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# Synthesis of 1,1-bisphosphono-2-aza-1,3-dienes, a new class of electron-deficient azadienes

Kurt G. R. Masschelein, Christian V. Stevens *

*Research Group SynBioC, Department of Organic Chemistry, Faculty of Bioscience Engineering, Ghent University, Coupure links 653, B-9000 Ghent, Belgium*

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ABSTRACT

1,1-Bisphosphono-2-aza-1,3-dienes are formed by 1,4-dehydrohalogenation of the corresponding *N*-(bisphosphonomethyl)-α-haloimines in moderate to good yields. The precursors could be formed by condensation of bisphosphono-amines and the corresponding α-haloaldehydes.



Bisphosphonates (BPs) are analogues of naturally occurring pyrophosphate (PPi) and are a major class of drugs for the treatment of bone diseases.[1] Besides their antiresorptive properties, several bisphosphonates are also potent growth inhibitors of some pathogenic trypanosomatids.[2]

2-Azadienes in general are recognized as useful intermediates in synthetic chemistry for the construction of both heterocyclic systems as well as acyclic polyfunctionalized compounds.[3] Although the synthesis and reactivity of azadienes are well-established, their synthesis is mainly focused on electron-rich and electronically neutral 2-azadienes (in view of the well-established Diels–Alder methodology).[4] Due to the lack of general methods for their synthesis and their less pronounced importance for inverse electron demand Diels–Alder methodology,[5] electron-poor azadienes have received much less attention.

Keeping in mind the importance of the bisphosphonates as therapeutic agents and the azadienes as building blocks for a wide variety of compounds, the synthesis of a new class of electron-deficient bisphosphono-azadienes is interesting and could lead to new synthetic methods for azaheterocycles.

Until now, only a few reports on the synthesis of phosphonylated azadienes or their precursors appeared in the literature.[6] In some of these reports, 1,4-dehydrohalogenation of suitable phosphonylated α-haloimines was used as a strategy for the synthesis of 2-aza-1,3-dienes.[6a] The α-haloimines were formed either by condensation of α-halo carbonyl compounds with 1-aminoalkylphosphonates[6a] or by α-chlorination of phosphonylated imines.[6c]

To make the new class of 1,1-bisphosphono-2-aza-1,3-dienes, both synthetic pathways towards the halogenated imines were evaluated. Condensation of tetraethyl aminomethylbisphosphonate **1** (prepared by condensation of dibenzylamine, triethyl phosphite and triethyl orthoformate and subsequent debenzylation)[7] and appropriate aldehydes **2** gave the imines **3** in good yields and purity (>95%). However, the subsequent α-chlorination with NCS in $CCl_4$ did not proceed as smoothly as expected. The reaction mixture contained three major compounds together with 12 less important side products. The failure of the α-chlorination is probably related to the difficult formation of the corresponding enamine, which is counteracted by the electron withdrawing N-substituent. Instead, in both cases the formation of unidentified side products was observed following the reaction by $^{31}P$ NMR at room temperature and at reflux temperature (Scheme 1).

Therefore, the halogenated imines **4** had to be synthesized using the condensation of α-halogenated aldehydes **5** and tetraethyl aminomethylbisphosphonate **1**. The synthesis of freshly prepared α-halogenated aldehydes **5a–e** was performed by chlorination using $SO_2Cl_2$ (Scheme 2 and Table 1).[8]

In case of isobutyraldehyde, chlorination with $SO_2Cl_2$ was performed using a literature procedure.[9] Also, the brominated aldehyde **5g** could be obtained in good yield (Scheme 3).[10]

With the halogenated aldehydes in hand, the condensation with tetraethyl aminomethylbisphosphonate **1** was evaluated. Stirring the reactants in dry $CH_2Cl_2$ at room temperature for a couple of hours proved sufficient to obtain the halogenated imines **4** in good yield and purity. However, during the evaporation of the solvent after filtration of the drying agent, colouring of the product was

* Corresponding author. Tel.: +32 9 2645957; fax: +32 9 2646243.
*E-mail address:* chris.stevens@UGent.be (C. V. Stevens).
URL: http://www.synbioc.ugent.be

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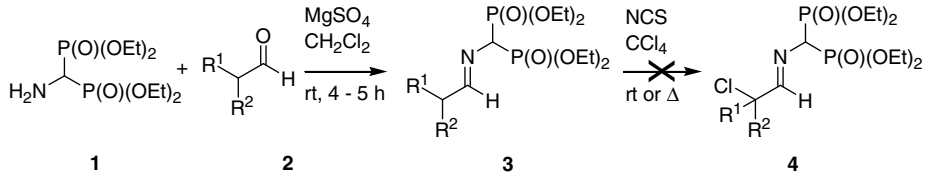
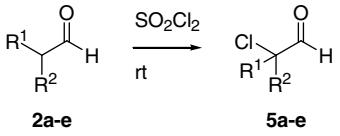



1 2 3 4

**Scheme 1.**



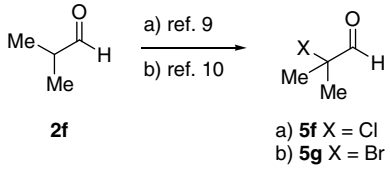

**2a-e** **5a-e**

**Scheme 2.**

**Table 1**
Synthesis of α-chlorinated aldehydes **5**

| Entry | Compound | Reaction time (min) | $R^1$ | $R^2$ | Yield[a] (%) |
|---|---|---|---|---|---|
| **2a** | **5a** | 30 | Ph | Ph | 75 |
| **2b** | **5b** | 30 | Me | Ph | 71 |
| **2c** | **5c** | 900 | Ph | H | 61 |
| **2d** | **5d** | 30 | $(CH_2)_5$ (*c*-Hex) | | 68 |
| **2e** | **5e** | 30 | Et | Et | 67 |

[a] After distillation.




**2f**

a) **5f** X = Cl
b) **5g** X = Br

**Scheme 3.**

observed. 1,4-Dehalogenation was already occurring which could be confirmed by $^1$H NMR and $^{31}$P NMR spectroscopy. When trying to purify the halogenated imines by chromatography, only the 1,1-bisphosphono-2-aza-1,3-dienes could be isolated.

Because of the ease of 1,4-dehalogenation, a one-step procedure for the synthesis of the 1,1-bisphosphono-2-aza-1,3-dienes starting from α-haloaldehydes **5** and tetraethyl aminomethylbisphosphonate **1** was evaluated. Therefore, 1.1 equiv of triethylamine was added to the in situ formed α-halogenated imines **4**. $^{31}$P NMR of the reaction mixture showed the formation of the desired azadienes **6**. After workup,[11] the 1,1-bisphosphono-2-aza-1,3-dienes were obtained as yellowish oils. In case of **6c,** a complex mixture was formed after workup. Following the reaction, $^{31}$P NMR revealed that condensation of **5c** and **1** immediately led to a lot of side products.

In general, in order to obtain the azadienes analytically pure, column chromatography was performed, however this resulted in a significant drop of the yields (Scheme 4 and Table 2).

**Table 2**
Synthesis of bisphosphono-azadienes **6**

| $R^1$ | $R^2$ | Product | Crude yield[a] (%) | Yield[b] (%) |
|---|---|---|---|---|
| Ph | Ph | **6a** | 88 | 63 |
| Me | Ph | **6b** | 92 | 58 |
| Ph | Cl | **6c** | Complex | 16 |
| $(CH_2)_5$(*c*-Hex) | | **6d** | 95 | 68 |
| Et | Et | **6e** | 93 | 56 |
| Me | Me | **6f** | 93[c]/89[d] | 63[c]/60[d] |

[a] After workup.
[b] After column chromatography.
[c] Using the chlorinated aldehyde.
[d] Using the brominated aldehyde.

In conclusion, a straightforward synthesis of a new class of phosphono-azadienes, that is, 1,1-bisphosphono-2-aza-1,3-dienes, was elaborated using a 1,4-dehydrohalogenation of phosphonylated α-chloroimines as a key step. The synthetic reactivity study of this new class of electron-deficient azadienes is currently under investigation and will be reported in due course.

## Acknowledgement

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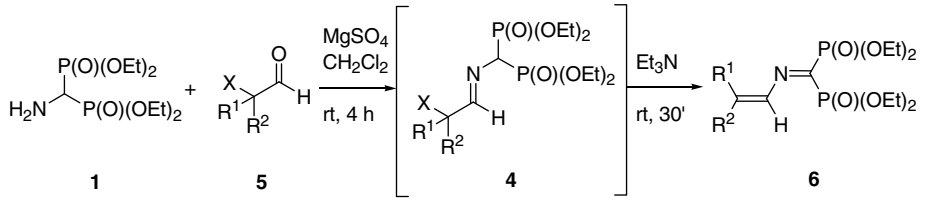
## References and notes

1. Graham, R.; Russell, G. *Ann. N.Y. Acad. Sci.* **2006**, *1068*, 367.
2. Docampo, R.; Moreno, S. N. J. *Curr. Drug Targets* **2001**, *1*, 51.
3. Jayakumar, S.; Ishar, M. P. S.; Mahajan, M. P. *Tetrahedron* **2002**, *58*, 379.
4. Boger, D. L. *Tetrahedron* **1983**, *39*, 2869.
5. (a) Boger, D. L. *Chem. Rev.* **1986**, *86*, 781; (b) Boger, D. L.; Patel, M. *Prog. Heterocycl. Chem.* **1989**, *1*, 30.
6. (a) Onys'ko, P. P.; Maidanovich, N. K.; Kim, T. V.; Kiseleva, E. I.; Sinitsa, A. D. *Zh. Obshch. Khim.* **1989**, *68*, 573; (b) Palacios, F.; Gil, M. J.; Martinez de Marigorta, E.; Rodriguez, M. *Tetrahedron Lett.* **1999**, *40*, 2411; (c) Stevens, C.; Gallant, M.; De Kimpe, N. *Tetrahedron Lett.* **1999**, *40*, 3457; (d) Palacios, F.; Gil, M. J.; Martinez de Marigorta, E.; Rodriguez, M. *Tetrahedron* **2000**, *56*, 6319; (e) Palacios, F.; Ochoa de Retana, A. M.; Martinez de Marigorta, E.; Rodriguez, M.; Pagalday, J. *Tetrahedron* **2003**, *59*, 2617; (f) Vanderhoydonck, B.; Stevens, C. V. *Synthesis* **2004**, 722; (g) Palacios, F.; Herrán, E.; Alonso, C.; Rubiales, G. *Arkivoc* **2007**, *iv*, 397–407; (h) Masschelein, K. G. R.; Stevens, C. V. *J. Org. Chem.* **2007**, *72*, 9248.
7. Kantoci, D.; Denike, J. K.; Wechter, W. J. *Synth. Commun.* **1996**, *26*, 2037. The debenzylation of tetraethyl dibenzylaminomethylbisphosphonate was performed with Pd–C (20%) in MeOH at room temperature under a $H_2$-atmosphere (stirring for 16 h).
8. Typical procedure for the synthesis of α-chloroaldehydes **5**: to the aldehyde in a flask equipped with an air cooler was added carefully 1.05 equiv of $SO_2Cl_2$ at




1 5 4 6

**Scheme 4.**

0 °C (in case of **5c** 2.1 equiv of $SO_2Cl_2$ was necessary and stirring was continued for 15 h). After stirring for 30 min at room temperature, the resulting mixture was poured into water. The water phase was extracted with $CH_2Cl_2$. The combined organic fractions were washed with a saturated $NaHCO_3$-solution and dried ($MgSO_4$). After filtration and evaporation, the crude chlorinated aldehydes **5** were obtained. To use the aldehydes in the following imination step, distillation was performed.

9. Stevens, C. L.; Gillis, B. T. *J. Am. Chem. Soc.* **1957**, *79*, 3448.
10. Tisdale, E. J.; Vong, B. G.; Li, H.; Kim, S. H.; Chowdhury, C.; Theodorakis, E. A. *Tetrahedron* **2003**, *59*, 6873.
11. Typical procedure for the synthesis of 1,1-bisphosphono-2-aza-1,3-dienes **6**: tetraethyl aminomethylbisphosphonate **1** (5.0 mmol) and an appropriate α-chloroaldehyde (5.0 mmol) were dissolved in 15 mL of dichloromethane. To this solution, anhydrous magnesium sulfate (2.5 mmol) was added. The reaction mixture was protected from moisture by a calcium chloride tube and was stirred for 4 h at room temperature. Triethylamine (5.5 mmol) was added to the mixture and the reaction was further stirred for 30 min. After evaporation of the solvent, the residue was dissolved in diethyl ether. The solids ($MgSO_4$ and triethylammonium salts) were removed by filtration and the solvent was evaporated in vacuo. If necessary, the residue was again dissolved in diethyl ether to remove the remaining triethylammonium salts. The crude product was purified by column chromatography on silica gel (100% EtOAc). Spectral data of diethyl [(diethoxyphosphoryl)-(2-methylpropenylimino)methyl]phosphonate **6f**: $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 1.36 (6H, t, $J$ = 7.2 Hz, 2 × P(O)OCH$_2$C$H_3$), 1.37 (6H, t, $J$ = 7.2 Hz, 2 × P(O)OCH$_2$C$H_3$), 1.98 (3H, s, $CH_3$), 2.10 (3H, s, $CH_3$), 4.20 (4H, q, $J$ = 7.2 Hz, 2 × P(O)OC$H_2$CH$_3$), 4.25 (4H, q, $J$ = 7.2 Hz, 2 × P(O)OC$H_2$CH$_3$), 7.73 (1H, br s, NCH). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 16.37 (d, $^3J_{CP}$ = 5.8 Hz, 2 × P(O)OCH$_2$C$H_3$), 16.43 (d, $^3J_{CP}$ = 5.8 Hz, 2 × P(O)OCH$_2$C$H_3$), 18.45 ($CH_3$), 23.90 ($CH_3$), 63.08 (d, $^2J_{CP}$ = 6.9 Hz, 2 × P(O)OCH$_2$CH$_3$), 63.46 (d, $^2J_{CP}$ = 6.9 Hz, 2 × P(O)OCH$_2$CH$_3$), 134.88 (dd, $^3J_{CP}$ = 34.6 Hz, $^3J_{CP}$ = 19.6 Hz, NCH), 151.56 (*C*=CHN), 153.06 (dd, $^1J_{CP}$ = 212.3 Hz, $^1J_{CP}$ = 129.2 Hz, C=N). $^{31}$P NMR (121 MHz, $CDCl_3$): $\delta$ 0.50 (d, $^2J_{PP}$ = 155.6 Hz), 8.77 (d, $^2J_{PP}$ = 155.6 Hz). IR (cm$^{-1}$) $\nu_{max}$: 1248 (P=O), 1014 (P–O). MS *m/z* (%): (ES, Pos) 356 (M+H$^+$, 100). Chromatography: EtOAc (100%) $R_f$ = 0.18.