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Oxidative Synthesis of Cyclic Acyl Aminals through Carbon–Carbon σ-Bond Activation

Danielle L. Aubele and Paul E. Floreancig*

Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260

florean+@pitt.edu

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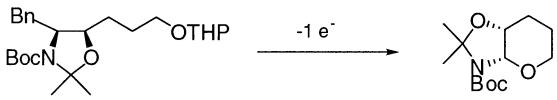
ABSTRACT



Acyliminium ions can be prepared through photoinitiated single-electron oxidation reactions of homobenzylic amides and carbamates. Cyclic acyl aminals are formed when these acyliminium ions are appended to nucleophiles such as hydroxyl, ether, and sulfonamide groups. The scope of these reactions is discussed along with mechanistic issues relating to the energetics, chemoselectivity, and stereoelectronic effects of bond activation.

Acyliminium ions have proven to be useful and versatile intermediates in organic synthesis,[1] serving as both potent electrophiles and initiators of sigmatropic rearrangement reactions. Conventional routes to form acyliminium ions employ either acid-mediated condensation reactions of primary amides and carbamates into aldehydes or solvolysis reactions of α-halo-, -alkoxy-, or -acetoxy-substituted amides.[2] Pioneering studies by Shono, Moeller, Yoshida, Mariano, and others[3−6] have shown that oxidative conditions can be employed to form acyliminium ions from *N*-acyl amino acids,[3] α-trialkylstannylalkyl amides,[4] α-trimethylsilylalkyl amides,[5] and even nonfunctionalized tertiary amides.[6] In addition to offering greater flexibility in acyliminium ion precursor selection, oxidative protocols have been shown to be efficacious for reactions in which substrates are not stable toward standard reaction conditions. We recently reported[7] a new cyclization reaction that proceeds through oxidatively generated oxonium ions. This carbon−carbon σ-bond activation process is initiated by photoinduced (medium-pressure mercury lamp, Pyrex filtration) single-electron oxidation reactions of homobenzylic ethers that contain pendent hydroxy and alkoxy groups (Figure 1). The selectivity for carbon−carbon bond activation in preference to carbon−hydrogen bond activation in these reactions can be attributed to the ability of the alkoxy group to stabilize the incipient cationic character at the homobenzylic position of the intermediate radical cation,[8] presaging that other electron-

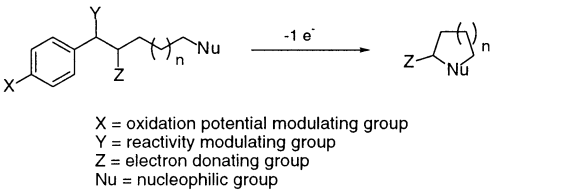


Figure 1. Generalized depiction of ETIC reactions.

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(2) Speckamp, W. N.; Hiemstra, H. *Tetrahedron* **1985**, *41*, 4367.
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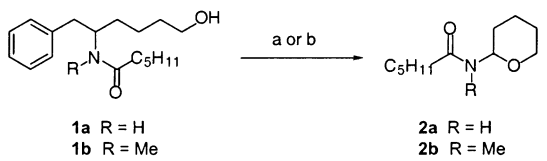
donating substituents could serve in the same capacity. In conjunction with our efforts to expand the scope of these electron transfer initiated cyclization (ETIC) reactions, we have demonstrated that homobenzylic amide and carbamate groups are also effective promoters of carbon−carbon bond activation, leading to a new oxidative route to acyliminium ions. In this communication we report electron transfer initiated cyclization reactions to form (*N*,*O*)- and (*N*,*N*)-acylaminals, discuss the mechanism and stereochemical outcomes of the reactions, and demonstrate the importance of electronic interactions and orbital overlap in predicting the reaction pathways for the intermediate radical cations.

We prepared substrate **1a** in order to test the ability of homobenzylic amide groups to serve as promoters of carbon−carbon bond activation. Exposing **1a** to stoichiometric oxidative cyclization conditions (*hν*, 2 equiv of *N*-methylquinolinium hexafluorophosphate ($NMQPF_6$), NaOAc, toluene, 1,2-dichloroethane) provided (*N*,*O*)-acylaminal **2a** in 86% yield (Figure 2).[9] Conducting the reaction under our



Reagents and conditions
a) *hν*, $NMQPF_6$, NaOAc, *tert*-butylbenzene, 1,2-dichloroethane, 86% for **2a**, 55% for **2b**. b) *hν*, $NMQPF_6$, O_2, NaOAc, $Na_2S_2O_3$, toluene, 1,2-dichloroethane, 75% for **2a**, 71% for **2b**.

Figure 2. Amides as electron-donating groups in ETIC reactions.

catalytic aerobic conditions[10] (*hν*, 0.025 equiv of $NMQPF_6$, O_2 aeration, NaOAc, $Na_2S_2O_3$, toluene, 1,2-dichloroethane) resulted in the isolation of **2a** in 75% yield. We employed the catalytic protocol for subsequent cyclization reactions because of the comparable efficiency and the significant facilitation of product purification that results from minimizing aromatic waste production. Tertiary amides are also competent substrates in these reactions, with **1b** undergoing cyclization to provide **2b** in 71% yield.

Our initial efforts at establishing the displacement mechanism and studying the functional group compatibility of these reactions are represented in Table 1. Alkyl groups are tolerated at the bis-homoallylic position for both secondary and tertiary amides. Regardless of whether substrates were single diastereomers or mixtures of diastereomers, the stereochemical outcomes of these reactions were identical (entries 2 and 3). These results are consistent with a mechanism in which discrete acyliminium ions are formed from mesolytic cleavages of benzylic carbon−carbon bonds in the substrate radical cations, in preference to the radical

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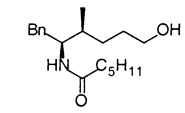
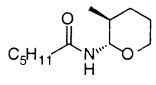
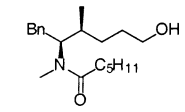
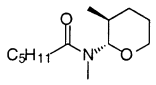
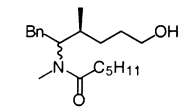
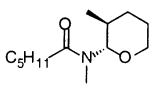
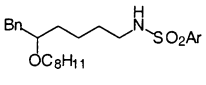
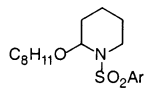
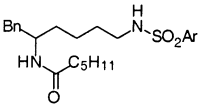
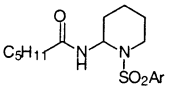
Table 1. Examples of Nitrogen Group Incorporation into ETIC Cyclizations[a]

Entry	Substrate	Product	Yield (%)	D.R.[b]
1	 **3**	 **4**	75	2:1
2	 **5**	 **6**	67	>19:1
3[c]	 **7**	 **6**	56	>19:1
4[d]	 **8**	 **9**	68	
5[d]	 **10**	 **11**	64	

[a] Reaction conditions: *hν*, $NMQPF_6$ (2.5 mol %), O_2, NaOAc, $Na_2S_2O_3$, DCE, PhMe. [b] Diastereomeric ratio. The major diastereomer is shown in the product column. Stereochemical assignments were based on ^1H NMR coupling constants. [c] 1:1 mixture of diastereomers. [d] Ar = *p*-$NO_2C_6H_4$.

cations undergoing associative, S_N2-type reactions. To discount the possibility that the observed product ratios could be ascribed to reaction through the associative pathway followed by equilibration, we resubjected both diastereomerically pure **4** and its *syn* diastereomer to the reaction conditions. While a small (approximately 10%) amount of epimerization was observed upon prolonged exposure, the rate was not sufficient to account for the observed product ratios. Cyclization of tertiary amides **5** and **7** were exceptionally stereoselective. We attribute this result to the enhanced allylic strain in conformer **12** relative to **13** (Figure 3).

In addition to hydroxyl groups, sulfonamides proved to be effective nucleophiles in these reactions (entries 4 and

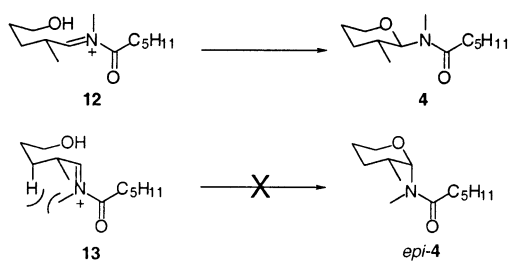


Figure 3. Stereocontrol in tertiary amide cyclizations.

5). The *p*-nitrobenzenesulfonamide group was selected because of its high oxidation potential and ease of cleavage.[11] Acyl aminal groups related to those in **9** and **11** are present in numerous aza-sugars that function as potent glycosidase inhibitors.[12]

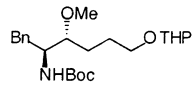
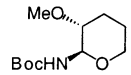
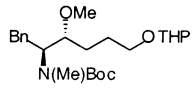
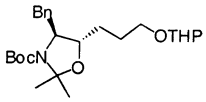
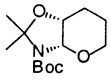
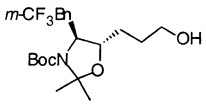
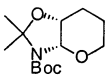
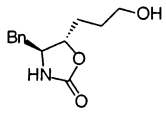
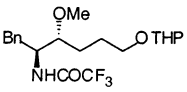
Incorporating oxygen-containing functional groups at the bis-homobenzylic position would provide a desirable increase in the utility of this method for complex molecule synthesis. Placing inductively electron-withdrawing groups in this position, however, will exert a detrimental effect on the reactivity of the intermediate radical cation. The relationship between structure and benzylic carbon−carbon bond strength in the radical cations of these substrates is expressed in eq 1.[13] In this relationship, BDE_{RC} defines the mesolytic bond dissociation energy of the benzylic carbon−carbon bond in the radical cation, BDE_S defines the homolytic bond dissociation energy of the same bond in the neutral substrate, OP_S defines the oxidation potential of the substrate, and OP_E defines the oxidation potential of the amidoalkyl radical that would result from a homolytic cleavage of the benzylic carbon−carbon bond. Therefore, increasing the oxidation potential of the amidoalkyl radical by adding an inductively electron withdrawing group is expected to increase BDE_{RC} and retard cyclization.

$$BDE_{RC} = BDE_S - OP_S + OP_E \qquad (1)$$

As shown in Table 2, alkoxy groups are tolerated for secondary amides but not tertiary amides. Acyloxazolidines are particularly effective substrates for these reactions, but cyclic carbamates do not react under our conditions (entries 3−5). We attribute this difference to the greater electron-withdrawing capacity of an acyloxy group relative to that of an alkoxy group, as predicted by eq 1. The failure of trifluoroacetamide **21** (entry 6) to react under these conditions provides further validation of the predictive utility of eq 1. While hydroxy groups and THP-ethers function equally well as nucleophiles, the substrates are often easier to handle as the THP-ether. The excellent diastereoselectivity observed in the cyclization of oxazolidines **17** and **19** was expected on the basis of the kinetic preference[14] of annulation reactions to provide *cis* ring junctions.

The efficient cyclization of oxazolidine **17** in contrast to the decomposition of methoxy-substituted tertiary carbamate **16** merits comment. The formation of the THP-ether of methyl 4-hydroxybutyrate from the oxidation of **16** indicates that homobenzylic carbon−carbon bond activation is a prominent reaction pathway for this substrate. This result is consistent with oxidation of the amide group in preference to the arene, in accord with the oxidation potentials of tertiary amides and carbamates being approximately 0.5 V lower than both secondary amides and carbamates[15] and monoalkylarenes.[16] Upon formation of the amide radical cation, both the benzylic and the homobenzylic carbon−carbon bonds are activated toward fragmentation (Figure 4). For **16** the preferred pathway appears to be cleavage of the homobenzylic carbon−carbon bond. Although σ-bonds between alkyl groups and benzyl groups are, in general, weaker than

Table 2. Incorporation of Oxygen-Containing Functional Groups at the Bis-Homobenzylic Position[a]

Entry	Substrate	Product	Yield (%)	D.R.[b]
1	 **14**	 **15**	63	2:1
2	 **16**	Decomposition		
3	 **17**	 **18**	88	>19:1
4	 **19**	 **18**	56	>19:1
5	 **20**	No Reaction		
6	 **21**	No Reaction		

[a] Reaction conditions: *hν*, $NMQPF_6$ (2.5 mol %), O_2, NaOAc, $Na_2S_2O_3$, DCE, PhMe. [b] Diastereomeric ratio. The major diastereomer is shown in the product column. Stereochemical assignments were based on ^1H NMR coupling constants.

(9) All new compounds were characterized by ^1H NMR, ^{13}C NMR, IR, and HRMS. See Supporting Information for details.

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(11) Fukuyama, T.; Jow, C.-K.; Cheung, M. *Tetrahedron Lett.* **1995**, *36*, 6373.

(12) (a) Ganem, B. *Acc. Chem. Res.* **1996**, *29*, 340. (b) Nishimura, Y.; Shitara, E.; Takeuchi, T. *Tetrahedron Lett.* **1999**, *40*, 2351. (c) Umezawa, H.; Aoyagi, T.; Komiyama, H.; Morishima, H.; Hamada, M.; Takeuchi, T. *J. Antibiot.* **1974**, *27*, 963.

(13) Popielarz, R.; Arnold, D. R. *J. Am. Chem. Soc.* **1990**, *112*, 3068.

(14) For example, see: Seebach, D.; Lamatsch, B.; Amstutz, R.; Beck, A. K.; Dobler, M.; Egli, M.; Fitzi, R.; Gautschi, M.; Herradon, B.; Hidber, P. C.; Irwin, J. J.; Locher, R.; Maestro, M.; Maetzke, T.; Mauriño, A.; Pfammater, E.; Plattner, E.; Schickli, C.; Schweizer, W. B.; Seiler, P.; Stucky, G. *Helv. Chim. Acta* **1992**, *75*, 913.

(15) Reed, R. C.; Wightman, R. M. In *Encyclopedia of Electrochemistry of the Elements*; Bard, A. J., Ed.; Marcel Dekker: New York, 1984; Vol. 15, p 83.

(16) Oxidation potentials of aromatic compounds can be estimated by applying Kochi's empirical relationship to the vertical ionization potential: Howell, J. O.; Goncalves, J. M.; Amatore, C.; Klasinc, L.; Wightman, R. M.; Kochi, J. K. *J. Am. Chem. Soc.* **1984**, *106*, 3698. For an extensive collection of vertical ionization potentials, see: Rosenstock, M.; Draxl, K.; Steiner, B. W.; Herron, J. T. *J. Phys. Chem. Ref. Data* **1977**, *6*, Suppl. 1.

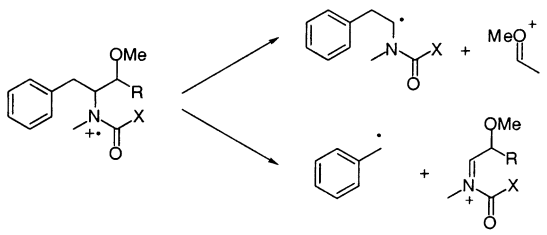

Figure 4. Reaction pathways for amide radical cations.

bonds between alkyl groups and alkoxyalkyl groups,[17] this cleavage can be attributed to the stability of the oxonium ion[18] that forms from homobenzylic bond cleavage.

Arnold, however, has demonstrated[19] that thermodynamic analyses of bond dissociations are valid only when proper orbital alignment can be achieved between the fragmenting carbon−carbon σ-bond and the SOMO and between the oxygen lone pair and the σ^*-orbital of the breaking carbon−carbon bond (Figure 5). Constraining the carbamate group

Figure 5. Ideal geometries for β-alkoxy carbamate radical cation carbon−carbon bond fragmentation.

and the ether oxygen in an oxazolidine ring prohibits these alignments. A model of **17** clearly shows that the dihedral angles between the endocyclic carbon−carbon bond and the carbamate SOMO and between the lone pair of the oxygen in the oxazolidine and the σ^*-orbital of the homobenzylic carbon−carbon bond cannot attain the proper alignment for bond cleavage. The dramatic influence of stereoelectronic effects on the kinetics of radical ion fragmentation processes strongly demonstrates the need for orbital alignment consideration in predicting reaction pathways.

The successful, though somewhat less efficient, cyclization of trifluoromethyl-substituted oxazolidine **19** (Table 2, entry 4) provides additional support for the reaction proceeding through amide oxidation. Incorporating the trifluoromethyl group is expected to increase the oxidation potential of the arene by approximately 0.3 V.[16] This would be expected to inhibit the reaction if the relevant pathway required the formation of the arene radical cation.

We have demonstrated that secondary and tertiary amides and carbamates function as effective homobenzylic substituents in promoting carbon−carbon σ-bond activation of alkylarene radical cations. This process constitutes a new oxidative method for forming acyliminium ions and leads to cyclization reactions to form both (*N*,*O*)- and (*N*,*N*)-acylaminals. Stereocontrol can be accomplished in these reactions when the tertiary amides and acyl oxazolidines are employed as homobenzylic substituents. Tertiary amides appear to be oxidized in preference to monosubstituted arenes, providing alternate fragmentation pathways. The radical cations of cyclic oxazolidines undergo preferential cleavage of the exocyclic carbon−carbon bond over to the endocyclic bond, demonstrating the importance of orbital alignment considerations in predicting the outcomes of these reactions.

Acknowledgment. This work was supported by the University of Pittsburgh and the Research Corporation through a Research Innovation Award. We thank Professor Dennis Curran for helpful discussions.

Supporting Information Available: Synthetic schemes for cyclization substrates and detailed experimental procedures, characterizations, and ^{1}H and ^{13}C NMR spectra for all cyclization products. This material is available free of charge via the Internet at http://pubs.acs.org.

OL026538M

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