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A NEW EFFICIENT SYNTHESIS OF ω -AMINOALKYLIDENE-1,1-BISPHOSPHONATE TETRAETHYLESTERS

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A NEW EFFICIENT SYNTHESIS OF ω -AMINOALKYLIDENE-1,1- BISPHOSPHONATE TETRAETHYLESTERS

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Bisphosphonates are interesting therapeutic agents in the management of bone diseases and since several years our laboratory has been developing the chemistry of 1,1-bisphosphonates. This paper describes an original synthesis of two aminoalkylidenebisphosphonates by first preparing the intermediate hydroxyalkylidenebisphosphonates which are transformed into amines via the azides.

Keywords: tetraethyl ω -aminoalkylidenebisphosphonates and ω -hydroxy-alkylidenebisphosphonates; methylidenebisphosphonate; amination

INTRODUCTION

Bisphosphonates are nonbiodegradable analogues of pyrophosphate with a high affinity for bone tissues¹. They are potent inhibitors of bone resorption and have been effectively used as therapeutic agents in the management of bone diseases such as Paget's disease², hypercalcemia of malignancy³ and prevention of osteoporosis⁴.

Since several years, our laboratory has been studying the drug targeting in bone and articulation therapy (bone cancers and metastases, inflammation, osteoporosis) by developing the chemistry of the 1,1 -gem-bisphosphonates. We showed recently that methotrexate amino-gembisphosphonic conjugates have an interesting antineoplastic

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activity against osteosarcoma in experimental animal models and that the labelled conjugates behave like a bone-seeking agent⁵.

So, we prepared the 1-aminomethylidenebisphosphonate (AMBP: $n = 0$), described by L. MAIER⁶, by electrophilic amination of methylidenebisphosphonate carbanion⁷. The 2-aminoethylidenebisphosphonate (AEBP: $n = 1$) was formed easily by addition of NH_3 in water on ethylidenebisphosphonate. But our laboratory has demonstrated that it was unstable, through heating or condensing on carboxylic acid, and underwent a retro-MICHAEL reaction⁸. The study of the stability of N-substituted 2-aminoethylidenebisphosphonates was developed recently⁹. These results led us to study an original and efficient preparation of the tetraethylesters of 3-aminopropylidenebisphosphonic acid **1a** and 4-aminobutylidenebisphosphonic acid **1b** (fig.1) and to continue the pharmacomodulation on the gem-bisphosphonate carrier.

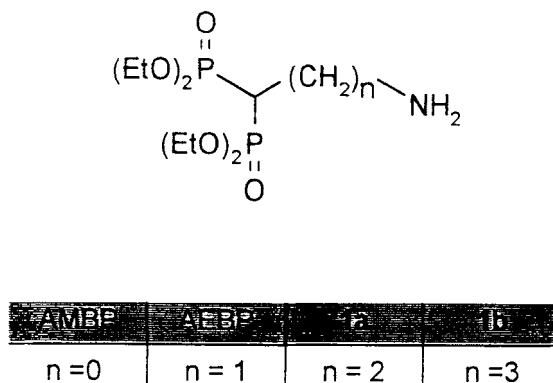


FIGURE 1

RESULTS AND DISCUSSION

The synthesis of these compounds **1** has been reported in the literature by carrying out the reaction of methylidenebisphosphonate¹⁰ carbanion **2** with nitrile compounds^{11, 12}. The nitrile functions were reduced into primary amines by catalytic hydrogenation with Pd/C (fig.2).

The delicate purification and the low yields led us to search for a new synthesis of the ω -aminoalkylidenebisphosphonates.

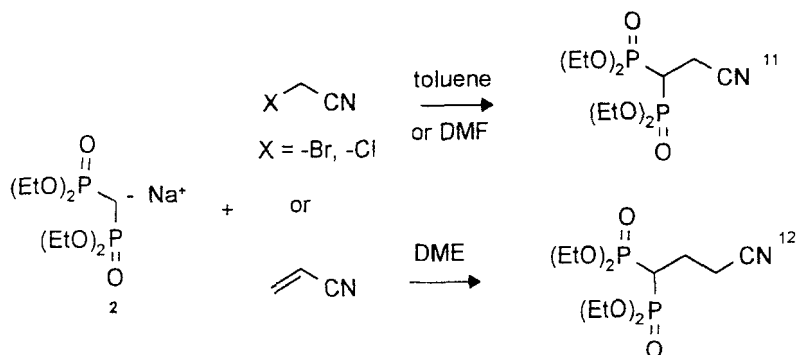
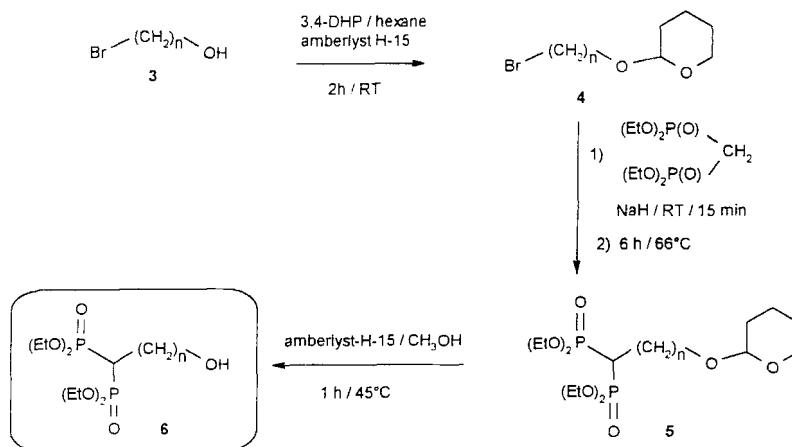


FIGURE 2

We first prepared the hydroxyalkylidenebisphosphonate analogues **6**. It seems that the preparation of these compounds has not been described precisely in the literature. It was reported that the condensation of the thallium (I) salt of tetraisopropylmethylidenebisphosphonate with the 2-iodoethyl tetrahydropyranyl ether gave **6** with a low yield¹³.

As a variation we chose the methylidenebisphosphonate carbanion **2** condensation with the commercial by available O-protected bromoalcohols; this is illustrated in scheme 1.

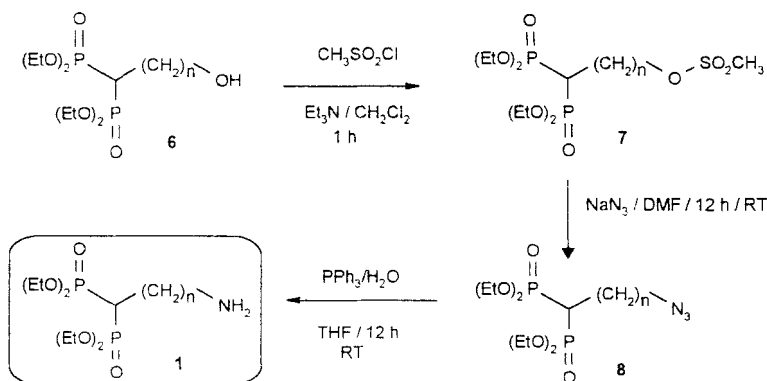


SCHEME 1

3,4-Dihydro-2H-pyran (3,4-DHP) was used as reagent to protect the primary alcohol¹⁴. The carbanion of the methylenedibisphosphonate **2** was prepared by action of sodium hydride at room temperature. The bromoalcohol was added as soon as the evolution of hydrogen ceased (15–30 minutes). The resulting mixture was heated at reflux for 8 hours. The compound **5** was isolated and the deprotection of the tetrahydropyranyl group was achieved by using Amberlyst H-15 in a methanolic solution of tetrahydropyranyl ester bisphosphonates **5**. This procedure is quite simple and easy and provides the hydroxyalkylidenes **6a** and **6b** with good yields. Moreover, these compounds are interesting molecules to develop other reactions like coupling with chloride acid or to obtain other functional groups.

We used these alcohols **6** to prepare the aminoalkylidenebisphosphonates **1** (scheme 2). The conversion of the primary alcohols into the corresponding primary amines is known in the literature¹⁵

For this purpose we prepared the mesylates **7** of the alcohols **6** by reaction with mesyl chloride. Subsequent nucleophilic attack by sodium azide allowed the azidation; this was followed by the STAUDINGER reaction¹⁶; finally the azide function **8** was reduced by triphenylphosphine with water¹⁷.



SCHEME 2

This standard method allows the preparation of the mesylate **7** and the azide **8** in good yields and the primary amines **1** are obtained quantitatively.

CONCLUSION

In summary, this study describes an original method to obtain the tetraethylesters of 3-aminopropylidenebisphosphonic acid **1a** and 4-aminobutylidenebisphosphonic acid **1b**. The hydroxyalkylidenebisphosphonates synthesized as intermediate could be potential building blocks for getting other bisphosphonates and/or for achieving other reactions. This method consists of several steps, but each reaction gives good yields.

EXPERIMENTAL SECTION

The primary chemical used were commercial products (Aldrich or Acros). The solvents were distilled both for the reactions and for chromatography. Tetrahydrofuran and dimethylformamide were dried with molecular sieves (4Å). The purity of products and the reaction progress were monitored on TLC plates (60F₂₅₄ Merck) and liquid chromatography was carried out on a silica gel column (Merck 60, 70–230 mesh). TLC revelation were carried out under a UV light (254 nm), by reagents : iodine, DITTER.

³¹P NMR spectra were recorded on a JEOL JNM-FX 100 FT spectrometer, the chemical shifts are reported in ppm to phosphoric acid as reference (85 % H₃PO₄ in heavy water) with positive values being downfield. ¹H and ¹³C NMR spectra were recorded on BRUCKER AC 300 spectrometer; the chemical shifts are reported in ppm using TMS (tetramethylsilane) in organic solvent (CDCl₃) as reference. Coupling constants J are reported in Hertz (Hz).

IR Spectra were recorded on RT IR COMEN spectrometer between KBr pastilles ; the absorption numbers are reported in cm⁻¹.

• Tetraethylmethylidene-1,1-bisphosphonate **2**

Prepared according to literature procedure ¹⁰

Spectral data

³¹P NMR δ : 19,4

¹H NMR δ : 1,4 (t,12H) ; 2,5 (t,2H,J²_{H-P}=20) ; 4,1(fqt,8H).

• Synthesis of bromoalcohol-O-protected **4**

A mixture of commercial bromoalcohol (40 mmol) and 3,4-dihydropyran (44 mmol) was added to a suspension of Amberlyst H15 (1g) in hexane (25 mL). The reaction mixture was stirred for 2h at room temperature. A residual solid was filtered and the filtrate was concentrated in vacuo. CH_2Cl_2 was added to the resulting residue and the mixture was washed with aqueous NaOH (2 %). The organic layer was dried (MgSO_4), filtered and concentrated to a residual oil which was purified by distillation under reduce pressure :

4a : 90 %; b.p. = 63–64°C/0,05 mbar; $\text{C}_7\text{H}_{13}\text{BrO}_2$; MW = 209,08 g.mol⁻¹

4b : 85 %; b.p. = 69–70°C/0,05 mbar; $\text{C}_8\text{H}_{15}\text{BrO}_2$; MW = 223,10 g.mol⁻¹

Spectral data : ¹H NMR

compound **4a** : δ 1,5 (m, 4H) ; 1,7 (m, 2H) ; 3,4 (t, 2H, $J^3_{\text{H-H}} = 6,9$) ; 3,6 (t, 2H) ; 3,7 (t, 2H) 4,6 (t, 1H).

compound **4b** : δ 1,5 (m, 4H) ; 1,7 (m, 2H) ; 2,1 (qt, 2H, $J^3_{\text{H-H}} = 6,4$) ; 3,4 (t, 2H) ; 3,5 (t, 2H) 3,8 (m, 2H) ; 4,5 (t, 1 H).

• Synthesis of tetraethyl ω -hydroxyalkylidenebisphosphonates O-protected **5**

22 mmol of tetraethyl methylidenebisphosphonate **2** were added dropwise, under nitrogen, to a suspension of sodium hydride (22 mmol) in THF (20mL). The reaction mixture was stirred for 15 min at room temperature. Bromoalcohol-O-protected **4** (1eq.) was added and the reaction mixture was heated at reflux for 6 hours. After cooling to room temperature, the mixture was neutralised by an aqueous solution saturated with ammonium chloride (30 mL) and extracted with diethyl ether (20 mL). The residual aqueous layer was extracted two times with CH_2Cl_2 the organic layers were combined, dried (Na_2SO_4), filtered and concentrated. The oil was purified by liquid chromatography, eluting with ethyl acetate.

5a : 80 % ; $\text{C}_{16}\text{H}_{34}\text{O}_8\text{P}_2$; MW = 416,38 g.mol⁻¹ ; Rf : 0.35 (ethyl acetate)

5b : 82 % ; $\text{C}_{17}\text{H}_{36}\text{O}_8\text{P}_2$; MW = 430,41 g.mol⁻¹ ; Rf : 0.4 (ethyl acetate)

Spectral data

³¹P NMR

compound **5a** : δ 23,8

compound **5b** : δ 23,9

¹H NMR

compound **5a** : δ 1,3 (t, 12H) ; 1,5–1,7 (m, 2H) ; 1,8–2,1 (m, 6H) ; 2,6 (tt, 1H, $J^2_{\text{H-P}} = 23$) ; 3,4 (t, 2H) ; 3,7 (t, 2H) ; 4,3 (fqt, 8H, $J^3_{\text{H-H}} = 8,1$) ; 4,6 (t, 1H).

compound **5b** : δ 1,3 (t, 12H,) ; 1,5–1,7 (m, 4H) ; 1,8–2,1 (m, 6H) ; 2,3 (tt, 1H, $J^2_{\text{H-P}} = 22,4$) ; 3,4 et 3,7 (tt, 2H) ; 3,5 et 3,8 (m, 2H) ; 4,2 (fqt, 8H, $J^3_{\text{H-P}} = 7,9$) ; 4,6 (t, 1H).

• Synthesis of tetraethyl esters ω-hydroxyalkylidenebisphosphonates **6**

10 mmol of alcohols O-protected **5** were added to a suspension of Amberlyst H15 (0,3g) in methanol (20mL). The mixture was heated at 45°C for 1h. After cooling, the reaction mixture was filtered and the methanol was removed in vacuo. The alcohols **6a**, **6b** were formed quantitatively. They are not purified by distillation because they undergo an intramolecular transesterification by heating ¹⁸.

6a : C₁₁H₂₅O₆P₂ ; MW = 315,26 g.mol⁻¹ ; Rf : 0.2 (ethyl acetate/ethanol : 9/1)

| 6a | C | H | P |
|-----------|--------|-------|--------|
| calc. | 41,9% | 7,99% | 19,64% |
| found | 41,71% | 8,2% | 19,2% |

6b ; C₁₂H₂₇O₆P₂ ; MW = 329,28 g.mol⁻¹ ; Rf : 0.32 (ethyl acetate)

| 6b | C | H | P |
|-----------|--------|-------|--------|
| calc. | 43,77% | 8,26% | 18,81% |
| found | 43,50% | 8,4% | 18,36% |

Spectral data

TABLE I

| Compound 6a | Compound 6b |
|--------------------|--------------------|
| | |

| <i>RMN ¹H</i> | |
|--|---|
| 1,3 (H ₁ , t, 12H) ; 1,7 (OH) ; 2,1 (H ₄ , tq, 2H, J ³ _{P-H} = 9,3, J ³ _{H-H} = 7) ; 2,6 (H ₃ , tt, 1H, J ² _{P-H} = 24) ; 3,8 (H ₅ , t, 2H) ; 4,2 (H ₂ , fqt, 8H, J ³ _{H-H} = J ³ _{P-H} = 7,5). | 1,3 (H, t, 12H) ; 1,6 (OH) ; 1,8 (H ₅ , qt, 2H); 2,1 (H ₄ , tq, J ³ _{P-H} = 9 Hz, J ³ _{H-H} = 7,3 Hz, 2H); 2,4 (H ₃ , tt, J ² _{P-H} = 24 Hz) ; 3,7 (H ₆ , t, 2H); 4,2 (H ₂ , fqt, J ³ _{P-H} = J ³ _{H-H} = 7,3 Hz, 8H). |
| <i>RMN ¹³C</i> | |
| 16,2 (C ₁) ; 27,9 (C ₄) ; 36,1 (C ₃ , t, J ¹ _{C-P} = 136) ; 61,5 (C ₅) ; 62,5 (C ₂). | 16,2 (C ₁) ; 21,6 (C ₅) ; 31,6 (C ₄) ; 35,8 (C ₃), t, J ¹ _{C-P} = 133) ; 61,7 (C ₆) ; 62,5 (C ₂). |
| <i>RMN ³¹P</i> | |
| 24,1 | 24,2 |

• Synthesis of ω-methylsulfonylalkylidenebisphosphonates 7

10 mmol of methanesulfonylchloride were added dropwise to a mixture of hydroxyalkylidenebisphosphonate **6** (10 mmol) and triethylamine (11 mmol) in CH₂Cl₂ (15 mL) cooled to 0°C.

At room temperature, the reaction mixture was stirred for 1 hour. Water (20 mL) was added and the mixture was shaken. The organic phase was dried (Na₂SO₄), filtered and evaporated under reduce pressure.

7a: 90% ; C₁₂H₂₈O₉P₂S ; MW = 410,35 g.mol⁻¹ ; Rf = 0,3 (ethyl acetate)

| 7a | C | H | S |
|-----------|--------|-------|-------|
| calc. | 35,12% | 6,87% | 7,81% |
| found | 34,90% | 7,02% | 7,50% |

7b: 84 % ; C₁₃H₃₀O₉P₂S ; MW = 424,38 g.mol⁻¹ ; Rf = 0,37 (ethyl acetate)

| 7b | C | H | S |
|-----------|--------|-------|-------|
| calc. | 36,79% | 7,12% | 7,55% |
| found | 36,51% | 7,34% | 7,18% |

Spectral data

³¹P NMR

7a: δ 22,8 and **7b** : δ 22,1

¹H NMR

7a: δ 1,3(t, 12H) ; 2,0 (tq, 2H, J³_{H-P} = 9,7, J³_{H-H} = 7,1) ; 2,2 (qt, 2H) ; 2,5 (tt, 1H, J²_{H-P} = 23,8) ; 3,0 (s, 3H) ; 3,7 (t, 2H) ; 4,2 (fqt, 8H, J³_{H-P} = 7,5).

7b: δ 1,3 (t, 12H) ; 2,1 (tq, 2H, $J^3_{\text{H-P}} = 9,5$, $J^3_{\text{H-H}} = 7,2$) ; 2,6 (tt, 1H, $J^2_{\text{H-P}} = 24,1$) ; 3,1 (s, 3H) ; 3,9 (t, 2H) ; 4,2 (fqt, 8H, $J^3_{\text{H-P}} = 7,4$).

• Synthesis of ω -azidoalkylidenebisphosphonates **8**

5 mmol of sodium azide were added through a powder funnel over 10 min to a solution of mesylate **7** (5 mmol) in DMF (15 mL). The reaction mixture was stirred at room temperature for 12 hours. The solution was concentrated in vacuo and the resulting residue was partitioned between CH_2Cl_2 and water. The organic layer was dried (Na_2SO_4), filtered and concentrated to give a yellow oil. The product was converted to **1** without further purification.

8a: 85 % ; $\text{C}_{11}\text{H}_{25}\text{N}_3\text{O}_6\text{P}_2$; MW = 357,27 $\text{g}\cdot\text{mol}^{-1}$; Rf = 0,4 (ethyl acetate)

| 8a | C | H | N |
|-----------|--------|-------|--------|
| calc. | 36,98% | 7,05% | 11,76% |
| found | 36,72% | 7,21% | 11,34% |

8b: 80 % ; $\text{C}_{12}\text{H}_{27}\text{N}_3\text{O}_6\text{P}_2$; MW = 371,30 $\text{g}\cdot\text{mol}^{-1}$; Rf = 0,5 (ethyl acetate)

| 8b | C | H | N |
|-----------|--------|-------|--------|
| calc. | 38,78% | 7,32% | 11,31% |
| found | 38,60% | 7,50% | 10,95% |

Spectral data

31P NMR

8a: δ 23,2

8b: δ 23,3

^1H NMR

8a: δ 1,3 (t, 12H) ; 1,9 (tq, 2H, $J^3_{\text{H-P}} = 9,2$, $J^3_{\text{H-H}} = 7,6$) ; 2,3 (tt, 1H, $J^2_{\text{H-P}} = 23,8$) ; 3,3 (t, 2H) ; 4,2 (fqt, 8H, $J^3_{\text{H-P}} = 7,8$).

8b: δ 1,3 (t, 12H) ; 1,8 (tq, 2H, $J^3_{\text{H-P}} = 9,8$; $J^3_{\text{H-H}} = 7,5$) ; 2,1 (qt, 2H) ; 2,3 (tt, 1H, $J^2_{\text{H-P}} = 24,2$) ; 3,2 (t, 2H) ; 4,2 (fqt, 8H, $J^3_{\text{H-P}} = 7,5$).

IR

8a: 2103 (νN_3) ; 1252 ($\nu \text{P=O}$) ; 1050 ($\nu \text{P-O-C}$)

8b: same vibrations

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RMN ¹H

1,3 (H₁, t, 12H) ; 1,6 (NH₂), 2,0 (H₄, 2H, tq, J³_{P-H} = 9,4, J³_{H-H} = 7,1) ; 2,3 (H₃, 1H, tt, J³_{H-H} = 7) ; 1,5 (NH₂) ; 1,7 (H₅, qt, 2H, J³_{P-H} = 24) ; 2,9 (H₅ t, 2H) ; 4,2 (H₂, fqt, 8H, (H₃, tt, 1H, J²_{P-H} = 24,3) ; 2,6 (H₆, t, 2H) ; J³_{H-H} = J³_{P-H} = 7). 4,2(H₂, fqt, 8H, J³_{H-H} = J³_{P-H} = 7).

RMN ¹³C

16,2 (C₁) ; 31,5 (C₄), 35,2 (C₃, t, J¹_{C-P} = 134, 1) ; 43,7 (C₅), 62,2 (C₂). 16,2 (C₁) ; 22,7 (C₅) ; 29,8 (C₄) ; 32,3 (C₃, t, J¹_{C-P} = 135,4) ; 41,5 (C₆) ; 62 (C₂).

RMN ³¹P

23,9

23,9

IR

1a: 3370, 3304 (ν_{N-H}) ; 1607 (δ_{N-H}) ; 1250 (ν_{P=O}) ; 1040 (ν_{P-O-C})

1b: same vibrations as compound **1a** for the fonctionnal groups.

References

- [1] O.L.M. BIJVOET, H.A. FLEISCH, R.E. CANFIELD, R.G.G. RUSSELL (eds.), « Bisphosphonates on bones » © Elsevier Science B.V. (1995).
- [2] D.K.J. HOSKING, *Drugs*, **40**, 829–840 (1990).
- [3] H. FLEISCH, *Drugs*, **42**, 919–944 (1991).
- [4] S.E. PAPAPLOULOS, J.O. LANOMAN, O.L.M. BIJVOET, C.W.G.M. LOWIX, R. VALKEMA, E.K.J. PAUWELS, P. VERMEIJ, *Bone*, **13**, S41–S49 (1992).
- [5] a – G. STURTZ, G. APPERE, K. BREISTOL, O. FOSTAD, G. SCHWARTSMANN, H.R. HENDRIKS, *Eur. J. Med. Chem.*, **27**, 825–833 (1993) – b – G. STURTZ, H. COUTHON, O. FABULET, M. MIAN, S. ROSINI, *Eur. J. Med. Chem.*, **28**, 899–903 (1993) – c – F. HOSAIN, R.P. SPENCER, H.M. COUTHON, G.L. STURTZ, *J. Nucl. Med.*, **37**, 105–107 (1996).
- [6] L. MAIER, *Phosphorus and Sulfur*, **11**, 311–322 (1981).
- [7] G. STURTZ, H. COUTHON, *C. R. Acad. Sci. Paris*, **t 316**, série II, 181–186 (1993).
- [8] G. APPERE, *Ph. D. Thesis*, 1990, U.B.O. Brest.
- [9] T. BAILLY, R. BURGADA, *Phosphorus, Sulfur and Silicon*, **86**, 217–228 (1994).
- [10] O.E.O. HORMI, E.O. PAJUNEN, A.K.C. AVALL, P. PENNAMEN, *Synth. Comm.*, **20**, 1865–1867 (1990).
- [11] E. BOSIES, A. ESSWEIN, F. BAUSS, *Ger. Offen.* DE 4,029,499 [CA 116-P235961s].
- [12] H. BIERE, C. RUFER, I. BOETTCHER, *Ger. Offen.* DE 3,225,469 [CA 100-P210141f].
- [13] D.W. HUTCHINSON, D.M. THORNTON, *Synthesis*, 135–137 (1990).
- [14] A. BONGINI, G. CARDILLO, M. ONENA, *Synthesis*, 618–620 (1979).
- [15] A.R. KATRITZKY, O. METH-COHN, C.W. REES, « Comprehensive Organic Functional Group Transformations » PERGAMON 1st ed. **2**, 308–310 (1995).
- [16] H. STAUDINGER, J. MEYER, *Helv. Chim. Acta*, **2**, 635–646 (1919).
- [17] N. KNOUZI, M. VAULTIER, R. CARRIE, *Bull. Soc. Chim. Fr.*, (5), 815–819 (1985).
- [18] G. STURTZ, A. PONDIVEN-RAPHALEN, *Phosphorus and Sulfur*, **36**, 39–52A (1988).