Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
Tetrahedron 61 (2005) 97–101

# Synthesis of an imidazolium-linked cyclophane from histamine

Semih Durmus, Jered C. Garrison, Matthew J. Panzner, Claire A. Tessier and Wiley J. Youngs*

*Department of Chemistry, The University of Akron, Akron, OH 44325-3601, USA*

Received 17 July 2004; revised 18 October 2004; accepted 20 October 2004

Available online 2 November 2004

**Abstract**—The synthesis and structural characterization of a dicationic imidazolium-linked cyclophane **7** is reported. In **7**, two imidazolium units that have histamine dihydrochloride as a precursor are bridged by two 2,6-bis(bromomethyl)-pyridine.


## 1. Introduction

Öfele[1] and Wanzlick[2] reported the first metal-*N*-heterocyclic carbene complexes synthesized from imidazolium salts in 1968. *N*-heterocyclic carbenes (NHC), also known as diaminocarbenes, are a class of ligands which have been shown to bind tightly to a wide variety of metals.[3] The synthesis of new imidazolium-linked cyclophanes is of interest to those working with *N*-heterocyclic carbenes because they serve as precursors which are easily converted to NHCs.

The chemistry of imidazolium-linked cyclophanes has been explored by our group[4] and others.[5] Our work involves the synthesis of cyclic ligand systems which can be reacted with a wide variety of transition metals in different oxidation states to afford new NHC metal complexes. Our interest in this area is the potential use of metal *N*-heterocyclic carbene complexes as medicinal agents. In 1998, Lin and co-workers reported the use of $Ag_2O$ to produce silver *N*-heterocyclic carbenes.[6] Recently, we have demonstrated Ag(I)–carbene complexes have novel antimicrobial properties.[7] We have also reported the synthesis of rhodium carbene complexes as models for novel radiopharmaceuticals.[8] In accordance with our pursuit of medicinal agents, we report herein, the use of the biological molecule histamine to synthesize a dicationic imidazolium-linked cyclophane with side chains. These side chains could be linked to various targeting groups to produce a targeted radioimmunoconjugate.

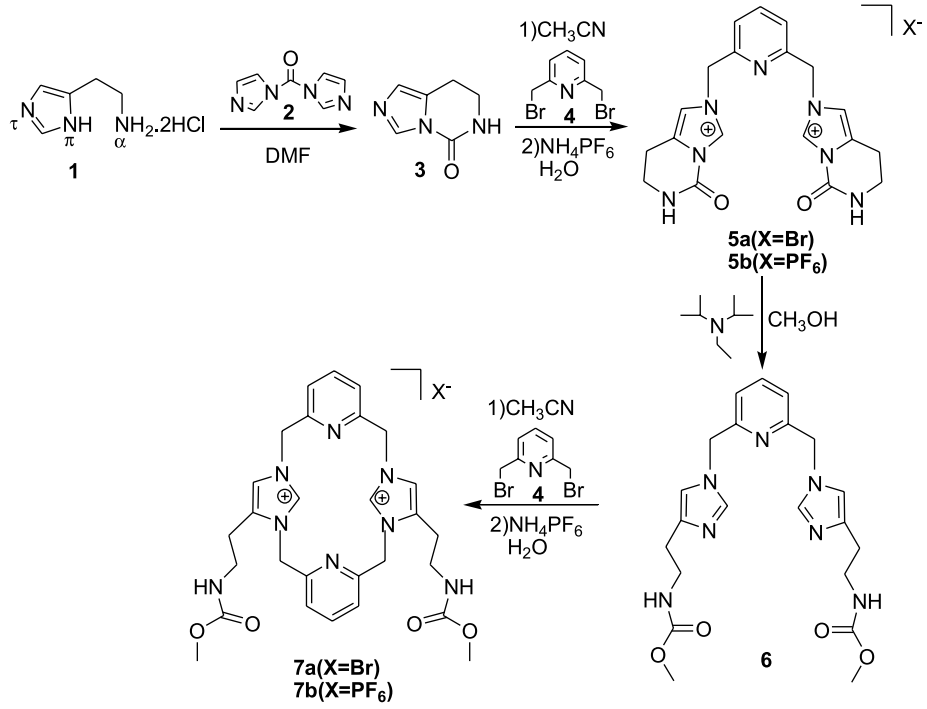
## 2. Results and discussion

Pyman and Van Der Merwe[9] reported the alkylation of histamine at the various positions, $N^{\pi}$, $N^{\alpha}$ and $N^{\tau}$[10] (Scheme 1). The selective alkylation of $N^{\tau}$ was obtained after the protection of $N^{\pi}$ and $N^{\alpha}$. Otherwise, electrophilic attack also occurs on both $N^{\pi}$ and $N^{\alpha}$. The reaction of histamine dihydrochloride (**1**) with 1,1′-carbonyl-diimidazole (**2**) gives the $N^{\pi}$ and $N^{\alpha}$ protected histamine (**3**) (Scheme 1).[11] The $^1H$ and $^{13}C$ NMR spectra are consistent with the structure of **3**.[11] Compound **3** was crystallographically characterized by single crystal X-ray diffraction. Crystals suitable for X-ray diffraction were obtained from a saturated solution in acetonitrile. The thermal ellipsoid plot of compound **3** is illustrated in Figure 1.

The condensation of 2,6-bis(bromomethyl)-pyridine (**4**) with **3** in acetonitrile gives the dicationic imidazolium salt, **5a**. Compound **3** is considerably less reactive than other imidazole derivatives when forming imidazolium salts. This is likely due to the electron withdrawing effects of the diamide protecting group making $N^{\tau}$ less nucleophillic. Anion exchange of **5a** with ammonium hexa-fluorophosphate in water yields the hexafluorophosphate salt **5b** (Scheme 1). The $^1H$ and $^{13}C$ NMR spectra for $[\mathbf{5}][PF_6]_2$ are consistent with the proposed structure. The most notable feature of the $^1H$ NMR spectrum is the presence of the imidazolium proton resonance at 9.76 ppm. This value is in the range of C–H acidic proton shift of imidazolium salts ($\delta = 8$–$10$).[12] In the $^{13}C$ spectrum of compound $\mathbf{5}[Br]_2$, signals due to C1 (C=O) and C6 (N–C–N) were seen at 145.01 and 153.15 ppm, respectively. Crystals of $[\mathbf{5}][PF_6]_2$ suitable for X-ray crystallography were obtained from a concentrated 1:1 water–acetonitrile mixture. The thermal ellipsoid plot of compound **5** is shown in Figure 2.

*Keywords*: Histamine dihydrochloride; Imidazolium-linked cyclophane.
* Corresponding author. Tel.: +1 330 972 5362; fax: +1 330 972 7370; e-mail: youngs@uakron.edu

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.10.056




**Scheme 1.** Synthesis of **7**.

Compound **5a** was deprotected by refluxing in methanol in the presence of *N*,*N*-diisopropylethylamine to obtain compound **6**. Colorless crystals of compound **6** were obtained from concentrated $CH_2Cl_2$ solution. The thermal ellipsoid plot of compound **6** is illustrated in Figure 3. $^1H$ and $^{13}C$ NMR spectra (DMSO-$d_6$) of compound **6** are consistent with the crystal structure. In the $^1H$ NMR spectrum of compound **6**, signal due to the protons on C5 and C5A were observed at 7.62 ppm conforming the change from imidazolium proton (C–$H^+$) to imidazole proton (C–H).

Condensation of **6** and **4** in acetonitrile yields the dicationic cyclophane, **7**$[Br]_2$. The hexafluorophosphate salt, **7**$[PF_6]_2$ was isolated by anion exchange with ammonium hexafluorophosphate in water. Suitable crystals of [**7**]$[PF_6]_2$ for X-ray crystallography were obtained from a concentrated 1:1 water–acetonitrile mixture. The thermal ellipsoid plot of compound **7** is shown in Figure 4. Cyclophane [**7**]$[PF_6]_2$ has an inner cavity that is suitable for complexation to a variety of metals. The distances N1–N4 and C9–C19 (distance between the centroids of imidazolium rings) are 5.081 and 4.862 Å, respectively. $^1H$ and $^{13}C$ NMR spectra (DMSO-$d_6$) of [**7**]$[PF_6]_2$ are consistent with the proposed structure. The imidazolium proton appears at 8.95 ppm in the $^1H$ NMR spectrum of [**7**]$[PF_6]_2$.

The reaction of [**7**]$[PF_6]_2$ with $Ag_2O$ in DMSO at 55 °C yields the silver complex of cyclophane **7**. The ESI-MS spectra showed $[M-H]^+$ at *m*/*z* 651.2. Further characterization of this compound is in progress.

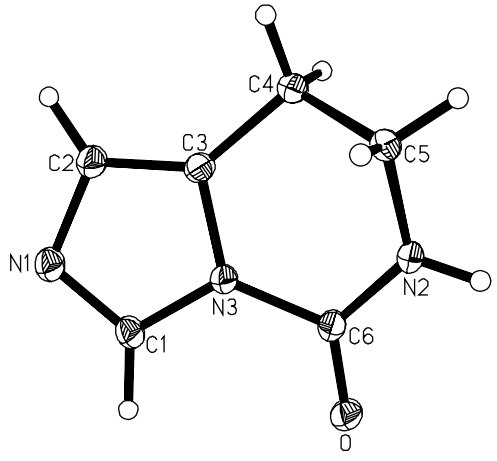



**Figure 1.** Molecular structure of **3** with thermal ellipsoids drawn at 50% probability.

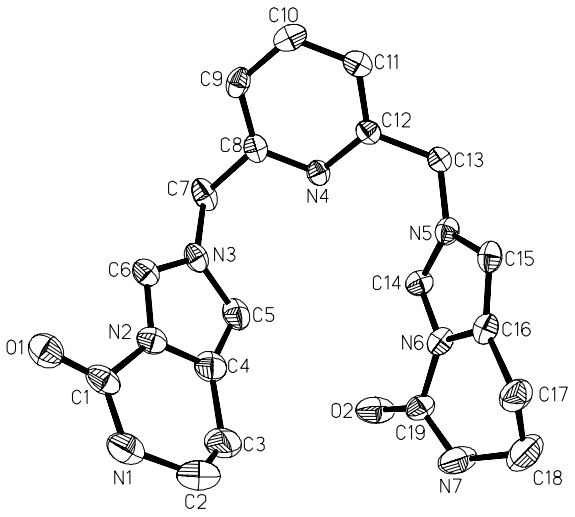



**Figure 2.** Molecular structure of dicationic portion of [**5**]$[PF_6]_2$ with thermal ellipsoids drawn at 50% probability. Hydrogen atoms have been omitted for clarity.