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An Efficient Approach to the Stereocontrolled Synthesis of Enamides[†]

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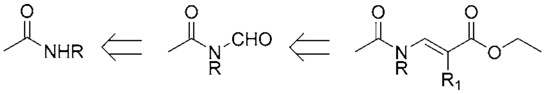
ABSTRACT



A fast, flexible, and efficient approach for the stereocontrolled synthesis of enamides has been developed starting from lactams and amides through the use of imides. This new approach provides access to enamide systems not easily or currently accessible through other approaches.

Enamides are very important subunits in various biologically active natural products and pharmaceutical drug lead compounds such as the antibiotic CJ-15,801 **1**, crocacin A **2**, the lituarines **3**, and the anti-insecticidal agent **4** (Figure 1).[1] Synthetically, enamides are highly reactive, which has made them key intermediates in the synthesis of a variety of heterocyclic compounds.[2]

The importance and relevance of enamides both as building blocks and target units has been reflected in the number of different approaches reported for their synthesis.[3,4]

The synthetic methods developed for the synthesis of enamide systems thus far enjoy varying degrees of success, particularly with regard to yield and control of the double bond stereochemistry. In a number of cases, the control of double bond geometry is almost nonexistent.

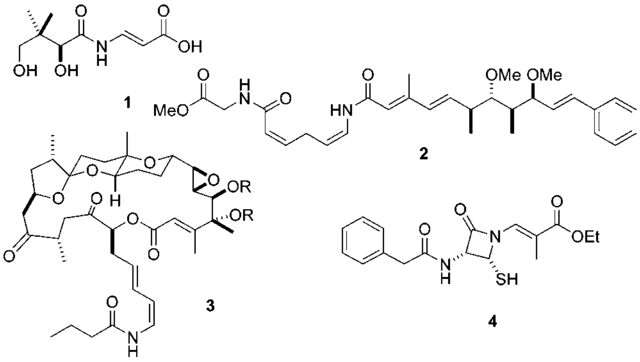


Figure 1. CJ-15,801 **1**, crocacin A **2**, lituarines **3**, and anti-insecticidal agent **4**.

A reliable, flexible, and stereoselective procedure for the synthesis of enamide units would greatly improve current approaches to the synthesis of enamide-bearing natural

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[†] Dedicated to the memory of Vincent R. J. Villa.

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(1) (a) Vidal, J. P.; Escale, R.; Girard, J. P.; Rossi, J. C.; Chantraine, J. M.; Aumelas, A. *J. Org. Chem.* **1992**, *57*, 5857. (b) Sugie, Y.; Dekker, K. A.; Hirai, H.; Ichiba, T.; Ishiguro, M.; Shiomi, Y.; Sugiura, A.; Brennan, L.; Duignan, J.; Huang, L. H.; Sutcliffe, J.; Kojima, Y. *J. Antibiot.* **2001**, *54*, 1060. (c) Kunze, B.; Jansen, R.; Hoefle, G.; Reichenbach, H. *J. Antibiot.* **1994**, *47*, 881.

(2) (a) McAlonan, H.; Murphy, J. P.; Nieuwenhuyzen, M.; Reynolds, K.; Sarma, P. K. S.; Stevenson, P. J.; Thompson, N. *J. Chem. Soc., Perkin Trans. 1*, **2002**, 69. (b) Shirokawa, S. I.; Kamiyama, M.; Nakamura, T.; Okada, M.; Nakazaki, A.; Hosowaka, S.; Kobayashi, S. *J. Am. Chem. Soc.* **2004**, *126*, 13604.

(3) For an excellent review on the synthesis of enamides, see: Tracey, M. R.; Hsung, R. P.; Antoline, J.; Kurtz, K. C. M.; Shen, L.; Slafer, B. W.; Zhang, Y. *Sci. Synth.* **2005**, *5*, 387.

(4) (a) Nicolaou, K. C.; Mathison, C. J. N. *Angew. Chem., Int. Ed.* **2005**, *44*, 5992. (b) Han, C.; Shen, R. C.; Su, S.; Porco, J. A. *Org. Lett.* **2004**, *6*, 27.

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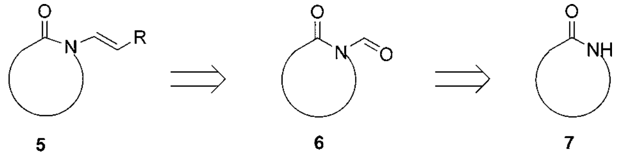
products and pharmaceutically relevant heterocyclic systems. We now report a novel and flexible approach that delivers enamides in good yields and with high selectivity.

In our approach, we envisioned the enamide unit as originating from the unprecedented Wittig olefination of the imide precursor **6**. The desired imide intermediate could in turn be obtained from the parent lactam unit **7** (Scheme 1).

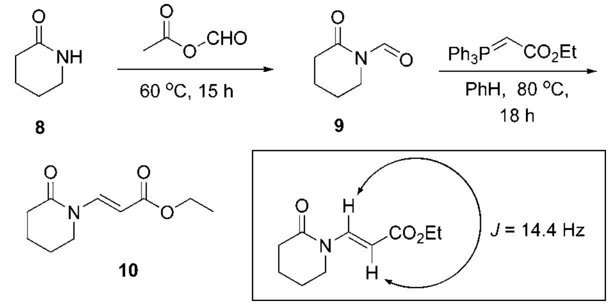
Scheme 1. Proposed Synthesis of Enamides from Imides



Our decision to focus on the imide functionality emanated from considering the formyl unit as potentially behaving as a pseudoaldehyde unit due to the original lactam carbonyl. It was reasoned that the nitrogen lone pair would be effectively delocalized into the lactam carbonyl, thus rendering the formyl group more reactive than a typical formamide. This approach would have the benefit of being able to take advantage of the myriad of aldehyde olefination conditions to stereoselectively generate polyfunctionalised enamides.[5]

Our initial formylation−olefination sequence studies began with lactam **8**, which upon formylation under nonstandard conditions using acetic formic anhydride generated the corresponding imide **9** in excellent yield (Scheme 2).[6]

Scheme 2



Treatment of imide **9** with ethyl triphenylphosphonoacetate in benzene proceeded cleanly to generate the desired *E*-enamide ester **10** in good yield and more importantly as a single isomer (Scheme 2). The double bond geometry was assigned on the basis of the alkene coupling constant (J = 14.4 Hz), on two-dimensional NOE experiments, and finally through X-ray crystallography (Figure 2).[7]

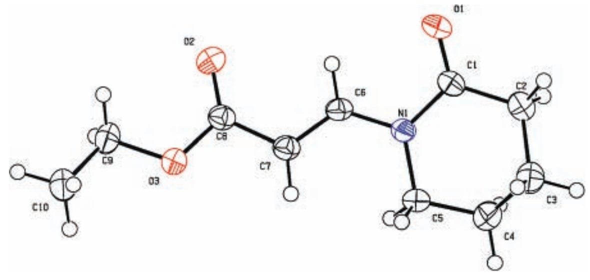
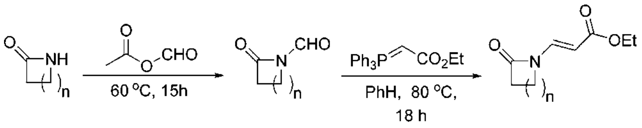


Figure 2. Crystal structure of valerolactam-derived enamide **10**.

Our newly developed conditions were then applied to a number of lactam analogues of various ring sizes to assess the reproducibility of this transformation. Treatment of 2-azetidinone **8a**, 2-pyrrolidinone **8b**, ϵ-caprolactam **8c**, 1-aza-2-cyclooctanone **8d**, and 2-azonanone **8e** with acetic formic anhydride successfully generated the desired *N*-formylimides (**9a**−**e**) in good yield after minimal purification. The lower yield observed for the generation of *N*-formylazetidinone **9a** compared to the other imides can possibly be explained through its lower boiling point and partial loss during solvent removal under vacuum (Scheme 3).

Scheme 3



n = 1	**8a**	56%	**9a**	77%	**10a**
n = 2	**8b**	75%	**9b**	66%	**10b**
n = 3	**8**	80%	**9**	47%	**10**
n = 4	**8c**	85%	**9c**	55%	**10c**
n = 5	**8d**	70%	**9d**	37%	**10d**
n = 6	**8e**	87%	**9e**	57%	**10e**

Olefination of the stable imide intermediates (**9a**−**e**) under Wittig conditions similar to those used before proceeded to provide cleanly the desired enamides (**10a**−**e**) in moderate to good yield and as a single *E*- double bond isomer in all cases.

Having demonstrated the ability of our procedure to generate lactam enamides efficiently and stereoselectively,

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(5) For other non-imide-based olefination approaches to the synthesis of enamides, see: (a) Paterson, I.; Cowden, C.; Watson, C. *Synlett* **1996**, 209. (b) Couture, A.; Deniau, E.; Grandclaudon, P. *Tetrahedron Lett.* **1993**, *34*, 1479.

(6) For traditional conditions for the formylation of lactams, see: (a) Gramain, J. C.; Remuson, R. *Synthesis* **1982**, 264. (b) Wells, G. J.; Bihovsky, R.; Hudkins, R. L.; Ator, M. A.; Husten, J. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1151.

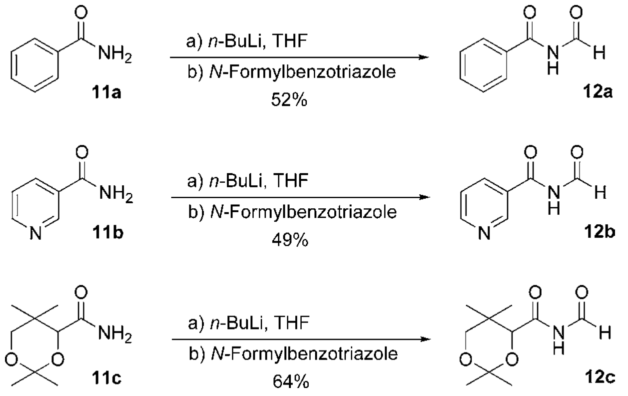
(7) The atomic coordinates for **10** (CCDC deposition no. CCDC603107) are available upon request from the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, U.K. The crystallographic numbering system differs from that used in the text; therefore, any request should be accompanied by the full literature citation of this paper.

we decided to test the flexibility of our conditions on acyclic amide-based systems.

Unfortunately, treatment of a sample of acyclic amides (**11a**−**c**) with acetic formic anhydride failed to generate the corresponding imides in greater than 20% conversion despite prolonged and more strenuous reaction conditions.

However, treatment of the amides (**11a**−**c**) with *N*-formylbenzotriazole and *n*-butyllithium proceeded cleanly to generate the expected imide units (**12a**−**c**) in good yields (Scheme 4).[8] Surprisingly, treatment of lactams (**8**, **8a**−**e**) under the same *N*-formylbenzotriazole and *n*-butyllithium conditions failed to generate any of the corresponding *N*-formyl imides.

Scheme 4



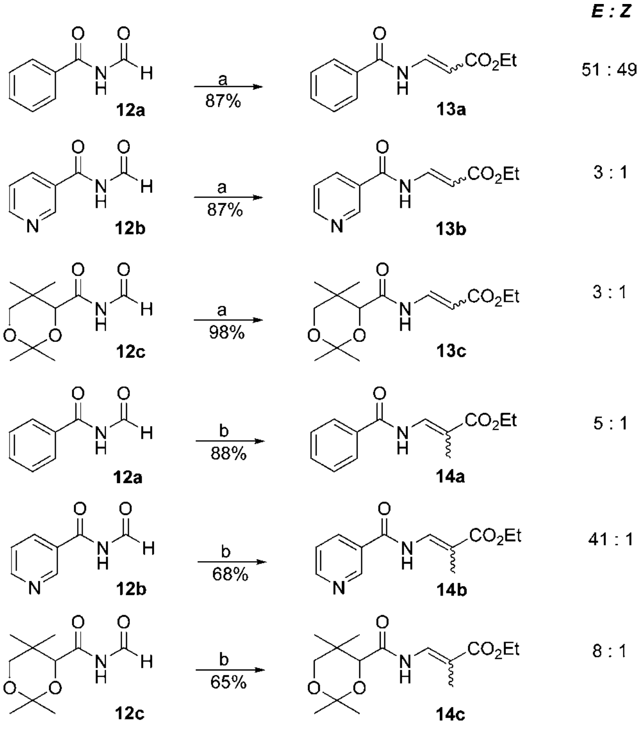
Rewardingly, subjecting the newly generated acyclic imides to the previously used olefination conditions afforded the desired enamides (**13a**−**c**) in excellent yields. In all cases, the *E*-enamide is the preferred isomer although various amounts of the *Z*-isomer are formed in these cases (Scheme 5).

The highly successful olefination of imides (**13a**−**c**) encouraged us to apply this approach to the synthesis of 2-methyl-substituted enamides. 2-Substituted enamides have proven to be remarkably difficult to access through traditional approaches with any degree of stereocontrol.

Hence, we are pleased to report that treatment of imides (**12a**−**c**) with the corresponding methyl-substituted phosphorus ylide proceeded to generate the desired 2-methyl-substituted enamides (**14a**−**c**) in good yields and with high *E*/*Z* selectivity (Scheme 5). Significantly, no double-bond isomerization has been detected under the reaction conditions.

Very recent results in our group indicate that imides can also be successfully olefinated using nonstabilized ylides to generate other functionalized enamide building blocks, for example, bromo enamide **15** (Scheme 6).

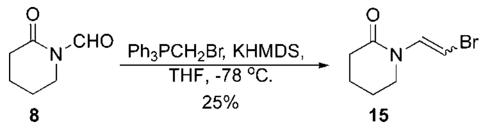
Scheme 5[a]



[a] Reagents and conditions: (a) Ph_3PCHCO_2Et, PhH, 95 °C; (b) $Ph_3PC(Me)CO_2Et$, PhH, 95 °C.

In conclusion, we have demonstrated that *N*-formylimides are a viable starting point for the efficient, flexible, and stereocontrolled synthesis of both simple and substituted enamide systems.

Scheme 6



We are currently working on the expansion and optimization of this method for the synthesis of more complicated enamide and dienamide systems, their synthetic derivatives, and their applications to natural product synthesis.

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Supporting Information Available: Experimental procedures and characterization data of the described compounds and intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

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[8] Couty, S.; Barbazanges, M.; Meyer, C.; Cossy, J. *Synlett* **2005**, 905.