Tetrahedron Letters 54 (2013) 840–842

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Complexation to $[Ru(bpy)_2]^{2+}$: the trick to functionalize 3,3′-disubstituted-2,2′-bipyridine

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ARTICLE INFO

Article history:
Received 6 September 2012
Revised 15 November 2012
Accepted 21 November 2012
Available online 10 December 2012

Keywords:
3,3′-Disubstituted-2,2′-bipyridine
Ruthenium complexes
Metalloligands

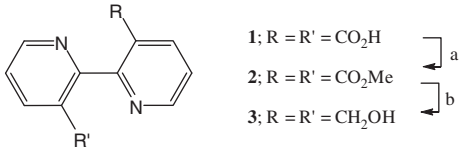
ABSTRACT

While many papers reported the synthesis and chemical transformations of *x*,*x*′-disubstituted-2,2′-bipyridine with *x* = 4, 5 or 6, this is not the case when *x* = 3. Though, such 3,3′-disubstituted-2,2′-bipyridines would be a useful building block for the design of new original complexes. Here we report the results of our investigation concerning the synthesis of members of this family. This study led to the formation of several $[(2,2'\text{-bipyridine})_2Ru(3,3'\text{-dialkylated-}2,2'\text{-bipyridine})]^{2+}$ complexes highlighting a surprising chemical behaviour of the 3,3′-disubstituted-2,2′-bipyridine ligand compared to its 4,4′, 5,5′ and 6,6′-homologues.

Bipyridine and in particular 2,2′-bipyridine is, to date, probably the most widely used ligand in coordination chemistry mainly for its availability, its robust redox stability and its relative ease of functionalization.[1] Literature contains countless examples of metal (Ru,[2,3] Fe,[4] Ir,[5] Os,[3,6] Cu[7] ...) complexes bearing one or more of this versatile building block. This enormous popularity of these classes of compounds is driven by the wide range of applications mainly related to their well defined redox and photophysical properties.[8,9] However, while many papers report the synthesis and/or chemical transformations of *x*,*x*′-dialkylated-2,2′-bipyridine with *x* = 4,[10–13] 5[14–16] or 6[17,18], syntheses of 3,3′-disubstituted-2,2′-bipyridines are still extremely challenging.[19] The main difficulty is related to the relative proximity of the nitrogen atom and the substituent of the opposite ring. This often leads to side reactions when 3,3′-benzylic positions have to be functionalized.

In this Letter we report our investigations in the preparation of ruthenium bis(2,2′-bipyridine) complexes bearing various 3,3′-disubstituted-2,2′-bipyridine as the third bidentate ligand. The synthesized compounds could be useful building blocks to access new families of polynuclear complexes.

In order to synthesize 3,3′-di(hydroxymethyl)-2,2′-bipyridine (**3**), the commercially available 2,2′-bipyridine-3,3′-dicarboxylic acid (**1**) was first esterified using the standard procedure into its corresponding methyl diester in good yield (Scheme 1).[20] However, in the next reduction step, while 3 equiv of $NaBH_4$ efficiently reduced the 4,4′ diester at room temperature in 3 h,[13] our attempts



Scheme 1. Synthesis of 3,3′-dihydroxymethyl-2,2′-bipyridine. (a) *N*,*N*′-Dicyclohexylcarbodiimide (DCC), MeOH, 3 h, 0 °C, 85%; (b) $LiAlH_4$, reflux, 2.5 days, 70%.

to reduce its 3,3′ homologue with $LiAlH_4$ (LAH, 1.6 equiv room temperature) yielded to very low conversion. Consequently, more drastic conditions were required and the reduction of the 3,3′ diester was achieved under reflux for 2.5 days using an excess of LAH (3.5 equiv). Surprisingly, the presence of substituents (phenyl, methyl and *tert*-butyl) at the 6,6′ positions greatly enhanced the reduction of the diesters. Only 2 h at room temperature in the presence of 1.6 equiv of LAH was needed to reduce the 6,6′-diphenyl homologue of **2** as reported by Hayashi and coll.[19] Using sodium bis(2-methoxyethoxy)aluminium hydride as a more powerful reducing agent in diethyl ether at 0 °C, diol **3** was formed in 84% yield.[21]

The substitution of the two hydroxyl groups by two potential leaving groups (chloride, tosylate, bromide) was also particularly difficult. After several unsuccessful attempts to introduce tosylate groups[22,23] or chloride substituents using $SOCl_2$, the substitution of the two hydroxyl groups by bromide was investigated. Despite our efforts using NBS and PPh_3[24,25] or an aqueous solution of HBr at room temperature[26–28] or at 110 °C[29] the desired dibromo

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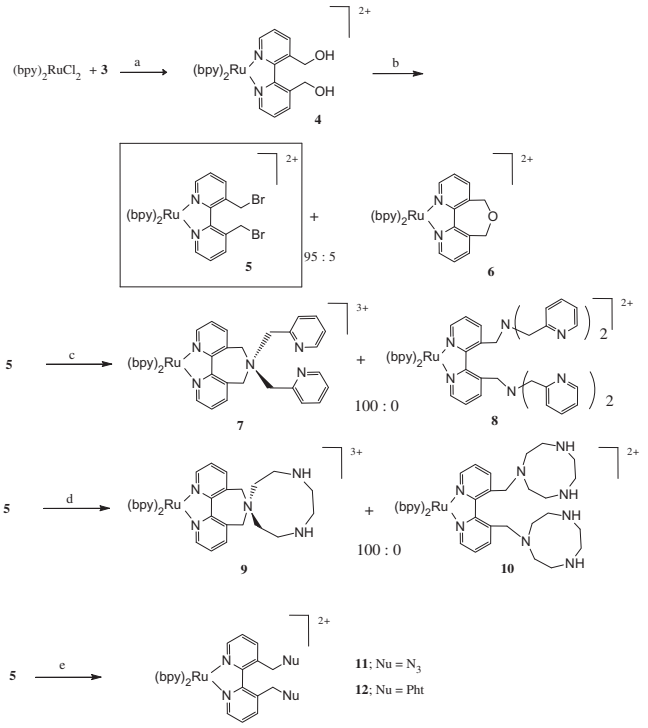
0040-4039/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2012.11.089

product was never obtained properly. A similar behaviour was observed by Meyer and coll. with 4,4′-di(bromomethyl)-2,2′-bipyridine.[30] The authors suggested that the problem was related to the close proximity of the nitrogen atom of one pyridine to the benzylic position of the second pyridine. In order to move away these functions from one to the other, the complexation of the ligand by its bipyridine moiety with a cation as template was envisaged. However Van der Waals repulsions between substituents in the 3,3′-positions might prevent chelation by avoiding a near *cis*-planar conformation required for an optimal coordination,. This is not the case with small substituents such as methyl groups, carboxylic acids and methyl esters as reported by Wallis and co-workers.[31] Notably, in these systems, pyridine rings are displaced from co-planarity by 30–35° and two diastereomeric forms (Δ, a*R*-Λ, a*R*/Λ, a*S*-Δ, a*S*) could be obtained.

Reaction of **3** with 1 equiv of $Ru(bpy)_2Cl_2,6H_2O$ in refluxing ethanol resulted in the formation of complex $[Ru(bpy)_2\mathbf{3}]^{2+}$ (**4**) in reasonable yield (57%; Scheme 2). The reaction proved to be highly stereoselective since a unique diastereomer was detected by ^1H NMR spectroscopy at room temperature. The relative configuration Λ, a*R*-(Δ, a*S*) was attributed by X-ray crystallography of a single crystal obtained by the slow diffusion of diethyl ether into a solution of the complex in a 3:1 acetone–MeOH mixture (Fig. 1; Table 1). It is worth to note that the same relative configuration was observed by Ashby and coll. for the $[(bpy)_2Ru(3,3'$-diamino-$2,2'$-bipyridine$]^{2+}$ complex.[32] In addition, an important dihedral angle of about 34° between the two pyridinyl moieties of the disubstituted ligand was observed, highlighting a noticeable steric strain between substituents. Moreover, two conformational forms, differing only by the position of one of the hydroxymethyl substituent, were observed in the crystal (65:35 ratio). Once again, the substitution of the two hydroxyl groups by bromide to form compound **5** was problematic. In the standard conditions (HBr 48% at reflux), the cyclic ether **6** was quantitatively formed as a result of



Scheme 2. Complexes synthesis. (a) EtOH, reflux, 4 h, 57%; (b) PBr_3 (large excess), CH_2Cl_2, reflux, 87%; (c) 1,2-bis(4-pyridyl)ethane, K_2CO_3, acetone, reflux, 78%; (d) 1,4,11-triazacyclononane, K_2CO_3, acetone, reflux, 42%; (e) For **11**: NaN_3, anhydrous DMF, 0 °C, 62%; For **12**: potassium phthalimide, DMF, rt, 24 h, 60%.

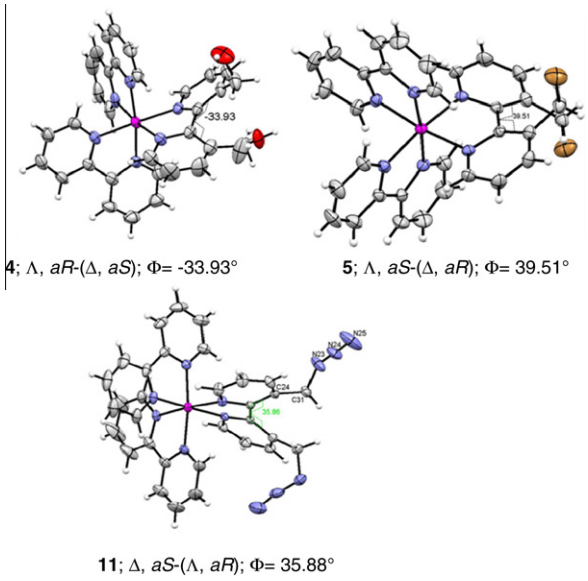


Figure 1. ORTEP view of **4**, **5** and **11** cations.

a unique substitution of one hydroxyl group by a bromide followed by direct intramolecular cyclization due to the proximity of the hydroxyl and bromide groups. A 46:54 mixture of **6** and **5** respectively was however obtained when the reaction was carried out with PBr_3 in dichloromethane at room temperature. This problem was addressed by adding a large excess of PBr_3 (100 equiv) directly into a highly concentrated refluxing solution of **4** in dichloromethane. In such conditions, a 5:95 mixture was obtained in favour of the dibromo product. After purification, **5** was obtained in 70% yield. Single crystals suitable for X-ray analysis were obtained by the slow diffusion of diethyl ether in a solution of the complex in a mixture of acetone and dichloromethane with a little amount of ethanol (Fig. 1). Surprisingly, a Λ, a*S*-(Δ, a*R*) relative configuration with a dihedral angle of 39.5° was determined underlining an unexpected isomerization of the complex during the substitution reaction. One may hypothesize the decoordination of the disubstituted ligand followed by a subsequent recoordination after conformational isomerization around the C2–C2′ axis to afford a more stable isomer. The observed important dihedral angle is without any doubt at the origin of the weak chelation of the disubstituted ligand even if Ru–N bond lengths involving the disubstituted ligand are nearly identical to the $Ru–N_{bpy}$ bonds (2.069 compared to 2.054 and 2.062 Å, respectively).

With the objective to synthesize compound **8** as an interesting metalloligand able to bind different metal cations, the substitution of the two bromide by 1,2-bis(4-pyridyl)ethane (BPA) was then investigated.

However, despite the use of a large excess of BPA (100 equiv), the cyclic ammonium product **7** was obtained as the unique product in good yield (78%). Despite the high concentration of BPA, cyclization occurred faster than intermolecular substitution of the remaining bromide by a second molecule of BPA. Similarly, when 1,4,11-triazacyclononane was used as nucleophile, the corresponding cyclic ammonium product **9** was formed, as detected by mass spectrometry. Compound **10** could not be detected. Consequently, in order to avoid such intramolecular cyclization, azide and phthalimide were used as nucleophile. In anhydrous DMF at 0 °C, the desired products **11** and **12** were obtained in 62 and 87% yields, respectively. Slow diffusion of diethyl ether into a solution of complex **11** in a 3:1 acetone:dichloromethane mixture afforded single crystals suitable for X-ray analysis. While an unexpected and unexplained isomerization was observed during the

Table 1
Selected crystallographic data for complexes [**4**][PF_6]$_2$, [**5**][PF_6]$_2$ and [**11**][PF_6]$_2$

Compound	2[**4**][PF_6]$_2$,0.39H_2O	4[**5**][PF_6]$_2$,8Et_2O	[**11**][PF_6]$_2$
Formula	$C_{73}H_{74.78}F_{24}N_{12}O_{7.39}P_4Ru_2$	$C_{160}H_{184}Br_8F_{48}N_{24}O_8P_8$ Ru_4	$C_{32}H_{26}F_{12}N_{12}P_2Ru$
Molecular weight	2020.46	4774.63	969.66
Colour	Orange	Orange	Orange
Crystal system	Monoclinic	Monoclinic	Monoclinic
Space group	P 2_1/c	C 2/c	P 2(1)/n
a [Å]	24.5602(8)	12.7396(4)	12.1165(2)
b [Å]	12.6187(5)	20.6339(7)	24.5613(5)
c [Å]	25.7537(9)	18.4614(5)	12.2965(2)
α [°]	90	90	90
β [°]	99.881	104.783	92.3794(16)
γ [°]	90	90	90
V [Å]^3	7	4692.3(3)	3
	863.1(5)		656.25(12)
Z	4	1	4
R Indices	R1 = 0.0513, wR2 = 0.0997	R1 = 0.0309, wR2 = 0.0549	R1 = 0.0391, wR2 = 0.0780

R1 = $\sum$ ||F0| − |Fc||/$\sum$ |F0| ; wR2 = {$\sum$ [w($F_0^2 - F_c^2)^2$]/$\sum$ [w($F_0^2)^2$]}$^{1/2}$ with w = 1/[$s^2(F_0^2)$ + (aP)^2 + bP] and $P = [2F_c^2 + \mathrm{Max}(F_0^2, 0)]/3$.

formation of the dibromo product **5** from diol **4**, (from a Λ, a*R*-(Δ, a*S*) to a Λ, a*S*-(Δ, a*R*) relative configuration), a similar behaviour was observed during the substitution of the two bromides by azide restoring the initial Λ, a*R*-(Δ, a*S*) relative configuration. For all complexes, a unique set of signals was observed by ^{1}H NMR spectroscopy.

In conclusion, we report here the results of our investigation into the intriguing chemistry of 3,3′-disubstituted-2,2′-dipyridine and related ruthenium based-complexes yielding the formation of compounds of interest such as **7**, **9**, **11** and **12**. To the difference with the 4,4′-, 5,5′ and 6,6′-related systems, the close proximities between (i) the pyridinyl nitrogen atom and the benzylic position of the second aromatic moiety in the free ligand and, (ii) the two benzylic positions once coordinated to a metal cation, lead to an interesting reactivity. First, despite our efforts, we were unable to introduce a leaving group such as bromide, chloride or tosylate at the two benzylic positions in the free ligand from the corresponding diol. It is assumed that such benzylic position is particularly unstable and undergoes a nucleophilic substitution involving a neighbouring group participation by the pyridinyl nitrogen atom. Second, the coordination to a metal cation leads to move away these two functions but, on the other hand moves closer the two benzylic positions one to the other. Due to Van der Waals' repulsions, this generates an important dihedral angle which is not high enough to avoid the formation of cyclized products when the two leaving groups have to be simultaneously substituted. Thanks to this proximity, two new original metalloligands, namely **7** and **9**, were synthesized in reasonable yields. Finally, without any doubt, the reported strategy will be of particular interest in the design of a new family of polynuclear complexes/catalysts.

Acknowledgment

We thank C. Lebrun (CEA Grenoble, DRFMC) for ESI-MS analyses.

Supplementary data

Supplementary data (Crystallographic data for **4**, **5** and **11** were deposited at the Cambridge Crystallographic Data Centre (CCDC) with the CCDC reference numbers: CCDC 858774 for [1][PF_6]$_2$, CCDC 858775 for [5][PF_6]$_2$ and CCDC 858776 for [11][PF_6]$_2$) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.11.089.

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