Phase-Transfer Catalysis in the *N*-Benzylation of Adenine

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A convenient phase-transfer catalysis in the *N*-benzylation of adenine is described. The benzylation of adenine with benzyl halides in a two-phase system containing phase-transfer catalyst gave 9-benzylated adenines as a major product accompanied with 3-benzylated adenines.

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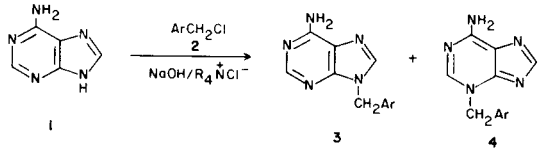
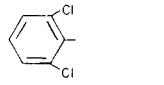
In connection with a study of the synthesis of the important coccidiostat aprinocid, 9-(2-chloro-6-fluorobenzyl)-adenine (**3d**) (1), we have investigated several alternative methods for the benzylation of adenine with the aim of maximizing 9-isomer formation (**3**) while minimizing that of 3-isomer (**4**). It was found that the 9-isomer is the major product (90-95%) resulting from benzylation reactions carried out with sodium adeninate in strictly anhydrous dipolar aprotic solvents (*e.g.*, DMF, DMSO and HMPA) but that the 3-isomer predominates (55%) in protic media (*e.g.*, aqueous ethanol) (2).



a) Ar = Ph



In this paper, we wish to report that by employing phase-transfer catalysis (3), it is possible to preserve the economical and operational advantages of reactions run in largely aqueous media while at the same time favoring 9-isomer formation. This high-yielding benzylation which produces a *ca.* 4 to 1 mixture of **3** to **4** together with a small amount of the N-7 isomer (*ca.* 1-2% by hplc assay), can be accomplished by heating adenine **1** in a two-phase system consisting of aqueous sodium hydroxide and an immiscible solvent (*e.g.*, hexanes, isooctane and benzene) containing a phase-transfer catalyst and the benzylating reagent **2**. The results are summarized in the Table. The pure 9-isomer **3a, 3c** and **3d** can be obtained by the sulfuric acid-prompted selective debenzylation of the 3-isomer which will be reported elsewhere (4).

EXPERIMENTAL

Melting points are uncorrected. Elemental analyses were performed by Mr. J. Gilbert and his associates, Merck Sharp & Dohme Research Laboratories. ^{1}H nmr spectra were recorded at 60 MHz with a Hitachi Perkin-Elmer R-24 A instrument. ^{13}C nmr spectra were obtained with a Varian CFT-20 spectrometer. Chemical shifts are reported in parts per million (δ) from internal TMS.

Table

Phase-Transfer Catalyzed *N*-Benzylation of Adenine (1)

Benzylating Agents **2**	Solvent	Catalyst	Reaction Time (hours)	Yield (%) (a)	Products **(3:4)**
2a	hexanes	aliquat 336 (d)	8	92	75:25 (b)
2b	hexanes	aliquat 336	10	82	80:20 (b)
2c	hexanes	aliquat 336	6	91	85:15 (c)
2c	benzene	aliquat 336	6	86	80:20 (c)
2c	hexanes	TEBAC (e)	6	40	60:40 (c)
2d	hexanes	aliquat 336	6	96	70:30 (c)
2d	isooctane	MTTAC (f)	18	82	80:20 (c)
2d	hexanes	adogen 440 (g)	20	97	82:18 (c)

(a) Yields of isolated products are reported as a mixture of **3** and **4**. The reaction was carried out at refluxing temperature. (b) Product ratios were obtained by ^{1}H nmr in (acetic acid-d_4): using N-9 CH_2/N-3 CH_2 peaks at 5.48/5.68 for **3a/4a**, at 5.68/5.85 for **3b/4b**. (c) Products ratios were obtained by hplc using a microporous, octadesylsilane bonded phase column with a methanol, aqeuous phosphate mobile phase at 35°. The mobile phase was prepared from 30 parts methanol plus 70 parts of 0.01*M* sodium hydrogen phosphate adjusted to *p*H 7.0 with phosphoric acid. Detection was by uv at 280 nm. The N-7 isomer was generally detected at less than 2.0%. (d) Aliquat 336: a mixture of $(n\text{-}C_8\text{-}C_{12})_3\overset{+}{N}\text{-}CH_3\ Cl^-$ (General Mills, Inc.). (e) TEBAC: $(CH_3CH_2)_3\overset{+}{N}\text{-}CH_2Ph\ Cl^-$ (Aldrich Chemical Co.). (f) MTTAC: Methyl trihydrogenated tallowammonium chloride (Ashland Chemical Co.). (g) Adogen 440: $(C_{16}\text{-}C_{18})_3\overset{+}{N}\text{-}CH_3\ Cl^-$ (Ashland Chemical Co.).

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General Benzylation Procedure.

A three-necked round bottomed flask equipped with a thermometer, reflux condenser, nitrogen inlet and an overhead mechanical stirrer is charged sequentially with 5 ml. of water, 2 ml. of 50% sodium hydroxide solution (0.039 mole) and 2.0 g. (0.015 mole) of adenine (98% pure). After the adenine dissolves a solution of benzylating reagent (0.016 mole) and phase-transfer catalyst (5 mole %) in 30-40 ml. of organic solvent is added. The system is stirred under reflux for the time indicated in the Table and then cooled to room temperature. The precipitated solids are filtered, washed with water (2 × 10 ml.) and dried *in vacuo* to give the crude benzylated adenine mixture of **3** and **4**. Results and methods of analysis are presented in the Table.

Isolation of **3d** and **4d**.

The crude benzylated adenine mixture (80% of **3d**, 18% of **4d** and 1.6 % of N^7 isomer by hplc assay) was recrystallized from glacial acetic acid-water mixture to give pure **3d**, m.p. 245-246°, lit (5) m.p. 245-246°; purity 99.8% by hplc assay; uv (0.1*N* methanolic sodium hydroxide): λ max 260 nm, $\epsilon = 15.93 \times 10^{-3}$; ^{1}H nmr (acetic acid-d_4): δ 5.68 (s, 2, CH_2), 7.20 (m, 3, aromatic protons), 8.08 (s, 1, H-8) and 8.41 (s, 1, H-2); ^{13}C nmr (trifluoroacetic acid): δ 43.4 (CH_2), 113.4 (C-5), 145.6 (C-8), 149.1 (C-2), 150.2 (C-4) and 150.7 (C-6) besides phenyl ring carbon signals; ms: m/e 277 (M^+).

Anal. Calcd. for $C_{12}H_9ClFN_5$: C, 51.90; H, 3.27; Cl, 12.77; F, 6.84; N, 25.22. Found: C, 52.17; H, 3.28; Cl, 12.87; F, 7.01; N, 24.49.

The mother liquor (acetic acid-water) was concentrated *in vacuo*, to give **4d** enriched crystals. This crude **4d** was treated with methanol-hydrogen chloride (23 weight %) to form the hydrochloride salt of **4d** which recrystallized from methanol, m.p. 253-254° dec.; purity 99.6% by hplc assay; uv (0.1*N* methanolic sodium hydroxide): λ max 275 nm, $\epsilon = 12.47 \times 10^{-3}$; ^{1}H nmr (acetic acid-d_4): δ 5.89 (s, 2, CH_2), 7.21 (m, 3, aromatic protons) and 8.48 (s, 2, H-2 and H-8); ^{13}C nmr (trifluoroacetic acid): δ 48.1 (CH_2), 113.3 (C-5), 147.6 (C-8), 148.4 (C-4), 149.9 (C-2) and 155.5 (C-6) besides phenyl ring carbon signals.

Anal. Calcd. for $C_{12}H_9ClFN_5$: C, 51.90; H, 3.27; Cl, 12.77; N, 25.22. Found: C, 51.67; H, 3.04; Cl, 12.81; N, 25.29.

The 9- and 3- Benzylated adenine derivatives (**3a-3c** and **4a-4c**) were isolated in a similar manner and the obtained physical properties are shown below.

Compound **3a**.

This compound had m.p. 231-232° [from ethanol, lit. (6) m.p. 230°]; ms: m/e 225 (M^+); ^{1}H nmr (acetic acid-d_4): δ 5.48 (s, 2, CH_2), 7.31 (s, 5, aromatic protons), 8.25 (s, 1, H-8) and 8.40 (s, 1, H-2); ^{13}C nmr (trifluoroacetic acid): δ 52.8 (CH_2), 113.3 (C-5), 145.2 (C-8), 149.4 (C-2), 150.1 (C-4) and 150.6 (C-6) besides phenyl ring carbon signals.

Compound **3b**.

This compound had m.p. 257-259° [from methanol, lit. (7) m.p. 256-257°]; ms: m/e 270 (M^+); ^{1}H nmr (acetic acid-d_4): δ 5.61 (s, 2, CH_2), 7.46 and 8.15 (d, each 2, aromatic protons) and 8.36 (broad s, 2, H-8 and H-2).

Anal. Calcd. for $C_{12}H_{10}N_6O_2$: C, 53.33; H, 3.73; N, 31.10. Found: C, 53.08; H, 3.61; N, 30.87.

Compound **3c**.

This compound had m.p. 265-266° (from acetic acid); ms: m/e 293 (M^+); uv (0.1*N* methanolic sodium hydroxide): λ max 260 nm, $\epsilon = 15.8 \times 10^{-3}$; ^{1}H nmr (acetic acid-d_4): δ 5.90 (s, 2, CH_2), 7.55 (s, 3, aromatic protons), 7.97 (s, 1, H-8) and 8.42 (s, 1, H-2).

Anal. Calcd. for $C_{12}H_9Cl_2N_5$: C, 48.99; H, 3.05; Cl, 24.11; N, 23.81. Found: C, 48.60; H, 3.20; Cl, 23.70; N, 23.61.

Compound **4a**.

This compound had m.p. 276-278° [from ethanol lit. (8) m.p. 278-280°, lit. (6) 275-277°]; ms: m/e 225 (M^+); ^{1}H nmr (acetic acid-d_4): δ 5.64 (s, 2, CH_2), 7.31 (s, 5, aromatic protons), 8.41 (s, 1, H-8) and 8.58 (s, 1, H-2); ^{13}C nmr (trifluoroacetic acid): δ 57.04 (CH_2), 113.3 (C-5), 147.4 (C-8), 148.3 (C-4), 150.3 (C-2) and 155.4 (C-6) besides phenyl ring carbon signals.

Compound **4b**.

This compound had m.p. 288-290° dec. (from acetic acid); ms: m/e 270 (M^+); ^{1}H nmr (acetic acid-d_4): δ 5.88 (s, 2, CH_2), 7.61 and 8.20 (d, each 2, aromatic protons), 8.43 (s, 1, H-8) and 8.65 (s, 1, H-2).

Anal. Calcd. for $C_{12}H_{10}N_6O_2$: C, 53.33; H, 3.73; N, 31.10. Found: C, 53.06; H, 3.61; N, 30.85.

Compound **4c**.

This compound had m.p. 287-290° (from DMF-water); ms: m/e 293 (M^+); uv (0.1*N* methanolic sodium hydroxide): λ max 275 nm, $\epsilon = 13.6 \times 10^{-3}$; ^{1}H nmr (acetic acid-d_4): δ 5.96 (s, 2, CH_2), 7.62 (s, 3, aromatic protons), 8.25 (s, 1, H-8), and 8.64 (s, 1, H-2).

Anal. Calcd. for $C_{12}H_9Cl_2N_5$: C, 48.99; H, 3.05; Cl, 24.11; N, 23.81. Found: C 48.63; H, 3.27; Cl, 23.80; N, 23.64.

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