Pergamon

Tetrahedron Letters, Vol. 36, No. 20, pp. 3489-3490, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)00572-2

Simple One-Step Synthesis of 3-Bromo- and 3,8-Dibromo-1,10-Phenanthroline: Fundamental Building Blocks in the Design of Metal Chelates

Dimitrios Tzalis, Yitzhak Tor,* Salvatorre Failla and Jay S. Siegel*

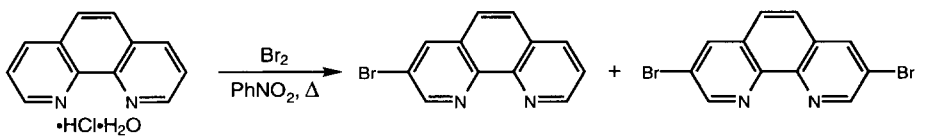
Department of Chemistry and Biochemistry
University of California at San Diego, La Jolla, CA 92093-0358

Abstract: Commercially available 1,10-phenanthroline monohydrochloride monohydrate (**1**) reacts with bromine to give 3-bromo-1,10-phenanthroline (**2**) and 3,8-dibromo-1,10-phenanthroline (**3**) as major products in a one step reaction.

Starting from 1,10-phenanthroline as a fiduciary metal binding site, one can readily imagine molecular scaffolds with applications to selective nucleic acid binding and cleavage, energy conversion systems, chemical sensors or probes, and the assembly of supramolecules in general.[1] Of particular interest, because of their spatial orientation and geometry, are phenanthrolines substituted in either the 3 or the 3 and 8 positions. These positions, however, have been traditionally difficult to functionalize, requiring low-yield multi-step Skraup reaction sequences which utilize carcinogens like bromoacrolein and produce arsenic-rich waste steams.[2] Conventional wisdom advises that simple bromination of phenanthroline is poor and unselective;[3] rewardingly, this turns out not to be the case when one starts from its HCl salt. Indeed, we now report a simple one-step procedure for the direct bromination of 1,10-phenanthroline at the 3- and 3,8 positions.

We have found that the treatment of the commercially available 1,10-phenanthroline monohydrochloride monohydrate (**1**) with bromine in nitrobenzene as a solvent gives 3-bromo-1,10-phenanthroline (**2**) and 3,8-dibromo-1,10-phenanthroline (**3**) as major products (Scheme). The synthesis is conceptually based on the bromination of quinoline salts described by Kress et al.,[4] and provides these two synthetically very useful starting materials in reasonable yields.

Scheme



In a typical procedure, a solution of **1** (10 g, 43 mmol) in nitrobenzene (20 ml) was heated to 130-140 °C in a 250 ml 3-neck flask. Bromine (3.3 ml, 64 mmol in 9.3 ml nitrobenzene) was added dropwise over a period of 1 h. Upon the addition of bromine, **1** went into solution. After stirring for 3 h at the same temperature, the reaction mixture was cooled to room temperature, treated with concentrated ammonium hydroxide (100 ml) and extracted with dichloromethane (3x50 ml). The combined organic layers were washed with water (3x50 ml) and dried ($MgSO_4$). Concentration in vacuum afforded a suspension of the products in nitrobenzene. The nitrobenzene was removed by dissolving the suspension in dichloromethane (10 ml) and filtering it through silica gel (300 ml) using dichloromethane as the eluent. After the nitrobenzene eluted out, the products were recovered by gradually increasing the polarity of the eluent up to 10% MeOH in CH_2Cl_2. Flash column chromatography (0.6 % MeOH in CH_2Cl_2) afforded **2** (3.6 g, 33 % yield) and **3** (2.4 g, 17 % yield) as white powders.[5] Higher solvent polarity (10% MeOH in CH_2Cl_2) elutes unreacted phenanthroline (*ca.* 4 g) that can be recycled.[6]

In summary, a practical and straightforward procedure for the direct bromination of the phenanthroline ring at the strategic 3- and 3,8- positions is reported.

Acknowledgments: This work was supported by the National Science Foundation (CHE-9307582) and the NATO collaborative research program.

References and Notes

1. For a recent review that summarizes recent applications of phenanthroline ligands in bioorganic chemistry, molecular recognition and supramoleuclar chemistry, see: Sammes, P. G.; Yahioglu, G. *Chem. Soc. Rev.* **1994**, 23, 327-334.
2. For the multi-step syntheses of bromo derivatives of 1,10-phenanthroline using the Skraup reaction, see: Case, F.H. *J. Org. Chem.* **1951**, *16*, 941-945.
3. For a monograph, see: Katritzky, A.R.; Taylor, R. *Electrophilic Substitution of Heterocycles: Quantitative Aspects* (Vol. 47 of *Adv. Heterocycl. Chem.*); Academic Press: San Diego, 1990. For an early review, see: Graham, B. in *The Chemistry of Heterocyclic Compounds* Allen, C.F.H. Ed, Interscience Publishers, Inc.: New York, 1958; pp. 386-456. A direct bromination reaction that gives low yields of di-, tri- and tetrabrominated phenanthrolines and traces of the 3- and 5-bromo derivatives has been reported: Denes, V.; Chira, R. *J. Prakt. Chem.* **1978**, *320*, 172-175.
4. Kress T. J.; Costantino S. M. *J. Heterocyclic Chem.* **1973**, *10*, 409-410.
5. 3-Bromo-1,10-phenanthroline **2**; m.p. 164-167 °C; HRMS calcd for $C_{12}H_7BrN_2$ $[M]^+$ 257.9793, found 257.9807; ^1H NMR ($CDCl_3$) δ 9.20 (dd, *J*=4.4, 1.5 Hz, 1H, H9), 9.19 (d, *J*=2.2 Hz, 1H, H2), 8.40 (d, *J*=2.2 Hz, 1H, H4), 8.26 (dd, *J*=8.1, 1.5 Hz, 1H, H7), 7.83 (d, *J*=8.8 Hz, 1H, H5), 7.72 (d, *J*=8.8 Hz, 1H, H6), 7.65 (dd, *J*=8.1, 4.4 Hz, 1H, H8). ^{13}C NMR ($CDCl_3$) δ 151.0, 150.6, 145.8, 144.2, 137.3, 136.0, 129.5, 128.5, 127.8, 125.3, 123.4, 119.8. **2** was also synthesized from 8-nitroquinoline by the Skraup reaction according to ref 2. 3,8-Dibromo-1,10-phenanthroline **3**; m.p. 270-273 °C; HRMS calcd for $C_{12}H_6Br_2N_2$ $[M]^+$ 335.8898, found 335.8890; ^1H NMR ($CDCl_3$) δ 9.20 (d, *J*=2.2 Hz, 2H, H2,9), 8.44 (d, *J*=2.2 Hz, 2H, H4,7), 7.78 (s, 2H, H5,6). ^{13}C NMR ($CDCl_3$) δ 151.5, 144.0, 137.5, 129.5, 126.8, 120.1.
6. Variations of the amount of bromine, reaction time, or temperature influence the outcome of the reaction. Attempts to push the reaction to completion or to higher conversions usually result in higher yields of **3** but at the same time lead to the generation of various other brominated derivatives. Under the present conditions, *ca.* 90 % of crude phenanthroline containing products can be accounted for as unsubstituted phenanthroline, **2** and **3**. The remaining 10% contains several other brominated by-products (5-bromo-, 3,5,8-tribromo- and 3,5,6,8-tetrabromo-1,10-phenanthroline) that can be removed by column chromatography.

(*Received in USA* 31 *January* 1995; *revised* 15 *March* 1995; *accepted* 21 *March* 1995)