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Phosphorus Ylides

Glycoconjugates via Phosphorus Ylides

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Abstract: A facile, high yielding access to rare chimeric compounds combining phosphorus ylides with complex glycosyl formamides is described. We determined X-ray structures gaining structural insight into this compounds class. In addition, data mining of similar compounds deposited within the Cam-

bridge Structural Database was performed. These derivatives could be used either as synthetic intermediates via the ylide functionalization and glyco chemical biology synthons or improving the pharmacokinetic properties of a potential bioactive molecule, exploiting the glycosyl moiety.

Introduction

Organophosphorus compounds and especially phosphorus ylides have been utilized in a wide variety of reactions of interest to synthetic chemists, specifically in the synthesis of naturally occurring products.^[1–7] Phosphorus ylides, endowed by unique electronic and molecular structures, are classed as special zwitterions, useful in diverse reactions; they are characterized by electron-rich carbanions, decisively nucleophilic. Thus, these moieties have received considerable interest as widely used reagents for linking synthetic building blocks with the formation of carbon–carbon double bonds, as the Wittig reaction^[8] and this has aroused much interest in the study of the synthesis, structures and properties of P-ylides and their derivatives. Most importantly, phosphorus ylides are readily obtainable from abundantly available inexpensive reagents and have been correspondingly researched in depth with respect to their reactive properties and their potential in both reagent preparation and industrial-level organic synthesis. Ylide preparation usually involves the treatment of a phosphonium salt (normally from phosphine and an alkyl halide) with a base.^[2,6,9–15] Moreover, a convenient synthesis of phosphorus ylides is based on the assembly of phosphine with acetylenic esters and a source of an acidic proton e.g. O–H,^[1,16] N–H,^[17–21] S–H^[22] and C–H^[2,23–26] groups.

However, the use of complex starting materials such as oligosaccharides is unknown in this multicomponent reaction and very often reactions fail when non trivial building blocks are used. In continuation to our interest in discovering novel glycoconjugates, we envision employing phosphorus ylides with

glycosyl moieties of interest giving access to rare sugar derivatives (Figure 1A, Figure 1B). These chimeric compounds, on one hand could serve as synthetic hubs and tools for the accomplishment of various syntheses taking advantage the labile phosphorus ylide moiety. For example, they could be employed in the Wittig reaction, which is a well investigated reaction, extensively used for derivatization of carbohydrates, important initial reagents in the synthesis of naturally occurring compounds. On the other hand, they could be employed in building molecules to bind specific targets or enhancing ADMET properties, e.g. transport properties through transporters and increase water solubility due to the attached sugar moieties^[27,28] or more importantly in the triphenylphosphonium-based modification of molecules facilitating mitochondria targeting.^[29] As we have successfully demonstrated in past,^[30] an effective strategy of combining two different chemical species, namely the aglycon part and the carbohydrate, is via multicomponent reactions (MCRs).

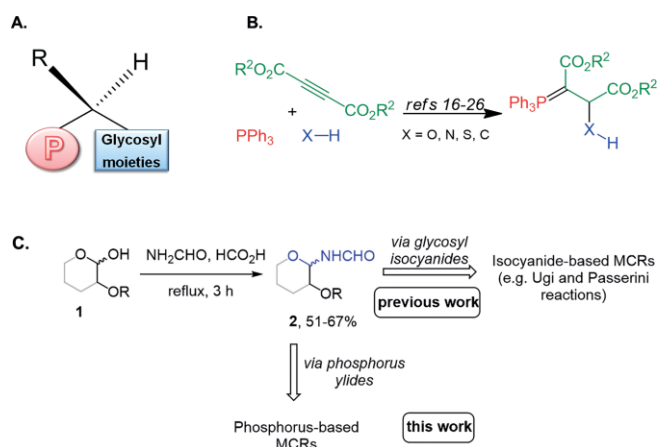


Figure 1. (A) Design of novel glycoconjugates consisting of phosphorus ylides and glycosyl moieties. (B) The established MCR utilizing an acidic proton; (C) MCR implementation of the glycosyl formamides towards molecules of interest via glycosyl isocyanides (previous work) and phosphorus ylides (this work).

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Supporting information and ORCID(s) from the author(s) for this article are available on the WWW under <https://doi.org/10.1002/ejoc.201900434>.

Results and Discussion

In our previous studies towards glycoconjugate synthesis^[31] we took advantage of our Leuckart–Wallach procedure towards glycosyl formamides which is the key intermediate, followed by their transformation to the corresponding isocyanides. Then, we applied certain isocyanide-based MCRs (IMCRs) in order to synthesize targeted libraries (Figure 1C). However, in the current study we employed the glycosyl formamide directly into a MCRs, via phosphorus ylides, exploiting its acidic N–H (Figure 1B, Figure C). Consequently, we exploit here a synthetic solution of successfully incorporating a phosphonium ylide into complex carbohydrates.

A representative series of mono-, di- and trisaccharides in order to test our synthetic plan was prepared (Figure 2). As described before,^[30,31] we performed the regio- and stereo-specifically reductive amination on the 1-OH-unprotected sugars **1**, affording the corresponding glucosyl (**2a**), galactosyl (**2b**), lactosyl (**2c**) and maltotriosyl (**2d**) formamides as β -anomers with Z-configuration in good yields.

Then, the reaction of the synthesized glycosyl formamides **2a–d** with triphenylphosphine **3** and dialkyl acetylenedicarboxylates (DMAD and DEAD) **4a,b** at r.t. in ethyl acetate as solvent was performed. It successfully afforded the organophosphorus compounds **5a–l** (a plausible mechanism is given in Supporting

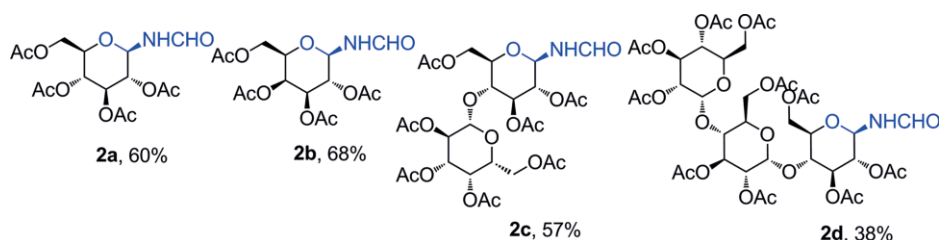
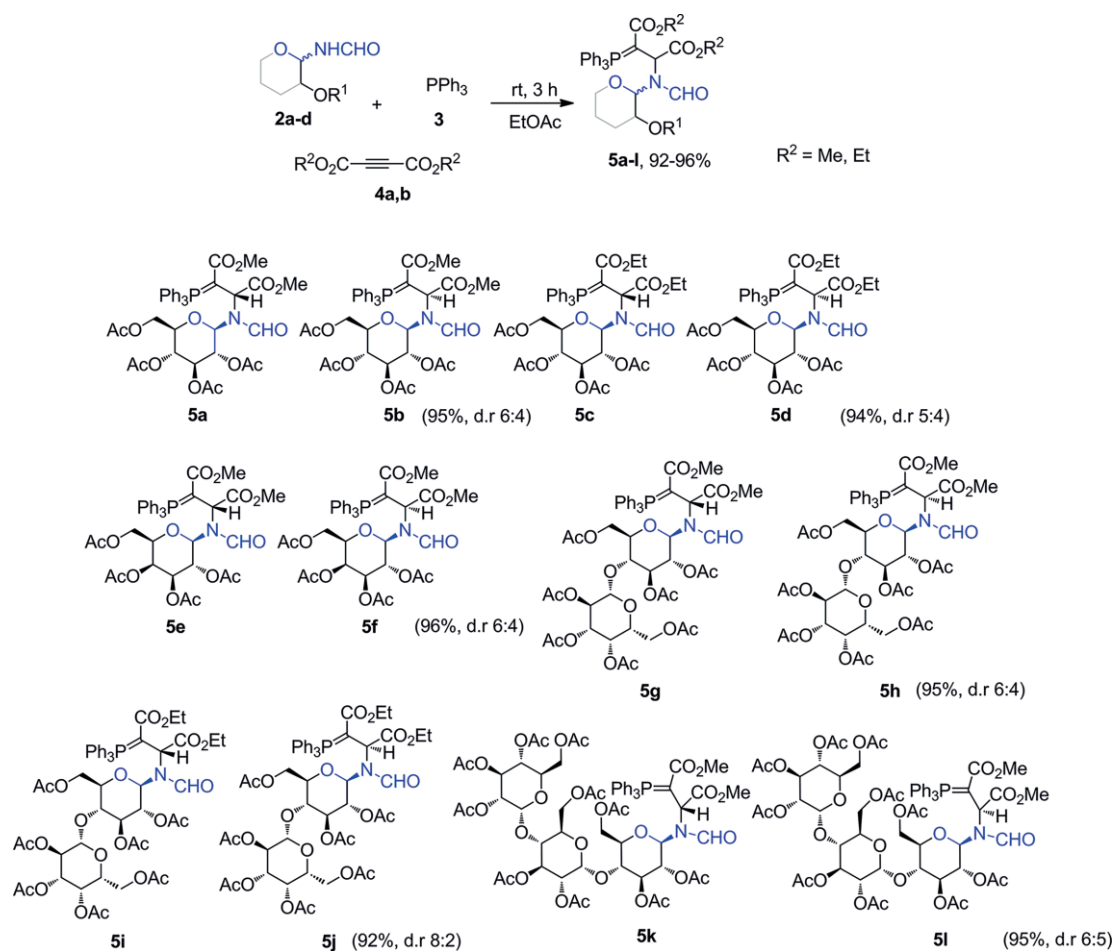


Figure 2. Sugar formamides **2a–d** employed in the current study.



Scheme 1. MCR of glycosyl formamides **2a–d**, triphenylphosphine **3** and acetylene dicarboxylates **4a,b** yielding organophosphorus derivatives **5**; diastereomer separation yielded the derivatives **5a–l**.

Information, SI) in quantitative yields (Scheme 1). Compounds **5**, incorporated both the phosphorus ylides and the sugar moieties, were obtained as diastereomeric mixtures (Scheme 1), which were separated by column chromatography.

Besides their spectroscopic characterization by means of ^1H NMR, ^{13}C NMR and ^{31}P NMR, we obtained compounds **5g** and **5i** in the crystalline form, allowing X-ray crystal structure determination (Figure 3). Due to the fact that the P=C bond is strongly conjugated with the adjacent carbonyl group, the rotation of the partially double bond C=C is slow in solution at r.t.^[32,33] As a result, the molecules in the crystal structures are in *E*-configuration (see the stereoscopic view in Figure 3).

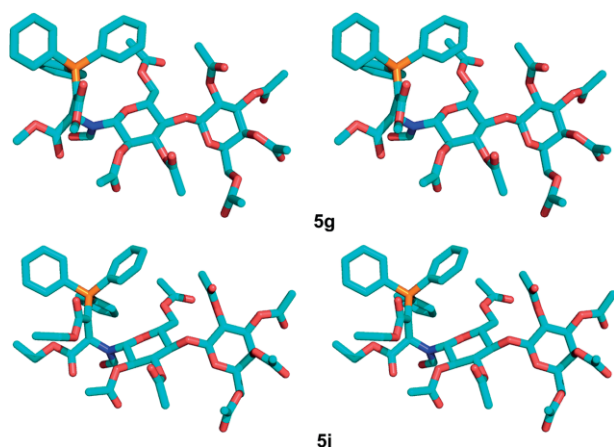


Figure 3. Stereoscopic view of the crystal structures of the organophosphorus compounds **5g** (CCDC 1888843) and **5i** (CCDC 1889525).

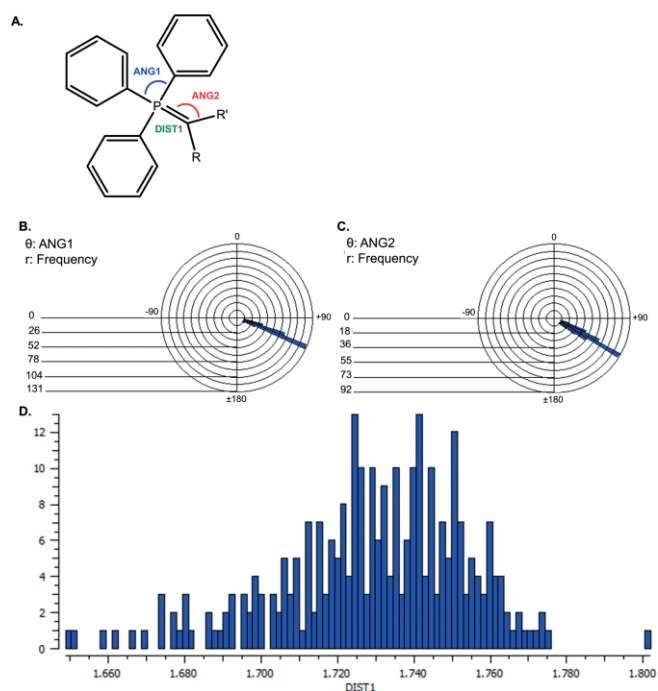


Figure 4. (A) The statistically investigated geometrical features of phosphorus ylides found in the CSD (245 hits). (B) Polar histogram of the C–P–C angle (namely ANG1, blue color) with a mean value of 111.9° . (C) Polar histogram of the P=C–R' angle (namely ANG2, red color) with a mean value of 120.4° . (D) Histogram of the P=C distance (namely DIST1, green color) with a mean value of 1.73 \AA .

In order to give a general perspective of the structural features of these phosphonium species, a data mining in the Cambridge Structural Database (CSD)^[34] revealed 245 crystal structures of organophosphorus compounds containing triphenylphosphorus ylides (Figure 4A). The structure and conformation of a phosphonium ylide is very important, e.g. the outcome of a Wittig reaction is strongly influenced by the above factors. Thus, the important geometrical features are depicted in Figure 4, with C–P–C (namely ANG1) and P=C–R' (namely ANG2) angles mean values being 111.9° and 120.4° , respectively (Figure 4B, Figure 4C). Furthermore, the mean value of P=C distance (namely DIST1) was defined as 1.73 \AA (Figure 4D).

The aforementioned *E*-configuration observed in the presented crystal structures is well justified by the C–C distance (DIST3, Figure 5A) being around 1.4 \AA , which is much shorter than a typical single bond. This observation strongly suggests

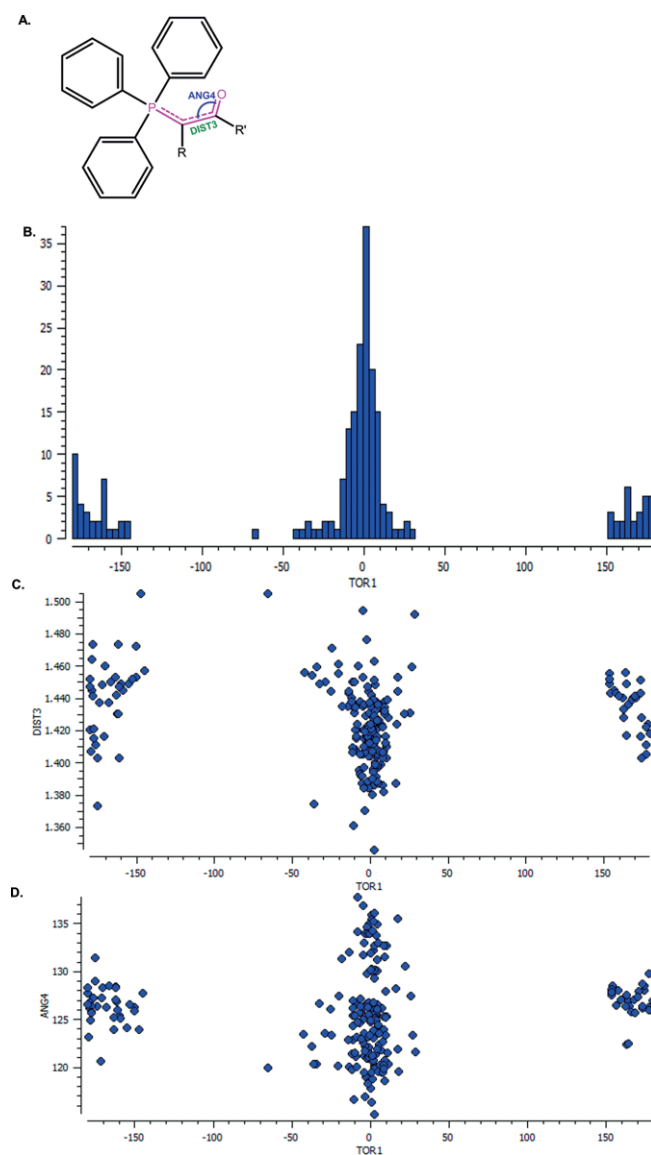


Figure 5. (A) Geometrical features of phosphorus ylides deposited in the CSD (147 hits). (B) Histogram presenting the torsion angle (TOR1) distribution, showing the synperiplanar conformation preference. (C) Scatterplot of TOR1 vs. DIST3. (D) Scatterplot of TOR1 vs. ANG4.

the conjugation of the P=C bond with the adjacent carbonyl group (Figure 5A). Additionally, the described resonance effect is leading to the slight elongation of the C=O (≈ 1.24 Å). A torsion angle analysis of structures of similar ylides deposited within the CSD has also confirmed an *E*-configuration preference. The P–C–O torsion angle (TOR1, magenta, Figure 5B) adopts a predominant synperiplanar conformation with values of -45° to $+45^\circ$. The strong conjugation effect can be verified by the delocalization of the π -system between the P=C and C=O (magenta, Figure 5A).^[35] Indeed, similarly to the determined crystal structures presented in this paper, the synperiplanar conformation (TOR1) of such type of molecules leads to shortening of the C–C distance (DIST3, mean value 1.43 Å), what suggests its partial double bond character (Figure 5C). At the same time, the C–C=O angle (ANG4, mean value 125.6°) decreases from a planar trigonal to a more tetrahedral conformation (Figure 5D).

Conclusions

In summary, we developed a high-yielding synthetic route towards complex glycoconjugates with unique features. Our described reaction works with complex building blocks such as the di- and trisaccharides **2c** and **2d** with more than 10 stereogenic centers. We envision that our developed strategy could be added to the phosphorus ylides arsenal of synthetic chemical biologists. Studies towards the selective uptake of these phosphonium compounds towards mitochondria are currently ongoing in our laboratory and will be reported in due course.

Experimental Section

Supporting Information (see footnote on the first page of this article): The Supporting information contains general procedures, characterization data of all the compounds, crystal structure determination and data mining of the CSD.

CCDC 1888843 (for **5g**), 1889525 (for **5i**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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Keywords: Phosphorus Ylides · Glycoconjugates · Glycosyl Formamides · Multi-Component Reactions · Chemical Biology

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