Short Communication

Synthesis of N^6-Aryl-2-methyladenosines

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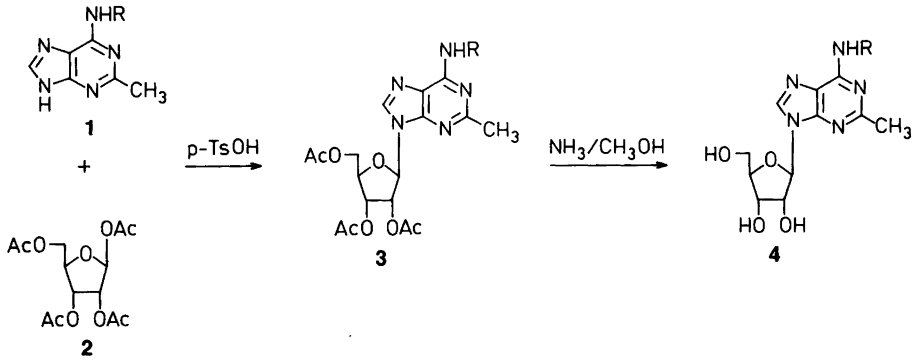

Scheme 1.

Purine derivatives are among the most ubiquitous of all naturally occurring heterocyclic compounds, their presence being associated with growth control.[1] Recently, a series of biologically active 2-methyl-N^6-aryladenines has been prepared by reacting 5-acetylamino-1*H*-imidazole-4-carboxamide hydrochloride and an appropriate substituted aniline in a mixture of phosphorus pentoxide and triethylamine hydrochloride at 180 °C.[2] (Scheme 1). We needed a series of compounds in order to investigate whether it is possible to enhance the biological activity of the 2-methyl-N^6-aryladenines by converting them to the corresponding 2-methyl-N^6-aryladenosines (**4**). The most attractive procedure for their preparation was assumed to be the fusion procedure used by Barascut *et al.*[3] to prepare N^6-benzyladenosine, but for the high-melting and insoluble starting materials a modification of this procedure is needed.

We have found that the high-melting 2-methyl-N^6-aryladenines (**1**) may be condensed with an excess of 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose, as described in the Experimental, to give 2′,3′,5′-tri-*O*-acetyl-2-methyl-N^6-aryladenosines (**3**). After work-up by chromatography, **3** is deacetylated by ammonolysis with a saturated solution of ammonia in methanol to give 2-methyl-N^6-aryladenosines (**4**).

The identification of **1a–b** and **4**, and the assignment of the structures of **4** as the β-anomers were confirmed by MS, ^{1}H NMR, and ^{13}C NMR (coupled and decoupled) measurements, together with reference data for similar compounds.[2,4–7]

Experimental

N^6-*Aryl-2-methyladenines* (**1a–b**) – *General procedure.* P_4O_{10} (55.5 g, 0.195 mol), triethylamine

Table 1. Preparation of **1** and **4**.

Compd. ( ) No.	R	Yield/%	M.p./°C (Solvent)
1a	$3,5\text{-}(CH_3)_2C_6H_3$	54	291–292 (DMF/H_2O)
1b	$3\text{-}CF_3C_6H_4$	45	295–296 (DMF/H_2O)
4a	C_6H_5	49	224–225 (CH_3OH/H_2O)
4b	$4\text{-}CH_3C_6H_4$	41	230–231 (CH_3OH/H_2O)
4c	$4\text{-}C_2H_5C_6H_4$	47	181–182 (CH_3OH)
4d	$3,5\text{-}(CH_3)_2C_6H_3$	28	190–191 (C_2H_5OH)
4e	$4\text{-}FC_6H_4$	49	255–256 (CH_3OH/H_2O)
4f	$3\text{-}CF_3C_6H_4$	28	169–170 (C_2H_5OH)
4g	$4\text{-}ClC_6H_4$	55	231–232 (CH_3OH)
4h	$3,4\text{-}Cl_2C_6H_3$	33	197–198 (C_2H_5OH)

hydrochloride (53.8 g, 0.391 mol) and the appropriate substituted aniline (0.391 mol) are mixed at room temperature. The reaction vessel, which is fitted with a drying tube, is then heated on an oil bath at 220 °C with mechanical stirring. When a clear, homogeneous mixture is obtained (ca. 30 min), the mixture is cooled to 180 °C, 5-acetylamino-1*H*-imidazole-4-carboxamide hydrochloride[2] (20.00 g, 0.0977 mol) is added, and the mixture is stirred for 18 h. The oil bath is allowed to cool to 120 °C and 2 M NaOH is cautiously added with stirring until pH > 10; the mixture separates into two layers. The strongly alkaline mixture is extracted 3 times with 200 ml of ether and the aqueous phase is neutralized with 4 M HCl (pH 6). The precipitate is collected, washed with water and recrystallized (Table 1).

N^6-*Phenyl-2-methyladenosine* (**4a**) – *Typical procedure.* **2** (12.09 g, 0.038 mol) is heated to 190 °C on an oil bath, **1** (0.02 mol) is added and the temperature is raised to 240 °C for 5 min to obtain a homogeneous melt. The melt is cooled to 190 °C, *p*-toluenesulfonic acid monohydrate (0.38 g, 0.002 mol) is added and the mixture is stirred for 45 min under vacuum (10 mmHg). The reaction mixture is allowed to cool to room temperature, chloroform (200 ml) is added and the mixture is stirred until the reaction cake is digested (30 min). The mixture is filtered and the chloroform is evaporated, giving a dark syrup. The syrup is flash-chromatographed on a silica-gel column with CH_2Cl_2/CH_3OH (49:1) as eluent, the appropriate fractions being collected and dried over Na_2SO_4. The solvent is evaporated and the resulting syrup is deacetylated by ammonolysis at room temperature with 175 ml of NH_3/CH_3OH (saturated at 0 °C) overnight. The solvent is evaporated and the product is precipitated by adding water (250 ml). The precipitate is collected, washed with water and recrystallized (Table 1).

^1H NMR (60 MHz, DMSO-d_6): δ 2.60 (s, 3H, 2-CH_3), 3.65–3.80 (m, 2H, 5′-H), 4.00–4.35 (m, 2H, 3′-H, 4′-H), 4.60–4.92 (m, 1H, 2′-H), 5.27 (d, 1H, *J* 4 Hz, 3′-OH), 5.47–5.70 (m, 2H, 2′-OH, 5′-OH), 6.03 (d, 1H, *J* 6 Hz, 1′-H), 6.93–8.08 (m, 5H, Ar-H), 8.57 (s, 1H, 8-H), 9.90 (s, 1H, N^6-H).

^{13}C NMR (15 MHz, DMSO-d_6): δ 87.9 (C-1′), 73.5 (C-2′), 70.8 (C-3′), 86.2 (C-4′), 61.8 (C-5′), 160.8 (C-2), 149.9 (C-4), 118.5 (C-5), 151.8 (C-6), 140.3 (C-8), 25.6 (2-CH_3), 139.7 (C-1″), 120.6 (C-2″), 128.3 (C-3″), 122.5 (C-4″).

MS [*m/z* (% rel. int.)]: 357 (35, M), 327 (2), 268 (28), 254 (52), 238 (6), 226 (53), 225 (99), 224 (100).

N^6-*(3,4-Dichlorophenyl)-2-methyladenosine* (**4h**). The same procedure as for **4a** is followed, with the exception that a larger quantity of **2** (22.28 g, 0.07 mol) and an oil bath temperature of 260 °C (5 min) were used to obtain a homogeneous melt.

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