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Photochemistry on Soluble Polymer Supports: Synthesis of Nucleosides

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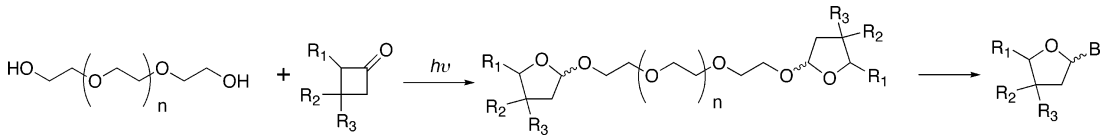
ABSTRACT



A new soluble polymer support synthesis of nucleosides is described. The photochemical ring expansion of cyclobutanones in the presence of poly(ethylene glycol) (PEG) results in polymer-supported ribosides. These photoadducts can be cleaved from the polymer under Vorbrüggen coupling conditions with TMS-protected purines and pyrimidines to give ribonucleosides. The method has been extended to include modified PEGs with dendritic end-groups in order to improve the loading levels for these coupling reactions.

The use of polymer supports has been the backbone of combinatorial chemistry and the production of chemical libraries for the identification of lead compounds of medicinal interest.[1] The development of a new nucleoside synthesis based on the photochemical ring expansion of cyclobutanones[2] has prompted us to adapt such methodology to a polymer support approach. Whereas cross-linked polystyrene beads have been used in solid-phase synthesis,[3] our earlier attempts to use these as supports for cyclobutanone photochemistry were not encouraging after observation of the low efficiency for photoconversion. This is largely due to light scattering and competing chromophore absorption associated with the resin. Furthermore, photodegradation of the polymer backbone was also observed. To circumvent these problems, we investigated the use of soluble polymer supports[4] for the key photochemical step in order to reinstate the advantages of homogeneity used in synthetic photochemistry. We chose poly(ethylene glycol) (PEG) as the support since these polymers do not possess interfering chromophores that could mask the cyclobutanone carbonyl group. These polymers are photostable and commercially available as polydispersed mixtures with a range of molecular weights. Furthermore, these polymers are recyclable and inexpensive. We have also prepared a class of modified PEGs containing dendritic end groups based on glycerol and pentaerythritol in order to improve loading capacities of these resins and yet maintain the attractive solubility properties of commercial PEG.[5]

A general method for preparation of nucleosides involves the use of the Vorbrüggen coupling of *O*-glycosides with TMS-protected purines or pyrimidines in the presence of a Lewis acid.[6] In the current investigation, we report the preparation of *O*-ribosides attached to both commercial and modified PEG by photochemical ring-expansion of cyclobutanones and the coupling of these ribosides with silylated purines and pyrimidines under Vorbrüggen coupling conditions. The photochemistry of cyclobutanones in the presence of alcohols gives *O*-ribosides as one of two principal pathways.[7] This is accompanied by moderate amounts (up

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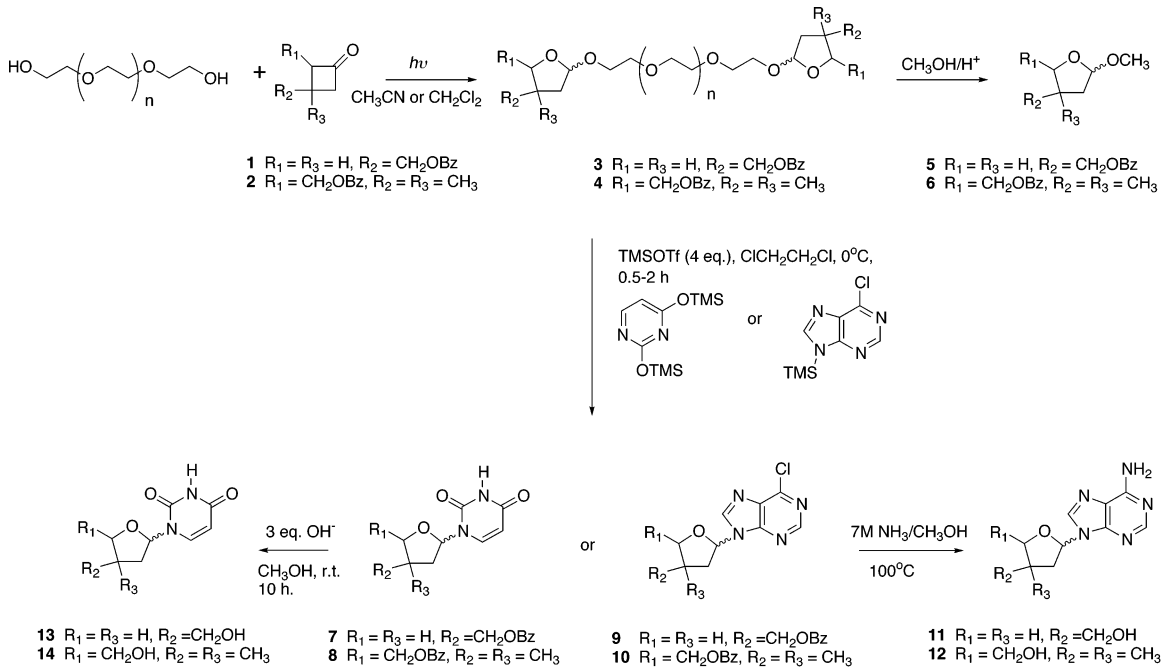

1 $R_1 = R_3 = H$, $R_2 = CH_2OBz$
2 $R_1 = CH_2OBz$, $R_2 = R_3 = CH_3$
3 $R_1 = R_3 = H$, $R_2 = CH_2OBz$
4 $R_1 = CH_2OBz$, $R_2 = R_3 = CH_3$
5 $R_1 = R_3 = H$, $R_2 = CH_2OBz$
6 $R_1 = CH_2OBz$, $R_2 = R_3 = CH_3$
13 $R_1 = R_3 = H$, $R_2 = CH_2OH$
14 $R_1 = CH_2OH$, $R_2 = R_3 = CH_3$
7 $R_1 = R_3 = H$, $R_2 = CH_2OBz$
8 $R_1 = CH_2OBz$, $R_2 = R_3 = CH_3$
9 $R_1 = R_3 = H$, $R_2 = CH_2OBz$
10 $R_1 = CH_2OBz$, $R_2 = R_3 = CH_3$
11 $R_1 = R_3 = H$, $R_2 = CH_2OH$
12 $R_1 = CH_2OH$, $R_2 = R_3 = CH_3$

to 30%) of cycloelimination products. The use of a polymer support such as PEG would enable the facile separation of the ring-expanded ribosides from these cycloelimination byproducts by precipitation of the polymer upon dilution with diethyl ether.[4] Furthermore, the Vorbrüggen coupling of the polymer-supported riboside enables both the cleavage and base substitution steps to occur by the same process.

Irradiation of cyclobutanones **1** and **2** (2−3 equiv per OH group in PEG) in acetonitrile or methylene chloride solutions containing PEG diol (MW 3400) resulted in photoadducts **3** and **4**, respectively.[8] Loading levels were determined by two independent methods: (1) methanol cleavage and recovery of methyl acetals **5**[9] and **6** or (2) NMR integration of the signals associated with the acetal or benzyl protons with those of the backbone methylene protons of PEG. The former method gives loading levels of 0.12−0.21 mmol/g for **3** (21−36% of theoretical) and 0.06−0.15 mmol/g for **4** (10−26%). The NMR integration method gives loading levels of 0.48 mmol/g (83% of theoretical) for **3** and 0.416 mmol/g (72% of theoretical) for **4.** Loading levels as determined by the chemical method represent lower limits since aromatic signals associated with the benzoate ester groups were observed for the residual PEG, indicating that cleavage of the tetrahydrofuranosides of polymer-supported substrates **3** and **4** under the methanolysis conditions was not complete and that other acid-catalyzed transformations of these acetals (e.g., ring-opening) were taking place competitively.

Reaction of photoadducts **3** and **4** with bis(trimethylsilylated) uracil or *N*-trimethylsily-6-chloropurine in the presence of trimethylsilyl triflate in 1,2-dichloroethane (typical Vorbrüggen coupling conditions[6]) gave the corresponding uracils **7** and **8**, respectively, or purines **9** and **10**, respectively, in yields ranging from 42 to 70%.[10] These conversions were comparable in efficiency to the transformations of methoxy acetals **5** and **6** to the same nucleosides under the Vorbrüggen conditions. Anomeric mixtures were obtained that showed some stereoselectivity. This selctivity differed slightly from that observed in the nucleosides derived from methoxy acetals **5** and **6** (see Table 1). The α- and

Table 1. Yields[a] and Stereoselectivity of Vorbrüggen Coupling Products

compd	% yields (α:β)[b]	deprotection products	% yields[c]
7 (from **3**)	42 (1.4:1)	**13α**	86
7 (from **5**)	83 (1.4:1)	**13*β***	94
8 (from **4**)	66 (1:1)	**14α**	91
8 (from **6**)	73 (1:1)	**14*β***	80
9 (from **3**)	61 (1:2)	**11α**	76
9 (from **5**)	25 (1:2.4)	**11*β***	85
10 (from **4**)	52 (1:1)	**12α**	65
10 (from **6**)	27.6 (3.7:1)	**12*β***	67

[a] Isolated yields. [b] Obtained from integration of ^{1}H NMR spectra of the anomeric mixture. [c] Yields for the deprotection step.

β-anomers (trans and cis, respectively) were separated at this stage by silica gel chromatography, and the stereochemistry assigned for **7**−**10** was based on the splitting patterns associated with the anomeric *N*-acetal proton.[11] Furthermore, the known benzoate-protected derivatives **7α** and **7*β*** showed ^{1}H NMR spectra that were similar to those reported in the literature.[9] Deprotection of the benzoate groups in anomeri-

(8) Typical reaction conditions for the preparation of **3** and **4**: 10.0 g (2.9 mmol) of HO−PEG_{3400}−OH (dried at 80° C under high vacuum for 30 min, 5.88 mmol of free OH groups) was dissolved in 500 mL of CH_3CN followed by addition of 6 mmol of cyclobutanone **1** or **2**. The solution was purged with argon and irradiated in nine Pyrex tubes using a medium-pressure Hg lamp (Hannovia, 450 W) for 20 h. After the solution was concentrated to 40−60 mL, cold anhydrous ether was added and diluted to 800 mL whereupon the polymer precipitated and was filtered off and subjected to ^{1}H NMR analysis.

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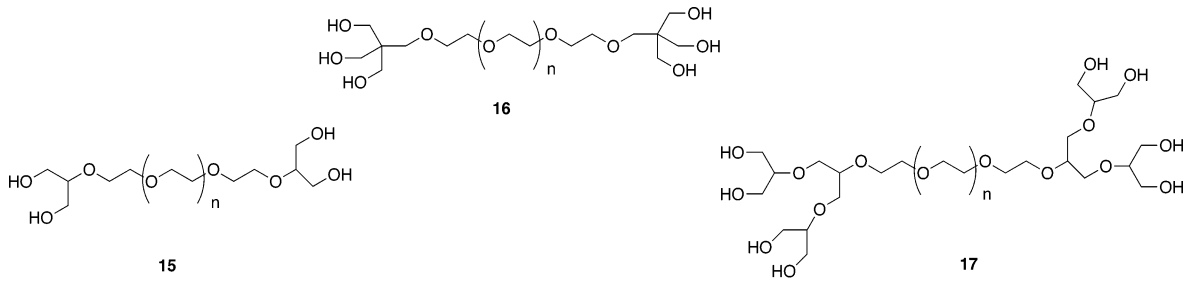

cally pure **7** and **8** was accomplished with methanolic hydroxide ion solutions, whereas deprotection and amination of **9** and **10** proceeded efficiently in 7 M methanolic ammonia solutions at 100 °C. The resultant deprotected nucleosides **11**−**14** were obtained anomerically pure.[12] Loading levels could be increased to about 85% of theoretical by the use of excess (3 equiv) cyclobutanone substrate. Nevertheless, the inherently limiting loading capacity of commercial PEG with only two terminal OH groups does not rival that for the functionalized cross-linked polystyrene resins or poly(vinyl alcohol) (PVA).[4] Our substrates are not suitable for coupling to PVA or alcohol dendrimers[13] because of the inefficient coupling of the photochemically generated oxacarbenes to secondary or tertiary alcohols. We have recently investigated the use of modified PEGs with dendrimeric end units based on glycerol or pentaerythritol[14] as soluble polymer supports in order to improve the low loading capacities of commercial PEG.[5] PEG hexitol **16** was prepared by coupling of pentaerythritol with PEG dimesylate, whereas polyols **15** and **17** were obtained from coupling of 1,3-dibenzyloxyglycerol and 1,3-bis(1,3-dibenzyloxyglyceroxy)-glycerol, respectively, with PEG dimesylate followed by deprotection of benzyl using hydrogenolysis.[5] The loading levels for modified PEGs **15**−**17**[5] were measured for the coupling of the photochemically derived carbene from ketone **2**. Although some improvement in loading levels is observed for **16** and **17** (see Table 2), these are not reflected with respect to their theoretical loading capacities. This observation, which has been observed for other coupling reactions,[5] is attributed to intramolecular hydrogen bonding and steric effects. Although conversion efficiencies can be improved in principle by using a stoichiometric excess of PEG, the hygroscopic nature of these polyethers along with the competing coupling reaction of the oxacarbene with water limits this approach. Thus, the use of modified PEGs with high loading levels (increased density of attached substrates) would represent a more efficacious method for anhydrous polymer support reactions.

Table 2. Loading Levels for Photochemical Coupling of Ketone **2** with Resins **15**−**17**

polymer	theoretical capacity (mmol/g)	measured loading (mmol/g)[a]
$PEG_{3200}(OH)_2$	0.59	0.42
$PEG(OH)_4$ (**15**)	1.12	0.48
$PEG(OH)_6$ (**16**)	1.64	0.88
$PEG(OH)_8$ (**17**)	2.07	1.12

[a] Loading levels were determined by ^{1}H NMR integration using the polymer backbone signal as an internal standard.

In summary, it has been shown that cyclobutanones can photoinsert into PEG (MW 3400) forming photoadducts that can act as polymer-supported glycosyl donors in Vorbrüggen coupling reactions to give ribonucleosides. This method has the advantage of by-passing the separation of the cyclo-elimination products associated with the photochemical step, thus eliminating time-consuming chromatography methods and the use of costly and environmentally unfriendly solvents. The inherently low loading levels for this coupling with commercial PEG can be improved with the use of modified PEGs with dendritic end-groups based on glycerol and pentaerythritol. The low cost and recyclable properties of PEG make these attractive candidates as supports for automated combinatorial synthesis of nucleosides. We are presently looking at other chemically modified PEGs in order to improve loading levels for the key photochemical coupling step.

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(10) Typical procedure: a suspension consisting of 6-chloropurine (0.67 g, 4.32 mmol), a few crystals of ammonium sulfate, hexamethyldisalazane (11.1 mL), and trichloromethylsilane (1.1 mL) was heated to reflux under argon until a clear solution was obtained. The volatile compounds were evaporated off, and the residue was coevaporated twice with 8 mL of dry toluene. The resulting mixture was cooled to room temperature and dissolved in 15 mL of 1,2-dichloromethane to which was added PEG−acetal **3** (3.48 g, 1.02 mmol, dried by coevaporation with 30−40 mL of toluene) and trimethylchlorosilane (0.14 mL, 1.0 mmol) in 20 mL of 1,2-dichloroethane under argon. To this mixture was added trimethylsilyl triflate (0.66 mL, 2.88 mmol), and the mixture was heated to reflux for 2 h. After cooling to room temperature, the solution was diluted with acetonitrile (30 mL) and the reaction quenched with 10 mL of saturated $NaHCO_3$. After stirring for 30 min, the organic layer was separated and dried over Na_2SO_4. After the solution was concentrated, cold anhydrous ether was added whereupon the polymer precipitated out and was filtered off. The filtrated was evaporated, and the residue was chromatographed on preparative TLC plates (repeated elution with 1:1 hexane/ethyl acetate) to give 0.088 g (0.24 mmol) of **9**α and 0.171 g (0.48 mmol) of **9**β.

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