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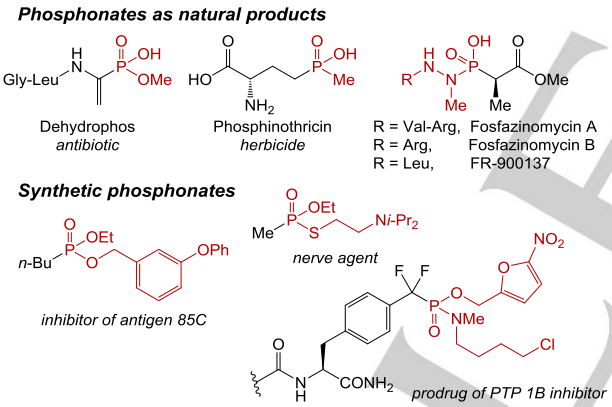
Chemoselective Activation of Diethyl Phosphonates: A Modular Synthesis of Biologically Relevant Phosphonylated Scaffolds

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

Abstract: Phosphonates have garnered considerable attention for years due to both their singular biological properties and their synthetic potential. State-of-the-art methodology for the preparation of mixed phosphonates, phosphonamidates, phosphonothioates and phosphinates relies 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, *via* chemoselective activation with triflic anhydride. This procedure enables flexible and even iterative substitution with a broad range of O, S, N and C-nucleophiles.

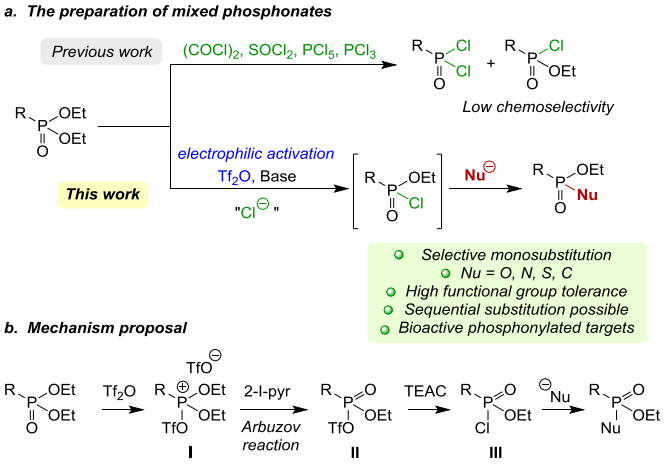
The phosphonate functional group remains a cornerstone of modern organic chemistry. Indeed, phosphonic acids and derivatives can be found in the backbone of a range of bioactive products (Scheme 1).[1] Among them, aminophosphonates are commonly used as analogs of aminoacids.[2] As phosphonates present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



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

The synthesis of phosphonates classically relies mainly on two different strategies: either the action of a trialkylphosphite on an alkyl halide (Michaelis-Arbuzov reaction)[4] or a metal-mediated coupling with dialkylphosphite.[5] Although these methods are efficient, they only lead to symmetrical phosphonates (i.e., phosphonates of the form $RP(O)(OR')_2$). In order to access mixed phosphonates, a general method consists of pre-forming either a dichloro- or a monochlorophosphonyl derivative from a readily available symmetrical phosphonate, using a strong chlorinating agent, or from a phosphonic acid ester with classical activation of acids. These intermediates can then be substituted by different nucleophiles as shown in Scheme 2a.[1e],[6] Depending on the chlorinating agent used, some lack of selectivity between mono- and disubstitution can be observed when phosphorus pentachloride was used.[7] Moreover those are somewhat harsh reagents with low functional group tolerance. However, milder chlorinating agents, such as oxalyl chloride, can be used to efficiently yield the mono-chlorinated product.[8] An elegant approach employing copper catalysis and diaryliodonium reagents has been developed to substitute phosphonates, but it is limited to aryloxy-modification.[9] Selective reductions[10],[11] or arylations[12] of arylphosphine 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]

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 to a range of not only phosphonates, but also phosphonamidates, phosphonothioates and phosphinates with a broad scope (Scheme 2a).[14]



Scheme 2. Substitutions of phosphonates and mechanism proposal (TEAC: tetraethylammonium chloride).

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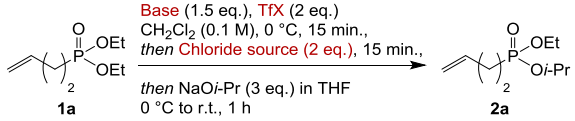
Phosphonates can be activated by triflic anhydride leading to the phosphonium **I**. Then an Arbuzov reaction can occur promoted by triflate and 2-iodo-pyridine (See SI for more details) to yield the mixed phosphonate **II**. Simple substitution by a chloride forms **III** which ultimately yields the expected product after addition of the deprotonated nucleophile (Scheme 1b). In contrast to reported work by Kang,[14] the replacement of the triflate by the pyridine on the intermediate **II** was not observed.

Table 1. Optimization of the reaction.



Entry	TfX	Base	Chloride source	%**2a**[a]	%**1a**	%other
1	Tf_2O	2-I-pyr	none	71	22	8
2	Tf_2O	pyridine	none	51	40	9
3	Tf_2O	2-I-pyr	TEAC[b]	89	11	0
4	TfCl	2-I-pyr	none	nd[c]	100	0
5[d]	Tf_2O	2-I-pyr	TEAC[b]	100	nd[c]	0

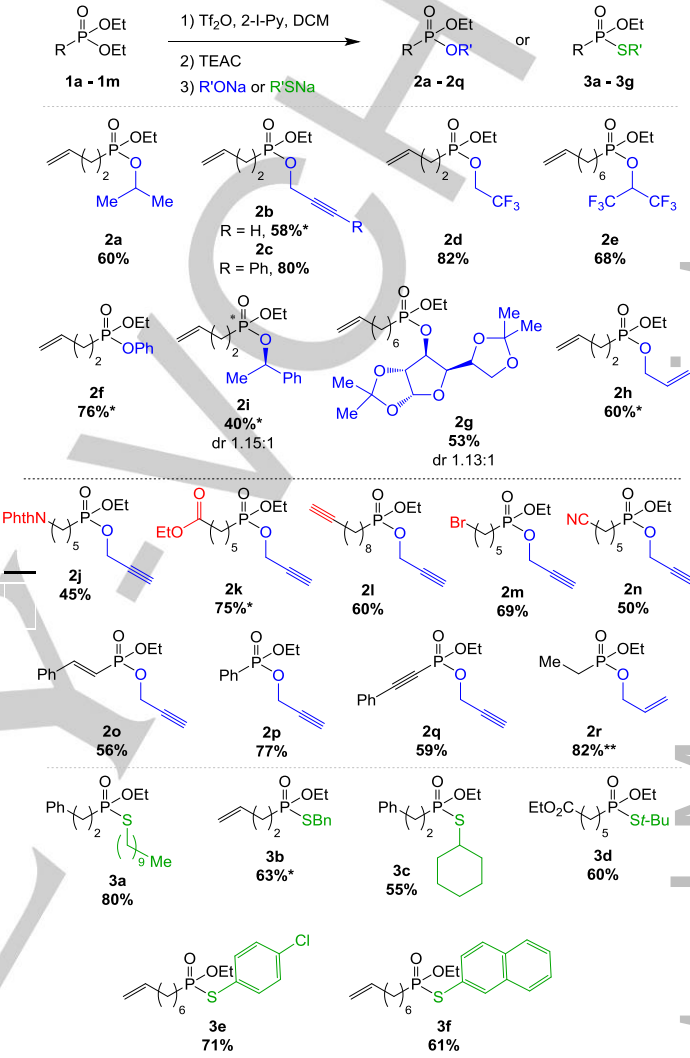
[a] Yields determined by ^{31}P NMR of the crude residue. [b] Tetraethylammonium chloride. [c] not detected. [d] with fully optimized conditions: To a solution of the phosphonate (0.2 mmol) in CH_2Cl_2 (4 mL) were added 2-iodopyridine (1.5 eq.) and triflic anhydride (2 eq.) at 0 °C. After 30 minutes, TEAC (2.5 eq.) was added at 0 °C. After 15 minutes, a solution of deprotonated nucleophile (4 eq.) in THF (2 mL) was added. Stirring at r.t. for 18 hours.

Our investigations started on the phosphonate **2a** as a substrate, using sodium isopropoxide as the nucleophile (Table 1, for full optimization details and mechanism investigation by ^{31}P NMR, see the Supporting Information). We found that reproducibly high yields of product could be obtained by employing 2-iodopyridine as a base (entry 1) compared to pyridine (entry 2). Using tetraethylammonium chloride as a chloride source (entry 3) avoided the formation of unidentified by-products. Trifluoromethanesulfonyl chloride did not yield to any conversion (entry 4). Ultimately, the optimized conditions allowed full conversion into the desired product (entry 5) resulting in a 60% isolated yield.

At first, we delineated the scope and limitations of this reaction using alcohols as nucleophiles. (Scheme 3) A large diversity of aliphatic alcohols efficiently delivered mixed phosphonates, including isopropyl **2a**, propargyl **2b**-**c**, allyl **2h** and electron-poor alkoxides such as trifluoroethyl **2d** and hexafluoroisopropyl **2e**. Phenol could also be used (**2f**). Interestingly, a protected furanose core could also be 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** are all well-tolerated. This unique chemoselectivity is all the more noteworthy as even a primary alkyl bromide **2m** is tolerated without competing S_N2-substitution taking place. The use of vinyl-, phenyl- or alkynylphosphonates was also possible (cf. **2o**, **2p** and **2q**). Finally, this method has been applied on 15 mmol scale in order 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 for the formation of phosphonothiates. Gratifyingly, a range of thiols including decanethiol **3a**, benzylmercaptan **3b** or the bulkier cyclohexanethiol **3c** and *tert*-butylthiol **3d** were all competent nucleophiles for this process. Finally, substitution with arylthiols allowed us to prepare **3e** and **3f**.



* tetrabutylammonium chloride used instead of tetraethylammonium chloride (TEAC); ** reaction has been set up on a 15 mmol scale.

Scheme 3. Scope of alcohol and thiol nucleophiles. Yields refer to isolated, pure compounds. To a solution of the phosphonate (0.2 mmol) in CH_2Cl_2 (4 mL) were added 2-iodopyridine (1.5 eq.) and triflic anhydride (2 eq.) at 0 °C. After 30 minutes, TEAC (2.5 eq.) was added at 0 °C. After 15 minutes, a solution of deprotonated nucleophile (4 eq.) in THF (2 mL) was added. Stirring at r.t. for 18 hours.

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, a nosyl phosphonamidate **4a** and the tosyl phosphonamidates **4b** and **4c** are readily accessed, the latter carrying a protected glycine moiety. Valuable amines such as morpholine, piperazine and difluoropyrrolidine could be added as their lithium amides in very good yields to prepare respectively **4d**, **4e** and **4f**. The acyclic methylallylamine and dimethylamine were also viable nucleophiles delivering the corresponding phosphonamidates **4g** and **4i** in lower yields whilst benzylamine afforded **4h** in good yield.

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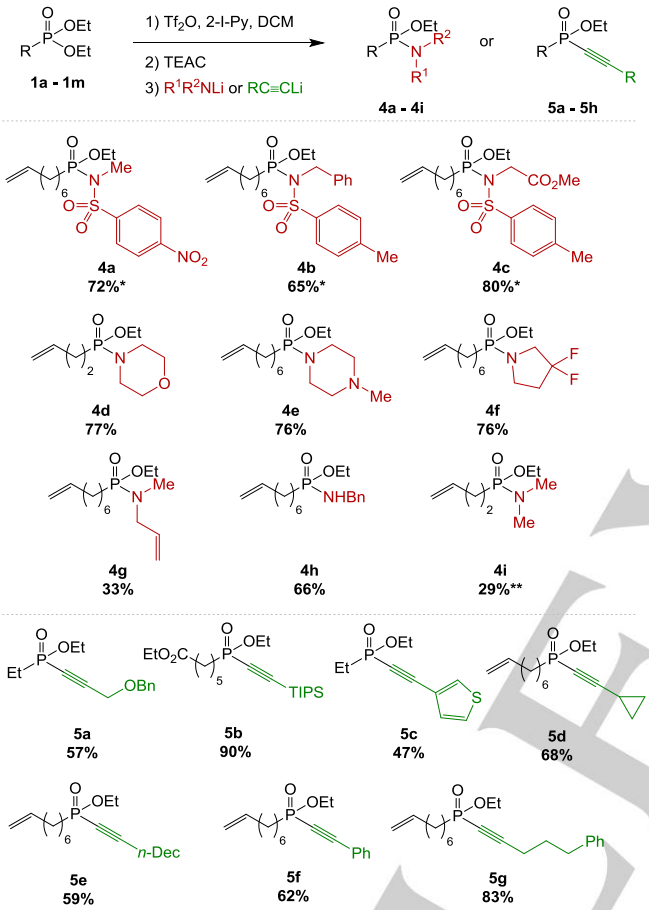
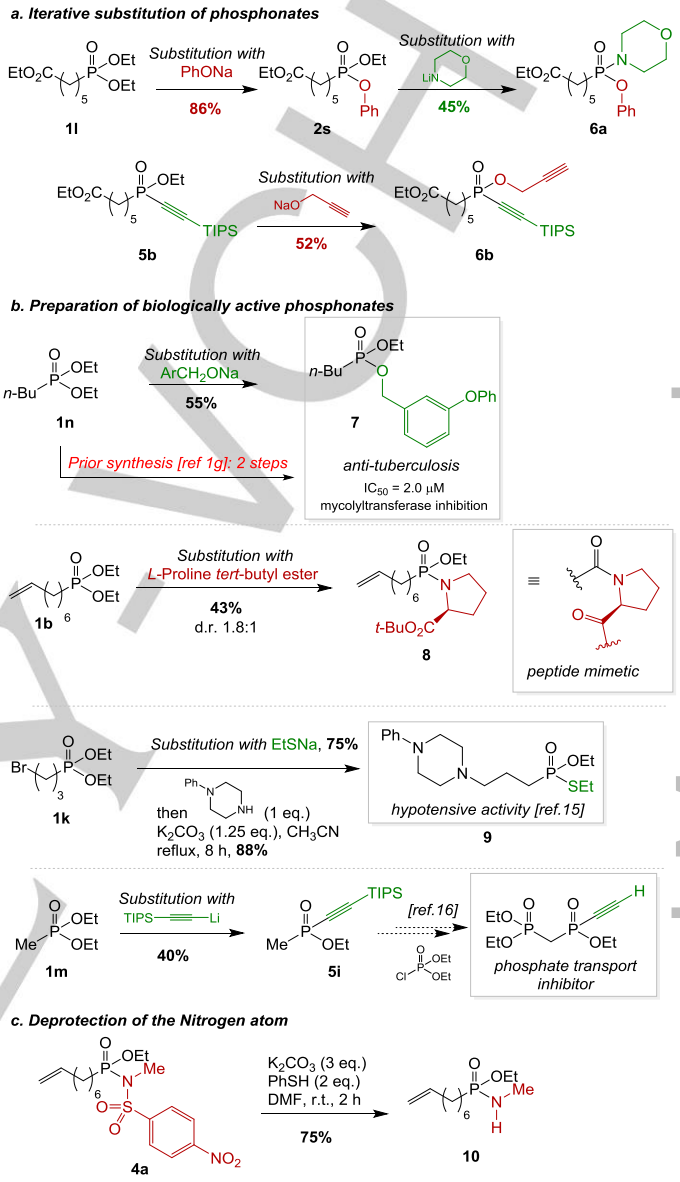
At this juncture, we envisioned that alkynes could be attractive nucleophiles in order to prepare phosphinates. The terminal alkynes were deprotonated with butyl lithium prior to addition (cf. Scheme 4). The use of a benzyl-protected propargyl alcohol allowed the formation of **5a** in good yield. Triisopropylsilylacetylene could also be used to yield the phosphinate **5b** in an excellent yield of 90%, and a thiophene ring was also tolerated (cf. **5c**). Phosphinates bearing alkyl chains such as cyclopropyl **5d**, decyl **5e**, or phenylpropyl **5g** were efficiently prepared. Phenylacetylene could also be used to form **5h**.



*Sodium hydride used for the deprotonation; ** tetrabutylammonium chloride used instead of tetraethylammonium chloride

Scheme 4. Scope of amine and alkyne nucleophiles. Yields refer to isolated, pure compounds. See SI for conditions. To a solution of the phosphonate (0.2 mmol) in CH_2Cl_2 (4 mL) were added 2-iodopyridine (1.5 eq.) and triflic anhydride (2 eq.) at 0 °C. After 30 minutes, TEAC (2.5 eq.) was added at 0 °C. After 15 minutes, a solution of deprotonated nucleophile (4 eq.) in THF (2 mL) was added. Stirring at r.t. for 18 hours.

Having demonstrated that a broad range of nucleophiles including heteroatoms performs competently in this substitution protocol, 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 the 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 the phosphinate **5b** with propargyl alcohol, affording the product **6b** in moderate yield.



Scheme 5. (a) Iterative substitution of phosphonates, (b) preparation of biologically active phosphonylated targets, (c) deprotection of the nosyl-phosphonamidate.

As mentioned in the introductory section, phosphonylated 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 anti-tuberculosis properties.[1f],[1g] This compound could be readily prepared through the novel methodology reported herein in a single step from commercially available diethyl butylphosphonate **1n** and the commercially available benzylic alcohol in 55% yield. Phosphonamidates are particularly interesting for the incorporation in peptide chains. In particular, phosphonamide surrogates of Glycine-Proline are appealing for their singular stability and reactivity due to the slightly pyramidal nitrogen atom.[15] In this context, we decided to

investigate the use of proline as nucleophile. In the event, phosphonamidate **8** was accessed in moderate yield. After preparation of the phosphonothioate **3g** from the phosphonate **1k**, displacement of the bromide with *N*-phenylpiperazine yielded **9**, a compound exhibiting hypotensive activity.[16] Furthermore, we prepared the phosphinate **5i** as a patented precursor to a phosphate transport inhibitor.[17] Finally, we showed that the nosyl group on the phosphonamidate **4a** could be efficiently cleaved in classical conditions to yield the deprotected compound **10** (Scheme 5c).

We 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. Through this procedure, a plethora of O, N, S and C-nucleophiles could be added to efficiently prepare mixed phosphonates, phosphonamidates, phosphonothioates or phosphinates respectively, several of them bioactive substances. We believe that the mild conditions and high functional group tolerance of this protocol are well suited for late-stage functionalization and the modular decoration of a phosphorus center in medicinal chemistry and agrochemistry.

Acknowledgements

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Keywords: phosphonate • phosphonamidate • phosphonothioate • phosphinate • triflic anhydride • chemoselectivity

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[14] During the preparation of this manuscript, the group of Kang 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). In that work, the authors reported the efficient addition of phenol derivatives and alcohols to an activated phosphonate. However, the addition of aliphatic alcohols appeared to be limited to phenylphosphonates on simple substrates. Moreover, the authors reported in the Supporting Information that nucleophiles such as amines or thiols were unsuccessful with their method.

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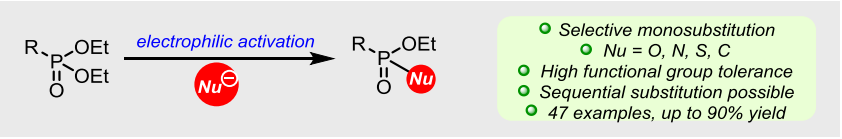

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