Chemoselective Activation of Diethyl Phosphonates: Modular Synthesis of Biologically Relevant Phosphonylated Scaffolds

Pauline Adler, Amandine Pons, Jing Li, Jörg Heider, Bogdan R. Brutiu, and Nuno Maulide*

Abstract: Phosphonates have garnered considerable attention for years owing to both their singular biological properties and their synthetic potential. State-of-the-art methods for the preparation of mixed phosphonates, phosphonamidates, phosphonothioates, and phosphinates rely on harsh and poorly selective reaction conditions. We report herein a mild method for the modular preparation of phosphonylated derivatives, several of which exhibit interesting biological activities, that is based on chemoselective activation with triflic anhydride. This procedure enables flexible and even iterative substitution with a broad range of O, S, N, and C nucleophiles.

The phosphonate functional group remains a cornerstone of modern organic chemistry. Indeed, phosphonic acids and derivatives thereof can be found in the scaffolds of a range of bioactive products (Scheme 1).[1] Among them, amino phosphonates are commonly used as analogues of amino acids.[2] As phosphonates present enhanced resistance towards hydrolysis, the phosphate moiety has proven very useful in the development of potential drugs and agrochemicals.[3]

The synthesis of phosphonates classically relies mainly on two different strategies, namely on either the action of a trialkyl phosphite on an alkyl halide (Michaelis–Arbuzov reaction)[4] or a metal-mediated coupling with dialkyl phosphite.[5] Although these methods are efficient, they only lead to symmetric phosphonates (i.e., phosphonates of the form RP(O)(OR′)₂). To access mixed phosphoryl phosphonates, a general method consists of preforming either a dichloro- or a mono-chlorophosphonyl derivative from a readily available symmetrical phosphonate with a strong chlorinating agent, or from a phosphonic acid ester with classical acid activation. These intermediates can then be substituted by different nucleophiles as shown in Scheme 2a.[6, 7] Depending on the chlorinating agent used, some lack of selectivity between mono- and disubstitution was observed when phosphorus pentachloride was used.[7] Moreover, these are somewhat harsh reagents with low functional group tolerance. However, milder chlorinating agents, such as oxalyl chloride, can be used to efficiently yield the monochlorinated product.[8] An elegant approach employing copper catalysis and diaryliodonium reagents has been developed to substitute phosphonates, but it is limited to arylxoy modifications.[9] Selective reductions[10, 11] or arylations[12] of aryl phosphate oxides or phosphonates have been achieved with different activating agents. The Atherton–Todd reaction is also an elegant approach for the synthesis of phosphonamidates and phosphoramidates with global inversion of configuration.[13]

Scheme 1. Selected examples of phosphonate-containing biologically active compounds.

Scheme 2. Substitutions of phosphonates and mechanistic proposal.

[1] Dr. P. Adler, Dr. A. Pons, Dr. J. Li, J. Heider, B. R. Brutiu, Prof. Dr. N. Maulide
Institute of Organic Chemistry
University of Vienna
Währinger Strasse 38, 1090 Vienna (Austria)
E-mail: nuno.maulide@univie.ac.at
Homepage: http://organicsynthesis.univie.ac.at

Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under:
https://doi.org/10.1002/anie.201806343.

© 2018 The Authors. Published by Wiley-VCH Verlag GmbH & Co. KGaA. This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.
Herein, we present an approach to the substitution of phosphonates. This strategy relies on electrophilic activation with triflic anhydride followed by the addition of a chloride source to selectively and transiently yield a monochlorophosphonyl species. In situ attack by a nucleophile then provides a simple and versatile approach for the synthesis of a range of not only phosphonates, but also phosphonamidates, phosphonothioates, and phosphinates (Scheme 2a).[^14]

Phosphonates can be activated with triflic anhydride to give phosphonium ion I. Then, an Arbuzov reaction can occur promoted by triflate and 2-iodopyridine (see the Supporting Information for details) to yield the mixed phosphonate II. Simple substitution with a chloride forms III, which ultimately generates the expected product after addition of the deprotonated nucleophile (Scheme 2b). In contrast to a report by Kang and co-workers,[^14] the replacement of the triflate by the pyridine on intermediate II was not observed.

Our investigations started with phosphonate 2a as the substrate and sodium isopropoxide as the nucleophile (Table 1; for full optimization details and mechanistic investigations by $^{31}$P NMR spectroscopy, see the Supporting Information). We found that reproducibly high yields of product were obtained when 2-iodopyridine was employed as the base (entry 1) instead of pyridine (entry 2). Using tetraethylammonium chloride as the chloride source (entry 3) avoided the formation of unidentified side products. The use of trifluromethanesulfonyl chloride did not lead to any conversion (entry 4). Ultimately, the optimized conditions allowed full conversion into the desired product (entry 5), which was isolated in 60% yield.

First, we delineated the scope and limitations of this reaction with alcohols as nucleophiles (Scheme 3). A broad range of aliphatic alcohols efficiently delivered mixed phosphonates, including isopropyl 2a, propargyl (2b, 2c), allyl (2h), and electron-poor alkoxides such as trifluoromethyl (2d) and hexafluoroisopropyl (2e). Phenol could also be used (2f). Interestingly, a protected furanose core was also incorporated (2g).

The reaction displays excellent functional group tolerance. Indeed, reactive functional groups such as a phthalimide-protected amine (2j), an ester (2k), or a nitrile (2n) were all well-tolerated. This unique chemoselectivity is all the more noteworthy as even a primary alkyl bromide (2m) is tolerated without competing S$_2$ substitution taking place. The use of vinyl, phenyl, or alkynyl phosphonates was also possible (2o–2q). Finally, this method was applied on 15 mmol scale to prepare 2.2 g of the phosphonate 2r in a very good 82% yield.

We then turned our attention to the extension of this method to the formation of phosphonothioates.
a range of thiols, including decanethiol (3a), benzyl mercaptan (3b), and the bulkier cyclohexanethiol (3c) and tert-butylthiol (3d), were all competent nucleophiles for this process. Finally, substitution with aryl thiols allowed us to prepare 3e and 3f.

Eager to access phosphonamidates by a similar process, we decided to study the addition of nitrogen nucleophiles (Scheme 4). We found that upon deprotonation with NaH, sulfonamides are competent partners in this reaction. Thus the nosyl phosphonamidate 4a and the tosyl phosphonamidates 4b and 4c were readily accessed, the latter carrying a protected glycine moiety. Valuable amines, such as morpholine, piperazine, and difluoropyrrolidine, were added as their lithium amides to prepare 4d, 4e, and 4f, respectively, in very good yields. The acyclic substrates methylallylamine and dimethylamine were also viable nucleophiles, delivering the corresponding phosphonamidates 4g and 4i in lower yields whilst benzyllamine afforded 4h in good yield.

At this point, we envisioned that alkynes could be attractive nucleophiles for the preparation of phosphinates. The terminal alkynes were deprotonated with n-butyllithium prior to addition (Scheme 4). The use of a benzyl-protected propargyl alcohol led to the formation of 5a in good yield. Triisopropylsilylacetylene could also be used to generate phosphinate 5b in an excellent yield of 90%, and a thiophene ring was also tolerated (5c). Phosphinates bearing alkyl chains such as cyclopropyl (5d), decyl (5e), or phenylpropyl (5f) were efficiently prepared. Phenylacetylene could also be used to form 5f.

Having demonstrated that a broad range of nucleophiles, including heteroatom nucleophiles, perform competently in this substitution reaction, we were intrigued by the possibility of achieving sequential double substitution. Indeed, as the products still carry one OEt moiety, we hypothesized that renewed activation and substitution would lead to an iterative procedure for decorating a phosphorus center in a flexible manner. Indeed, starting from phosphonate 1l, a first substitution with phenol yielded the mixed phosphonate 2s in high yield. Renewed activation of 2s enabled displacement with morpholine to form the modularly assembled phosphonamidate 6a in moderate yield (Scheme 5a). An iterative substitution was also possible on phosphinate 5b with propargyl alcohol, affording product 6b in moderate yield.

As mentioned in the introduction, phosphorylated compounds exhibit a wide range of biological activities. We therefore envisaged the preparation of various bioactive targets using this method (Scheme 5b). For instance, the mixed phosphonate 7 presents antituberculosis properties. This compound was readily prepared using the novel method reported herein in a single step from commercially available diethyl butylphosphonate (1m) and the commercially available benzyl alcohol derivative in 55% yield. The incorporation of phosphonamidates into peptide chains is particularly interesting. In particular, phosphonamide surrogates of glycine-proline are appealing for their singular stability and reactivity, which are due to the slightly pyramidal nitrogen atom. In this context, we decided to investigate the use of proline as a nucleophile. Phosphonamidate 8 was indeed accessed in moderate yield. After preparation of phosphonothioate 3g from phosphonate 1k, displacement of the bromide with N-phenylpiperazine yielded 9, a compound exhibiting hypotensive activity. Furthermore, we prepared phosphinate 5h as a patented precursor to a phosphate transport inhibitor. Finally, the nosyl group on phosphonamidate 4a could be efficiently cleaved under classical conditions to yield the deprotected compound 10 (Scheme 5c).

In conclusion, we have developed a mild electrophilic activation method that enables the chemoselective substitution of phosphonates in the presence of a range of functional groups such as esters, nitriles, or halides. By following this procedure, a plethora of O, N, S, and C nucleophiles can be added to efficiently prepare mixed phosphonates, phosphonamides, phosphonothioates, and phosphinates, respectively (several of them are bioactive substances). We believe that the mild conditions and high functional group tolerance of this procedure are well suited for late-stage functionalization.
Conflict of interest

The authors declare no conflict of interest.

Keywords: phosphonates · phosphoramidates · phosphonates · phosphonothioates · triflic anhydride

How to cite: Angew. Chem. Int. Ed. 2018, 57, 13330–13334
Angew. Chem. 2018, 130, 13514–13518

[1] a) G. P. Horsman, D. L. Zeochel, Chem. Rev. 2017, 117, 5704–5783; b) A. J. Wiemer, D. F. Wiemer in Phosphorus Chem. 1 (Ed.: J.-L. Montchamp), Springer International Publishing, Cham, 2014, pp. 115–160; c) W. W. Metcalf, W. A. van der Donk, Annu. Rev. Biochem. 2009, 78, 65–94; d) M.-H. Chen, Z. Chen, B.-A. Song, P. S. Bhadury, S. Yang, X.-J. Cai, D.-Y. Hu, W. Xue, S. Zeng, J. Agric. Food Chem. 2009, 57, 1385–1388; e) J. G. Boutsellis, X. Yu, Z.-Y. Zhang, R. F. Borch, J. Med. Chem. 2007, 50, 856–864; f) S. Gobec, I. Plantan, J. Mravljak, R. A. Wilson, G. S. Besra, D. Kikelji, Bioorg. Med. Chem. Lett. 2004, 14, 3559–3562; g) S. Gobec, I. Plantan, J. Mravljak, U. Švajger, R. A. Wilson, G. S. Besra, S. L. Soares, R. Appelberg, D. Kikelji, Eur. J. Med. Chem. 2007, 42, 54–63.

[2] a) V. P. Kukhar, H. R. Hudson, Aminosphosphonic and Aminophosphoric Acids: Chemistry and Biological Activity, Wiley, Chichester, New York, 2000; b) A. Woschek, W. Lindner, F. Hammerschmidt, Adv. Synth. Catal. 2003, 345, 1287–1298.

[3] F. Orsini, G. Sello, M. Sisti, Curr. Med. Chem. 2010, 17, 264–289.

[4] a) A. Michaelis, R. Kaehe, Ber. Dtsch. Chem. Ges. 1898, 31, 1048–1055; b) A. E. Arbusov, J. Russ. Phys. Chem. Soc. 1906, 38, 687; c) A. K. Bhattacharya, G. Thyagarajan, Chem. Rev. 1981, 81, 415–430.

[5] a) K. M. Kem, N. V. Nguyen, D. J. Cross, J. Org. Chem. 1981, 46, 5188–5192; b) W. J. Ruan, A. Hassner, Eur. J. Org. Chem. 2001, 1259–1266; c) D. Gelman, L. Jiang, S. L. Buchwald, Org. Lett. 2003, 5, 2315–2318; d) M. Kake, A. Ziad, J. Stawinski, Org. Lett. 2008, 10, 4637–4640; e) J. Xu, P. Zhang, Y. Gao, Y. Chen, G. Tang, Y. Zhao, J. Org. Chem. 2013, 78, 8176–8183.

[6] From symmetric phosphonates: a) X. Morise, P. Savignac, J.-M. Denis, J. Chem. Soc. Perkin Trans 1 1996, 2179; b) M. de F. Fernandez, C. P. Vlaar, H. Fan, Y.-H. Liu, F. R. Fronczek, R. P. Hammer, J. Org. Chem. 1995, 60, 7390–7391; c) P. Fourgeaud, C. Midrier, J.-P. Gors, J.-N. Yelle, D. Virieux, Tetrahedron 2010, 66, 758–764; d) J. Motoyoshiya, T. Kusaura, K. Kokin, S. Yokoya, Y. Takaguchi, S. Narita, H. Aoyama, Tetrahedron 2001, 57, 1715–1721; for selected examples from hydrogen phosphonates: e) K. A. Fredrikssen, M. Amedjoukou, Eur. J. Org. Chem. 2016, 474–482; f) M. Quintilliani, J. Balzarini, R. A. Wilson, G. S. Besra, D. Kikelji, Angew. Chem. Int. Ed. 2013, 52, 9111–9119; g) M. Van Overtveldt, T. S. A. Heugebaert, I. Verstraetens, D. Geilen, J. Biomed. Chem. 2015, 13, 5260–5264.

[7] a) L. Maier, Phosphorous Sulfur Silicon Relat. Elem. 1990, 47, 465–470; b) B. Iorga, D. Carmichael, P. Savignac, C. R. Acad. Sci. Ser. IIc: Chim. 2000, 3, 821–829.

[8] For selected recent reports, see: a) B. J. Foust, M. M. Poe, N. A. Lentini, C.-H. C. Hsiao, A. J. Wiemer, D. F. Wiemer, ACS Med. Chem. Lett. 2017, 8, 914–918; b) S. Bag, R. Jayarajan, R. Mondal, D. Maiti, Angew. Chem. Int. Ed. 2017, 56, 3182–3186; Angew. Chem. 2017, 129, 3230–3234; c) K. Seth, M. Bera, M. Brochetta, S. Agasti, A. Das, A. Gandini, A. Porta, G. Zanoni, D. Maiti, ACS Catal. 2017, 7, 7732–7736.

[9] M. Fañanás-Mastral, B. L. Feringa, J. Am. Chem. Soc. 2014, 136, 9894–9897.

[10] N. P. Kenny, K. V. Rajendran, D. G. Gilheaney, Chem. Commun. 2015, 51, 16561–16564.

Acknowledgements

We are thankful to the ERC (CoG VINCAT), the FWF (P30266 to N.M. and M0247 to A.P.), and the DFG (Grant MA 4861/2-1) for supporting this work. The University of Vienna is gratefully acknowledged for continued generous support of our research programs.

and the modular decoration of phosphorus centers in medicinal and agricultural chemistry.
During the preparation of this manuscript, Kang and co-workers reported a similar approach for the formation of mixed phosphonates (H. Huang, J. Denne, C.-H. Yang, H. Wang, J. Y. Kang, *Angew. Chem. Int. Ed.* 2018, 57, 6624–6628; *Angew. Chem.* 2018, 130, 6734–6738). In that work, the authors reported the efficient addition of phenol derivatives and alcohols to an activated phosphate. However, the addition of aliphatic alcohols appeared to be limited to phenylphosphonates on simple substrates. Moreover, the authors reported in the Supporting Information that the use of nucleophiles such as amines or thiols was unsuccessful with their method.

Manuscript received: June 1, 2018
Revised manuscript received: July 14, 2018
Accepted manuscript online: August 1, 2018
Version of record online: September 11, 2018