Tetrahedron Letters 53 (2012) 5290–5292

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

The preparation of N-substituted aminomethylidenebisphosphonates and their tetraalkyl esters via reaction of isonitriles with trialkyl phosphites and hydrogen chloride. Part 1

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ARTICLE INFO

Article history:
Received 9 May 2012
Revised 4 July 2012
Accepted 19 July 2012
Available online 27 July 2012

Keywords:
Aminobisphosphonate
Bisphosphonate
Bisphosphonic acid
Aminomethylidenebisphosphonate
Aminomethylidenebisphosphonic acid
Isonitrile
Proton-assisted nucleophilic addition
Addition reactions

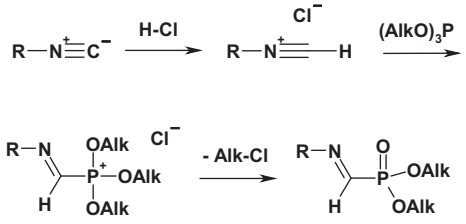
ABSTRACT

The reaction of isonitriles with trialkyl phosphites in the presence of hydrogen chloride gives tetraalkyl N-substituted aminomethylidenebisphosphonates via *N*-methylideneaminium (isonitrilium) salts. Hydrolysis or dealkylation of these tetraalkyl esters gives N-substituted aminomethylidenebisphosphonic acids in high yields.

In 1974, Pudovik et al.[1] described the preparation of tetraalkyl phenylaminomethylidenebisphosphonates ($PhNHCH[P(O)(OR)_2]_2$) by treating phenylisonitrile with dialkyl phosphonates in the presence of catalytic amounts of an alkali metal alkoxide. Later the same authors published[2] an extension of this reaction to substituted phenylisonitriles, and reported the preparation of tetraalkyl arylaminomethylidenebisphosphonates in 58–75% yield. It is hard to believe, but this potentially useful method for the preparation of aminobisphosphonates was totally overlooked by the 'bisphosphonate society'.[3] Moreover, we found that this paper has only one citation.[4]

Although on the list of so-called bisphosphonate drugs, there is only one example of an aminobisphosphonate, which possesses an $N–C(PO_3H_2)_2$ moiety, namely cycloheptylaminomethylidenebisphosphonic acid (incadronic acid, Astellas Pharma, formerly Yamanouchi Pharma). Many groups have published papers concerning the synthesis and biological activity of N-substituted aminomethylidenebisphosphonates.[5] These compounds were prepared by the reaction of amines with trialkyl orthoformates and dialkyl phosphonates. It is interesting that this reaction was well known to chemists long before Suzuki et al. claimed it in many patents issued to Nissan Chemical Ind. (the first examples in 1978 and 1979),[6] and then by Takeuchi and co-workers as claimed in many patents issued to Yamanouchi Pharmaceutical (the first in 1988),[7a] and finally published in 1993.[7b] We (M.S.) knew this procedure from personal discussions with Hans Gross.

In continuation of our research on the reaction of trialkyl phosphites with onium salts,[8] we turned our attention to isonitrilium salts which could be generated from isonitriles. According to published data,[9] isonitriles are C-bases with high affinity for protons, therefore they should be easily converted into the corresponding *N*-methylideneaminium (isonitrilium) salts using hydrogen chloride, for example. Next, the isonitrilium salt should react with a



Scheme 1.

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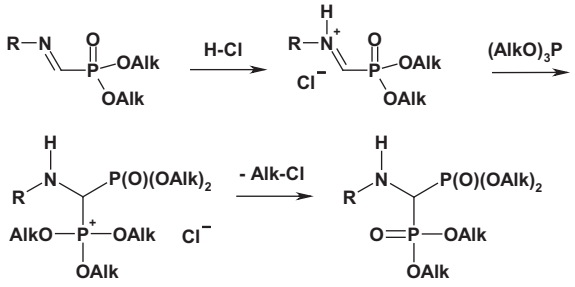
http://dx.doi.org/10.1016/j.tetlet.2012.07.085



Scheme 2.

nucleophilic trialkyl phosphite to give the intermediate phosphonium salt, which should spontaneously transform into the corresponding dialkyl N-substituted iminomethylidenephosphonate (Scheme 1).

The dialkyl N-substituted iminoalkylidenephosphonate is obviously a stronger base than the starting isonitrile, therefore it should react instantly with another molecule of hydrogen chloride to give the corresponding iminium salt—a very strong electrophile. This should react with a second molecule of the trialkyl phosphite to give another intermediate phosphonium salt, which, as we described earlier,[8] should be spontaneously transformed, as in the last step in the Arbuzov reaction, to give the final tetraalkyl N-substituted aminomethylidenebisphosphonate (Scheme 2).

Indeed, when we examined the reaction of butylisonitrile with triethyl phosphite in the presence of greater than stoichiometric amounts of hydrogen chloride in an aprotic solvent (CH_2Cl_2, e.g.), at a temperature below −10 °C (to prevent dealkylation of the starting triethyl phosphite), we found, by means of ^{31}P NMR spectroscopy, that the crude reaction mixture contained as much as 88% of tetraethyl butylaminomethylidenebisphosphonate, traces of unreacted triethyl phosphite, and about 10% of diethyl phosphonate. The crude tetraethyl butylaminomethylidenebisphosphonate was hydrolyzed by refluxing with 6 M HCl in water to give butylaminomethylidenebisphosphonic acid in 61% yield, based on the starting isonitrile. Similar results were obtained when other isonitriles were employed, for example: 2-methylpropylisonitrile gave a 77% yield of the corresponding aminobisphosphonic acid, pentylisonitrile—86%, 3-methylpentylisonitrile—98%, benzylisonitrile—95%, and cyclohexylisonitrile—82%. The tetraethyl ester obtained from *t*-butylisonitrile gave after hydrolysis, only aminomethylidenebisphosphonic acid in 91% yield. Thus it was dealkylated using a known procedure[10] with bromotrimethylsilane to give *t*-butylaminomethylidenebisphosphonic acid in 76% yield. Also tetraethyl phenylaminomethylidenebisphosphonate (obtained from phenylisonitrile) was dealkylated using the same procedure, and gave phenylaminomethylidenebisphosphonic acid in 99% yield.[11]

In summary, the protocol described in this Letter represents a very efficient method for the preparation[12] of tetraalkyl esters of N-substituted aminomethylidenebisphosphonic acids as well as N-substituted aminomethylidenebisphosphonic acids. Moreover, it offers enormous opportunity to link an aminomethylidenebisphosphonate moiety to a broad spectrum of other compounds. By applying this sequence of reactions, we have prepared a very large collection—hundreds of N-substituted derivatives of aminomethylidenebisphosphonates—starting from easily available isonitriles. We will publish these results soon.

Acknowledgement

Financial support of our research by the National Science Centre is appreciated (grant N204 122240).

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3. Contrary to the very long history of hydroxyalkylidenebisphosphonates,[13] that of aminoalkylidenebisphosphonates is rather short. The first syntheses of *N*-unsubstituted aminobisphosphonates via the reaction of nitriles with phosphorus trihalides, were described by Lerch and Kottler[14] in 1957. About ten years later, the same chemistry was applied for the synthesis of aminobisphosphonates as 'complex formers' by Blaser, Germscheid, and Worms.[15] In 1959, Kreutzkamp and Cordes[16] described the first examples of N-substituted aminobisphosphonates from the reaction of PhC(Cl) = NPh with $P(OEt)_3$, and then with $HP(O)(OEt)_2$. Later, many preparations of aminobisphosphonates were described by Gross and Costisella (first paper[17]) starting from dialkylformamide acetals and dialkyl phosphonates, or the so-called 'α-substituted phosphonates', mainly formylphosphonate derivatives. Searching Chemical Abstracts we found as many as 3439 structures and more than 1600 references to them. Most of the early development in this area was done by chemists from companies including: Dr. Karl Thomae, Therachemie, Henkel, Albright & Wilson, Procter & Gamble, Joh A. Benckiser, Benckiser-Knapsack, Nissan Chemical Ind., and Yamanouchi Pharmaceutical.
   It is worth noting that many applications of aminobisphosphonates were described even earlier than their syntheses. For example, in 1965 Berth and Reese[18] patented 'derivatives for protecting of hair', and Smith and Dixon[19] patented 'stabilization of phosphate salts'. The first pharmaceutical application of aminobisphosphonate was reported in 1968 by Francis,[20] who patented a 'composition for inhibiting anomalous deposition and mobilization of calcium phosphate in human tissue'.
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11. This chemistry was previously described in part in two Polish patents: (a) Soroka, M.; Goldeman, W.; Kluczyński, A. Polish Patent PL208806, 2011; *Chem. Abstr.* **2011**, *155*, 241101; (b) Soroka, M.; Goldeman, W.; Kluczyński, A. Polish Patent PL208807, 2011; *Chem. Abstr.* **2011**, *155*, 271405. However, both patents are printed in Polish, and therefore without the literature background, we would like to publish this excellent method for the synthesis of aminomethylidenebisphosphonic acids, especially the tetraalkyl esters.
12. *General procedure:* To a cold (ca. −10 °C, ice/NaCl stirred bath) solution of isonitrile (0.050 mol) and trialkyl phosphite (0.10 mol) in CH_2Cl_2 (100 mL) was added dropwise a cold (ca. −10 °C) solution of ~4 M HCl (0.15 mol in 1,4-dioxane, 38 ml). The mixture was stirred for about 1 h at the same temperature (the ice-NaCl bath must also be stirred). Further CH_2Cl_2 (100 mL) was added, and the reaction washed with cold (~0 °C) saturated $NaHCO_3$ solution (5 × 100 mL), dried (anhydrous Na_2SO_4), and evaporated under vacuum to give the dialkyl N-substituted aminomethylidenebisphosphonate, which was practically pure for most applications.
    For the preparation of N-substituted aminomethylidenebisphosphonic acids, the mixture from the above reaction was evaporated under vacuum, and the residue was refluxed with HCl in H_2O (6 M, 300 mL) for about 8 h. The hydrolysate was evaporated under vacuum using a water bath (final

temperature ~100 °C), the residue dissolved in H_2O (100 mL), and the solution evaporated again. This procedure (dissolution/evaporation) was repeated 3–5 times to give the final crystalline N-substituted aminomethylidenebisphosphonic acid, which could be recrystallized from boiling H_2O, if necessary. Spectroscopic data for representative example: *n*-butylaminomethylidenebisphosphonic acid: white solid; ^{31}P NMR {^1H} (D_2O + NaOD, 121 MHz): δ 16.48 (s), ^1H NMR (D_2O + NaOD, 300 MHz): δ 0.70 (t, J = 7.3 Hz, 3H, CH_3), 1.14 (sextet, J = 7.3 Hz, 2H, CH_2CH_3), 1.31 (quin, J = 7.3 Hz, 2H, $CH_2CH_2CH_3$), 2.50 (t, J = 17.3 Hz, 1H, CHP), 2.75 (t, J = 7.3 Hz, 2H, NCH_2); ^{13}C NMR (D_2O + NaOD, 75 MHz): δ 13.49 (s, CH_3), 19.86 (s, CH_2CH_3), 31.61 (s, NCH_2CH_2), 50.82 (t, J = 5.6 Hz, NCH_2), 59.52 (t, J = 129.5 Hz, CH); IR (KBr): 3207, 3070, 2963, 2934, 2876, 2791, 2257, 1652, 1589, 1566, 1467, 1428, 1388, 1352, 1216, 1196 (P = O), 1132, 1049 (P-O), 1030 (P-O), 965, 929, 913, 810, 780, 738, 704, 575, 524, 512, 463, 430 cm^{-1}.

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