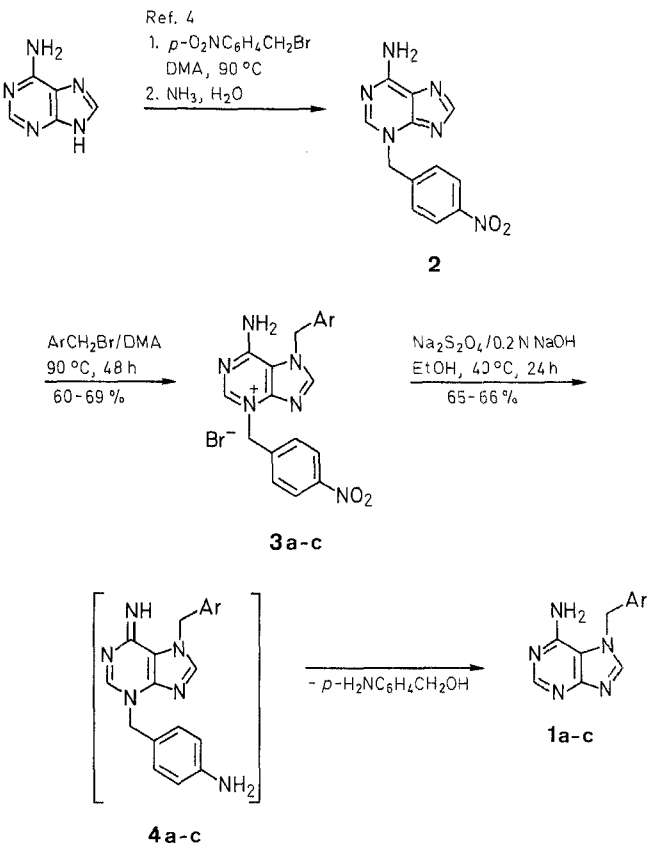

4-Nitrobenzyl as a *N*-Protective Group in *N*-Heterocycles: An Easy Access to 7-Arylmethyladenines from 3-(4-Nitrobenzyl)-adenine

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The 4-nitrobenzyl group is used as a *N*-3 protective group in adenine to direct further alkylation (benzylation) at the 7-position. In the obtained 7-arylmethyl-3-(4-nitrobenzyl)adenines, this protective group is removed, presumably as quinonimine methide, by reduction of the nitro group by the use of sodium dithionite, thus leaving 7-arylmethyladenines.

Selective alkylation at the 7-position of 3-benzyladenine, followed by hydrogenolytic cleavage of the benzyl group, allows a practical access to 7-alkyladenines.[1] However, 7-benzyladenine was not satisfactorily obtained by this method, because of the poor selectivity of the 3-benzyl group cleavage in 3,7-benzyladenine.[1] Alternative methods for the preparation of 7-alkyladenines being less effective,[2] we sought a way to extend the above route to the preparation of 7-arylmethyladenines by seeking a *N*-3 protective group that could be removed by a way other than hydrogenolysis. The 4-nitrobenzyl group, which was expected to be removable as quinonimine methide (1-imino-4-methylene-1,4-dihydrobenzene),[3] after reduction of the nitro group, gave us satisfactory results, as exemplified by the synthesis of the three 7-arylmethyladenines **1a–c** reported here.

1, 3	Ar
a	C_6H_5
b	3-$CH_3OC_6H_4$
c	3,5-$(CH_3O)_2C_6H_3$

Alkylation of adenine with 4-nitrobenzyl bromide in dimethylacetamide (DMA) at 90 °C afforded 3-(4-nitrobenzyl)adenine (**2**), which was easily separated from its isomers by recrystallization.[4] Heating of compound **2** with the appropriate arylmethyl bromide at 90 °C in dimethylacetamide for several hours provided the salts of substituted 3,7-dibenzyladenines **3a–c** (Table 1). Reduction of the nitro group in these products in slightly alkaline aqueous ethanolic solution at 50 °C gave the resulting aminobenzyl derivatives **4a–c**, which decomposed *in situ* to leave the expected 7-benzyladenines **1a–c** (Table 2) and 4-aminobenzyl alcohol.

The structures of compounds **1a–c** were confirmed by their UV spectral data (Table 3), typical of *N*-7 substituted adenines.[5]

Table 1. 7-Arylmethyl-3-(4-nitrobenzyl)adeninium Bromides **3** Prepared

Product	Yield (%)	mp (°C)	Molecular Formula[a]	MS (70 eV) *m/z* (%)	^{1}H-NMR (DMSO-d_6/TMS) δ
3a	60	180–183	$C_{19}H_{16}N_6O_2 \cdot HBr$ (360.4 + 81)	360 (M^+, 27)	5.75, 5.82 (2s, 4H, $2CH_2$); 7.28 (s, 5H, C_6H_5); 7.6–8.3 (m, 4H, $O_2NC_6H_4$); 8.83–9.12 (2s, 2H, H-2, H-8 purine)
3b	69	244	$C_{20}H_{18}N_6O_3 \cdot HBr$ (390.4 + 81)	390 (M^+, 100)	3.73 (s, 3H, CH_3O); 5.63 (s, 4H, $2CH_2$); 6.6–7.5 (m, 4H, $CH_3OC_6H_4$); 7.6–8.3 (m, 4H, $O_2NC_6H_4$); 8.85, 9.12 (2s, 2H, H-2, H-8 purine)
3c	64	257	$C_{21}H_{20}N_6O_4 \cdot HBr$ (420.4 + 81)	420 (M^+, 41)	3.67 (s, 6H, $2CH_3O$); 5.70 (s, 4H, $2CH_2N$); 6.3–6.5 [m, 3H, $(CH_3O)_2C_6H_3$]; 7.6–8.3 (m, 4H, $O_2NC_6H_4$); 8.77, 9.03 (2s, 2H, H-2, H-8 purine)

[a] Satisfactory microanalyses obtained: C ±0.28, H ±0.05, N ±0.38, Br ±0.19 (**3a, c** analyze as monohydrates).

Table 2. 7-Arylmethyladenines **1** Prepared

Product	Yield (%)	mp (°C)	Molecular Formula[a] or Lit. mp (°C)	MS (70 eV) *m/z* (%)	^{1}H-NMR (DMSO-d_6/TMS) δ
1a	66	235	236–238 (dec)[1]		5.70 (s, 2H, CH_2); 6.82 (s, 2H, NH_2); 7.02–7.43 (m, 5H, C_6H_5); 8.25, 8.45 (s, 2H, H-2, H-8 purine)
1b	66	271	$C_{13}H_{13}N_5O$ (255.3)	255 (M^+, 82)	3.72 (s, 3H, CH_3O); 5.65 (s, 2H, CH_2); 6.5–7.5 (m, 6H, $CH_3OC_6H_4$, NH_2); 8.25, 8.47 (2s, 2H, H-2, H-8 purine)
1c	65	205	$C_{14}H_{15}N_5O_2$ (285.3)	285 (M^+, 90)	3.68 (s, 6H, $2CH_3O$); 5.58 (s, 2H, CH_2); 5.95 [m, 3H, $(CH_3O)_2C_6H_3$]; 6.80 (s, 2H, NH_2); 8.23, 8.45 (2s, 2H, H-2, H-8 purine)

[a] Satisfactory microanalyses obtained: C ±0.25, H ±0.13, N ±0.30.

Table 3. UV Spectral Data of 7-Arylmethyladenines **1**

1	0.1 NHCl λ_{max} (nm)	log ε	0.1 NNaOH λ_{max} (nm)	log ε
a[a]	273	4.13	271	4.00
b	273	4.15	272	4.03
c	273	4.17	272	4.01

[a] Lit.[6] (0.1 N HCl) λ_{max} = 274 nm (log ε = 4.13); (0.01 N NaOH) λ_{max} = 272 nm (log ε = 3.98).

This easy access to 7-arylmethyl adenines is undoubtedly also valuable for the synthesis of any other 7-substituted adenines containing neither nitro nor similar reducible groups. Moreover, our results demonstrate that latent 4-aminobenzyl groups like 4-nitrobenzyl, or latent 2-amino, 2- and 4-hydroxybenzyl groups[3] are possible *N*-protective groups in *N*-heterocycles.

Melting points were determined on a Maquenne heating block. The microanalyses were run by the Laboratoire Central de Microanalyses du CNRS. The mass spectra were recorded on a Varian Mat 112 spectrometer, the ^{1}H-NMR spectra on a Varian EM 360 spectrometer, and the UV spectra on a Kontron-Uvikon 860 spectrometer.

7-Arylmethyl-3-(4-Nitrobenzyl)adenine Hydrobromides (3); General Procedure:

3-(4-Nitrobenzyl)adenine (**2**;[4] 4.59 g, 17 mmol) is dissolved by heating in freshly distilled DMA (100 mL). The arylmethyl bromide is added and the mixture is heated at 90 °C with stirring for 48 h. After cooling to room temperature, the solvent is evaporated *in vacuo*. The viscous residue is triturated in Et_2O (100 mL) and then solidified. After filtering with suction, the solid is dissolved with heating in 1 N aq. HBr (200 mL). Reprecipitation is obtained by cooling to room temperature and neutralization to pH 7 with 5 N aq. NH_3. Filtration, drying in high vacuum at 100 °C and recrystallization from EtOH afford analytically pure substituted 3,7-dibenzyladenines as their hydrobromide salts **3a–c** (Table 1).

7-Arylmethyladenines (1); General Procedure:

To a suspension of **3** (2.5 mmol) and sodium dithionite (1.74 g, 10 mmol) in EtOH (100 mL) is added 0.2 N aq. NaOH (100 mL, 20 mmol). The mixture is stirred at 40 °C for 24 h. After cooling to room temperature, the solution is concentrated under reduced pressure to a volume of 70 mL. The precipitate obtained is filtered with suction, washed water (2 × 25 mL) and then dried *in vacuo* at 100 °C. Analytical samples of **1a–c** (Table 2) are obtained by recrystallization in water/EtOH.

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