ORGANIC LETTERS

2004
Vol. 6, No. 6
929−931

New Method for the Synthesis of Diversely Functionalized Imidazoles from N-Acylated α-Aminonitriles

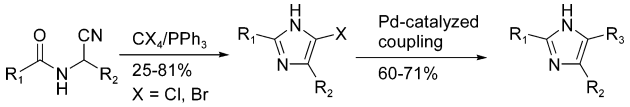
Yong-Li Zhong,* Jaemoon Lee, Robert A. Reamer, and David Askin

Department of Process Research, Merck Research Laboratories, P. O. Box 2000, Rahway, New Jersey 07065

yongli_zhong@merck.com

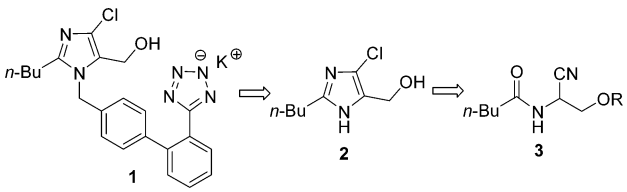
Received December 12, 2003

ABSTRACT



A new general method for the synthesis of medicinally important diversely functionalized imidazoles from N-acylated α-aminonitriles has been developed. N-Acylated α-aminonitriles were reacted with triphenylphosphine and carbon tetrahalide to afford 2,4-disubstituted 5-halo-1*H*-imidazoles in good yield. This new methodology was applied for the synthesis of 2-butyl-4-chloro-5-hydroxymethylimidazole. These halo-imidazoles can be directly converted to 2,4,5-trisubstituted imidazoles through palladium-catalyzed coupling reactions.

The synthesis of substituted imidazoles has received significant attention due to their known biological activity and diverse medicinal uses.[1] Despite this high level of interest, few general methods to assemble the functionalized imidazole ring have been reported.[2] Merck's Losartan (Cozaar) **1**, a nonpeptide angiotensin II receptor antagonist for the treatment of hypertension,[3] contains a 2,4,5-trisubstituted imidazole **2**. In our search for enabling synthetic technologies for a general synthesis of the imidazole system, we reasoned that imidazole **2** could be prepared via activation of N-acylated α-aminonitrile **3** followed by cyclization, chlorination, and tautomerization. Herein, we describe our efforts to effect the described set of chemical transformations, which provide the desired imidazole product in a one-pot protocol.



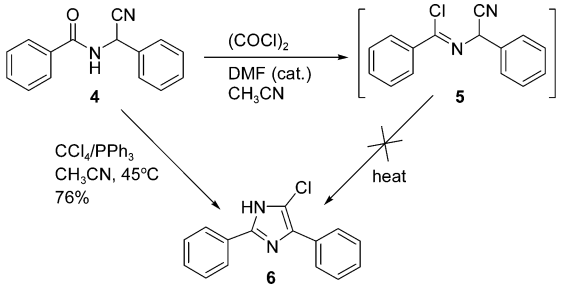
We initially explored the described process with N-benzoylated 2-phenylglycinonitrile **4**, which was prepared via benzoylation of 2-phenylglycinonitrile with either benzoyl chloride or benzoic anhydride. Treatment of the N-acylated α-aminonitrile **4** under Vilsmeier conditions with oxalyl chloride in the presence of a catalytic amount of DMF in acetonitrile at ambient temperature (Scheme 1) resulted in the formation of imidoyl chloride **5**, which slowly decom-

(1) (a) Claiborne, C. F.; Liverton, N. J.; Nguyen, K. T. *Tetrahedron Lett.* **1998**, *39*, 8939. (b) Laufer, S.; Wagner, G.; Kotschenreuther, D. *Angew. Chem., Int. Ed.* **2002**, *41*, 2290. (c) Bilodeau, M. T.; Cunningham, A. M. *J. Org. Chem.* **1998**, *63*, 2800. (d) Kang, U. G.; Shechter, H. *J. Am. Chem. Soc.* **1978**, *100*, 651. (e) Sarshar, S.; Zhang, C.; Moran, E. J.; Krane, S.; Rodarte, J. C.; Benbatoul, K. D.; Dixon, R.; Mjalli, A. M. M. *Bioorg. Med. Chem.* **2000**, *10*, 2599. (f) Zhang, C.; Sarshar, S.; Moran, E. J.; Krane, S.; Rodarte, J. C.; Benbatoul, K. D.; Dixon, R.; Mjalli, A. M. M. *Bioorg. Med. Chem.* **2000**, *10*, 2603. (g) Shilcrat, S. C.; Mokhallalati, M. K.; Fortunak, J. M. D.; Pridgen, L. N. *J. Org. Chem.* **1997**, *62*, 8449.

(2) Only the wide range of benzimidazoles can be prepared from 1,2-diaminobenzene and related compounds. For reviews on the synthesis of imidazoles, see: (a) Grimmett, M. R. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Potts, K. T., Eds.; Pergamon Press: New York, 1984; Vol. 5, pp 457−497. (b) Grimmett, M. R. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Shinkai, I., Eds.; Pergamon Press: New York, 1996; Vol. 3, pp 77−220. (c) Grimmett, M. R. In *Imidazole and Benzimidazole Synthesis*; Academic Press: New York, 1997. For recent imidazole syntheses, see: (d) Sezen, B.; Sames, D. *J. Am. Chem. Soc.* **2003**, *125*, 5274. (e) Tan, K. L.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2002**, *124*, 13964. (f) Sisko, J.; Kassick, A. J.; Mellinger, M.; Filan, J. J.; Allen, A.; Olsen, M. A. *J. Org. Chem.* **2000**, *65*, 1516. (g) Sisko, J. *J. Org. Chem.* **1998**, *63*, 4529. (h) Groarke, M.; McKervey, M. A.; Nieuwenhuyzen, M. *Tetrahedron Lett.* **2000**, *41*, 1275. (i) Rolfs, A.; Liebscher, J. *J. Org. Chem.* **1997**, *62*, 3480. (j) Matsumura, K.; Kuritani, M.; Shimadzu, H.; Hashimoto, N. *Chem. Pharm. Bull.* **1976**, *24*, 960. (k) Roesler, P. P.; Kille, G.; Fleury, J.-P. *Bull. Soc. Chim. Fr.* **1967**, 545.

10.1021/ol036423y CCC: $27.50
Published on Web 02/20/2004

Scheme 1

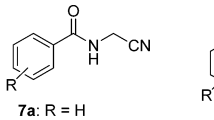
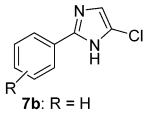
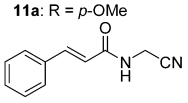
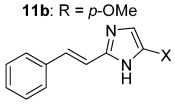
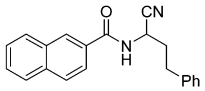
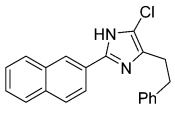
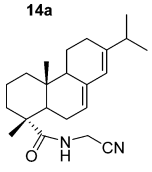
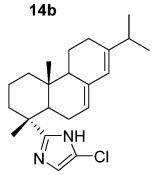
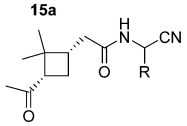
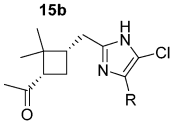
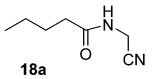
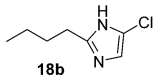
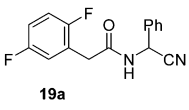
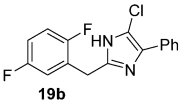


poses at 50 °C.[4] Cyclized product **6** was not detected. The same results were observed using thionyl chloride or phosphorus oxychloride in place of oxalyl chloride. This result implies that imidoyl chloride **5** is not a viable intermediate for the cyclization to imidazole **6**. In contrast, it was found that treatment of compound **4** with 1.0 equiv of triphenylphosphine and 1.0 equiv of carbon tetrachloride at room temperature in acetonitrile gradually generated 5-chloro-2,4-diphenyl-1*H*-imidazole **6** as observed by NMR and HPLC-MS. Further development led to the use of 2.5 equiv of triphenylphosphine and 2.5 equiv of carbon tetrachloride at 45 °C. Under the optimized conditions, **6** was isolated in 76% yield after silica gel chromatography.

The scope of this new synthetic method for the efficient construction of 2,4,5-trisubstituted imidazole was investigated by employing these optimized conditions. The results are summarized in Table 1. All substrates shown in the table were prepared from appropriate 2-aminoacetonitrile, 2-phenyl-2-aminoacetonitrile, or 2-(2′-phenylethyl)-2-aminoacetonitrile via acylation with commercially available carboxylic acid or acid chloride. A variety of substrates, including both functionalized aromatic (entries 2−8) and aliphatic (entries 9−12) N-acylated α-aminonitriles were effectively cyclized to the chloroimidazoles. Reactions with a substrate containing a quaternary center (entry 9) proceeded smoothly.

On the basis of the detailed studies performed by Tomoskozi et al. on the Ph_3P-CCl_4-mediated chlorination of alcohol and some intermediates observed through NMR

Table 1. Synthesis of 2,4-Disubstituted 5-Haloimidazoles from N-Acylated α-Aminonitriles[a]

entry	substrate	product	conditions[b]	yield (%)[c]
			PPh_3/CCl_4 45 °C, 4-16h	
1	**7a**: R = H	**7b**: R = H		52
2	**8a**: R = *o*-OMe	**8b**: R = *o*-OMe		71
3	**9a**: R = *o*-Br	**9b**: R = *o*-Br		74
4	**10a**: R = *m*-OMe	**10b**: R = *m*-OMe		40
5	**11a**: R = *p*-OMe	**11b**: R = *p*-OMe		72
			PPh_3/CX_4 45 °C, 16 h	
6	**12a**	**12b**: X = Cl		70
7	**12a**	**13b**: X = Br		25
			PPh_3/CCl_4 45 °C, 12 h	
8	**14a**	**14b**		67 (95)[d]
			PPh_3/CCl_4 45 °C, 13 h	
9	**15a**	**15b**		38
			PPh_3/CCl_4 45 °C, 16 h	
10	**16a**: R = H	**16b**: R = H		68
11	**17a**: R = Ph	**17b**: R = Ph		72
			PPh_3/CCl_4 45 °C, 16 h	
12	**18a**	**18b**		68
			PPh_3/CCl_4 45 °C, 16 h	
13	**19a**	**19b**		74 (79)[d]

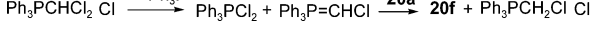
[a] Procedure: See Supporting Information for a detailed procedure. [b] PPh_3 (2.5 equiv), CCl_4 (2.5 equiv). [c] Isolated yield. [d] Assay yield by HPLC.

experiments,[5] a possible mechanism for the new imidazole synthesis via cyclization of N-acylated α-aminonitriles is proposed (Scheme 2). The formation of the intermediate **20b** takes place by the reaction of dichlorotriphenylphosphorane and (dichloromethylene)triphenylphosphorane or (chloromethylene)triphenylphosphorane with N-acylated α-aminonitrile **20a**. This process could lead to the novel seven-membered ring intermediate **20c**, which could undergo ring-opening, intramolecular addition, and then tautomerization to generate imidazole **20f**.

(3) (a) Carini, D. J.; Duncia, J. V.; Aldrich, P. E.; Chiu, A. T.; Johnson, A. L.; Pierce, M. E.; Price, W. A.; Santella, J. B., III; Wells, G. J.; Wexler, R. R.; Wong, P. C.; Yoo, S.-E.; Timmermans, P. B. M. W. M. *J. Med. Chem.* **1991**, *34*, 2525 and references therein. (b) Shi, Y.-J.; Frey, L. F.; Tschaen, D. M.; Verhoeven, T. R. *Synth. Commun.* **1993**, *23*, 2623 and references therein. (c) Larsen, R. D.; King, A. O.; Chen, C. Y.; Corley, E. G.; Foster, B. S.; Roberts, F. E.; Yang, C.; Lieberman, D. R.; Reamer, R. A.; Tschaen, D. M.; Verhoeven, T. R.; Reider, P. J.; Lo, Y. S.; Rossano, L. T.; Brookes, A. S.; Meloni, D.; Moore, J. R.; Arnett, J. F. *J. Org. Chem.* **1994**, *59*, 6391. (d) Griffiths, G. J.; Hauck, M. B.; Imwinkelried, R.; Kohr, J.; Roten, C. A.; Stucky, G. C. *J. Org. Chem.* **1999**, *64*, 8084 and references therein.

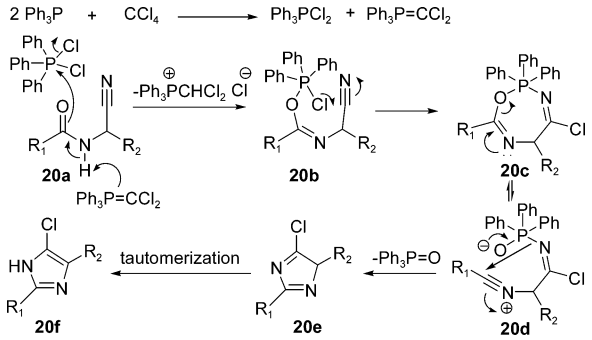
(4) (a) Pure imidoyl chloride **5** is stable (mp 78−79 °C); see: Suvalova, E. A.; Chudakova, T. I.; Onys'ko, P. P.; Sinitsa, A. D. *Zh. Obshch. Khim.* **1987**, *57*, 1514. (b) Imidoyl chloride **5** cannot be converted to imidazole **6** in the presence of various bases, e.g., pyridine, triethylamine, and DBU. Under these conditions, imidoyl chloride **5** slowly decomposed. No imidazole was detected. (c) We did not observe the formation of imidoyl chloride **5** by HPLC under our optimized reaction conditions (PPh_3/CCl_4, acetonitrile). However, treatment of N-benzoylated *β*-aminonitrile under standard conditions (PPh_3/CCl_4, acetonitrile, 45 °C) afforded imidoyl chloride in high yield. The cyclized product was not observed.

(5) (a) Tomoskozi, I.; Gruber, L.; Radics, L. *Tetrahedron Lett.* **1975**, 2473. (b) The reaction of **4** to **6** in CD_3CN was monitored by ^1H NMR at 0 °C. It was observed that the intermediate **20e** slowly tautomerized to **20f**. The byproduct (chloromethyl)triphenylphosphonium chloride was identified by NMR studies.



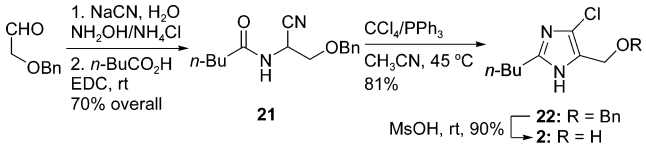
(c) This reaction requires a free amide N−H bond. In our control experiment, no reaction was observed when N-benzoylated *N*-methyl-α-aminonitrile was subjected to the standard reaction conditions (PPh_3/CCl_4, acetonitrile, 45 °C) as determined by HPLC. (d) The reaction can be carried out at 0 °C. Attempts to observe intermediate **20c** by NMR (^1H, ^{13}C, and ^{31}P NMR) at 0 °C and room temperature were unsuccessful.

Scheme 2



A demonstration of the utility of this new reaction was showcased in the synthesis of 2-butyl-4(5)-chloro-5(4)-hydroxymethyl-1*H*-imidazole **2**, a key intermediate for the synthesis of Cozaar **1** (Scheme 3). The imidazole precursor

Scheme 3

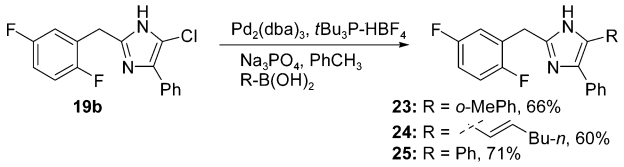


21 was simply prepared in 70% overall yield from the reaction of benzyloxyacetaldehyde and sodium cyanide,[6] followed by acylation with valeric acid. Treatment of **21** with 2.5 equiv of PPh_3 and 2.5 equiv of CCl_4 in acetonitrile at 45 °C gave imidazole **22** in 81% isolated yield. Deprotection of **22** with methanesulfonic acid in chloroform[7] furnished the Cozaar intermediate **2** in 90% yield.

To further demonstrate the utility of this method, the synthesis of 2,4,5-trisubstituted imidazoles was investigated

(6) Deng, S.-L.; Liu, D.-Z. *Synthesis* **2001**, 2445 and references therein.

Scheme 4



from the 5-chloroimidazole products. Employing the Suzuki coupling conditions developed by Fu et al. ($Pd_2(dba)_3$, $^tBu_3P{\cdot}HBF_4$, K_3PO_4)[8] allowed direct coupling of the unprotected 2,4-disubstituted 5-chloro-1*H*-imidazole **19b** with various aryl/vinyl boronic acids in good yield without optimization (Scheme 4). To the best of our knowledge, this is the first example of a Suzuki coupling with an unprotected 5-chloroimidazole as the substrate.

In conclusion, we have developed a mild and general method for the efficient synthesis of pharmacologically important diversely functionalized 2,4,5-trisubstituted imidazoles from N-acylated α-aminonitriles. We have shown that other functional groups could be easily introduced to the resulting unprotected 5-chloroimidazoles by the Suzuki cross-coupling reaction.

Acknowledgment. We thank Dr. Thomas J. Novak for mass spectrometric assistance and Dr. Jingjun Yin and Dr. Michael Palucki for helpful discussions.

Supporting Information Available: Full experimental details and spectral data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL036423Y

(7) Matterson, D. S.; Man, H.-W., Ho, O. C. *J. Am. Chem. Soc.* **1996**, *118*, 4560.

(8) (a) For a review of palladium-catalyzed coupling reactions of aryl chloride, see: Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176. (b) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **1998**, *37*, 3387. (c) Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020. (d) Yin, J.; Rainka, M. P.; Zhang, X.-X.; Buchwald, S. L. J. *Am. Chem. Soc.* **2002**, *124*, 1162.