Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 45 (2004) 4511–4513
Tetrahedron Letters

One-pot synthesis of 1-hydroxymethylene-1,1-bisphosphonate partial esters

Evelyne Migianu, Isabelle Mallard, Nadia Bouchemal and Marc Lecouvey*

Laboratoire de chimie Structurale Biomoléculaire (UMR 7033-CNRS). UFR S.M.B.H. Université Paris 13. 74, Rue Marcel Cachin, F-93017 Bobigny Cedex, France

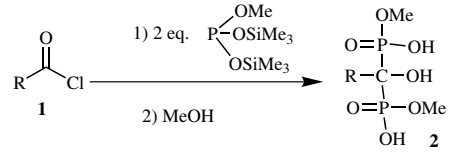
Received 3 February 2004; revised 7 April 2004; accepted 9 April 2004

Abstract—A selective one-pot procedure of synthesis of 1-hydroxymethylene-1,1-bisphosphonic partial trimethylesters and *P*,*P*-, *P*,*P*′-diesters was described.

1-Hydroxymethylene-1,1-bisphosphonates (HMBP) are an important class of drugs used in the treatment of bone diseases involving excessive bone destruction or resorption such as Paget's disease, osteoporosis and bone metastases.[1,2] They are structural analogues of naturally pyrophosphates and are completely resistant to enzymatic hydrolysis. More recently, bisphosphonates have been used for treatment of metastatic cancer.[3] It has been shown that these compounds were able to inhibit bone metastases proliferation in prostate or breast cancer.[4–6] Unfortunately, the bioavailability of these derivatives is very poor because of their strong hydrophilicity and powerful complexation of divalent metal cations. In fact, only 3–7% of the drug is metabolised.[7] A prodrug strategy should be a satisfying solution to increase the gastrointestinal absorption. Few studies about the design of bisphosphonate prodrugs have been reported in the literature.[8,9] Ezra et al. have shown that the introduction of a dipeptide as the side chain in bisphosphonate increased the efficiency of the drug significatively.[10] Another interesting approach is the modification of the phosphonic acid function it-self, by introducing an ester group. The presence of suitable hydrophobic groups should be able to decrease the hydrophilicity of the drug and consequently increase its bioavailability. The best choice seems to synthesise HMBP tetraesters. Unfortunately, these derivatives are not stable at physiologic pH as they rearrange themselves into phosphonophosphate pentaesters.[11]

This problem should be minimized by using partial esters. Only one method has been described to prepare such HMBP partial esters. The procedure first requires the synthesis of HMBP tetraesters, which are regioselectively dealkylated by different metal halides or trimethylsilyliodide.[12]

In this letter, we reported a new one-pot procedure to introduce one or several methyl group(s) on each acid function of the two phosphonic acid groups. This work is based on a previous publication demonstrating the efficiency of the reaction of tris(trimethylsilyl) phosphite and acid chlorides for the synthesis of HMBP tetraacids.[13] The same strategy was used to prepare HMBP *P*,*P*′-diesters **2** where one methyl group can be positioned on each phosphorus atom. Thus, the treatment of an acid chloride at room temperature with 2 equiv of methyl bis(trimethylsilyl) phosphite (synthesised using the procedure described by Sekine et al.[14]), followed by methanolysis during 1 h leaded to HMBP *P*,*P*′-diesters **2** (Scheme 1).



Scheme 1.

Keywords: Bisphosphonate silylated phoshite.
* Corresponding author. Tel.: +33-0148387709; fax: +33-0148387625; e-mail: m.lecouvey@smbh.univ-paris13.fr

0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2004.04.047

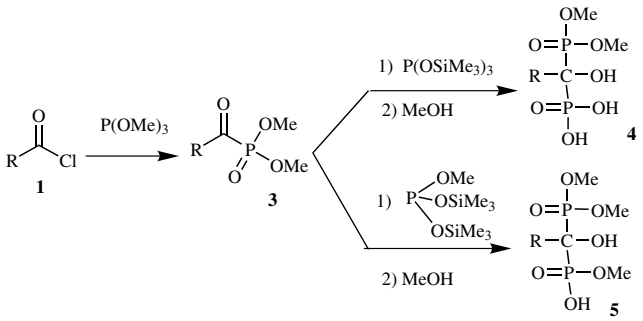
Table 1. HMBP partial esters **2** produced according to Scheme 1

Entry	R	Solvent	T °C	HMBP partial esters	Yield %	^{31}P $\{^1H\}$ NMR (D_2O) ppm
1	Me	—	25	**2a**	90	23.9
2	Pr	—	25	**2b**	90	24.0
3	*i*-Pr	—	25	**2c**	95	24.1
4	Bn	—	25	**2d**	90	20.8
5	Ph	—	25	**2e**	90	18.5
6	*p*-Br–C_6H_4	THF	25	**2f**	90	17.3
7	*p*-H_3C–C_6H_4	THF	25	**2g**	90	17.0
8	*p*-H_3CO–C_6H_4	THF	25	**2h**	90	17.8
9	*p*-O_2N–C_6H_4	THF	−70	**2i**	84	15.6

As shown in Table 1, this procedure was very efficient in aliphatic or aromatic series. The treatment of the acid chloride **1** with 2 equiv of methyl bis(trimethylsilyl) phosphite at room temperature leaded to the dimethyl bis(trimethylsilyl) ester of 1-trimethylsiloxymethylene-1,1-bisphosphonic acid in a single step within few minutes. This synthesis was based on an Arbuzov reaction to give a methyl trimethylsilyl α-ketophosphonate followed by an immediate addition of a second equivalent of methyl bis(trimethylsilyl) phosphite. The reaction was strongly exothermic and no side reaction could be detected by ^{31}P $\{^1H\}$ NMR. In particular, for the benzyl acetyl chloride, it has been shown that the Arbuzov reaction from this substrate and trimethyl phosphite did not lead to the α-ketophosphonate but to the enol form instead.[15] After 1 h of methanolysis, HMBP *P*,*P*′-diesters **2a**–**e** were obtained in very good yields and purity. Note that the solid acid chlorides (entries 6–9) were first solubilized in THF. The reaction was carried out at room temperature except for substrate **2i**. In that case, it was necessary to work at −70 °C due to the high reactivity of *p*-nitrobenzoyl chloride that leaded to the phosphonophosphonate rearrangement at room temperature. ^{31}P $\{^1H\}$ NMR spectroscopy was used throughout to follow the progress of the reaction and to analyze the purity of the products. The multiplicity of ^{31}P $\{^1H\}$ NMR signals offered an unambiguous method to assign the amounts and the type of substituents on each phosphorus atom. In decoupled ^{31}P spectroscopy, symmetrical HMBP *P*,*P*′-diesters **2** were easily identified by a single line at 20–25 ppm for aliphatic compounds (entries 1–4) and at 15–19 ppm for aromatic compounds (entries 5–9).

The HMBP *P*,*P*-diesters **4** and the HMBP triesters **5** were prepared by addition of the tris(trimethylsilyl) phosphite or methyl bis(trimethylsilyl) phosphite on α-ketophosphonate (prepared in situ via a standard Arbuzov reaction) followed by methanolysis (Scheme 2).

As shown in Table 2, the synthesis of the HMBP *P*,*P*-dimethyl esters **4** and the synthesis of the HMBP trimethyl esters **5** were also very efficient both in aliphatic or aromatic series. The first Arbuzov reaction between trimethylphosphite and acid chloride was carried out at −10 °C and monitored by ^{31}P $\{^1H\}$ NMR. After 2 h of reaction, the ^{31}P $\{^1H\}$ NMR spectrum showed the apparition of a single peak ($-5 < \delta < 0$ ppm) different from the starting product ($\delta = 140$ ppm), characteristic of the α-ketophosphonate **3**. The addition of tris(trimethylsilyl) phosphite or methyl bis(trimethylsilyl) phosphite on the intermediate **3** for 30 min furnished after methanolysis (2 h), the HMBP *P*,*P*-dimethyl esters **4** or the HMBP trimethyl esters **5**, respectively. After vacuum evaporation of volatile fractions, the products **4** and **5** were obtained without need for purification; no side products were observed. In reactions using mixed phosphites such as methyl bis(trimethylsilyl) phosphite, one of the trimethylsilyl groups was always lost preferentially.



Scheme 2.

The ^{31}P $\{^1H\}$ NMR spectra of compounds **4** and **5** showed the presence of two separate doublets with equal $^2J_{P-P}$ coupling constants. The ^{31}P $\{^1H\}$ NMR chemical shifts were very sensitive to the number of ester groups on the phosphorus atoms and to substituents on the central carbon. HMBP *P*,*P*-dimethyl esters **4** were easily identified based on their ^{31}P chemical shifts (entries 10–15) because of a large difference (about 8–9 ppm) between the doublet of $P(O)(OMe)_2$ and the doublet of $P(O)(OH)_2$. The use of the coupled ^{31}P NMR spectroscopy allowed us to identify two different signals of phosphorus atoms of HMBP *P*,*P*-dimethyl esters **4**. The chemical shift of phosphonic acid fragment was always observed downfield.

In the case of HMBP trimethyl esters **5**, the shift differences were less important (lower than 3 ppm). As previously, the ^1H coupled ^{31}P NMR spectroscopy experiments allowed unambiguous attribution of phosphorus signals: the chemical shift of the phosphorus having two methyl groups was always higher than the chemical shift of the phosphorus bearing one methyl group. Also, the $^2J_{P-P}$ coupling constants were again very sensitive to the number of ester groups bonded to

Table 2. HMBP partial esters **4**–**5** produced via Scheme 2

Entry	R	Solvent	T °C	HMBP partial esters	Yield %	^{31}P{^{1}H} NMR (D_2O) ppm
10	Me	—	25	**4a**	95	29.1, d; 19.9, d $^{2}J_{P-P} = 36$ Hz
11	Pr	—	25	**4b**	95	28.4, d; 20.0, d $^{2}J_{P-P} = 35$ Hz
12	*i*-Pr	—	25	**4c**	93	29.0, d; 19.4, d $^{2}J_{P-P} = 35$ Hz
13	Ph	—	25	**4d**	91	23.6, d; 12.9, d $^{2}J_{P-P} = 23$ Hz
14	*p*-Br–C_6H_4	—	25	**4e**	92	23.2, d; 12.6, d $^{2}J_{P-P} = 24$ Hz
15	*p*-H_3C–C_6H_4	—	25	**4f**	80	22.9, d; 14.1, d $^{2}J_{P-P} = 25$ Hz
16	*p*-H_3CO–C_6H_4	—	25	**4g**	96	23.1, d; 13.7, d $^{2}J_{P-P} = 23$ Hz
17	Me	—	25	**5a**	84	20.4, d; 18.6, d $^{2}J_{P-P} = 47$ Hz
18	Pr	—	25	**5b**	81	21.0, d; 18.6, d $^{2}J_{P-P} = 47$ Hz
19	*i*-Pr	—	25	**5c**	80	20.9, d; 19.5, d $^{2}J_{P-P} = 47$ Hz
20	Ph	—	25	**5d**	90	16.7, d; 14.5, d $^{2}J_{P-P} = 47$ Hz
21	*p*-Br–C_6H_4	—	25	**5e**	93	15.9, d; 13.7, d $^{2}J_{P-P} = 42$ Hz
22	*p*-H_3C–C_6H_4	—	25	**5f**	97	17.1, d; 13.7, d $^{2}J_{P-P} = 48$ Hz

phosphorus atoms. In all cases, the value of $^{2}J_{P-P}$ coupling constants for HMBP *P*,*P*-dimethyl esters **4** are less important than the value of $^{2}J_{P-P}$ coupling constants for HMBP trimethyl esters **5**. Moreover, the $^{2}J_{C-P}$ coupling constants for the central carbon were sensitive to the number of ester groups on the phosphorus atoms, approximately 149 Hz for $P(O)(OMe)_2$, 140 Hz for P(O)(OMe)(OH) and 128 Hz for $P(O)(OH)_2$ groups.

In conclusion, we have developed a new and efficient one-pot synthesis of HMBP partial esters from various aromatic or aliphatic acid chlorides. This procedure makes these very useful compounds readily accessible in high yields and should find wide applications in biological fields.[16]

References and notes

1. Fleisch, H. *Prog. Mol. Subcell. Biol.* **1999**, *23*, 197–216.
2. Fleisch, H. *Eur. Spine J.* **2003**, *12*(Suppl. 2), S142–146.
3. Green, J. R. *Cancer* **2003**, *97*, 840–847.
4. Mercadante, S. *Curr. Urol. Rep.* **2002**, *3*, 244–249.
5. Clezardin, P.; Fournier, P.; Boissier, S.; Peyruchaud, O. *Curr. Med. Chem.* **2003**, *10*, 173–180.
6. Fleisch, H. *Breast Cancer Res.* **2002**, *4*, 30–34.
7. Lin, J. H. *Bone* **1996**, *18*, 75–85.
8. Niemi, R.; Turhanen, P.; Vepsalainen, J.; Taipale, H.; Jarvinen, T. *Eur. J. Pharm. Sci.* **2000**, *11*, 173–180.
9. Vepsalainen, J. J. *Curr. Med. Chem.* **2002**, *9*, 1201–1208.
10. Ezra, A.; Hoffman, A.; Breuer, E.; Alferiev, I. S.; Monkkonen, J.; El Hanany-Rozen, N.; Weiss, G.; Stepensky, D.; Gati, I.; Cohen, H.; Tormalehto, S.; Amidon, G. L.; Golomb, G. *J. Med. Chem.* **2000**, *43*, 3641–3652.
11. Fitch, S. J.; Moedritzer, K. *J. Am. Chem. Soc.* **1962**, *84*, 1876–1879.
12. Turhanen, P. A.; Ahlgren, M. J.; Jarvinen, T.; Vepsalainen, J. J. *Synthesis* **2001**, *4*, 633–637.
13. Mallard, I.; Bailly, T.; Burgada, R.; Leroux, Y. *Tetrahedron Lett.* **2001**, *42*, 8475–8478.
14. Sekine, M.; Futatsugi, T.; Yamada, K.; Hata, T. *J. Chem. Soc., Perkin Trans. 1* **1982**, *11*, 2509–2514.
15. El Manouni, D.; Leroux, Y.; Burgada, R. *Phosphorus, Sulfur Silicon Relat. Elem.* **1989**, *42*, 73–84.
16. Lecouvey, M.; Leroux, Y.; Kraemer, M.; Crepin, M.; El Manouni, D.; Louriki, M. PCT Int. Appl. WO 03008425, 2003; *Chem. Abstr.* **2003**, *138*, 122736.