Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Convenient and Efficient Synthesis for a Series of Ether Bis-Imidazoles and Their Derivatives

Cheng-He Zhou [a b] , Xiao-Rong Gu [a] , Ru-Gang Xie [a] & Meng-Shen Cai [b]

[a] Department of Chemistry , School of Sciences, Sichuan Union University , Chengdu, 610064, P. R. China

[b] Department of Bioorganic Chemistry , State Key Laboratory of Natural and Biomimetic Drugs, School of Pharmaceutical Sciences, Beijing Medical University , Beijing, 100083, P. R. China

Published online: 17 Sep 2007.

To cite this article: Cheng-He Zhou , Xiao-Rong Gu , Ru-Gang Xie & Meng-Shen Cai (1999) Convenient and Efficient Synthesis for a Series of Ether Bis-Imidazoles and Their Derivatives, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 29:7, 1217-1222, DOI: 10.1080/00397919908086093

To link to this article: http://dx.doi.org/10.1080/00397919908086093

SYNTHETIC COMMUNICATIONS, 29(7), 1217–1222 (1999)

CONVENIENT AND EFFICIENT SYNTHESIS FOR A SERIES OF ETHER BIS-IMIDAZOLES AND THEIR DERIVATIVES

Cheng-He Zhou[a,b], Xiao-Rong Gu[a], Ru-Gang Xie[a*], Meng-Shen Cai[b*]

[a] Department of Chemistry, School of Sciences, Sichuan Union University, Chengdu 610064, P. R. China

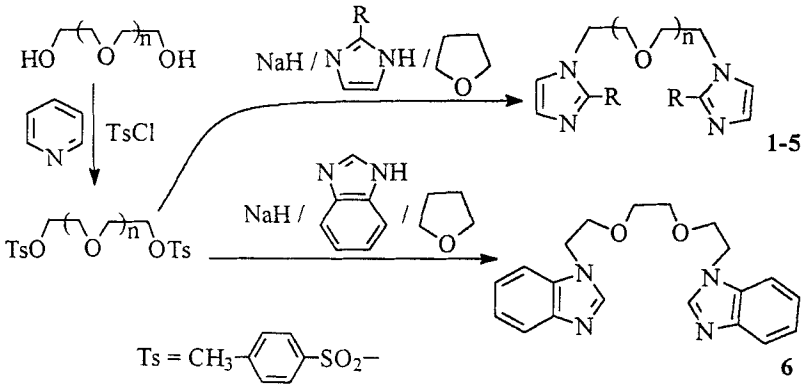
[b] Department of Bioorganic Chemistry, State Key Laboratory of Natural and Biomimetic Drugs, School of Pharmaceutical Sciences, Beijing Medical University, Beijing 100083, P. R. China

ABSTRACT: A simple, convenient and efficient synthesis for a series of ether bis-imidazoles and their derivatives from oligo-ethyleneglycols, imidazole, 2-methylimidazole, and benzimidazole is reported. All these compounds obtained were characterized by MS, ^{1}HNMR and elemental analysis.

In last about thirty years multi-ether compounds such as crown ethers and non-cyclic crown ethers have received extensive studies in host-guest interaction, ionophore and supramolecular chemistry[1-4]. As a part of the histidine unit in protein, imidazole plays a very important role in biological system. For examples, in the active center of metalloenzymes, the metal copper of plastocycanine and the Zn^{2+} ion of both carboxypeptidase and thermolysin are respectively bound to two imidazoles, while in non-metalloenzymes the catalytic sites of Ribonuclease A also

* To whom correspondence should be addressed

contain two imidazole rings which act as both acid and basic catalysts in the hydrolytic cleavage of RNA. Imidazole-based biomimetic models and macrocycles, especially recent imidazolium cyclophanes[5-8] have been paid increasing attention. In spite of this, only one literature, to our knowledge, reported the synthesis of ether bis-imidazoles **1-2** in about 68% yields by condensation of imidazole and 2-methylimidazole with di-ethyleneglycol in toluene and 85% H_3PO_4 at 240-250°, and investigated them as catalysts in manufacture of polyurethane foams[9]. However, their other potential applications in pharmaceutical, complex, biomimetic and supramolecular chemistry had not been mentioned. Multi-ether bis-imidazoles and their derivatives have not been hitherto observed. Here we will report a mild, convenient and efficient synthesis for a series of ether bis-imidazoles and their derivatives from oligo-ethyleneglycols, imidazole, 2-methylimidazole and benzimidazole. The synthetic route is shown in scheme I. The open chain ether bis-imidazoles and their derivatives might possess potential fungicidal and insecticidal activity, and may be used as multidentate ligands to bind metal ions. Their zinc and copper metal complexes will be employed as carboxypeptidase and plastocyanine metalloenzyme models. These ether bis-imidazole compounds are also important intermediates for the synthesis of ether-imidazolium cyclophanes and imidazole crown ethers.



1, n = 1, R = H; **2**, n = 1, R = CH_3 **3**, n = 2, R = H;
4, n = 2, R = CH_3; **5**, n = 3, R = H

Scheme I

(MS) were measured on a Finnigan MAT 4510 spectrometer at 70ev. Elemental analyses were performed with a Carlo Erba 1106. Analytical TLC was performed glass sheets coated with a 0.2 mm layer of silica gel produced by *Qing Dao Marine Chemical Co.* Tetrahydrofuran was purified following standard purification method. All other chemicals and reagents were obtained commercially.

Preparation of the oligo-ethyleneglycol ditosylates:

The multi-ether ditosylates were prepared in good yields by the reaction of commercial di-, tri- and tetra-ethyleneglycol in pyridine respectively with *p*-toluenesulfonyl chloride according to literature[10].

General Procedure for the Synthesis of the ether bis-imidazoles and their derivatives(1-6):

To a well-stirred suspension of 60 mmol of sodium hydride in 20 ml dry tetrahydrofuran, 50 mmol imidazole, 2-methylimidazole or benzimidazole was added slowly. The resulting mixture was stirred for 15 min, and then allowed to rise to 50-60 °C. A solution of 25 mmol of oligo-ethyleneglycol ditosylates in 50 ml tetrahydrofuran was added dropwise 8-10 hr. After the reaction was complete, the mixture was filtered, and thoroughly washed with hot anhydrous tetrahydrofuran. All the tetrahydrofuran solutions were combined, and then concentrated under reduced pressure. The remaining crude product was subjected to column chromatography on silica gel using acetone-methanol (5/1-2/1, v/v) as eluent affording pure desired multi-ether bis-imidazoles and their derivatives(**1-6**). The related data are collected as follows:

Bis-imidazole **1**: Yield 85.2%; colorless liquid; EI-MS: M/Z = 207[M^++1], 139[M^+-Im[14]], 95[$ImCH_2CH_2^+$], 81[$ImCH_2^+$]; ^{1}HNMR(δ ppm): 7.52(s, 2H, Im2-H), 7.05(s, 2H, Im4 -H), 6.88(s, 2H, Im5-H), 4.05-4.10(m, 4H, NCH_2), 3.62-3.70 (m, 4H, OCH_2); Anal. Calcd. for $C_{10}H_{14}N_4O$: C 58.24, H 6.84, N 27.17; Found: C 57.91, H 6.91, N 27.32.

Bis-2-methylimidazole **2**: Yield 92.3%; colorless oil; EI-MS: M/Z = 234[M^+], 219[M^+-CH_3], 153[M^+-MIm[14]], 125[M^+-$MImCH_2CH_2$], 109[$MImCH_2CH_2^+$], 95 [$MImCH_2^+$], 82[$MImH^+$]; ^{1}HNMR(δ ppm): 6.88-6.97 (s, 4H, MIm4,5-H), 3.95-

The ether bis-imidazoles were synthesized by the reaction of imidazole with the oligo-ethyleneglycol ditosylates which were easily obtained starting from

commercial oligo-ethyleneglycols and *p*-toluenesulfonyl chloride[10]. The strong base particularly favors the reaction to give excellent yields of desired products. The fact shows that the imidazole anions are highly susceptible to electrophilic attack, and alkylation occurs rapidly at the nitrogen atom, while byproducts are suppressed effectively[11-12]. It is specially pointed out that the addition of ditosylates all at once decreases the formation of products, instead of the dropwise addition. In the same reaction condition, the reactions of imidazole derivatives such as 2-methylimidazole and benzimidazole with a series of multi-ether ditosylates all also produce high yields of target compounds. In contrast to the former, the reaction gives low yields in the absence of base or by the use of weak base such as potassium carbonate or sodium carbonate. This synthetic method provides a mild, simple, convenient and highly efficient procedure that allows the large-scale preparation of desired ether bis-imidazoles and their derivatives which have a wide range of potential applications.

All these ether bis-imidazoles and their derivatives **1-6** are easily soluble in water, chloroform, acetone, ethanol and methanol. Their structures were characterized by EI-MS, ^{1}HNMR and elemental analysis. The elemental analyses are in good agreement with compounds **1-6** respectively. The EI-MS spectra reveal that the molecular 'ion' peaks and fragmentation peaks are in accordance with the given structures of **1-6**. In ^{1}HNMR spectra, for all these ether bis-imidazoles and their derivatives the NCH_2 protons give a larger value of chemical shift *ppm* than the OCH_2 hydrogens. The 2-position protons of benzimidazole in compound **6** shift downfield, with respect to imidazole 2-position protons in bis-imidazoles **1**, **3** and **5**. Due to the N-alkylation of 1-position in both imidazole and 2-methylimidazole, the ether bis-imidazoles and bis-methylimidazoles **1-5** desplay a highfield signal of the 5-position hydrogen in imidazole ring, compared with the 4-position hydrogen[13].

Experimental

^{1}HNMR spectra were recorded on a VXR-300S zdsnmr instrument in $CDCl_3$, and chemical shifts were reported with TMS as the internal standard. Mass spectra 4.07(m, 4H, NCH_2), 3.58-3.66(m, 4H, OCH_2), 2.48(s, 6H, CH_3); Anal. Calcd. for $C_{12}H_{18}N_4O$: C 61.52, H 7.74, N 23.91; Found: C 61.05, H 7.58, N 24.17.

Bis-imidazole **3**: Yield 89.8%; colorless liquid; EI-MS: M/Z = 251[M^++1], 139[M^+- OCH_2CH_2Im], 124[M^+-$CH_2OCH_2CH_2Im$], 95[$ImCH_2CH_2^+$], 82[$ImCH_3^+$],

68 [ImH$^+$]; ^{1}HNMR(δ ppm): 7.59(s, 1H, Im2-H), 7.52(s, 1H, Im2-H), 7.05(s, 2H, Im4-H), 6.97(s, 1H, Im5-H), 6.88(s, 1H, Im5-H), 4.06-4.11(m, 4H, NCH_2), 3.62-3.69(m, 4H, OCH_2), 3.52(s, 2H, OCH_2), 3.13(s, 2H, OCH_2); Anal. Calcd. for $C_{12}H_{18}N_4O_2$: C 57.58, H 7.25, N 22.38; Found: C 57.19, H 7.34, N 22.46.

Bis-2-methylimidazole **4**: Yield 90.4%; colorless oil; EI-MS: M/Z = 278[M$^+$], 197[M$^+$-MIm], 170[M$^+$+1-MImCH$_2$CH$_2$], 109[MImCH$_2$CH$_2^+$], 82[MIm$^+$]; ^{1}HNMR(δ ppm): 6.89-6.95(m, 4H, MIm4,5-H), 3.95-4.08(m, 4H, NCH_2), 3.59-3.65(m, 4H, OCH_2), 3.48(s, 2H, OCH_2), 3.24(s, 2H, OCH_2), 2.44(s, 6H, CH_3); Anal. Calcd. for $C_{14}H_{22}N_4O_2$: C 60.41, H 7.97, N 20.13; Found: C 60.27, H 8.06, N 20.38.

Bis-imidazole **5**: Yield 88.6%; colorless liquid; EI-MS: M/Z = 294[M$^+$], 184[M$^+$+1-OCH$_2$CH$_2$Im], 169[M$^+$-CH$_2$OCH$_2$CH$_2$Im], 155[M$^+$-CH$_2$CH$_2$OCH$_2$CH$_2$Im], 95[CH$_2$CH$_2$Im$^+$], 68 [ImH$^+$]; ^{1}HNMR(δ ppm): 7.51(s, 2H, Im2-H), 6.90-7.10(s, 4H, Im4,5-H), 4.71(s, 4H, NCH_2), 4.00-4.20(m, 4H, OCH_2), 3.70-3.80(m, 4H, OCH_2), 3.10(s,4H, OCH_2); Anal. Calcd. for $C_{14}H_{22}N_4O_3$: C 57.13, H 7.53, N 19.03; Found: C 56.88, H 7.59, N 18.92.

Bis-benzimidazole **6**: Yield 84.6%; colorless oil; EI-MS: M/Z = 351[M$^+$+1], 233[M$^+$-BIm^{14}], 206[M$^+$+1-BImCH$_2$CH$_2$+], 175[M$^+$-BImCH$_2$CH$_2$OCH$_2$], 145 [BIm CH$_2$CH$_2^+$], 118 [BImH$^+$]; ^{1}HNMR(δ ppm): 7.79-7.96(m, 2H, BIm2-H), 7.27-7.39(m, 8H, BIm-H), 4.20-4.26(m, 4H, NCH_2), 3.42-3.76(m, 8H, OCH_2), Anal. Calcd. for $C_{20}H_{22}N_4O_2$: C 68.55, H 6.33, N 15.99; Found: C 68.47, H 6.28, N 16.16.

Acknowledgment: We are grateful to the China Postdoctoral Science Foundation, the Special Funds of State Educational Committee for Doctorate Scientific Research and the National Natural Science Foundation of P. R. China.

References and notes

1. Atwood, J. L., Davies, J. E., Macnicol, D. D., Vogtle, F. and Lehn, J.-M., *Comprehensive Supramolecular Chemistry, Vol. 1-2 and 9-10,* Pergamon Press, New York, **1996**.

2. Wu, C.-T., *Crown Ether Chemistry*, Science Press, Beijing, **1992**(Ch).
3. Ma, J. C. and Dougherty, D. A., *Chem. Rev.* **1997**, 97, 1303.
4. Silva, A.P., Gunaratne, H. Q. N., Gunnlaugsson, T., Huxley, A. J. M., McCoy, C. P., Rademacher, J. T. and Rice, T. E., *Chem. Rev.* **1997**, 97, 1515.
5. Luo, M.-M., Guo, S.-J., Zhou, C.-H. and Xie, R.-G., *Heterocycles* **1995**, 41, 1421.
6. Zhou, C.-H., Xie, R.-G. and Zhao, H.-M., *Org. Prep. Proc. Int.* **1996**, 28, 345.
7. Alcalde, E., Gisbert, M., Alvarez-Rua, C. and Garcia-Granda, S., *Tetrahedron* **1996**, 52, 15189, and references therein.
8. Rajakumar, P. and Srisailas, M., *Tetrahedron Lett.* **1997**, 38, 5323.
9. Nakatani, K. and Nakasugi, N., *Jpn Kokai Tokkyo Koho JP 02, 160 768[90, 160, 768]*, **1990**.
10. Dale, J. and Kristiansen, P. O., *Acta Chem. Scand.* **1972**, 26, 1471.
11. Katritzky, A. R. and Rees, C. W., *Comprehensive Heterocyclic Chemistry I, Vol. 5*, Pergamon Press, New York, **1984**, pp382-383.
12. Katritzky, A. R. and Rees, C. W. and Scriven, E. F. V., *Comprehensive Heterocyclic Chemistry II, Vol. 3*, Pergamon Press, Oxford, **1996**, pp102-119.
13. Katritzky, A. R. and Rees, C. W. and Scriven, E. F. V., *Comprehensive Heterocyclic Chemistry II, Vol. 3*, Pergamon Press, Oxford, **1996**, pp84-86.
14. Im =  , MIm =  , BIm = 

Accepted June 27, 1998