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An Efficient Synthesis of Aromatic 1-Hydroxymethylene-1, 1-bisphosphonates from Aldehydes

Yu Li XIE*, Qin ZHU, Xing Rong QIN, Yu Yuan XIE[1]

State Key Laboratory of Drug Research, Shanghai Institute of Materia Medica, Shanghai Institutes for Biological Sciences, Shanghai 200031

Abstract: A simple and efficient procedure for synthesis of 1-hydroxymethylene-1,1-bisphosphoates from aldehydes is described. This method was applied to the synthesis of novel catechol substituted bisphosphonates as the anti-osteoporosis agents.

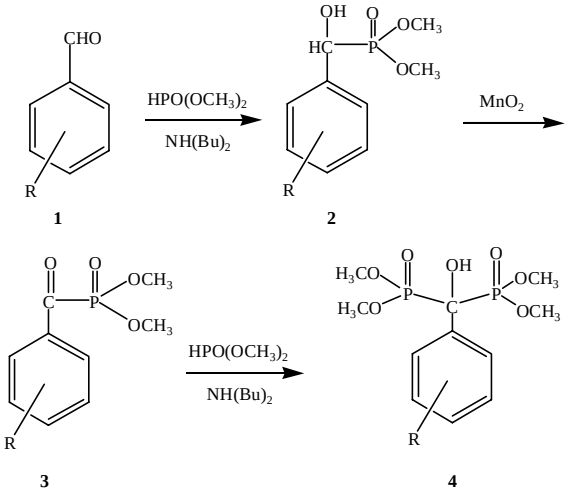
Keywords: Bisphosphonate, aldehydes, catechol, anti-osteoporosis.

Bisphosphonates(BPs), as the stable analogues of pyrophosphate, contain two phosphonate groups attached to a single carbon atom, forming a "P-C-P" structure that are completely resistant to enzymatic hydrolysis. The 1-hydroxymethylene-1, 1-bisphosphonates(HMBP) as the most effective compounds, are widely used in the treatment of a number of diseases characterized by an abnormal calcium metabolism such as Paget's disease of bone, myeloma, and osteoporosis[1,2]. Recently, there has been considerable interest on aromatic BPs because of their novel biological properties as anti-inflammatory, anti-neoplastic and lipid lowering agents[3,4]. However, more surprisingly, we recently found some of catechol substituted HMBP not only inhibit osteoclasts but also stimulate the proliferation of osteoblasts *in vitro*[5]. This result suggests they might offer distinct advantage over currently available BPs to selectively act on osteoblasts rather than other cell types.

Several methods have been reported for the synthesis of HMBP[6]. However, the common method that involves the reaction of a carboxylic acid and phosphorus trichloride was limited to only the compounds with alkyl substituent , not allowing the synthesis of aromatic analogues[7,8]. As described in the literatures[3,9], aromatic HMBP can be indirectly obtained from acid chlorides and trimethylphosphite. Unfortunately, in this case, Michaelis-Arbuzov reaction of trialkyl phosphite and acid chloride is carried out in the harsh acidic conditions and the products need to be purified by distillation. Consequently it is not suitable for the polyfunctional substrates. Furthermore, we have failed to synthesize some catechol derivatives in which we are in particular interest by this method. In this communication, we report a very mild and efficient method for the preparation of aromatic HMBP from aldehydes (**Scheme 1**).

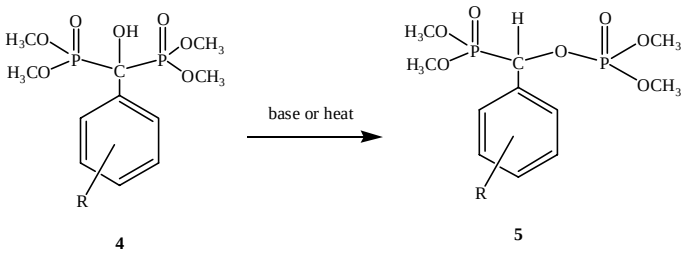
*E-mail: yyxie@mail.shcnc.ac.cn

Scheme 1



As shown in **Scheme 1**, α-hydroxyphosphonate **2** can be easily obtained by the addition of dimethylphosphite to aldehydes in the presence of catalytic amount di-*n*-butylamine based on Pudovik reaction. Treatment of **2** with 5 equiv of freshly prepared active MnO_2 in $CHCl_3$ at room temperature led to α-ketophosphonate **3** within 24 h. Compound **3** does not need to be purified and reacts directly with dimethylphosphite and 10% equiv of di-*n*-butylamine to give the corresponding BPs derivatives in good yields. Addition reaction was carried out in ether at -5-0°C for 1 h. The products can be conveniently collected from the reaction mixture after precipitation and allow an easy recrystallization to analytical purity.

Scheme 2



Bisphosphonate **4** is not stable thermically or under basic conditions due to the rearrangement into the phosphonophosphate **5** (**Scheme 2**)[10]. The addition of dimethylphosphite was strongly exothermic, but no side reaction was observed at 0°C except for the substrate **1e**. In this case, it was necessary to work at -5°C for good result. In this

reaction, the choice of solvent was found to be important since in chloroform, for example, the ^{31}PNMR measurements indicated that the initially formed bisphosphonate **4** showed some tendency to rearrange even though at -5°C. Fortunately, it was found that the bisphosphonate **4** was only slightly soluble in ether, so that in this solvent the product precipitated as it formed thus preventing subsequent rearrangement.

Table 1 HMBP derivatives **4a-4j** produced *via* **Scheme 1**

Entry[a]	R	Formula	Yield[b] (%)	Elemental analysis(%) Calcd		Found	
				C	H	C	H
4a	3,4-2OCH$_3$	$C_{13}H_{22}O_9P_2$	36.5	40.63	5.73	40.44	5.95
4b	3,4-CH$_2$O$_2$	$C_{12}H_{18}O_9P_2$	57.5	39.13	4.89	39.44	4.95
4c	3-OCH$_3$-4-OAc	$C_{14}H_{22}O_{10}P_2$	39.0	40.78	5.34	40.39	5.65
4d	3,4-2OAc	$C_{15}H_{22}O_{11}P_2$	41.2	40.91	5.00	40.58	4.95
4e	2,3-2OCH$_3$	$C_{13}H_{22}O_9P_2$	42.4	40.63	5.73	40.55	5.98
4f	3-Cl	$C_{11}H_{17}ClO_7P_2$	49.2	36.82	4.74	36.77	4.62
4g	4-OCH$_3$	$C_{12}H_{20}O_8P_2$	52.2	40.68	5.65	40.54	5.55
4h	H	$C_{11}H_{18}O_7P_2$	61.3	40.74	5.56	40.71	5.66
4i	2-OCH$_3$	$C_{12}H_{20}O_8P_2$	43.5	40.68	5.65	40.43	5.57
4j	4-Cl	$C_{11}H_{17}ClO_7P_2$	51.5	36.82	4.74	36.75	4.55

a) New compounds **4a-4e** were confirmed by ^{1}HNMR, ^{1}PNMR and EI[11]. b) Isolated yield.

As shown in **Table 1**, 5 catechol derivatives of HMBP were successfully prepared in moderate yields by this method. In the other cases, it also gives good results. In conclusion, the procedure described herein allowed to introduce the 1-hydroxymethylene-1,1-bisphosphonic groups from various aromatic aldehydes. To our knowledge, synthesis of HMBP from aldehydes was carried out for the first time. The hydrolyzed bisphosphonates have been tested *in vitro* for anti-osteoporosis activities and the results will be reported elsewhere.

References and Notes

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11. Spectral data of compound **4a**: ^{1}H-NMR($CDCl_3$) δ ppm: 3.60-3.81（m, 12H, PO(OCH$_3$)$_2$）; 3.88-3.98（d, 6H, -OCH$_3$）; 4.35(s, 1H , -OH); 6.69-7.42(m, 3H, Ar-H). ^{31}PNMR($CDCl_3$) δ: 19.6ppm. EI（*m/z*）: 384（M$^+$）; 275（M$^+$- PO(OCH$_3$)$_2$）. **4b**: ^{1}H-NMR($CDCl_3$) δ ppm: 3.60-3.81 (m, 12H, PO(OCH$_3$)$_2$）; 4.35(s, 1H , -OH); 5.29(s, 2H, -OCH$_2$O-); 6.79(m, 1H, Ar-H); 7.22-7.31(m, 2H, Ar-H). ^{31}PNMR($CDCl_3$) δ: 19.2ppm. EI（*m/z*）: 368（M$^+$）; 259（M$^+$-PO(OCH$_3$)$_2$）. **4c**: ^{1}H-NMR($CDCl_3$) δppm: 2.55(s, 3H, -OCCH$_3$); 3.62-3.85（m, 12H, PO

$(OCH_3)_2$）; 3.98（d, 3H, -OCH_3）; 4.55(s, 1H , -OH); 6.69-7.42(m, 3H, Ar-H). ^{31}PNMR ($CDCl_3$) δ: 19.4 ppm. EI（*m/z*）:412（M^+）; 303（M^+- $PO(OCH_3)_2$）. **4d**:^{1}H-NMR($CDCl_3$) δ ppm: 2.53-2.56(d, 6H, -$OCCH_3$); 3.62-3.90（m, 12H, $PO(OCH_3)_2$）; 4.55(s, 1H , -OH); 6.67-7.45(m, 3H, Ar-H). ^{31}PNMR($CDCl_3$) δ: 19.3 ppm. EI（*m/z*）: 440（M^+）; 331（M^+- $PO(OCH_3)_2$）. **4e**: ^{1}H-NMR($CDCl_3$) δ ppm: 3.62-3.85（m, 12H, $PO(OCH_3)_2$）; 3.89-3.96（d, 6H, -OCH_3）; 4.40(s, 1H, -OH); 7.02-7.69(m, 3H, Ar-H). ^{31}PNMR($CDCl_3$) δ: 19.8ppm. EI（*m/z*）: 384（M^+）; 275（M^+- $PO(OCH_3)_2$）。

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