A Convenient Synthesis of 8-Alkyl- and 8-Alkylthio-2-(4-pyridyl)adenines

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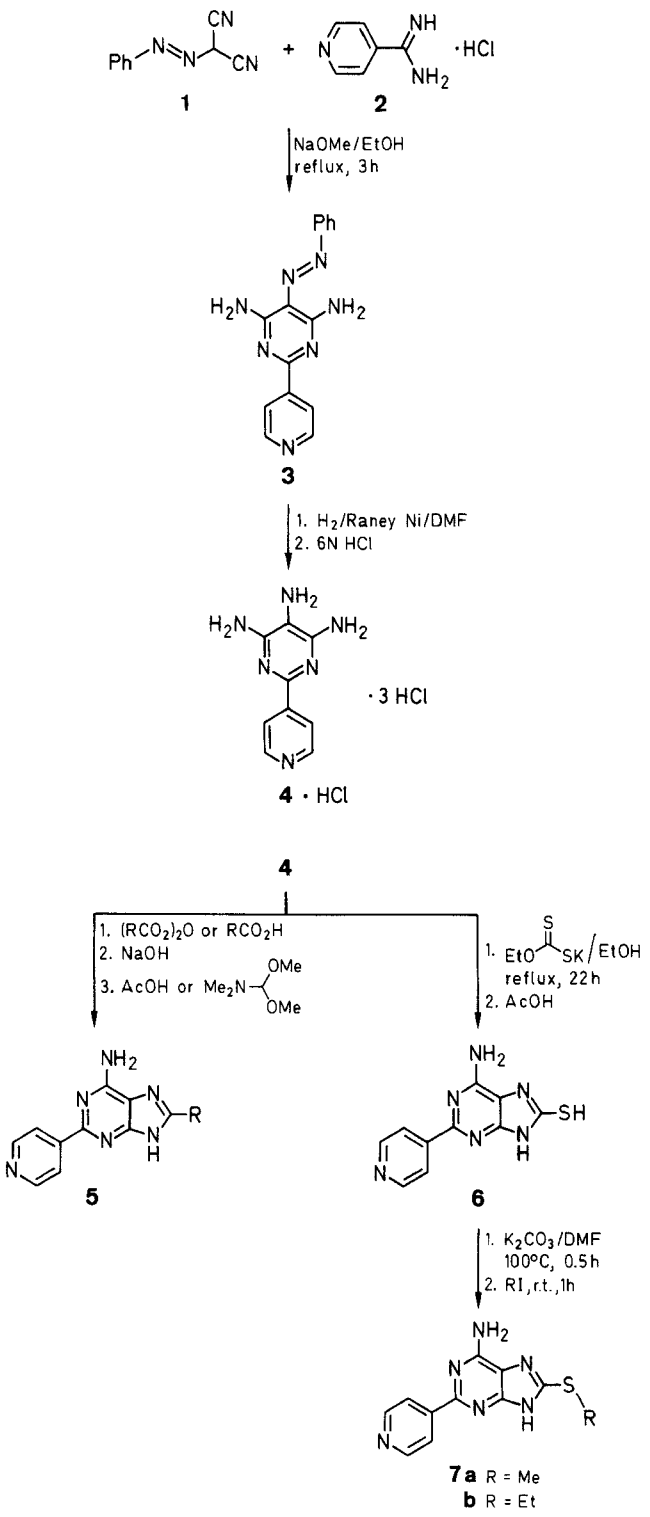
Several 8-alkyl-2-(4-pyridyl)adenine analogs **5** were prepared by reacting 4,5,6-triaminopyrimidine **4** with acid anhydrides, acids or dimethylformamide dimethyl acetal. 8-Mercapto-2-(4-pyridyl)-adenine (**6**), prepared by treating **4** with *O*-potassium *O*-ethyl dithiocarbonate was alkylated to give 8-alkylthioadenine derivatives **7**.

8-Alkyl-2-(4-pyridyl)adenines **5** were needed for the evaluation of their cardiotonic activity. Although there are numerous examples of 2,8-disubstituted adenines reported in the literature, only a very few are those of 8-alkyl-2-aryladenines. In 1959, 2-(3-pyridyl)adenine[2] was synthesized by heating a mixture of 4,6-diamino-5-nitroso-2-(3-pyridyl)pyrimidine, formamide, formic acid, and sodium dithionite. In 1971, 8-methyl-2-phenyladenine[3] was prepared by the reduction of 7-acetylamino-5-phenylfurazano[3,4-*d*]pyrimidine which in turn was synthesized in several steps from benzamidine. 8-Alkyl(aryl)adenines have been prepared by the acid,[4,5] base[6] and thermal[7] cyclization of 5-acylamino-4-aminopyrimidines. Our approach to **5** utilizes the reaction of triaminopyrimidine **4** with acid anhydrides or acids without the isolation of intermediate amides.

The requisite triaminopyrimidine **4** was prepared from phenylazomalononitrile (**1**)[8] and isonicotinamidine hydrochloride (**2**)[9] by the procedure reported by Baddiley et al.[10] for the preparation of 4,5,6-triaminopyrimidines. Triaminopyrimidine **4** was treated with acid anhydrides or high boiling acids at 190–200 °C for several hours and the resulting mixtures were dissolved in aqueous sodium hydroxide and then acidified with acetic acid to give 8-alkyl-2-(4-pyridyl)adenines **5** in 43–74% yields.

The 8-(alkylthio)-2-(4-pyridyl)adenines **7** required for structure activity relationship studies were prepared by the alkylation of thiol **6**, which in turn was prepared by reacting *O*-potassium *O*-ethyl dithiocarbonate with triaminopyrimidine **4**. Treatment of **4** with dimethylformamide dimethyl acetal gave adenine **5j**.



4,6-Diamino-5-phenylazo-2-(4-pyridyl)pyrimidine (3):
To a stirred mixture of isonicotinamidine hydrochloride (**2**; 15.8 g, 0.1 mol) and NaOMe (5.4 g, 0.1 mol) in EtOH (100 mL) is added phenylazomalononitrile (**1**;[8] 17 g, 0.1 mol). The resulting mixture is refluxed for 3 h and then poured into water (250 mL). The precipitated brown solid is collected, washed with water, and recrystallized from EtOH affording the title compound; yield: 28.4 g (85%); mp 299–301 °C.

$C_{15}H_{13}N_7$ (291.3) calc. C 61.85 H 4.50 N 33.60
found 61.99 4.33 33.68

^{1}H-NMR (CF_3CO_2D/TMS): δ = 7.45–8.04 (m, 5H, C_6H_5), 8.94, 9.23 (A_2B_2, 4H, C_5H_4N).

4,5,6-Triamino-2-(4-pyridyl)pyrimidine Trihydrochloride (4 · HCl):
A mixture of **3** (35 g, 0.12 mol) and Raney Ni (2.5 g) in DMF (300 mL) is hydrogenated at 70–80 °C at 50 psi until the uptake of H_2 stops. After cooling to r.t., the catalyst is separated by filtration and the filtrate is concentrated to near dryness under vacuum. The residue is dissolved in 6 N HCl (300 mL), heated on a steam bath for 1 h and then treated with charcoal. The filtrate is concentrated to near dryness and the red solid residue is recrystallized from

5	R	5	R
a	Me	**f**	$CH_2CH_2CO_2H$
b	Et	**g**	CH_2NHAc
c	Pr	**h**	$CH_2C_6H_4OMe$-4
d	*i*-Pr	**i**	CH_2OH
e	*t*-Bu	**j**	H

Table. Compounds **5b–h** Prepared

Product	Yield[a] (%)	mp (°C) (solvent)	Molecular Formula[b]	^{1}H-NMR (CF_3CO_2D/TMS)[c] δ, J (Hz)
5b	68	>300 (*i*-PrOH)	$C_{12}H_{12}N_6$ (240.3)	1.69 (t, 3H, J = 7, $CH_2C\underline{H}_3$), 3.46 (q, 2H, J = 7, $C\underline{H}_2CH_3$), 9.03 (s, 4H, C_5H_4N)
5c	60	>320 (EtOH)	$C_{13}H_{14}N_6$ (254.3)	1.26 (t, 3H, $CH_2CH_2C\underline{H}_3$), 2.17 (m, 2H, $CH_2C\underline{H}_2CH_3$), 3.42 (t, 2H, J = 7, $C\underline{H}_2CH_2CH_3$), 9.05 (s, 4H, C_5H_4N)
5d	52	248–251 (EtOH)	$C_{13}H_{14}N_6 \cdot 2CH_3SO_3H$ (440.5)	1.72 [d, 6H, J = 6, $CH(C\underline{H}_3)_2$], 3.18 (s, 6H, 2 × CH_3SO_3), 3.75 (m, 1H, $C\underline{H}(CH_3)_2$, 9.02 (s, 4H, C_5H_4N)
5e	43	272–274[d]	$C_{14}H_{16}N_6$ (268.3)	1.79 [s, 9H, $C(CH_3)_3$], 9.03 (s, 4H, C_5H_4N)
5f	74	>320[d]	$C_{13}H_{12}N_6O_2$ (284.3)	3.1 (m, 2H, $CH_2C\underline{H}_2CO_2$), 4.0 (m, 2H, $C\underline{H}_2CH_2CO_2$), 9.02 (s, 4H, C_5H_4N)
5g	55	>325 (DMF/MeOH)	$C_{13}H_{13}N_7O$ (283.3)	2.35 (s, 3H, CH_3CO), 5.1 (s, 2H, CH_2N), 9.0, 9.13 (A_2B_2, 4H, C_5H_4N)
5h	58	286–289 (EtOH)	$C_{18}H_{16}N_6O$ (332.4)	4.04 (s, 3H, OCH_3), 4.75 (s, 2H, CH_2), 7.18, 7.45 (A_2B_2, 4H_{arom}), 9.01 (s, 4H, C_5H_4N)

[a] Yield of isolated product.
[b] Satisfactory microanalyses for C, H and N were obtained within ±0.45% of the theoretical values.
[c] Recorded on a Varian HA 100spectrometer.
[d] Did not need recrystallization.

MeOH and collected; yield: 25.8 g (69%); mp > 320°C.

$C_9H_{10}N_6 \cdot 3HCl$ (311.7) calc. C 34.69 H 4.21 N 26.97
found 35.13 4.03 26.89

^{1}H-NMR (CF_3CO_2D/TMS): δ = 8.85, 9.17 (A_2B_2, 4H, C_5H_4N).

8-Methyl-2-(4-pyridyl)adenine Dihydrochloride (5a):
A mixture of **4** (as the free base, 49 g, 0.24 mol) and acetic anhydride (500 mL) is refluxed with stirring for 22 h and then concentrated under vacuum. The resulting residue is dissolved in hot aq NaOH and treated with charcoal. The filtrate is acidified with AcOH and the resulting yellow precipitate after collection, is recrystallized as the dihydrochloride from EtOH; yield: 49 g (68%); mp > 310°C.

$C_{11}H_{10}N_6 \cdot 2HCl$ (299.2) calc. C 44.16 H 4.04 N 28.09
found 44.38 4.21 28.17

^{1}H-NMR (CF_3CO_2D/TMS): δ = 3.13 (s, 3H, CH_3), 9.05 (s, 4H, C_5H_4N).

8-Alkyl-2-(4-pyridinyl)adenines 5b–h; General Procedure:
A mixture of **4** (20.2 g, 0.1 mol) and the appropriate acid anhydride or acid (0.4 mol) is heated in an oil bath at 190–200°C for 4 h and then cooled to r.t. The resulting dark brown mixture is dissolved in aq NaOH by heating on a steam bath and then decolorized with charcoal. The filtrate is acidified with AcOH and the resulting precipitate is collected, washed with water and recrystallized (Table).

8-Hydroxymethyl-2-(4-pyridyl)adenine (5i):
A stirred mixture of **4** (10.1 g, 0.05 mol) and 70% aq glycolic acid (20 mL) is heated in an oil bath at 210–220°C for 3.5 h using an air condenser to allow the water to evaporate. After cooling to r.t., the resulting mixture is dissolved in hot aq NaOH and treated with charcoal. The filtrate is acidified with AcOH and the resulting precipitate is collected, washed with water, and dried; yield: 6.7 g (55%); mp > 300°C.

Treatment of **5i** with methanesulfonic acid in ethanol affords the dimethanesulfonate; mp 256–258°C.

$C_{11}H_{10}N_6O \cdot 2CH_3SO_3H$ (434.5) calc. C 35.94 H 4.18 N 19.34
found 35.94 4.32 19.32

^{1}H-NMR (CF_3CO_2D/TMS): δ = 3.18 (s, 6H, 2 × CH_3SO_3), 5.56 (s, 2H, CH_2O), 8.98, 9.2 (A_2B_2, 4H, C_5H_4N).

2-(4-Pyridyl)adenine (5j):
A stirred mixture of **4** (20.2 g, 0.1 mol) and dimethylformamide dimethyl acetal (15 mL, 0.12 mol) in DMF (50 mL) is heated under reflux for 7 h and then cooled to r.t. Filtration affords a tan crystalline product; yield: 13.5 g (63%); mp 340°C.

$C_{10}H_8N_6$ (212.2) calc. C 56.60 H 3.80 N 39.60
found 56.38 3.71 39.23

^{1}H-NMR (CF_3CO_2D/TMS): δ = 9.19 (s, 4H, C_5H_4N), 9.53 (s, 1H, H-8).

8-Mercapto-2-(4-pyridyl)adenine (6):
A stirred mixture of **4** (40.4 g, 0.2 mol) and *O*-potassium *O*-ethyl dithiocarbonate (60 g, 0.37 mol) in EtOH (600 mL) is refluxed for 22 h and then concentrated under reduced pressure. The yellow solid residue is dissolved in hot water and filtered. The filtrate is acidified with acetic acid and the resulting yellow solid is collected, washed with water and dried; yield: 45 g (92%); mp > 330°C.

Treatment of a suspension of **6** in EtOH with 1 equiv of methanesulfonic acid gives the monomethanesulfonate; mp > 330°C.

$C_{10}H_8N_6 \cdot CH_3SO_3H$ (340.4) calc. C 38.82 H 3.55 N 24.69
found 38.64 3.53 24.75

^{1}H-NMR (CF_3CO_2D/TMS): δ = 3.16 (s, 3H, CH_3SO_3), 8.8, 9.2 (A_2B_2, 4H, C_5H_4N).

8-(Methylthio)-2-(4-pyridyl)adenine Dimethanesulfonate (7a):
A stirred mixture of **6** (12.2 g, 0.05 mol) and milled anhydrous K_2CO_3 (10 g, 0.07 mol) in DMF (100 mL) is heated on a steam bath for 0.5 h. MeI (3.5 mL, 0.057 mol) is added at r.t. and the resulting mixture is stirred for 1 h and then concentrated to near dryness under reduced pressure. The residue is quenched with water, neutralized with AcOH, collected, and washed with water. Treatment of the dry product with 2 equiv of $MeSO_3H$ in EtOH gives the salt; yield: 16.7 g (74%); mp 221–223°C (dec).

$C_{11}H_{10}N_6S \cdot 2CH_3SO_3H$ (450.5) calc. C 34.66 H 4.03 N 18.65
found 34.73 4.12 18.38

^{1}H-NMR (CF_3CO_2D/TMS): δ = 3.1 (s, 3H, SCH_3), 3.23 (s, 6H, 2 × CH_3SO_3), 8.9, 9.17 (A_2B_2, 4H, C_5H_4N).

8-(Ethylthio)-2-(4-pyridyl)adenine Dimethanesulfonate (7b):
Compound **7b** is prepared by the procedure used for the preparation of product **7a**; yield: 65%; mp 168–170°C (dec).

$C_{12}H_{12}N_6S \cdot 2CH_3SO_3H$ (464.5) calc. C 36.20 H 4.34 N 18.09
found 36.31 4.48 18.16

^{1}H-NMR (CF_3CO_2D/TMS): δ = 1.67 (t, 3H, J = 7 Hz SCH_2CH_3), 3.17 (s, 6H, 2 × CH_3SO_3), 3.66 (q, 2H, J = 7 Hz SCH_2CH_3), 9.0, 9.16 (A_2B_2, 4H, C_5H_4N).

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Errata and Addenda

1990

Chang, Y.-H.; Uang, B.-J.; Wu, C.-M.; Yu, T.-H.
Synthesis **1990**, 1033. The correct country in the address of the Authors on page 1033 in both cases should be, Taiwan, Republic of China.

1991

Marchand, A. P.; Reddy, G. M. *Synthesis* **1991**, 198.
The following correction was received from Professor Marchand. Shortly after the appearance of our paper, we became aware of a comparable study of ultrasonic acceleration of the reduction of polycyclic 1,2-dicarbonylethylene and 1,2-dicarbonylcyclobutane derivatives with zinc/acetic acid (Chou, T.-C.; Hong, F.-T.; Chuang, K.-S. *Tunghai J.* **1987**, *28*, 659). We thank Professor Teh-Chang Chou of having brought this paper to our attention.

Lesher, G. Y.; Singh, B. *Synthesis* **1991**, 211.
Note the correct spelling of Dr. Singh's forename is Baldev.

Takeda, K.; Ayabe, A.; Suzuki, M.; Konda, Y.; Harigaya, Y. *Synthesis* **1991**, 689. In footnote d of Table 2 on page 690 the correct quantity of 4-dimethylaminopyridine (DMAP) should be 0.033g, 0.05 mmol.