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Synthetic Nucleosides and Nucleotides. XIII.[1] Stannic Chloride Catalyzed Ribosylation of Several 6-Substituted Purines

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Condensation of adenine (**1a**) with 1-O-acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose (**2a**) in acetonitrile in the presence of stannic chloride at room temperature gave blocked nucleoside. After removal of the benzoyl group, adenosine (**4a**) was obtained in 78% overall yield. When 1,2,3,5-tetra-O-acetyl-β-D-ribofuranose (**2b**) was used instead of **2a** in the same reaction, 2′,3′,5′-tri-O-acetyladenosine (**3b**) was obtained in 77% yield. In both cases, the α-isomer or 1-, 3- or 7-riboside could not be detected in the reaction.

In an application of this reaction, 6-chloropurine (**1b**) and purin-6-yl benzyl disulfide (**1c**) were coupled with **2a** or **2b** followed by reaction with thiourea or β-mercaptoethanol to give 2′,3′,5′-tri-O-acyl-6-thioinosine (**3c**). Coupling of 6-methylthiopurine (**1d**) with **3a** after deblocking of the acyl group yielded 9-β-D-ribofuranosyl-6-methylthiopurine in 75% yield. In addition, 2,6-dichloropurine (**1e**) coupled with **2b** under the same conditions to give 9-β-D-ribofuranosyl-2,6-dichlororopurine tri-O-acetate in 81% yield.

Keywords——stannic chloride; ribosylation; adenine; 6-mercaptopurine riboside; 6-chloropurine; purin-6-yl benzyldisulfide

Several methods have been proposed for the synthesis of purine nucleosides utilizing the 1-O-acylated sugar derivatives rather than the less stable glycosyl halides.[3–7] More recently, various elegant stannic chloride-catalyzed glycosylations of silylated purine with fully acylated sugars have been reported.[8,9] However, it is still necessary to develop a simpler and more general method for the synthesis of purine nucleosides having biological activity.

A versatile alternative to these synthetic methods appeared to be the utilization of 6-substituted purines without any protecting groups in the stannic chloride-catalyzed ribosylation reaction. In this paper, we report several examples of this synthetic procedure. The reaction conditions are similar to those described for the synthesis of 5-fluoro-[10] and 5-alkylpyrimidine nucleosides,[11] using Friedel-Crafts catalysts.

Adenine (**1a**) was suspended in dry acetonitrile with one equivalent of 1-O-acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose (**2a**). To this suspension was added two equivalents of stannic chloride in dry acetonitrile. After 3 hr, all solid materials had disappeared. After usual work-up, the resulting thin-layer chromatographically homogeneous (silica gel, chloroform–methanol, 9 : 1, v/v) gum (2′,3′,5′-tri-O-benzoyladenosine) was treated with methanolic ammo-

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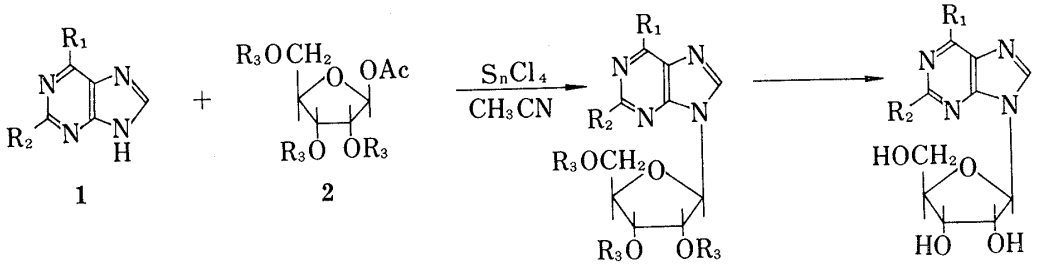
nia at 50° for 10 hr. After work-up, adenosine was obtained in crystalline form in 78% yield. No α-isomer or 1-, 3- or 7-riboside was detected in contrast to the results of the trimethylsilyl method.[9] When 1,2,3,5-tetra-O-acetyl-β-D-ribofuranose (**2b**) was used instead of **2a**, crystalline 2′,3′,5′-tri-O-acetyladenosine (**3b**), mp 173—174°, was obtained in 77% isolated yield. The structure was identified by comparison of the ultraviolet (UV) and infrared (IR) spectra with those of an authentic specimen[12] and by mixed melting point determination.

6-Chloropurine (**1b**) was reacted with **2a** or **2b** to form the corresponding acylated ribonucleosides which showed the same IR spectra as authentic specimens.[13] These were converted to crystalline 2′,3′,5′-tri-O-acyl-6-thioinosine[14,15] in 75—85% isolated yield. Similar condensation of purin-6-yl benzyl disulfide[16] with **2b** gave the tri-O-acetate of 9-β-D-ribofuranosylpurin-6-yl benzyl disulfide, which was then converted to crystalline 2′,3′,5′-tri-O-acetyl-6-thioinosine (**3d**) by treatment with β-mercaptoethanol in ethanol at room temperature. The coupling of 6-methylthiopurine (**1d**) with **2b** under similar conditions followed by treatment with alkali gave crystalline 9-β-D-ribofuranosyl-6-methylthiopurine (**4c**)[15] in good yield. As a typical example of a 2,6-disubstituted purine derivative, 2,6-dichloropurine (**1e**) was coupled with **2b** to give the crystalline tri-O-acetate of 9-β-D-ribofuranosyl-2,6-dichloropurine[17] in good yield. Application of this method to other pentofuranose nucleoside analogs is in progress in our laboratory.



1a : $R_1=NH_2$, $R_2=H$
1b : $R_1=Cl$, $R_2=H$
1c : $R_1=-S-S-CH_2-C_6H_5$, $R_2=H$
1d : $R_1=SCH_3$, R_2H
1e : $R_1=R_2=Cl$

2a : R_3=benzoyl
2b : R_3=acetyl
Ac=acetyl

Chart 1

Experimental

General——Melting points were determined on a Yanaco MP-3 apparatus and are uncorrected. UV spectra were recorded on a Shimadzu UV-300 recording spectrometer or Shimadzu model Double-40 multi-convertible spectrophotometer. IR spectra were obtained on a Hitachi 215 grating infrared spectrophotometer. Thin-layer chromatography (TLC) was performed with pre-coated silica-gel plates, 60 F_{254} (Merck), and column chromatography with Wako-gel C-200. Adenine, 6-chloropurine, 6-methylthiopurine, 2,6-dichloropurine, 1,2,3,5-tetra-O-acetyl-β-D-ribofuranose and 1-O-acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose were purchased from Waldhof (Germany).

Synthesis of Adenosine——Adenine (**1a**) (135.1 mg, 1 mmol) was suspended in a solution of **2a** (505 mg, 1 mmol) in 50 ml of anhydrous acetonitrile. Stannic chloride (2 mmol) in 20 ml of the same solvent was added and the mixture was stirred at room temperature. After 30 min, the reaction mixture became clear. Thin-layer chromatographic analysis of this solution (silica gel, chloroform–methanol, 9: 1, v/v) showed three spots with *Rf* values of 0.1, 0.42 and 0.81, corresponding to adenine, benzoylated nucleoside and **2a**,

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respectively. On further stirring the reaction mixture overnight, the TLC spots corresponding to sugar and adenine almost disappeared. The reaction mixture was concentrated to a small volume (*ca.* 5 ml), and sodium bicarbonate (600 mg) and distilled water (2 ml) were added. When the vigorous evolution of carbon dioxide had ceased, the mixture was evaporated down under reduced pressure at 37° (bath temperature). The residual glassy gum was extracted with hot chloroform (50 ml × 3) and the combined extracts were filtered and evaporated down. This product contained a small amount of unchanged sugar derivative, and the mixture was applied to a column of silica gel (2.5 cm × 15 cm). The column was washed with chloroform–ethyl acetate (9: 1, v/v) (300 ml) and then eluted with chloroform–methanol (9: 1, v/v) (300 ml). The eluate was concentrated under reduced pressure to give a colorless foam which was homogeneous on TLC. However, it could not be crystallized from several solvent systems tested. The foam (600 mg) was treated with 50 ml of methanol saturated with ammonia at 0° in a sealed vessel and then heated at 50° for 10 hr. The solvent was evaporated off under reduced pressure and the residue was mixed with distilled water (10 ml) and extracted with chloroform (3 ml × 5) to remove benzamide. The aqueous layer was evaporated to give a colorless solid, which was redissolved in 2 ml of distilled water at reflux temperature. This solution was kept overnight in a freezer, yielding fine silky crystals, 208 mg (78%). mp 223—224.5°. UV, $\lambda_{max}^{H_2O}$ nm: 260; $\lambda_{max}^{0.01N\ HCl}$ nm: 258. This compound was identified as adenosine by mixed melting point determination and by IR and paper chromatography. The mother liquor of the crystallization was checked by paper and thin-layer chromatography (Avicel SF cellulose plate, 10 cm × 10 cm, normal butanol–acetic acid–water = 4: 1: 5, v/v/v; isobutyric acid-0.5 N ammonium hydroxide = 4: 1 and isopropanol–conc.NH_4OH = 7: 3, v/v); it gave a single spot corresponding to adenosine.

Synthesis of 2′,3′,5′-Tri-O-acetyladenosine (**3b**)——Adenine (1 mmol) was coupled with **2b** (318 mg, 1 mmol) in dry acetonitrile (50 ml) in the presence of stannic chloride (2 mmol). After work-up similar to that described above, acetylated nucleoside was obtained. This sample was purified by column chromatography on silica gel (2.5 cm × 15 cm), and crystallized from boiling ethanol to give colorless needles 302 mg (77%), mp 174—176°. The compound was identified as 2′,3′,5′-tri-O-acetyladenosine[12] by mixed melting point determination and by comparison of the UV and IR spectra with those of authentic material prepared according to the literature.[12]

Synthesis of 2′,3′,5′-Tri-O-acetyl-6-thioinosine (**3d**)——Method A: 6-Chloropurine (**1b**) (154.6 mg, 1 mmol) was coupled with **2b** (1 mmol) in the presence of stannic chloride (2 mmol). The resulting syrupy nucleoside showed an IR spectrum identical with that of authentic 9-β-D-ribofuranosyl-6-chloropurine tri-O-acetate.[13] This was treated with a slight excess of thiourea (90 mg) in refluxing ethanol (20 ml). After a few hours, a white solid began to separate from the reaction mixture. The mixture was allowed to stand overnight at 4°, then the solid was collected by filtration, washed with ethanol and air-dried. This sample was crystallized from boiling ethanol to give colorless tiny needles 320 mg (78%). mp 252—253° (lit. 253°).[14] This compound was identified as 2′,3′,5′-tri-O-acetyl-6-thioinosine by mixed melting point determination and comparison of the UV and IR spectra with those of an authentic specimen.[14]

Method B: Purin-6-yl benzyl disulfide (**1c**) (274 mg, 1 mmol) was condensed with **2b** in a manner similar to that described above. After neutralization and evaporation of the reaction mixture, it was extracted with chloroform (30 ml × 3). The combined extracts were evaporated to dryness and subjected to silica gel column (2.5 cm × 15 cm) chromatography. The column was first washed with chloroform–ethyl acetate (9: 1, v/v) (200 ml) and then eluted with chloroform–ethyl acetate (4: 1, v/v) (300 ml). The fractions which contained the product were combined and evaporated to dryness. The UV spectrum of this compound showed maxima at 286 and 305 nm in ethanol, which are characteristic of 9-β-D-ribofuranosylpurin-6-yl benzyl disulfide.[16] This spectrum shifted immediately to 340 nm when the compound was treated with β-mercaptoethanol. The UV absorption maximum at 340 nm is characteristic of 9-β-D-ribofuranosylpurine (6-thioinosine). β-Mercaptoethanol (2 eq.) in 2 ml of ethanol was added to a solution of the reaction product (**3c**) in 30 ml of ethanol with stirring at room temperature. After a few minutes, white precipitates began to separate. After stirring for a further 3 hr, the mixture was stored in a refrigerater for 10 hr. The precipitates were collected by filtration, washed with ethanol and crystallized from boiling ethanol to give fine needles, 357 mg (85%). mp 248—252°. Recrystallization from the same solvent gave pure material which melted at 252—253°. The compound was identified as 2′,3′,5′-tri-O-acetyl-6-thioinosine by mixed melting point determination and comparison of the UV and IR spectra with those of an authentic specimen.[14]

When **2a** was used instead of **2b** in the coupling reaction (Method A or Method B), 2′,3′,5′-tri-O-benzoyl-6-thioinosine[15] was obtained in 75 and 84% yields, respectively.

9-β-D-Ribofuranosyl-6-methylthiopurine (**4c**)——Stannic chloride (1.5 mmol) was added to a solution of 6-methylthiopurine (**1d**) (166 mg, 1 mmol) and **2b** (1 mmol) in dry acetonitrile (50 ml), under continuous stirring. The reaction proceeded smoothly, as described above, and after similar work-up, tri-O-acetyl nucleosides (400 mg) was obtained together with a small amount of the sugar derivative. The product was directly treated with methanolic sodium methoxide (100 ml) and stirred for 18 hr at room temperature. The solvent was removed under reduced pressure, and the sticky residue was triturated with ether and ethanol to give solid material, which was crystallized from boiling ethanol. This compound, 223.7 mg, mp 165—167°, was identified as 9-β-D-ribofuranosyl-6-methylthiopurine[15] by mixed melting point determination and comparison of the UV and IR spectra with those of an authentic specimen.[15]

Synthesis of 2,6-Dichloro-9-β-D-(2′,3′,5′-tri-O-acetyl)-ribofuranosylpurine——Condensation of 2,6-dichloropurine (**1e**) (189 mg, 1 mmol) with **2b** (1 mmol) was carried out in the presence of stannic chloride (1.5 mmol). After work-up, tri-O-acetyl nucleoside was extracted with ethyl acetate (50 ml×3) and concentrated. The resulting slightly yellow syrup was dissolved in ethanol (3 ml). The solution was kept in a refrigerator overnight to give 360 mg (81%) of colorless needles, mp 161—162° (lit. 158—159°).[3] This compound was identified as the desired compound by mixed melting point determination and comparison of the UV and IR spectra with those of an authentic specimen prepared by the fusion method.[3]

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Synthesis of *s*-Triazolo[3,2-*b*]-1,3,4-thiadiazoles and *s*-Triazolo[3,2-*b*]benzimidazoles

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Treatment of 2-amino-1,3,4-thiadiazole and 2-amino-1-methylbenzimidazole with *O*-mesitylenesulfonylhydroxylamine gave the 2,3-diamino-1,3,4-thiadiazolium and 2,3-diamino-1-methylbenzimidazolium salts, respectively. These salts were transformed into 6-substituted *s*-triazolo[3,2-*b*]-1,3,4-thiadiazoles and 2-substituted 4-methyl-*s*-triazolo-[3,2-*b*]benzimidazoles by treatment with acylating agents.

Keywords——bridgehead nitrogen heterocycles; 2-amino-1,3,4-thiadiazole; 2-amino-1-methylbenzimidazole; *O*-mesitylenesulfonylhydroxylamine; cyclization

Fused 5–5 heteroaromatic ring systems with bridgehead nitrogen have recently been the subject of extensive investigations.[2] Previously we reported the synthesis of thiazolo[3,2-*b*]-*s*-triazoles (**1**).[3] The findings that some of these compounds have potent antifungal activity prompted us to synthesize related fused triazole derivatives. In this paper, we report a simple synthesis of *s*-triazolo[3,2-*b*]-1,3,4-thiadiazoles (**4**) and *s*-triazolo[3,2-*b*]benzimidazoles (**7**).

The starting 2,3-diamino-1,3,4-thiazolium salt **3** and 2,3-diamino-1-methylbenzimidazolium salt **6** were synthesized by reaction of the parent heterocycles **2** and **5** with *O*-mesitylenesulfonylhydroxylamine (MSH)[4] in 86 and 70% yields, respectively. Cyclization of these diamine salts **3** and **6** to *s*-triazole derivatives **4** and **7** was effected by heating with acetic anhydride, propionic anhydride, or benzoyl chloride at 200°. The structures of **4** and **7** were readily assigned on the bases of spectral data and elemental analyses (see "Experimental").

Experimental[5]

Materials——2-Amino-1,3,4-thiadiazole (**2**)[6] and 2-amino-1-methylbenzimidazole (**5**)[7] were prepared according to the literature.

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