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Synthesis of 1-[1-(diphenoxyphosphoryl)alkyl]-3,4,6-trimethylglycolurils

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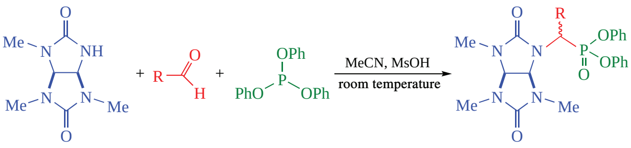
The reaction of 1,3,4-trimethylglycoluril, aliphatic aldehydes and triphenyl phosphite in the presence of methanesulfonic acid affords new phosphorus-containing derivatives of glycoluril. The thus formed diastereomers of 1-[1-(diphenoxyphosphoryl)alkyl]-3,4,6-trimethylglycolurils were separated by reverse-phase HPLC.



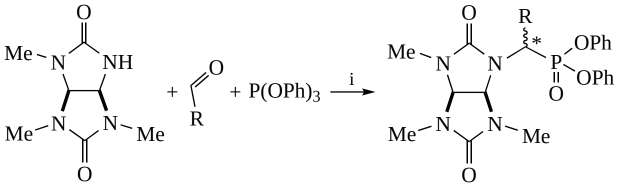
Keywords: 1,3,4-trimethylglycolurils, phosphonates, diastereomers, Birum–Oleksyszyn reaction, triphenyl phosphite, one-pot synthesis.

The chemistry of glycolurils (bicyclic bisureas) is steadily developing. A special attention is paid to the methods for synthesizing new derivatives of glycolurils and their analogues and precursors, as well as the study of their properties.[1–6] The literature describes methods for obtaining phosphorus-containing glycoluril derivatives[7–9] some of which exhibit catalytic activity in three-component reactions.[7,8]

In order to expand the glycoluril diversity, we have performed herein the introduction of phosphonate group into a glycoluril molecule using a three-component Birum–Oleksyszyn reaction (a case of the Kabachnik–Fields reaction). This reaction is widely employed to prepare various ureido and carbomoyl phosphonates used for further hydrolysis into α-amino phosphonates.[10–15]

1,3,4-Trimethylglycoluril **1** bearing only one reaction centre and simplest aliphatic aldehydes were chosen as the convenient initial substrates (Scheme 1). The choice of triphenyl phosphite was due to the higher reactivity of aryl phosphites in comparison with alkyl phosphites and alkyl chloridophosphites.[16,17] Trimethylglycoluril **1** was prepared *via* one-pot synthesis by the reaction between 1-methylurea and glyoxal and subsequent treatment of the intermediate 4,5-dihydroxy-1-methylimidazolidin-2-one with 1,3-dimethylurea.[18]

Based on the ^{1}H and ^{31}P NMR data of the products obtained (see Scheme 1), the reaction does not proceed stereoselectively and gives racemic mixtures of diastereomers **4a–d** (**4a′–d′** and **4a′′–d′′**) in close ratios in all cases. ^{1}H NMR spectrum of sample **4a** contains two multiplets for C*H*(Me)P(O) proton in the ranges of 4.46–4.65 and 4.56–4.70 ppm. This spectrum also contains four doublet signals of bridging methine protons of the glycoluril moiety in the range of 5.06–5.50 ppm. ^{31}P NMR spectrum of sample **4a** consists of two signals at 18.33 and 18.56 ppm. Moreover, in its ^{13}C NMR spectrum several principal signals are doubled, for example, methyl groups of the CH(CH_3)P(O) fragment for the diastereomers are manifested at 12.96 and 15.17 ppm.



1 **2a–d** **3** **4a–d**

a R = Me, *dr* 46:54, 56%
b R = Et, *dr* 53:47, 51%
c R = Pr^n, *dr* 57:43, 63%
d R = *n*-C_5H_{11}, *dr* 60:40, 33%

Scheme 1 *Reagents and conditions*: i, MsOH, MeCN, room temperature, 60 min. In the *dr* ratios, the first value relates to the diastereomer with lower HPLC retention time.

With the use of HPLC on the reversed stationary phase, we were able to preparatively separate individual racemic diastereomers **4a′–c′** (lower retention times) and **4a′′–c′′**. Apparently, the diastereomers with better sterically accessible hydrophobic groups are characterized by the higher retention. Although each individual diastereomer was characterized by ^{1}H, ^{13}C and ^{31}P NMR, the true assignment of the configuration within such chemotype of compounds currently remains a challenge. Anyway, ^{1}H NMR spectra of compounds of type **4a′** contain characteristic signals for CH–CH methine protons in a narrow region at δ 5.11 (d, J = 8.7 Hz) and δ 5.27 (dd, J = 8.6, 1.7 Hz), while for compound **4a′′** such signals are recorded in a wider area at δ 5.06 (d, J = 8.5 Hz) and δ 5.40 (dd, J = 8.5, 1.0 Hz). In addition, compound **4a′′** is characterized by a downfield shift of the signals for methine protons (m, δ 4.56–4.70 ppm) compared to similar signals of compound **4a′** (m, δ 4.46–4.65 ppm). The resonance of phosphorus atoms of compound **4a′′**, on the contrary, is shifted upfield (18.33 ppm) relative to compound **4a′** (s, δ 18.56 ppm).

In summary, the reaction of 1,3,4-trimethylglycoluril **1**, triphenyl phosphite and aliphatic aldehydes affords racemic mixtures of diastereomers of 1-[1-(diphenoxyphosphoryl)alkyl]-3,4,6-trimethylglycolurils. The results of the conducted studies may be a basis for expanding the preparative horizon for the synthesis of new phosphorylated glycoluril derivatives by involving other aldehydes and bicyclic bisureas in this reaction.

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*Online Supplementary Material*s

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2023.09.015.

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