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One-Step Synthesis of Complex Nitrogen Heterocycles from Imines and Alkyl-Substituted Maleic Anhydrides

Yuchen Tang, James C. Fettinger, and Jared T. Shaw*

Department of Chemistry, University of California, One Shields Avenue, Davis, California 95616

shaw@chem.ucdavis.edu

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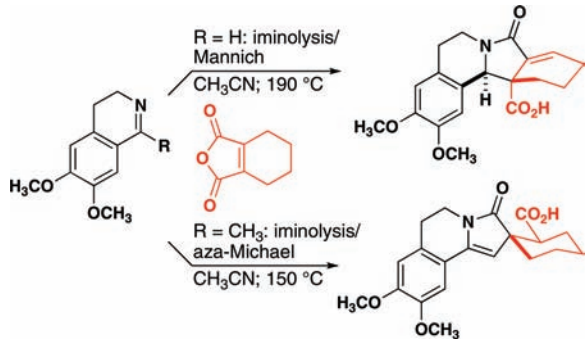
ABSTRACT



Substituted maleic anhydrides react with imines to form polycyclic lactam products. Diastereoselectivity can be controlled by altering the reaction conditions in some cases, and regiochemistry is dictated by the structure of the allylic substituents on the anhydride. Cyclic imines, including dihydro-β-carbolines and dihydroisoquinolines, exhibit the highest level of reactivity in these new annulation reactions.

Five-membered ring heterocycles are common structural subunits in polycyclic natural products[1] and medicinal leads.[2] A one-step synthesis of γ-lactams is possible from imines and succinic anhydrides through a formal cycloaddition process, as first demonstrated by Castagnoli.[3] Favorable substrates for this reaction have substituents, such as an aromatic ring, capable of stabilizing an enolate intermediate formed from iminolysis of the anhydride.[4] Our own studies revealed that a thioether substituent enabled the synthesis of γ-lactams in high yield and with a high level of diastereoselectivity.[5] The acylation step was shown to be reversible, and this finding led to the discovery of a new four-component synthesis of γ-lactams.[6] Our ongoing studies of the iminolysis mechanism prompted us to explore the possibility of accessing a zwitterionic enolate intermediate from a maleic anhydride by a prototropic shift to provide allylic stabilization (Scheme 1). We envisioned that zwitterion **3**, resulting from iminolysis of anhdyride **2**, could isomerize to **4**. Attack of the α- or γ-position of the dienolate

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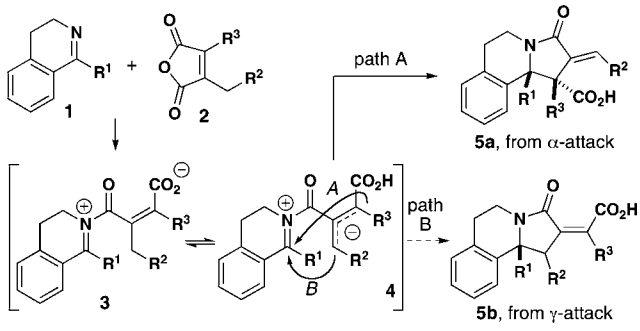
Scheme 1. Potential Reaction Pathways of Imines with Substituted Maleic Anhydrides



would lead to products **5a** or **5b**, respectively. Herein we report our preliminary findings on the synthesis of unsaturated lactams from the reactions of imines **6a**−**e** with maleic anhydrides **7a**−**d** (Figure 1).

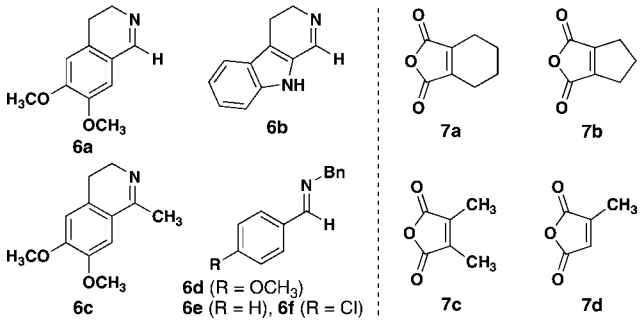


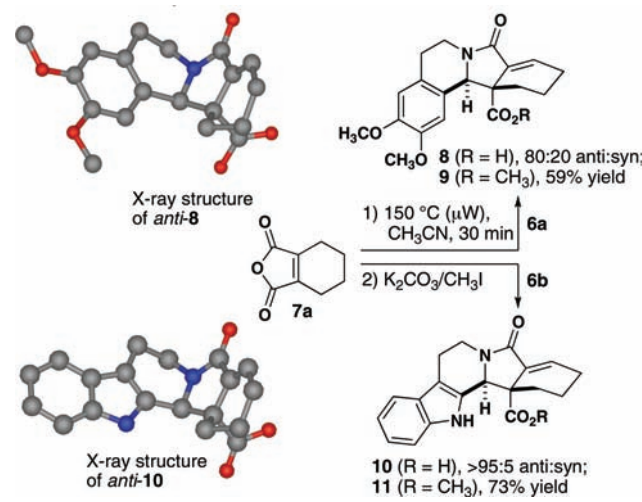
Figure 1. Imines (**6a**−**e**) and substituted anhydrides (**7a**−**d**).

Tetrahydrophthalic anhydride **7a** reacted with imines **6a** and **6b** to form the anticipated formal cycloaddition products (Scheme 2). In both cases reaction by path A, i.e., attack of the α-carbon of the presumed dienolate on the iminium ion, was observed. Dihydroisoquinoline **6a** and dihydrocarboline **6b** each reacted with high diastereoselectivity and in acceptable yields as judged by converting initially formed acids **8** and **10** to their respective methyl esters **9** and **11**. The *anti* configuration of the major isomer in each case was identified through X-ray crystallographic analysis.[7]

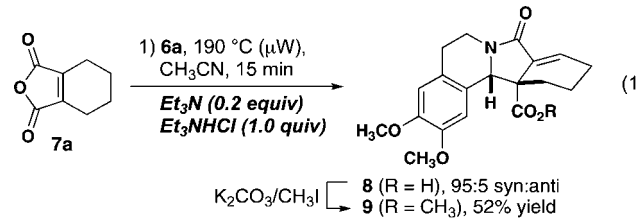
The diastereoselectivity of the reaction of **6a** with tetrahydroisoquinoline **7a** is reversed when the reaction is conducted in the presence of triethylamine and triethylammonium hydrochloride (eq 1). Density functional theory calculations for the two diastereomeric core structures indicate that *syn*-**8** is more stable by 1.4 kcal/mol, suggesting that the alternate conditions enable equilibration of the less stable and presumably kinetically formed *anti*-**8**.[8] It is

(7) Data summaries for all of the X-ray crystal structures are provided in Supporting Information. In addition, crystallographic information files (CIF) files have been deposited in the Cambridge Crystallographic Database (CCDB).

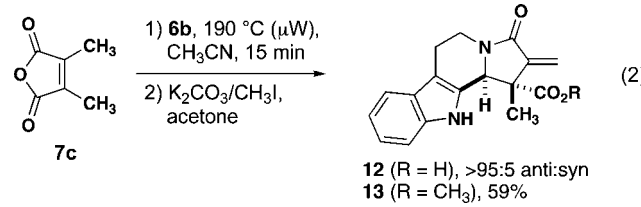
Scheme 2. Polycyclic Products from the Reactions of Anhydride **7a** with Imines **6a** and **6b**



noteworthy that lactam **8** has all of the structural features and the correct stereochemistry of the natural product jamtine *N*-oxide[9] and several related alkaloids[10] from the medicinal plant *Cocculus hirsutus*. Independent syntheses of jamtine, the presumed biosynthetic precursor of jamtine *N*-oxide, have cast doubt on the core structures of these natural products.[11]



Methyl- and dimethyl-substituted anhydrides **7c** and **7d** were also investigated. No reaction with imines **6a** or **6d,e** was observed in either case. Only the reaction of **6b**, which shows the highest reactivity of all of the imines, was observed to react with **7c** to provide exomethylene-substituted lactam **12** in good yield and high diastereoselectivity (eq 2). The configuration of methyl ester **13** could not be determined and is tentatively assigned on the basis of analogy to **8** and **10**.



Acyclic imines derived from aromatic aldehydes (**6d**−**f**) react with anhydride **7a** to provide [6,5]-fused lactams with yields and selectivities that depend on the substituents of the aromatic ring (Scheme 1, Table 1). Electron-rich imine

Scheme 3. Reactions of Acyclic Imines **6d−f** with **7a**

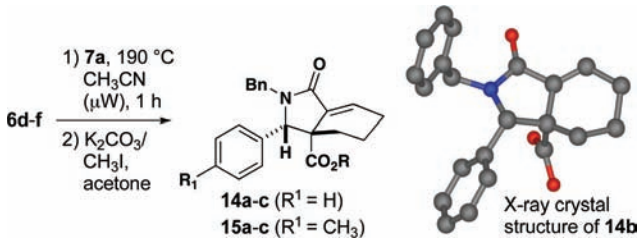


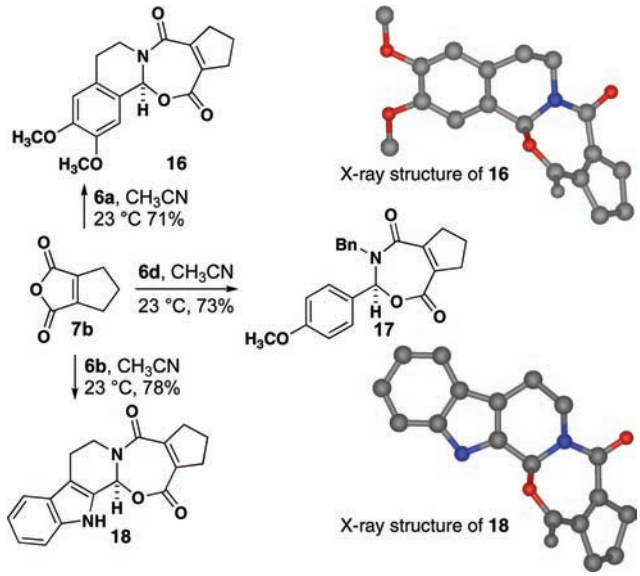
Table 1. Reactions of Acyclic Imines with Anhydride **7a**

imine	R^1	dr (**14a−c**)	yield (%)
6d	OCH_3	>95:5 (**14a**)	70 (**15a**)
6e	H	>95:5 (**14b**)	51 (**14b**)
6f	Cl	50:50 (**14c**)	45 (**15c**)

6d reacts in high yield and with high (>95:5) diastereoselectivity when heated for 1 h. This reduced reactivity of acyclic imines, when compared to cyclic imines, is consistent with previous observations in reactions of homophthalic anhydride.[4c] Although benzaldehyde-derived imine **6e** reacts with similar diastereoselectivity, incomplete conversion and a correspondingly lower yield is observed. *p*-Chlorophenyl imine **6f** gave poor conversion. The relative configuration of **14b** was demonstrated by X-ray crystallography, and those of **14a** and **14c** are assigned by analogy on the basis of their similar ^{1}H NMR spectra.

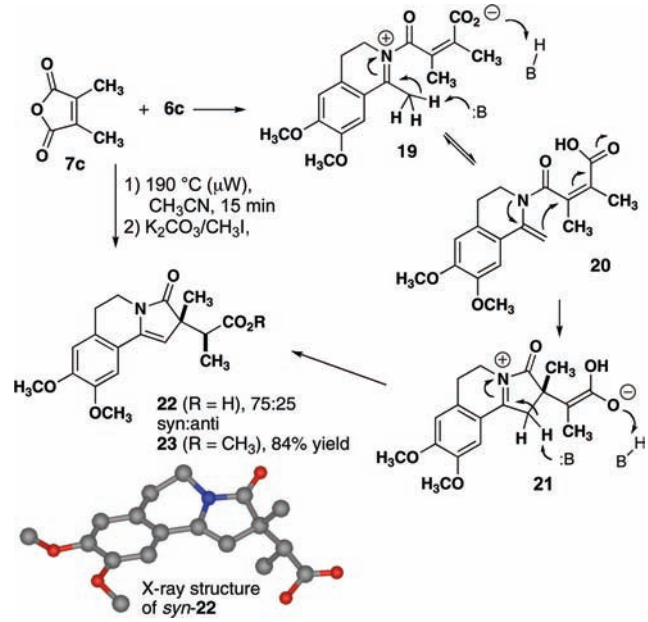
Cyclopentane-fused maleic anhydride **7b** exhibited interesting reactivity with imines (Scheme 4). Upon mixing the imines **6a** with anhydride **7b**, a precipitate instantly formed. Although the ^{1}H NMR spectrum of the product of **6a** and **7b** initially appeared to be consistent with one of the anticipated adducts, X-ray crystallographic analysis revealed the product to be *N*,*O*-acetal **16**. Similar *N*,*O*-acetal products were formed with **6b** and **6c**. Although a similar structure is proposed as an intermediate in the reactions of succinic anhydrides,[3] continued heating of **16** failed to produce any lactam products.

Scheme 4. Reactions of **7b** with Imines **6a**, **6b**, and **6d**



We next turned our attention to the reactions of ketimine **6c**. Although ketimines are known to be less reactive toward homophthalic anhydride,[12] we reasoned that **6c** might be sufficiently reactive based on the higher reactivity of cyclic imines **6a** and **6b** relative to their acyclic analogues. Upon heating **6c** and **7c**, we observed conversion to a new product (Scheme 5). Although the ^{1}H NMR spectrum suggested the expected fused lactam had formed, X-ray crystallographic analysis of the major diastereomer indicated a completely different reaction manifold had produced tricyclic unsaturated lactam **22**. This product arises from acylation of the imine followed by prototropic shift to enamide carboxylic acid **20**.

Scheme 5



(8) Relative energies (B3LYP/6-31+G(d,p) + unscaled zero point energy corrections) for the core compounds lacking the methoxy groups were calculated by Prof. D. J. Tantillo, UC Davis (djtantillo@ucdavis.edu). See Supporting Information.

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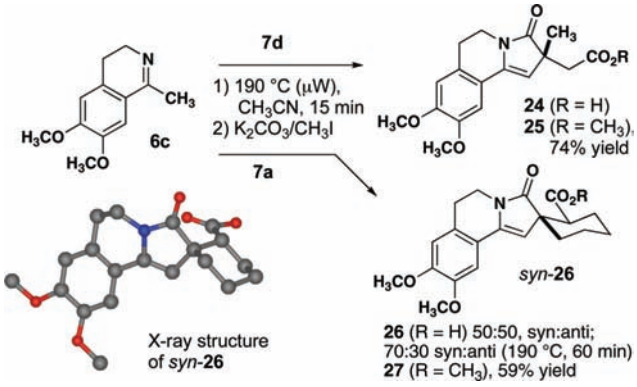
This intermediate is poised for an intramolecular Michael-type addition of the enamide to the unsaturated acid and formation of **22** after elimination.[13] A modest preference (75:25) for the formation of the *syn* isomer depicted is observed, and the configuration was determined by X-ray crystallographic analysis. Anhydrides **7d** and **7a** reacted similarly to produce **24** and **26**, respectively, the latter case consisting of 50:50 mixture of the two diastereomers. Continued heating of **26** under the reaction conditions shifted to a 70:30 mixture favoring the *anti* isomer for which X-ray crystallographic analysis confirmed the structural assignment (Scheme 6).

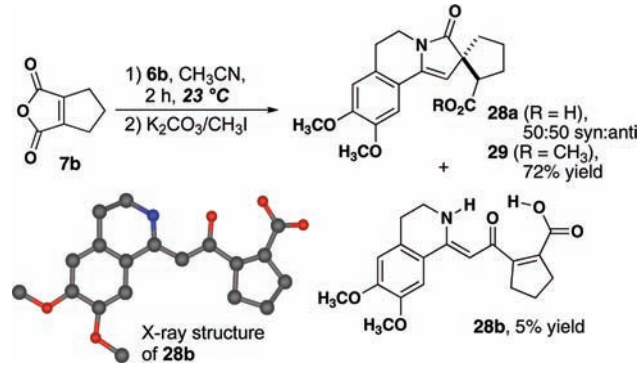
Scheme 6



Anhydride **7b** exhibited higher reactivity toward imine **6b** (Scheme 7). Upon mixing at room temperature, a reaction occurred immediately and the expected product of conjugate addition (**28a**) was formed as a mixture of diastereomers. A small quantity of direct *C*-acylation product **28b** was also isolated as a precipitate. This result is consistent with the *C*-acylation of 2-methyl-substituted pyridines by acetic and trifluoroacetic anhydride that has been previously observed[14] and is a testament to the increased reactivity of **7b**.

In summary, we have discovered a series of new reactions between imines and substituted maleic anhydrides to produce complex, polycyclic lactams in a single step. Aldimines react in a new manifold that was predicted by the acylation/Mannich mechanism previously observed for succinic and homophthalic anhydrides. Ketimine **6c** produces related lactam products through an entirely new acylation/aza-

Scheme 7



Michael reaction of anhydrides via an enamide intermediate. The polycyclic products of these new reactions are reminiscent of dihydroisoquinoline and β-carboline natural products and will be useful in target-oriented and diversity-oriented synthesis efforts.

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Supporting Information Available: Experimental procedures for the preparation of all new compounds and X-ray crystallographic data (including CIF files) for **8**, **10**, **14b**, **16**, **18**, **22**, **26**, and **28b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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