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Nitro-Mannich/Lactamization Cascades for the Direct Stereoselective Synthesis of Pyrrolidin-2-ones

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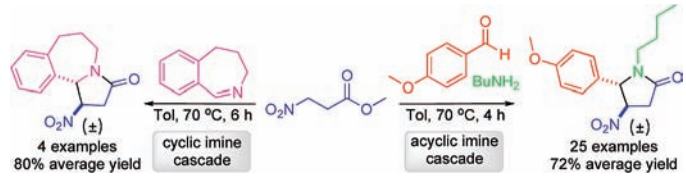
ABSTRACT



An efficient three-component nitro-Mannich/lactamization cascade of methyl 3-nitropropanoate with in situ formed acyclic imines for the direct preparation of pyrrolidinone derivatives has been developed. The reaction is easy to perform, broad in scope, and highly diastereoselective and may be extended to cyclic imines allowing the direct formation of polycyclic pyrrolidinone derivatives.

Chemical entities containing pyrrolidine and pyrrolidinone heterocycles are common among natural products and pharmaceutical compounds ranging from the simple to the architecturally complex[1−4] (Figure 1).

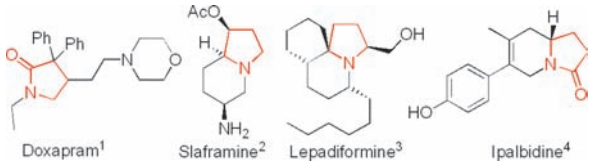


Figure 1. Pyrrolidine and pyrrolidinone ring-containing natural products and pharmaceutical molecules.

Although numerous elegant methods[5] exist for their preparation, we recognized that a direct, synthetically powerful route to these structures could involve a nitro-Mannich[6]/lactamization cascade[7] of 3-nitropropanoate esters with imine substrates, made in situ or otherwise. Thus, in a continuation of our studies into the stereoselective synthesis of nitrogen-containing heterocyclic compounds, herein we describe a new development of our work

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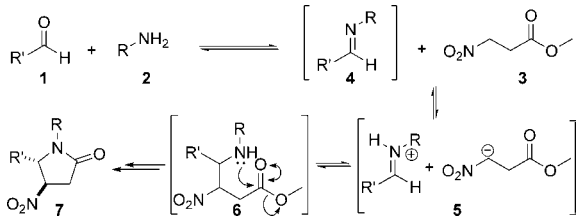
leading to an efficient cascade reaction of three components: nitroester, amine, and aldehyde.

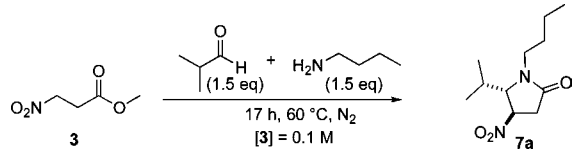
Scheme 1. Nitro-Mannich/Lactamization Cascade for the Synthesis of Pyrrolidin-2-one Derivatives



Our proposed cascade is shown in Scheme 1. Treatment of an amine **2** with an aldehyde **1** leads to the rapid formation of the imine intermediate **4** which undergoes proton exchange with the acidic nitroalkane **3**.[8] This mutually reactive ion pair **5** should then undergo carbon−carbon bond formation to give the nitro-Mannich product **6** which, through favorable positioning of the amine and the ester functionality, is poised to undergo irreversible lactamization.

Initial studies to probe reactivity were performed using methyl-3-nitropropanoate **3**, isobutyraldehyde, and butylamine. Solvents, ranging from polar protic to apolar aprotic, were screened, and the reactivity was assessed by measuring conversion by ^{1}H NMR against an internal standard. The results are presented in Table 1. Previous studies on nitro-

Table 1. Solvent Screen in the Nitro-Mannich/Lactamization Cascade



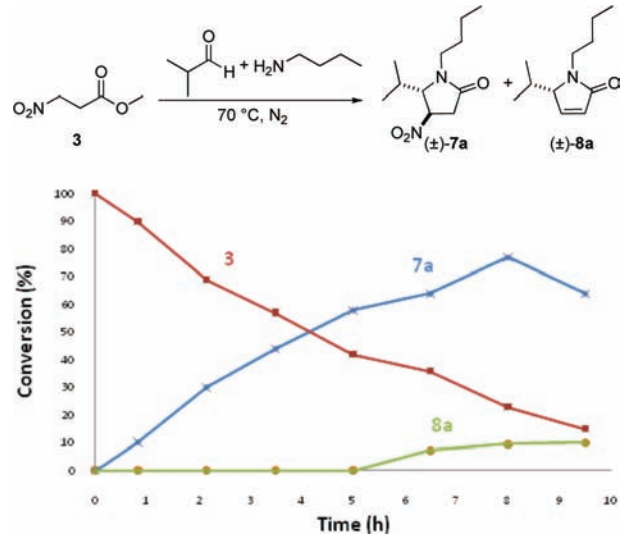
entry	solvent	^{1}H NMR yield (%)[a]	dr
1	water	~0	-
2	MeOH	17	>98:2
3	MeCN	40	>98:2
4	THF	43	>98:2
5	toluene	51	>98:2
6	hexane	72	>98:2
7	neat	4	-

[a] Against 1,3,5-tribromobenzene (0.3 equiv) as an internal standard.

Mannich/lactamization cascades in our group have shown that polar protic solvents were preferred for the synthesis of piperidin-2-one derivatives. However, in the present case of five-membered ring formation, little or no conversion was observed in water or methanol (entries 1 and 2). Pleasingly, aprotic solvents gave better results (entries 3−6), with hexane (entry 6) providing the highest conversion. In all cases, only a single diastereomeric product was observed in the reaction mixture.

Subsequent optimization was required to improve the rate of the reaction and the conversion. Increasing the temperature to 70 °C and concentration to 0.4 mol/L resulted in a significant decrease in the reaction time from 24 to 7 h, but the conversion remained below 80%. Further ^{1}H NMR studies were undertaken to investigate the cause of the incomplete conversion. Interestingly, above 60% conversion, smooth formation of **8a**, presumably through base elimination, was visible (Scheme 2). Accordingly, the reaction was

Scheme 2. Composition of the Reaction Mixture Over Time



repeated in the presence of acid to decrease the pH, thereby suppressing any base-catalyzed elimination pathway. Pleasingly, in toluene in the presence of benzoic acid, rapid and complete conversion to a single diastereomer of the desired product was witnessed, providing **7a** in a gratifying 72% isolated yield.

Further experiments revealed that the optimal conditions for the synthesis of the pyrrolidin-2-one product benefitted from an inert atmosphere, degassed (but not necessarily anhydrous) toluene, a temperature of 70 °C, a concentration of 0.4 mol/L, and an excess of aldehyde and amine (1.5 equiv) with respect to methyl-3-nitropropanoate **3**. Furthermore, the presence of acid was found to increase the reaction rate with the preferred quantity being 1 equiv with respect to the amine.

With optimal conditions identified, the scope of the reaction with respect to both the amine and the aldehyde component was investigated. The results are presented in Schemes 3 and 4. Initially, primary amines ranging from

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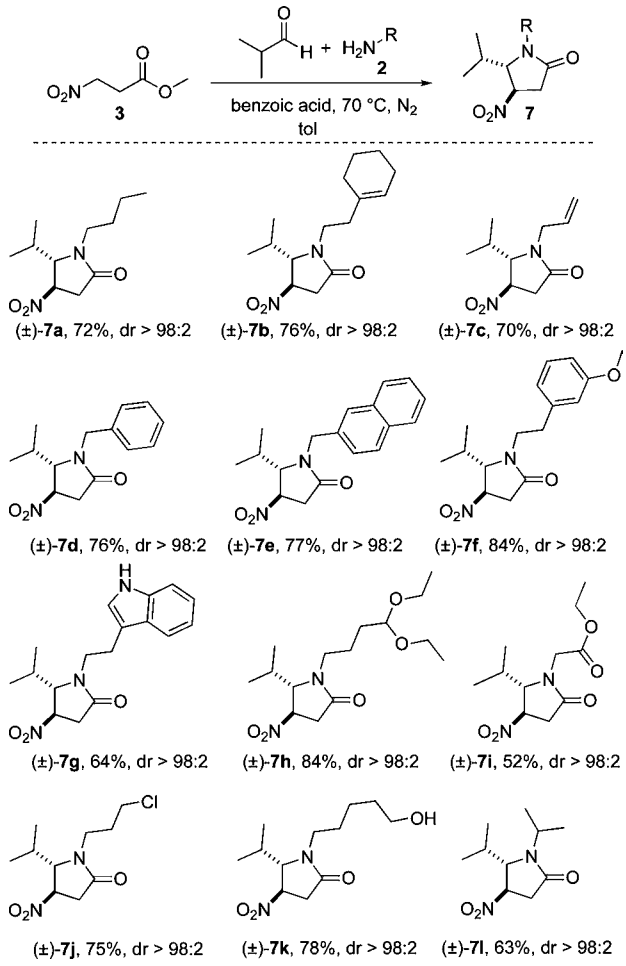
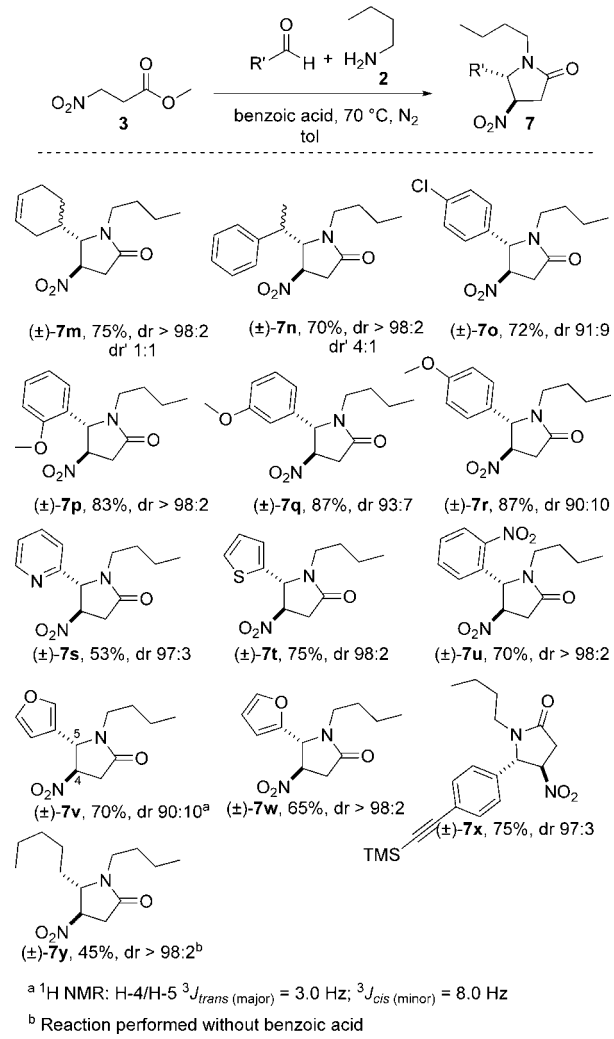
Scheme 3. Scope of Nitro-Mannich/Lactamization Cascade with Respect to the Amine Component



Scheme 4. Scope of Nitro-Mannich/Lactamization Cascade with Respect to the Aldehyde Component



[a] ^{1}H NMR: H-4/H-5 $^3J_{trans\ (major)}$ = 3.0 Hz; $^3J_{cis\ (minor)}$ = 8.0 Hz

[b] Reaction performed without benzoic acid

linear to sterically hindered and carrying various functional groups such as esters, acetals, halides, alcohols, and heterocycles were reacted with isobutyraldehyde to give products **7a**−**7l**. Reaction yields ranged from 52−84%, and excellent diastereoselectivity was obtained.

Next, the scope with respect to the aldehyde component was probed using butylamine. Simple aliphatic aldehydes gave excellent diastereocontrol. For example, with isobutyraldehyde a single diastereomeric product was formed in high yield. High selectivity was also obtained with hexanal (dr > 98:2); however, only a moderate yield was obtained due to competing side reactions. Interestingly, when chiral racemic α-branched aldehydes were employed only two of the possible four diastereomers were formed with no to moderate diastereoselection in good yield (**7m**−**n**). *o*-, *m*-, or *p*-substituted aromatic and heteroaromatic aldehydes ranging from electron-rich to electron-poor gave excellent yields and good to excellent diastereocontrol (**7o**−**x**, crude dr range, 90:10 to >98:2).

The trans stereochemistry of the major diastereomer was unambiguously determined by single-crystal X-ray analysis of compound **7t** (Figure 2).[9] By comparison of the ^{1}H NMR coupling constants [$^3J_{trans}$ (H-5/H-4) range from 1.0 to 3.0 Hz], the stereochemistry of the other compounds (**7a** to **7y**) was assigned by analogy.

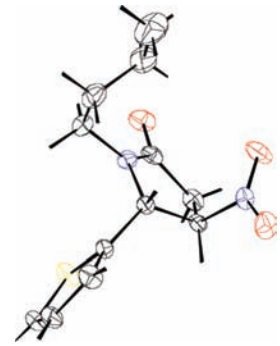


Figure 2. Structure of **7t** showing thermal ellipsoids drawn at 50% probability (disorder omitted for clarity).

Extension of the methodology to cyclic imines allowed the formation of polycyclic pyrrolidinone derivatives **10**. A

range of six- and seven-membered ring imines **9** (Figure 3), prepared by literature procedures,[10] were reacted with

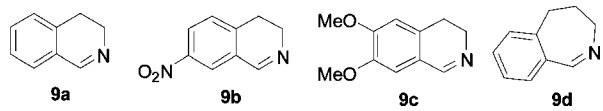


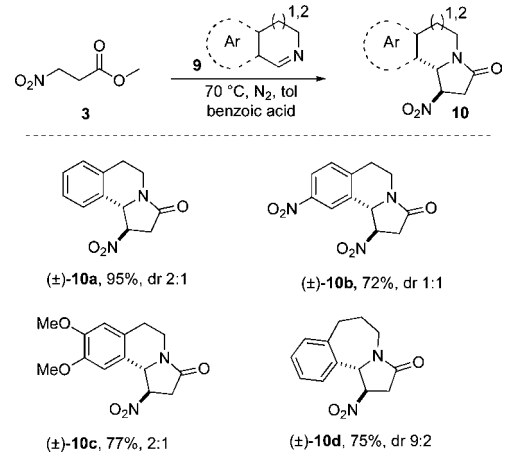
Figure 3. Cyclic imine starting materials.

methyl-3-nitropropanoate **3** in toluene with benzoic acid at 70 °C, and the results are presented in Scheme 5. The reactivity was similar to those of aliphatic imines, and the products were formed in excellent yields. However, a lower diastereoselectivity was observed in all cases (1:1 to 4.5:1 dr).

In all cases, separation of the two diastereoisomeric products was possible. Resubjection of the minor or major diastereomer, arising from imine **9c**, to the reaction conditions resulted in the same 2:1 ratio favoring the major diastereoisomer. This was clear evidence of a thermodynamic origin of stereocontrol in the nitro-Mannich/lactamization cascade of methyl-3-nitropropanoate **3** with acyclic and cyclic imines and is consistent with our previous observations[7b] relating to postcyclization epimerization at the stereocenter bearing the nitro functionality.

In summary, an efficient diastereoselective nitro-Mannich/lactamization reaction cascade of methyl 3-nitropropanoate

Scheme 5. Cyclic Imine Nitro-Mannich/Lactamization Cascade



with cyclic and acyclic imines for the direct preparation of mono- and multicyclic pyrrolidinone derivatives has been developed. The reaction is easy to perform and broad in scope. Further developments of this reaction and its application in total synthesis are ongoing in our laboratory, and the results will be disclosed in due course.

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Supporting Information Available: Experimental procedures and spectroscopic data for products **7a**−**y** and **10a**−**d** and a CIF file of compound **7t**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) Data were collected at low temperature [Cosier, J.; Glazer, A. M. *J. Appl. Cryst.* **1986**, *19*, 105−107.] using an Enraf-Nonius KCCD diffractometer [Otwinowski, Z.; Minor, W. *Processing of X-ray Diffraction Data Collected in Oscillation Mode Methods Enzymol*; Carter, C. W., Sweet, R. M., Eds.; Academic Press, 1997; p 276]. The crystal structure of **7t** was solved using SIR92 [Altomare et al. *J. Appl. Cryst.* **1994**, *27*, 435] and refined using the CRYSTALS software suite [Betteridge et al. *J. Appl. Cryst.* **2003**, *36*, 1487], as per the Supporting Information (CIF file). Crystallographic data (excluding structure factors) for **7t** have been deposited with the Cambridge Crystallographic Data Centre (CCDC 747540), and copies of these data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif.

(10) See Supporting Information for details.