yielded 0.010 g (30%) of the methoxylated product and 0.007 g (ca. 23%) of the starting material. When the reaction was scaled up the current efficiency of the reaction dropped even more dramatically. In this experiment, 0.112 g (0.48 mmol) of amide **15** was electrolyzed at a constant current of 7.5 mA until 6.3 F of current had been passed. The electrolysis led to the formation of 0.023 g (18%) of the methoxylated product and 0.051 g (45%) of the recovered starting material. Conditions for the oxidation of **15** that afforded mass balances and yields of oxidized product comparable to the other cases studied were not found. The spectral data for methoxylated product **16** were as follows: TLC R_f = 0.5 using ether as eluant (*p*-anisaldehyde stain); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22 (t, 1 H, J = 7.8 Hz), 6.84–6.74 (m, 3 H), 5.46 (d, $^1/_2$ H, J = 4.7 Hz, methine proton α to OMe for one of the amide rotomers), 4.85 (d, $^1/_2$ H, J = 4.6 Hz, methine proton α to OMe for one of the amide rotomers), 3.79 (s, 3 H), 3.65–3.23 (m, 2 H), 3.65 and 3.23 (2 s, 3 H, methyl ether on the pyrrolidine ring for both amide rotomers), 3.10–2.90 (m, 2 H), 2.80–2.57 (m, 2 H), 2.10–1.60 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) 172.7, 172.5, 159.8, 143.2, 143.0, 129.5, 120.8, 114.2, 114.1, 111.4, 88.6, 87.0, 56.3, 54.9, 53.8, 45.8, 45.3, 36.3, 35.7, 31.2, 31.1, 30.6, 30.5, 22.6, 20.7; IR (neat/NaCl) 2926, 1656, 1601, 1415, 1262, 1154, 1083 cm^{-1}; GCMS (35 eV) m/e (rel intensity) 231 (M^+ – MeOH, 2), 135 (231 – C_5H_8NO, 5), 121 (C_8H_9O, 13), 91 (4), 79 (2), 78 (1), 77 (3), 70 (6), 69 (C_4H_7O, 100); HRMS (EI) m/e calcd for $C_{15}H_{21}NO_3$ – OCH_3, 232.1337, found 232.1324; calcd for $C_{15}H_{21}NO_3$ – $HOCH_3$ 231.1259, found 231.1264.

General Procedure for Constant Potential Electrolysis: Synthesis of 2-Methoxy-*N*-(4-pentenoyl)pyrrolidine (7). To a cool, oven-dried 25-mL 3-necked flask was added 78 mg (0.51 mmol) of compound **6**, 1.5 g (5 mmol) of tetraethylammonium tosylate, 0.5 mL of methanol, and 4.5 mL of acetonitrile. The reaction was degassed by sonication for 5 min. The flask was then fitted with two carbon rod electrodes and a Ag/AgCl reference electrode. The electrodes were arranged such that the anode was placed into the reaction through the center neck of the flask, and the reference electrode was as close to the anode as possible. The reaction was then electrolyzed at a constant potential of +1.65 V. After 2 F of charge had been passed, the reaction was concentrated in vacuo and then immediately chromatographed through silica gel using 20% ether/dichloromethane as eluant to afford 74 mg (79%) of the methoxylated product along with ca. 10 mg (13%) of the recovered starting material: TLC R_f = 0.41 using ether (*p*-anisaldehyde stain); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.96–5.82 (m, 1 H), 5.46 (d, 0.5 H, J = 4.9 Hz, methine proton α to OMe for one of the amide rotomers), 5.10 (d, 0.5 H, J = 1.6 Hz, methine proton α to OMe for one of the amide rotomers), 5.04–4.98 (m, 2 H), 3.68–3.55 (m, 2 H), 3.39, 3.30 (2 s, 3 H), 2.57–2.38 (m, 4 H), 2.22–1.63 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.4, 173.2, 138.2, 138.0, 115.6, 115.5, 89.1, 87.4, 56.7, 54.2, 46.3, 45.7, 34.1, 33.5, 31.6, 31.1, 29.2, 28.7, 23.0, 21.1; GCMS (35 eV) m/e (rel intensity) 169 (M^+, 0.6), 168 (M^+ – 1, 6), 151 (8), 138 (M^+ – OCH_3, 1), 128 (3), 86 (12), 85 (9), 70 (100), 69 (97), 68 (66).

Methyl 2-Methoxy-2-(3-methoxyphenyl)acetate (5). Compound **5** was generated from methyl (3-methoxyphenyl)acetate using the constant potential conditions described above. The spectral data for the slightly impure product were as follows: TLC R_f = 0.65 using 50% ether/dichloromethane (*p*-anisaldehyde stain); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (t, 1 H, J = 7.9 Hz), 7.04–6.99 (m, 2 H), 6.91–6.87 (m, 1 H), 4.76 (s, 1 H), 3.82 (s, 3 H), 3.72 (s, 3 H), 3.41 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) 171.4, 160.1, 137.7, 129.8, 119.8, 114.8, 112.3, 82.4, 57.2, 55.2, 52.3; IR (neat/NaCl) 2999, 2952, 2836, 1748, 1600, 1489, 1434, 1258, 1177, 1109, 1039, 1014 cm^{-1}; MS (70 eV) m/e (rel intensity) 210 (M^+, 1), 151 (M^+ – CO_2CH_3, 100), 136 (151 – CH_3, 13), 108 (22), 91 (17), 65 (7); HRMS (EI) m/e calcd for $C_{11}H_{14}O_4$ 210.0892, found 210.0898.

Competition Experiment between Methyl (3-Methoxyphenyl)acetate (4) and 4-Pentenoylpyrrolidine (6). To a cool, oven-dried 25-mL 3-neck flask were added 88 mg (0.49 mmol) of **4**, 1.5 g (5 mmol) of tetraethylammonium tosylate, and then a solution of 76 mg (0.49 mmol) of **6** in 0.5 mL of methanol and 4.5 mL of acetonitrile. The reaction was degassed by sonication for 5 min, and then the flask was fitted with two carbon rod electrodes and a reference electrode as described earlier. The reaction was electrolyzed at a constant potential of +1.65 V. After 2 F of charge had been passed, the reaction mixture was concentrated in vacuo and then immediately chromatographed through silica gel using 50% ether/dichloromethane as eluant. The reaction afforded 65 mg (74%) of **4**, 14 mg (13%) of **5**, 37 mg (49%) of **6**, and 40 mg (45%) of **7**.

Competition Experiment between Methyl (4-Methoxyphenyl)acetate and 4-Pentenoylpyrrolidine (6). This competition experiment was run in a fashion identical with the one reported above. In this case, silica gel chromatography led to the isolation of 64 mg of a 2.2:1 mixture of the monooxidized methyl 2-methoxy-2-(4-methoxyphenyl)acetate and the dioxidized methyl 2,2-dimethoxy-2-(4-methoxyphenyl)acetate. NMR analysis of this mixture indicated that ca. 42 mg (40% yield) of the mixture was the monoxidized product while ca. 22 mg (18% yield) of the mixture was the dioxidized product. In addition, 34 mg (37%) of the starting ester was isolated from the competition experiment along with 59 mg (77%) of starting amide **6** and a small amount (ca. 4 mg, 4%) of the amide methoxylation product **7**. The spectral data for the mixture of benzylic oxidation products were as follows: TLC R_f = 0.33 in dichloromethane (*p*-anisaldehyde stain); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (d, 2 H, J = 8.6 Hz, dimethoxylated product), 7.37 (d, 2 H, J = 8.8 Hz, monomethoxylated product), 6.91 (d, 2 H, J = 8.6 Hz, both products), 4.73 (s, 1 H, benzylic methine proton in the monomethoxylated product), 3.81

(s, 3 H, aryl methoxy group in both products), 3.72 (s, 3 H, methyl ester protons in both products), 3.38 (s, 3 H, monomethoxylated product), 3.30 (s, 6 H, dimethoxylated product); ^{13}C NMR (75 MHZ, $CDCl_3$) 171.6, 169.8, 160.2, 128.7, 128.2, 114.1, 113.7, 101.5, 81.9, 56.9, 55.1, 52.7, 52.1, 50.1; IR (neat/NaCl) 3000, 2952, 2837, 1750, 1611, 1512, 1248, 1173, 1106 cm^{-1}; GCMS for the monomethoxylated product (35 eV) m/e (rel intensity) 210 (M^+, 2), 151 ($M^+ - CO_2CH_3$, 100), 136 (151 - CH_3, 20), 135 (151 - CH_4, 38), 108 (16), 91 (11), 77 (14); GCMS for the dimethoxylated product (35 eV) m/e (rel intensity) 209 ($M^+ - OCH_3$, 5), 181 ($M^+ - CO_2CH_3$, 80), 135 (181 - C_2H_6O, 100), 92 (14), 77 (28), 59 (32).

$TiCl_4$ Cyclization Reactions. General Procedure: Synthesis of 1,2,3,5,6,10b-Hexahydro-8-methoxy-5-oxopyrrolo[2,1-*a*]isoquinoline (17a) and 1,2,3,5,6,10b-Hexahydro-10-methoxy-5-oxopyrrolo[2,1-*a*]isoquinoline (18a). To a -78 °C solution of 102 mg (0.41 mmol) of methoxylated amide **2a** in 0.78 mL of dichloromethane was added 0.126 mL (1.15 mmol) of titanium tetrachloride (99.9%). After stirring at -78 °C for 1 h, the reaction mixture was allowed to warm to room temperature and then quenched with 2 mL of saturated potassium carbonate. The reaction mixture was stirred for 20 min, and then the water and organic layers were separated. The aqueous layer was extracted 8–10 times with dichloromethane, and the combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The crude reaction was chromatographed through silica gel using 50% ether/dichloromethane as eluant to afford 64.4 mg (72%) of a 2.9:1 (assigned by capillary column GC analysis) ratio of **17a**:**18a**. Careful chromatography led to separation of the two isomers. The spectral data for the major isomer, **17a**, were as follows: TLC R_f = 0.2 using 50% ether/dichloromethane (*p*-anisaldehyde stain); ^1H NMR (300 MHz, $CDCl_3$) δ 7.11 (d, 1 H, J = 9.3 Hz), 6.80 (dd, 1 H, J = 9.3 and 5.4 Hz), 6.72 (d, 1 H, J = 5.4 Hz), 4.58 (m, 1 H), 3.80 (s, 3 H), 3.85–3.36 (m, 4 H), 2.62 (p, 1 H, J = 5.7 Hz), 2.19–1.80 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) 167.6, 159.2, 134.5, 128.6, 125.1, 112.4, 112.3, 59.0, 55.1, 44.4, 38.7, 31.7, 22.9; IR (neat/NaCl) 3040, 3020, 2960, 2940, 2880, 2840, 1700, 1660, 1520, 1460, 1330, 1320, 1040 cm^{-1}; MS (35 eV) m/e (rel. intensity) 218 (M^+ + 1, 6), 217 (M^+, 33), 216 (M^+ - 1, 45), 189 (15), 186 ($M^+ - CH_3O$, 10), 185 (M^+ - MeOH, 3), 151 (53), 149 ($M^+ - C_4H_8N$, 13), 148 (22), 110 (15), 83 (25), 71 (100); HRMS (EI) m/e calcd for $C_{13}H_{15}NO_2$ 217.1103, found 217.1111. The spectral data for the minor isomer, **18a**, were as follows: mp = 134–136 °C; TLC R_f = 0.4 using 50% ether/dichloromethane (*p*-anisaldehyde stain); ^1H NMR (300 MHz, $CDCl_3$) δ 7.22 (app t, 1 H, J_{av} = 7.6 Hz), 6.78 (d, 1 H, J = 7.6 Hz), 6.77 (d, 1 H, J = 7.6 Hz), 4.58 (m, 1 H), 3.83 (s, 3 H), 3.61 (s, 2 H), 3.77–3.47 (m, 2 H), 2.96 (p, 1 H, J = 5.7 Hz), 2.11–1.60 (m, 3 H); IR (neat/NaCl) 3020, 2940 br, 1700, 1600, 1560, 1480, 1420, 1330, 1290, 1120, 1080, 1010, 990, 950 cm^{-1}; MS (35 eV) m/e (rel intensity) 218 (M^+ + 1, 14), 217 (M^+, 33), 216 (M^+ - 1, 100), 189 (50), 186 ($M^+ - CH_3O$, 25), 185 (M^+ - MeOH, 3), 161 (64), 160 (96); HRMS (EI) m/e calcd for $C_{13}H_{15}NO_2$ 217.1103, found 217.1103. Anal. Calcd for $C_{13}H_{35}NO_2$: C, 71.86; H, 6.96; N, 6.45. Found: C, 71.15; H, 7.01; N, 6.20.

1,2,3,5,6,10b-Hexahydro-9-hydroxy-8-methoxy-5-oxopyrrolo[2,1-*a*]isoquinoline (17b). Using the conditions described above, 45 mg (0.13 mmol) of the methoxylated amide **13b** was cyclized to afford 24 mg (59%) of the tricyclic amide **17b**: mp 237.8–239.1 °C; TLC R_f = 0.3 using 10% methanol/ether (*p*-anisaldehyde stain); ^1H NMR (300 MHz, $CDCl_3$) δ 6.78 (s, 1 H), 6.65 (s, 1 H), 5.71 (br s, 1 H), 4.59–4.52 (m, 1 H), 3.89 (s, 3 H), 3.73–3.44 (m, 4 H), 2.92 (m, 1 H), 2.20–1.79 (m, 3 H); IR (neat/NaCl) 3260, 3080, 2980, 2952, 2926, 1622, 1592, 1518, 1457, 1437, 1409, 1365, 1336, 1312, 1281, 1243, 1216, 1204, 1167, 1123, 1094, 1020, 981, 939, 886, 862, 847, 772, 739, 710, 667 cm^{-1}; MS (35 eV) m/e (rel intensity) 234 (M^+ + 1, 10), 233 (M^+, 69), 232 (M^+ - 1, 77), 218 (M^+ - Me, 4), 217 (4), 216 (12), 205 (17), 191 (6), 176 (100), 163 (23); HRMS (EI) m/e calcd for $C_{13}H_{15}NO_3$ 233.1052, found 233.1068. Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.22; H, 6.48; N, 5.91.

1,2,3,5,6,10b-Hexahydro-8,10-dimethoxy-9-hydroxy-5-oxopyrrolo[2,1-*a*]isoquinoline (17c). Using the conditions described above, 31 mg (0.08 mmol) of methoxylated amide **13c** was cyclized to afford 26 mg (90%) of the desired tricyclic amide compound **17c**: mp 177.3–179.9 °C; TLC R_f = 0.28 using 10% methanol/ether (*p*-anisaldehyde stain); ^1H NMR (300 MHz, $CDCl_3$) δ 6.43 (s, 1 H), 5.67 (br s, 1 H), 4.62–4.55 (m, 1 H), 3.90 (s, 3 H), 3.89 (s, 3 H), 3.71–3.45 (m, 4 H), 2.82 (m, 1 H), 2.15–1.70 (m, 3 H); IR (neat/NaCl) 3350, 3015, 2925, 2849, 1631, 1454, 1426, 1415, 1343, 1315, 1282, 1208, 1186, 1154, 1120, 1108, 1077, 1067, 1029, 1009, 948, 911, 902, 844, 834, 647, 628, 611 cm^{-1}; MS (35 eV) m/e (rel intensity) 264 (M^+ + 1, 8), 263 (M^+, 52), 248 (M^+ - Me, 6), 235 (27), 232 (M^+ - MeO, 23), 206 (100), 192 (11); HRMS (EI) m/e calcd for $C_{14}H_{17}NO_4$ 263.1158, found 263.1142.

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Supplementary Material Available: ^1H and ^{13}C NMR spectra for **1c**, **2c**, **3b**, **6**, **7**, **13b**, **13c**, **15**, **16** and **17a** (20 pages). Ordering information is given on any current masthead page.