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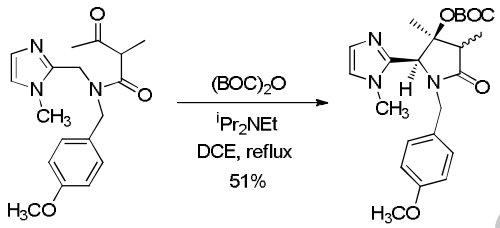

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Intramolecular cyclization of alkylimidazoles

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ABSTRACT

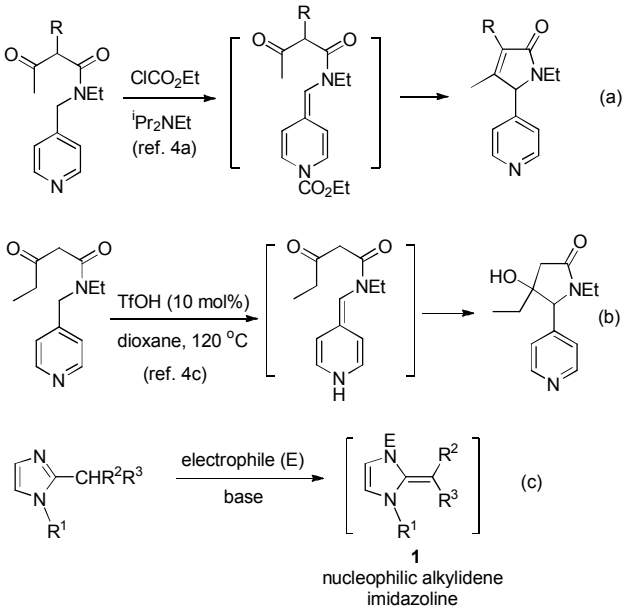
1,2-Dialkylimidazoles can be converted to nucleophilic 2-alkylidene imidazolines upon treatment with $(BOC)_2O$ under mild conditions. Incorporation of a β-keto amide carbonyl electrophile in the 2-alkylimidazole side chain results in intramolecular aldol-like cyclization to afford imidazole-functionalized γ-lactams. Positioning of a ketone electrophile in a 1-alkyl side chain results in cyclization at the 2-position to afford fused ring imidazoles through a similar reaction manifold. Efficient transfer of a BOC group from an intermediate N-acyl imidazolium species to a nucleophilic center in the cyclized product appears to be an important feature of these reactions.

1. Introduction

Azaheterocycles occupy positions of unparalleled importance in natural product and medicinal chemistry.[1] Owing to the wide range of biological activities exhibited by N-heterocyclic natural products and unnatural pharmacologic agents, developing new synthetic strategies to both synthesize azaheterocycles and manipulate existing azaheterocyclic ring systems remain important objectives.

In this context, we have begun examining the reactivity of aromatic N-heterocycles, such as pyridine, toward new dearomatization manifolds leading to functionalized dihydropyridines and piperidines.[2,3] As part of these studies, we have also begun examining the reactivity of alkylidene dihydropyridines (anhydrobases) with the aim of expanding the synthetic utility of these readily accessible intermediates.[4] Toward this end, we recently reported successful intramolecular benzylic cyclizations of 4-substituted pyridines via anhydrobase intermediates generated by transient electrophilic activation of pyridine substrates with ethyl chloroformate (Scheme 1a).[4a,b] Subsequently, we found that similar cyclizations could be effected in the presence of Brønsted acid catalysts, presumably via formation of enamine-like intermediates (Scheme 1b).[4c]

Imidazoles offer similar opportunities for generation of nucleophilic alkylidene imidazolines (**1**) via electrophilic activation (Scheme 1c).[5] Consequently, appropriately substituted 2-alkylimidazoles and/or 1,2-dialkylimidazoles should also be capable of participating in intramolecular cyclizations analogous to those depicted in Scheme 1a,b. Indeed, a few examples of *intermolecular* aldol- and Mannich-type condensations involving electrophilic activation of 1,2-dialkyl imidazoles have been reported.[6] More recently, the reactivity of alkylidene imidazolines toward other electrophiles (e.g., activated alkyl halides) has been examined as well.[7] Finally, several studies have explored the reactivity of methylene and alkylidene imidazolines toward various transition metal fragments.[8] Notably, imidazolines such as **1** represent deoxy analogues of intermediates potentially encountered in imidazolium-based N-heterocyclic carbene-catalyzed transformations of aldehydes (i.e., Breslow intermediates), thus further stimulating interest in reactive species of this type.[9]

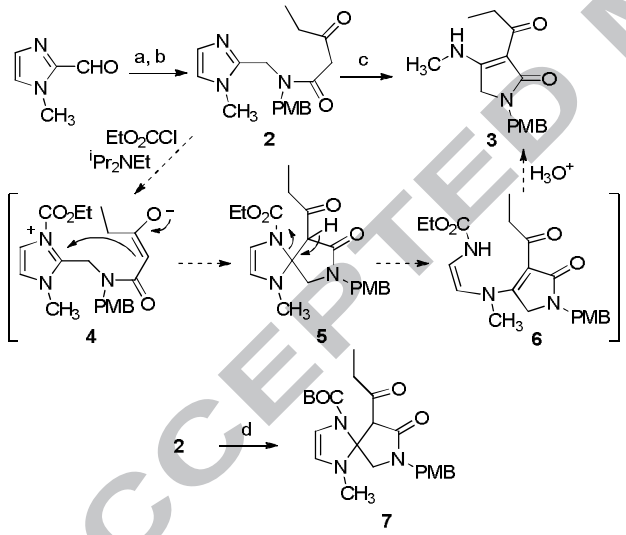


Scheme 1

Given the general importance of imidazole-based heterocycles in natural product/medicinal chemistry[10] coupled with increasing interest in the chemistry of alkylidene imidazolines and our previous experiences with pyridine anhydrobases, we set out to explore intramolecular reaction manifolds available to relatively simple 1,2-disubstituted imidazoles in the presence of electrophilic activating agents. We report the preliminary results of this study that has resulted in identification of reaction conditions leading to successful preparation of imidazole-substituted lactams from 2-alkylimidazole precursors and formation of pyrrolo[1,2-*a*]imidazoles from 1-alkylimidazoles.

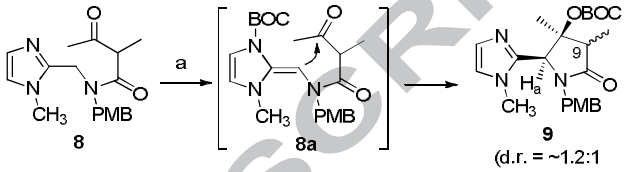
2. Results and discussion

Our study began with the straightforward preparation of imidazole **2** starting from 1-methylimidazole-2-carboxaldehyde (Scheme 2).[11] This compound was then subjected to reaction conditions previously found to be effective in promoting formation and intramolecular aldol-like cyclization of pyridine-derived anhydrobases.[4a] In this instance, however, none of the expected imidazole-substituted lactam was obtained, instead lactam **3** was isolated, albeit in modest yield. We speculate that **3** arises from electrophilic activation of the imidazole ring with EtO_2CCl followed by nucleophilic addition of the activated methylene to afford spirocyclic intermediate **5**. Base-promoted elimination/ring opening of the imidazoline then gives **6**. Addition of TFA/H_2O induces enamine hydrolysis to yield the observed product. Consistent with this mechanistic rationale, changing the electrophilic activating agent to $(BOC)_2O$ and omitting the acid treatment resulted in conversion of **2** to spirocycle **7**, although again in modest isolated yield.



Scheme 2. Reagents and conditions. (a) (i) *p*-$CH_3OC_6H_4CH_2NH_2$, mol. sieves; (ii) $NaBH_4$, 76%. (b) methyl 3-oxovalerate, $PhCH_3$, reflux, 75%. (c) (i) EtO_2CCl (1.5 equiv), $^iPr_2NEt$ (2 equiv), $Ti(O^iPr)_4$ (0.5 equiv), THF, reflux; (ii) TFA, H_2O, reflux, 25%. (d) $(BOC)_2O$ (1.5 equiv), $^iPr_2NEt$ (2 equiv), DCE, reflux, 41%.

In previous studies involving manipulation of pyridine anhydrobases equipped with β-amido carbonyl side chains, it was observed that substituents on the activated methylene group promoted benzylic cyclization at the expense of competing spirocyclization.[4a] To probe for similar effects in the imidazole series, substrate **8**, bearing a methyl group at the dicarbonyl-activated carbon, was treated with $(BOC)_2O$ and $^iPr_2NEt$ in refluxing DCE. Disappearance of starting material was observed to be complete after ~12 h, and imidazole-substituted lactam **9** was isolated in good yield (51%, as a ~1:1 mixture of diastereomers[12]) after purification by flash column chromatography (Scheme 3). The formation of **9** is consistent with the expected reaction manifold involving imidazole activation by $(BOC)_2O$ followed by deprotonation to generate a nucleophilic imidazoline (**8a**) that reacts with the pendant carbonyl electrophile. Transfer of the BOC group to the resulting oxyanion (by intra- and/or intermolecular acylation) then completes the transformation. Slow evaporation of an EtOAc/hexane solution of **9** deposited single crystals suitable for X-ray analysis. Fortuitously, both diastereomers were found to be present in the crystal as shown in Figure 1 (relative occupancy 0.6:0.4), thus establishing the relative stereochemistry of both products.[13]



Scheme 3. Reagents and conditions. (a) $(BOC)_2O$ (1.5 equiv), $^iPr_2NEt$ (2 equiv), DCE, reflux, 51%.

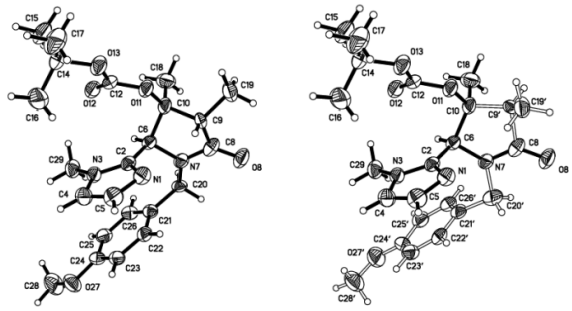
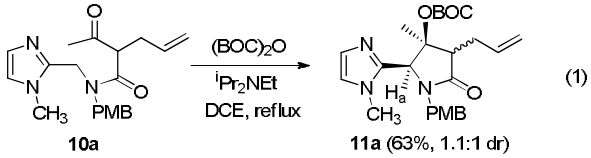
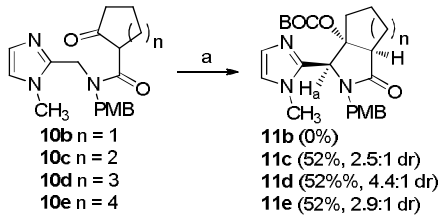


Figure 1. X-ray structure of **9** showing the molecular structure of both diastereomers that differ in relative configuration at C9/C9' (Scheme 3).

Several other imidazoles bearing α-alkyl-β-ketoamide substituents at the 2-position were subjected to these cyclization conditions as well, and the results are summarized in Eq. 1 and Scheme 4. In each case diastereomeric ratios were estimated by comparison of ^{1}H-NMR resonances corresponding to H_a. Relative stereochemistry in **11a** (Eq. 1) was assigned by analogy to **9** (*vide supra*). Cyclopentanone-derived substrate **10b** did not undergo cyclization (Scheme 4). The other cycloalkanone-imidazoles (**10c-e**) gave the reaction to afford imidazole-substituted lactams (**11c-e**) in comparable yields, each as inseparable mixtures of two diastereomers. A NOESY spectrum obtained on cycloheptyl adduct **11d** allowed assignment of relative stereochemistry in both the major and minor diastereomer according to the correlations indicated in Figure 2. The presumed reactive conformations leading to these diastereomeric products are also illustrated. Relative stereochemistry of the major diastereomer in **11c** and **11e** has been tentatively assigned as shown in Scheme 4 by analogy to **11d**.



(1)



Scheme 4. Reagents and conditions. (a) $(BOC)_2O$ (1.5 equiv), $^iPr_2NEt$ (2 equiv), DCE, reflux.

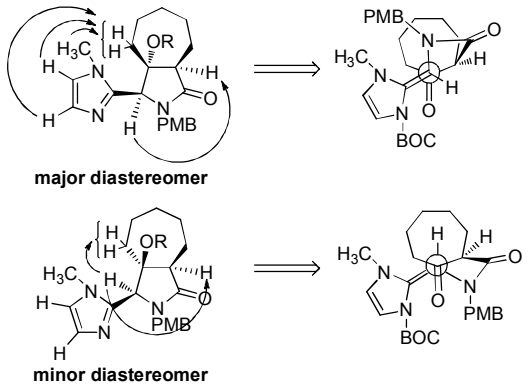
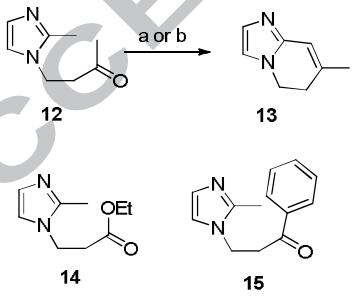


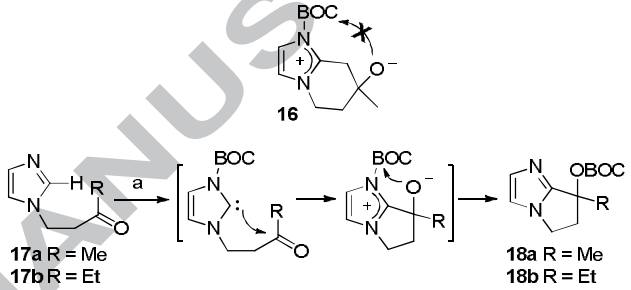
Figure 2. NOESY correlations in **11e** (R = BOC).

We next turned our attention to the preparation of fused-ring imidazo-derivatives via intramolecular cyclization of *N*-alkyl-2-methylimidazoles under reaction conditions expected to generate nucleophilic imidazoline intermediates. Thus, exposure of **12**[14] to $(BOC)_2O$ in refluxing DCE resulted in complete consumption of starting material within 30 minutes, and imidazo[1,2-*a*]dihydropyridine **13** was obtained, albeit in impure form, in 44% yield after chromatography (Scheme 5).[15] No added base was used in this process as *tert*-butoxide anion should be generated upon reaction of the imidazole with $(BOC)_2O$.[6b,c,16] Efforts to improve this transformation revealed that performing the reaction at room temperature in acetonitrile gave comparable results, but the yield of **13** never rose above ~40%. Moreover, structurally related substrates such as **14** and **15** afforded intractable reaction mixtures under both sets of conditions.



Scheme 5. Reagents and conditons. (a) $(BOC)_2O$, DCE, reflux, 44%. (b) $(BOC)_2O$, CH_3CN, rt, 41%.

A common feature in successful intramolecular cyclization reactions involving imidazoline intermediates described above (Schemes 3-4) and mechanistically analogous intermolecular transformations of 2-alkylimidazoles reported previously[6] is the transfer of an electrophilic activating group (e.g., *tert*-butoxy carbonyl) from an imidazolium ring to a nucleophilic oxygen generated in the course of aldol-like condensation. Conversion of **12** to **13**, however, necessitates formation of an intermediate oxyanion that is structurally impeded from participating in an intramolecular acyl transfer involving a BOC-substituted imidazolium species (**16**). To probe the importance of this feature in reactions leading to fused-ring imidazo products, 2-unsubstituted imidazoles **17** were treated with $(BOC)_2O$ with the aim of generating nucleophilic acyl imidazolium carbenes capable of participating in intramolecular cyclizations to give oxyanion intermediates.[17] Indeed, both **17a**,**b** were transformed to the pyrrolo[1,2-*a*]imidazoles **18a**,**b** in virtually quantitative yield according to NMR analysis of crude products (Scheme 6). Unfortunately, both compounds proved to be unstable, readily decomposing upon attempted purification, thus characterization was performed on impure material obtained directly from reaction mixtures. Nonetheless, the difference in reactivity between **17** and **12** seemingly supports the notion that a pathway for facile conversion of acyl imidazolium intermediates to stable imidazoles is an important parameter in successful intramolecular cyclizations of *in situ*-generated 2-alkylidene imidazolines and imidazolium carbenes.



Scheme 6. Reagents and conditions. (a) $(BOC)_2O$, CH_3CN, rt, 12 h, 100%.

3. Conclusions

In conclusion, we have demonstrated that nucleophilic 2-alkylidene imidazolines can be generated from 1,2-dialkylimidazoles under mild conditions and that these reactive intermediates are capable of participating in intramolecular cyclization reactions with appropriately positioned electrophiles. Specifically, aldol-like cyclizations of keto-amide side chains attached to the 2-position of imidazole substrates were found to proceed in reasonable yield to deliver imidazole-substituted γ-lactam products. Results from attempts to prepare fused ring imidazo[1,2-*a*]dihydropyridines and pyrrolo[1,2-*a*]imidazoles via intramolecular cyclization of 2-methylimidazoles and 2-unsubstituted imidazoles, respectively, indicate that the ability to regenerate a stable imidazole at the conclusion of the cyclization event by transfer of an acyl activating group to a nucleophilic center in the newly-formed ring may be an important feature of successful transformations. These results show the potential to generate functionalized imidazole derivatives by manipulation of peripheral substituents. Current studies seek to further define the synthetic utility of alkylidene imidazolines in organic and organometallic reaction manifolds.

Acknowledgments

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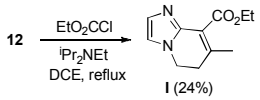
Supplementary Material

Experimental procedures, compound characterization data, ^{1}H-, ^{13}C-NMR spectra, and crystallization data (cif file) can be found in the online version of this article at doi: 10.1016/j.tetlet.xxxx.xx.xxx.

References and notes

1. (a) *Progress in Heterocyclic Chemistry*; Gribble, G. W.; Joule, J. A., Eds; Elsevier; Oxford, 2014; Vol. 26. (b) Vitaku, E.; Smith, D. T.; Njardarson, J. T. *J. Med. Chem.* **2014**, doi: 10.1021/jm501100b. (c) Ritchie, T. J.; Macdonald, S. J. F.; Peace, S.; Pickett, S. D.; Luscombe, C. N. *Med. Chem. Commun.* **2012**, *3*, 1062-1069.
2. (a) Parameswarappa, S. G.; Pigge, F. C. *Org. Lett.* **2010**, *12*, 3434-3437. (b) Parameswarappa, S. G.; Pigge, F. C. *Tetrahedron Lett.* **2011**, *52*, 4357-4359.
3. Bull, J. A.; Mousseau, J. J.; Pelletier, G.; Charette, A. B. *Chem. Rev.* **2012**, *112*, 2642-2713.
4. (a) Parameswarappa, S. G.; Pigge, F. C. *J. Org. Chem.* **2012**, *77*, 8038-8048. (b) Pawar, L.; Pigge, F. C. *Tetrahedron Lett.* **2013**, *54*, 6067-6070. (c) Lansakara, A. I.; Farrell, D. P.; Pigge, F. C. *Org. Biomol. Chem.* **2014**, *12*, 1090-1099.
5. Zificsak, C. A.; Hlasta, D. J. *Tetrahedron* **2004**, *60*, 8991-9016.
6. (a) Trofimov, B. A.; Andriyankova, L. V.; Nikitina, L. P.; Belyaeva, K. V.; Mal'kina, A. G.; Afonin, A. V.; Ushakov, I. A. *Tetrahedron Lett.* **2013**, *54*, 4693-4696. (b) Zificsak, C. A.; Hlasta, D. J. *Tetrahedron Lett.* **2005**, *46*, 4789-4792. (c) Deng, Y.; Hlasta, D. J. *Tetrahedron Lett.* **2002**, *43*, 189-192. (d) Gallagher, T. F.; Adams, J. L. *Tetrahedron Lett.* **1989**, *30*, 6599-6602.
7. (a) Knappke, C. E. I.; Arduengo, III, A. J.; Jiao, H.; Neudörfl, J.-M.; von Wangelin, A. J. *Synthesis* **2011**, 3784-3795. (b) Knappke, C. E. I.; Neudörfl, J.-M.; von Wangelin, A. J. *Org. Biomol. Chem.* **2010**, *8*, 1695-1705.
8. (a) Kronig, S.; Jones, P. G.; Tamm, M. *Eur. J. Inorg. Chem.* **2013**, 2301-2314. (b) Song, G.; Li, X.; Song, Z.; Zhao, J.; Zhang, H. *Chem. – Eur. J.* **2009**, *15*, 5535-5544. (c) Fürstner, A.; Alcarazo, M.; Goddard, R.; Lehmann, C. W. *Angew. Chem. Int. Ed.* **2008**, *47*, 3210-3214. (d) Viciano, M.; Feliz, M.; Corberán, R.; Mata, J. A.; Clot, E.; Peris, E. *Organometallics* **2007**, *26*, 5304-5314. (e) Kuhn, N.; Bohnen, H.; Kreutzberg, J.; Bläser, D.; Boese, R. *J. Chem. Soc., Chem. Commun.* **1993**, 1136-1137.
9. DiRocco, D. A.; Oberg, K. M.; Rovis, T. *J. Am. Chem. Soc.* **2012**, *134*, 6143-6145.
10. Boiani, M.; González, M. *Mini-Rev. Med. Chem.* **2005**, *5*, 409-424.
11. A UV active PMB protecting group was employed to aid TLC analysis of reaction mixtures.
12. Diastereomeric ratio was estimated based on relative integration of singlets corresponding to H_a in the ^{1}H-NMR spectrum.
13. This structure has been deposited with the Cambridge Structural Database. CCDC No. 1035872
14. Liu, B. K.; Wu, Q.; Qian, X. Q.; Lv, D. S.; Lin, X. F. *Synthesis* **2007**, 2653-2659.
15. The structure of **13** was assigned on the basis of ^{1}H-, ^{13}C-NMR and HRMS. Impurities appearing in the aliphatic region of the ^{1}H-NMR spectrum are attributed to the presence of $(BOC)_2O$ in the reaction. Numerous attempts to obtain a homogeneous sample by repeated column chromatography and distillation were unsuccessful. Interestingly, using EtO_2CCl and $^{i}Pr_2NEt$ in place of $(BOC)_2O$ led to formation of **I** in low yield.



I (24%)

16. $(BOC)_2O$ alone may be sufficient to mediate the cyclizations illustrated in Schemes 2-4 as well, but this was not attempted.
17. For related intermolecular transformations, see reference 6b,c and: (a) Zhao, Y.; Lei, M.; Yang, L.; Han, F.; Li, Z.; Xia, C. *Org. Biomol. Chem.* **2012**, *10*, 8956-8959. (b) Joyce, E.; McArdle, P.; Aldabbagh, F. *Synlett* **2011**, 1097-1100. (c) Shen, Y.; Cai, S.; He, C.; Lin, X.; Lu, P.; Wang, Y. *Tetrahedron* **2011**, *67*, 8338-8342. (d) Trofimov, B. A.; Andriyankova, L. V.; Belyaeva, K. V.; Mal'kina, A. G.; Nikitina, L. P.; Afonin, A. V.; Ushakov, I. A. *Eur. J. Org. Chem.* **2010**, 1772-1777. (e) Cruz-Acosta, F.; de Armas, P.; García-Tellado, F. *Synlett* **2010**, 2421-2424.