A Facile Procedure for the Reduction of Azido Nucleosides to Amines Using Polymer Bound Triphenylphosphine

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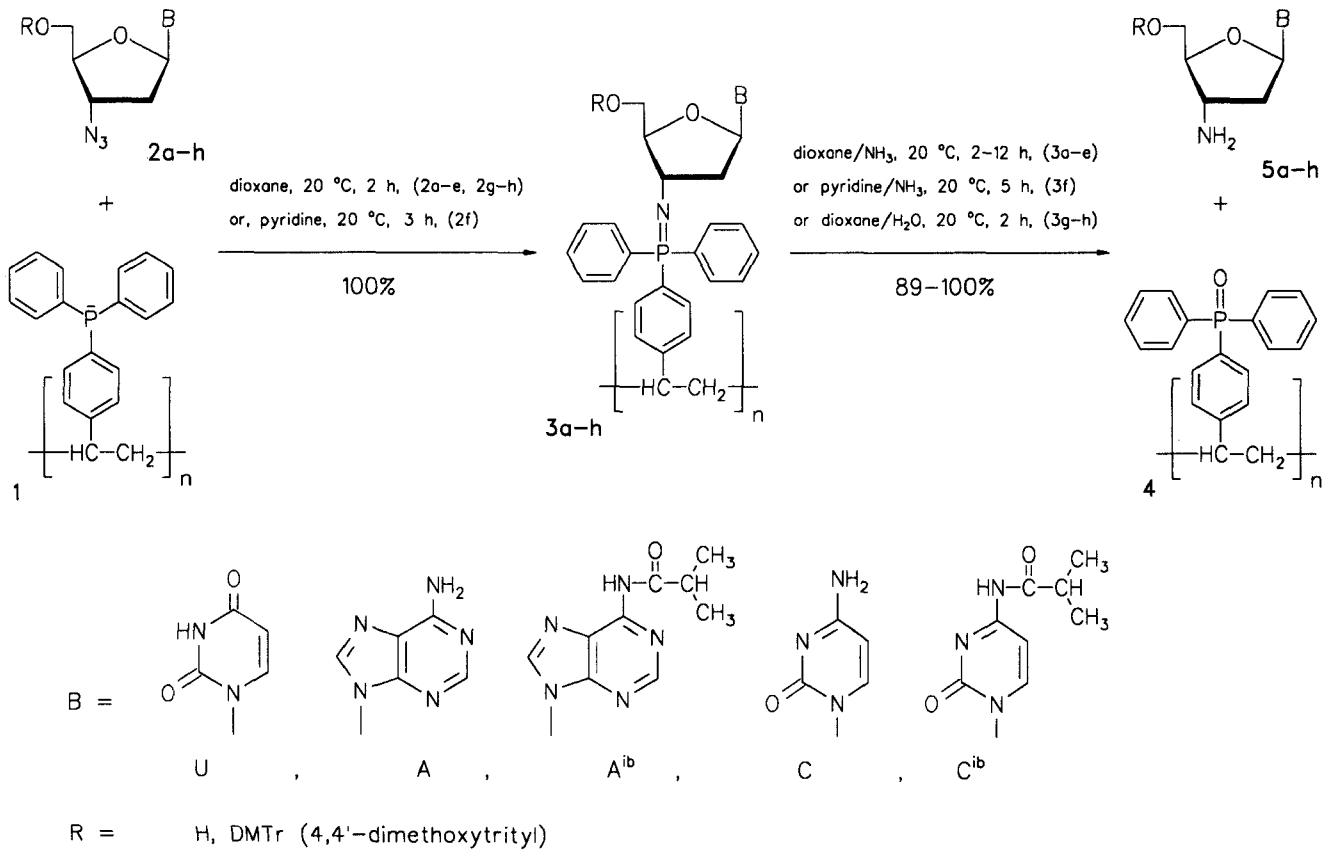
A very convenient reduction of azido nucleosides to amines under mild conditions using polystyryl diphenylphosphine resin is described. The method requiers only a filtration and evaporation process for product isolation.

Nucleosides in which the carbohydrate part is replaced by an aminosugar has been intensively investigated during the past two decades.[1-7] The reaction of nucleosides having the azido group at the sugar moiety with triphenylphosphine represents one of the most convenient synthetic methods for the clean, mild and good yielding reduction of the azido group to amines.[4-7] However, considering its utilisation in small-scale reactions, the necessary chromatographic separation of triphenylphosphine oxide, which is formed in the reaction, represents in fact, a shortcoming and sometimes a limitation of the method itself.

As a result of this we had the idea to modify the procedure by replacing triphenylphosphine with a polymer supported triarylphosphine. Therefore, we have chosen the commercially available polystyryl diphenylphosphine resin **1** for the reduction. It has already successfully been used in Wittig reactions,[8] for the acetalization of carbonyl compounds,[9] for the conversion of alcohols to alkyl chlorides[10] and for the conversion of epoxides to halohydrins.[11] The most important feature of our procedure is represented by its very simplified workup that in principle requires only filtration of the suspended polymeric material, which completely removes the polymer supported triphenylphosphine oxide **4** and evaporation of the filtrate for the isolation of pure products **5a–h**. Thus, we were able to obtain quantitative yields avoiding any chromatographic separations.

The general procedure which was performed in two steps is illustrated in the Scheme. Dioxane and pyridine were used as solvents. The reaction of 3′-azido-2′,3′-dideoxynucleosides **2a–h** with the polystyryl diphenylphosphine resin **1** leads to the formation of the phosphine imines **3a–h** which were hydrolysed by addition of either concentrated ammonia or water.

Dioxane was used as the solvent for the reduction of unprotected 3′-azido-2′,3′-dideoxynucleosides **2a–c** and base protected compounds **2d–e, 2g–h**. The hydrolysis was performed using either concentrated ammonia in



Scheme

case of compounds **2a–e** or water for compounds **2g–h**. The use of water instead of concentrated ammonia keeps the base protection intact. The 5′-protected 3′-azido-2′,3′-dideoxynucleoside **2f** was reduced in pyridine as solvent and the hydrolysis was achieved by adding concentrated ammonia. Thus, we were able to reduce also protected nucleosides in almost quantitative yields without cleaving the protecting group. The purity of the products **5a–h** was proved by reverse phased HPLC and ^{1}H NMR spectroscopy. Data were completely identical with authentic samples prepared by traditional reductions[1–5] (Table). The advantage of having a reaction which requires only a filtration and evaporation process for product isolation is not diminished by the higher cost of polystyryl diphenylphosphine resin in comparison with triphenylphosphine, particularly if one considers that the polymer bound phosphine oxides can be readily reduced to the phosphine form with trichlorosilane.[8,10] The high yield and the simplicity of the procedure demonstrate its advantage compared to the palladium-catalyzed reduction introduced by Horwitz[14] and Prusoff.[15]

All reagents were obtained commercially and used without further purification. Dioxane and pyridine (containing less than 0.01% H_2O) were obtained from Fluka AG (Switzerland) and stored over 4Å molecular sieves. The preparation of the different azido nucleosides was carried out according to procedures described in the literature.[1–5] Polystyryl diphenylphosphine resin **1** was purchased from Fluka AG (Switzerland). HPLC was performed on Shimadzu LC-6B system with an UV detector operating at 260 nm. Columns were packed with RP18 and eluted with 40 mM KH_2PO_4 (pH 4.2) containing a linear gradient of MeCN from 0% to 4% in 20 min and from 4% to 30% in 25 min. ^{1}H NMR was performed using a Bruker AM 300 spectrometer.

Reduction of Unprotected and Base Protected 3′-Azido-2′,3′-dideoxynucleosides 2a–e and 2g–h Using Polymer Supported Triphenylphosphine 1; General Procedure:

Polymer supported PPh_3 **1** (0.33 g, loaded with ca. 3 mmol PPh_3/g resin) was suspended in anhydr. dioxane (5 mL) and the appropriate 3′-azido-2′,3′-dideoxynucleoside **2** (200 μmol) was added. The suspension was slightly shaken for 2 h at r.t. After that time concentrated ammonia (4 mL, 32%) (for **2a–e**) or H_2O (2 mL) (for **2g–h**) was added, respectively. After shaking for another 2 h, the suspension was filtered and the residual solid was washed with H_2O (3 × 10 mL). The ammonolysis was performed overnight to deprotect the nucleobases completely as it is required for compound **2d–e**. The solution was filtered and lyophilised to give the amino nucleosides as white powders in almost quantitative yield (Table).

Reduction of 5′-Protected 3′-Azido-5′-dimethoxytrityl-2′,3′-dideoxynucleoside 2f Using Polymer Supported Triphenylphosphine 1; General Procedure:

Polymer supported PPh_3 **1** (0.33 g, loaded with ca. 3 mmol PPh_3/g resin) was suspended in anhydr. pyridine (5 mL) and the 3′-azido-5′-dimethoxytrityl-2′,3′-dideoxynucleoside (**2f**; 111 mg, 200 μmol) was added. The suspension was slightly shaken for 3 h at r.t. After that time concentrated ammonia (4 mL, 32%) was added. The mixture was shaken for another 5 h, filtered and the residual solid was washed with $CHCl_3$ (3 × 10 mL). The combined organic layers were evaporated under reduced pressure to afford 3′-amino-5′-dimethoxytrityl-2′,3′-dideoxynucleoside **(5f)** as a colorless oil; yield: 94 mg (89%).

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Table. Reduction of Azides **2** to Amino Nucleosides **5** Using Polymer Bound Triphenylphosphine

Azide	R	B	HPLC Retention Time of **2** (min)	Reaction Time (h)	Product	R	B	Yield (%)	HPLC Retention Time of **5** (min)	^{1}H NMR (DMSO-d_6/TMS) δ, J (Hz)
2a[5]	H	U	14.70	2 + 2	**5a**[1,2]	H	U	~100	2.13	2.05 (m, 2H, H-2′), 3.36 (m, 3H, H-4′ + 3′-NH_2), 3.58 (m, 3H, H-3′, H-5′), 5.60 (d, 1H, J = 8.0, H-5), 6.06 (t, 1H, J = 5.8, H-1′), 7.91 (d, 1H, J = 8.0, H-6)
2b[3,12]	H	A	–	2 + 2	**5b**[3,4]	H	A	98	7.02	2.67 (m, 2H, H-2′), 3.68–4.10 (m, 4H, H-3′, 4′, 5′), 6.31 (dd, 1H, $J_{1',2'}$ = 5.0, $J_{1',2''}$ = 6.5 H-1′), 7.95 (s, 11H, H-2), 8.20 (s, 1H, H-8)[a]
2c[5]	H	C	–	2 + 2	**5c**[1,2]	H	C	~100	1.90	2.00 (m, 2H, H-2′), 3.31 (m, 3H, H-4′ + 3′-NH_2), 3.59 (m, 3H, H-3′, 5′), 5.70 (d, 1H, J = 7.5, H-5), 6.09 (t, 1H, J = 5.8, H-1′), 7.10 (br s, 2H, 4-NH_2), 7.85 (d, 1H, J = 7.5, H-6)
2d[b]	H	A^{ib}	20.54	2 + 12	**5d**[4]	H	A	93	7.02	see **5b**
2e[b]	H	C^{ib}	20.66	2 + 12	**5e**[1,2]	H	C	94	1.90	see **5c**
2f[c]	DMTr	U	–	3 + 5	**5f**	DMTr	U	89	–	2.26 (m, 2H, H-2′), 3.47 (m, 2H, H-5′), 3.69 (m, 2H, H-3′, 4′), 3.80 (s, 6H, OCH_3), 5.39 (d, 1H, J = 8.1, H-5), 6.18 (dd, 1H, $J_{1',2'}$ = 3.4, $J_{1',2''}$ = 6.6, H-1′), 7.95 (d, 1H, J = 8.1, H-6)[d]
2g[b]	H	A^{ib}	20.54	2 + 2	**5g**	H	A^{ib}	~100	–	–
2h[b]	H	C^{ib}	20.66	2 + 2	**5h**	H	C^{ib}	98	15.12	1.04 (d, 6H, J = 6.8, CH_3), 2.23 (m, 3H, H-2′, CH), 2.72 (m, 2H, H-5′), 3.60 (m, 2H, H-3′, 4′), 5.96 (dd, 1H, $J_{1',2'}$ = 3.7, $J_{1',2''}$ = 6.6, H-1′), 7.20 (d, 1H, J = 7.5, H-5), 8.43 (d, 1H, J = 7.5, H-6)

[a] Measured in D_2O.
[b] The protection of the exocyclic amino group of **2b** and **2c** was performed according to standard procedure.[13]
[c] The 5′-hydroxyl function was protected using 4,4′-dimethoxytrityl chloride.[13]
[d] Measured in $CDCl_3$.

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