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N-AMINATION OF UNSYMMETRICALLY SUBSTITUTED PYRIMIDINES. SYNTHESIS OF ISOMERIC N-AMINOPYRIMIDONES

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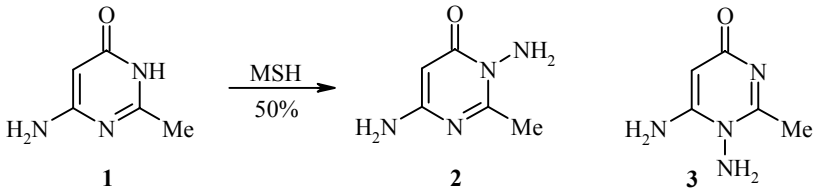
N-Amination of 6-amino-2-methyl-4-pyrimidone with O-(mesitylenesulfonyl)hydroxylamine leads to the 3-amino derivative. The isomeric 1,6-diamino-2-methyl-4-pyrimidone was obtained by the N-amination of the O-benzoyl derivative of the initial pyrimidone and removal of the benzoyl protection.

Keywords: O-(mesitylenesulfonyl)hydroxylamine, 4-pyrimidones, N-amination.

In N-amination reactions of azines with electrophilic aminating agents the most reactive sites are nitrogen atoms with electron-donating substituents, such as amino and alkoxy groups, located in the *ortho* position. Annular nitrogen atoms of the amide type are also extremely reactive when located beside an exocyclic carbonyl group, since such compounds are usually aminated as the anion [1,2].

We have studied the regiodirectivity of amination with O-(mesitylenesulfonyl)hydroxylamine (MSH) of pyrimidone **1** containing two nonequivalent annular nitrogen atoms belonging to the most reactive group.



Pyrimidone **1** is aminated as the sodium salt in methanol at room temperature. It turned out that the sole reaction product was the N-aminopyrimidone **2**, isolated in 50% yield. The structure of N-aminopyrimidone **2** was established by X-ray analysis (Fig. 1, Tables 1, 2). The remainder of the reaction mixture was a mixture of the initial pyrimidone **1** and sodium mesitylenesulfonate. Formation of N-aminopyrimidone **3** was not observed.

By comparing literature and our data it is possible to affirm with a sufficient degree of confidence that on amination of 4-pyrimidone anions the nitrogen atom next to the carbonyl group is the most reactive, and for a wide range of 4-pyrimidones the amination reaction will be directed at the $N_{(3)}$ atom independent of the nature of the substituent at position 6 of the pyrimidine ring.

With the aim of broadening the synthetic potential of the amination reaction we investigated the possibility of applying it to the synthesis of the second possible isomeric amination product of pyrimidone **1**, namely the aminopyrimidone **3**. Since the sole product of the direct amination of compound **1** is pyrimidone **2**, we decided to take advantage of an indirect route linked with the introduction of a carbonyl group into the N-aminopyrimidine.

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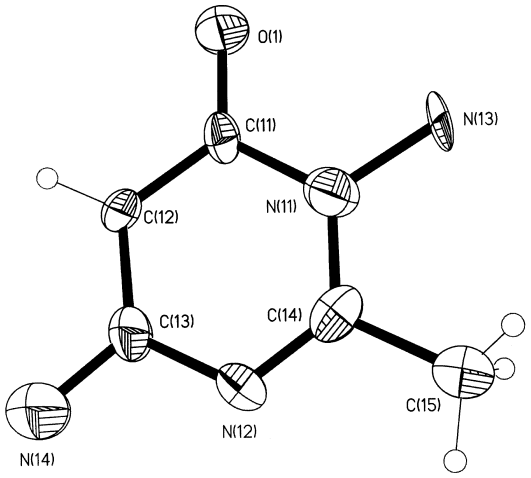
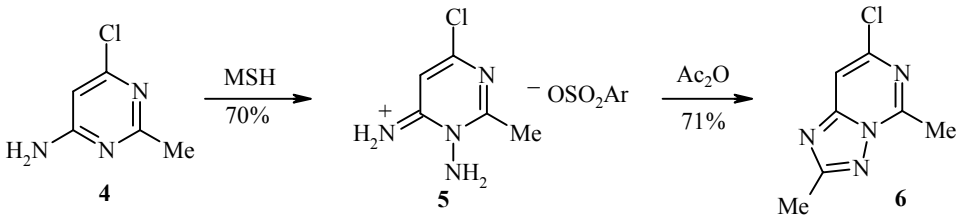


Fig. 1. Structure of N-aminopyrimidone **2** according to X-ray analysis.

For this, the N-aminopyrimidine **5** was synthesized in 70% yield by the amination of chloropyrimidine **4** in chloroform at room temperature. The direction of the amination and the position of the amino group in compound **5** was established by converting the latter into triazolopyrimidine **6**.



Here and subsequently Ar = 2,4,6-$Me_3C_6H_2$

However all attempts to replace the halogen in compound **5** by oxygen proved to be unsuccessful, since destruction of the pyrimidine ring occurred under the reaction conditions.

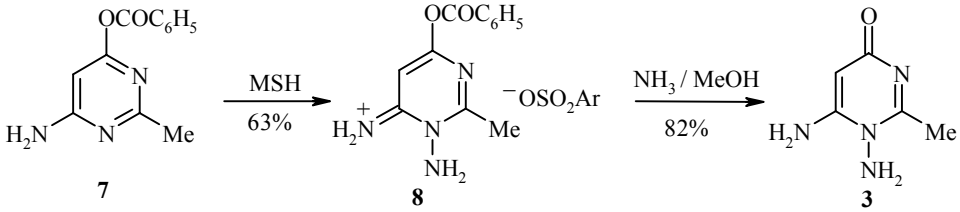
TABLE 1. Bond Lengths in N-Aminopyrimidone **2** according to X-Ray Data

Bond	*l*, nm	Bond	*l*, nm	Bond	*l*, nm
C(11)–O(1)	125.5(8)	C(23)–N(22)	143.0(11)	C(41)–O(4)	121.7(9)
C(11)–C(12)	138.5(8)	C(24)–N(22)	130.0(9)	C(41)–N(41)	142.1(9)
C(11)–N(11)	139.6(9)	C(24)–N(21)	136.4(11)	C(41)–C(42)	144.5(9)
C(12)–C(13)	138.9(10)	C(24)–C(25)	151.9(11)	C(42)–C(43)	134.4(10)
C(13)–N(14)	132.1(9)	C(31)–O(3)	125.2(9)	C(43)–N(42)	135.1(8)
C(13)–N(12)	138.1(10)	C(31)–N(31)	141.8(10)	C(43)–N(44)	138.9(8)
C(14)–N(12)	129.3(9)	C(31)–C(32)	143.5(10)	C(44)–N(42)	132.3(7)
C(14)–N(11)	134.9(11)	C(32)–C(33)	134.4(10)	C(44)–N(41)	134.0(9)
C(14)–C(15)	152.8(11)	C(33)–N(32)	133.8(8)	C(44)–C(45)	148.7(10)
C(21)–O(2)	124.3(8)	C(33)–N(34)	139.0(8)	N(11)–N(13)	141.8(7)
C(21)–C(22)	137.5(8)	C(34)–N(32)	132.4(7)	N(21)–N(23)	140.4(7)
C(21)–N(21)	139.5(9)	C(34)–N(31)	135.8(9)	N(31)–N(33)	145.9(7)
C(22)–C(23)	138.6(10)	C(34)–C(35)	148.2(9)	N(41)–N(43)	147.3(7)
C(23)–N(24)	133.2(9)				

TABLE 2. Valence Angles in N-Aminopyrimidone **2** according to X-Ray Data

Angle	ω, deg.	Angle	ω, deg.
O(1)–C(11)–C(12)	125.1(6)	N(32)–C(34)–C(35)	118.3(6)
O(1)–C(11)–N(11)	118.5(6)	N(31)–C(34)–C(35)	121.9(5)
C(12)–C(11)–N(11)	116.4(7)	O(4)–C(41)–N(41)	119.9(6)
C(11)–C(12)–C(13)	119.9(6)	O(4)–C(41)–C(42)	128.4(8)
N(14)–C(13)–N(12)	113.9(8)	N(41)–C(41)–C(42)	111.6(7)
N(14)–C(13)–C(12)	124.4(7)	C(43)–C(42)–C(41)	121.2(7)
N(12)–C(13)–C(12)	121.6(6)	C(42)–C(43)–N(42)	122.8(6)
N(12)–C(14)–N(11)	125.7(7)	C(42)–C(43)–N(44)	121.5(6)
N(12)–C(14)–C(15)	116.4(8)	N(42)–C(43)–N(44)	115.7(7)
N(11)–C(14)–C(15)	117.9(7)	N(42)–C(44)–N(41)	121.2(6)
O(2)–C(21)–C(22)	125.2(6)	N(42)–C(44)–C(45)	118.1(7)
O(2)–C(21)–N(21)	117.7(6)	N(41)–C(44)–C(45)	120.6(6)
C(22)–C(21)–N(21)	117.1(7)	C(14)–N(11)–C(11)	119.9(6)
C(21)–C(22)–C(23)	119.6(6)	C(14)–N(11)–N(13)	120.6(6)
N(24)–C(23)–C(22)	125.5(7)	C(11)–N(11)–N(13)	119.5(6)
N(24)–C(23)–N(22)	111.4(8)	C(14)–N(12)–C(13)	116.4(8)
C(22)–C(23)–N(22)	123.0(6)	C(24)–N(21)–C(21)	120.0(6)
N(22)–C(24)–N(21)	126.7(7)	C(24)–N(21)–N(23)	119.5(6)
N(22)–C(24)–C(25)	114.8(9)	C(21)–N(21)–N(23)	120.4(6)
N(21)–C(24)–C(25)	118.5(7)	C(24)–N(22)–C(23)	113.5(8)
O(3)–C(31)–N(31)	118.8(6)	C(34)–N(31)–C(31)	124.3(5)
O(3)–C(31)–C(32)	129.4(8)	C(34)–N(31)–N(33)	115.7(5)
N(31)–C(31)–C(32)	111.8(8)	C(31)–N(31)–N(33)	120.0(6)
C(33)–C(32)–C(31)	121.6(7)	C(34)–N(32)–C(33)	120.2(6)
N(32)–C(33)–C(32)	122.3(6)	C(44)–N(41)–C(41)	124.3(5)
N(32)–C(33)–N(34)	116.0(7)	C(44)–N(41)–N(43)	117.4(5)
C(32)–C(33)–N(34)	121.7(6)	C(41)–N(41)–N(43)	118.3(6)
N(32)–C(34)–N(31)	119.8(6)	C(44)–N(42)–C(43)	118.9(7)

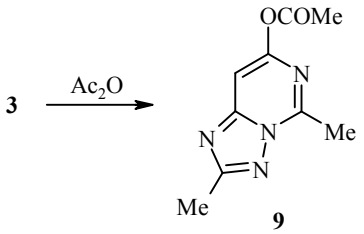
A different route gave a result. Pyrimidone **1** was converted into benzoyloxypyrimidine **7**, which was subjected to amination with O-(mesitylenesulfonyl)hydroxylamine. The sole reaction product isolated in 63% yield was the diaminopyrimidine salt **8**. Treatment of salt **8** with methanolic ammonia solution led to the formation of N-aminopyrimidone **3** in 82% yield.



7 **8** **3**

The differences in the ^{1}H and ^{13}C NMR spectra of compounds **2** and **3** were not large and did not enable a conclusion to be made, based on just these spectra, on the position of the N-amino group in each of them. But they were completely adequate to confirm the nonidentity of the two substances. The structure of

N-aminopyrimidone **3** was also demonstrated by a chemical route. On treating N-aminopyrimidone **3** with acetic anhydride the triazolopyrimidine **9** was obtained.



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EXPERIMENTAL

The ^{1}H NMR spectra were obtained on a Bruker DPX 300 (300 MHz) instrument in DMSO-d_6. The X-ray structural analysis was carried out using a Kappa CCD diffractometer. Solution was carried out by the direct method using SHELXS-86 (Sheldrick, 1990) and SHELXL-93 (Sheldrick, 1993) programs.

Due to its dangerously explosive nature O-(mesitylenesulfonyl)hydroxylamine was not isolated in the pure state, but was obtained directly before use and was put into the reaction without further purification [2].

3,6-Diamino-2-methyl-3H-4-pyrimidone (2). Sodium (0.23 g) was first dissolved in methanol (25 ml), then pyrimidone **1** (1.25 g, 10 mmol) was added. A solution of the equivalent quantity of O-(mesitylenesulfonyl)hydroxylamine in methanol was added dropwise. The reaction mixture was left for 1 day at ~20°C. The methanol was evaporated, the solid residue was extracted with boiling ethyl acetate (4 × 50 ml). The ethyl acetate was evaporated, and the dry residue recrystallized from methanol. N-Aminopyrimidone **2** (0.70 g, 50%) was obtained; mp 181-182°C. ^{1}H NMR spectrum, δ, ppm: 2.34 (3H, s, CH_3); 5.08 (1H, s, 5-H); 5.45 (2H, s, N–NH_2); 6.24 (2H, s, 6-NH_2). Found, %: C 42.83; H 5.72; N 40.12. $C_5H_8N_4O$. Calculated, %: C 42.85; H 5.75; N 39.98.

1,6-Diamino-4-chloro-2-methylpyrimidinium Mesitylenesulfonate (5). A solution of the equivalent quantity of O-(mesitylenesulfonyl)hydroxylamine in chloroform (50 ml) was added dropwise to a solution of pyrimidine **4** [3] (4.0 g, 28 mmol) in chloroform (200 ml). After a few minutes the reaction product began to precipitate as a solid. The reaction mixture was stored for 1 day at ~20°C. The precipitated solid was filtered off and dried. Salt **5** (7 g, 70%) was obtained; mp 249°C. ^{1}H NMR spectrum, δ, ppm: 2.66 (3H, s, 2-CH_3); 6.28 (2H, s, N–NH_2); 7.00 (1H, s, 5-H); 9.02 (1H, s, 6-NH_2); 9.54 (1H, s, 6-NH_2); 2.16 (3H, s, CH_3); 2.49 (6H, s, $(CH_3)_2$); 6.73 (2H, s, Ar). Found, %: C 46.74, H 5.34; N 15.51. $C_5H_7ClN_4.C_9H_{12}O_3S$. Calculated, %: C 46.86; H 5.34; N 15.61.

7-Chloro-2,5-dimethyl[1,2,4]triazolo[1,5-*c*]pyrimidine (6). A mixture of salt **5** (360 mg, 1 mmol) and acetic anhydride (1 ml) was heated for 15 min at a bath temperature of 180°C. A 20% solution of potassium carbonate (20 ml) was poured into the reaction mixture, which was then extracted with chloroform (3 × 15 ml). The extract was dried with magnesium sulfate, and evaporated to dryness in vacuum. Triazolopyrimidine **6** (130 mg, 71%) was obtained; mp 110°C. ^{1}H NMR spectrum, δ, ppm: 2.51 (3H, s, CH_3); 2.84 (3H, s, CH_3); 7.86 (1H, s, 8-H). Found, %: C 46.05; H 3.85; N 30.72. $C_7H_7ClN_4$. Calculated, %: C 46.04; H 3.86; N 30.68.

4-Amino-6-benzoyloxy-2-methylpyrimidine (7). A solution of benzoyl chloride (7.72 g, 55 mmol) in acetonitrile (15 ml) was added dropwise over 4 h with stirring to a suspension of the sodium salt obtained from pyrimidine **1** (6.25 g, 50 mmol) in acetonitrile (25 ml) ~20°C. The reaction mixture was stirred for a further 2 h. The precipitate of sodium chloride was filtered off, and the filtrate evaporated in vacuum. The oily residue rapidly crystallized. The crystals were washed on the filter with ether and pyrimidine **7** (8.60 g, 76%) was obtained; mp 161-162°C. ^{1}H NMR spectrum, δ, ppm: 2.32 (3H, s, CH_3); 6.10 (1H, s, 5-H); 7.08 (2H, s, NH_2); 7.60 (2H, t, Ph); 7.77 (1H, t, Ph); 8.08 (2H, d, Ph). Found, %: C 63.04; H 4.92; N 18.24. $C_{12}H_{11}N_3O_2$. Calculated, %: C 62.87; H 4.84; N 18.33.

1,6-Diamino-4-benzoyloxy-2-methylpyrimidinium Mesitylenesulfonate (8). A solution of the equivalent quantity of O-(mesitylenesulfonyl)hydroxylamine in chloroform (30 ml) was added dropwise to a solution of pyrimidine **7** (6.87 g, 30 mmol) in chloroform (150 ml). The reaction mixture was left for 3 h at ~20°C. The precipitated solid was filtered off and dried. Salt **8** (8.35 g, 63%) was obtained; mp 213-214°C. ^{1}H NMR spectrum, δ, ppm: 2.71 (3H, s, 2-CH_3); 6.28 (2H, s, N–NH_2); 6.96 (1H, s, 5-H); 8.97 (1H, s, 6-NH_2); 9.59 (1H, s, 6-NH_2); 7.65 (2H, t, C_6H_5); 7.80 (1H, t, C_6H_5); 8.11 (2H, d, C_6H_5); 2.16 (3H, s, CH_3), 2.49 (6H, s, 2CH_3); 6.73 (2H, s, Ar_{MS}). Found, %: C 56.72; H 5.42; N 12.59. $C_{12}H_{12}N_4O_2.C_9H_{12}O_3S$. Calculated, %: C 56.74; H 5.44; N 12.60.

1,6-Diamino-2-methyl-3H-4-pyrimidone (3). A 10 M solution of ammonia in methanol (3.0 ml) was added with stirring at ~20°C to a suspension of salt **8** (4.44 g, 10 mmol) in ethanol (80 ml). The salt dissolved completely. A precipitate began to form in the reaction mixture after stirring for 30 min. After 1 h the precipitate was filtered off. After evaporating the filtrate to 40% initial volume an additional amount of solid was obtained, which was combined with the first portion. Pyrimidone **3** (1.15 g, 82%) was obtained; mp >230°C (decomp.). ^{1}H NMR spectrum, δ, ppm: 2.33 (3H, s, CH_3); 4.93 (1H, s, 5-H); 5.45 (2H, s, N-NH_2); 6.32 (2H, s, 6-NH_2). Found, %: C 42.10; H 5.78; N 40.25. $C_5H_8N_4O$. Calculated, %: C 42.85; H 5.75; N 39.98.

7-Acetoxy-2,5-dimethyl[1,2,4]triazolo[1,5-*c*]pyrimidine (9). A mixture of pyrimidone **3** (140 mg, 1 mmol) and acetic anhydride (1 ml) was heated for 15 min at a bath temperature of 180°C. The excess of acetic anhydride was distilled in vacuum, and the residual crystalline substance was sublimed in vacuum at 1 mm Hg. Triazolopyrimidine **9** (110 mg, 52%) was obtained; mp 95°C. ^{1}H NMR spectrum, δ, ppm: 2.33 (3H, s, CH_3); 2.50 (3H, s, CH_3); 2.84 (3H, s, CH_3); 7.54 (1H, s, 8-H). Found, %: C 51.61; H 4.91; N 27.24. $C_9H_{10}N_4O_2$. Calculated, %: C 52.42; H 4.89; N 27.17.

REFERENCES

1. Y. Tamura, J. Minamikawa, and M. Ikeda, *Synthesis*, 1 (1977).
2. A. Yu. Ivanov, V. P. Tsyrenov, N. G. Antonov, P. S. Lobanov, and A. A. Potekhin, *Khim. Geterotsikl. Soedin.*, 807 (2002).
3. Z. Foldi, G. V. Fodar, I. Demjen, H. Szeker, and J. Halmos, *Ber.*, **75**, 755 (1942).