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Controlled Oxidation of Pyrroles: Synthesis of Highly Functionalized γ-Lactams

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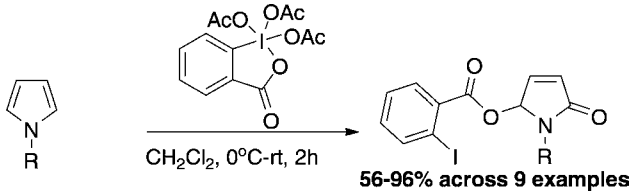
ABSTRACT



The oxidation of pyrroles usually leads to uncontrolled polymerization and decomposition. To overcome this problem, the controlled oxidation of substituted pyrroles with Dess-Martin periodinane is reported. This strategy yields a range of 5-aroyloxypyrrolinones.

Dearomatization of substituted aromatic systems is a powerful and widely used synthetic strategy for the preparation of carbo- and heterocyclic rings.[1,2] This transformation may be achieved by numerous methods including enzymatic,[3] photochemical,[4] radical,[5] transition-metal mediated,[6] reductive[7] (Birch reduction/catalytic hydrogenation), oxidative,[8] or electrochemical[9] approaches. While these processes are most widely applied to aromatic hydrocarbons, the dearomatization of aromatic heterocycles is a powerful method to prepare nonaromatic heterocycles that are ubiquitous in bioactive molecules and natural products. Aromatic heterocycles are attractive building blocks due to their stability and ready availability. This can be exemplified by the ability of pyrroles to undergo substitution followed by partial reduction to pyrrolines[10−12] or catalytic hydrogenation to pyrrolidines (Scheme 1, a and b).[13] The importance of these reductive methods is highlighted by their application in the synthesis of natural products and bioactive molecules, such as hyacinthacine A_1 (**1a**),[14] 1-epiaustraline (**1b**),[15] and anisomycin (**2**).[10b,16]

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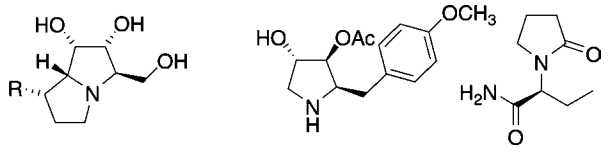


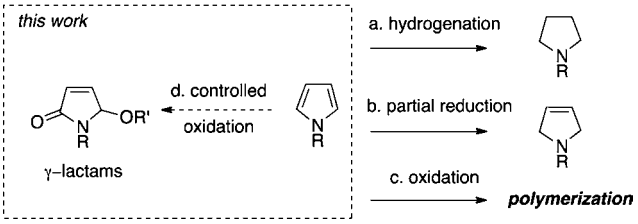
1a R = H, hyacinthacine A_1
1b R = OH, 1-epiaustraline

2 anisomycin

3 levitiracetam

As a compliment to these reductive methods, the oxidation of pyrrole has the potential to yield the important γ-lactam skeleton. The γ-lactam skeleton is a building block for synthesis[17] and possesses useful biological activity.[18] For example, Levitiracetam (**3**) is currently used in the management of epileptic disorders.[19] While there are numerous methods for the synthesis of γ-lactams, these generally require the synthesis of specific acyclic precursors.[20] As such, there is still a need for more general methods to construct γ-lactams from simple, readily available aromatic starting materials.

Scheme 1. Potential Dearomatization Reactions of Pyrroles



Unfortunately, in contrast to the efficient reductive processes, controlled oxidations of pyrrole have been hampered by the propensity for polymerization to occur under oxidizing or acidic conditions, yielding polypyrrole (Scheme 1, c).[21] The handful of reports on the oxidation of pyrrole demonstrated that pyrrolinones can be obtained by the use of singlet oxygen[22,23] and peroxides.[24] These have not been widely adopted as synthetic protocols due to low yields as a result of significant accompanying decomposition. Recently Lubricks et al. have demonstrated a controlled palladium catalyzed acetoxylation of pyrrole with phenyliodonium acetate.[25] During their investigations they observed the formation of pyrrole-2,5-diones and 5-functionalized pyrrolidin-2-ones as overoxidation productions in some instances when the reaction was carried out at elevated temperatures. Alp et al. also reports the oxidation of *N*-tosylpyrrole with 1 equiv of phenyliodine bis(trifluoroacetate) (PIFA) to reveal a γ-lactam species, and a 5-hydroxy-γ-lactam when reacted with 2 equiv of PIFA.[26] However, this reaction was only demonstrated with a *single* electron-poor example and it has also been reported by Kita et al. that the oxidation of electron-rich pyrroles with PIFA/Lewis acid combinations results in the formation of bipyrroles via Scholl oxidation rather than the formation of pyrrolinones.[27]

We envisaged that through judiscious choice of hypervalent iodine reagent and reaction conditions that selective oxidation of readily available electron-rich pyrroles[28] to γ-lactams should be possible. Such a method would avoid the limitation of using a sulfonyl protecting group at nitrogen and provide a compliment to current reductive methods for the synthetic manipulation of pyrroles (Scheme 1, d). Herein, we report a metal-free, controlled oxidation of pyrroles with the Dess-Martin periodinane reagent yielding 5-aroyloxy-γ-lactams.

Initial experiments following the PIFA method of Alp[26] with *N*-methyl pyrrole resulted in the formation of a complex mixture of products in poor and inconsistent yields due to decomposition of the starting material. This outcome was attributed to the high electron density of the *N*-alkyl pyrrole in comparison to the *N*-tosylated species.

Due to the nonselective reactivity of PIFA, alternate hypervalent iodine oxidants were screened and Dess-Martin periodinane was found to be effective. Interestingly, as part of Kita's bipyrrole method development, they found Dess-Martin periodinane to cause decomposition of electron-rich pyrroles.[27] However, we found that when *N*-methylpyrrole (**4a**) was added slowly to 2.5 equiv of Dess-Martin periodinane at 0 °C polymerization was prevented and the 5-aroyloxy-γ-lactam **6a** was formed as the major product after a reductive workup (Table 1). To our surprise the compound contained an *ortho*-iodobenzoyloxy moiety at C5 and only trace amounts of a 5-acetoxy-derivative were observed in the crude NMR. Unlike other oxidations with Dess-Martin periodinane, we see the incorporation of an organic fragment of the oxidant into the product.[29]

We postulate that the slow addition of pyrrole limits polymerization due to its rapid consumption in the

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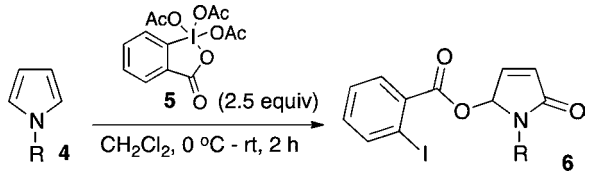
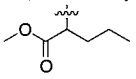
presence of excess oxidant. Using 1 equiv of oxidant with *N*-methylpyrrole results in the formation of the same 5-aroyloxy-γ-lactam **6a** in 31% yield instead of a mono-oxidized product, indicating that the intermediate formed is more reactive and consumed faster than the starting pyrrole. It was also shown that trace amounts of water helped facilitate the reaction, as demonstrated in the comparison of bench grade solvent to anhydrous solvent under a nitrogen atmosphere (81% yield compared to 65% under anhydrous conditions). This is similar to previous oxidations with Dess-Martin periodinane in which trace amounts of water can help to promote the oxidation of alcohols.[30]

A range of *N*-alkyl pyrroles (**4**) were oxidized with the Dess-Martin periodinane reagent (**5**) under our conditions to yield the corresponding 5-aroyloxy-γ-lactams **6** in good to excellent yield (Table 1). Both *N*-alkyl and *N*-aryl substituents are tolerated, and the parent pyrrrole (**4h**) gives the lactam **6h** in a 56% yield. Compound **6g** was formed as a 1:1 mixture of diastereoisomers. Compounds of this type, which can be synthesized in two steps from amino esters, could be used for the synthesis of the anti-epileptic drug levitiracetam and derivatives.

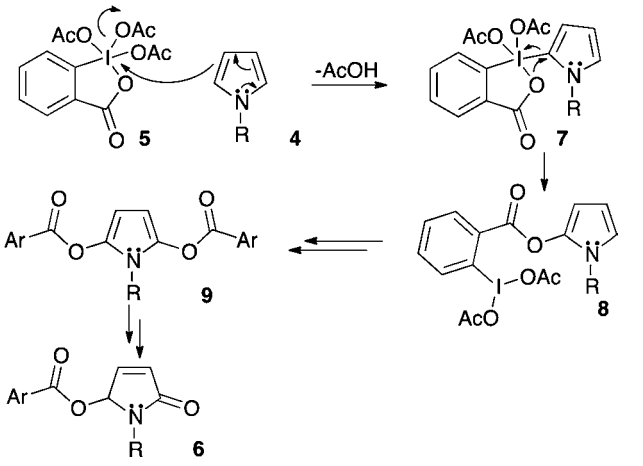
Table 1. Oxidation of Pyrroles to 5-Aroyloxy-γ-lactams with Dess-Martin Periodinane[a]



entry	-R	product	yield
4a	-Me	**6a**	81%
4b	-Et	**6b**	83%
4c	-*p*-C_6H_4-Me	**6c**	88%
4d	-*p*-C_6H_4-OMe	**6d**	93%
4e	-CH_2-(*p*-C_6H_4-Me)	**6e**	93%
4f	-2-(3,4-dimethyoxyphenyl)ethyl	**6f**	96%
4g		**6g**	88%
4h	-H	**6h**	56%

Based upon the results of Lubricks[25] that showed pyrroles react with phenyliodonium acetate to form an iodonium intermediate, we postulated a similar mechanism (Scheme 2). The electrophilic aromatic substitution of pyrrole onto the iodine atom of Dess-Martin periodinane would give a similar intermediate **7** to that reported by Lubriks. This can be followed by a selective migration of the oxygen atom of the benzoate onto C2 of the pyrrole to give **8**. Once formed, the electron-rich intermediate **8** is more reactive than the starting pyrrole and substitution is repeated to form 2,5-diaroyloxypyrrole **9** as an intermediate that is either hydrolyzed *in situ* or upon reductive workup. Attempts to follow the reaction by ^{1}H NMR and IR to observe either an iodonium intermediate or the 2,5-diaroyloxypyrrole intermediates were not successful, as only the starting material and the resonances of the pyrrolinone system were visible. This indicates that the reaction intermediates are short-lived on the NMR time scale and that the 2,5-diaroyloxypyrrole **9** intermediate is hydrolyzed *in situ*, as the product pyrrolinone **6a** had formed before aqueous workup.

Scheme 2. Proposed Mechanism of Oxidation with Dess-Martin Periodinane

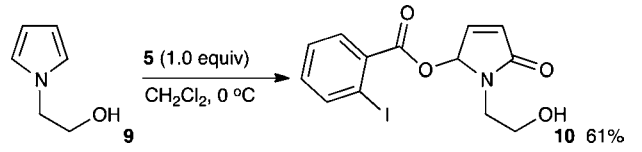


While the proposed mechanism is plausible, there is one clear curiosity. The addition of trace amounts of water to the Dess-Martin periodinane is believed to aid in the dissociation of an acetate group from the iodine core making iodine more electrophilic.[30] This would help promote the attack of the electron-rich pyrroles to form an iodonium intermediate. However, what is not clear is why migration of the benzoate O-atom would be favored almost exclusively over one of the acetate groups. Trace amounts of the acetoxy species are always observed; however, this is proposed to form from the *in situ* generation of acetic acid, which exchanges for the benzoate group. Support for this hypothesis is seen when the benzoate lactam is stirred in AcOH/CH_2Cl_2 to slowly produce the acetoxylated product. An alternative mechanism would be the direct attack of the electron-rich pyrrole on the benzoate O-atom of the Dess-Martin periodinane; however, there is no precedent for such a reaction.

The Dess-Martin periodinane is commonly used to oxidize primary and secondary alcohols to their corresponding carbonyls,[29,30] so, as a competitive oxidation, *N*-(2-hydroxyethyl)pyrrole (**9**) was subjected to the oxidative reaction conditions. Interestingly, the 5-aroyloxy-γ-lactam **10** with the alcohol functionality still intact was the major product when treated with 1 equiv of oxidant. This gives further evidence to the reactivity of pyrroles toward Dess-Martin periodinane, indicating a selectivity over alcohols (Scheme 3).

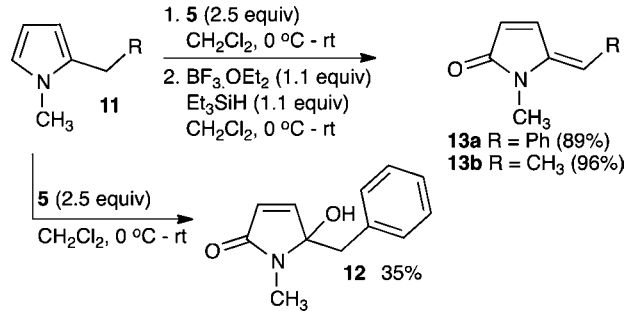
(30) Meyer, S.; Schreiber, S. *J. Org. Chem.* **1994**, 7549.

Scheme 3. Chemoselective Oxidation of Pyrrole over a Primary Alcohol with Dess-Martin Periodinane



The method has also been expanded to the oxidation of 2-substituted pyrroles. Initial oxidations of 2-benzyl-*N*-methyl pyrrole (**11a**, R = Ph) proceeded to give the 5-benzyl-5-hydroxy-γ-lactam **12** in only 35% isolated yield. As this decrease in yield was due to the instability of **12** during isolation, an attempted *in situ* hydroxyl group reduction with $BF_3 \cdot OEt_2/Et_3SiH$ was employed. However, alkene **13a** (R = Ph) was provided in 89% yield (Scheme 4). This two-step methodology was also applied to 2-ethyl-*N*-methyl pyrrole (**11**, R = CH_3), resulting in the corresponding product (**13**, R = CH_3) in 96% yield. The formation of the *E* isomer **13a** was supported by NMR with a signal observed between the *N*-methyl group and the proton of the exocyclic alkene in the nOe.

Scheme 4. Oxidation of 2-Alkyl-*N*-methyl Pyrroles

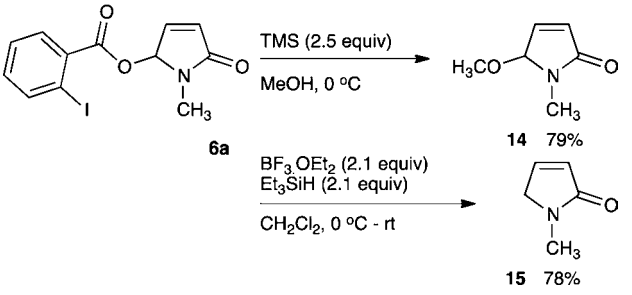


The extension of the oxidation to other substitution patterns was not as selective with 3-benzyl-*N*-methylpyrrole yielding a 3:2 mixture of isomers (see Supporting Information for details) while 2,5-dialkylpyrroles underwent decomposition.

(31) Issa, F.; Fischer, J.; Turner, P.; Coster, M. J. *J. Org. Chem.* **2006**, *71*, 4703.

The resulting 5-aryloxy-α,β-unsaturated-γ-lactams **6a**–**h** are highly functionalized compounds, and to demonstrate their potential utility in synthesis we carried out a series of reactions typical of the functionality present (Scheme 5). The aroyloxy group can be exchanged with MeOH/HCl to generate the 5-methoxy-γ-lactam[31] **14**, while simply heating the compound in a solution of methanol furnishes the same product but in a reduced yield of 48%. The aminal group can be reduced with $BF_3 \cdot OEt_2/Et_3SiH$ to yield the 5-unsubstituted-γ-lactam **15**.[31]

Scheme 5. Reaction of 5-Aroyloxypyrrolinones



In conclusion, we have developed a new method for the controlled oxidation of *N*-alkylpyrroles resulting in high yields of 5-aroyloxy-γ-lactams. These lactams are highly functionalized and therefore are excellent building blocks for synthesis. Further investigations to expand the substrate scope of the controlled oxidation with the Dess-Martin periodinane reagent as well as mechanistic studies are underway in our laboratory.

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Supporting Information Available. Experimental details and spectral ^{1}H NMR of compounds **6a**–**g**, **10**, **12**, **13a**–**b**, **14**, and **15**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.