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A facile synthesis of aminomethylene bisphosphonates through rhodium carbenoid mediated N–H insertion reaction. Application to the preparation of powerful uranyl ligands

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Abstract

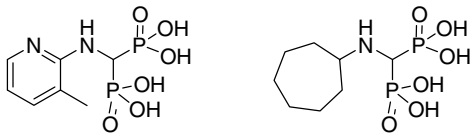
A straightforward procedure ensuring the anchoring of bisphosphonate moiety onto aromatic amines is described. The procedure yields aminoaryl 1,1-bisphosphonates known to display multiple biological activities. The described methodology has also been applied to the synthesis of ligands whose uranyl-binding properties have been studied.

Keywords: Carbenoids; Insertions; Rhodium; Bisphosphonates; Uranyl

Aminomethylene 1,1-bisphosphonates are known to display important biological activities. They are powerful inhibitors of the enzyme farnesyl pyrophosphate synthase (FPPS), a key regulatory enzyme in the mevalonate pathway. The blockade of this pathway is a concept that has found widespread clinical use; bisphosphonate drugs thus display therapeutic properties for several human pathologies such as osteoporosis,[1] rheumatoid arthritis,[2] and cancer.[3] In addition, aminomethylene bisphosphonates have interesting activities against many parasites including trypanosamid parasites.[4]

The structure of the side chain connected through the N-atom to the geminal carbon has a huge influence on the biological activities. Scheme 1 shows examples of important aminomethylene bisphosphonate drugs with aromatic (NE-97220) or aliphatic (incadronate, YM-175) side chains.

Classical synthetic routes to aminomethylene bisphosphonates involve acid catalyzed reactions of nitriles with phosphorous acid or phosphites,[5] condensation of amines



Scheme 1. Examples of aminomethylene bisphosphonates used clinically.

with ethylorthoformate and phosphites,[6] bisphosphorylation of formamides,[7] Beckman rearrangement of oximes in the presence of phosphites,[8] and reductive amination of carbonyl derivatives with aminomethyldiphosphonate.[9]

In connection with our efforts to develop new synthetic routes to bisphosphonates,[10] we recently developed a Cu-carbenoid O–H insertion reaction that allows an easy anchoring of the bisphosphonate moiety into alcohols and phenols.[11] In the present Letter, we describe the corresponding reaction with amine substrates as a new method for aminomethylene bisphosphonate preparation.

The use of in situ generated metallacarbenoid species for the transfer of a carbene moiety from a diazo source to organic substrates has a long history of successful applications in organic synthesis.[12] Although N–H insertion

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reactions of metal carbenoid intermediates have been widely explored (especially the intramolecular version),[13] no reaction was described with tetraethyl diphosphonodiazomethane **1** probably due to the very low reactivity of this particular diazo compound.[14]

We first investigated the reaction of aniline, used as a model substrate, with **1** in the presence of a series of putative catalysts. Reactions were conducted under refluxed toluene (Table 1).

Contrary to our previous finding showing a superior activity of copper over rhodium complexes for the O–H insertion reaction involving **1**,[11] $Rh_2(NHCOCF_3)_4$ was found to be the best catalyst for the reaction of **1** with aniline affording almost quantitative yield of the expected aminomethylene bisphosphonate **2a** with a loading of only 1% mol (Table 1, entry 2). This dirhodium complex was first identified by Moody and co-workers as an interesting catalyst for O–H insertion reactions involving α-diazo phosphonate compounds.[15]

We therefore looked at the scope of this reaction by applying the procedure to a variety of aromatic amines (Table 2).

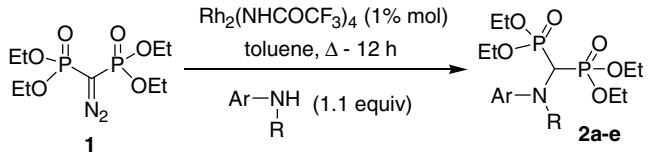
The reaction worked successfully on several aniline derivatives bearing either electronwithdrawing or donating groups (Table 2, entries 1–4) and was also efficient on secondary aromatic amine (Table 2, entry 5) affording the desired aminobisphosphonates in good yields. However, despite our efforts, all attempts trying to apply this method on aliphatic amines were unsuccessful. These nucleophilic amines are known to coordinate to the metal[13g] and to a certain extent poison the catalyst.[16]

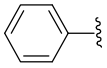
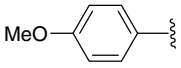
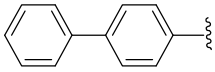
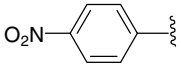
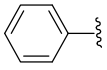
Besides their biological importance, bisphosphonates are also known for their ability to strongly chelate metals. Dipodal and tripodal ligands bearing bisphosphonates moieties are particularly interesting for uranyl sequestration.[17] Encouraged by the efficiency of the above-described methodology, we investigated the use of this new insertion reaction for the construction of dipodal bisphosphonate ligands by using diamines as starting materials (Table 3). Deprotection of the bisphosphonate moieties was easily carried out by conventional treatment with TMSBr.[18]

Ligands **3a**–**d** were obtained in moderate yields through double N–H insertion of aromatic diamines. The deprotection step of the corresponding dipodal bisphosphonates occurred quantitatively and the final products were recovered by precipitation with Et_2O.

We then investigated the uranyl-binding properties of these ligands by employing a colorimetric method that we previously described.[17] This method is based on competitive uranium binding using Sulfochlorophenol S (SCP) as

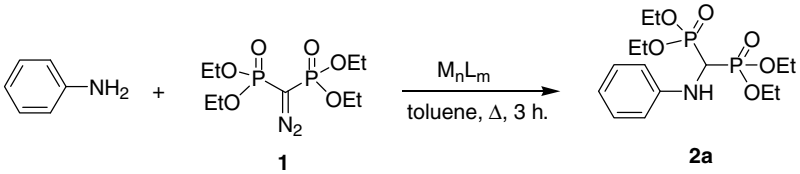
Table 2
Scope of the N–H insertion reaction involving aromatic amines[a]



Entry	Ar	R	Product	Isolated yield (%)
1		H	**2a**	80
2		H	**2b**	87
3		H	**2c**	78
4		H	**2d**	76
5		Me	**2e**	66

[a] Reactions were conducted with 1.1 equiv of $PhNH_2$ and 1 equiv of **1**.

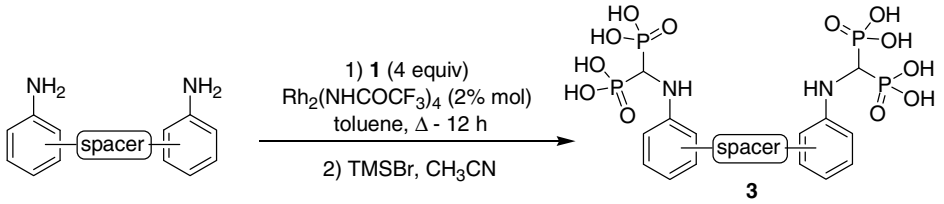
Table 1
Optimization of the insertion reaction involving diazo compound **1** and aniline[a]

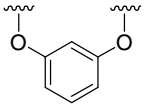
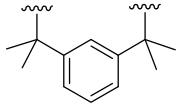


Entry	M_nL_m (% mol)	Yield of **2a**[b] (%)
1	$Rh_2(NHCOCF_3)_4$ (3%)	99
2	$Rh_2(NHCOCF_3)_4$ (1%)	**97**
3	$Rh_2(OCOCH_3)_4$ (1%)	2
4	ScOTf (1%)	1
5	$Yb(OTf)_3$ (1%)	n.d.
6	AgOTf (1%)	4
7	$Cu(OTf)_2$ (1%)	72
8	$[Ru(pcym)Cl_2]_2$ (1%)	36

[a] Reactions were conducted with 1.1 equiv of $PhNH_2$ and 1 equiv of **1**.
[b] ^{31}P NMR yields.

Table 3
Preparation of bis-aminomethylene bisphosphonates through double insertion reaction of **1** on diamines

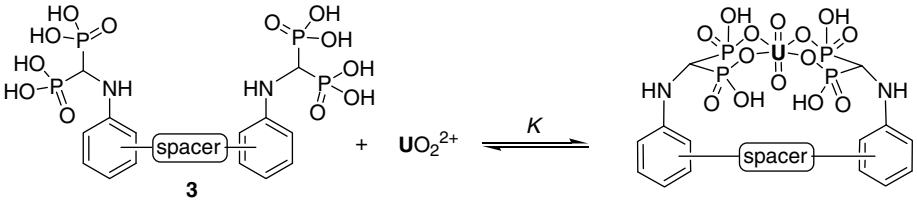


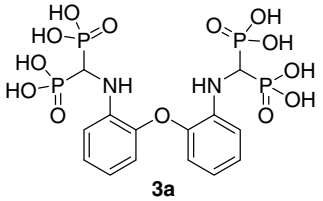
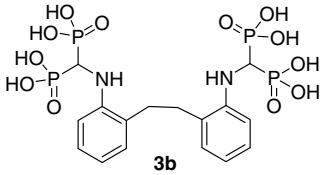
Entry	Spacer	Product	Global isolated yield (%)
1	(*o*) –O–	**3a**	49
2	(*o*) –CH_2–CH_2–	**3b**	48
3	(*p*) 	**3c**	50
4	(*p*) 	**3d**	47

chromophoric reference chelate. In aqueous solution, this dye compound displays a violet color whereas the SCP/UO_2 complex is blue. The conditional association constants (K_{cond}) of the bisphosphonate ligands **3a**–**d** toward UO_2^{2+} were therefore easily determined by following the disappearance of the preformed SCP/UO_2 at biologically relevant pH values (pH 5.5, 7.4, and 9). The results (Table 4) indicate the strong uranyl binding properties of these ligands with K_{cond} up to $\sim 10^{17}$ at pH 7.4.

As expected, higher association constants were observed with ligands constructed with a spacer of sufficient size separating the bisphosphonate chelating functions (compare entries 2–4 with entry 1, Table 4). A decrease of the uranyl binding properties of ligands **3a**–**d** was also

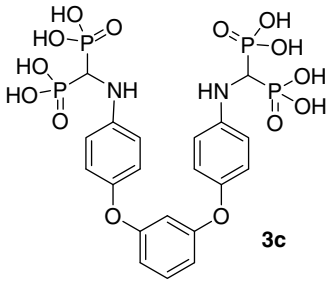
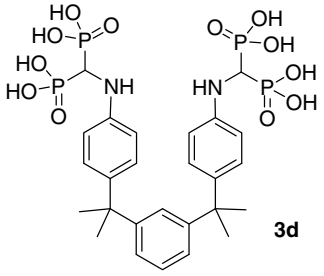
Table 4
UO_2^{2+}-binding properties of ligands **3**



Entry	**3**	K_{cond}		
		pH 5.5	pH 7.4	pH 9
1	 **3a**	$10^{12.8}$	$10^{15.6}$	$10^{17.6}$
2	 **3b**	$10^{12.7}$	$10^{16.8}$	$10^{18.8}$

(*continued on next page*)

Table 4 (*continued*)

Entry	3	K_{cond}		
		pH 5.5	pH 7.4	pH 9
3	 **3c**	10^{15}	$10^{16.7}$	$10^{17.6}$
4	 **3d**	10^{15}	$10^{16.7}$	$10^{17.8}$

observed under acidic pH. This phenomenon might be explained by the protonation of the amine function resulting in the formation of ammonium ion which might undergo repulsive electrostatic interactions with the metal cation.

In conclusion, we have developed a simple and practical method providing a direct entry to the anchoring of the bisphosphonate moiety onto aromatic amine starting materials through C–N bond formation.[19] The presented procedure is complementary to known protocols and, in regard to its simplicity and efficiency, is of particular interest for the straightforward synthesis of aromatic aminobisphosphonate products.

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18. McConnell, R. L.; Coover, H. W. *J. Am. Chem. Soc.* **1956**, *78*, 4450–4452.
19. *Typical procedure for aminoaryl 1,1-bisphosphonates preparation*: To a solution of aromatic amine (0.35 mmol, 1.1 equiv) and $Rh_2(NHCOCF_3)_4$ (2 mg, 3.18 μmols) in 3 mL of dry toluene was added diazo-phosphonate **1** (0.318 mmol, 1 equiv) dissolved in 3 mL of dry toluene. The mixture was heated under reflux for 12 h, then evaporated under reduced pressure. The residue was purified by flash chromatography on silica column (dichloromethane/acetone 60/40) to afford the desired product. All new compounds have been characterized by ^{1}H NMR, ^{13}C NMR, ^{31}P NMR, IR and mass spectroscopy. *Selected data*: Compound **2b**: ^{1}H NMR (400 MHz, DMSO) (δ ppm): 1.11 (t, $J = 7.2$ Hz, 6H); 1.17 (t, $J = 7.2$ Hz, 6H); 3.62 (s, 3H); 3.94–4.09 (m, 8H); 4.39 (dt, $^2J_{H-P} = 22.8$ Hz; $^3J_{NH-H} = 10.8$ Hz, 1H); 5.24 (dt, $^3J_{NH-P} = 3$ Hz; $^3J_{NH-H} = 10.8$ Hz, NH); 6.68 (d, $J = 8.8$ Hz, 2H); 6.81 (d, $J = 8.8$ Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) (δ ppm): 16.24–16.38 (m); 51.72 (t, $J = 147$ Hz); 55.59 (OMe); 63.15 (d, $J = 3.5$ Hz); 63.18 (d, $J = 3.5$ Hz); 63.62 (d, $J = 3.5$ Hz); 63.65 (d, $J = 3.5$ Hz); 114.64; 115.28; 140.37; 153.06. ^{31}P NMR (160 MHz, $CDCl_3$) (δ ppm): 17.99 (s, 2P). IR (NaCl): ν 3491; 2984; 1514; 1243; 1026; 974 cm^{-1}. MS (ESI/TOF) m/z: 432 (100%, $[M+23]^+$). HRMS: Calcd for $C_{16}H_{29}NO_7NaP_2$: 432.1317 m/z. Found: 432.1331 m/z. Compound **3a**: This ligand was prepared according to the above-described procedure using 4 equiv of **1**. After purification by flash chromatography, the tetraethyl esters were deprotected by treatment with TMSBr (12 equiv) in 10 mL CH_3CN. The mixture was heated under reflux for 3 h, then quenched with 1 mL of water. After refluxing for additional 15 min, the solvents were evaporated and co-evaporated with MeOH. Resulting residues were dissolved in a minimum of MeOH and precipitated with ether. The resulting slurry was decanted, washed with ether and dried under high vacuum in the presence of P_2O_5. ^{1}H NMR (400 MHz, MeOD) (δ ppm): 4.31 (t, $J_{H-P} = 21.6$ Hz, 2H); 6.74 (t, $J = 7.2$ Hz, 2H); 6.86 (d, $J = 7.2$ Hz, 2H); 6.99–7.08 (m, 4H). ^{13}C NMR (100 MHz, MeOD) (δ ppm): 50.68 (t,$J = 144$ Hz); 112.86; 116.99; 117.99; 126.09; 137.83; 143.85. ^{31}P NMR (160 MHz, MeOD) (δ ppm): 16.20 (s, 4P). MS (ESI/TOF) m/z: 549 (100%, $[M+1]^+$).