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Highly Efficient and Versatile Synthesis of Lactams and *N*-Heterocycles via Al(OTf)$_3$-Catalyzed Cascade Cyclization and Ionic Hydrogenation Reactions

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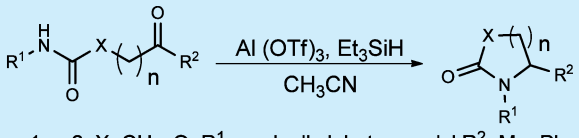
Supporting Information

ABSTRACT: The discovery and development of an efficient and versatile method for the synthesis of *N*-substituted lactams is described. Pyrrolindinones, piperidones, and structurally related heterocycles were formed by Al(OTf)$_3$-catalyzed cascade cyclization and ionic hydrogenation reactions of corresponding nitrogen substituted ketoamides in good yields.



N-Substituted lactams constitute an important class of chemical structures that have found widespread applications in agrochemicals, pharmaceuticals (Figure1), and other industries.[1]

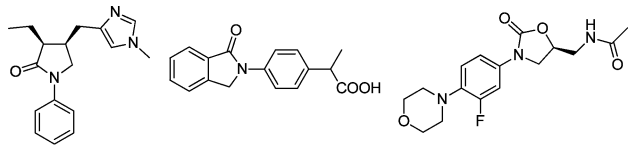
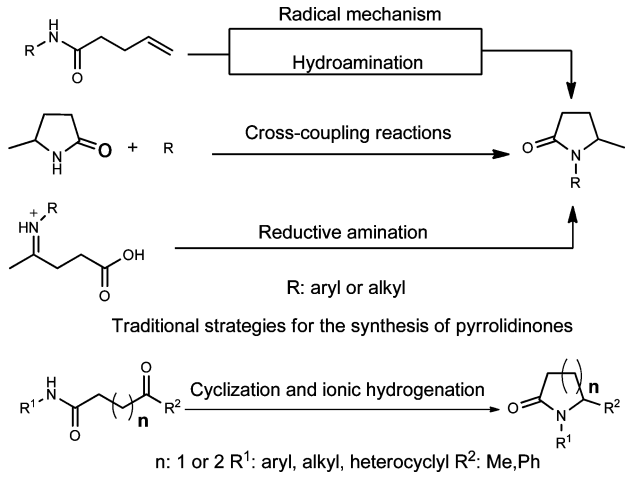


Figure 1. Pharmacologically active nitrogen substituted lactams.

Because lactam derivatives have great influence in their properties, efficient methods for the preparation of this structural unit are highly desirable. In the past few decades, several approaches to lactams have been developed (Scheme 1). Nicolaou and Li et al. reported that pyrrolidinones could be formed by unactivated alkenes via a radical mechanism.[2,3] Che et al. and Hartwig also used alkenes as starting material to afford pyrrolidinones by a hydroamination method.[4,5] Baudoin and co-workers reported a novel method for preparing *N*-arylated lactams that relied on the Pd-catalyzed coupling reaction.[6] In addition, transition-metal-catalyzed reductive amination methods were developed to convert levulinic acid to pyrrolidinones in one pot.[7] During studies on the methodology of the construction of heterocycles, we discovered that Al(OTf)$_3$-catalyzed cascade cyclization and ionic hydrogenation reactions could generate five- and six-membered heterocycles with substitution of various groups in good yields under conventional conditions.

The idea was based on our recent finding that tetralins could be obtained from arene-1,4-diones with a combination of $TiCl_4$/Et_3SiH.[8] Encouraged by this result, we conceived that

Scheme 1. Strategies for the Synthesis of Pyrrolidinones and Piperidones



such a combination might be utilized though Lewis acid catalyzed cyclization and ionic hydrogenation to provide pyrrolidinones from *N*-substituted γ-ketoamides. 4-Oxo-*N*-phenylpentanamide **1a** was initially employed as a substrate with the $TiCl_4$ /Et_3SiH/CH_2Cl_2 system in our investigation. Hydroxyamide **1c** was detected as the major product while only 10% *N*-phenyl pyrrolidinone (**1b**) was obtained (Table1, entry 1). Further study was performed to investigate the effects of different solvent systems and various Lewis or Brønsted acid catalysts for intramolecular cyclization of γ-ketoamide **1a**. As shown in Table 1, CH_3CN proved to be superior and resulted in a 30% yield among the solvents tested (Table 1, entries 1–

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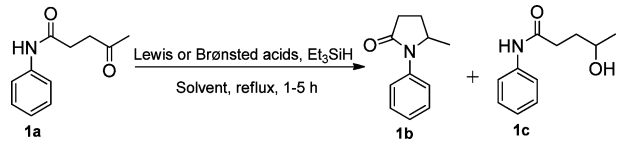
Table 1. Optimization of the Reaction Conditions[a]



				yield[b] (%)	
entry	catalyst (equiv)	solvent	time (h)	**1b**	**1c**
1	$TiCl_4$ (2.0)	CH_2Cl_2	5	10	65
2	$TiCl_4$ (2.0)	THF	5	25	30
3	$TiCl_4$ (2.0)	CH_3CN	4	30	45
4	$TiCl_4$ (2.0)	toluene	5	0	50
5	$SnCl_4$ (2.0)	CH_3CN	4	8	50
6	$AlCl_3$ (2.0)	CH_3CN	4	29	69
7	CF_3COOH (2.0)	CH_3CN	3	76	0
8	$Al(OTf)_3$ (2.0)	CH_3CN	1	97	0
9	$Al(OTf)_3$ (1)	CH_3CN	1	98	0
10	$Al(OTf)_3$ (0.5)	CH_3CN	1	98	0
11[c]	$Al(OTf)_3$ (0.5)	CH_3CN	1	80	0
12[d]	$Al(OTf)_3$ (0.5)	CH_3CN	1	45	0
13	$Al(OTf)_3$ (0.2)	CH_3CN	2	85	0

[a]All reactions were performed at reflux for 1−5 h with 1.0 mmol of **1a**, the indicated amount of Lewis or Brønsted acid, and 2.0 equiv of Et_3SiH in 5.0 mL of the indicated solvent. [b]Isolated yields. [c]1.5 equiv of Et_3SiH. [d]1.0 equiv of Et_3SiH.

4). Then, attention was turned to screen various Lewis or Brønsted acids (Table 1, entries 5−8) to facilitate the cyclization step. Notably, $Al(OTf)_3$ (Table 1, entry 8) was found to be more generally effective than other agents. The yield of **1b** was significantly increased to 97% with 2 equiv of $Al(OTf)_3$ after only 1 h. To further optimize the reaction parameters, the catalyst loadings were reduced to 1, 0.5, and 0.2 equiv, leading to 98%, 98%, and 85% yields, respectively (Table 1, entries 9, 10, and 13). The amount of Et_3SiH was also observed to affect the yield of **1b** (Table 1, entries 10−12). The best result was found that **1a** was added into CH_3CN with $Al(OTf)_3$ (0.5 equiv)/Et_3SiH (2 equiv) and refluxed for 1 h to afford **1b** in 98% yield.

After the optimized reaction conditions were established, we examined the scope and limitation of this cascade process for the assembly of 5-methyl-*N*-(aryl,alkyl)-2-pyrrolidinones. Both amides from anilines or alkylamines were used to explore the scope of the reaction. To our delight, the reaction was unbiased to aryl (Table 2, entries 1−12) or alkyl (Table 2, entries 13−16) substitution on the nitrogen atom. It was found that all compounds with electron-donating groups (Table 2, entry 6), electron-withdrawing groups (Table 2, entries 1, 7−9, and 11), and halides(Table 2, entries 1−3, 10, and 11) situated at the *ortho*, *meta*, or *para* position at the aniline phenyl ring proceeded smoothly and in good yields. It was noteworthy that the nitro group substituted compound (Table 2, entry 8) was converted into the corresponding product in good yield, which was reported as being difficult to prepare under normal conditions.[2] The heterocycle substituted ketoamides (Table 2, entries 17 and 18) were also found to work well in the current reaction system. In addition, structure diverse pyrrolidinones (Table 2, entries 19−23) had also been obtained in moderate to good yields. Encouraged by the results above, the generality of this catalytic system was further tested in the reaction of *δ*-ketoamides. Corresponding piperidones (Table 2, entries 24−28) had been achieved, which represented another class of

Table 2. Assembly of *N*-Substituted Pyrrolidinones and Piperidinones from Ketoamides[a]

entry	R^1	R^2	n	substrate	product	yield[b][%]
1	4-FC_6H_4	Me	1	**2a**	**2b**	94
2	4-ClC_6H_4	Me	1	**3a**	**3b**	90
3	4-BrC_6H_4	Me	1	**4a**	**4b**	81
4	4-MeC_6H_4	Me	1	**5a**	**5b**	80
5	4-EtC_6H_4	Me	1	**6a**	**6b**	83
6	4-$MeOC_6H_4$	Me	1	**7a**	**7b**	81
7	4-$CF_3C_6H_4$	Me	1	**8a**	**8b**	92
8	4-$NO_2C_6H_4$	Me	1	**9a**	**9b**	83
9	4-CNC_6H_4	Me	1	**10a**	**10b**	84
10	3-ClC_6H_4	Me	1	**11a**	**11b**	81
11	2-FC_6H_4	Me	1	**12a**	**12b**	86
12		Me	1	**13a**	**13b**	80
13	*n*-Pentyl	Me	1	**14a**	**14b**	82
14	Cyclohexyl	Me	1	**15a**	**15b**	82
15	-$CH_2CO_2CH_3$	Me	1	**16a**	**16b**	60
16	Benzyl	Me	1	**17a**	**17b**	88
17	3-thienyl	Me	1	**18a**	**18b**	50
18	5-quinolyl	Me	1	**19a**	**19b**	65
19	Ph	Ph	1	**20a**	**20b**	96
20	4-$CF_3C_6H_4$	Ph	1	**21a**	**21b**	86
21	4-$MeOC_6H_4$	Ph	1	**22a**	**22b**	82
22	Benzyl	Ph	1	**23a**	**23b**	75
23				 **24a**	 **24b**	50
24	Ph	Me	2	**25a**	**25b**	80
25	4-ClC_6H_4	Me	2	**26a**	**26b**	90
26	4-$MeOC_6H_4$	Me	2	**27a**	**27b**	97
27	4-$CF_3C_6H_4$	Me	2	**28a**	**28b**	71
28	3-thienyl	Me	2	**29a**	**29b**	72

[a]Reaction conditions: All reactions were performed at reflux for 1−4 h with 1.0 mmol of **1a**, 0.5 equiv of $Al(OTf)_3$, and 2.0 equiv of Et_3SiH in 5.0 mL of dry acetonitrile. [b]Yield of isolated product.

important heterocycle compounds of significant bioactive interest.[9]

This $Al(OTf)_3$-catalyzed cascade cyclization and ionic hydrogenation reaction was considered to provide an efficient alternative method for the formation of the C−N bond, which might enable the construction of structure diverse lactams from a vast array of building blocks. Remarkably, isoindolinones, oxazolidinone, and dihydroquinazolinone were readily assembled from the corresponding *N*-aryl amides, carbamates, and open-chain ureas, respectively, with good yields (Table 3).

The X-ray crystal structure of representative target molecule **20b** (CCDC 969129) was elucidated (Figure 2), showing that the desired intramolecular cyclization of ketoamide had been achieved by this protocol.

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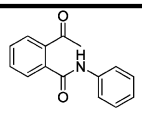
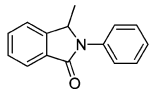
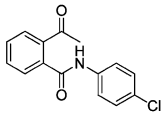
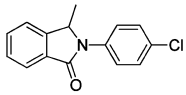
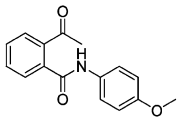
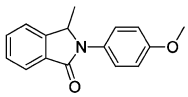
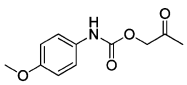
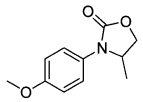
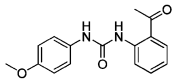
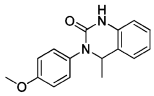
Table 3. Assembly of Isoindolinones, Oxazolidinone, and Dihydroquinazolinone Catalyzed by $Al(OTf)_3$[a]

entry	substrate	product	yield[b](%)
1	 **30a**	 **30b**	75
2	 **31a**	 **31b**	71
3	 **32a:**	 **32b**	81
4	 **33a**	 **33b**	65
5	 **34a**	 **34b**	73

[a]Reaction conditions: All reactions were performed at reflux for 1−4 h with 1.0 mmol of **1a**, 0.5 equiv of $Al(OTf)_3$, and 2.0 equiv of Et_3SiH in 5.0 mL of dry acetonitrile. [b]Yield of isolated product.

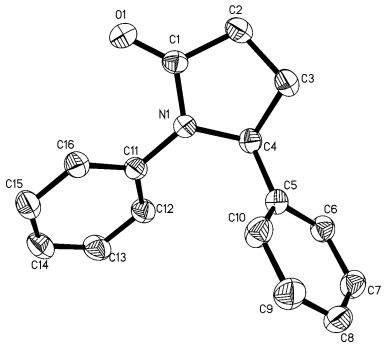


Figure 2. X-ray crystal structure of compound **20b**.

In conclusion, we have developed an efficient and verstaile $Al(OTf)_3$-catalyzed cascade cyclization and ionic hydrogenation method for *N*-substituted lactams preparation. The reaction is applicable to a wide range of substrates with various functional groups to afford the corresponding pyrrolidinones, piperidones, and structure related heterocycles in moderate to good yields. The ease of preparation of the nitrogen substituted precursors, the mild reaction conditions, and the efficiency of this reaction that enable cyclization and hydrogenation to be attainable in one step make this protocol an attractive methodology in organic synthesis.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data for all compounds and X-ray crystal structure data (CIF) for compound **20b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Brickner, S. J.; Barbachyn, M. R.; Hutchinson, D. K.; Manninen, P. R. *J. Med. Chem.* **2008**, *51*, 1981. (b) Das, S.; Addis, D.; Knopke, L. R.; Bentrup, U.; Junge, K.; Bruckner, A.; Beller, M. *Angew. Chem., Int. Ed.* **2011**, *50*, 9180. (c) Lei, A.; Waldkirch, J. P.; He, M.; Zhang, X. *Angew. Chem., Int. Ed.* **2002**, *41*, 4526. (d) Manzer, L. E. U.S. Patent 6,818,593, 2004.

(2) Nicolaou, K. C.; Zhong, Y.-L.; Baran, P. S. *Angew. Chem., Int. Ed.* **2000**, *39*, 625.

(3) (a) Li, Z.; Song, L.; Li, C. *J. Am. Chem. Soc.* **2013**, *135*, 4640. (b) Lu, H.; Li, C. *Tetrahedron Lett.* **2005**, *46*, 5983.

(4) Liu, X.-Y.; Li, C.-H.; Che, C.-M. *Org. Lett.* **2006**, *8*, 2707.

(5) Schlummer, B.; Hartwig, J. F. *Org. Lett.* **2002**, *4*, 1471.

(6) Guyonnet, M.; Baudoin, O. *Org. Lett.* **2012**, *14*, 398.

(7) (a) Wei, Y.; Wang, C.; Jiang, X.; Xue, D.; Li, J.; Xiao, J. *Chem. Commun.* **2013**, *49*, 5408. (b) Huang, Y. B.; Dai, J. J.; Deng, X. J.; Qu, Y. C.; Guo, Q. X.; Fu, Y. *ChemSusChem* **2011**, *4*, 1578. (c) Du, X. L.; He, L.; Zhao, S.; Liu, Y. M.; Cao, Y.; He, H. Y.; Fan, K. N. *Angew. Chem., Int. Ed.* **2011**, *50*, 7815.

(8) Li, G.; Xiao, Q.; Li, C.; Wang, X.; Yin, D. *Tetrahedron Lett.* **2011**, *52*, 6827.

(9) (a) Elworthy, T. R.; Brill, E. R.; Caires, C. C.; Kim, W.; Lach, L. K.; Tracy, J. L.; Chiou, S. S. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2523. (b) Miller, T. A.; Ghosh, J.; Myers, C. E.; Macdonald, T. L. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1913.