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Diastereoselective Synthesis of 1,3,5-Trisubstituted 4-Nitropyrrolidin-2-ones via a Nitro-Mannich/Lactamization Cascade

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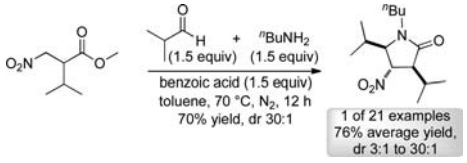
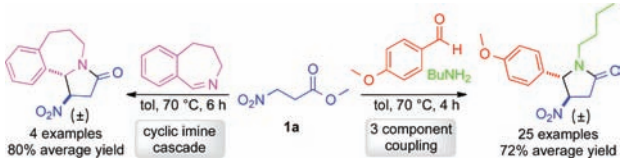
ABSTRACT



A versatile one-pot nitro-Mannich/lactamization cascade for the direct synthesis of 1,3,5-trisubstituted 4-nitropyrrolidin-2-ones has been developed. The reaction is easy to perform and broad in scope, and high levels of diastereoselectivity can be achieved.

In recent times, the nitro-Mannich[1] reaction has emerged as a powerful synthetic tool for the construction of important intermediates and building blocks. We recently described[2] an efficient nitro-Mannich/lactamization cascade[3] of methyl 3-nitropropanoate for the direct preparation of pyrrolidin-2-ones[4] (Scheme 1).

Scheme 1. Previous Work: One-Pot Synthesis of Pyrrolidinones



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(1) (a) Mühlstädt, M.; Schulze, B. *J. F. Prakt. Chemie, Band 317 Heft 6* **1975**, 919. (b) Snyder, H. L.; Hamlin, E. *J. Am. Chem. Soc.* **1950**, *72*, 5082. (c) Ma, J.; Wang, S. H.; Tian, G. R. *Synth. Commun.* **2006**, *36*, 1229. (d) Westermann, B. *Angew. Chem., Int. Ed.* **2003**, *42*, 151. (e) Garcia Ruano, J. L.; Haro, T.; Singh, R.; Cid, M. B. *J. Org. Chem.* **2008**, *73*, 1150. (f) Sharikov, R. R.; Dokichev, T. V.; Biglova, R. Z.; Vlasova, N. M.; Baibulatova, N. Z.; Talipov, R. F. *Chem. Heterocycl. Compd.* **2008**, *44*, 43. (g) Desai, M. C; Thadeio, P. F.; Lefkowitz, S. L. *Tetrahedron Lett.* **1993**, *34*, 5831. (h) Desai, M. C; Lefkowitz, S. L. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 2083. (i) Nara, S.; Tanaka, R.; Eishima, J.; Hara, M.; Takahashi, Y.; Otaki, S.; Foglesong, R. J.; Hugues, P. F.; Turkington, S.; Kanda, Y. *J. Med. Chem.* **2003**, *46*, 2467. (j) Tanaka, R.; Rubio, A.; Harn, N. K.; Gernet, D.; Grese, T. A.; Eishima, J.; Hara, M.; Yoda, N.; Ohashi, R.; Kuwabara, T.; Soga, S.; Akinaga, S.; Nara, S.; Kanda, Y. *Bioorg. Med. Chem.* **2007**, *15*, 1363. (k) Pei, Z.; Li, X.; von Geldern, T. W.; Longenecker, K.; Pireh, D.; Stewart, K. D.; Backes, B. J.; Lai, C.; Lubben, T. H.; Ballaron, S. J.; Beno, D. W. A.; Kempf-Grote, A. J.; Sham, H. L.; Trevillyan, J. M. *J. Med. Chem.* **2007**, *50*, 1983. (l) Anderson, J. C.; Stepney, G. J.; Mills, M. R.; Horsfall, L. R.; Blake, A. J.; Lewis, W. *J. Org. Chem.* **2011**, *76*, 1961.

(2) Pelletier, S. M.-C.; Ray, P. C.; Dixon, D. J. *Org. Lett.* **2009**, *11*, 4512.

(3) (a) Xu, F.; Corley, E.; Murry, J. A.; Tschaen, D. M. *Org. Lett.* **2007**, *9*, 2669. (b) Jakubec, P.; Helliwell, M.; Dixon, D. J. *Org. Lett.* **2008**, *10*, 4267. (c) Hynes, P. S.; Stupple, P. A.; Dixon, D. J. *Org. Lett.* **2008**, *10*, 1389. (d) Jakubec, P.; Cockfield, D. M.; Dixon, D. J. *J. Am. Chem. Soc.* **2009**, *131*, 16632. (e) Xu, F.; Corley, E.; Zacuto, M.; Conlon, D. A.; Pipik, B.; Humphrey, G.; Murry, J. A.; Tschaen, D. M. *J. Org. Chem.* **2010**, *61*, 1343. (f) Imashiro, R.; Uehara, H.; Barbas, C. F., III. *Org. Lett.* **2010**, 12. (g) Kyle, A. F.; Jakubec, P.; Cockfield, D. M.; Cleator, E.; Skidmore, J.; Dixon, D. J. *Chem. Commun.*, **2011**, *47*, 10037. (h) Jakubec, P.; Kyle, A. F.; Calleja, J.; Dixon, D. J. *Tetrahedron Lett.* **2011**, *52*, 6094.

(4) (a) Roberson, C. W.; Woerpel, K. A. *J. Org. Chem.* **1999**, *64*, 1434. (b) Krawczyk, H.; Albrecht, L.; Wojciechowski, J.; Wolf, W. M.; Krajewska, U.; Rozalski, M. *Tetrahedron* **2008**, *64*, 6307. (c) Dieter, R. K.; Lu, K. *Tetrahedron Lett.* **1999**, *40*, 4011. (d) Basavaiah, D.; Rao, J. S. *Tetrahedron Lett.* **2004**, *45*, 1621. (e) Song, Y. S.; Lee, C. L.; Lee, K.-J. *J. Heterocycl. Chem.* **2003**, *40*, 939. (f) Snider, B. B.; Neubert, B. J. *J. Org. Chem.* **2004**, *69*, 1633. (g) Berlin, S.; Ericsson, C.; Engman, L. J. *Org. Chem.* **2003**, *68*, 8386. (h) Elford, T. G.; Hall, D. G. *Tetrahedron Lett.* **2008**, *49*, 6995.

(5) (a) Kazmierski, W. M.; Andrews, W. C.; Furfine, E. S.; Spaltenstein, A.; Wright, L. L. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5689. (b) Sherrill, R. G.; Andrews, W. C.; C.; Bock, W. J.; Davis-Ward, R. G.; Furfine, E. S.; Hazen, R. J.; Rutkowske, R. D.; Spaltenstein, A.; Wright, L. L. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 81.

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In order to extend this chemistry to enable the synthesis of biologically active compounds[5,6] and natural products[7] (Figure 1), we required a method of introducing an alkyl substituent alpha to the lactam carbonyl. A range of conditions to directly alkylate the previously synthesized pyrrolidin-2-ones were attempted but failed to yield any of the desired products.

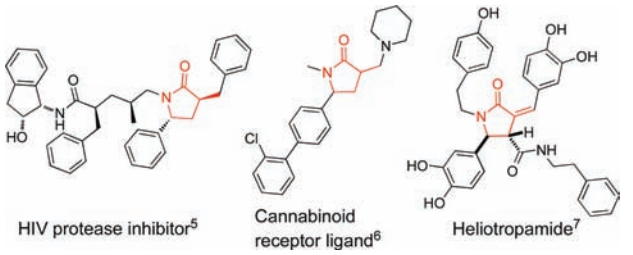


Figure 1. Pyrrolidin-2-one natural products and biologically active compounds.

Accordingly, and in order to circumvent this issue, we decided to investigate an alternative route in which the methyl 3-nitropropanoate was *C*-alkylated *prior* to the nitro-Mannich/lactamization cascade. In relation to our previously published work, this development would raise new issues of reactivity, reaction scope, and diastereoselection in the products and as such was a worthy pursuit. Herein we wish to report our findings leading to a diastereoselective synthesis of 1,3,5-trisubstituted 4-nitropyrrolidin-2-ones *via* a nitro-Mannich/lactamization cascade.

Following modified literature procedures,[8] methyl 2-benzyl-3-nitropropanoate **1b** was synthesized in one scaleable step from the parent methyl 3-nitropropanoate **1a**. With **1b** in hand, a range of preliminary experiments to identify conditions for a nitro-Mannich lactamization cascade were performed using isobutyraldehyde (1.5 equiv), butylamine (1.5 equiv), and benzoic acid (1.5 equiv) in a range of solvents at 70 °C for a fixed time of 12 h. Although little product was observed in methanol, pleasingly with ethyl acetate, diethyl ether, and tetrahydrofuran as solvents, the reactions were efficient and the diastereoselectivities were moderate. Further screening revealed hexane and toluene to be optimal with respect to both reaction yield and diastereoselectivity (Table 1). Additional studies revealed that variations to the dilution, the temperature, the nature of the acid, and the stoichiometry of the reagents had no significant influence on the reaction dr which remained at ~4.5:1.

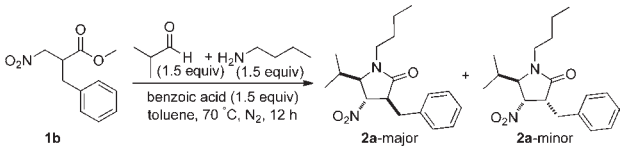
With optimal reaction conditions established, the scope of the reaction and the degree of stereocontrol possible

(6) Enz, A.; Feuerbach, D.; Frederiksen, M. U.; Gentsch, C.; Hurth, K.; Müller, W.; Nozulak, J.; Roy, B. L. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 1287.

(7) Guntern, A.; Ioset, J.-R.; Queiroz, E. F.; Sándor, P.; Foggin, C. M.; Hostettmann, K. *J. Nat. Prod.* **2003**, *66*, 1550.

(8) (a) O'Neil, I. A.; Bhamra, I.; Gibbsons, P. D. *Chem. Commun.* **2006**, 4545. (b) Seebach, D.; Henning, R.; Mukhopadhyay, T. *Chem. Ber.* **1982**, *115*, 1705.

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

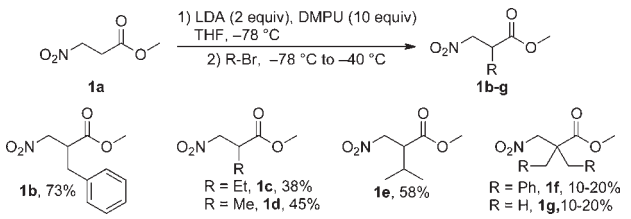


entry	solvent	^{1}H NMR yield (%)[a]	dr
1	MeOH	29	–
2	EtOAc	62	3:1
3	Et_2O	84	3.5:1
4	THF	60	3.5:1
5	Hexane	92	4.5:1
6	Toluene	93	4.5:1

[a] ^{1}H NMR yield measured against an internal standard.

in the formation of the fully substituted pyrrolidin-2-one products remained to be investigated. First, a range of alkyl substituted methyl 3-nitropropanoate starting materials were synthesized using a modification of literature procedures (Scheme 2).[8] The desired monoalkylated nitroesters **1b**–**e** were isolated in moderate to good yields (38% to 73%), and in some cases, gem-alkylated nitroesters **1f**–**g** were obtained as a minor side product of the reaction (10–20% yield).

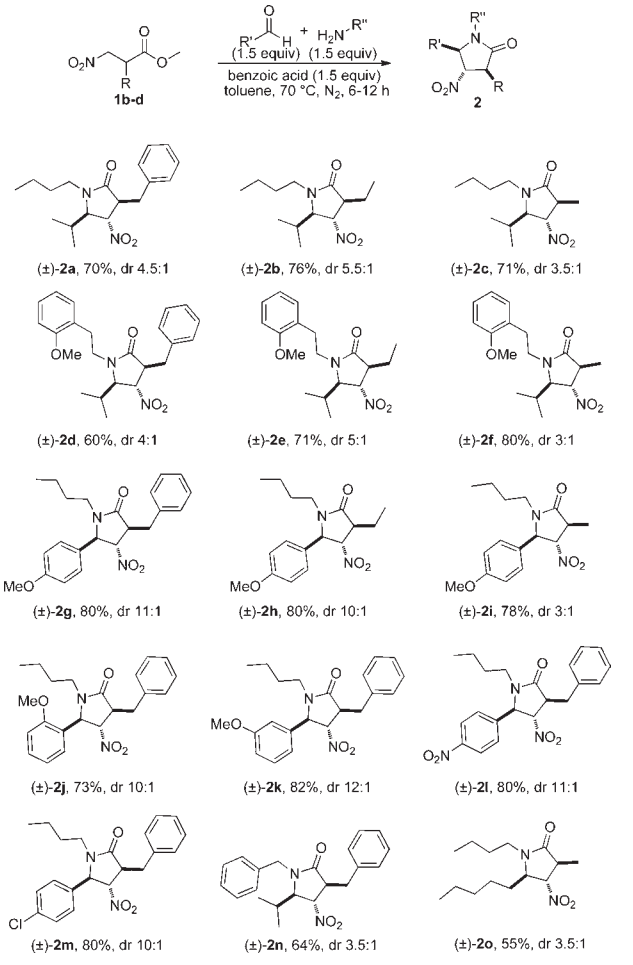
Scheme 2. Synthesis of α-Substituted Methyl 3-Nitropropanoates



Initially with alkyl-substituted nitropropanoate methyl esters **1b**–**d**, we probed the scope of the nitro-Mannich/lactamization reaction using 1.5 equiv respectively of amine, aldehyde, and benzoic acid in toluene at 70 °C. The results are presented in Scheme 3. Initially, the reaction was performed using isobutyraldehyde and butylamine. Pleasingly, monosubstituted alkylnitroesters **1b**–**1d** all provided the desired products **2a**–**2c**. Reaction yields averaged 73%, and moderate to good diastereoselectivities (ranging from 3.5:1 to 5.5:1 dr) were obtained. Substituting butylamine for 2-(2-methoxyphenyl)ethanamine gave similar results with isobutyraldehyde (**2d**–**2f**). In each case, the 2-methylsubstituted nitroester starting material **1d** gave a lower diastereoselectivity than the analogous benzyl substituted or ethyl substituted starting materials, **1b** and **1c** respectively. With the sterically hindered gem-dialkylated starting material (**1f** and **1g**) no reactivity under these conditions was

observed. Interestingly, when *p*-methoxybenzaldehyde was employed in the cascade, a significant increase in diastereocontrol was observed. With ethyl and benzyl substituted nitroesters the diastereoselectivity was greater than 10:1. This high level of diastereocontrol was maintained through ortho (**2j**), meta (**2k**), and para (**2g**) substitution around the ring and for electron-rich (**2g**), electron-poor (**2l**), and halide substituted (**2m**) rings.

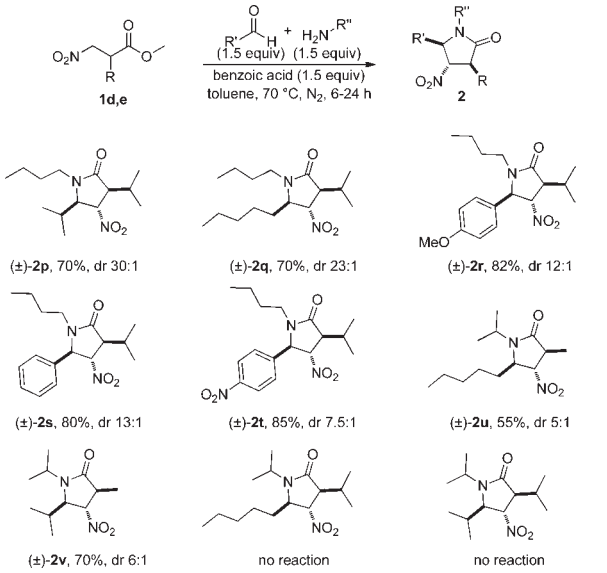
Scheme 3. Scope of Nitro-Mannich/Lactamization Cascade



The *trans*/*trans* relative stereochemistry of the major diastereomer was unambiguously determined by single crystal X-ray analysis of compounds **2a** and **2l**. By comparison of the ^{1}H NMR coupling constants, the stereochemistry of the major diastereoisomer of pyrrolidinones **2b**−**k** and **2m**−**o** was assigned by analogy. Similarly, the *trans*/*cis* relative stereochemistry of the minor diastereoisomers of the reaction was assigned by analogy to that of **2n** which was unambiguously determined by single crystal X-ray analysis;[9] see Supporting Information for details.

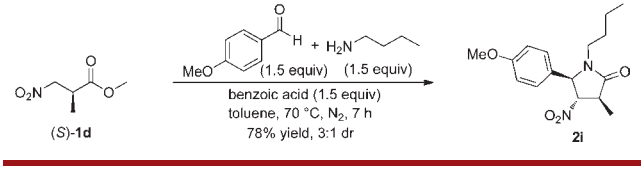
Analysis of the data from Scheme 3 suggested that the degree of diastereocontrol varied as a function of the steric demand of the reagents. Accordingly sterically demanding methyl 2-isopropyl-3-nitropropanoate **1e** was investigated (Scheme 4), and indeed good to excellent diastereocontrol ranging from 7.5:1 for **2t** to 30:1 for **2p** was observed. Using the hindered amine, isopropylamine, also gave rise to improved dr (5:1 for **2u** vs 3.5:1 for **2o**), but the reaction is significantly slower and when reacted with 3-isopropyl-nitroester **1e**, no formation of product was observed.

Scheme 4. Influence of Steric Hindrance on the Diastereocontrol



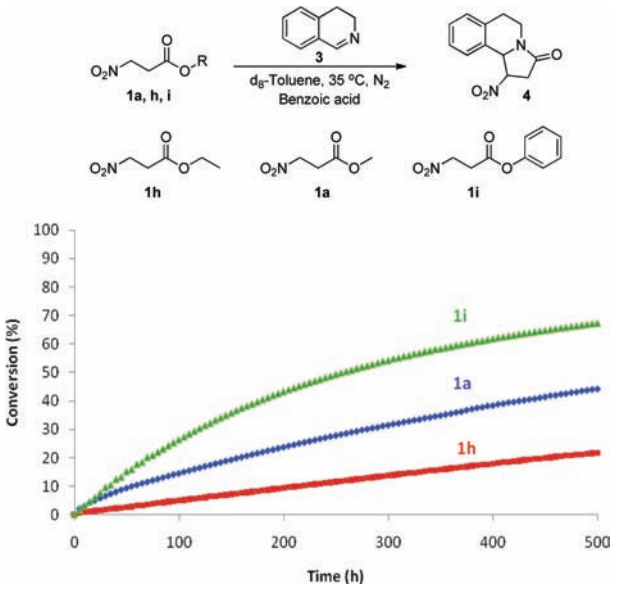
In order to begin to rationalize these data, the major and the minor diastereoisomer of **2c**, once separated, were subjected to simulated reaction conditions. After 48 h at 70 °C, no epimerization was observed. Furthermore, subjection of (*S*)-**1d** to the cascade reaction with *p*-methoxybenzaldehyde and butylamine afforded (+)-**2i** in >99% ee: racemization was not occurring at any point in the reaction pathway between **1d** and **2i** (Scheme 5).

Scheme 5. Cascade Reaction with Enantiopure Substrate



(9) Data for **2a** and **2l** were collected at 100 K using a Bruker Apex II diffractometer and solved and refined using SHELXTL [G. M. Sheldrick, G. M. *Acta Crystallogr*. **2008**, *A64*, 112–122]. Data for **2n** were collected at 150 K[Cosier, J.; Glazer, A. M. *J. Appl. Crystallogr*. **1986**, *19*, 105−107] using a Nonius KCCD Diffractometer[Otwinowski, Z.; Minor, W. *Processing of X-ray Diffraction Data Collected in Oscillation Mode, Methods in Enzymology*; Carter, C. W., Sweet, R. M., Eds.; Academic Press: 1997; p 276], solved with SIR92 [Altomare, A.; Cascarano, G.; Giacovazzo, C.; Guagliardi, A.; Burla, M. C.; Polidori, G.; Camalli, M. *J. Appl. Crystallogr*. **1994**, *27*, 435] and refined with CRYSTALS [Betteridge, P. W.; Carruthers, J. R.; Cooper, R. I.; Prout, K.; Watkin, D. J. *J. Appl. Crystallogr*. **2003**, *36*, 1487. Cooper, R. I.; Thompson, A. L.; Watkin, D. J. *J. Appl. Crystallogr*. **2010**, *43*, 1100–1107]. Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre (CCDC 853455 - 853457) and can be obtained via www. ccdc.cam.ac.uk/data_request/cif.

Scheme 6. Investigation of the Rate-Determining Step



Further studies were undertaken, using a cyclic imine **3** as a model substrate, to establish which one of the nitro-Mannich or the lactamization reactions was the rate-determining step. Three nitroesters **1a**, **1h**, and **1i** bearing different ester groups (ethyl **1h**, methyl **1a**,[10] and phenyl **1i**) were synthesized and reacted with 3,4-dihydroisoquinoline **3** and benzoic acid in deuterated toluene in an NMR tube at 35 °C. The conversion to **4** was measured by ^{1}H NMR spectroscopy at 10 min intervals over 8 h, and the results are displayed in Scheme 6. As shown in the graph, the reaction speed varies strongly with the ester substituent: the reaction with **1h** is approximately twice as slow as the reaction with **1a** and approximately three times slower than the reaction with **1i**. Hence, the rate increases with decreasing size or increasing reactivity of the ester moiety. By assuming that exchanging ethyl for methyl or phenyl does not significantly affect the pK_a of the carbon bearing the nitro group, these results suggest that lactamization is rate-determining. It is therefore reasonable that the origin of diastereocontrol lies in the favorable pseudoequatorial positioning of the substituents during the lactamization step and not during the nitro-Mannich reaction, which we suspect is reversible.

In summary, an efficient diastereoselective nitro-Mannich/lactamization reaction cascade of methyl 2-alkyl 3-nitropropanoate with imines generated *in situ* has been developed. This versatile extension of our previous work now allows direct, diastereoselective preparation of 1,3,5-trisubstituted 4-nitropyrrolidin-2-one derivatives. The diastereocontrol is likely to originate during the rate-determining lactamization step of this reaction cascade.

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Supporting Information Available. Experimental procedures and spectroscopic data for products **1a**–**f** and **2a**–**v**. This material is available free of charge via the Internet at http://pubs.acs.org.

(10) Prepared according to literature. (a) Griesser, H.; Ohrlein, R.; Schwab, W.; Ehrler, R.; Jager, V. *Org. Synth.* 2004, Coll. Vol. *10*, 577. (b) Silva, P. C.; Costa, J. S.; Pereira, V. L. P. *Synth. Commun.* **2001**, *31*, 595.