A New Alkylation Reagent for Seleno- and Thio-Substituted Nucleosides and Related Compounds

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The mixture of dialkyl disulfide (or diselenide) and tri-*n*-butylphosphine was found to be a new alkylation reagent for seleno- and thio-substituted nucleosides and related compounds.

5′-Deoxy-5′-(methylthio)adenosine is known to inhibit the transmethylation reactions of *S*-adenosyl-L-methionine in vitro.[1,2] Its analogues were usually prepared by multistep syntheses.[3-5] Recently, a convenient method was reported for the synthesis of 5′-*S*-alkylthio-5′-deoxyribonucleosides and nucleotides.[6,7] For example, after treatment of adenosine with dimethyl disulfide and tri-*n*-butylphosphine in DMF for 24 h, 5′-*S*-methylthio-5′-deoxyadenosine was isolated in 73% yield.[7] However, in application of this reaction to synthesize some 5′-*S*-alkylthio-5′-deoxy-6-thio (or seleno) ribonucleosides from the corresponding 6-thio (or seleno) ribonucleosides, we have found that the reaction took an unexpected course.

After treatment of 6-seleno-9-(β-D-ribofuranosyl)purine[8,9] with excess of dimethyl disulfide and tri-*n*-butylphosphine in DMF at room temperature for 2 h, instead of the expected 5′-*S*-methylthio-5′-deoxy-6-selenoinosine, 6-methylseleno-9-(β-D-ribofuranosyl)purine (I)[10] was isolated in 63% yield. Other examples of this reaction are indicated in Scheme I and Table I. Structures of these compounds were verified by elemental analysis, uv, and NMR data and compared with authentic samples.

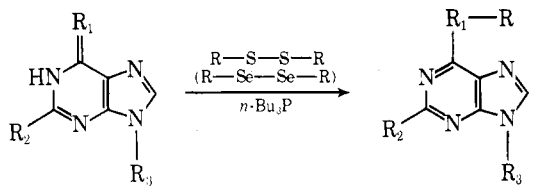
In order to explore the limitation of this new methylation reagent, 6-selenopurine was treated with a variety of disulfides (or diselenides) and tri-*n*-butylphosphine. After treatment of 6-selenopurine with dibenzyl disulfide and tri-*n*-butylphosphine in DMF for 2 h, ultraviolet spectral monitoring indicated that 6-selenopurine [λ_{max} (MeOH) 362 nm] was completely converted to 6-benzylselenopurine [λ_{max} (MeOH) 302 nm]. However, after the mixture was distilled in vacuo at 125 °C and the residue washed with petroleum ether and then recrystallized from H_2O, the product isolated was 6-benzylthiopurine [λ_{max} (MeOH) 292 nm]. This unexpected side re-

Table I. Alkylthio- and Alkylselenopurines Prepared by the Reaction of Thio- and Selenopurines with a *n*-Butylphosphine and Dialkyl Disulfide[a]

Thio- (or seleno-) purines	Dialkyl disulfide	Product	Reaction time	Yield %	NMR, δ
6-Seleno-9-(β-D-ribofuranosyl)purine[8,9]	Me-S-S-Me	I[10]	2 h	63	8.77 (1 H) 8.73 (1 H) 6.07 (1 H) 2.60 (3 H)
6-Selenopurine[12]	Me-S-S-Me	II[12]	Overnight	50	8.77 (1 H) 8.54 (1 H) 2.63 (3 H)
6-Mercaptopurine[13]	Me-S-S-Me	III[20]	Overnight	54	8.70 (1 H) 8.43 (1 H) 2.70 (3 H)
6-Mercaptopurine riboside[14]	Me-S-S-Me	IV[21,22]	4 h	12	8.77 (1 H) 8.71 (1 H) 6.07 (1 H) 2.71 (3 H)
6-Selenoguanosine[10,15,16]	Me-S-S-Me	V[10]	3 h	32	8.21 (1 H) 6.53 (2 H) 5.85 (1 H) 2.50 (3 H)
8-Selenoguanosine[17]	Me-S-S-Me	VI[17]	1 h	33	6.35 (2 H) 5.68 (1 H) 2.48 (3 H)
4-Thiouracil[18,19]	Me-S-S-Me	VII[23]	Overnight	35	7.43 (1 H) 6.18 (1 H) 2.48 (3 H)
6-Seleno-9-(β-D-ribofuranosyl)purine 3′,5′-cyclic phosphate[9,16]	Me-S-S-Me	VIII[9]	2 h	75	8.73 (1 H)[9] 8.51 (1 H) 2.19 (3 H) 8.70 (1 H)
6-Mercaptopurine[13]	Bzl-S-S-Bzl	IX[24]	2 days	50	8.40 (1 H) 7.27 (5 H) 4.67 (2 H) 8.70 (1 H)
6-Selenopurine[12]	Bzl-Se-Se-Bzl	X	2 days	45	8.40 (1 H) 7.27 (5 H) 4.70 (2 H)

[a] Satisfactory analytical data (±0.4% for C, H, N) for all new compounds (I, II, III, VI, IX, X) were submitted for review.

Scheme I

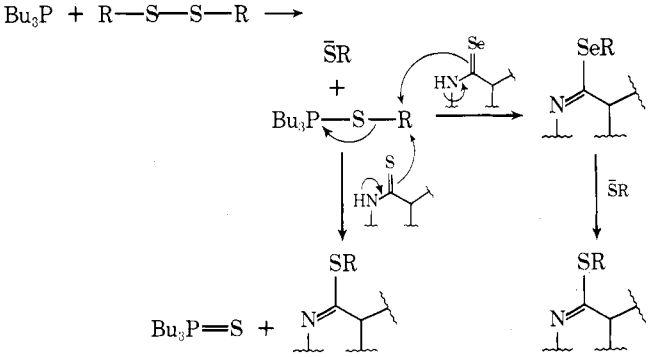


I-X

I	$R = CH_3$,	R_1 = Se,	R_2 = H,	R_3 = β-D-ribofuranosyl
II	$R = CH_3$,	R_1 = Se,	R_2 = H,	R_3 = H
III	$R = CH_3$,	R_1 = S,	R_2 = H,	R_3 = H
IV	$R = CH_3$,	R_1 = S,	R_2 = H,	R_3 = β-D-ribofuranosyl
V	$R = CH_3$,	R_1 = Se,	$R_2 = NH_2$,	R_3 = β-D-ribofuranosyl
VI	8-seleno-guanosine			8-methylseleno-guanosine
VII	4-thiouracil			4-methyl-thiouracil
VIII	$R = CH_3$,	R_1 = Se,	R_2 = H,	R_3 = 3′,5′-cyclic phosphoribosyl
IX	$R = C_6H_5CH_2$,	R_1 = S,	R_2 = H,	R_3 = H
X	$R = C_6H_5CH_2$,	R_1 = Se,	R_2 = H,	R_3 = H

action is presumably due to the fact that the benzylseleno group was displaced by the benzylthio group at elevated temperatures. Indeed, when 6-benzylselenopurine was treated with dibenzyl disulfide and tri-*n*-butylphosphine in DMF and the reaction mixture was distilled at 125–130 °C, 6-benzylthiopurine was isolated. 6-Benzylselenopurine also reacted with benzyl mercaptide anion in refluxing DMF to give 6-benzylthiopurine. Treatment of 6-mercaptopurine with dibenzyl disulfide and tri-*n*-butylphosphine gave 6-benzylthiopurine as expected. Likewise, 6-selenopurine reacted with dibenzyl diselenide and tri-*n*-butylphosphine to give 6-benzylselenopurine.

The mechanism of this alkylation reaction is probably similar to those proposed by Kharasch et al.[11] for the dealkylation of dialkyl disulfide by mercaptide anion and can be shown as follows:



These results demonstrate that the mixture of dialkyl disulfide (or deselenide) and tri-*n*-butylphosphine was a new alkylation reagent for seleno- and thio-substituted nucleosides and related compounds.

Experimental Section

Ultraviolet spectra were determined on a Perkin-Elmer Model 402 spectrophotometer. NMR spectra were measured on a Varian A-60A spectrometer in Me_2SO-d_6 with Me_4Si as the internal standard. Elemental analyses were performed by Midwest Microlab, Indianapolis, Ind.

In a typical experiment, a solution of 400 mg (1.15 mmol) of 6-seleno-9-(β-D-ribofuranosyl)purine,[8,9] 1 g (10 mmol) of dimethyl disulfide, and 2 g (10 mmol) of tri-*n*-butylphosphine in 5 ml of DMF was stirred at room temperature for 2 h. The solution was evaporated and the oily residue was distilled at reduced pressure. Ether was added into the residue and the precipitates were filtered by suction and dried to give 250 mg (63%) of I.[10] The analytical sample was recrystallized from H_2O.

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Registry No.—I, 30902-29-5; II, 58540-76-4; III, 50-66-8; IV, 342-69-8; V, 30902-27-3; VI, 55921-92-1; VII, 35551-31-6; VIII, 56477-18-0; IX, 724-34-5; X, 58540-77-5; 6-seleno-9-(β-D-ribofuranosyl)purine, 40093-99-0; 6-selenopurine, 5270-30-4; 6-mercaptopurine, 50-44-2; 6-mercaptopurine riboside, 653-58-7; 6-selenoguanosine, 29411-74-3; 8-selenoguanosine, 55921-90-9; 4-thiouracil, 591-28-6; 6-seleno-9-(β-D-ribofuranosyl)purine 3′,5′-cyclic phosphate, 56477-08-8; Me-S-S-Me, 624-92-0; Bzl-S-S-Bzl, 150-60-7; Bzl-Se-Se-Bzl, 1482-82-2; tri-*n*-butylphosphine, 998-40-3.

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