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Synthesis, characterization and crystal structure of 6-Chloro-4,4′-dimethyl-2,2′-bipyridine and 4,4′-Dimethyl 2,2′-bipyridine N-Oxide

Eleonora Conterosito [a], Claudio Magistris [b], Claudia Barolo [b], Gianluca Croce [a], Marco Milanesio [a], *

[a] Dipartimento di Scienze e Innovazione Tecnologica, Università del Piemonte Orientale, Viale T. Michel 11, Alessandria, 15121, Italy
[b] Dipartimento di Chimica, NIS Interdepartmental Centre, Università degli Studi di Torino, Via P. Giuria 7, Torino, 10125, Italy

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ABSTRACT

The synthesis, the NMR characterization and the crystal structure of 6-Chloro 4,4′-dimethyl 2,2′-bipyridine and of the reaction intermediate 4,4′-Dimethyl 2,2′-bipyridine N-Oxide are here reported. The target compound crystallizes in the orthorhombic system while the intermediate is monoclinic. In both structures, the molecules are linked by weak interactions. The structure of the reaction intermediate N-oxide is characterized by a dihedral angle between the two phenyl rings of 161.77° while the other is almost planar with a dihedral angle of 179.15°. The crystal packing was investigated, also with the aid of Hirshfeld surface analysis. In the N-oxide reaction intermediate the packing is governed by CH–O interactions, while in the product the packing is simply driven by minimizing the voids and thus maximizing the density, with a prevalence of H•••H and C•••H contacts, as indicated by fingerprint decomposition analysis.

1. Introduction

2,2′-Bipyridines have enjoyed considerable success as ligands in metal complexes, thanks to their ability to coordinate a variety of metal ions in different oxidation states [1]. Their simple structure favoured the application of a wide range of synthetic strategies, in order to extend the π-conjugated system and tune their physical and photochemical properties [2–4]. This resulted in a vast array of technological applications, ranging from solar energy conversion [5] to redox electrocatalysis [6].

Unsymmetrically substituted 2,2′-bipyridines, in particular, retain a considerable interest for the possibility of tuning the electronic properties in donor-acceptor conjugated systems, as well as in the construction of versatile metallo-supramolecular architectures [7,8]. In fact unsymmetrical substitution with a halogen represents a preferred route to metal-catalysed cross-coupling reactions, typically used to extend the π-conjugation.

In this paper we report the synthesis and the structural determination of 6-chloro 4,4′-dimethyl 2,2′-bipyridine (**3**) and its synthetic intermediate 4,4′-dimethyl-2,2′-bipyridine N-oxide (**2**) together with their synthesis and characterization (MS, ^{1}H and ^{13}C NMR). 4,4′-Dimethyl-2,2′-bipyridine N-oxide (**2**), an intermediate in the synthesis of 4-(aminomethyl)-4′-methyl-2,2′-bipyridine dihydrochloride hydrate[3] and 4-(bromomethyl)-4′-methyl-2,2′-bipyridine dihydrobromide,[3] is usually synthesized by treatment of 4,4′-dimethyl 2,2′-bipyridine (**1**) with 3-chloroperbenzoic acid.[1,3] The synthesis of 6-Chloro 4,4′-dimethyl 2,2′-bipyridine (**3**) has been reported either by chlorination with $POCl_3$ of the N-oxide (**2**) [9], or through coupling of 2-chloropicoline with 2-bromopicoline [10]. It is a useful building block in the synthesis of 6-phosphanyl bipyridine ligands for electrochemical CO_2 reduction,[5] and tridentate azole-pyridine ligands for Co complexes [11]. The synthesis route is reported in Scheme 1.

2. Experimental

2.1. Reactants and instrumentation

All the chemicals were purchased from Sigma Aldrich and used without further purification. GC–MS spectra were recorded on a Thermo Finnigan Trace GC with a cross-linked methyl silicone capillary column, coupled to a Thermo Finnigan Trace MS mass

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* Corresponding author.
E-mail address: marco.milanesio@uniupo.it (M. Milanesio).

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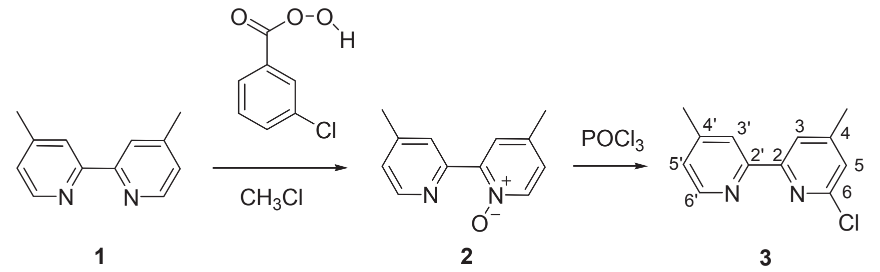

Scheme 1. Synthesis route. 1st Step: oxidation of 4,4′-Dimethyl 2,2′-bipyridine (**1**) to 4,4′-Dimethyl 2,2′-bipyridine N-Oxide (**2**); 2nd Step: chlorination of the N-Oxide to 6-Chloro 4,4′-dimethyl 2,2′-bipyridine (**3**).

spectrometer equipped with an electronic impact source (EI). ^{1}H NMR (200 MHz) and ^{13}C NMR (50 MHz) spectra were recorded on a Bruker Avance 200 NMR spectrometer.

2.2. Synthesis and crystallization

2.2.1. 4,4′-Dimethyl 2,2′-bipyridine N-oxide (2)

A solution of freshly crystallized 3-chloroperbenzoic acid (31.30 g, 0.18 mol) in $CHCl_3$ (1.2 L) was slowly dropped (3 h) into a solution of 4,4′-Dimethyl 2,2′-bipyridine **1** (33.42 g, 0.18 mol) in $CHCl_3$ (0.6 L) in ice bath, and let under stirring at r.t. for 48 h. The solvent was evaporated and the residue neutralized with 1 M K_2CO_3 and heated at 95 °C for 30 min, in order to filter the unreacted **1**; the solution was extracted with $CHCl_3$, dried over Na_2SO_4 and evaporated. The crude product (light brown solid, 27.97 g, $\eta = 77\%$) was used in the following step; it was further purified by chromatography (EtOAc/MeOH = 9/1) before proceeding to crystallization [1,6].

^{1}H NMR ($CDCl_3$): $\delta = 8.70$ (t, J = 0.8 Hz, $H_{3'}$), 8.54 (d, J = 5.0 Hz, $H_{6'}$), 8.18 (d, J = 6.7 Hz, H_6), 7.91 (d, J = 2.7, H_3), 7.14 (dq, $J_{5',6'} = 5.0$, $J_{5',3'} = 0.8$ Hz, $H_{5'}$), 7.04 (dd, $J_{5,6} = 6.7$, $J_{5,3} = 2.7$ Hz, H_5), 2.41 (s, CH_3), 2.36 (s, CH_3) [1,6].

^{13}C NMR ($CDCl_3$): 149.7, 149.1, 147.6, 146.6, 140.1, 137.4, 128.4, 126.5, 126.59, 126.1, 125.3, 21.4, 20.5.

GC–MS (EI): *m/z* (%) = 201 (41), 200 (77, M^+), 199 (77), 184 (70), 183 (68), 172 (62), 171 (100), 157 (40), 156 (58), 144 (69), 142 (32), 132 (81), 119 (65), 93 (37), 92 (72).

2.2.2. 6-Chloro 4,4′-dimethyl 2,2′-bipyridine (3)

Freshly distilled $POCl_3$ (50 mL) was carefully mixed with **2** (21.40 g, 0.11 mol) in ice bath, then let to room temperature under stirring and finally heated under reflux for 6 h; $POCl_3$ was distilled and, after cooling, the solid was cautiously poured in a becher containing ice (fumes), neutralized with Na_2CO_3 and extracted several times with CH_2Cl_2. The organic phase was dried over Na_2SO_4 and evaporated; elution with PE/EtOAc = 8/2 gave the pure product as white solid, g 18.70 ($\eta = 80\%$) [9].

^{1}H NMR ($CDCl_3$): $\delta = 8.47$ (d, J = 5.0 Hz, H_{Ar}), 8.18 (s, H_{Ar}), 8.12 (s, H_{Ar}), 7.11-7.07 (m, $2H_{Ar}$), 2.38 (s, CH_3), 2.37 (s, CH_3) [9,10].

^{13}C NMR ($CDCl_3$): 156.5, 154.5, 151.3, 150.9, 149.0, 148.3, 125.2, 124.6, 124.6, 122.3, 120.6, 120.6, 21.2, 21.0.

GC–MS (EI): *m/z* (%) = 220 (43), 219 (39), 218 (100, M^+), 184 (38), 183 (93), 181 (37), 168 (35), 92 (44), 91 (33), 90 (34).

2.3. XRD data collection and refinement

Single-crystal diffraction data were collected using an Oxford Xcalibur CCD area detector diffractometer with graphite monochromator and Mo–Kα ($\lambda = 0.71069$ Å) radiation. Data reduction and absorption corrections were performed using CrysAlisPRO [12] 171.34.44. Single crystal structure solution was performed by direct methods using SIR2011 [13] and refinement with full-matrix least-squares employing SHELXL-2013 [14] with ShelXle GUI [15]. Crystal data, data collection and structure refinement details are summarized in Table 1 and reported in details in Table S1–S4 and Table S5–S8 in the supplementary information file. H atoms were originally found in the difference Fourier map and then inserted in the model. All C-bound H atoms were then placed in the expected positions, with C–H = 0.97 (phenyl) or 0.95–1.00 Å (methyl), and refined as riding atoms on their carrier atoms, with $U\mathrm{iso}(H_{Ar}) = 1.2U\mathrm{eq}(C)$ for aromatic H atoms and $U\mathrm{iso}(H_{Me})$ $1.5U\mathrm{eq}(C)$ for methyl H atoms.[1] Structural illustrations have been drawn with CCDC Mercury [16] and Crystal Explorer 3.1 [17]. Crystal Explorer 3.1 [17] was used to perform Hirshfeld surface analysis.

2.4. Hirshfeld analyses

Hirshfeld surfaces were generated by the program Crystal Explorer 3.1 [17] All bond lengths to hydrogen were automatically modified to typical standard neutron values [18] (C–H = 1.083 Å, N–H = 1.009 Å and O–H = 0.983 Å), while the CIF files of crystals 1–4 were read into the Crystal Explorer software program for calculations. We are aware that this analysis has some limitations for very weak interactions, like H•••H and C•••H contacts [19], and the results were carefully checked by visual inspection of the crystal packing.

3. Results and discussion

6-Chloro 4,4′-dimethyl 2,2′-bipyridine (**3**) was synthesized as previously reported, through mono-oxidation of 4,4′-Dimethyl 2,2′-bipyridine (**1**) with 3-chloroperbenzoic acid [1,6], and selective chlorination of the crude N-Oxide (**2**) with $POCl_3$ [9]. All the products were characterized through MS and NMR spectroscopy.

The crystal structures of **2** and **3** were solved (structures and crystal packing features are reported Fig. 1 and Fig. 2 respectively) and compared with relevant literature data. The conformational features of the molecules and the packing of the molecule with (**2**) and without (**3**) the N-oxide moiety were analysed. The reaction product **3** crystallizes in Pbca (Fig. 2) space group while **2** crystallizes in P21/n (Fig. 1).

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[1] Cif file of the structures of compound 2 and 3 were submitted to CCDC with numbers CCDC-1429846 and CCDC-1429847 respectively.