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Deprotection of α-imidazole/benzimidazole ribonucleosides by catalytic carbon tetrabromide initiated photolysis

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Abstract—Several protected benzimidazole and imidazole α-ribonucleosides were deprotected in excellent yield at ambient temperature using CBr_4 initiated photolysis in methanol at ambient temperature. No selectivity was observed and both trityl and isopropylidene groups were deprotected under the reaction conditions.

5,6-Dimethyl-α-D-ribofuranosylbenzimidazole,[1] the lower axial ligand in coenzyme B_{12} plays an as yet unknown role in the enzymatic activation of coenzyme B_{12} for carbon–cobalt bond homolysis. We have consequently pursued cobalamins with altered axial nucleosides in order to investigate the role, if any, of the axial base. Although some B_{12} analogues can be prepared by guided biosynthesis,[2] using fermentation of certain bacteria, many important derivatives require semi-synthesis/partial synthesis. Semi-synthesis of cobalamins[3–5] with altered axial nucleotide ligands is best achieved by coupling cobyric acid[6,7] with a suitable ribonucleoside phosphodiester. The synthesis of such phosphodiesters requires several steps, including selective glycosylation to make ribonucleosides in the α-configuration,[8–11] protection and deprotection. We have recently reported the synthesis of indoline and dimethylindoline ribonucleosides[10] in the α-configuration using 2-fluoro-1-methylpyridinium tosylate as a condensing reagent.[11] Deprotection of these unstable α-nucleosides[8–11] while retaining the α-configuration is crucial. Trityl (Tr), dimethoxytrityl (DMTr) and isopropylidene groups are commonly used for the protection of the 5-hydroxyl and 2,3-hydroxyl groups in both carbohydrate and nucleoside chemistry.[12] For α-ribonucleosides, protection of the 2′, 3′, and 5′ positions is required for selectivity in the glycosylation reaction. Strong acids such as formic acid[13] and trifluoroacetic acid (TFA)[14] are typically used for the deprotection of trityl and isopropylidene groups. Most of these methods suffer from low yields and the use of strongly acidic conditions, which can cause deglycosylation or decomposition of α-ribonucleosides.

While trityl and dimethoxytrityl ethers are selectively deprotected to the corresponding alcohols by CBr_4 in methanol at reflux under neutral reaction conditions,[15] at these temperatures imidazole ribonucleosides isomerize from the α- to the β-anomer. In this letter, we report a mild and highly efficient deprotection of trityl and isopropylidene protecting groups without any deglycosylation or anomerization, in high yield using substoichiometric amounts of carbon tetrabromide. Thus, α-ribonucleosides of imidazole and benzimidazole were readily deprotected by photoirradiation using catalytic carbon tetrabromide (CBr_4) in methanol at ambient temperature. Although selective deprotection of trityl versus isopropylidene groups of β-ribonucleosides and sugars has been achieved using photolysis,[16] the present photolysis protocol shows no selectivity in trityl/isopropylidene deprotection for the α-ribonucleosides.

The photolysis reactions were carried out in glass vials using a high pressure Xe–Hg photolysis lamp (254 nm principal wavelength) for 30 min–1.0 h at ambient temperature (Scheme 1). Complete conversion of the starting material was confirmed by TLC (methanol/methylene chloride 8:2) as well as ^1H NMR. After completion, the methanol was removed under reduced pressure, and water (10 mL) and methylene chloride (10 mL) were added. After stirring for 10 min, the aqueous layer was separated and evaporated under reduced pressure to afford a viscous oil containing the desired compound in

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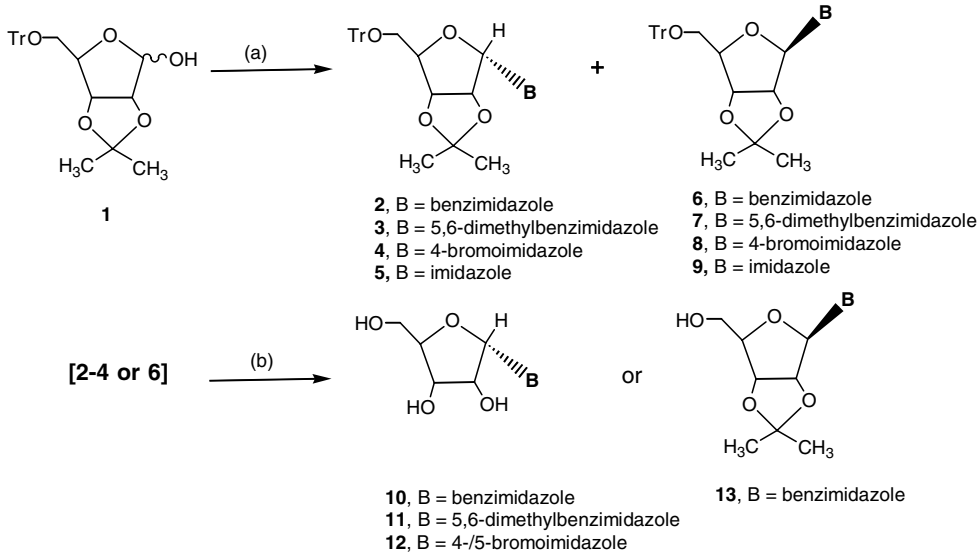
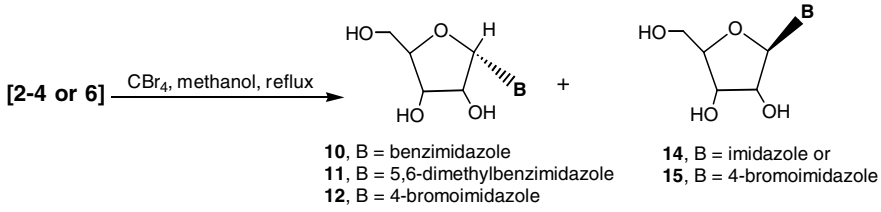


Scheme 1. Preparation and deprotection of α-benzimidazole and imidazole ribonucleosides by photoirradiation. Reagents and conditions: (a) TMS-protected benzimidazole/imidazole bases, 2-fluoromethyl pyridinium tosylate, DIEA, methylene chloride, −30 °C to 0 °C. (b) Methanol, carbon tetrabromide, 20 °C, photolysis.



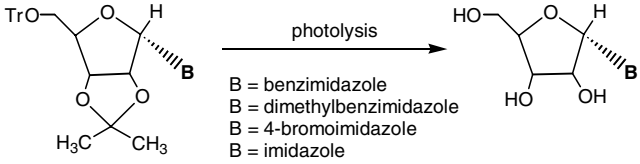
Scheme 2. Deprotection of α/β-benzimidazole and imidazole ribonucleosides by carbon tetrabromide at reflux temperature.

excellent yield. Increasing the amount of carbon tetrabromide from 0.05 to 0.5 equiv decreased the reaction time but also decreased the observed yield (Table 1). β-Ribonucleosides of benzimidazole, dimethylbenzimidazole and 2,3-*O*-(1-methylethylidene)-5-*O*-(triphenylmethyl)-α/β-D-ribofuranose[17] were also deprotected under similar conditions in yields of 80%, 85% and 80%, respectively.

In contrast, deprotection of the α-ribonucleosides of imidazole and 4-bromoimidazole with excess carbon tetrabromide (1–3 equiv) at reflux in methanol (Scheme 2) produced mixtures of α- and β-anomers (Table 2). These reactions take 5–6 h for complete removal of trityl and isopropylidene groups. With less carbon tetrabromide, the reaction is very sluggish and complete deprotection takes 10–12 h. However, in the case of the benzimidazole and 5,6-dimethylbenzimidazole α-ribonucleosides, we observed only 5% anomerization under reflux conditions, possibly due to the more bulky bases compared to the imidazole and 4-bromoimidazole α-ribonucleosides.

α-Ribonucleosides of imidazole and benzimidazole can be prepared by coupling their corresponding TMS protected bases with 2,3-*O*-(1-methylethyledene)-5-*O*-(triphenylmethyl)-α/β-D-ribofuranose[17] by using 2-fluoro-1-methylpyridinium tosylate as a condensing reagent.[18] Both corresponding α- and β-ribonucleosides can be easily separated by repeated flash silica gel chromatography and the structure and anomeric configurations of these ribonucleosides were established by 2D NMR spectroscopy (COSY, HMQC and NOESY).

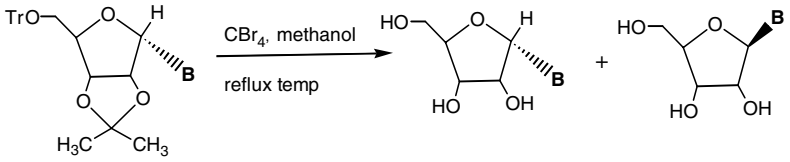
Table 1. Photolysis reaction conditions and yields



S. No.	Reactant (**B**)	CBr_4[a]	Reaction time	Yield (%)[b]
1	α-Benzimidazole	0.05	1.0 h	95
2	α-Benzimidazole[19]	0.5	20 min	75–80
3	α-5,6-DMBz[c]	0.05	1.0 h	98
4	α-5,6-DMBz[c]	0.5	10–20 min	75
5	α-Imidazole	0.05	50 min	86
6	α-4-Bromoimidazole	0.05	1.0 h	90
7	β-Benzimidazole	0.05	1.0 h	85
8	β-5,6-DMBz[c]	0.05	1.0 h	85

[a] Equiv of CBr_4.
[b] Isolated yields.
[c] 5,6-DMBz = 5,6-dimethylbenzimidazole.

Table 2. Reaction conditions and yields under reflux conditions in methanol and carbon tetrabromide



S. No.	Reactant (**B**)	CBr_4[a]	Reaction time (h)	Yield α-anomer (%)[b]	Yield β-anomer (%)[b]
1	α-Benzimidazole	1–2	5–6	95	0
2	α-Benzimidazole	0.5	10–12	85	5
3	α-5,6-DMBz[c]	2	5–6	75	0
4	α-5,6-DMBz[c]	0.5	10–12	70–80	5
5	α-Imidazole	2	4–5	60–70	30
6	α-4-Bromoimidazole	3	4–5	80	20

[a] Equiv of CBr_4.
[b] NMR yields.
[c] 5,6-DMBz = 5,6-dimethylbenzimidazole.

Acknowledgements

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19. (α-D-Ribofuranosyl)benzimidazole (**10**): A solution of 1-(5-*O*-triphenylmethyl-2,3-*O*-isopropylidene-α-D-ribofuranosyl)benzimidazole (60 mg, 0.107 mmol), and carbon tetrabromide (0.05 equiv) in methanol (1 mL) was photolysed using a high pressure Xe–Hg photolysis lamp (254 nm principal wavelength) for 30 min–1.0 h with completion of reaction being monitored by TLC. After completion, the methanol was removed under reduced pressure and the residue was dissolved in water (5 mL) and washed thoroughly with methylene chloride to remove the triphenylmethanol and carbon tetrabromide. The aqueous layer was separated and concentrated under reduced pressure afforded viscous oil in 90% yield. ^{1}H NMR (D_2O): δ 3.86 (dd, $J = 4.7$. 8.0 Hz, 1H, 5′), 3.98 (dd, $J = 2.6$, 10.0 Hz, 1H, 5′), 4.49 (t, $J = 4.7$ Hz, 1H, 3′), 4.55 (q, 1H, 4′), 4.85 (t, $J = 4.7$ Hz, 1H, 2′), 6.60 (d, $J = 4.7$ Hz, 1H, 1′), 7.60–7.64 (m, 2H, Ar), 7.75 (dd, 1H, Ar), 7.81 (dd, 1H, Ar), 9.39 (s, 1H, imidazole); ^{1}H NMR (CD_3OD): δ 3.72 (dd, $J = 4.05$. 8.5 Hz, 1H, 5′), 3.81 (dd, $J = 3.24$, 9.39 Hz, 1H, 5′), 4.34 (t, $J = 4.5$ Hz, 1H, 3′), 4.44 (q, 1H, 4′), 4.73 (t, $J = 5.27$ Hz, 1H, 2′), 6.55 (d, $J = 5.2$ Hz, 1H, 1′), 7.59–7.62 (m, 2H, Ar), 7.79–7.81 (m, 1H, Ar), 7.91–7.93 (m, 1H, Ar), 9.52 (s, 1H, imidazole); ^{13}C NMR (D_2O): δ 63.78 (CH_2, 5′), 73.33 (3′), 74.10 (2′), 88.22 (4′), 90.21 (1′), 115.61 (CH), 117.15 (CH), 129.35 (CH), 129.62 (CH), 132.58 (Cquat), 132.83 (Cquat), 142.17 (CH); HRMS: *m/z*: 251.1031 (calcd for $C_{14}H_{15}N_2O_4$; 251.1026) (M+H); MS: (FAB) *m/z* 253, 251, 133, 120.