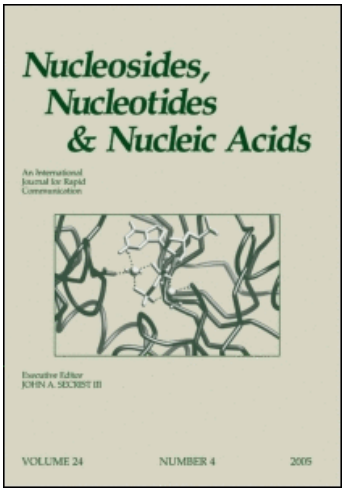

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SYNTHESIS OF *N*-ARYLINOSINES

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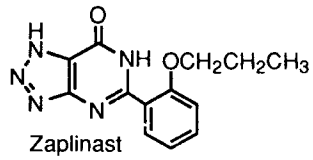
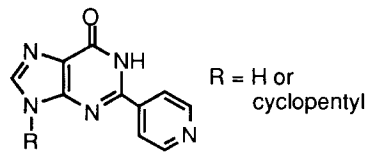
ABSTRACT: 2',3',5'-Tri-*O*-(tetrahydropyran-2-yl)inosine **1** was treated with iodobenzene or 2-bromopyridine in the presence of cuprous oxide in pyridines to give the N^1-aryl derivatives **2a,b**. Deprotection of the products afforded N^1-arylinosines **3a,b**.

INTRODUCTION

Introduction of aryl group onto 2-carbon of purine base has been attracted much attention since the development of Zaplinast[1]. Subramanyam *et al* also reported that the 2-(pyridin-4-yl)purines were competitive AMPA receptor antagonists.[2] Recently, we reported a method to introduce a phenyl group at the 3-nitrogen of uridine or thymidine. Therefore, we planned to explore the biological activity of *N*-arylionsines. In this paper, methods for the synthesis of *N*-phenyl **3a** or pyridin-2-yl derivative **3b** of inosine are described.



Zaplinast

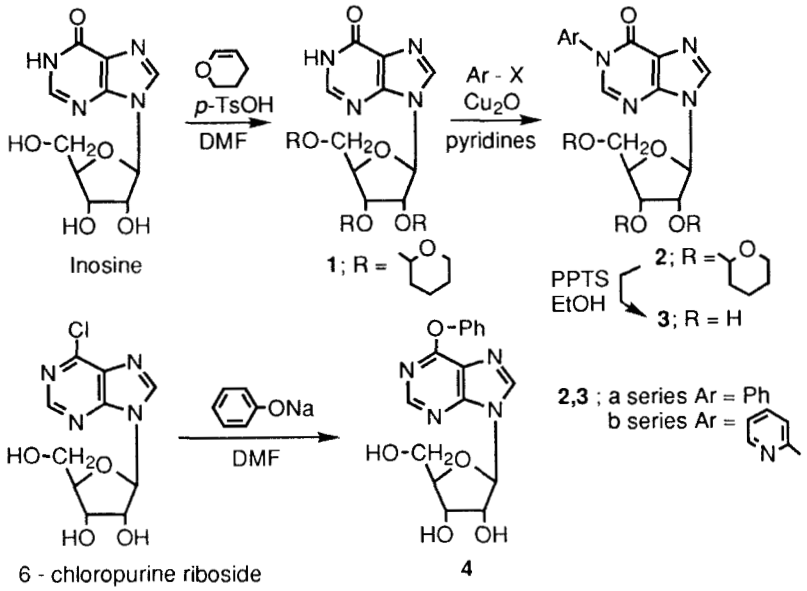


R = H or cyclopentyl

SYNTHESIS

By analogy with earlier method[3] sugar hydroxyl groups of inosine were protected with tetrahydropyran-2-yl group to give **1**. Then, compound **1** was treated with iodobenzene in the presence of cuprous oxide in 2,4,6-trimethylpyridine to give the N^1-phenyl product (**2a**) in 31% yield. Deprotection of compound **2a** with pyridinium *p*-toluenesulfonate (PPTS) in EtOH gave a target product (**3a**) in good yield. Introduction of a phenyl group was suggested by mass and ^{1}H NMR spectra as well as elemental analysis. Since formation of the 6-methoxy product besides N^1-methyl product has been

reported in the reaction of inosine derivatives with diazomethane, [4),5)] 6-phenoxypurine riboside (**4**) was prepared from 6-chloro congener and compared with **3a** by the spectro-



scopic methods. The ^{1}H-NMR spectrum of **3a** revealed appearance of two singlet at 8.44 and 8.40 attributable to base protons (H-8, H-2), whereas 8.75 and 8.48 ppm in *O*-phenyl derivative (**4**). In contrast to simple UV spectrum of **4** (λmax; 253 nm), compound **3a** showed three absorption maximum at 273, 252 and 244 nm. These result unequivocally demonstrated that **3a** is N^1-phenyl derivative. Introduction of pyridine at 1-nitrogen was also examined. Thus compound **1** was refluxed with 2-bromopyridine in the presence of cuprous oxide in pyridine to give the pyridin-2-yl derivative **2b** in good yield. But no *N*-substituted product was not detected in the similar reaction of **1** with 3-bromopyridine, suggesting that the reagent is less active toward nucleophilic displacement compared with 2-bromopyridine. An attempt to prepare N^1-(pyridin-4-yl)inosine was also unsuccessful. Deprotection of **2b** with PPTS in EtOH gave N^1-(pyridine-2-yl)inosine (**3b**) in 69%.

EXPERIMENTAL

Melting points (mp) were determined using a Yanagimoto micro-melting point apparatus (hot stage type) and are uncorrected. UV spectra were recorded with a Shimadzu UV-190 digital spectrometer. Low-resolution mass spectra were obtained on a JEOL JMS-AX500 mass spectrometer in the direct-inlet mode. ^{1}H-NMR spectra were recorded on a Varian UNITY 200 (200 MHz) or UNITY 600 (600 MHz) in $CDCl_3$ (or dimethyl sulfoxide (DMSO-d_6) with tetramethylsilane as an internal standard.

2',3',5'-Tri-*O*-(tetrahydropyran-2-yl)inosine 1 3,4-Dihydro-(2*H*)-pyran (30 ml) was added to the solution of inosine (10 g, 37.3 mmol) in DMF (80 ml), then ice-cooled. *p*-Toluenesulfonic acid (7.5g, 43.6 mmol) was dissolved to the solution and stirring was continued at 0°C for 3 hr. After neutralization with triethylamine, the solution was evaporated and the residue was dissolved in benzene (500 ml). The organic layer was washed with water three times (600 ml), dried over $MgSO_4$ and concentrated to a small volume. The solution was chromatographed over a column of silica gel G (5.2×30 cm) with 0-10% EtOH in CH_2Cl_2 (4 l) to give a caramel, which was crystallized from EtOH to give white crystals (11.9g, 61%). mp 189-190.5°C. Anal. Calcd for $C_{25}H_{36}N_4O_8$: C, 57.68; H, 6.97; N, 10.76. Found: C, 57.56; H, 7.23; N, 10.59. MS *m/z*: 520 (M^+). UV λmax MeOH 248 nm.

2',3',5'-Tri-*O*-(tetrahydropyran-2-yl)-1-*N*-phenylinosine 2a Iodobenzene (1.1 ml, 10 mmol) was added to a solution of **1** (1.04 g, 2 mmol) and cuprous oxide (286 mg, 2 mmol) in 2,4,6-trimethylpyridine (10 ml) and the mixture was heated under N_2 atmosphere at 190°C overnight. After cooling, the insolubles were filtered off and the solution was diluted with CH_2Cl_2 (100 ml). The organic layer was successively washed with 10% AcOH three times (300 ml) and water (100 ml), dried over $MgSO_4$ and concentrated to a small volume. The solution was chromatographed over a column of silica gel G (3.0×32 cm) with 0-5% EtOH in CH_2Cl_2 (1.5 l) to give a caramel (369 mg, 31%). MS *m/z*: 596 (M^+). UV λmax MeOH 275, 253, 247 nm.

1-*N*-Phenylinosine 3a A solution of **2** (270 mg, 0.45 mmol) and PPTS (130 mg, 0.52 mmol) in EtOH (6 ml) was heated at 50°C overnight. The solution was concentrated to a small volume, which was chromatographed over a column of silica gel G (2.5×35 cm) with 0-25% EtOH in CH_2Cl_2 (1.6 l) to give a solid. The precipitate and the solid were combined and recrystallized from EtOH to give a caramel (102 mg, 65%). MS *m/z*: 344 (M^+). UVλmax MeOH 273, 252, 244 nm. ^{1}H-NMR (DMSO-d_6) δ: 8.44, 8.40 (each 1H, s, H-8, H-2), 7.49-7.58 (5H, m, C_6H_5-), 5.92 (1H, d, J = 5.6 Hz, H-1'), 5.55 (1H, d, J = 6.3 Hz, 2'-OH), 5.27 (1H, d, J = 5.1 Hz, 3'-OH), 5.11 (1H, dd, J = 5.9, J = 5.1 Hz, 5'-OH), 4.52 (1H, q, J = 5.6 Hz, H-2'), 4.15 (1H, m, H-3'), 3.97 (1H, m, H-4'), 3.68 (1H, ddd, J = 12.0, J = 5.1, J = 4.2 Hz, H-5'a), 3.58 (1H, ddd, J = 12.0, J = 5.9, J = 3.9 Hz, H-5'b).

2',3',5'-Tri-*O*-(tetrahydropyran-2-yl)-1-*N*-(pyridin-2-yl)inosine 2b 2-Bromopyridine (0.96 ml, 10 mmol) was added to a solution of **1** (1.04 g, 2 mmol) and cuprous oxide (286 mg, 2 mmol) in pyridine (10 ml) and the mixture was refluxed under N_2 atmosphere overnight. After cooling, the insolubles were filtered off and the filtrate was evaporated to give a syrup, which was evaporated azeotropically with toluene three times (100 ml). The pale brownish caramel was dissolved in a small amount of CH_2Cl_2

and subjected to silica gel column chromatography as described in the section of **2a** to give a caramel (1.02 mg, 86%). MS *m/z*: 598 (M^++1). UV λmax MeOH 255, 248 nm (sh).

1-*N*-(Pyridin-2-yl)inosine 3b A solution of **2b** (721 mg, 1.2 mmol) and PPTS (500 mg, 2 mmol) in EtOH (12 ml) was heated at 50°C for 3 hr. After cooling, the crystals were collected by filtration to give **3b** (289 mg, 69%). mp 205-207°C. *Anal.* Calcd for $C_{15}H_{15}N_5O_5 \cdot 0.2\ H_2O$: C, 51.63; H, 4.45; N, 20.07. Found: C, 51.83; H, 4.42; N, 19.65. MS *m/z*: 345 (M^+). UV λmax MeOH 254, 248 (sh) nm. ^{1}H-NMR (DMSO-d_6) δ: 8.56 (1H, s, H-2), 8.46 (1H, s, H-8), 7.56 - 8.61, (4H, m, C_5H_4N-), 5.93 (1H, d, J = 5.8 Hz, H-1'), 5.50 (1H, br s, 2'-OH), 5.23 (1H, br s, 3'-OH), 5.08 (1H, br s, 5'-OH), 4.52 (1H, dd, J = 5.8, 5.0 Hz, H-2'), 4.16 (1H, dd, J = 5.0, 3.8 Hz, H-3'), 3.97 (1H, m, H-4'), 3.68 (1H, dd, J = 12.1, 4.1 Hz, H-5'a), 3.58 (1H, dd, J = 12.1, 4.1 Hz, H-5'b).

6-Phenoxypurine Riboside 4 Sodium hydride (60% in oil, 160 mg, 4 mmol) was added to a solution of phenol (471 mg, 5 mmol) in dry DMF (5 ml), then 6-chloropurine riboside (287 mg, 1 mmol) was added. The solution was stirred at room temperature for 1 hr, neutralized with AcOH and evaporated. The residue was dissolved in a small volume of EtOH and chromatographed over a column of silica gel G (2.5×35 cm) with 0-20% EtOH in CH_2Cl_2 (2 l) to give a caramel (70 mg, 21%). MS *m/z*: 344 (M^+). UV λmax MeOH 253 nm. ^{1}H-NMR (DMSO-d_6) δ: 8.75, 8.48 (each 1H, s, H-8, H-2), 7.25-7.55 (5H, m, C_6H_5-), 6.02 (1H, d, J = 4.7 Hz, H-1'), 5.52 (1H, br s, 2'-OH), 5.27 (1H, br s, 3'-OH), 5.13 (1H, br s, 5'-OH), 4.61 (1H, t, J = 4.7 Hz, H-2'), 4.19 (1H, m, H-3'), 3.97 (1H, q, J = 3.4 Hz, H-4'), 3.5-3.77 (2H, m, H-5').

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