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A Straightforward Synthesis of 5-Bromo and 5,5'-Dibromo-2,2'-Bipyridines

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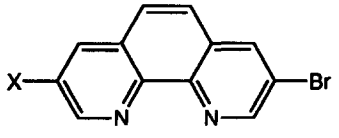
Key Words: 5-bromo- and 5,5'-dibromo substituted 2,2'-bipyridines; radical decarboxylative bromination

Abstract: We herein report on the selective synthesis of 5-bromo-2,2'-bipyridine **2** and 5,5'-dibromo-2,2'-bipyridine **3** by direct bromination of 2,2'-bipyridine hydrobromide salt **1**, as well as by radical decarboxylative bromination of the corresponding acid chlorides.

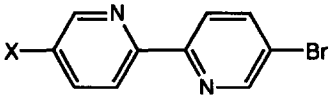
There is nowadays much interest in the design of polytopic ligands suitable for the preparation of oligonuclear metal complexes which are of particular relevance in many fields of research such as energy transfer processes and metal-ion-induced self-assembling phenomena.[1-3] Oligopyridines have extensively been used as fundamental metal binding sites in this kind of systems. We have recently been interested in bromo- and triflate-substituted oligopyridines as building blocks for the preparation, by Pd-catalyzed cross-coupling reactions, of ditopic ligands with the metal binding sites connected through an acetylenic-type bridge.[4] Complexation of these entities afforded materials with outstanding photophysical properties.[5,6]

Later, we turned our attention to the 5- and 5'-positions of the bipyridyl core and, starting from 5-bromo-bpy and 5,5'-dibromo-bpy (bipy = 2,2'-bipyridine), we applied the same strategy to the synthesis of linear rigid rod-like complexes of nanometric dimension.[7] Halo-substituted oligopyridines are also convenient derivatives for the preparation of formyl-substituted pyridines which could be used in further steps for the preparation of stable organic radicals which display an interesting magnetic behaviour.[8]

The recent communication by Siegel and coworkers[9] that 1,10-phenanthroline monohydrochloride monohydrate undergoes bromination at the 3- and 3,8-positions prompts us to report our various findings concerning the synthesis of 5-bromo-2,2'-bipyridine **2** and 5,5'-dibromo-2,2'-bipyridine **3**.



X = H or Br

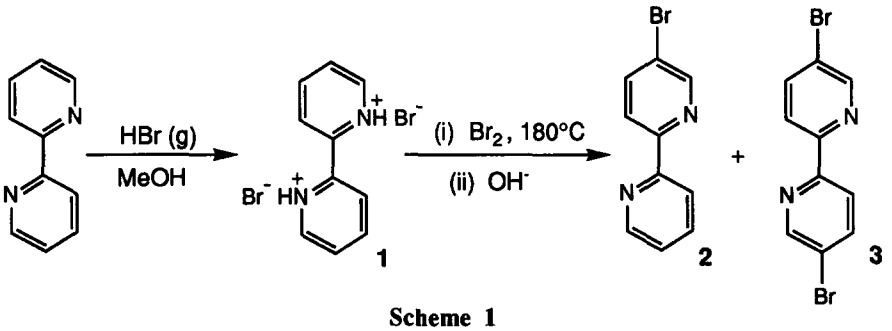


2 X = H; **3** X = Br

It was Burstall[10] in 1938 who first obtained these bpy-products by direct bromination of 2,2'-bipyridine hydrobromide salts in a stream of bromine vapours. At that time, however, the structure of these products could not be unambiguously assigned. Compound **3** has also been prepared at very high temperature

(> 220°C) from 2,5-dibromopyridine and copper (Ullmann's reaction), but the yields were exceedingly poor.[11] Regioselective monolithiation of 2,5-dibromopyridine at position 5 and subsequent treatment with $CuCl_2$, followed by oxidative dimerization with O_2 provided an isomer of compound **3**.[12] Later, the synthesis of **3** has been described by a complicated multi-step procedure[13] and there are no more reports on the synthesis of **2**.

In this communication, we wish to describe the synthesis of **2** and **3** by a modification of Burstall's procedure (Scheme 1). The structures of compounds **2** and **3** resulting from this reaction are for the first time clearly elucidated by comparing their spectroscopic properties with the compounds prepared independently by a novel procedure (vide infra).

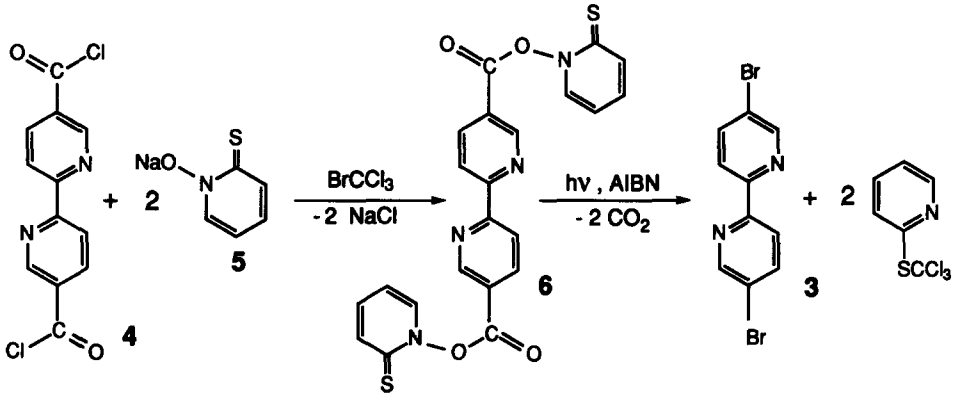


Scheme 1

The synthesis of the starting material **1** was performed by bubbling HBr(gas) into an anhydrous methanolic solution of bpy during 40 min. The precipitate formed was collected and dried in vacuum (98%). In a typical bromination experiment, product **1** (6.0 g, 18.9 mmol) and bromine (6.0 g, 37.6 mmol) were heated to 180°C in a sealed tube during 72 h. The mixture was then allowed to cool and the hard solid was powdered and treated with Na_2SO_3 to remove unreacted bromine, then basified with sodium hydroxide. The resulting aqueous solution was extracted with CH_2Cl_2 (6 x 100 ml). Partial evaporation of the solvent led to precipitation of compound **3**, together with unreacted bipyridine. The solid was filtered and the two products separated by chromatography on silica gel (CH_2Cl_2) yielding 2.47 g of pure compound **3** and 1.53 g of unreacted bpy. The filtrate was then evaporated to dryness and the residue purified by flash silica-chromatography (CH_2Cl_2 as eluent). This yielded 530 mg of mono-substituted compound[14] **2** (yield: 12%), and 300 mg of product **3** (total yield: 42%).[15] Variations of the amount of bromine and reaction time influence the ratio of monobromo- versus dibromo-derivatives as well as the overall chemical conversion of starting salt **1**. Short reaction periods (24 h) increase the yield of derivative **2** to 46%. Higher conversions (two weeks) resulted in higher yields of derivative **3** (51%) and lower yields of **2** (15%), but at the same time led to the formation of other polybrominated compounds, which have not been isolated and characterized. An analogous observation has been made during the bromination of phenanthroline.[9]

In order to unambiguously assigned the molecular structure of these compounds (a proof of structure was lacking in Burstall's report[10]) we have synthesized **3** and **2** by a novel procedure (Scheme 2) based on Barton's radical decarboxylative bromination.[16] This reaction has to the best of our knowledge never been used before with pyridine-based acid chlorides. Thus, reaction of 5,5'-dichlorocarbonyl-2,2'-bipyridine[17] **4** with the pyrithione sodium salt **5** in $BrCCl_3$ yielded the intermediate ester **6**, which was photolysed *in situ* to

give by a radical chain reaction 5,5'-dibromo-2,2'-bipyridine **3**. In a typical experiment compound **4** (2.25 g, 8 mmol) and AIBN (550 mg) were added to a suspension of dry pyrithione sodium salt (2.56 g, 17 mmol) in freshly distilled $BrCCl_3$ under argon. The mixture was heated to 100°C and stirred for 20 h under visible light exposure. It was allowed to cool and the solvent was evaporated. Filtration through alumina and recrystallisation from hexane afforded 1.09 g of **3** as white needles. Isolation of the intermediate thiohydroxamic ester **6** is straightforward, but does not increase the yield of the decarboxylative bromination. From a practical point of view, the synthetic procedure is easily performed in a one-pot reaction without isolation of the intermediate ester **6**. Spectroscopic data for products **3** obtained in the two synthetic procedures are identical and thus unambiguously prove the regioselectivity of the direct bromination.



Scheme 2

Compound **2** has also been prepared by a decarboxylative bromination reaction of 5-chlorocarbonyl-2,2'-bipyridine. This last product has been prepared by chromium(VI)-oxide oxydation in sulphuric acid of 5-methyl-2.2'-bipyridine (obtained by a Kröhnke synthesis[19]) followed by reaction with $SOCl_2$.[20] Here again the regioisomer obtained by direct bromination of the salt and the one prepared by a modified Barton reaction have identical spectroscopic properties.

As a conclusion, two practical procedures are described for bromination of 2,2'-bipyridine at the 5- and 5,5'-positions, uncontaminated by positional isomers. The first one uses direct bromination of 2,2'-bipyridine hydrobromide salts at 180°C and the second a decarboxylative bromination of the corresponding acid chloride in the presence of a radical initiator and $BrCCl_3$ as chain carrier.

Therefore, the present procedures are quite useful for convenient synthesis of numerous oligopyridine derivatives. Further studies on these reactions are under current investigation in our laboratory.

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14. 5-bromo-2,2'-bipyridine **2**: R_f = 0.30 (SiO_2, CH_2Cl_2); m.p. 74/75 °C; FAB^+ (m-NBA, m/z, rel. intensity): 235.0/237.0 $[M+H]^+$, 100%; ^1H NMR (CD_2Cl_2) δ 8.69 (d, ^4J = 2.3 Hz , 1H, H6), 8.62 (large-d,^4J = 3.9 Hz , 1H, H6'), 8.36 (d, ^3J = 7.8 Hz , 1H, H3'), 8.32 (d, ^3J = 8.5 Hz , 1H, H3), 7.92 (dd, ^3J = 8.5, ^4J = 2.3 Hz , 1H, H4), 7.79 (td, ^3J = 7.8 Hz, ^4J = 1.8 Hz, 1H, H4'), 7.30 (ddd, ^3J = 7.8 Hz, ^3J = 3.9, ^4J = 1.2 Hz , 1H, H5'). ^{13}C NMR (CD_2Cl_2) δ 156.1, 151.1, 150.2, 140.4, 137.9, 125.0, 123.2, 122.1, 121.7. Elemental analysis: Calc. for $C_{10}H_7N_2Br$ (M_r = 235.085): C, 51.09; H, 3.00; N, 11.92; Found: C, 50.92; H, 2.90; N, 11.83.
15. 5,5'-dibromo-2,2'-bipyridine **3**: R_f = 0.30 (SiO_2, CH_2Cl_2); m.p. 203/205 °C; FAB^+ (m-NBA, m/z, rel. intensity): 315.0 $[M+H]^+$, 100%; ^1H NMR (CD_2Cl_2) δ 8.71 (d, ^4J = 2.1 Hz , 2H, H6,6'), 8.31 (d, ^3J = 8.5 Hz , 2H, H3,3'), 7.96 (dd, ^3J = 8.5 Hz, ^4J = 2.1 Hz , 2H, H4,4'); Elemental analysis: Calc. for $C_{10}H_6N_2Br_2$ (Mr = 313.980): C, 38.25; H, 1.93; N, 8.92; Found: C, 38.17, H, 1.85, N, 8.79.
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