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Deoxygenation of 5-*O*-benzoyl-1,2-isopropylidene-3-*O*-imidazolylthiocarbonyl-α-D-xylofuranose using dimethyl phosphite: an efficient alternate method towards a 3′-deoxynucleoside glycosyl donor

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Abstract

An efficient radical deoxygenation reaction of thiocarbonylimidazolyl activated glycoside analogue using dimethyl phosphite as hydrogen source and radical chain carrier was performed as a key step in a multi step synthesis towards a common 3-deoxy glycosyl donor for 3′-deoxynucleosides. This method has safety and cost advantages compared to the generally used radical reduction reagents.

Keywords: 3′-Deoxynucleosides; Barton–McCombie deoxygenation; Thiocarbonylimidazolyl; Dimethyl phosphite

The removal of the 3′-hydroxy group in nucleoside analogues, leading to the corresponding 3′-deoxy compounds is a well-known chemical modification, explored by several research groups in the aim to improve the antiviral and/or antineoplastic,[1–5] or more recently the anti-SARS-CoV[6,7] activities of modified nucleosides.

The chemical route of these compounds involves a deoxygenation reaction on the 3 position of the furanose moiety of either a nucleoside or a glycoside precursor. Indeed, in nucleoside and glycoside chemistry, deoxygenation is a common transformation which is generally carried out effectively by radical reduction. In the original Barton–McCombie method,[8] thionocarbonates or xanthates are efficiently reduced using tributyltin hydride (*n*-Bu_3SnH) which is the hydrogen atom source, and the corresponding tin radical (*n*-$Bu_3Sn^{\bullet}$) is the radical chain carrier. However, as this reagent is toxic, expensive and harmful for the environment and produces tin byproducts that are difficult to remove from the final product, considerable efforts were done in the development of alternate radical reagents.

Tributylgermanium hydride[9,10] and silanes, such as triethylsilane or tris-trimethylsilylsilane,[11] reveal to be as efficient as *n*-Bu_3SnH. Furthermore, they are superior reagents from ecological and practical points of view since they are less or even non-toxic and work-up procedures are easier. However, their cost is a serious drawback making their use not a cheap alternative to tin hydride.

In the beginning of the 1990s, Barton et al. reported that reagents containing a P–H bond such as dimethyl and diethyl phosphites[12] and hypophosphorous acid or its salts[13,14] are efficient hydrogen sources and chain carriers for radical reductions of various thionocarbonates and xanthates. These reagents are commercially available, cheap and far less toxic than organotin compounds, which make them almost an ideal alternative.

Since then, however not much attention was paid to the general use or development of these reagents, as only few reports resumed it.[15–17] Moreover, we would like to stress

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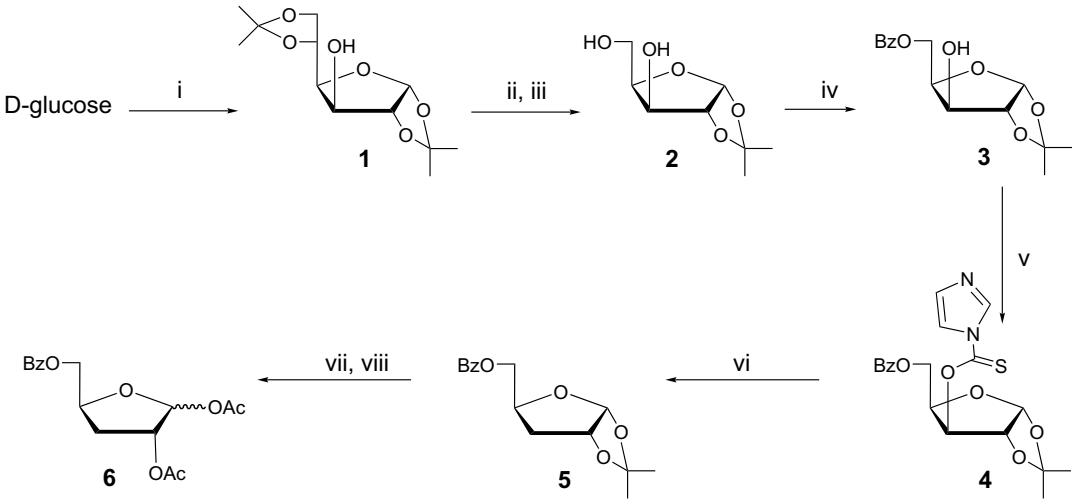
on the fact that although deoxygenation reaction is very common, particularly in nucleoside chemistry, these radical reduction reagents remain widely unpopular or even somewhat unknown despite their numerous practical advantages and low cost.[18]

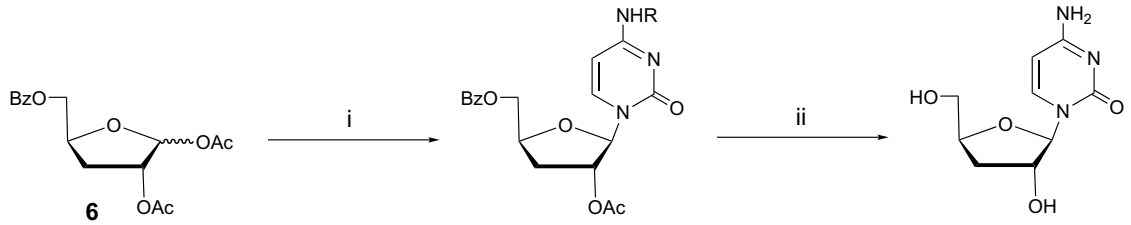
We focused on the deoxygenation reaction using dimethyl phosphite with a view to prepare some 3′-deoxy-oligoribonucleotides. Hence, we needed a universal glycosyl donor, namely, the α,β-1,2-di-*O*-acetyl-5-*O*-benzoyl-3-deoxyribofuranose **6**. This compound can be readily obtained after the radical reduction of the suitably activated analogue of the 3-hydroxy-xylofuranose **3**. Thionocarbonates[12–14,16] or xanthates[12–16] are the activators that are reported to be successfully used with the P–H bond containing reducing reagents. However, we wished to concentrate on the use of thiocarbonylimidazolyl activated compounds, as they are more easily and efficiently prepared from a simple reaction of the corresponding hydroxyl analogue with 1,1′-thiocarbonyldiimidazole (TCDI).[18–20] To our knowledge, only one case of a free radical reduction of a thiocarbonylimidazolyl nucleoside by a P–H bond containing reagent was ever reported using 10 M equiv of it and the reaction yield was rather low.[17] Thus, we decided to investigate the free radical deoxygenation of 5-*O*-benzoyl-1,2-isopropylidene-3-*O*-imidazolylthiocarbonyl-α-D-xylofuranose **4** by dimethyl phosphite as a key step reaction in a multi gram scale synthesis towards the glycosyl precursor for 3′-deoxynucleosides **6** (Scheme 1).

The 3-*O*-imidazolylthiocarbonyl derivative **4** was prepared in four steps starting from D-glucose as depicted in Scheme 1. First, hydroxyl groups 1, 2, 5 and 6 were protected as isopropylidene bridges, leading to di-acetone-D-glucose **1**. Efficient 'dehomologation' of the di-*O*-isopropylidenehexofuranose was carried out by a sequential selective acid-catalyzed hydrolysis of the terminal acetal and oxidative cleavage of the corresponding diol, followed by reduction of the resulting aldehyde, as previously reported by Robins et al.[21] The resulting xylofuranose **2**[21] was selectively benzoylated on the primary hydroxyl giving **3**[22] and after work-up the crude was directly treated with 1.2 M equiv of TCDI which reacted with the sole remaining hydroxyl providing the desired 3-*O*-imidazolylthiocarbonyl derivative **4** in good yield (58% from D-glucose) after silica gel chromatography.[23] This compound was then reacted with dimethyl phosphite and portion-added benzoyl peroxide in boiling dioxane, following Barton's protocol.[13] Reduction proceeded smoothly and the desired deoxy sugar **5**[22] was obtained after evaporation, under vacuum, of the solvents and the dimethyl phosphite excess and eventually chromatography purification.[24] It is worth noting that using only 10 M equiv of dimethyl phosphite gave low yields, and best results were obtained when 30–50 M equiv was used, as yields rose from good to excellent (80–93%). Finally, a two-step 'one-pot' procedure of acidic hydrolysis of the 1,2-*O*-isopropylidene protection followed by 1,2-*O*-acetylation, provided the expected 3-deoxy glycosyl donor **6**.[25] As an example for glycosylation, we successfully coupled **6** with either N^4-benzoyl- or N^4-acetyl-cytosine using Vorbrüggen's conditions,[26] providing 3′-deoxycytidine[5,27] with a 90% yield after ammonia deprotection (Scheme 2).

In conclusion, we report an efficient alternative for free radical deoxygenation reaction of thiocarbonylimidazolyl activated glycoside analogue using cheap and convenient dimethyl phosphite as hydrogen source and radical chain carrier. Reaction proceeds smoothly and with good yields. The present method is useful for the preparation of a common 3-deoxy glycosyl donor for 3′-deoxynucleosides. We believe that good reaction yields and safety and cost advantages of this method would make it more applicable on laboratory or industrial scale.



Scheme 1. Reagents and conditions: (i) acetone, H_2SO_4, $CuSO_4$, rt, 24 h, 80%; (ii) H_5IO_6, AcOEt, rt, 2 h; (iii) $NaBH_4$, EtOH, rt, 1 h 30, 80%; (iv) BzCl, pyridine, 0 °C, 1 h 30; (v) TCDI, 1,2-dichloroethane, reflux, 2 h, 90%; (vi) dimethyl phosphite, $(BzO)_2$, dioxane, reflux, 2 h 30, 93%; (vii) AcOH-80%, reflux, 2 h, then Na_2CO_3 neutr; (viii) Ac_2O, DMAP, pyridine, rt, overnight, 80%.



Scheme 2. Reagents and conditions: (i) N^4-acetyl or N^4-benzoyl-cytosine, BSA, CH_3CN, reflux, 1 h, then TMSOTf, rt, 5 h; (ii) NH_4OH-28%, THF/MeOH – 2:1 (v/v), 50 °C, 6 h, 90%.

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23. *NMR data for compound* **4**: ^{1}H NMR: ($CDCl_3$, 400 MHz) δ 8.30 (1H, s), 7.92 (2H, dd, $^3J = 8.5$ Hz, $^4J = 1.4$ Hz), 7.52 (1H, d, $J = 1.3$ Hz), 7.50 (1H, m, $^3J = 7.4$ Hz, $^4J = 1.3$ Hz), 7.36 (2H, t, $J = 8.0$ Hz, $J = 7.4$ Hz), 7.00 (1H, d, $J = 1.1$ Hz), 5.98 (1H, d, $J = 3.7$ Hz), 5.93 (1H, d, $J = 2.9$ Hz), 4.73–4.70 (2H, m), 4.53 (2H, m), 1.52, 1.29 (6H, 2s). ^{13}C NMR: ($CDCl_3$, 100 MHz) δ 182.2, 165.9, 136.9, 133.4, 131.0, 129.8, 129.2, 128.5, 117.7, 112.9, 104.9, 84.3, 82.8, 76.7, 61.1, 26.6, 26.2.
24. *Experimental protocol for deoxygenation step:* Compound **4** (2.3 g, 5.7 mmol) was dissolved in 60 mL of anhydrous dioxane and 27 mL of dimethyl phosphite (290 mmol, 50 mol equiv) was added. The mixture was heated to reflux and treated with six 0.5 mL portions of benzoyl peroxide (0.4 g, 3.5 mmol; dissolved in 3 mL of dry dioxane), added each 20 min. The reaction mixture was stirred under reflux for 1 h after the last addition of benzoyl peroxide, and then cooled to room temperature. It was diluted with ethyl acetate and the solvents were evaporated on an oil pump (0.2 mbar, 80 °C). The crude reaction mixture was purified on silica gel chromatography using a gradient of ethyl acetate (0–10%) in cyclohexane, providing after evaporation pure **5** as white crystals (1.46 g, 93%).
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