Synthesis of \(N^6\)-Aryl-2-methyladenosines

Jesper Andersen, Erik S. Andreassen and Erik B. Pedersen

Department of Chemistry, Odense University, DK-5230 Odense M, Denmark


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\begin{align*}
\text{NHR} & \quad \text{NHR} \\
\text{1} & \quad \text{AcO} \\
& \quad \text{AcO} \\
& \quad \text{AcO} \\
& \quad \text{AcO}
\end{align*}
\]

\[
\begin{align*}
\text{p-TsOH} & \quad \text{AcO} \\
\text{3} & \quad \text{NH}_3/\text{CH}_3\text{OH} \\
& \quad \text{HO} \\
& \quad \text{HO} \\
& \quad \text{HO}
\end{align*}
\]

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-acylamino-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-\(\beta\)-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 \(\beta\)-anomers were confirmed by MS, \(^1\)H NMR, and \(^13\)C NMR (coupled and decoupled) measurements, together with reference data for similar compounds.\(^4-7\)

Experimental

\(N^6\)-Aryl-2-methyladenines (1a-\(b\)) – General procedure. \(\text{P}_4\text{O}_{10}\) (55.5 g, 0.195 mol), triethylamine
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-acyl-

amino-1H-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).

\(^1\)H NMR (60 MHz, DMSO-\(d_6\)): \(\delta\) 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-\(d_6\)): \(\delta\) 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.

**References**


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