On the Chichibabin Amination of Pyrimidine and *N*-Alkylpyrimidinium Salts Using Liquid Ammonia/Potassium Permanganate [1]

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Treatment of the 2-*R*-pyrimidines (**1**, R = methyl, ethyl, *i*-propyl and *t*-butyl) with potassium amide/liquid ammonia/potassium permanganate leads to amination at C-4(6). The yields of the 4(6)-amino compounds **3** increase in the order 2-methyl (10%), 2-ethyl (30%), 2-*i*-propyl (45%) and 2-*t*-butyl (60%). Treatment of the 2-R-*N*-methylpyrimidinium salts (**4**, R = hydrogen, methyl) with liquid ammonia/potassium permanganate leads to a regiospecific imination at C-6, the corresponding 2-R-1,6-dihydro-6-imino-1-methylpyrimidines **6** being obtained in 80-85% yield. It is proved by ^{15}N-labelling that no ring opening is involved in these imination reactions. Treatment of the imino compounds with base leads to the corresponding 2-R-6-methylaminopyrimidines **8**, involving, as proved by ^{15}N-labelling, an ANRORC-mechanism. 2-*t*-Butyl-1-ethylpyrimidinium tetrafluoroborate (**9b**) when treated with liquid ammonia/potassium permanganate undergoes *N*-deethylation, 2-*t*-butylpyrimidine being exclusively formed.

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Amination of 2-Alkylpyrimidines.

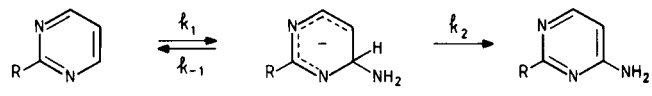
We have reported that pyrimidine can conveniently be aminated into 4-aminopyrimidine when treated with liquid ammonia/potassium amide/potassium permanganate at −33° [2]. As by-product a small amount of 2-aminopyrimidine has been obtained. Using the same procedure 5-bromo- and 5-phenylpyrimidine [2] too could be easily aminated into the corresponding 4-amino compounds. Due to the high electrophilicity of the pyrimidine ring in 5-nitropyrimidine, this compound only needs the weak nucleophilic ammonia and potassium permanganate to be aminated. At −33° 4-amino-5-nitropyrimidine is obtained, at −60° the 2-amino-5-nitro compound [3]. In order to complement further the generality and applicability of this very convenient amination procedure we extended our study to the amination of 2-R-pyrimidines (R = methyl-, ethyl-, *i*-propyl-, *t*-butyl) **1a-d**.

When 2-methylpyrimidine (**1a**) was dissolved in a solution of potassium amide in liquid ammonia, subsequently an equimolar amount of potassium permanganate was added during stirring and the solution was then stirred for half an hour, after work-up 4-amino-2-methylpyrimidine (**3a**) was obtained (10%), 83% of **1a** could be recovered. Thus, the reaction with **1a** occurs much slower than with pyrimidine. This is not unexpected. The methyl group is in the strong basic medium deprotonated and the anion formed is strongly deactivated for nucleophilic attack. Since in the series methyl-, ethyl-, *i*-propyl the acidity of the hydrogen on the α-carbon atom is decreasing, a consequence is that the formation of the covalent σ-adduct **2**, being the supposed intermediate in these aminations, is more favoured. This has been found indeed. Compound **1b** gave a 4-amino-2-ethylpyrimidine (**3b**) in 30% yield, from **1c** 4-amino-2-*i*-propylpyrimidine (**3c**) was isolated in 45% yield and from 2-*t*-butylpyrimidine (**1d**) the 4-amino compound **3d** was obtained in 60% yield.

Attempts to establish the intermediacy of σ-adducts by measuring solutions of **1a-1d** in liquid ammonia/potassium amide (thus, in the absence of potassium permanganate) were *not* successful. Not any indication of adduct formation (even in the case of the 2-*t*-butyl compound) was obtained.

Apparently, for the compounds **1a-1d** the equilibrium **1** ← **2** lies far to the left ($k_1 \leq k\text{-}1$) and k_2 is low compared to k-1. In the presence of an oxidant the formation of the product **3** is considerably increased and the equilibrium $k_1/k\text{-}1$ shifts to the right. This result is in contrast to the one found with the parent compound pyrimidine, which is known to undergo a very efficient adduct formation into **2** (R = H). The conclusion seems justified that without an alkyl group at C-2, the equilibrium **1** (R = H) ← **2**(R = H) lies far to the right ($k_1 \geq k\text{-}1$).

Scheme I



1 2 3

a) R = CH_3, b) R = C_2H_5, c) R = i-C_3H_7, d) R = t-C_4H_9

Amination of *N*-Alkylpyrimidinium Salts.

It has been reported that *N*-alkylazinium salts (*i.e.* *N*-alkylpyridinium-, *N*-alkylquinolinium- and *N*-alkylisoquinolinium salts) [4] easily undergo a regiospecific covalent addition with liquid ammonia. It takes place at the carbon,

adjacent to the ring nitrogen, although in cases where the *N*-alkyl group is large (*t*-butyl group) addition at the para position of the ring nitrogen has also been observed [5]. We recently found that these σ-adducts can easily be oxidized by potasssium permanganate into the 1-alkyl-2-imino-1,2-dihydroazines. Since also *N*-alkylpyrimidinium salts easily undergo a regiospecific covalent addition in liquid ammonia we become interested whether by oxidation with permanganate iminopyrimidines could be prepared.

When a solution of 1-methylpyrimidinium iodide **4a** in liquid ammonia was treated with potassium permanganate, in 80% yield 1,6-dihydro-6-imino-1-methylpyrimidine (**6a**) was formed. Its structure was confirmed by conversion of **6a** into 1,6-dihydro-1-methyl-6-oxopyrimidine (**7a**) on treatment with acid. When the amination was carried out in ^{15}N-labelled ammonia, containing 5.3% ^{15}N, it was found that **6a*** also contained 5.3% ^{15}N, but that **7a** obtained from **6a*** by acid treatment was not ^{15}N-labelled. This result shows that during the amination no ring opening was involved. Since **4a**, has been reported to give the σ-adduct **5a** when dissolved in liquid ammonia, it seems reasonable to assume that **5a** is the intermediate in the oxidation.

When the reaction mixture, obtained from **4a** and liquid ammonia/potassium permanganate was directly treated with an aqueous solution of potassium hydroxide interestingly enough *not* **6a**, but the isomeric (4)6-methylaminopyrimidine (**8a**) was obtained (90-95%). Heating of **8a** with acid gave **7a**. Carrying out the same procedure as described above using, however, ^{15}N-labelled ammonia (5.3% ^{15}N), we found that **8a*** contained 5.3% ^{15}N and that **7a*** obtained from **8a*** also contained 5.3% ^{15}N. It is evident that during base treatment **6a** has undergone an ANRORC Dimroth-type rearrangement into **8a** (see Scheme II). Similar results were obtained with 1,2-dimethylpyrimidinium iodide (**4b**). See Experimental.

Treatment of 2-ethyl (**9a**)-, 2-*i*-propyl (**9b**)- and 2-*t*-butyl-1-ethylpyrimidinium tetrafluoroborate (**9c**) with liquid ammonia/potassium permanganate gave reaction mixtures, in which *N*-dealkylated product was present. Increase of the size of the alkyl group at C-2 leads to increasing amounts of dealkylated product. In fact, from **9c** exclusively 2-*t*-butylpyrimidine (**1d**) was formed. From **9a** and **9b** respectively, a mixture of the corresponding imino compounds **10a,b** and 2-ethylpyrimidine (**1b**) or 2-*i*-propylpyrimidine (**1c**), respectively, was found, as indicated by the ^1H-nmr spectra of the crude reaction mixtures. The ratio imino compound/N-dealkylated product is for R = ethyl larger than for R = *i*-propyl.

Scheme III

9 10

a) R = C_2H_5, b) R = i-C_3H_7, c) R = t-C_4H_9

EXPERIMENTAL

Melting points are uncorrected. Mass spectra are determined on an AEI MS-902 mass spectrometer equipped with a VG ZAB console. The ^1H-nmr spectra are recorded on a Varian EM-390 spectrometer equipped with a Varian EM-3940 variable temperature controller with DSS or TMS as internal standard (δ = 0 ppm).

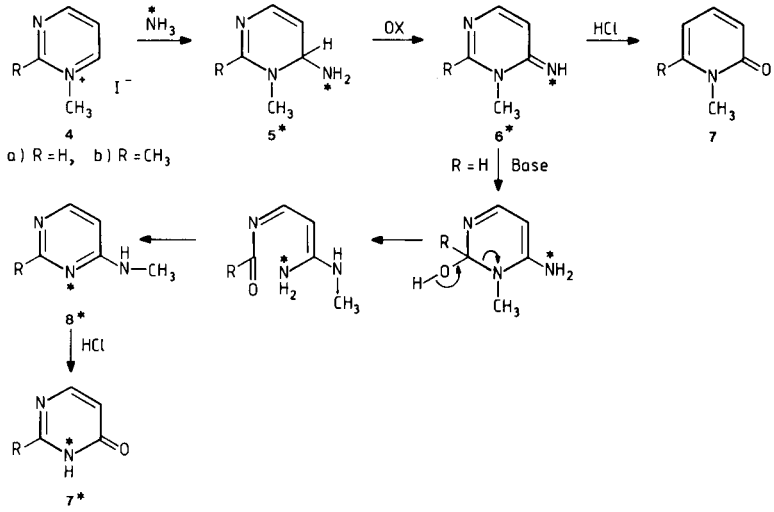
Starting Materials and Reference Compounds.

2-Methylpyrimidine (**1a**), 2-ethylpyrimidine (**1b**), 2-*i*-propylpyrimidine (**1c**) and 2-*t*-butylpyrimidine (**1d**) were donated by DSM (Dutch States Mines). 1-Methylpyrimidinium iodide (**4a**) [6] and 1,2-dimethylpyrimidinium iodide (**4b**) [7] and 1,6-dihydro-1-methyl-6-oxopyrimidine (**7a**) [8] were prepared according to procedures described in the literature.

1,2-Diethylpyrimidinium Tetrafluoroborate (**9a**).

A solution of 20 mmoles of **1b** in 20 ml of methylene chloride was refluxed for 5 hours with 22 mmoles of triethyloxonium tetrafluoroborate.

Scheme II



After cooling the solvent was evaporated off and the residue obtained recrystallized from methanol-ether, yield, 70-75%; mp 109-110°; ^{1}H-nmr (deuterated methanol): δ 9.31 (dd, H_4), 9.17 (dd, H_6), 7.96 (dd, H_5), 4.60 (q, N-CH_2), 3.31 (q, C-CH_2), 1.62 (t, CH_3) and 1.48 (t, CH_3).

Anal. Calcd. for $C_8H_{13}BF_4N_2$: C, 42.89; H, 5.85; M.W. 224.02. Found: C, 42.64; H, 5.88.

1-Ethyl-2-isopropylpyrimidinium Tetrafluoroborate (**9b**).

This compound was prepared from **1c** in a similar way as described above for **9a**, yield, 70%, mp 69-71°; ^{1}H-nmr (deuterated methanol): δ 9.40 (dd, H_4), 9.21 (dd, H_6), 8.02 (dd, H_5), 4.78 (q, N-CH_2), 3.73 (m, C-H), 1.65 (t, CH_3), 1.51 (d, 2 CH_3).

Anal. Calcd. for $C_9H_{15}BF_4N_2$: C, 45.41; H, 6.35; M.W. 238.05. Found: C, 45.08; H, 6.36.

1-Ethyl-2-*t*-butylpyrimidinium Tetrafluoroborate (**9c**).

This compound was prepared from **1d** in a similar way as described for the preparation of **9a**, yield 50%, mp 143-144°; ^{1}H-nmr (deuterated water): δ 9.28 (dd, H_4), 9.12 (dd, H_6), 8.03 (dd, H_5), 4.87 (q, N-CH_2), 1.63 (t, CH_3), 1.58 (s, *t*-C_4H_9).

Anal. Calcd. for $C_{10}H_{17}BF_4N_2$: C, 47.65; H, 6.80; M.W. 252.07. Found: C, 47.94; H, 6.62.

4-Methylamino-2-methylpyrimidine (**8b**).

This compound was prepared according to a modified literature procedure. An amount of 1.28 g (10 mmoles) of 4-chloro-2-methylpyrimidine [9] was heated with an 40% aqueous solution of methylamine at 120° for 15 hours in a sealed tube. After cooling, the solution was diluted with water and extracted with chloroform. After removing of the solvent from the chloroform extracts, 1.1 g (90%) of **8b** was obtained, mp 86-87° (from petroleum ether (40-60°) (lit [10] 90°). The ^{1}H-nmr and microanalytical data are identical to those reported.

General Amination Procedure for the 2-Alkylpyrimidines **1a-1d**.

Four mmoles of **1a-1d** was added to a solution of 16 mmoles of potassium amide in liquid ammonia. This solution was stirred for a few hours at −33°. Then 4 mmoles of potassium permanganate were added to this solution, whereupon an additional half hour of stirring took place. Ammoniumchloride was added and ammonia was evaporated off. The residue obtained was extracted with chloroform, the chloroform extracts dried on magnesium sulphate and then the solvent evaporated off *in vacuo*. The residue obtained from the compounds **1a**,**1b** was subjected to chromatography, using silcon, and petroleum ether as eluent. The residue obtained from **1c**,**1d** was direct crystallized from petroleum ether 40-60°. The result obtained for the different compounds are as follows:

Amination of **1a**.

4-Amino-2-methylpyrimidine (**3a**) was obtained in a yield of 10%, mp 204-205° (lit [11] 202-203°); exact mass 109.0639. Calcd. for $C_5H_7N_3$: 109.0640. Compound **1a** could be recovered in 83% yield.

Amination of **1b**.

4-Amino-2-ethylpyrimidine (**3b**) was obtained in a yield of 30%, mp 180-181° (lit [12] 183°); exact mass 123.0796. Calcd. for $C_6H_9N_2$: 123.0796. Compound **1b** was recovered in 60% yield.

Amination of **1c**.

4-Amino-2-*i*-propylpyrimidine (**3a**) was obtained in a yield of 45%, mp 159-160° (from petroleum ether 40-60°); exact mass 137.0950. Calcd. for $C_7H_{11}N_3$: 137.0953; ^{1}H-nmr (deuteriochloroform/methanol-d_4): δ 8.08 (d, H_6), 6.30 (d, H_5), 2.94 (m, C-H), 1.22 (d, 2 CH_3).

Anal. Calcd. for $C_7H_{11}N_3$: C, 61.28; H, 8.08; M.W. 137.18. Found: C, 61.03; H, 8.09.

Amination of **1d**.

4-Amino-2-*t*-butylpyrimidine (**3d**) was obtained in a yield of 60%, mp 152-153° (from petroleum ether 40-60°); exact mass: 151.1105. Calcd. for $C_8H_{13}N_3$: C, 151.1109; ^{1}H-nmr (deuteriochloroform/methanol-d_4): δ 8.06 (d, H_6), 6.10 (d, H_5), 1.24 (s, t-C_4H_9).

Anal. Calcd. for $C_8H_{13}N_3$: C, 63.54; H, 8.66; M.W. 151.21. Found: C, 63.28; H, 8.72.

General Procedure for the Imination of the *N*-Alkylpyrimidinium Salts **4a**, **4b**, **9a-9c**.

Five mmoles of the appropriate salt was added to a solution of 5 mmoles of potassium permanganate in 40-50 ml of liquid ammonia. This solution was stirred for 4 hours at −33°. The ammonia was evaporated off and the residue obtained extracted with chloroform. After drying the combined extracts with magnesium sulphate, the solvent was evaporated off *in vacuo*. The ^{1}H-nmr and mass spectral data were recorded of the crude mixture before product isolation was carried out. The results obtained are as follows:

Imination of **4a**.

1,6-Dihydro-6-imino-1-methylpyrimidine (**6a**) was obtained in a yield of 80-85%; exact mass 109.0639. Calcd. for $C_5H_7N_3$: 109.0640; ^{1}H-nmr (deuteriochloroform): δ 7.87 (s, H_2), 7.38 (d, H_4), 6.25 (d, H_5), 5.90 (br, s, NH), 3.51 (s, CH_3). These data are in agreement with those reported for this compound in the literature [13]. Compound **6a** could be isolated in crystalline form as its hydroiodide salt.

Heating of crude **6a** with concentrated hydrochloric acid at 125° for 12 hours in a sealed tube gave a reaction mixture from which, after neutralization and by extraction with chloroform, 1,6-dihydro-1-methyl-6-oxopyrimidine (**7a**) was isolated (75-80%), mp 128-129° (lit [8] 125-126°), mp picrate of **7a**, 178-179° (lit [8] 175-176°). Mixed melting point determination with an authentic specimen gave no depression.

Treatment of crude **6a** with a weak basic solution for some hours gave 4(6)-methylaminopyrimidine (**8a**), yield 90-95%, mp 71-72° (lit [13] 70-71°); exact mass 109.0641. Calcd. for $C_5H_7N_3$: 109.0640; ^{1}H-nmr (deuteriochloroform): δ 8.58 (s, H_2), 8.20 (d, H_4), 6.32 (d, H_5), 6.20 (broad NH): 2.93 (d, CH_3).

Imination of **4b**.

1,6-Dihydro-1,2-dimethyl-6-iminopyrimidine (**6b**) was isolated in 80% yield; exact mass 123.0795. Calcd. for $C_6H_9N_3$: 123.0796; ^{1}H-nmr (deuteriochloroform): δ 7.13 (d, H_4), 6.05 (d, H_5), 5.72 (br, s, NH), 3.40 (s, N-CH_3), 2.36 (s, C-CH_3); mp hydroiodide salt 242-245° (lit [10] 246°).

Heating of crude **6b** with acid following the same procedure as given for **6a** into **7a**, gave 1,6-dihydro-1,2-dimethyl-6-oxopyrimidine (**7b**); mp 62-63° (lit [14] 63-65°); exact mass: 124.0630. Calcd. for $C_6H_8N_2O$: 124.0637; ^{1}H-nmr (deuteriochloroform): δ 7.70 (d, H_4), 6.25 (d, H_5), 3.41 (s, N-CH_3), 2.47 (s, C-CH_3).

Heating of **6b** with a weak basic solution gave compound **8b** being identical with the compound, prepared independently (see above).

Imination of **9a**.

By nmr spectroscopy of the crude reaction mixture it could be established that besides some 1,6-dihydro-1,2-diethyl-6-iminopyrimidine (**10a**), as main product 2-ethylpyrimidine was obtained. No efforts were made to isolate **10a**.

Imination of **9b**.

By ^{1}H-nmr spectroscopy it is evident that mainly 2-*i*-propylpyrimidine is formed, together with 1,6-dihydro-1-ethyl-2-*i*-propyl-6-iminopyrimidine (**10b**).

Imination of **9c**.

Attempts to iminate **9c** were unsuccessful. Only *N*-dealkylation was observed, 2-*t*-butylpyrimidine being formed.

Conversion of the 4-Methylaminopyrimidines **8a**, **8b** into the Corresponding 4-Oxopyrimidines **7a**, **7b**.

Heating of **8a**, **8b** with concentrated hydrochloric acid gave the corresponding 2-R-3,4-dihydro-4-oxopyrimidine (R = H, CH_3) being identical with reference compounds.

Amination of **1a** with ^{15}N-labelled Ammonia.

The procedure was the same as described above for unlabelled ammonia.

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