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Synthesis of β,γ-Unsaturated Lactams via a Magnesium Iodide Promoted Ring Expansion of Secondary Methylenecyclopropyl Amides

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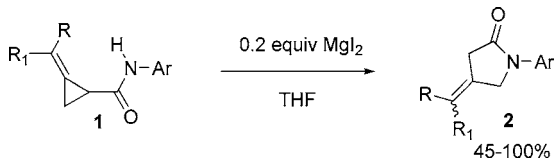
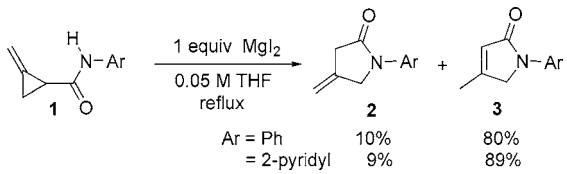
ABSTRACT



A novel and efficient route to *exo*-β,γ-unsaturated lactams from substituted and non-substituted secondary methylenecyclopropyl amides is reported. Subsequent modification of the resulting *exo*-β,γ-unsaturated lactams provides access to several pharmaceutically relevant scaffolds.

The use of highly strained methylenecyclopropanes (MCPs) as precursors for the synthesis of carbo- and heterocyclic compounds is a rapidly growing area of investigation.[1,2,3] Recently, we reported a divergent MgI_2-mediated ring expansion of secondary methylenecyclopropyl amides to give α,β-unsaturated lactams.[3b] During the course of that study, we isolated small amounts of a surprisingly stable[4] exocyclic β,γ-unsaturated lactam byproduct (Scheme 1). A survey of the literature revealed that although many reported routes exist to acyclic β,γ-unsaturated amides,[5] there are currently no methods for the synthesis of exocyclic β,γ-unsaturated lactams, despite their possible use as building blocks for a variety of related natural and pharmaceutically interesting compounds.[6] This observation prompted us to pursue a selective route to these unusual scaffolds. To this end, we

Scheme 1. Initial MgI_2 Ring Expansion[3b]



(1) For a recent review on the preparation of MCPs, see: Brandi, A.; Goti, A. *Chem. Rev.* **1998**, *98*, 589.

(2) For a recent review of MCPs used for the preparation of heterocyclic compounds, see: Brandi, A.; Cicchi, S.; Cordero, F. M.; Goti, A. *Chem. Rev.* **2003**, *103*, 1213. For recent selected references on the synthetic utility of MCPs, see: (a) Shi, M.; Liu, L.-P.; Tang, J. *J. Am. Chem. Soc.* **2006**, *128*, 7430. (b) Liu, L.-P.; Shi, M. *J. Org. Chem.* **2004**, *69*, 2805. (c) Ryu, J.-S.; Yanwu, L.; Marks, T. J. *J. Am. Chem. Soc.* **2003**, *125*, 12584. (d) Itazaki, M.; Nishihara, Y.; Osakada, K. *J. Org. Chem.* **2002**, *67*, 6889. (e) Fürstner, A.; Aïssa, C. *J. Am. Chem. Soc.* **2006**, *128*, 6306. (f) Huang, J.-W.; Shi, M. *J. Org. Chem.* **2005**, *70*, 3859. (g) Shi, M.; Liu, L.-P.; Tang, J. *J. Org. Lett.* **2006**, *8*, 4043. (h) Smolensky, E.; Kapon, M.; Eisen, M. S. *Organomet.* **2005**, *24*, 5495. (i) Kamikawa, K.; Shimizu, Y.; Takemoto, S.; Matsuzaka, H. *Org. Lett.* **2006**, *8*, 4011. (j) Shi, M.; Shao, L.-X.; Xu, B. *Org. Lett.* **2003**, *5*, 579. (k) Xu, B.; Shi, M. *Org. Lett.* **2003**, *5*, 1415. (l) Fujita, M.; Hanagiri, S.; Okuyama, T. *Tetrahedron Lett.* **2006**, *47*, 4145.

(3) For our contributions to this area, see: (a) Lautens, M.; Han, W. *J. Am. Chem. Soc.* **2002**, *124*, 6312. (b) Lautens, M.; Han, W.; Liu, J. H.-C. *J. Am. Chem. Soc.* **2003**, *125*, 4028. (c) Scott, M. E.; Han, W.; Lautens, M. *Org. Lett.* **2004**, *6*, 3309. (d) Scott, M. E.; Lautens, M. *Org. Lett.* **2005**, *7*, 3045.

(4) Single point calculations using Spartan at the RB3LYP level show an energy difference of 17.7 kcal/mol between the more stable endo product **3g** and the less stable exo product **2g**.

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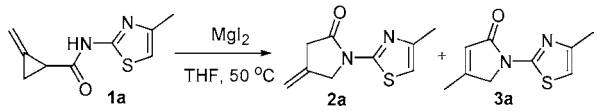
report a selective method for the preparation of *exo*-β,γ-unsaturated lactams via a MgI_2-mediated ring expansion of secondary methylenecyclopropyl amides.

Initial investigations established that although THF and MgI_2 were optimal as both solvent and Lewis acid for the reaction, use of dilute reaction conditions and substoichiometric amounts of MgI_2 were crucial to obtaining the exo isomer in excellent yield and selectivity (Table 1).

Table 1. Effect of Catalyst Loading and Concentration on Reaction Selectivity and Yield



MgI_2 loading (equiv)	concentration (M)	yield[a] (%)	**2a**:**3a** ratio[b]
1.0	0.10	75	1:6.3
0.5	0.10	53	1:2.0
0.2	0.10	49	1:1.3
0.2	0.05	91	>10:1
0.2	0.02	96	>20:1
0.2	0.005	98[c]	>20:1

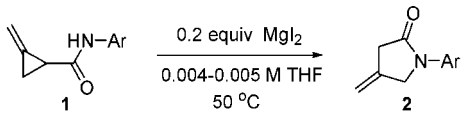
[a] Yield of the major isomer as determined by HPLC. [b] Determined by crude ^{1}H NMR. [c] Isolated yield.

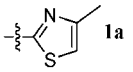
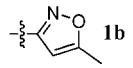
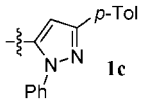
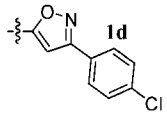
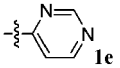
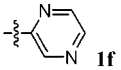
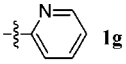
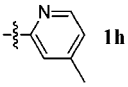
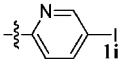
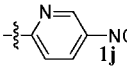
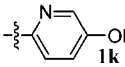
Subjecting a variety of secondary aromatic methylenecyclopropyl amides to the reaction conditions gave the desired *exo*-β,γ-unsaturated lactam products in good to excellent yields and selectivities (Table 2). Interestingly, although several substituted azoles (entries 1−3) afforded the corresponding ring-expanded products in excellent yield and selectivity, use of an analogous isoxazole substrate bearing an oxygen adjacent to the amido functionality resulted in no observable ring expansion (entry 4), suggesting that a nitrogen atom adjacent to the amido functionality was crucial to obtaining the desired exo product in good selectivity and yield.

(5) See, for example: (a) Concellón, J. M.; Bernad, P. L.; Bardales, E. *Chem. Eur. J.* **2004**, *10*, 2445. (b) Luo, F.-T.; Lu, T.-Y.; Xue, C. *Tetrahedron Lett.* **2003**, *44*, 7249. (c) Janecki, T.; Bodalski, R.; Wieczorek, M.; Bujacz, G. *Tetrahedron* **1995**, *51*, 1721. (d) Murahashi, S.-I.; Imada, Y.; Nishimura, K. *Tetrahedron* **1994**, *50*, 453. (e) Nakanishi, S.; Yamamoto, T.; Furukawa, N.; Otsuji, Y. *Synthesis* **1994**, 609. (f) Mitsudo, T.; Suzuki, N.; Kondo, T.; Watanabe, Y. *J. Org. Chem.* **1994**, *59*, 7759. (g) Deng, M.-Z.; Li, N.-S.; Huang, Y.-Z. *J. Chem. Soc., Chem. Commun.* **1993**, 65. (h) Fu, G. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **1992**, *114*, 7324. (i) Larock, R. C.; Ding, S. *Tetrahedron Lett.* **1989**, *30*, 1897. (j) Yamaguchi, M.; Hamada, M.; Kawasaki, S.; Minami, T. *Chem. Lett.* **1986**, 1085. (k) Majewski, M.; Mpango, G. B.; Thomas, M. T.; Wu, A.; Sniekus, V. *J. Org. Chem.* **1981**, *46*, 2029. (l) Jenkins, P. R.; Gut, R.; Wetter, H.; Eschenmoser, A. *Helv. Chim. Acta* **1979**, *62*, 1922. (m) Chan, K.-K.; Saucy, G. *J. Org. Chem.* **1977**, *42*, 3828. (n) Büchi, G.; Cushman, M.; Wüest, H. *J. Am. Chem. Soc.* **1974**, *96*, 5563. (o) Rossi, R.; Ingrosso, G. *Tetrahedron Lett.* **1969**, *27*, 2235.

(6) (a) Royles, B. J. L. *Chem. Rev.* **1995**, *95*, 1981. (b) Henning, H.-G.; Gelbin, A. *Adv. Heterocycl. Chem.* **1993**, *57*, 139. (c) Eberle, M.; Ziegler, H.; Cederbaum, F.; Ackermann, P. Patent WO 2002053560, 2002. (d) Weinstock, J. U.S. Patent 3,984,559, 1976. (e) Merchant, J. R.; Hakim, M. A.; Pillay, K. S.; Patell, J. R. *J. Med. Chem.* **1971**, *14*, 1239. (f) Zou, D.; Dasse, O.; Evans, J.; Higgins, P.; Kintigh, J.; Knerr, L.; Kondru, R.; Schwartz, E.; Zhai, H.-X. Patent WO 03/030897, 2003.

Table 2. Reaction Scope for Unsubstituted Secondary Methylenecyclopropyl Amides



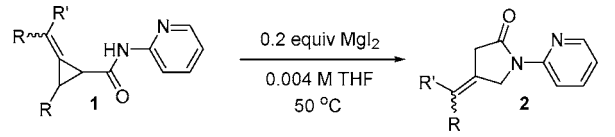
entry	MCP	time (h)	yield[a] (%)	exo:endo ratio[b]
1	 **1a**	12	98	>20:1
2	 **1b**	12	92	>20:1
3	 **1c**	60	79 (90)[c]	>20:1
4	 **1d**	24	trace	-
5	 **1e**	4	93	17:83
6	 **1f**	12	81[d]	9:1
7	 **1g**	12	93	9:1
8	 **1h**	2.5	92	3:1
9	 **1i**	7	99	>20:1
10	 **1j**	4	100	1:3
11	 **1k**	34	55[e]	3:1

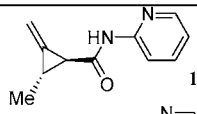
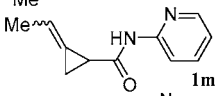
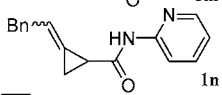
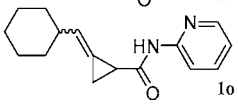
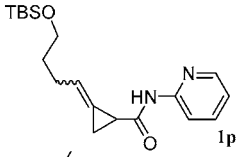
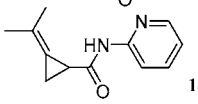
[a] Isolated combined yield of both the exo and endo products. [b] Based on crude ^{1}H NMR. [c] Yield based on recovered starting material. [d] Carried out at 0.01 M in THF. [e] Carried out at 60 °C.

Extension of these reaction conditions to 2-pyrimidine (entry 5), 2-pyrazine (entry 6), and a variety of substituted 2-pyridine systems (entries 7−11) gave the ring-expanded products in excellent yields and in modest to excellent selectivities, depending on the electronic nature of the heteroaromatic ring. In particular, mild electron-withdrawing groups and electron-rich groups (entries 6−9, 11) gave the exo product in moderate yields but high selectivity. Conversely, electron-withdrawing groups were found to afford the ring-expanded products in excellent yields, albeit in poor exo selectivity (entries 5 and 10). Attempts to improve these ratios by further decreasing the catalyst loading, reaction time, and/or concentration were unsuccessful.

We next examined the impact of substitution on the methylenecyclopropane ring (Table 3). Interestingly, MCPs substituted at either the exo methylene or cyclopropyl carbon

Table 3. Reaction Scope for Substituted Secondary Methylenecyclopropyl Amides



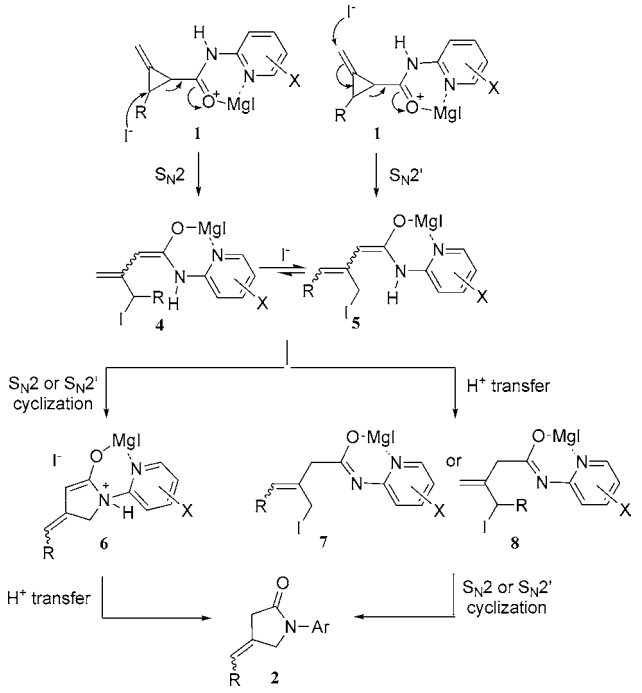
entry	MCP	time (h)	yield[a] (%)	exo:endo ratio[b]
1	 **1l**	12	82	>20:1
2	 **1m**	19	63	>20:1
3	 **1n**	26.5	64	>20:1
4	 **1o**	24	75	>20:1
5	 **1p**	38	71	>20:1
6	 **1q**	48.5	39 (45)[c]	>20:1

[a] Isolated combined yield of both the exo and endo products. [b] Based on crude ^{1}H NMR. [c] Yield based on recovered starting material.

afforded the same product, suggesting a common reaction intermediate. In all cases, yields of the ring-expanded products were moderate to good with high selectivities of the exo product. For products bearing a trisubstituted olefin, the exo products were obtained as mixtures of *E* and *Z* isomers with the *Z* isomer being the major product.[7]

Mechanistically, we propose that the reaction proceeds by initial iodide ring opening via an S_N2 or S_N2' pathway to generate the vinylogous enolate **4** or **5** (Scheme 2). Although we note that either pathway is possible, orbital constraints favor an S_N2 mechanism. Iodide-mediated isomerization of the intermediate allylic iodide[8,9] would then account for the observation that both the exo methylene-substituted and cyclopropyl-substituted starting materials give the same product (Table 3, entries 1 and 2). Enolate protonation and cyclization of **7** or **8**[10] then affords the observed products, although the relative order of these two steps may depend

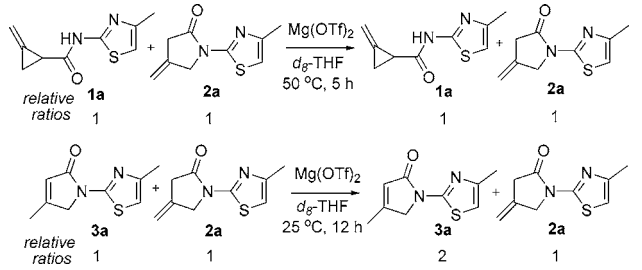
Scheme 2. Proposed Reaction Mechanism



on the electronic properties of the aromatic group. Furthermore, although either pathway is possible, we believe that protonation of the enolate followed by cyclization is more likely because this mechanism avoids the necessity for proper enolate geometry as required for a cyclization/proton-transfer route.

We also undertook additional studies to investigate the interconversion of the reaction products and, in particular, the erosion of the initial exo:endo ratio that was observed in some examples. Preliminary experiments in which the exo product was resubjected to the reaction conditions did not lead to isomerization (Scheme 3). However, in the presence

Scheme 3. Product Interconversion Studies



of the endo product at room temperature, the exo lactam underwent isomerization to the more thermodynamically stable endo isomer without any evidence of decomposition. We suspect that this unknown product isomerization pathway explains the moderate selectivies obtained with electron-rich substrates (Table 2, entry 11).[11]

Although the resulting exo pyrrolidinone products tend to be base-sensitive, it was possible to carry out synthetic

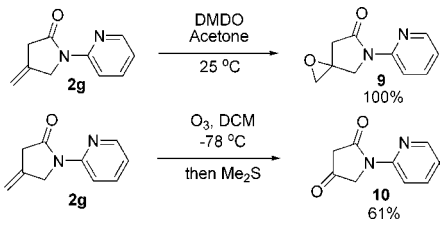
(7) See Supporting Information for details.

(8) For an example of an iodide-mediated S_N2' reaction of allylic iodides, see: McDowell, C. A.; Lossing, F. P.; Henderson, I. H. S.; Farmer, J. B. *Can. J. Chem.* **1956**, *34*, 345.

(9) Although the major route of isomerization is likely via S_N2' attack of iodide, there is a possibility that trace I_2, either generated in situ or as an impurity in the commercial MgI_2, could lead to allylic iodide isomerization. For instance, see: (a) Sibbett, D. J.; Noyes, R. M. *J. Am. Chem. Soc.* **1953**, *75*, 761. (b) Sibbett, D. J.; Noyes, R. M. *J. Am. Chem. Soc.* **1953**, *75*, 763. (c) Cain, W. P.; Noyes, R. M. *J. Am. Chem. Soc.* **1959**, *81*, 2031.

transformations to gain access to a variety of pharmaceutically relevant scaffolds. For example, treatment of the 2-pyridyl pyrrolidinone **2g** with DMDO cleanly afforded epoxide **9** with no evidence of *N*-oxide formation, even in the absence of a pyridyl protecting group (Scheme 4).[12] Such

Scheme 4. Product Modification



epoxides could prove to be useful building blocks for the preparation of a family of CCR2 chemokine receptor antagonists.[6f] Alternatively, the same 2-pyridyl pyrrolidinone could be treated with ozone to access the corresponding β-keto-derivative **10** in good yield. Such keto-derivatives are noteworthy since they belong to a class of tetramic acid derivatives that typically possess a broad range of biological activities.[6a−e]

In summary, we have described a selective ring expansion of secondary MCP amides to *exo*-pyrrolidinones using catalytic MgI_2 at high dilution. Further examination of the reaction scope and mechanism is ongoing.

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

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(10) Although an S_N2' ring-closing pathway (5-*endo-trig)* is unfavored by Balwin's rules, similar 5-*endo-trig* ring-closing reactions have been reported for the synthesis of pyrrolidines. See, for example: (a) Padwa, A.; Norman, B. H. *J. Org. Chem.* **1990**, *55*, 4801. (b) Craig, D.; Jones, P. S.; Rowlands, G. J. *Synlett* **1997**, 1423. (c) Auvray, P.; Knochel, P.; Normant, J. F. *Tetrahedron Lett.* **1985**, *26*, 4455. (d) Berry, M. B.; Craig, D.; Jones, P. S.; Rowlands, G. J. *Chem. Commun.* **1997**, *22*, 2141. (e) Jones, A. D.; Knight, D. W. *Chem. Commun*. **1996**, 915. (f) Dell'Erba, C.; Mugnoli, A.; Novi, M.; Pani, M.; Petrillo, G.; Tavani, C. *Eur. J. Org. Chem*. **2000**, 903. (g) Chang, K. T.; Jang, H. Y.; Kim, Y. K.; Park, K. H.; Lee, W. S. *Heterocycles* **2001**, *55*, 1173.

(11) For **1k** (Table 2, entry 11), initial ^{1}H NMR analysis showed only **2k** along with unreacted starting material. Extensive formation of the endo isomer (**3k**) along with significant amounts of decomposition were observed after prolonged heating.

(12) Typically, oxidation with DMDO occurs preferentially at the pyridyl nitrogen first, then at the alkene. Often in situ protecting groups such as BF_3·Et_2O are used to reverse this selectivity. See, for example: (a) Ferrer, M.; Sànchez-Baeza, F.; Messeguer, A.; Diez, A.; Rubiralta, M. *J. Chem. Soc. Chem. Commun*. **1995**, 293. (b) Ferrer, M.; Sànchez-Baeza, F.; Messeguer, A. *Tetrahedron* **1997**, *53*, 15877.