Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron Letters 47 (2006) 5451–5453
Tetrahedron Letters

Synthesis of 1,5-disubstituted 4-haloimidazoles from α-aminonitriles

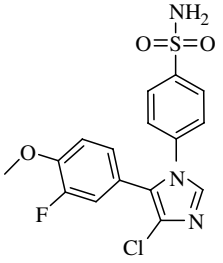
Vijaykumar G. Pawar,[a] Wim M. De Borggraeve,[a,*] Koen Robeyns,[b] Luc Van Meervelt,[b] Frans Compernolle[a] and Georges Hoornaert[a]

[a]*Molecular Design and Synthesis, K.U.-Leuven, Celestijnenlaan 200F, B-3001 Leuven, Belgium*
[b]*Biochemistry, Molecular and Structural Biology, K.U.-Leuven, Celestijnenlaan 200F, B-3001 Leuven, Belgium*

Received 30 April 2006; revised 23 May 2006; accepted 30 May 2006

Abstract—Synthesis of pharmaceutically important 1,5-disubstituted-4-haloimidazoles starting from α-aminonitriles is described. Some 1D and 2D NMR spectral features of these imidazoles are discussed.

Imidazole is a common moiety in a large number of natural products and pharmaceutically active compounds.[1–5] Etomidate, cimetidine, omeprazole and lansoprazole are examples of drugs containing imidazoles.[6,7] Recently 1,5-disubstituted-4-chloroimidazole **1** (Cimicoxib, UR-8880) (Fig. 1) was found to be a highly potent and selective COX-2 inhibitor for the treatment of inflammatory diseases and pain.[8–11] Substituted imidazoles can be prepared by a variety of synthetic methods.[12] A method which gives 1,5-disubstituted imidazoles includes base-induced cycloaddition of sulfonylmethyl isocyanides with imines. This method is also used for the synthesis of COX-2 inhibitor **1**.[13] Merck researchers recently developed a mild method for the synthesis of substituted imidazoles starting from N-acylated α-aminonitriles.[14] Here we would like to report our preliminary results for the direct synthesis of 1,5-disubstituted-4-chloroimidazoles starting from α-aminonitriles.

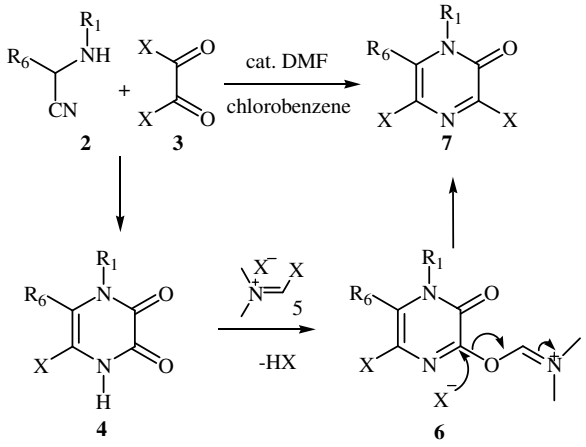


COX-2 inhibitor

1

Figure 1.

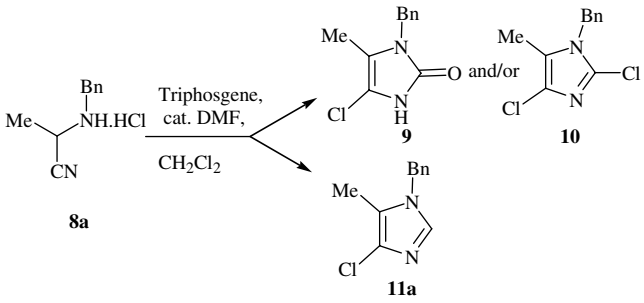
In our laboratory we synthesize dihalo-2(1*H*)pyrazinones **7** by treating α-aminonitriles **2** with oxalyl halide in the presence of a catalytic amount of DMF (Scheme 1).[15,16] In analogy with this synthesis we were expecting the formation of chloroimidazolidinone **9** or dichloroimidazoles **10** upon treating α-aminonitriles with phosgene or phosgene equivalents. However, instead of forming **9** and/or **10**, formation of 1,5-disubstituted-4-chloroimidazoles **11a** was observed in very low yields upon treating α-aminonitrile **8a** with triphosgene in the presence of catalytic amounts of DMF (Scheme 2).



Scheme 1.

Keywords: Imidazole; α-Aminonitriles; Triphosgene; Vilsmeier reagents.
* Corresponding author. Tel.: +32 16 327693; fax: +32 16 327990; e-mail: Wim.DeBorggraeve@chem.kuleuven.be

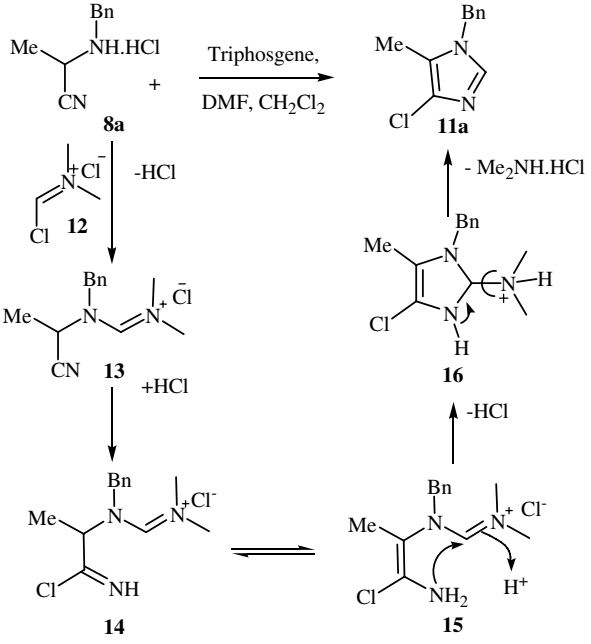
0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.05.181



Scheme 2.

When the α-aminonitriles **8** were treated just with the phosgene equivalent without addition of DMF, the formation of 1,5-disubstituted-4-chloroimidazole **11a** was not observed.[17] The formation of this product can only be explained by the involvement of the Vilsmeier reagent formed in situ (proposed mechanism for the formation of the imidazoles is shown in Scheme 3).[18] Nucleophilic attack of the secondary amine of the α-aminonitrile **8** to the chloromethyleneiminium salt **12** led to loss of HCl. Subsequent addition of HCl on the nitrile group and further tautomerization enables internal attack of the second amine on the electrophilic carbon of the iminium salt. This intermediate **16** loses dimethylammonium chloride and the five-membered imidazole ring forms.

In order to avoid the use of triphosgene and to make the synthesis more practical, we tried to directly use the commercially available Vilsmeier reagent **12**.[19] Indeed, when α-aminonitrile **8a** was treated directly with the Vilsmeier reagent, chloromethyleneineiminium salt **12**, the imidazole **11a** was obtained exclusively.[20] The structure of this product was confirmed by mass spectroscopy, 1D and 2D NMR experiments: Figure 2 shows characteristic HMBC correlations for imidazole **11a**.



Scheme 3.

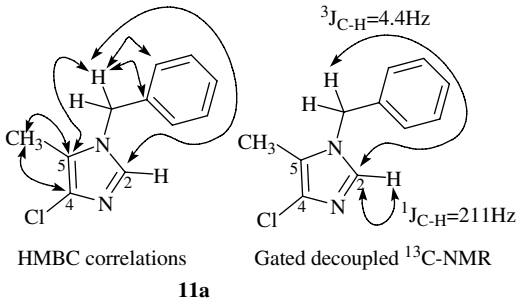


Figure 2.

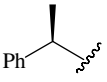
Moreover gated decoupled ^{13}C NMR spectra of **11a** showed a doublet of triplets (dt) for the C^2-carbon at 134.6 ppm with $^1J_{C-H} = 211$ Hz and $^3J_{C-H} = 4.4$ Hz (Fig. 2).

Using this method with different aminonitriles **8a–f** as starting materials, we synthesized a diverse set of imidazoles **11a–f** (Table 1).

Good quality crystals of compound **11d** were obtained from chloroform. Figure 3 shows the X-ray crystal structure of this compound.[21]

Since the Vilsmeier reagent was used in this synthesis, one might expect problems of formylation of activated aromatic rings. However this formylation did not seem to compete with imidazole formation. Only in the case

Table 1.

α-Amino-nitrile	Product	R^1	R^2	Yield (%)
8a	**11a**	Bn	Me	55
8b	**11b**		*p*-Methoxy-phenyl	65
8c	**11c**	Bn	Bn	52
8d	**11d**	Ph	Ph	45
8e	**11e**	Ph_2CH	H	56
8f	**11f**	PMB	Me	62

Bn = Benzyl, PMB = *p*-Methoxybenzyl.

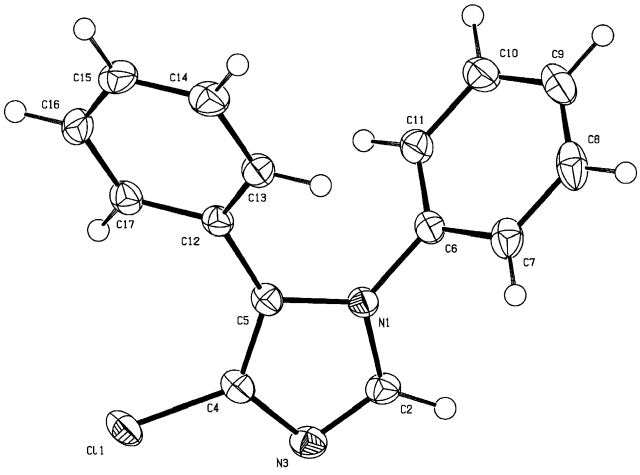
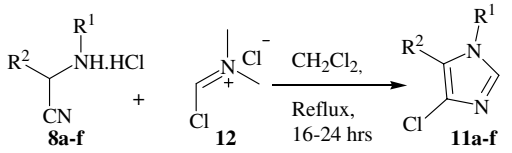
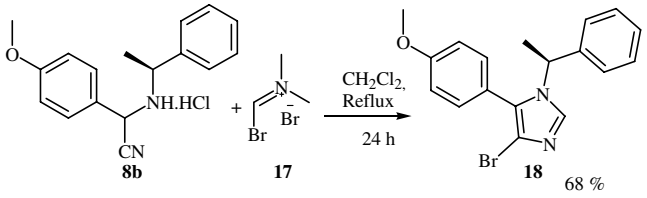


Figure 3. X-ray crystal structure of **11d**.



Scheme 4.



Scheme 5.

of **8e** and **8f** on prolonged heating (36 h), traces of formylated product were detected by mass spectroscopy (Scheme 4).

In order to check the scope of the method, we used bromomethyleneiminium salt **17** in order to try to form the bromoderivative **18**. Bromoimidazole **18** was obtained in 68% yield as a colorless oil upon reaction of amino nitrile **8b** with the Vilsmeier reagent **17** in dichloromethane for 24 h (Scheme 5). The presence of the bromine atom in the compound formed was easily seen in the mass spectrum where M^+ and M^++2 ion peaks were observed in a 1:1 ratio. The structure of the compound was also confirmed by NMR spectroscopy.

In conclusion, we have developed a new mild, short and simple method for the small scale synthesis of pharmaceutically important 1,5-disubstituted 4-chloroimidazoles from α-aminonitriles. Moreover, 4-bromoimidazole was also synthesized by using the bromomethyleneiminium salt as a reagent. At the moment we are trying to improve the yields of this reaction on a large scale. The functionalization of the 4-position of these 4-haloimidazoles using palladium-catalyzed methods is also in progress.

Acknowledgements

V.P. thanks K.U.-Leuven for the fellowship received (DB/05/015). W.M.D.B. (Postdoctoral fellow of the FWO—Vlaanderen) thanks the FWO for a postdoctoral fellowship received.

References and notes

1. Adams, J. L.; Boehm, J. C.; Kassis, S.; Gorycki, P. D.; Webb, E. F.; Hall, R.; Sorenson, M.; Lee, J. C.; Ayrton, A.; Griswold, D. E.; Gallagher, T. F. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 3111–3116.
2. Greenlee, W. J.; Siegl, P. K. S. *Annu. Rep. Med. Chem.* **1992**, *27*, 59–68.
3. Rizzi, J. P.; Nagel, A. A.; Rosen, T.; McLean, S.; Seeger, T. *J. Med. Chem.* **1990**, *33*, 2721–2725.
4. Shapiro, G.; Gomez-Lor, B. *J. Org. Chem.* **1994**, *59*, 5524–5526.
5. Shilcrat, S. C.; Mokhallalati, M. K.; Fortunak, J. M. D.; Pridgen, L. N. *J. Org. Chem.* **1997**, *62*, 8449–8454.
6. Beggs, W. H.; Andrews, F. A.; Sarosi, G. A. *Life Sci.* **1981**, *28*, 111–118.
7. Delgado, J. N.; Remers, W. A. *Wilson and Gisvold's Textbook of Organic Medicinal and Pharmaceutical Chemistry*, 10th ed.; Lippincott-Raven: Philadelphia, New York, 1998.
8. Sorbera, I. A.; Ramis, I.; Uriach, J. *Drugs Future* **2004**, *29*, 325–330.
9. Almansa, C.; Alfon, J.; de Arriba Alberto, F.; Cavalcanti Fernando, L.; Escamilla, I.; Gomez Luis, A.; Miralles, A.; Soliva, R.; Bartroli, J.; Carceller, E.; Merlos, M.; Garcia-Rafanell, J. *J. Med. Chem.* **2003**, *46*, 3463–3475.
10. Almansa, C.; Gonzalez, C.; Patent Appl. WO 2000023426 A1.
11. Almansa Rosales, C.; Gonzales Gonzales, C. Patent Appl. WO 2003016285 A1.
12. Grimmett, M. R. *Sci. Synth.* **2002**, *12*, 325–528.
13. Van Leusen, A. M.; Wildeman, J.; Oldenziel, O. H. *J. Org. Chem.* **1977**, *42*, 1153–1159.
14. Zhong, Y.; Lee, J.; Reamer, R. A.; Askin, D. *Org. Lett.* **2004**, *6*, 929–931.
15. Vekemans, J.; Pollers-Wieërs, C.; Hoornaert, G. *J. Heterocycl. Chem.* **1983**, *20*, 919–923.
16. De Borggraeve, W. M.; Verbist, B. M. P.; Rombouts, F. J. R.; Pawar, V. G.; Smets, W. J.; Kamoune, L.; Alen, J.; Van der Eycken, E. V.; Compernolle, F.; Hoornaert, G. J. *Tetrahedron* **2004**, *60*, 11597–11612.
17. Only formation of *N*-acylated product was observed by mass spectroscopy.
18. Reports which describe the use of Vilsmeier reagents in the synthesis of imidazoles (a) Acharya, A. N.; Thai, C.; Ostresh, J. M.; Houghten, R. A. *J. Comb. Chem.* **2002**, *4*, 496–500; (b) Srinivas, K.; Nair, C. K. S.; Ramesh, S.; Pardhasaradhi, M. *Synthesis* **2004**, *4*, 506–508.
19. The reaction of α-aminonitriles with Vilsmeier reagent **12** formed in situ by DMF/$POCl_3$ was not clean.
20. Typical experimental procedure: Vilsmeier reagent **12** (0.9 mmol) was added to the dichloromethane solution (2 mL) of α-aminonitrile hydrochloride salt **8a** (0.3 mmol) and the reaction mixture was refluxed under argon for 16–24 h. Upon completion of the reaction, the reaction was quenched with ammonium chloride solution and extracted with dichloromethane (3 × 5 mL) and finally with brine. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography using ethylacetate/heptane as eluent. The desired imidazole **11a** was obtained as a yellow colored oil (55%). ^{1}H NMR (400 MHz, $CDCl_3$): 7.47 (s, 1H, H-2, Imd), 7.28–7.4 (M, 3H, Ph), 7.08 (d, 2H, *ortho* Ph), 5.04 (s, 2H, CH_2Ph), 2.07 (s, 3H, CH_3) ^{13}C NMR (100 MHz): 135.1 (C, *ipso* Ph), 134.6 (CH, C-2, Imd), 129.1 (CH, *meta* Ph), 128.4, (CH, *para* Ph), 126.8 (CH, *ortho* Ph), 126.7 (C, C-4 Imd), 122.7 (C, C-5 Imd), 49.8 (CH_2, CH_2Ph), 8.24 (CH_3, Me) EIMS: *m*/*z* % 206 (62, $M^{+\cdot}$), 91 (100, $C_6H_5CH_2^+$) HRMS: calculated for $C_{11}H_{11}ClN_2$: 206.0611, found 206.0608.
21. Crystallographic data (excluding structure factors) for compound **11d** has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 610456. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].