Heterocyclic Chemistry: Benzoyl Peroxide Oxidation of Pyrimidines

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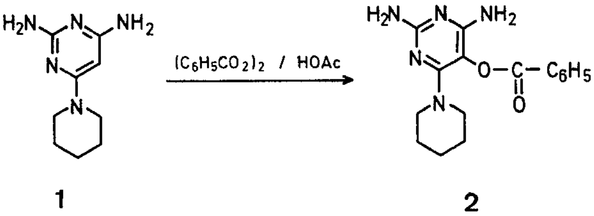
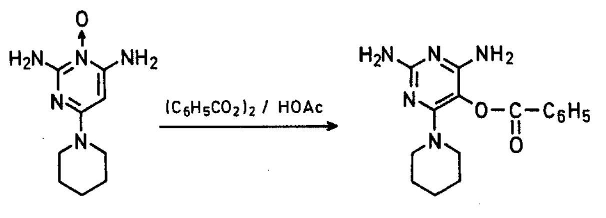
The introduction of a 5-oxygen function at pyrimidine C-5 has been accomplished by condensation reactions, hydrolysis of 5-halo compounds, and nitrous acid decomposition of 5-aminopyrimidines. This chemistry has been reviewed[1]. The direct oxidation of pyrimidine at C-5 has received little attention. Hull has extended the Elbs persulfate oxidation to pyrimidines which have at least one activating group[2]. The Fenton reagent has also been used for pyrimidine oxidations at C-5[3]. The literature cites no general preparation of 5-oxygenated triaminopyrimidines. Such a method is described below.

Benzoyl peroxide in acetic acid cleanly oxidizes triaminopyrimidines at the electron rich C-5 to give 5-O-benzoyl triaminopyrimidines. For example, 2,4-diamino-6-piperidinopyrimidine (**1**) and its 3-oxide **3** both undergo this reaction to give **2** and **4** in yields of 48% and 42%, respectively.



1 **2**

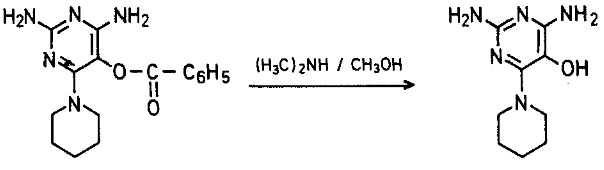


3 **4**

This oxidation has also succesfully been applied to 2,4,6-triaminopyrimidine, 2,4-diamino-6-(*N*-ethylamino)pyrimidine, and 2,4-diamino-6-(*N*,*N*-di-*n*-butylamino) pyrimidine in yields of 15%, 19%, and 38% respectively.

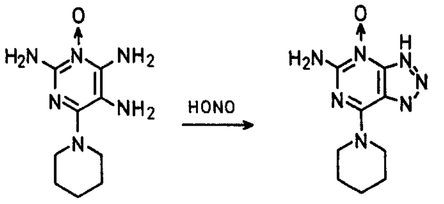
Competitive oxidation pathways appear in solvents such as dichloromethane, chloroform, acetonitrile, and methanol. Compound **1**, for example, is converted to **2** by one equivalent of benzoyl peroxide in 21% yield in dichloromethane and in 48% yield in acetic acid. Compound **3** shows a similar solvent preference. Although oxidation is slower in acetic acid, the selectivity for oxidation at C-5 is much greater.

The benzoyl groups of compounds **2** and **4** were removed by dimethylamine in methanol. The product 5-hydroxy compounds are identified by their spectral properties. Good elemental analysis could not be obtained because of the air sensitivity of these products.



2 **5**

Alternative routes to these C-5-oxidized triaminopyrimidines were explored. Hull's modified Elbs persulfate oxidation[2] on compounds **1** and **3** failed in our hands to give clean reactions. The nitrous acid deamination of **6** not unexpectedly produced **7** rather than the deaminated 5-hydroxy compound.



6 **7**

2,4-Diamino-6-piperidino-5-pyrimidinol Benzoate (2):

A mixture of 2,4-diamino-6-piperidinopyrimidine (2.00 g, 0.985 mmol) and benzoyl peroxide[4] (2.38 g, 9.85 mmol) in glacial acetic acid (10 ml) was stirred under nitrogen for 5.5 h. The mixture was concentrated *in vacuo* and chromatographed (silica gel, 4% methanol in dichloromethane) to give an oil. This was crystallized as its acetic acid salt from dichloromethane and hexane to give the product; yield: 1.75 g (48%); m.p. (decomp.): 164°. The free base was prepared by partition between dichloromethane and aqueous sodium hydrogen carbonate; m.p. (decomp.): 122°.

$C_{16}H_{19}N_5O_2$	calc.	C 61.32	H 6.11	N 22.35
(313.4)	found	61.23	6.24	22.18

M.S.: $m/e = 313$ (M^{+}).

2,4-Diamino-6-piperidino-5-pyrimidinol-3-oxide Benzoate (4):

A mixture of 2,4-diamino-6-piperidinopyrimidine 3-oxide (2.0 g, 9.57 mmol) and 2.20 g (9.57 mmol) of benzoyl peroxide[4] (2.20 g, 9.57 mmol) was stirred in glacial acetic acid (25 ml) for 18 h under nitrogen. The mixture was concentrated *in vacuo* and chromatographed (silica gel, 9% methanol and 1% ammonium hydroxide in dichloromethane) to give product; yield: 2.37 g. The salt was prepared by treatment with 6 *N* hydrogen chloride in ether. The salt was recrystallized from ethyl acetate to give the pure product; yield: 1.45 g (42%); m.p. (decomp.): 152°.

^{1}H-N.M.R. ($CDCl_3$, on free base): $\delta = 1.40$ (br s, 6H, $(CH_2)_3$), 3.40 (br s, 4H, $N(CH_2)_2$), 6.45 (br t, 4H, 2 (NH_2)), 7.50 (m, 3H, Ar), 8.01 ppm (m, 2H, Ar).

$C_{16}H_{19}N_5O_3 \cdot HCl \cdot H_2O$	calc.	C 51.41	H 5.88	N 18.74	Cl 9.48
(373.8)	found	51.32	5.55	18.68	9.56

2,4-Diamino-6-piperidino-5-pyrimidinol (5):

A sample of the acetic acid salt of **2** (300 mg, 0.798 mmol) was partitioned between dichloromethane and aqueous sodium hydrogen carbonate. The organic phase was dried over sodium sulfate and concentrated *in vacuo*. A solution of dimethylamine (2 ml) in methanol (5 ml) was added to the residue. The mixture was stirred at 0° for 6 h. The product was precipitated by addition of acetone, filtered, and dried to give the air sensitive product; yield: 100 mg (60%); m.p. (decomp.): 149°.

M.S.: $m/e = 209$ ($M^{\oplus}$).

5-Amino-7-piperidino-1*H*-*v*-triazolo[4,5-*d*]pyrimidine-4-oxide Hydrochloride (7):

A solution of sodium nitrite (0.74 g, 11.0 mmol) in water (5.0 ml) was dropped into a solution of 2,4,5-triamino-6-piperidinopyrimidine (2.80 g, 10.8 mmol) in 2*N* aqueous hydrochloric acid (50 ml) at 0°. After 30 min, the resultant precipitate was filtered, washed with acetone, and dried to give the product; yield: 1.93 g (67%); m.p. (decomp.): 226°.

$C_9H_{13}N_7O \cdot HCl$	calc.	C 39.78	H 5.19	N 36.09	Cl 13.05
(271.7)	found	39.47	5.18	35.92	13.47

2,4-Diamino-6-dibutylamino-4-pyrimidol Benzoate, Acetate (1:3): Recrystallized from dichloromethane and cyclohexane with a trace of acetic acid; m.p. 124–126°.

$C_{19}H_{27}N_5O_2 \cdot 1/2\ HOAc$	calc.	C 62.65	H 7.51	N 18.57
(377.4)	found	62.53	7.74	18.73

2,4-Diamino-6-*N*-ethylamino-5-pyrimidol Benzoate:

Recrystallized from dichloromethane; m.p. (decomp.) 155–6°.

M.S.: $m/e = 273$ ($M^{\oplus}$).

$C_{13}H_{15}N_5O_2 \cdot 2/3\ HOAc$	calc.	C 54.94	H 5.68	N 22.35
(313.3)	found	54.37	5.88	22.06

2,4,6-Triamino-5-pyrimidol Benzoate:

Recrystallized from methanol and acetonitrile; m.p. (decomp.) 196–200°.

$C_{11}H_{11}N_5O_2$	calc.	C 53.87	H 4.52	N 28.56
(245.2)	found	53.79	4.56	29.08

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[1] D. J. Brown in *Heterocyclic Compounds*, A. Weissberger, Ed., Vol. 16 "*The Pyrimidines*", Wiley-Interscience, New York, 1962.

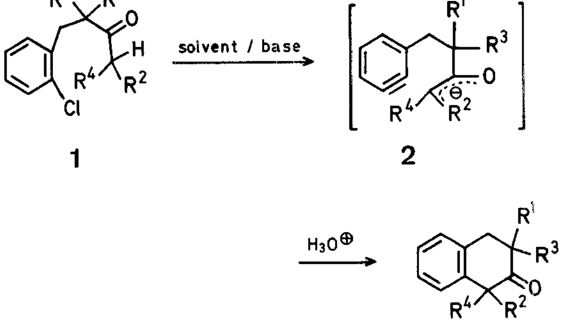
[2] R. Hull, *J. Chem. Soc.* **1956**, 2033.

[3] A. Cies, A. Lefier, M. Ravier, C. Nofre, *Compt. Rend.* **254**, 504 (1962).

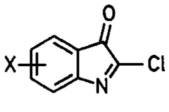
[4] Recrystallized from dichloromethane/methanol.

Errata

B. Loubinoux, P. Caubere, *Synthesis* **1974**, 201–203;
The formula scheme (p. 201) should be:

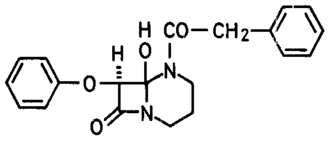


J. Grimshaw, W. J. Begley, *Synthesis* **1974**, 496–498;
The formula **2** in Table 1 (p. 497) should be:



2

A. K. Bose, J. C. Kapur, M. S. Manhas, *Synthesis* **1974**, 891–894;
The formula for compound **18** (p. 891) should be:

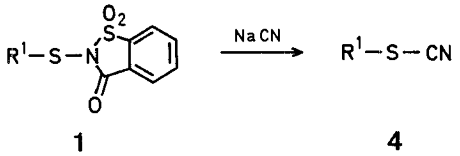


18

H. R. Kricheldorf, E. Leppert, *Synthesis* **1975**, 49–50;
The last entry in the first column of the Table (p. 50) should be: *N*-phenyl-*N*-methylimido.

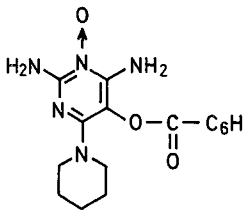
S. Kasina, J. Mematollahi, *Synthesis* **1975**, 162–163;
The name of compound **2** should be:
5,10-dioxo-5*H*,10*H*-diimidazo[3,4-*a*; 3′,4-*d*]pyrazine.

M. Furukawa, T. Suda, A. Tsukamoto, S. Hayashi, *Synthesis* **1975**, 165–167;
The reaction scheme **1**→**4** (p. 166) should be:



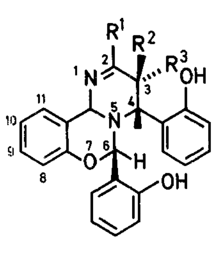
H. Singh, S. Sharma, R. N. Fyer, *Synthesis* **1975**, 325–326;
The name of the title compounds **2** should be:
5-oxobenzimidazo[2,1-*b*][1,3]benzoxazines.

J. M. McCall, R. E. TenBrink, *Synthesis* **1975**, 443–444;
The formula for compound **4** should be:



4

S. Kambe, T. Takajo, K. Saito, T. Hayashi, A. Sakurai, H. Midorikawa, *Synthesis* **1975**, 802–804;



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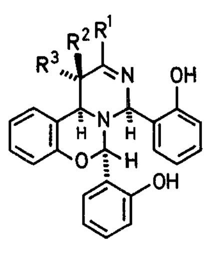

7

The names for compounds **6** should be:
6a: 4,6-Bis[2-hydroxyphenyl]-3,3-dimethyl-3,4-dihydro-11b*H*-pyrimido[1,2-*c*][1,3]benzoxazine
6b: 4,6-Bis[2-hydroxyphenyl]-2,3,3-trimethyl-3,4-dihydro-11b*H*-pyrimido[1,2-*c*][1,3]benzoxazine
6c: 4,6-Bis[2-hydroxyphenyl]-2-methyl-3-phenyl-3,4-dihydro-11b*H*-pyrimido[1,2-*c*][1,3]benzoxazine

The names for compounds **7** should be:
7b: 4,6-Bis[2-hydroxyphenyl]-1,1,2-trimethyl-1,4-dihydro-11b*H*-pyrimido[3,4-*c*][1,3]benzoxazine
7c: 4,6-Bis[2-hydroxyphenyl]-1-methyl-2-phenyl-1,4-dihydro-11b*H*-pyrimido[3,4-*c*][1,3]benzoxazine