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An Efficient Synthesis of Tetrasubstituted Imidazoles from *N*-(2-Oxo)-amides

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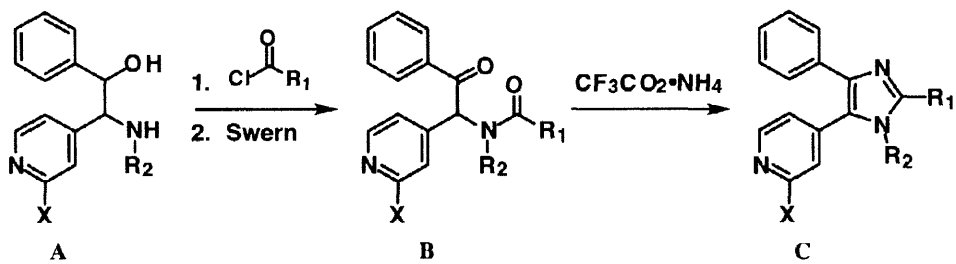
Abstract: *N*-(2-Oxo)-amides were efficiently converted to tri- and tetra- substituted imidazoles under neutral reaction conditions upon treatment with neat ammonium trifluoroacetate.

Appropriately substituted diaryl imidazoles are known inhibitors of p38 MAP kinase.[1] As part of our program to develop inhibitors of p38 kinase, we required a regioselective synthesis of tetrasubstituted imidazoles bearing 5-(2-fluoropyridyl) and 4-aryl groups, which would allow incorporation of a diverse array of substituents at the one and two positions. Methods for the synthesis of highly substituted imidazole rings are limited and generally cannot be carried out under neutral conditions.[2] Herein, we report an efficient synthesis of tetrasubstituted imidazoles under neutral reaction conditions. This synthesis readily allows for the variation of substitutions at the one and two positions.

Amino alcohols **A** (Scheme 1) were coupled with either acid chlorides or carboxylic acids to give the corresponding amides. The resulting products afforded *N*-(2-oxo)-amides **B** by oxidation under Swern conditions. When these dicarbonyl compounds were heated with ammonium trifluoroacetate,[3] good to excellent yields of the desired imidazole **C** were obtained. The use of known conditions[4] for similar transformations, which utilize refluxing acetic acid in the presence of excess ammonium acetate, were unsuccessful for these systems.[5]

Scheme 1



A **B** **C**

The scope of this ring forming reaction was explored for a variety of compounds and the results are summarized in Table 1. Although the method tolerates a versatile array of subtitutents, when R_2 is sterically hindered R_1 appears to be limited to small groups.[6] The reaction conditions were consistent and the yields ranged from 59 - 87%. For a typical experiment, the substrates were combined with 10 equivalents of ammonium trifluoroacetate and heated to 150 °C until the contents liquefied. After five minutes, the heat was removed and water added to the flask before solidification occurred. The products were then extracted from the aqueous solution with ethyl acetate.

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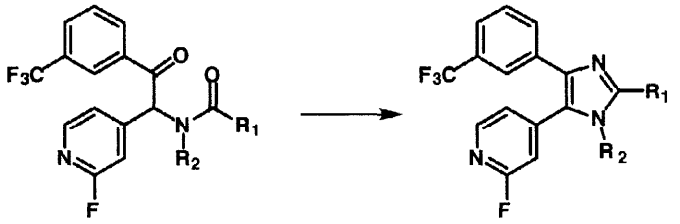
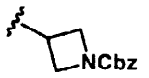
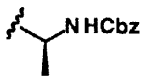
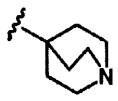
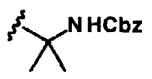
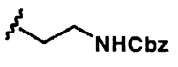
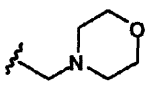
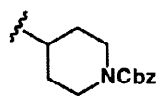
Table 1

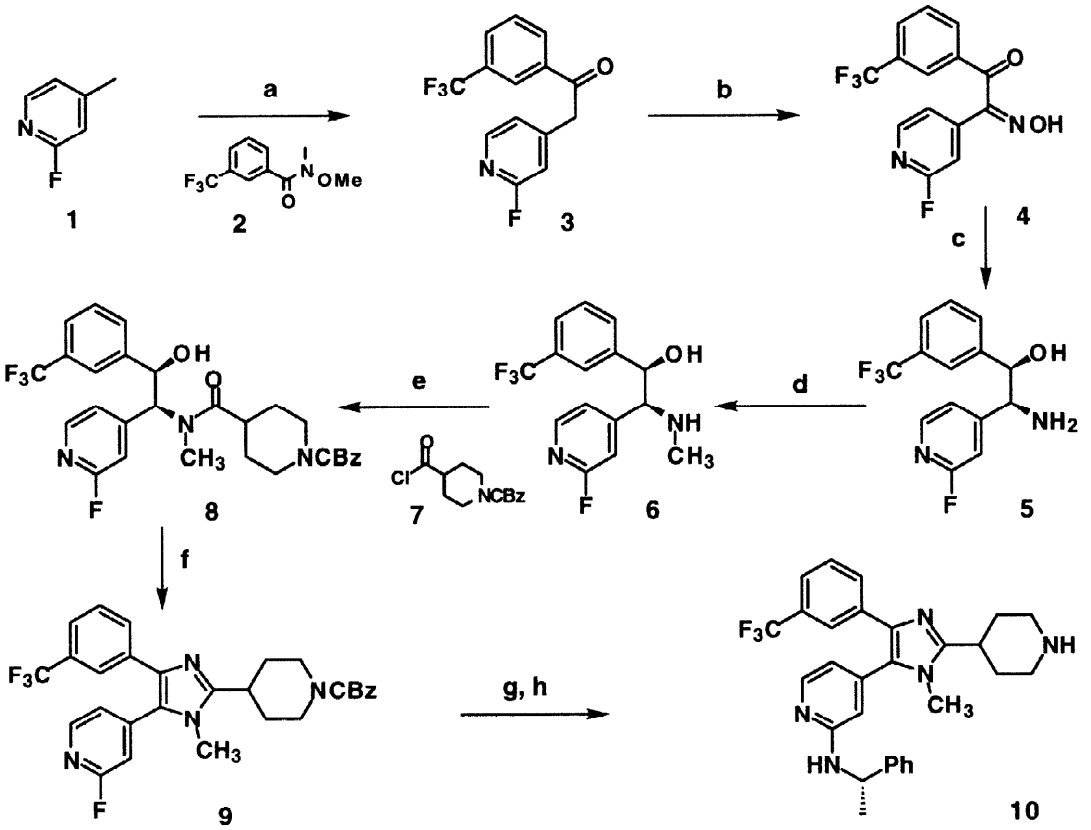


Entry	R_1	R_2	Yield
1		CH_3	75%
2		CH_3	70%
3		CH_3	75%
4		CH_3	72%
5		CH_3	70%
6		CH_3	75%
7		CH_3	85%
8		H	87%
9			59%

In our efforts to synthesize p38 inhibitors, compound **10** (L-790,070) was of particular interest. Toward this end, lithiation of 4-methyl-2-fluoropyridine **1** followed by the addition of Weinreb amide **2** afforded ketone **3**. The product ketone was converted to the "syn" amino alcohol **5**[7] via the keto-oxime **4** by palladium catalyzed reduction. Formylation of primary amine **5** followed by borane reduction produced the desired *N*-methyl amine **6**. This compound was then acylated with acid chloride **7**, and the resulting alcohol was oxidized

to the ketone under Swern conditions. The keto-amide was then heated in neat ammonium trifluoroacetate to afford imidazole **9**. The 2-fluoropyridine **9** served as a useful intermediate and was further elaborated by reactions with amines. For example, the addition of (S)-α-methylbenzyl amine to **9** provided the targeted kinase inhibitor **10**.

Scheme 2



Reagents and Conditions: a) *n*-BuLi (1.05 equiv.), **1**, THF at -78 °C, then **2** (80%); **b)** *t*-BuONO, HCl, ethanol at -5 °C for 1 hr, then 2 hrs at 23 °C (95%); **c)** 10% Pd / C (30% by wt. of substrate), H_2 (1 atm) in ethanol for 12 hrs (91%); **d)** ethyl formate (as solvent) refluxed 10 hrs (100%); BH_3•THF (3.0 equiv.) in THF at 24 °C, 2 hrs (85%); **e)** **7** (1.1 equiv.) **6**, triethylamine (1.5 equiv.) in methylene chloride at 25 °C, 20 min. (95%); **f)** DMSO (2.5 equiv.) and oxalyl chloride (2.0 equiv.) in methylene chloride at -78 °C, then **8**. After 2 hrs triethylamine (3.0 equiv.) and warm to 23 °C; Unpurified ketone from **8** in ammonium trifluoroacetate (as solvent) at 150 °C for 5 min. (86%); **g)** (-)-α-methylbenzylamine (5 equiv.) at 150 °C for 12 hrs (76%); **h)** 10% Pd / C (30% by wt. of substrate) and H_2 (1 atm) in ethanol for 4 hrs (98%).

In conclusion, we have described a mild and efficient method for the synthesis of imidazoles which allows for the convenient variation of the substituents at the one and two positions.

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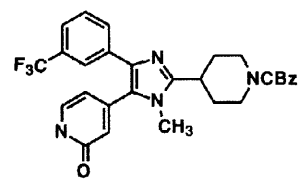
1. (a) J. C. Lee, J. T. Laydon, P. C. McDonnell, T. F. Gallagher, S. Kumar, D. Green, D. McNulty, M. Blumenthal, J. R. Heys, S. W. Landvatter, J. E. Strickler, M. M McLaughlin, I. R. Siemens, S. M. Fisher, G. P. Livi, J. R.White, J. L. Adams, P. R. Young *Nature* **1994**, *372*, 739; (b) J. C. Lee, U. Prabhakar, D. E. Griswold, D. Dunnington, P. R. Young, A. Badger *Circulatory Shock* , **1995**, *44*, 97.
2. (a) R. Gompper; *Chem. Ber.* **1957**, *90* , 374. (b) E. Beccalli, L. Majori, A. Marchesini, C. Torricelli, *Chem . Lett.* **1980**, 657. (c) H. Alper, S. Amaratunga, *J. Org. Chem.* **1982**, *47*, 3595.
3. Substitution of ammonium trifluoroacetate with ammonium acetate lead to decomposition of starting materials. The subdued nucleophilicity of the trifluoroacetate anion results in conditions sufficiently mild to accommodate the fluoropyridine moiety.
4. (a) M. R. Grimmett in *Advances in Heterocyclic Chemistry;* A. R. Katritzky, A. J. Boulton, Ed.; Academic Press: New York, **1970**; Vol 12, p 103. (b) M. R. Grimmett in *Advances in Heterocyclic Chemistry*; A. R. Katritzky, A. J. Boulton, Ed.; Academic Press: New York, **1980**, Vol 27, p 241.
5. The use of these reaction conditions resulted in the decomposition of starting materials. The sole isolated product was characterized as the imidazole pyridone. We suggest that the pyridone is formed via acetate addition to the fluropyridine followed by hydrolysis upon aqueous work up.



6. The synthesis of keto-amides bearing sterically hindered R_2 groups was difficult due to competitive acylation on oxygen (with the exception of acetyl chloride (entry 9)). Attempts to migrate the acyl group in the ester products to nitrogen were unsuccessful.
7. Relative stereochemistry was assigned by formation of the oxazolidinone with phosgene and determined by NOE.