CYCLOADDITION REACTIONS OF DEOXYRIBOSYLPROPYNOATES

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GRAPHICAL ABSTRACT

Abstract Pure anomers of either α or β 3-(2-deoxyribofuranosyl)propynoates reacted with the tetr methylcyclobutadiene–aluminum trichloride complex to yield the corresponding diastereoisomeric Dewar benzenes. Thermal- or ultraviolet light–initiated rearrangement gave rise to highly substituted C-aryldeoxyribosides as single anomers. The same compounds as well as other substituted deoxyribosides were obtained also by transition metal–mediated cycloaddition reactions.

Keywords C-Aryldeoxyribosides; cycloaddition; cyclotrimerization; Dewar benzenes; unnatural nucleosides

INTRODUCTION

Various C-substituted glycosides (natural as well as the synthetic ones) exhibit a range of biological properties. C-Aryldeoxyribosides may serve as a typical example, because of their application as artificial DNA components.[1] One of the possible pathways to this class of compounds is a transformation of the triple bond of 1-ethynyldeoxyribosides, prepared from the corresponding halogenose,[2] into the desired functionalized products, as has been demonstrated by our group[3] and others.[4] [2+2+2]-Cyclotrimerization to aryldeoxyribosides[3b] and the use of

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Sonogashira reaction conditions for syntheses of deoxyribosylbutenolides\textsuperscript{[3c]} and substituted alkynyldeoxyribosides,\textsuperscript{[3d,4b,4c]} indolyldeoxyribosides,\textsuperscript{[3e]} cyclopentenones bearing deoxyribosyl moiety,\textsuperscript{[4a]} and triazolyldeoxyribosides\textsuperscript{[4d,4e]} may serve as typical examples. 3-(2-Deoxyribofuranosyl)propynoates are interesting building blocks that could be used for further transformations by hitherto unstudied cycloaddition reactions. First of all, the presence of the electron-deficient triple bond makes this compound an attractive substrate for cycloaddition with other unsaturated compounds, (e.g., cyclobutadiene or its analogs), giving rise to Dewar benzenes. Secondly, it is an interesting substrate for catalytic or stoichiometric cyclotrimerizations with alkynes furnishing substituted 1-aryldideoxyribosides.

Dewar benzenes (DBs) are fascinating compounds possessing strained [2.2.0]-bicyclohexadiene frameworks, which can undergo thermal or photochemical rearrangement to the benzene ring. The first synthetic methodology for the preparation of DB was developed in the early 1960s.\textsuperscript{[5]} It was quickly also followed by other procedures that enabled preparation of a variety of variously substituted DBs.\textsuperscript{[6,7]} Probably the most versatile and simple procedure for synthesis of alkyl-substituted Dewar benzenes is based on the reaction of aluminum trichloride with 2 equivalents of an alkyne (e.g., 2-butyne)\textsuperscript{[6]} with another alkyne bearing electron-accepting groups (e.g. ester groups). The initial step gives rise to a complex compound that can be formally described as tetramethylcyclobutadiene–AlCl\textsubscript{3} complex,\textsuperscript{[8]} which reacts (in the presence of dimethylsulfoxide, DMSO) with the activated alkyne to yield the corresponding DB. Interestingly, application of DBs in organic synthesis has been rather rare and that could be to some extent attributed to difficulties regarding the synthesis of these compounds, owing to their specific substitution patterns. Nonetheless, over the span of several decades some interesting applications have been found. The reaction of tetraalkylcyclobutadiene complex has been used for the synthesis of DB polymers and permethylated ladderanes,\textsuperscript{[9]} chiral DBs,\textsuperscript{[10]} phenyl-substituted DBs that served as substrates to study electronic effect on the rearrangement to benzenes,\textsuperscript{[11]} conjugates with ferrocene,\textsuperscript{[12]} ter- and quaterphenyls,\textsuperscript{[13]} and unsymmetrically substituted fluorenes,\textsuperscript{[14]} and finally they could also be used as a protecting group.\textsuperscript{[15]} In all of these cases the DBs have been used as precursors of the correspondingly substituted benzene rings.

RESULTS AND DISCUSSION

We envisioned that by conversion of the anemic ethynyldeoxyriboside 1\textgreek{a} and 1\textgreek{b}\textsuperscript{[a]} into the corresponding propynoate 3\textgreek{a} and 3\textgreek{b} a suitable substrate for the synthesis of DBs will be obtained. However, we initially had to solve the problem of separation of the anemic mixture of 1\textgreek{a} and 1\textgreek{b} into the anomerically pure substances. The conventional method is based on separation by using preparative high-performance liquid chromatography (HPLC), which is not convenient, especially when larger quantities are required. We assumed that perhaps adding a suitable and easily removable functional group at the end of the triple bond in 1 could considerably change physical properties of both anomers. This could then result in an easy separation of both anomers by using a simple column chromatography. The choice of the tert-butyldimethylsilyle (TBDMS) group proved to be the case, and the whole process was as follows: lithiation of 1\textgreek{a} and 1\textgreek{b} anomic mixture with lithium diisopropylamide.
(LDA) followed by the reaction with TBDMS-Cl provided a mixture of the silylated ethynyldeoxyribosides. The ensuing column chromatography on silica gel provided 2α and 2β in 38% and 20% yields (58% combined yield), respectively. Deprotection of the obtained anomers with tetrabutylammonium fluoride (TBAF) afforded the corresponding 1α and 1β in 93% and 87% yields. Having obtained the pure anomers, the subsequent reactions were done either with α or β compound. Lithiation of 1α or 1β with LDA and the reaction with methyl chloroformate gave the corresponding propynoates 3α/3β in 72% and 79% isolated yields, respectively (Scheme 1).

The reaction of 3α with tetramethylcyclobutadiene–AlCl3 complex proceeded uneventfully to furnish the corresponding Dewar benzene 4α as a 3/2 inseparable mixture of diastereoisomers in 38% isolated yield (40% of 3α remained unreacted). In a similar manner the reaction with 3β was carried out, yielding the Dewar benzene 4β as a 1/1 inseparable mixture of diastereoisomers in 42% isolated yield (43% of 3β remained unreacted) (Scheme 2).

Later we found out that the whole reaction sequence from 1 to 4 could be also done with the anomeric mixture, forming the anomeric mixture of Dewar benzenes 4α and 4β (combined yield 48%), which, because of sufficient differences in the polarity of both anomers, was after this step separated into the individual anomers by column chromatography.

The obtained Dewar benzenes were stable under ambient conditions. Although it was demonstrated that substituted Dewar benzenes could be easily rearranged to the corresponding benzene derivatives under thermal conditions (>150 °C) with a reasonable reaction rate, in the case of 4α/4β considerable degradation was observed during the course of this reaction. This was not surprising, taking into account the presence of the sugar moiety, which easily undergoes dehydration. To avoid this undesirable side process, the rearrangement was carried out conveniently at 20 °C under UV irradiation in a quartz test tube that yielded the corresponding (2-deoxyribofuranosyl) arenes 5α/5β in 69 and 35% isolated yields, respectively (Scheme 3). It is worth noting

Scheme 1. Separation of anomers and synthesis of propynoates 3α/3β.
that after the rearrangement only one stereoisomer was obtained, indicating unrestricted free rotation around the bond connecting the deoxyribose and aryl moiety at 20 °C (restricted rotation was not observed even at −50 °C).

With propynoates 3 on hand we also decided to test their reactivity with other alkynes under cyclotrimerization conditions. Firstly, the reaction of 3α or 3β with tetramethylzirconacyclopentadiene, prepared from dibutyl zirconocene and 2-butyne, in the presence of a stoichiometric amount of CuCl[16] was carried out as an alternative

Scheme 2. Synthesis of Dewar benzenes 4α and 4β.

Scheme 3. Rearrangement of 4α or 4β to respective C-aryldeoxyribosides 5α or 5β.
approach to $5\alpha$ or $5\beta$ (Scheme 4). In both cases full consumption of the starting material was observed, providing complex reaction mixtures out of which $5\alpha$ or $5\beta$ were isolated as single products in 33 and 25% yields, respectively. Unlike in reactions with other sterically hindered propynoates,[16d] the formation of the Dewar benzene derivatives 4 was not detected.

Secondly, the reactions of $3\alpha$ or $3\beta$ with 1,6-heptadiyne in the presence of a catalytic amount of RhCl(PPh$_3$)$_3$ (10 mol%) furnished dihydroindenes $6\alpha/6\beta$ in poor (18 and 14%) isolated yields (Scheme 4). The use of CpRuCl(COD) provided the same products in somewhat better isolated yields of 24 and 28%. The structures of $6\alpha$ and $6\beta$ were unequivocally confirmed by their X-ray analyses (Fig. 1). Catalytic

![Scheme 4. Reactions of 3 to give 5 or 6.](image)

![Figure 1. X-ray structure of 6α and 6β. Displacement ellipsoids are scaled to the 30% probability level.](image)
cyclotrimerization of $\text{3}_\alpha$ and $\text{3}_\beta$ with 1,7-octadiyne was also attempted but it did not provide the expected products. This observation is not wholly surprising because similar results have been observed before by others\cite{17} and also by us\cite{3a} and could be best explained by the Thorpe–Ingold effect.\cite{18} In these cases the unreacted starting material was detected in the 40–45% range. The rather poor isolated yields could be probably attributed to considerable steric hindrance of the triple bond, which reduces its reactivity. The diynes used were completely consumed, presumably by self-cyclotrimerization, providing oligomeric products.

**CONCLUSION**

We have developed a simple method for separation of 1-ethynlydeoxyribose anomers and prepared 3-(2-deoxyribofuranosyl)propynoates $\text{3}_\alpha$ and $\text{3}_\beta$. These compounds were used as starting material for cycloaddition reactions, which yielded the corresponding Dewar benzenes 4, which could be converted into (2-deoxyribofuranosyl) arenes 5 upon photochemical rearrangement. In addition, they were used as substrates for reactions with zirconacyclopentadienes and in catalytic cyclotrimerization (Rh and Ru catalysis) with 1,7-heptadiene, giving rise to the corresponding 1-(2-deoxyribofuranosyl)dihydroindenones 6. During the course of these cycloaddition reactions anomerization was not observed.

**EXPERIMENTAL**

**Methyl 3-[3,5-Di-O-(4-toluoyl)-2-deoxy-\text{-}\alpha-D-ribofuranosyl]-1,4,5,6-tetramethylbi-cyclo-[2.2.0]hexa-2,5-diene-2-carboxylate (4\alpha)***

2-Butyne (0.25 mL, 3.15 mmol) was added to a stirred suspension of powdered anhydrous aluminum chloride (0.21 g, 1.58 mmol) in dry CH$_2$Cl$_2$ (10 mL) at–15 °C. After 15 min propynoate $\text{3}_\alpha$ (0.65 g, 1.50 mmol) was added to the resulting complex at–15 °C and the mixture was stirred for 1.5 h at–15 °C. DMSO (2 mL) was added, and the reaction mixture was stirred for another 0.5 h, while warming up to room temperature. The mixture was poured onto crushed ice and extracted with CH$_2$Cl$_2$ (3 × altogether with 20 mL). The combined organic layers were dried over anhydrous MgSO$_4$, filtered, and concentrated under vacuum. Column chromatography on silica gel (5/1 hexane/EtOAc) afforded an inseparable mixture of diastereomers (DS1–DS2 3:2 ratio) of Dewar benzene deoxyribosides (4\alpha) as a colorless oil (0.31 g, 38%): \( ^1\)H NMR (600 MHz, CDCl$_3$) DS1: \( \delta \) 7.94–7.92 (m, 2H), 7.91–7.86 (m, 2H), 7.24–7.21 (m, 4H), 5.51–5.47 (m, 1H), 5.30 (apt t, \( J = 7.5 \) Hz, 1H), 4.58–4.49 (m, 3H); 3.62 (s, 3H), 2.81 (apt dt, \( J = 13.6, 7.6 \) Hz, 1H), 2.41 (s, 3H), 2.40 (s, 3H), 2.30 (ddd, \( J = 13.0, 7.3, 4.9 \) Hz, 1H), 1.62–1.60 (m, 6H), 1.30 (s, 3H), 1.24 (s, 3H), DS2: \( \delta \) 7.94–7.92 (m, 2H), 7.91–7.86 (m, 2H), 7.24–7.21 (m, 4H), 5.51–5.47 (m, 1H), 5.33 (apt t, \( J = 7.8 \) Hz, 1H), 4.58–4.49 (m, 3H), 3.67 (s, 3H), 2.87 (apt dt, \( J = 13.6, 7.6 \) Hz, 1H), 2.41 (s, 3H), 2.40 (s, 3H), 2.23 (ddd, \( J = 13.3, 7.8, 5.0 \) Hz, 1H), 1.62–1.60 (m, 6H), 1.31 (s, 3H), 1.25 (s, 3H), \( ^{13} \)C NMR (150 MHz, CDCl$_3$) DS1: \( \delta \) 168.15, 166.32, 163.88, 144.65, 143.93, 143.74, 142.04, 138.97, 130.12–129.06 (multiple peaks, 10C), 127.06, 126.88, 80.97, 76.21, 75.62, 64.80, 56.06, 54.24, 50.85, 36.72, 21.63, 21.62, 11.26, 11.18, 10.74, 10.43; DS2: \( \delta \) 168.97, 166.17,
Methyl 2-[3,5-Di-O-(4-toluoyl)-2-deoxy-\(\alpha\)-D-ribofuranosyl]-3,4,5,6-tetramethyl-benzoate (5\(\alpha\))

\(n\)-BuLi 1.6 M (1.38 mL, 2.2 mmol) was added dropwise to a solution of zirconocene dichloride (0.33 g, 1.1 mmol) in THF (6 mL) at \(-78^\circ\)C. After 1 h of stirring, 2-butyne (0.32 mL, 4.0 mmol) was added and the reaction mixture was stirred for another hour, while warming up to ambient temperature. Then, propynoate 3\(\alpha\) (0.44 g, 1.0 mmol) and CuCl (0.20 g, 2.0 mmol) were added and the reaction was stirred for 96 h. Afterwards 1 M HCl (8 mL) was poured into the reaction and the mixture was extracted with ether (3 \times 8 mL). The organic layer was dried over anhydrous MgSO\(_4\), filtered, and concentrated under reduced pressure. Column chromatography of the residue on silica gel (5/1 hexane/EtOAc) furnished 5\(\alpha\) (0.18 g, 33\%) as a colorless oil: \(^1\)H NMR (600 MHz, CDCl\(_3\)) \(\delta\) 7.94–7.89 (m, 4H) 7.21–7.20 (m, 2H), 7.12–7.19 (m, 2H) 4.57–4.56 (m, 2H), 4.55–4.54 (m, 1H), 3.82 (s, 3H), 2.98 (ddd, \(J=13.0, 6.6, 6.6\) Hz, 1H), 2.40 (s, 3H), 2.39 (s, 3H), 2.33 (ddd, \(J=12.7, 10.3, 7.9\) Hz, 1H), 2.21 (s, 6H), 2.20 (s, 3H), 2.17 (s, 3H); \(^{13}\)C NMR (150 MHz, CDCl\(_3\)) \(\delta\) 171.78, 166.31, 166.28, 143.88, 143.69, 136.35, 134.56, 133.04, 130.39, 130.18, 129.79, 129.65, 129.56, 129.02, 129.01, 127.10, 126.80, 80.37, 78.35, 75.38, 64.91, 51.42, 39.33, 21.63, 21.61, 17.04, 16.49, 16.32, 15.98; IR (KBr) \(\nu_{max}\) 3037, 2989, 2947, 2920, 1724, 1613, 1449, 1429, 1305, 1371, 1275, 1198, 1180, 1108, 1021, 991, 749 cm\(^{-1}\); HRMS (m/z) for C\(_{33}\)H\(_{36}\)O\(_7\)Na (M + Na) calcd 567.2359, found: 567.2349; \(R_f\) (5/1 hexane/EtOAc) = 0.34 (silica-gel plate).

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SUPPLEMENTAL MATERIAL

Supplemental data for this article can be accessed on the publisher’s website.

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