ORGANIC LETTERS

2005
Vol. 7, No. 4
609−611

Synthesis of Trisubstituted Imidazoles by Palladium-Catalyzed Cyclization of *O*-Pentafluorobenzoylamidoximes: Application to Amino Acid Mimetics with a C-Terminal Imidazole

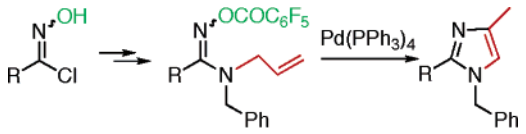
Shazia Zaman, Kitamura Mitsuru,[†] and Andrew D. Abell*

Department of Chemistry, University of Canterbury, Private Bag 4800, Christchurch, New Zealand, and Department of Chemistry, Graduate School of Science, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo, Japan

andrew.abell@canterbury.ac.nz

Received November 17, 2004

ABSTRACT



R = $PhCH_2$, $Ph(CH_2)_2$, CO_2Me, (*S*)-BocHNCHCH$_2$Ph, (*S*)-BocHNCHMe, (*S*)-BocHNCHCH$_2$CHMe$_2$

1-Benzyl-4-methylimidazoles with a range of substituents at the 2-position are prepared from *O*-pentafluorobenzoylamidoximes on treatment with catalytic amounts of $Pd(PPh_3)_4$ and triethylamine. The sequence provides access to optically active amino acid mimetics with a C-terminal imidazole.

Imidazoles are an important class of heterocycle with an ability to behave as ligands in metalloenzymes[1] and nonnatural metal complexes.[2] They are components of a number of highly significant biomolecules, including the essential amino acid histidine (and related compounds), biotin, and the pilocarpine alkaloids.[3] An imidazole ring has also been used as a component of nonnatural cyclic peptides[4] and as a stable ester isostere for use in peptidomimetics.[5,6] As such, a good deal of interest exists in developing new and efficient methods for the synthesis and functionalization of imidazoles: 2-functionalized imidazoles are typically prepared by metalation of an imidazole followed by reaction with an electrophile[7] (e.g., an aldehyde or isocyanate) or, more recently, by reaction of an azolium ylide with a reactive carbonyl.[8]

In this paper, we present a new synthesis of 2-substituted 1-benzyl-4-methylimidazoles based on a palladium(0)-catalyzed amino Heck reaction (an electrophilic amination sequence) of amidoximes and the application of this methodology to the preparation of amino acid mimetics containing a C-terminal imidazole; see **12a**−**c**. Mimetics of this type

[†] The University of Tokyo.

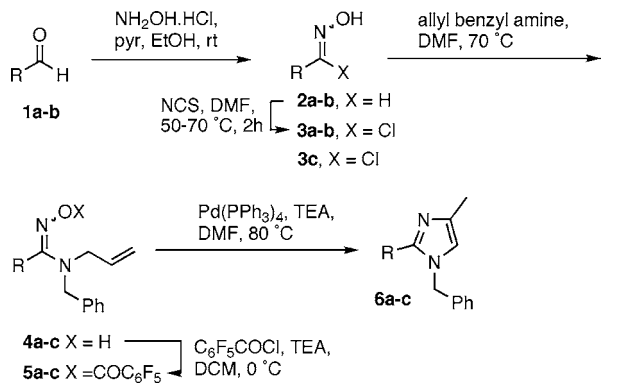
(1) Vallee, B. L.; Auld, D. S. *Biochemistry* **1990**, *29*, 5647.
(2) Omotowa, B. A.; Shreeve, J. M. *Organometallics* **2004**, *23*, 783. Liu, J.; Zhao, Y.; Zhou, Y.; Li, L.; Zhang, T. Y.; Zhang, H. *Org. Biomol. Chem.* **2003**, *1*, 3227.
(3) Grimmett, M. R. In *Comprehensive Heterocyclic Chemistry II*: Katritzky, A. R.; Ress, C. W.; Scriven, E. F. V., Eds.; Pergamon Press: Oxford, 1996: Vol. 3, pp 77−220.
(4) Haberhauer, G.; Rominger, F. *Eur. J. Org. Chem.* **2003**, 3209.
(5) Von Geldern, T. W.; Kester, J. A.; Bal, R.; Wu-Wong, J. R.; Chiou, W.; Dixon, D. B.; Opgenorth, T. J. *J. Med. Chem.* **1996**, *39*, 968. Predgen, L. N.; Mokhallalati, M. K.; Mcguire, M. A. *Tetrahedron Lett.* **1997**, *38*, 1275.
(6) Dhanak, D.; Christmann, L. T.; Darcy, M. G.; Keenan, R. M.; Knight, S. D.; Lee, J.; Ridgers, L. H.; Sarau, H. M.; Shah, D. H.; White, J. R.; Zhang, L. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1445.
(7) Pinkerton, F. H.; Thames, S. F. *J. Heterocycl. Chem.* **1972**, *9*, 67.
(8) Hlasta, D. J. *Org. Lett.* **2001**, *3*, 157. Deng, Y.; Hlasta, D. J. *Tetrahedron Lett.* **2002**, *43*, 189.

10.1021/ol047628p CCC: $30.25
Published on Web 01/19/2005

are known, being prepared by reaction of an optically active aldehyde derivative of an amino acid with NH_3 in 40% glyoxal and DMF.[5] However, problems with racemization have been noted with this method.[6] This is, to our knowledge, the first report of an imidazole synthesis based on a metal-catalyzed C−N bond formation reaction. Related methodology has been reported for the preparation of pyrroles and a number of azaheterocycles, including azaazulenes, spiroimines, and pyridinium derivatives.[9−11]

We first demonstrated the feasibility of the methodology using simple amidoximes as depicted in Scheme 1. Reaction

Scheme 1[a]



[a] Key: **a**, R = $PhCH_2$; **b**, R = $Ph(CH_2)_2$; **c**, R = CO_2Me.

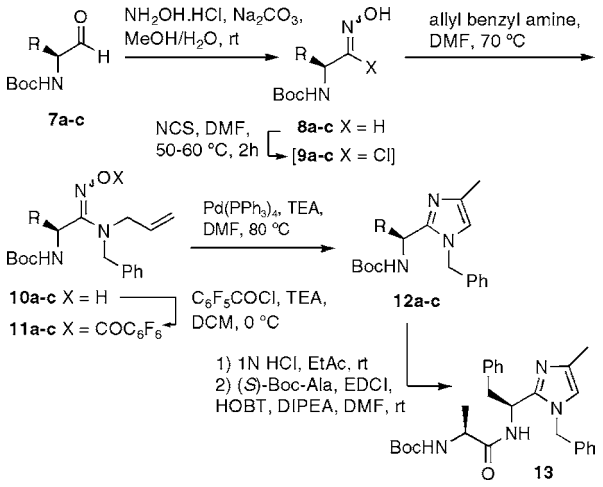
of aldehydes **1a** and **1b** with hydroxylamine in the presence of pyridine gave the aldoximes, (*E*/*Z*)-**2a**[12] (75%, 1:1) and (*E*/*Z*)-**2b**[13] (72%, 3:2), respectively. These were then separately treated with NCS, in dry DMF at 70 °C, to give the corresponding hydroxamoyl chlorides **3a** and **3b**, which were not isolated but simply coupled, in situ, with allyl benzylamine in DMF to give **4a** (63%) and **4b** (61%), respectively, as single isomers, tentatively assigned the (*E*)-configuration.[14] In a separate experiment, **2b** was treated with NCS and the crude product analyzed by ^{1}H NMR to show **3b** as a single isomer, which was isolated in 87% yield, characterized, and tentatively assigned the (*E*)-configuration.[14] This sample of **3b** was then reacted with allyl benzylamine in DMF to give the same isomer of **4b**, as per the in situ experiment. The hydroxamoyl chloride **3c**, prepared as an *E*/*Z* mixture (6:5) from glycine methyl ester hydrochloride,[15] was also reacted with allyl benzylamine in DMF to give **4c** (75%) as a 6:5 mixture of isomers (Scheme 1).

The key substrates for the amino Heck reactions (**5a**−**c**) were then prepared by reacting the samples of (*E*)-**4a**, (*E*)-**4b**, and (*E*/*Z*)-**4c** (isomer ratio of 6:5) with TEA and pentafluorobenzoyl chloride in DCM at 0 °C to give (*E*)-**5a** and (*E*)-**5b** as single isomers and (*E*/*Z*)-**5c** (isomer ratio of 4:1) in 83, 87, and 88% yields, respectively. An *N*,*O*-pentafluorobenzoyloxime was chosen for use in the subsequent amino Heck sequence since this group is known to suppress the competing Beckman rearrangement.[10]

The *N*,*O*-pentafluorobenzoyl amidoximes **5a**,**b** were treated with 10 mol % $Pd(PPh_3)_4$ and 5 equiv of TEA in DMF, at 80 °C for 30 min, to give the desired imidazoles **6a**,**b** in 72 and 70% yields, respectively. The amino Heck cyclization of **5c** was slower. Its consumption (as determined by TLC) required 3 h at 80 °C, and the desired imidazole **6c** was isolated in 30% yield. The lower yield in this case is unlikely to be linked to the presence of two isomers of the substrate **5c**, since the outcome of other amino Heck reactions are reported to be independent of the geometry of the substrate oxime.[10,11] The amino Heck cyclizations of **5a**−**c** are thought to proceed by oxidative addition of Pd(0) to the N−O bond to give an alkylideneaminopalladium(II) intermediate.[16] Olefin insertion into this species, followed by elimination of palladium hydride gives a dihydroimidazole, which finally isomerizes under the reaction conditions to the imidazole.

With the simple imidazoles **6** in hand, we next set about extending the methodology to amino acid-based examples; see **12** in Scheme 2. As mentioned earlier, an imidazole has

Scheme 2[a]



[a] Key: **a**, R = $PhCH_2$; **b**, R = Me; **c**, R = CH_2CHMe_2.

been used in this context as a stable ester isostere at the C-terminus of a peptidomimetic.[5,6] The key starting aldehydes **7a**−**c** were prepared by DIBALH reduction of (*S*)-*N*-Boc-

(9) Kitamura, M.; Narasaka, K. *Chem. Record* **2002**, *2*, 268. Kitamura, M.; Chiba, S.; Saku, O.; Narasaka, K. *Chem. Lett.* **2002**, 606. Tsutsui, H.; Narasaka, K. *Chem. Lett.* **1999**, 45. Tsutsui, H.; Narasaka, K. *Chem. Lett.* **2001**, 526.

(10) Tsutsui, H.; Narasaka, K.; Kitamura, M. *Bull. Chem. Soc. Jpn.* **2002**, *75*, 1451.

(11) Zaman, S.; Kitamura, M.; Narasaka, K. *Bull. Chem. Soc. Jpn.* **2003**, *76*, 1055.

(12) Boucher, J.-L.; Delaforge, M.; Mansuy, D. *Biochemistry* **1994**, *33*, 7811.

(13) Lam, P. Y. S.; Adams, J. J.; Clark, C. G.; Calhoun, W. J.; Luettgen, J. M.; Knabb, R. M.; Wexler, R. R. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1795.

(14) It has been noted that *O*-alkyl hydroxamoyl chlorides isomerize to the thermodynamically stable (*E*)-isomer and that these react stereospecifically to give an (*E*)-amidoxime (Johnson, J. E.; Nalley, E. A.; Kunz, Y. K.; Springfield, J. R. *J. Org. Chem.* **1976**, *41*, 252. Johnson, J. E.; Todd, S. L.; Dutson, S. M.; Ghafouripour, A.; Alderman, R. M.; Hotema. M. R. *J. Org. Chem.* **1992**, *57*, 4648). Note that the substituent priorities of **2** and **3/4** are different such that the respective (*E*)-isomers have opposite relative configurations.

Phe-OMe, (*S*)-*N*-Boc-Ala-OMe, and (*S*)-*N*-Boc-Leu-OMe, respectively. Treatment of each of these aldehydes with hydroxylamine hydrochloride in the presence of Na_2CO_3[17] gave the (*E*/*Z*)-α-amino aldoximes **8a** (79%, 2:1), **8b** (72%, 3:1), and **8c** (83%, 3:2), which were purified by column chromatography and recrystallization.[18] A one-pot treatment of these oximes with NCS, as for **2** in Scheme 1, gave the hydroxamoyl chlorides **9a**−**c**, which were reacted in situ with allyl benzylamine to give the amidoximes **10a**−**c** as mixtures of isomers.[18]

Treatment of separate samples of **10a**−**c** with TEA and pentafluorobenzoyl chloride, as for **4**, gave single isomers of the substrates for the amino Heck reaction, **11a**−**c** in 61, 63, and 31% yields, respectively.[18] These were then subjected to the amino Heck reaction conditions to give the C-terminal amino acid mimetics **12a**−**c** in good yield. In particular, the (*S*)-Phe- and (*S*)-Leu-based amidoximes **11a** and **11c** cyclized smoothly in 1 h to give the optically active imidazole derivatives **12a** (70%) and **12c** (56%), while (*S*)-Ala-based **12b** was isolated in 68% yield after a comparatively shorter reaction time of 30 min. The reactions work well, and ^{1}H NMR of the crude product revealed a turnover of 90−95% in all cases; however, the isolated yields are some what lowered by difficulties in removing the triphenylphosphine oxide byproduct. Finally, the *N*-Boc group of the Phe-based imidazole **12a** was removed on treatment with 1 N HCl, and the resulting free amine coupled with (*S*)-Boc-Ala under standard conditions to give **13** (>95% de by ^{1}H and ^{13}C NMR), thus suggesting that little or no racemization had occurred in the preparation of the imidazole.

In summary, new methodology has been developed for the synthesis of 1-benzyl-4-methylimidazoles with a range of substituents at the 2-position based upon a palladium-mediated amino Heck reaction of an amidoxime, itself derived from the corresponding aldehyde. The sequence is simple and efficient and can be used to prepare optically active amino acid mimetics containing a C-terminal imidazole.

Acknowledgment. We thank Professor Koichi Narasaka (University of Tokyo, Japan) and Dr. Owen Curnow (University of Canterbury, Christchurch, New Zealand) for their useful suggestions.

Supporting Information Available: General methods of preparation and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL047628P

(15) Abbott, S. D.; Lane-Bell, P.; Sidhu, K. P. S.; Vederas, J. C. *J. Am. Chem. Soc*. **1994**, *116*, 6513.

(16) Related radical cyclization has been reported; see: Gennet, D.; Zard, S. Z.; Zhang, H. *Chem. Commun.* **2003**, 1870.

(17) Chung, Y. J.; Ryu, E. J.; Keum, G.; Kim, H. *Bioorg. Med. Chem.* **1996**, *4*, 209.

(18) Assignment of isomers is ambiguous and, in any event, unimportant since both react in the subsequent amino Heck reactions. However, the literature suggests that for the amidoximes, the (*Z*)-isomer would be major (Sauve, G.; Rao, V. S.; Lajoie, G.; Belleau, B. *Can. J. Chem.* **1985**, *63*, 3089).