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Synthesis of Substituted Imidazoles via Organocatalysis

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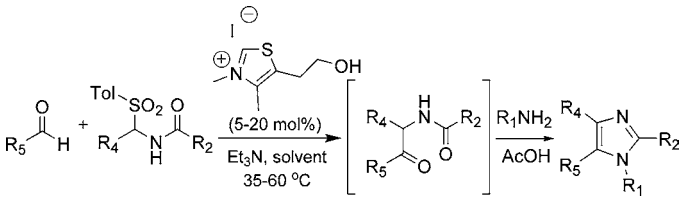
ABSTRACT

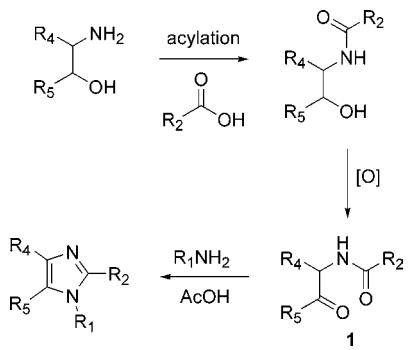


A one-pot synthesis of substituted imidazoles is described. The cornerstone of this methodology involves the thiazolium-catalyzed addition of an aldehyde to an acyl imine to generate the corresponding α-ketoamide in situ followed by ring closure to the imidazole in a one-pot sequence. The extension of this methodology to the one-pot synthesis of substituted oxazoles and thiazoles is also described.

The prevalence of imidazoles in natural products and pharmacologically active compounds has instituted a diverse array of synthetic approaches to these heterocycles.[1] However, despite intensive effort, only a handful of general methodologies exist for the construction of highly substituted imidazoles. Recently, several 4,5-diaryl-substituted imidazoles have been identified as potent inhibitors of p38 MAP kinase[2] and thus have rekindled an increased interest in obtaining tri- and tetrasubstituted imidazoles via absolute regiocontrolled processes. For example, elegant approaches based on van Leusen's TosMIC chemistry[3] have been reported;[4] however, this methodology has not been demonstrated to provide *direct* access to tetrasubstituted imidazoles, and subsequent activation/substitution is necessary.

A promising alternative approach that has received attention is the synthesis of α-ketoamide derivatives that are subsequently converted to the corresponding imidazoles via cyclization with an amine. Unfortunately, the synthesis of α-ketoamides (**1**) is nontrivial and in many instances involves multistep sequences starting from 1,2-amino alcohols (Scheme 1).[5]

Scheme 1



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(1) For imidazole syntheses, see: (a) Grimmett, M. R. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Boulton, A. J., Eds.; Academic: New York, 1980; Vol. 27, p 241. (b) Grimmett, M. R. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Boulton, A. J., Eds.; Academic: New York, 1970; Vol. 12, p 103. (c) Sisko, J. *J. Org. Chem.* **1998**, *63*, 4529. (d) Shilcrat, S. C.; Mokhallalati, M. K.; Fortunak, J. M. D.; Pridgen, L. N. *J. Org. Chem.* **1997**, *62*, 8449. (e) Horne, D. A.; Yakushijin, K.; Büchi, G. *Heterocycles* **1994**, *39*, 139. (f) Nunami, K.; Yamada, M.; Fukui, T.; Matsumoto, K. *J. Org. Chem.* **1994**, *59*, 7635. (g) Lantos, I.; Zhang, W. Y.; Shui, X.; Eggleston, D. S. *J. Org. Chem.* **1993**, *58*, 7092. (h) Ritter, L. A. *J. Org. Chem.* **1987**, *52*, 2714.

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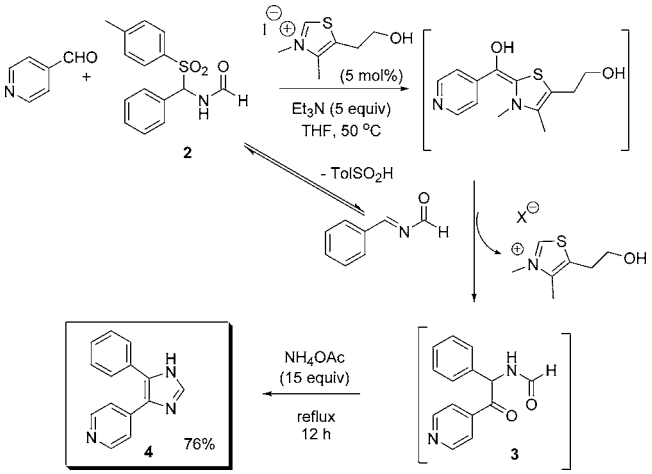
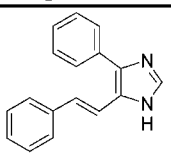
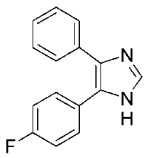
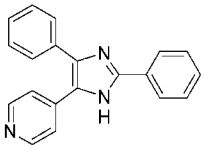
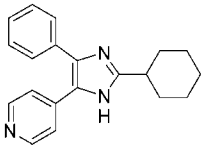
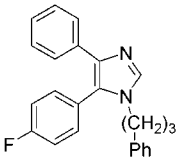
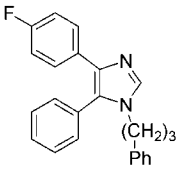
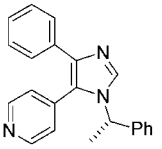
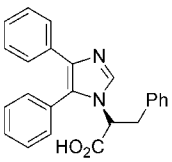
Scheme 2



The use of organic molecules as catalysts has provided attractive alternatives to the more traditional metal-catalyzed variants and in many cases has obviated the need for prior activation of the requisite nucleophile in a separate step.[6] On the basis of this concept, we recently reported the thiazolium-catalyzed acyl anion addition of aldehydes to acyl imines yielding α-ketoamides in high yields.[7] In this Letter, we disclose the application of this methodology to a novel one-pot synthesis of substituted imidazoles that allows for easy manipulation of the substituents around the imidazole core.

The conversion of α-ketoamides to the corresponding imidazoles has traditionally been achieved in refluxing acetic acid with excess ammonia or primary amine.[1a] We anticipated that these conditions would be compatible with a one-pot synthesis of substituted imidazoles in conjunction with the mild conditions developed for the organo-catalyzed synthesis of ketoamides (5−20 mol % thiazolium catalyst, excess Et_3N, CH_2Cl_2 or THF, 35−60 °C).[7] To test our hypothesis, we generated in situ ketoamide **3** via thiazolium-catalyzed acyl anion addition of 4-pyridinecarboxaldehyde to α-amido sulfone **2**[8] in THF. Addition of NH_4OAc (15 equiv) directly to the reaction mixture followed by heating provided a 76% yield of the 4,5-disubstituted imidazole **4** after 12 h (Scheme 2).

Table 1. One-Pot Synthesis of Di- and Trisubstituted Imidazoles

entry	product	isolated yield[a]
1	 **5**	47%[b] 68%[c]
2	 **6**	82%[c]
3	 **7**	78%[c]
4	 **8**	55%[b] 82%[c]
5	 **9**	35%[b] 58%[c]
6	 **10**	42%[b] 61%[c]
7	 **11**	83%[c] >98% ee
8	 **12**	48%[b] 73%[c] >98% ee

[a] Reaction yields and isolations were not optimized and represent the result of a single experiment. [b] Product isolated by crystallization from the crude product mixture. [c] Product isolated by SiO_2 chromatography.

In an effort to expand the scope, we set out initially to synthesize several di- and trisubstituted imidazoles. Our results are summarized in Table 1. In each case, the thiazolium-catalyzed coupling between the aldehyde and

(2) (a) Lee, J. C.; Laydon, J. T.; McDonnell, P. C.; Gallagher, T. F.; Kumar, S.; Green, D.; McNully, D.; Blumenthal, M.; Heys, J. R.; Landvatter, S. W.; Strickler, J. E.; McLaughlin, M. M.; Siemens, I. R.; Fisher, S. M.; Livi, J. P.; White, J. R.; Adams, J. L.; Young, P. R. *Nature* **1994**, *372*, 739. (b) Lee, J. C.; Prabhakar, U.; Griswold, D. E.; Dunnington, D.; Young, P. R.; Badger, A. *Circulatory Shock* **1995**, *44*, 97.

(3) van Leusen, A. M.; Wildeman, J.; Oldenziel, O. H. *J. Org. Chem.* **1977**, *42*, 1153.

(4) (a) Boehm, J. C.; Smientana, J. M.; Sorenson, M. E.; Garigipati, R. S.; Gallagher, T. F.; Sheldrake, P. L.; Bradbeer, J.; Badger, A. M.; Laydon, J. T.; Lee, J. C.; Hillegass, L. M.; Griswold, D. E.; Breton, J. J.; Chabot-Fletcher, M. C.; Adams, J. L. *J. Med. Chem.* **1996**, *39*, 3929. (b) Sisko, J.; Kassick, A. J.; Mellinger, M.; Filan, J. J.; Allen, A.; Olson, M. A. *J. Org. Chem.* **2000**, *65*, 1516.

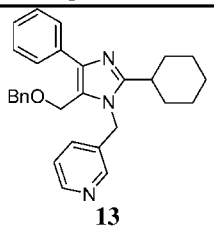
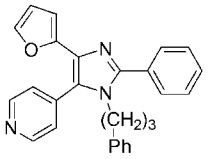
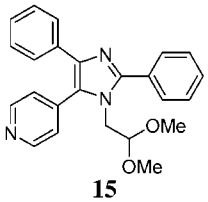
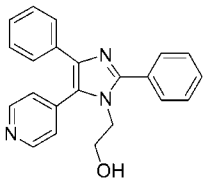
(5) (a) Bleicher, K. H.; Gerber, F.; Wüthrich, Y.; Alanine, A.; Capretta, A. *Tetrahedron Lett.* **2002**, *43*, 7687. (b) Claiborne, C. F.; Liverton, N. J.; Nguyen, K. T. *Tetrahedron Lett.* **1998**, *39*, 8939. (c) Lee, H. B.; Balasubramanian, S. *Org. Lett.* **2000**, *2*, 323.

α-amido sulfone was monitored to completion by HPLC analysis followed by addition of the appropriate amine (5 equiv) and acetic acid (5 equiv). The reaction was then heated to reflux and monitored by HPLC for imidazole formation.[9] This modular approach allows for the installation of various substituents around the imidazole core by simply choosing the desired aldehyde (5-position), amido sulfone (2- and 4-positions), and amine (1-position).[10] For example, access to regioisomeric imidazoles **9** and **10** is readily achieved (entry 5 vs 6, Table 1) by simply switching the fluorine substituent on the starting aldehyde and amido sulfone. Furthermore, chiral imidazoles can be obtained by incorporating chiral amines or amino acids (entries 7 and 8, Table 1) as the amine counterpart. Imidazole **12** (Table 1, entry 8) is of particular interest since 2-imidazol-1-yl alkanoic acids have been implicated as angiotensin II receptor antagonists, and their syntheses have traditionally involved multistep sequences or resolutions.[11] In several cases, we were pleased to find that the imidazole products could be isolated by direct crystallization from the crude product mixture (entries 1 and 4−7, Table 1) by the simple addition of water.

Only scarce reports on the direct synthesis of tetrasubstituted imidazoles exist. Most methodologies rely on the regiocontrolled synthesis of *trisubstituted* imidazoles followed by installation of the fourth substituent via N-alkylation,[12] metal-activated coupling,[13] or imidazole *N*-oxides.[14] One direct approach to tetrasubstituted imidazoles involves cycloaddition of munchnone derivatives; however, the versatility of this methodology is limited to *N*-methyl imidazoles.[15] An alternative synthesis of tetrasubstituted imidazoles via 1,2,4-thiadiazolium salts has also been reported but again appears to suffer from providing only *N*-methyl derivatives.[16] A more recent report utilizes microwave radiation to condense benzonitrile derivatives with benzil in the presence of primary amines to obtain the corresponding tetrasubstituted imidazoles.[17] The significant shortfall of this methodology is the necessity to use symmetrical benzil due to a lack of indiscriminant regiocontrol for the 4- and 5-positions in the process.

To address this shortcoming, we also applied the current methodology to the construction of highly functionalized tetrasubstituted imidazoles (Table 2). The advantage here over existing protocols is that the regiochemistry of the substituents is set in a single step with no apparent limitation to the amine incorporated in the 1-position. Again, the choice of starting aldehyde (5-position), α-amido sulfone (2- and 4-positions), and amine (1-position) dictates the desired

Table 2. One-Pot Synthesis of Tetrasubstituted Imidazoles

entry	product	isolated yield[a]
1	 **13**	22%
2	 **14**	76%
3	 **15**	80%
4	 **16**	75%

[a] Reaction yields were not optimized and represent the result of a single experiment. Products isolated by SiO_2 chromatography.

(6) Recent advances from other laboratories include the use of secondary amines to catalyze Friedel−Crafts, Diels−Alder, 1,3-dipolar cycloaddition, and Michael reactions: (a) Paras, N. A.; MacMillan, D. W. C. *J. Am. Chem. Soc*. **2001**, *123*, 4370. (b) Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc*. **2000**, *122*, 4243. (c) Jen, W. S.; Wiener, J. J. M.; MacMillan, D. W. C. *J. Am. Chem. Soc*. **2000**, *122*, 9874.

(7) Murry, J. A.; Frantz, D. E.; Soheili, A.; Tillyer R.; Grabowski, E. J. J.; Reider, P. J. *J. Am. Chem. Soc*. **2001**, *123*, 9696.

(8) Sisko, J.; Mellinger, M.; Sheldrake, P. W.; Baine, N. H. *Org. Synth.* **1999**, *77*, 198.

(9) See Supporting Information for experimental details.

(10) Limitations set forth in the thiazolium-catalyzed coupling (ref 7) also apply here, where aliphatic and electron-rich aromatic aldehydes, as well as enolizable α-amido suflones, give lower yields in the initial coupling due to competing side reactions (enamide formation) and/or lower reactivity.

(11) Palkowitz, A. D.; Steinberg, M. I.; Thrasher, K. J.; Reel, J. K.; Hauser, K. L.; Zimmerman, K. M.; Wiest, S. A.; Whitesitt, C. A.; Simon, R. L.; Pfeifer, W.; Lifer, S. L.; Boyd, D. B.; Barnett, C. J.; Wilson, T. M.; Deeter, J. B.; Takeuchi, K.; Riley, R. E.; Miller, W. D.; Marshall, W. S. *J. Med. Chem.* **1994**, *37*, 4508. Zaderenko, P.; Lopez, P.; Ballesteros, P.; Takumi, H.; Toda, F. *Tetrahedron: Asymmetry* **1995**, *6*, 381. Zaderenko, P.; Lopez, M. C.; Ballesteros, P. *J. Org. Chem.* **1996**, *61*, 6825. Birkett, P. R.; King, H.; Chapleo, C. B.; Ewing, D. F.; Mackenzie, G. *Tetrahedron* **1993**, *49*, 11029. Messina, F.; Botta, M.; Corelli, F.; Schneider, M. P.; Fazio, F. *J. Org. Chem.* **1999**, *64*, 3767.

(12) A common problem associated with the N-alkylation of 2,4,5-trisubstituted imidazoles is the formation of both possible regioisomers that are often difficult to separate. See: (a) Liverton, N. J.; Butcher, J. W.; Claiborne, C. F.; Claremon, D. A.; Libby, B. E.; Nguyen, K. T.; Pitzenberger, S. M.; Selnick, H. G.; Smith, G. R.; Tebben, A.; Vacca, J. P.; Varga, S. L.; Agarwal, L.; Dancheck, K.; Forsyth, A. J.; Fletcher, D. S.; Frantz, B.; Hanlon, W. A.; Harper, C. F.; Hofsess, S. J.; Kostura, M.; Lin, J.; Luell, S.; O'Neil, E. A.; Orvillo, C. J.; Pang, M.; Parsons, J.; Rolando, A.; Sahly, Y.; Visco, D. M.; O'Keefe, S. J. *J. Med. Chem.* **1999**, *42*, 2180. (b) Wagner, G. K.; Kotschenreuther, D.; Zimmermann, W.; Laufer, S. A. *J. Org. Chem.* **2003**, *68*, 4527.

(13) Fukumoto, Y.; Sawada, K.; Hagihara, M.; Chatani, N.; Murai, S. *Angew. Chem., Int. Ed.* **2002**, *41*, 2779−2781. Lipshutz, B. H.; Hagen, W. *Tetrahedron Lett.* **1992**, *33*, 5865. For the use of imidazolium ylides to introduce substituents in the 2-position, see: Hlasta, D. J. *Org. Lett.* **2001**, *3*,157.

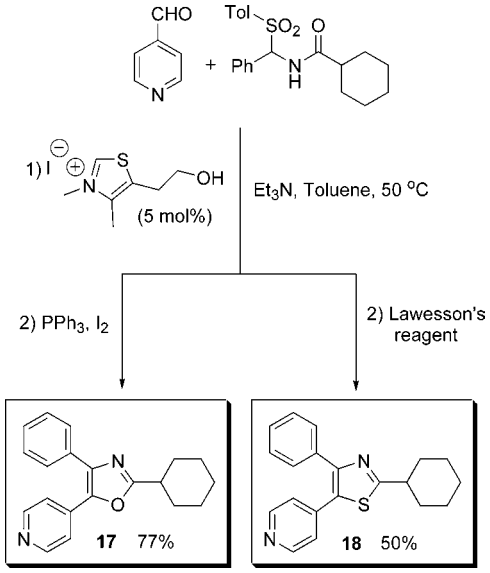
(14) Laufer, S.; Wagner, G.; Kotschenreuther, D. *Angew. Chem., Int. Ed.* **2002**, *41*, 2290.

(15) Consonni, R.; Croce, P. D.; Ferraccioli, R.; La Rosa, C. *J. Chem. Res.* **1991**. 188.

(16) Rolfs, A.; Liebscher, J. *J. Org. Chem.* **1997**, *62*, 3480.

(17) Balalaie, S.; Hashemi, M. M.; Akhbari, M. *Tetrahedron Lett.* **2003**, *44*, 1709.

Scheme 3



regiochemistry in the resulting tetrasubstituted imidazole. The mild conditions utilized in the current methodology allow for the introduction of functionalities that are relatively sensitive to highly acidic or basic media. For example, the use of aminoacetaldehyde dimethyl acetal as the amine substrate for imidazole **15** exemplifies this fact. Furthermore, 4-aryl-5-pyridinyl-tetrasubstituted imidazoles **13**−**15** (entries 2−4, Table 2) are representative of a general class of highly potent p38 kinase inhibitors.[12a]

Further application of this methodology allows for the synthesis of other 1,3-azoles. For example, in situ generation of the ketoamide followed by addition of triphenylphosphine/iodine or Lawesson's reagent furnishes the corresponding oxazole or thiazole, respectively, in good yield (Scheme 3).[18] In this respect, rapid access to imidazoles, oxazoles, and thiazoles with analogous substitution patterns can be realized utilizing the same starting materials.

In summary, we have identified a one-pot synthesis of highly functionalized di-, tri-, and tetrasubstituted imidazoles from readily available starting materials utilizing a thiazolium-catalyzed synthesis of α-ketoamides. The methodology can also be applied to gain access to substituted oxazoles and thiazoles. Given the generality of this method and the diversity of the heterocycles obtained, we feel this methodology should find general synthetic utility.

Supporting Information Available: Representative experimental procedure and characterization data (^{1}H and ^{13}C NMR) for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) For recent syntheses of oxazoles, see: (a) Hodgetts, K. J.; Kershaw, M. T. *Org. Lett.* **2002**, *4*, 2905. (b) Morwick, T.; Hrapchak, M.; DeTuri, M.; Campbell, S. *Org. Lett.* **2002**, *4*, 2665. (c) Dhar, T. G. M.; Guo, J.; Shen, Z.; Pitts, W. J.; Gu, H. H.; Chen, B. C.; Zhao, R.; Bednarz, M. S.; Iwanowicz, E. J. *Org. Lett.* **2002**, *4*, 2091. (d) Clapham, B.; Lee, S.-H.; Koch, G.; Zimmerman, J.; Janda, K. D. *Tetrahedron Lett.* **2002**, *43*, 5407. (e) Pandit, C. R.; Polniaszek, R. P.; Thottathil, J. K. *Synth. Commun.* **2002**, *32*, 2427. (f) Wipf, P.; Miller, C. P. *J. Org. Chem.* **1993**, *58*, 3604. For recent syntheses of thiazoles, see: (f) Hodgetts, K. J.; Kershaw, M. T. *Org. Lett.* **2002**, *4*, 1363. (g) Kazzouli, S. E.; Berteina-Raboin, S.; Mouaddib, A.; Guillaumet, G. *Tetrahedron Lett.* **2002**, *43*, 3193. See also: You, S-, L.; Kelly, J. W. *J. Org. Chem.* **2003**, *68*, 9508.