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Synthesis of dicobalt hexacarbonyl 5-*p*-tolylethynyl-2′-deoxyuridine†

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Reactions of 5-*p*-tolylethynyl-2′-deoxyuridine and 3′,5′-di-*O*-acetyl-5-*p*-tolylethynyl-2′-deoxyuridine with $Co_2(CO)_8$ in THF gave 5-*p*-tol$C_2[Co_2(CO)_6]$-2′-deoxyuridine and 3′,5′-di-*O*-acetyl-5-*p*-tol$C_2[Co_2(CO)_6]$-2′-deoxyuridine (92 and 66%).

Inert, stable molecules containing redox-active centers are valuable as probes of biological systems. In particular, transition metal complexes attached to a nucleoside, nucleotide, or oligonucleotide at site-specific locations are of interest for analytical applications (DNA/RNA sequencing, hybridization assays), therapeutic uses (anticancer, antiviral pharmaceuticals), and structural and mechanistic studies (DNA-mediated electron and energy transfer).[1,2]

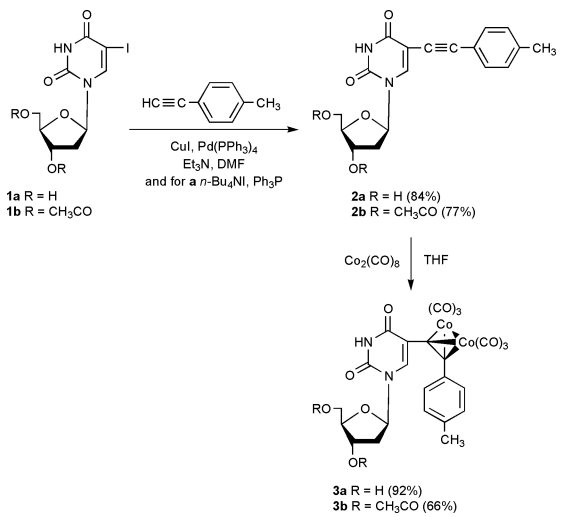
Acetylenes and their higher homologues (polyynes) have been found to promote strong electronic communication between terminal subunits and to favor rigid, rod-like structures, which have found an application in molecular wires design.[3] Interest in the utilization of the ethynyl (acetylenic) fragment for modification of nucleoside bases has resulted in a great number of contributions in recent years.[4] The linear, sp carbon chain facilitates exact positioning of the metal containing moiety for oligonucteotide arrays, and provides an opportunity for metal–nucleobase communication.

We are interested in synthetic exploration and utilization of the metal complexes covalently attached to nucleobases at non-hydrogen bonding sites. Targeted metallo-nucleosides serve as models and, after determining their basic properties, as precursors for the corresponding metal-derivatized oligonucleotides.[5] Nucleosides with a linked metal complex can subsequently be converted into phosphoramidites (building blocks for solid-phase synthesis) to access metallo-oligonucleotides.[6,7] Alternatively, modification during automated solid-phase synthesis,[8] or postmodifications of available oligonucleotides can be used to incorporate the relatively sensitive transition metal functionality.[9]

We have extended metal–alkynyl–nucleoside chemistry to the (μ-acetylene)dicobalt hexacarbonyl complexes because: (i) the alkyne C–C–C angles in this type of cluster are reduced to *ca.* 140°, placing the aryl (*p*-tolyl) sensor in a new rigid position relative to the base, (ii) the electrochemistry of relevant complexes containing the (μ-acetylene)dicobalt carbonyl unit $–C_2[Co_2(CO)_6]–$ is well documented, and provides evidence that coordination of the redox-active Co_2 cluster does not quench communication along an alkyne unit,[10] (iii) the dicobalt hexacarbonyl complex is a key intermediate for further synthetic transformations.[11]

We have prepared the 5-*p*-tolylethynyl-2′-deoxyuridine (**2a**) at room temperature by Sonogashira coupling,[12] as we also observed that elevated temperature leads to cyclization product.[13] A DMF solution of unprotected iodouridine **1a** (1.0 equiv.) and Et_3N (2.0 equiv.), when treated with excess $HC{\equiv}CC_6H_4CH_3$ (1.2 equiv.) in the presence of $Pd(PPh_3)_4$ (0.11 equiv.), *n*-Bu_4NI (1.0 equiv.), Ph_3P (1.0 equiv.), and CuI (0.1 equiv.), gave after 2.5 h and workup **2a** as a white powder in 84% yield (Scheme 1). 5-Arylalkynyl uridines with unprotected hydroxyl groups are reportedly difficult to purify,[14] and the observed yields are moderate.[15] Separation from ammonium salts is usually accomplished by protection/chromatography/deprotection,[14] quenching with ion-exchange resin,[15,16] or multiple column chromatography. Since relevant 5-alkynyl uridines are precursors for potent anti-VZV agents,[4c,15] we have optimized an isolation of **2a**. Two subsequent precipitations (MeOH and $CHCl_3$) provided material without any detectable trialkylammonium, $Pd(PPh_3)_4$, or Ph_3P impurities (by NMR). Silica gel short column chromatography ($CHCl_3$–CH_3OH) allowed the removal of traces of unreacted **1a**,‡ and afforded spectroscopically pure **2a**. The 5-*p*-tolylethynyl substituted 2′-deoxyuridine **2a** was characterized by NMR, IR, and UV–vis spectroscopy. A combination of NMR techniques (^1H, $^{13}C\{^1H\}$, ^{13}C, and COSY) allowed assignment of signals based upon the coupling constants pattern. When 3′,5′-di-*O*-acetyl-5-iodo-2′-deoxyuridine **1b** was treated in a classical manner (50 °C) with $HC{\equiv}CC_6H_4CH_3$, $Pd(PPh_3)_4$, Et_3N, and CuI, the 3′,5′-di-*O*-acetyl-5-*p*-tolylethynyl-2′-deoxyuridine (**2b**) was readily isolated by single silica gel column chromatography (hexane–ethyl acetate) in 77% yield.

As shown in Scheme 1, the acetylated 5-*p*-tolylethynyl-2′-deoxyuridine **2b** and $Co_2(CO)_8$ were combined in THF (1 : 2 mol ratio). The latter compound is known to form relatively stable dicobalt hexacarbonyl complexes, which participate in the Pauson–Khand reaction.[11] After 1.5 h, column chromatography gave a brown–red relatively air-stable powder, which showed properties consistent with the dicobalt hexacarbonyl complex of 3′,5′-di-*O*-acetyl-5-*p*-tolylethynyl-2′-deoxyuridine (**3b**), in 66% unoptimized yield. The unprotected nucleoside **2a**, which contains potentially reactive hydroxyl groups was similarly reacted. Workup gave 5-*p*-tol$C_2[Co_2(CO)_6]$-2′-deoxyuridine (**3a**) in 92% yield. The protected cobalt complex was pursued also in order to produce material suitable for X-ray



Scheme 1

† Electronic supplementary information (ESI) available: experimental section, NMR and mass spectra and cyclic voltammograms. See http://www.rsc.org/suppdata/cc/b1/b109501c/

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structural analysis. However, crystallization efforts for both **3a** and **3b** were not successful.

The ^{1}H and ^{13}C NMR spectra supported the structural assignments of **3a** and **3b**.§ First, the CoCO signals appeared at 200.5 and 199.2 for **3a** and **3b**. Second, the C≡C ^{13}C signals showed chemical shifts (96.7, 86.4 and 93.6, 81.1 ppm, DMSO-d_6 and $CDCl_3$) characteristic for phenylalkynyl–cobalt ligands.[17] Distinctive changes occurred as referred to free alkynes **2a** and **2b** (91.8, 82.1 and 94.0, 79.7 ppm, acetone-d_6 and $CDCl_3$). Third, the $-C_6H_4-$ ^{13}C signals exhibited a reversed order of chemical shifts for the *m*/*o* carbons, as established by a gated decoupling experiment for **3b**. We were unable to resolve the *i*/*p* carbon multiplicity due to the low intensity of the signals. The IR ν_{CoCO} values were essentially identical to those reported for other, chiral alkynyl–cobalt complexes (2094–2023 *vs.* 2096–2020 cm^{-1}).[18] MS spectra exhibited strong parent ions and adequate fragmentation for **3a** and **3b**. The latter complex also gave correct elemental analysis.¶ Thermal stability of the unprotected cobalt nucleoside was determined by DSC: **3a** endothermically decomposed at 125 °C (T_e) without melting.[19] Although alkynyl precursor **2a** exhibited fluorescence ($\lambda_{em}/\lambda_{ex}$ = 401/311 nm, MeOH), we were not able to observe well pronounced emission signals for **3a**.

The cobalt complexes exhibit one, irreversible oxidation potential at room temperature ($E_{p,a}$/V = 0.99, **3a**; 1.06 **3b**, CH_2Cl_2), as established by cyclic voltammetry. Both are stable in chlorinated ($CHCl_3$, 1,2-dichloroethane), polar (acetone, DMSO), or protic (MeOH) solvents, and also towards silica gel. The study towards synthetic utilization of cobalt nucleosides is in progress.

In conclusion, we have synthesized modified nucleoside bearing electrochemical 'reporter' groups.

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Notes and references

‡ This step may be omitted on the route to **3a**.

§ *NMR data*: **3a** (acetone-d_6): ^{1}H 10.32 (s, 1H, N3), 8.43 (s, 1H, H6), 7.53 (AB, *J* 8.0 Hz, 2H, *m*-$C_6H_4CH_3$), 7.19 (AB, *J* 8.0 Hz, 2H, *o*-$C_6H_4CH_3$), 6.43 (t, *J* 6.9 Hz, 1H, H1′), 4.52 (br, 1H, OH5′), 4.43 (d, *J* 2.7 Hz, 1H, OH3′), 4.24 (t, *J* 4.5 Hz, 1H, H3′), 4.06–4.02 (m, 1H, H4′), 3.83–3.68 (m, 2H, H5′), 2.32 (s, 3H, CH_3), 2.08–2.02 (m, 2H, H2′); ^{13}C{^{1}H} 200.5 (CoCO), 160.8 (C4), 150.8 (C2), 139.8 (C6), 138.8 (*i*-$C_6H_4CH_3$), 136.3 (*p*-$C_6H_4CH_3$), 130.6 and 130.2 (*m*,*o*-$C_6H_4CH_3$), 113.6 (C5), 89.2 (C4′), 86.4 (C1′), 96.7 and 86.2 ($C{\equiv}CC_6H_4$), 73.1 (C3′), 63.3 (C5′), 41.9 (C2′), 21.4 (CH_3). **3b** ($CDCl_3$): ^{1}H 9.73 (s, 1H, N3), 7.91 (s, 1H, H6), 7.43 (AB, *J* 7.8 Hz, 2H, *m*-$C_6H_4CH_3$), 7.16 (AB, *J* 7.8 Hz, 2H, *o*-$C_6H_4CH_3$), 6.32 (dd, *J* 8.6, 5.1 Hz, 1H, H1′), 5.14 (d, *J* 5.7, 1H, H3′), 4.38–4.22 (m, 2H, H5′), 4.17–4.02 (m, 1H, H4′), 2.56 (dd, *J* 14.0, 4.9 Hz, 2H, H2′), 2.35 (s, 3H, CH_3), 2.12 and 1.81 (2s, 2 × 3H, 2 $COCH_3$); ^{13}C 199.2 (s, CoCO), 170.5, 170.3 (m, 2 $COCH_3$), 160.8 (d, *J* 9.5 Hz, C4), 150.0 (d, *J* 8.7 Hz, C2), 138.5 (m, *i*-$C_6H_4CH_3$), 135.4 (dd, *J* 180.4, 2.7 Hz, C6), 135.2 (t, *J* 8.1 Hz, *p*-$C_6H_4CH_3$), 129.8 (dqnt, *J* 159.2, 5.7 Hz, *o*-$C_6H_4CH_3$), 129.3 (dd, *J* 159.4, 6.2 Hz, *m*-$C_6H_4CH_3$), 113.8 (d, *J* 3.9 Hz, C5), 93.6 (td, *J* 7.7, 2.8 Hz, $C{\equiv}CC_6H_4$), 85.5 (dm, *J* 170.8 Hz, C1′), 82.5 (dm, *J* 149.6 Hz, C4′), 81.1 (s, $C{\equiv}CC_6H_4$), 74.4 (dm, *J* 162.0 Hz, C3′), 63.9 (td, *J* 148.5, 1.7 Hz, C5′), 38.1 (dd, *J* 139.4, 131.3 Hz, C2′), 21.5 (qt, *J* 126.4, 4.2 Hz, CH_3), 21.1 (q, *J* 130.0 Hz, $COCH_3$), 20.4 (q, *J* 129.8 Hz, $COCH_3$).

¶ Anal. Calc. for $C_{28}H_{22}Co_2N_2O_{13}$: C, 47.21; H, 3.11. Found: C, 46.81; H, 3.43%.

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