Organometallic Nucleoside Analogues: An Adenine-Analogue Fischer Carbene Complex¹

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Abstract: A six-step synthesis of a nucleoside analogue Fischer carbene complex has been developed starting from D-ribo-1,4-lactone. The key steps involve a stoichiometric metathesis of exoglycal 3 with pentacarbonyl[(diphenyl)carbene]chromium to give chromium furanosylidene 4, its ring-opening aminolysis with the nucleobase adenine and a Mitsunobu recylisation leading to imino-L-lyxo-furanosylidene complex 6 with inversion of configuration.

Key words: carbene complexes, carbohydrates, chromium complexes, glycosylidene complexes, nucleosides

Saccharides play a central role in the chemistry of life.² They are involved in structural backbones, in energy storage as well as in intercellular molecular recognition processes such as infection, tumor-cell growth and cell adhesion. The monosaccharides ribose and deoxyribose, when attached to N-heterocyclic nucleobases, serve as building blocks for the nucleosides adenosine, cytidine, thymidine, uridine, and guanosine, which form nucleotides upon phosphorylation. On the other hand, organometallic chemistry has received increasing interest directed towards biological and pharmaceutical targets which has been referred to as ‘bioorganometallic chemistry’; in some cases organometallic functionalities have been shown to improve the performance of drugs.³ Following our ongoing interest in the organometallic – and in particular metal carbene⁴ – chemistry of sugars⁵ we turned our attention to the incorporation of nucleobases into glycosylidene complexes. Now we report the first example of a nucleoside analogue Fischer carbene complex.

The synthesis starts from the commercially available D-ribo-1,4-lactone 1 which was protected as 5-benzyl-2,3-isopropylidene derivative 2 (steps a,b,²) (Scheme 1). Olefination with the Petasis reagent⁷ afforded the exo-glycal 3 as a colourless waxy solid in 50–70% yield depending on the quality of the Petasis reagent (step c). Freshly prepared Cp₂TiMe₃ increases the yield by 10–20%.

The transformation of exo-glycal 3 into furanosylidene complex 4 has been achieved by a stoichiometric metathesis reaction using pentacarbonyl(diphenylcarbene)chromium (step d), a strongly electrophilic carbene complex handled at temperatures ≤ 30 °C. Its modification into the α-heteroatom-stabilized oxacyclopentylidene complex provides the thermodynamic driving force for the metathesis reaction.⁸ Heptane solutions of exo-glycal 3 and pentacarbonyl(diphenylcarbene)chromium were prepared at −45 °C and combined. The mixture was stirred and allowed to warm to room temperature while the progress of the reaction was monitored using FT-IR and TLC.⁹ After flash chromatography ribosylidene complex 4 was obtained in 47% yield as an orange oil and was characterized by a down-field ¹³C NMR-signal at 341.5 ppm (carbene-C).

Alkoxycarbene complexes readily undergo aminolysis upon reaction with amines.¹⁰ The rate of the reaction depends on the nature of the amine and significantly decreases with increasing steric bulk of the amine. Based on this experience we expected the primary amino group in the nucleobase adenine to be more reactive than the secondary amino functionality. In contrast to rapid aminolysis reactions characteristic for primary amines the ring-opening aminolysis of 4 by adenine required 24 hours to afford a 76% yield of acyclic mono-deprotected aminocarbene complex 5 as a yellow powder reflecting the reduced nucleophilicity of the nucleobase. Aminolysis with primary amines may result in the formation of E/Z-isomers with respect to the carbene-nitrogen bond, which are configurationally stable at ambient temperature. Under the aminolysis conditions used aminocarbene complex 5 – characterized by an ¹³C NMR up-field shift to 274.9 ppm for the carbene-C – was obtained as a single isomer within the accuracy of ¹H NMR-spectroscopy (step e); a low-field signal at 10.22 ppm (in CDCl₃) for the NH group attached to the carbene carbon suggests an E-stereochemistry.¹¹,¹²

Recyclization of 5 to give iminofuranosylidene complex 6 faces two problems. First, it has to overcome the poor nucleophilicity of the aminocarbene nitrogen, which is even less nucleophilic than that encountered in carboxylic amides; second, the unprotected hydroxy group at C-4 is only a modest leaving group. However, its leaving group ability can be efficiently enhanced under Mitsunobu conditions (step f)¹² which allow for the recyclization to give nucleoside-type complex 6, although in modest yield (29%) reflecting the substitution pattern at the carbene nitrogen atom. Since the Mitsunobu reaction is known to occur with clean inversion of configuration the D-ribose skeleton is modified into the L-lyxose backbone. This protocol takes advantage of a metal carbene based methodol-

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ogy to transform readily available D-sugars into their less common L-imino analogues and, in particular, provides a synthetic access to novel organometallic nucleoside analogues.

Since the metal carbene bond is prone to oxidation, addition and insertion reactions, nucleoside analogues of type 6 are promising candidates for subsequent structural elaboration, in particular oxidative cleavage or photo-induced carbonylation reactions leading to lactams or C-glycosides.

In conclusion we have developed a synthetic route to a nucleoside analogue Fischer carbene complex. It allows one to address novel nucleoside derivatives bearing also a non-natural configuration along with an organometallic functionality suitable for further C–C-bond formation.

All reactions were carried out under dry argon using Schlenk techniques. The solvents used for reactions and chromatography were dried by standard procedures and then saturated with argon.

Silica gel [(Merck silica gel 60 (0.63–0.200)] was degassed at high vacuum and stored under argon prior to use for chromatography. A 500 Watt sunlamp was used for the photochemical reactions. Thin layer chromatography was performed using foils from Merck (Typ 500), F254) with UV-detection; carbohydrate functionalities were detected by a spray containing H2SO4 (20%), HOAc (50%) and EtOH (30%). FT-IR: Nicolet Magna. EI-MS: Kratos MS 50. NMR: Bruker AM-250, Bruker AM-400, Bruker DRX 500.

2,5-Anhydro-1-deoxy-5-O-benzyl-3,4-O-isopropylidene-D-ribohex-1-enitol (3)
The synthesis of 3 was performed in analogy to the literature. A solution of lactone 2 (5.07 g, 18.20 mmol) and Cp2TiMe2 (8.36 g, 40.16 mmol) in toluene (100 mL) was stirred in the dark for 48 h at 65–70 °C under argon until TLC (petroleum ether–EtOAc, 5:1) indicated consumption of starting material. The brownish reaction mixture was concentrated, and the remaining syrup – after dilution with a minimum amount of toluene – was subjected to column chromatography on silica gel (eluent containing 1% of Et3N; petroleum ether–EtOAc, 20:1 → 5:1) to afford 3.51 g (12.7 mmol, 70% yield) of a colourless syrup.

1H NMR (250 MHz, CDCl3): δ = 7.35 (m, 5 H, Ph), 5.05 (app. t, J = 5.84 Hz, 1 H, H-3), 4.62 (app. t, J = 5.86 Hz, 1 H, H-4), 4.50 (s, 1 H, H-1b), 4.14 (m, 1 H, H-5), 4.43 (s, 2 H, CH2Ph), 4.23 (br s, 1 H, H-1a), 3.70 (m, 1 H, H-6'), 3.54 (app. dd, J = 3.41, 4.45 Hz, 1 H, H-6), 1.52 (s, 3 H, CH3), 1.37 (s, 3 H, CH3).

1C NMR (125 MHz/CDCl3): δ = 162.6 (C-2), 137.4 (ipso-C), 127.0 (Ph), 112.3 (CMe2), 84.1 (C-1), 83.8 (C-5), 80.3 (C-4), 79.6 (C-3), 73.0 (CH2OBn) 70.1 (CH2Ph), 26.8, 25.6, (2x, CH3).

Pentacarbonyl[5-O-benzyl-2,3-O-isopropylidene-D-ribofuranosylidene]chromium (4)
exo-Glycal 3 (3.72 g, 13.46 mmol) was dissolved in n-heptane (11 mL) at −45 °C and added to pentacarbonyl(diphenylcarbene)chromium (5.25 g, 14.65 mmol). The solution was allowed to warm to r.t. and was stirred for another 3 h until monitoring by IR indicated the consumption of the carbene complex. The solvent was evaporated, and the residue was purified by chromatography over silica gel (petroleum ether–EtO, CH2Cl2, 10:1) to give 4 as an orange oil (2.88 g, 6.36 mmol, 47%).

IR (petroleum ether): 2067 (m), 1949 (vs) cm−1.

1H NMR (250 MHz, CDCl3): δ = 7.30 (m, 5 H, Ph), 5.20 (d, J = 6.23 Hz, 1 H, H-2), 4.62 (app. t, J = 6.23 Hz, 1 H, H-3), 4.57 (s, 2 H, CH2Ph), 4.13 (dd, J = 6.34, J = 6.62 Hz, 1 H, H-4), 3.70 (dd, J = 9.4, J = 2.3 Hz, 1 H, H-5'), 3.58 (dd, J = 9.58, 6.96 Hz, 1 H, H-5), 1.46 (s, 3 H, CH3), 1.37 (s, 3 H, CH3).

1C NMR (125 MHz/CDCl3): δ = 341.5 (carbene-C), 224.0 (trans-CO), 216.1 (cis-CO), 137.3 (ipso-C), 126.6 (5 C, Ph), 112.7 (CMe2), 80.4 (C-5), 78.1 (C-4), 72.3 (C-3), 69.2 (CH2Ph), 62.0 (C-2), 27.6, 26.2, (2x, CH3).

FAB-MS: m/z (%) = 454.0 (20) M+, 370 (90, M− 3 CO), 314.0 (56, M− 4 CO).

Pentacarbonyl[1-adeno-1-deoxy-5-O-benzyl-2,3-O-isopropylidene-D-ribofuranosylidene] chromium (5)

Adenine (1.3 equiv) was added to a solution of 4 (2.88 g, 6.36 mmol) in DMF (500 mL). The flask was placed into an ultrasonic bath for several minutes to promote complete dissolution of adenine. Then the mixture was stirred for another 3 h until monitoring by IR indicated the consumption of the carbene complex. The solvent was evaporated, and the residue was purified by chromatography over silica gel (petroleum ether–EtOAc, CH2Cl2, 10:1) to give 4 as an orange oil (2.88 g, 6.36 mmol, 47%).

1C NMR (125 MHz/CHCl3): δ = 162.6 (C-2), 137.4 (ipso-C), 127.0 (Ph), 112.3 (CMe2), 84.1 (C-1), 83.8 (C-5), 80.3 (C-4), 79.6 (C-3), 73.0 (CH2OBn) 70.1 (CH2Ph), 26.8, 25.6, (2x, CH3).

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Adenine (1.3 equiv) was added to a solution of 4 (2.88 g, 6.36 mmol) in DMF (500 mL). The flask was placed into an ultrasonic bath for several minutes to promote complete dissolution of adenine. Then the mixture was stirred for 24 h. The yellow solution was...
extracted with Et₂O and dried over Na₂SO₄. After removal of the solvent the residue was purified by flash chromatography over silica gel (petroleum ether–Et₂O, 1:2) to give 2.84 g (4.83 mmol, 76%) of a yellow powder.

IR (petroleum ether): 2056 (m), 1965 (m), 1948 (vs) cm⁻¹.

¹H NMR (250 MHz, CDCl₃): δ = 10.50 (br s, 1 H, H-2''), 10.22 (s, 1 H, NH), 7.90 (s, 1 H, H-7'), 7.35–7.28 (5 H, Ph) 4.98 (app. dd, 1 H, J = 8.77, 8.2 Hz, 1 H, H-2), 4.62 (app. t, J = 6.34 Hz, 5.10, 1 H, H-3), 4.54 (s, 2 H, CH₂Ph), 4.13 (dd, J = 6.83, 6.34 Hz, 1 H, H-4), 3.71 (dd, J = 9.52, 8.2 Hz, 1 H, H-Sb), 3.54 (dd, J = 6.83, 2.93 Hz, 1 H, H-5a), 2.62 (br s, 1 H, OH), 1.42 (s, 3 H, CH₃), 1.34 (s, 3 H, CH₃).

¹³C NMR (125 MHz, CDCl₃): δ = 274.9 (carbene-C), 224.2 (C-4), 161.2 (C-4), 146.1 (C-7), 137.9 (ipso-C), 137.2 (ipso-C), 128.0 (5 C, Ph), 109.1 (C-2), 79.9 (C-3), 72.3 (C-2), 69.3, 69.5 (CH₂Ph, C-4), 25.7, 21.2, (2 s, CH₃).

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References


(9) IR-Absorptions of pentacarbonyl/diphenylcarbene/chromium: 2062 (m), 1977 (s), 1960 (vs) cm⁻¹.


(15) UV-irradiation of iminofuranosylidene complex 6 in MeOH with a 500 W sunlamp resulted in a modest yield (10%) of methyl 25-adeno-6-O-benzyl-2,5-dideoxy-3,4-O-isopropylidene-L-lyxo-hexitol-2-ulose. A single set of NMR-signals (including ¹JH,C₃,Φ = 8.04 Hz indicative of a vicinal coupling constant) suggests a diastereoselective formation of the β-C-iminoglycoside as previously observed under similar conditions for the pyranose series.¹³α