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Aza-Wittig Reaction of Sugar Isothiocyanates and Sugar Iminophosphoranes: An Easy Entry to Unsymmetrical Sugar Carbodiimides

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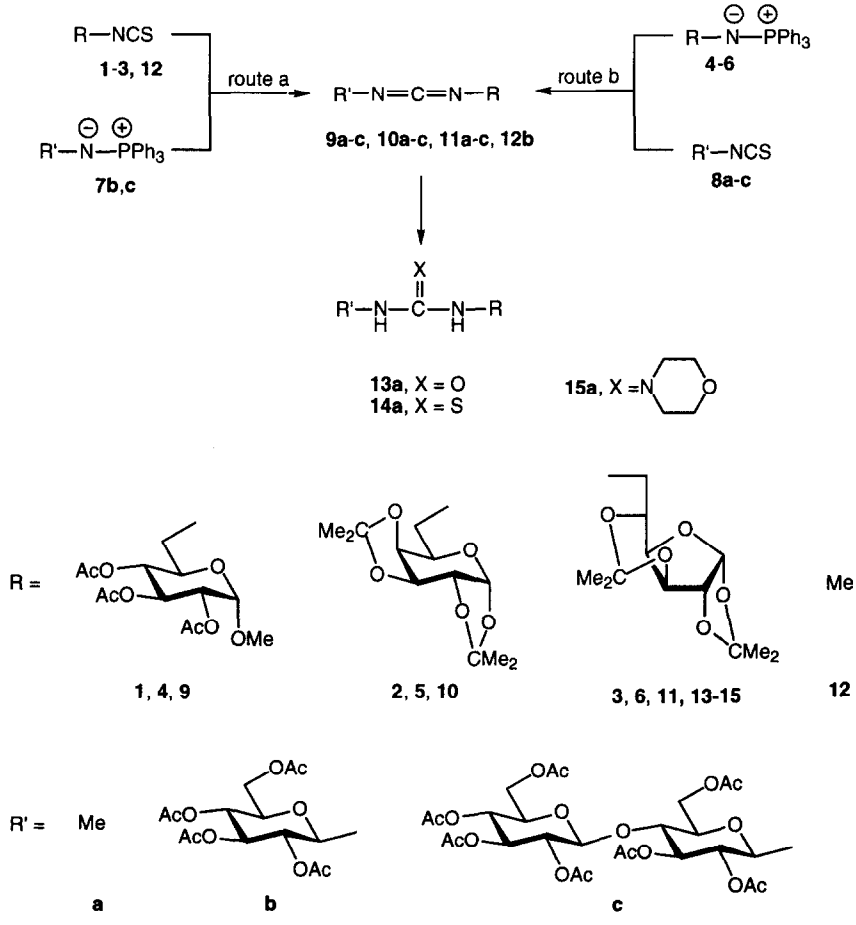
Abstract: Aldohexose derivatives possessing a triphenylphosphoranylideneamino substituent at the primary (C-6) position exhibit an increased reactivity towards the aza-Wittig condensation with isothiocyanates as compared with glycosyl phosphinimines. The reaction is particularly fast and efficient in the case of glycosyl isothiocyanates and has been exploited in the preparation of (1→6)-linked pseudooligosaccharides incorporating carbodiimide bridges. These compounds are excellent starting materials for the preparation of sugar ureas, thioureas and guanidines by reaction with the appropriate nucleophile. © 1997 Elsevier Science Ltd.

Cabodiimides are among the most important compounds in organic synthesis, useful both as precursors of a variety of functional groups and as condensing agents in the preparation of nucleotides and peptides.[1] Moreover, they are able to undergo a plethora of heterocyclization reactions leading to various complex azaheterocycles, including biologically active structures.[2] In spite of their impressive synthetic potential, examples of sugar carbodiimides are scarce,[3] and there are no reports on unsymmetrical sugar carbodiimides. In the frame of a program aimed at the synthesis of antigenic oligo(glycosyl)phosphate bioisosters, we have been interested in the preparation of (1→6)-linked pseudodisaccharides incorporating three-atom functionalities as phosphodiester surrogates.[4] Such compounds may be employed for the development of diagnostic tests, vaccines or as enzyme inhibitors, by analogy with the promising results obtained with backbone-modified antisense oligonucleotide isosters.[5] In this context, (1→6)-linked glycosyl carbodiimidosugars appear as very atractive synthetic intermediates, since carbodiimides can be easily transformed into urea, thiourea and guanidine derivatives by standard methodologies.

From the range of general methods available for the construction of the carbodiimide functionality,[1,2,6] the intermolecular aza-Wittig type reaction of iminophosphoranes (λ^5-phosphazenes, phosphine imines)[7] and heterocumulenes (isocyanates, isothiocyanates) looks the most attractive, since it takes place under neutral conditions compatible with all common OH protecting groups and may be conceived for convergent strategies in the synthesis of unsymmetrical complex structures. In a first approach, two alternative synthetic pathways were considered: (a) the reaction of glycosyl phosphinimines with 6-deoxy-6-isothiocyanato sugars and (b) the converse condensation of glycosyl isothiocyanates and triphenylphosphoranylidene derivatives of 6-amino-6-deoxy aldohexoses (Scheme 1). Both the isothiocyanates and the iminophosphoranes are readily accessible in

multi-gram scale by isothiocyanation of sugar halides or amino sugars[8] and by Staudinger reaction of sugar azides with triphenylphosphine,[3c,9] respectively. Results indicated a much lower reactivity for iminophosphorane groups located at the anomeric position as compared with their methylene counterparts. Thus, using methyl isothiocyanate (**8a**) as a model substrate, the aza-Wittig condensation with the 6-deoxysugar derivatives **4-6** was complete within 1 h (→**9a-11a**)[10] in dry toluene at room temperature using a stoechiometric proportion of the reagents. An even faster transformation was observed for the mono- and disaccharide glycosyl isothiocyanates **8b** and **8c** (→**9b-11b** and **9c-11c**, respectively).[10] In contrast, no reaction was observed by treatment of 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl phosphinimine (**7b**) with methyl isothiocyanate (route a) under identical reaction conditions after several days. By refluxing in toluene for 2 h, the corresponding glucosyl carbodiimide **12b** was obtained in moderate yield (40%), and similar results were achieved for the coupling of **7b,c** with the sugar isothiocyanates **1-3**. The formation of side products, probably arising from the reaction of either unreacted iminophosphorane or isothiocyanate with the formed carbodiimide, complicates the purification step in these cases.[1,11]



Scheme 1

The above differences in reactivity must obviously be ascribed to the particular electronic properties of the anomeric position of carbohydrates. The electron withdrawing (-I) effect of the glucopyranosyl ring results in the stabilization of the negatively charged anomeric nitrogen atom in glycosyl phosphinimines, with a subsequent decrease in its nucleophilicity. On the other hand, the increased reactivity of anomeric isothiocyanato groups is in agreement with a higher contribution of the R—N^-—C^+=S form to the ground state of glycosyl isothiocyanates.

In conclusion, we have shown that 6-amino-6-deoxy-6-phosphoranylidene sugars and glycosyl isothiocyanates are ideally suited to undergo aza-Wittig condensation between themselves, or with other iminophosphoranes or isothiocyanates, under mild conditions. The reactive sugar iminophosphorane can be generated in the reaction medium from the corresponding sugar azide, and further C=N bond formation, with extrusion of triphenylphosphine thioxide, takes place within minutes and with total control of the anomeric configuration. The resulting unsymmetric carbodiimides are stable enough to be isolated in pure form (70-90% yield) after flash chromatography. Nevertheless, formation of 10-15% of the corresponding ureas could not be avoided during the chromatographic process. Alternatively, the carbodiimides may be transformed in situ into urea, thiourea and guanidine derivatives by reaction with the appropriate nucleophile, as illustrated for the model compounds **13a-15a** (Scheme 1).[10] The preparation of a series of oligo(glycosyl)phosphate isosters incorporating these functional groups by using this approach is currently sought in our laboratories.

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10. All carbodiimides **9a-c**, **10a-c**, **11a-c**, **12b** gave the characteristic IR absorption at 2135-2150 cm^{-1} and ^{13}C resonance (125,7 MHz, $CDCl_3$) at 137-140 ppm (δ_{NCN}). Data for **9a**: $[\alpha]_D^{20}$ +107.7 (*c* 1.0, CH_2Cl_2). Data for **9b**: $[\alpha]_D^{20}$ +65.2 (*c* 1.9, CH_2Cl_2). Data for **9c**: $[\alpha]_D^{20}$ +44.5 (*c* 1.6, CH_2Cl_2). Data for **10a**: $[\alpha]_D^{20}$ -103.5 (*c* 1.0, CH_2Cl_2). Data for **10b**: $[\alpha]_D^{20}$ -51.5 (*c* 0.8, CH_2Cl_2). Data for **10c**: $[\alpha]_D^{20}$ -28.8 (*c* 1.2, CH_2Cl_2). Data for **11a**: $[\alpha]_D^{20}$ +22.3 (*c* 0.9, CH_2Cl_2). Data for **11b**: $[\alpha]_D^{20}$ +9.6 (*c* 0.9, CH_2Cl_2). Data for **11c**: $[\alpha]_D^{20}$ +15.0 (*c* 1.0, CH_2Cl_2). Data for **12b**: $[\alpha]_D^{20}$ -11.5 (*c* 1.0, CH_2Cl_2). Compounds **13a**, **14a** and **15a** were obtained by coupling of carbodiimide **11a** with H_2O, H_2S and morpholine, respectively. Data for **13a**: $[\alpha]_D^{20}$ +14.0 (*c* 1.1, CH_2Cl_2); ^{13}C NMR (125.7 MHz, $CDCl_3$): 159.3 ppm (CO urea). Data for **14a**: $[\alpha]_D^{20}$ +6.4 (*c* 0.9, CH_2Cl_2); ^{13}C NMR (125.7 MHz, $CDCl_3$): 183.0 ppm (CS). Data for **15a**: $[\alpha]_D^{20}$ +34.4 (*c* 1.1, CH_2Cl_2); ^{13}C NMR (125.7 MHz, $CDCl_3$): 161.2 ppm (C=N). Compounds **9a-c**, **10a-c**, **11a-c**, **12b**, **13a-15a** gave microanalyses (C, H, N, S) in agreement with the proposed structures.

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