A Convenient Method for Regioselective C-5 Halogenation of 4(3*H*)-Oxo-7*H*-pyrrolo[2,3-*d*]pyrimidines

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N-7, *O*-Disilylation of 4(3*H*)-oxo-7*H*-pyrrolo[2,3-*d*]pyrimidines provides a convenient method for activation of these compounds toward regiospecific halogenation at C-5. The sequence is conveniently carried out without isolation of the silylated derivatives and desilylation is spontaneous upon addition of water to the reaction mixture.

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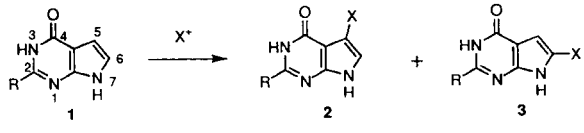
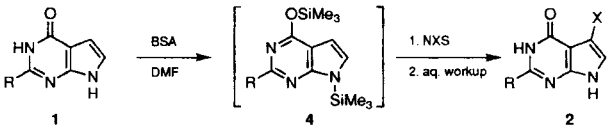
Direct halogenation of 4(3*H*)-oxo-7*H*-pyrrolo[2,3-*d*]-pyrimidines to the corresponding 5-halo derivatives is not synthetically useful due to poor regioselectivity or, apparently in some cases, preferential halogenation at C-6 [1,2].

Figure



For example, reaction of 2-pivaloylamino-4(3*H*)-oxopyrrolo[2,3-*d*]pyrimidine (**1c**) with one equivalent of *N*-iodosuccinimide was reported to give a mixture of 5 and 6 iodides along with the 5,6-diiodide and starting material [2]. The preparation of 4(3*H*)-oxo-5-iodo-7*H*-pyrrolo[2,3-*d*]pyrimidines (**2**), useful intermediates for the synthesis of pyrrolopyrimidine-based antifolate compounds, has been (indirectly) accomplished by deliberate diiodination of **1** with two equivalents of *N*-iodosuccinimide and selective reduction of the resulting 5,6-diiodides with zinc in acetic acid [2,3]. On the other hand, replacement of the 4-oxo group of **1** with, for example, alkoxy or chloro substituents, gives rise to derivatives which readily undergo regiospecific halogenation at C-5 [1,4]. The conversion of the 4-oxo compounds to these derivatives and re-establishment of the 4-carbonyl group after halogenation is, however, an inconvenient process which requires relatively harsh conditions [5]. We wish to report that silylation of pyrrolo[2,3-*d*]pyrimidines **1** in DMF solution, followed immediately by treatment of the resulting silylated derivatives **4** with halogenating agents (Scheme), conveniently provides the corresponding 4(3*H*)-oxo-5-halo-7*H*-pyrrolo-[2,3-*d*]pyrimidines **2** in good yield.

Scheme



1	R	2	R	X
a	H	**a**	H	I
b	CH_3	**b**	H	Br
c	$(CH_3)_3CCONH$	**c**	CH_3	I
		d	CH_3	Br
		e	$(CH_3)_3CCONH$	I
		f	$(CH_3)_3CCONH$	Br

Silylation of **1** effectively converts the C-4 carbonyl group to its silyl enol ether, thus meeting the electronic configurational requirements for regioselective halogenation at C-5. Bis(trimethylsilyl)acetamide (BSA) was found to be the reagent of choice for the silylation step, with two moles per mole of substrate giving the disilylated intermediate **4** at a convenient rate at 40° in DMF. Two equivalents of BSA were required in order to avoid the formation of mixtures of monosilylated derivatives and unreacted **1** in addition to **4**. The iodination of **1c** after exposure to one equivalent of BSA, for example, gave rise (after workup) to 8-10% of the 5,6-diiodide of **1c** and a reduced yield (60%) of the desired **2e** [6]. Both the *N*-7 and *O*-silyl substituents in the halogenated product were unstable toward hydrolysis under mild conditions such that desilylation was spontaneous during ordinary aqueous workup (see Experimental).

The structures of the products **2** were established by comparison of the proton nmr spectra of **2a, 2c** and **2e** [2] with authentic samples prepared by the method of Taylor, *et al.* [7]. The 5 and 6 protons in the unhalogenated **1c** have been reported to be found at δ 6.37 and 6.92 (DMSO) respectively [8]. The finely split signals at around δ 7.1 in **2a-2f** correlate closely with the reported value for the C-6 proton in **2e** (δ 7.12, J = 1.8 Hz) [2]. The regiochemical preference for halogenation was indeed impressive; in all cases no evidence for the presence of the isomeric 6-halo compounds **3** could be detected in the nmr spectra of the crude products.

The procedure is applicable to both bromination and iodination of 4(3*H*)-oxo-7*H*-pyrrolo[2,3-*d*]pyrimidines with

the requisite *N*-halosuccinimides (Table), and yields have been good in most cases. The reaction could be carried out in dichloromethane solution (entry 6), underscoring the marked improvement in solubility of the silylated intermediates **4** as compared to the starting pyrrolopyrimidines **1**. In this case, desilylation was carried out in DMF after removal of the dichloromethane under vacuum in order to standardize the isolation of the product with the other experiments. Elemental iodine (entry 7) was relatively unreactive toward **1c** as compared to *N*-iodosuccinimide. Some diiodination occurred during the reaction of **1c** with iodine monochloride (entry 8), suggesting that premature desilylation may have taken place during the halogenation step in that case. Addition of imidazole to the reaction mixture did not completely eliminate diiodination. Chlorination of silylated intermediate **4c** with *N*-chlorosuccinimide (entry 10) did not proceed beyond 50% conversion under the conditions used for bromination and iodination, and separation of the product from unreacted starting material by chromatography proved to be difficult and was not accomplished. The product, **2g**, was assigned the 5-chloro structure on the basis of nmr data obtained on the mixture after subtraction of signals due to the starting material **1c**.

Table. Halogenation of N-7,O-Disilylated 4(3*H*)-oxo-7*H*-pyrrolo[2,3-*d*]-pyrimidines

Entry	Substrate	Reagent	Solvent	Product	Yield
1	**1a**[a]	NIS	DMF	**2a**	88
2	**1a**	NBS	DMF	**2b**	75
3	**1b**[b]	NIS	DMF	**2c**	87
4	**1b**	NBS	DMF	**2d**	84
5	**1c**[c]	NIS	DMF	**2e**	83
6	**1c**	NIS	CH_2Cl_2	**2e**	71[d]
7	**1c**	I_2	DMF	**2e**	10
8	**1c**	ICl	DMF	**2e**	41[e]
9	**1c**	NBS	DMF	**2f**	63
10	**1c**	NCS	DMF	**2g**	50[f]

[a] Prepared by a literature [9] method. [b] Prepared by a literature [10] method. [c] Prepared by a literature [2] method. [d] Desilylation step was carried out in DMF-water after evaporation of the dichloromethane. [e] Reaction carried out in the presence of imidazole. Product was purified by silica chromatography. [f] Reaction was incomplete under the conditions of the general procedure and the product was not separable from starting material by chromatography in several systems. Yield was estimated by nmr.

The procedure described herein is suitable for the large scale preparation of 5-bromo and iodo compounds **2**. Kilogram quantities of **2e** have, for example, been successfully prepared from **1c**.

EXPERIMENTAL

General Procedure for the Preparation of 4(3*H*)-Oxo-5-halo-7*H*-pyrrolo[2,3-*d*]pyrimidines **2**.

To a solution of 1.0 g of the 4-hydroxypyrrolopyrimidine **1** in 20 ml of dry DMF was added bis(trimethylsilyl)acetamide (2.2 equivalents) and the resulting solution stirred at 40° for about two hours. Completeness of silylation was indicated by nmr analysis of an aliquot showing disappearance of the N-3 and N-7 proton signals. The reaction was cooled to ambient temperature and the halogenating reagent (see Table 1, equivalents) was added in one portion [11]. The reaction mixture was protected from light and stirred at ambient temperature until completion [12] was indicated by nmr analysis (disappearance of pyrrole C-H doublets and emergence of a single finely split doublet). The mixture was poured into 50 ml of water with stirring. A mild exotherm was observed, followed by precipitation of the crude product. After stirring for 1-2 hours, the product was collected by filtration, washed with water, dried, and reslurried in 10 volumes of 10% methanol in chloroform. Filtration and drying gave the 5-halogenated 4(3*H*)-oxo-7*H*-pyrrolo[2,3-*d*]pyrimidines **2**.

4(3*H*)-Oxo-5-iodo-7*H*-pyrrolo[2,3-*d*]pyrimidine (**2a**).

This compound was obtained by iodination of 4(3*H*)-oxo-7*H*-pyrrolo[2,3-*d*]pyrimidine (**1a**) as a colorless solid, mp 248-253° dec, lit [3] mp >245°; ^{1}H nmr (DMSO-d_6): δ 7.17 (d, J = 2.4 Hz, 1H), 7.80 (d, J = 2.3 Hz, 1H), 11.8 (br s, 1H), 12.1 (br s, 1H); ^{13}C nmr (DMSO-d_6): δ 53.8, 107.3, 125.5, 143.6, 147.9, 157.8; ir (potassium bromide pellet): ν 3061, 1668, 1591, 1370, 1212, 973, 777 cm^{-1}; uv (ethanol): λ max 268 nm (ε 8,870), 224 nm (ε 13,300); ms: m/z 261 (M$^+$).

4(3*H*)-Oxo-5-bromo-7*H*-pyrrolo[2,3-*d*]pyrimidine (**2b**).

This compound was obtained by bromination of 4(3*H*)-oxo-7*H*-pyrrolo[2,3-*d*]pyrimidine (**1a**) as a colorless solid, mp 269-271° dec, lit [4] mp 270-271° dec; ^{1}H nmr (DMSO-d_6): δ 7.17 (d, J = 2.4 Hz, 1H), 7.80 (d, J = 2.3 Hz, 1H), 11.9 (br s, 1H), 12.2 (br s, 1H); ^{13}C nmr (DMSO-d_6): δ 89.3, 105.5, 120.4, 144.3, 147.4, 157.5; ir (potassium bromide pellet): ν 3095, 1665, 1591, 1372, 988, 891 cm^{-1}; uv (ethanol): λ max 266 nm (ε 10,100), 219 nm (ε 14,500).

2-Methyl-4(3*H*)-oxo-5-iodo-7*H*-pyrrolo[2,3-*d*]pyrimidine (**2c**).

This compound was obtained by iodination of 2-methyl-4(3*H*)-oxo-7*H*-pyrrolo[2,3-*d*]pyrimidine (**1b**) as a colorless solid, mp 270-275° dec; ^{1}H nmr (DMSO-d_6): δ 2.23 (s, 3H), 7.08 (d, J = 2.2 Hz, 1H), 11.7 (br s, 1H), 11.9 (br s, 1H); ^{13}C nmr (DMSO-d_6): δ 20.8, 53.6, 105.0, 124.8, 148.6, 153.1, 158.6; ir (potassium bromide pellet): ν 3064, 1668, 1599, 1301, 1027, 970, 809 cm^{-1}; uv (ethanol): λ max 273 nm (ε 9,900), 224 nm (ε 14,200).

Anal. Calcd. for $C_7H_6IN_3O$: C, 30.57; H, 2.20; N, 15.28. Found: C, 30.30; H, 2.16; N, 14.99.

2-Methyl-4(3*H*)-oxo-5-bromo-7*H*-pyrrolo[2,3-*d*]pyrimidine (**2d**).

This compound was obtained by bromination of 2-methyl-4(3*H*)-oxo-7*H*-pyrrolo[2,3-*d*]pyrimidine (**1b**) as a colorless solid, mp 300-305° dec; ^{1}H nmr (DMSO-d_6): δ 2.23 (s, 3H), 7.07 (d, J = 2.1 Hz, 1H), 11.7 (br s, 1H), 11.9 (br s, 1H); ^{13}C nmr (DMSO-d_6): 20.8, 89.1, 103.2, 119.6, 148.1, 153.5, 158.2; ir (potassium bromide pellet) ν 3069, 1673, 1601, 1300, 1195, 1032, 987, 809 cm^{-1}; uv (ethanol): λ max 267 nm (ε 8,800), 224 nm (ε 13,200); ms: m/z 229, 227 (M$^+$).

Anal. Calcd. for $C_7H_6BrN_3O$: C, 36.87; H, 2.65; N, 18.42. Found: C, 36.64; H, 2.65; N, 18.13.

N-[4(3*H*)-Oxo-5-iodo-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]-2,2-dimethylpropionamide (**2e**).

This compound was obtained by iodination of *N*-[4(3*H*)-oxo-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]-2,2-dimethylpropionamide (**1c**) as a colorless solid, mp 255-260° dec, lit [2] mp >240° dec; ^{1}H nmr (DMSO-d_6): δ 1.20 (s, 9H), 7.07 (d, J = 2.0 Hz, 1H), 10.7 (br s, 1H), 11.7 (br s, 1H), 11.8 (br s, 1H); ^{13}C nmr (DMSO-d_6): δ 26.3, 39.7, 54.1, 103.8, 125.0, 146.9, 147.9, 156.5, 180.9; ir (potassium bromide pellet): ν 3241, 1682, 1656, 1616, 1576, 1239, 938, 783 cm^{-1}; uv (ethanol): λ max 295 nm (ε 13,750), 230 nm (ε 13,700).

N-[4(3*H*)-Oxo-5-bromo-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]-2,2-dimethylpropionamide (**2f**).

This compound was obtained by bromination of *N*-[4(3*H*)-oxo-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]-2,2-dimethylpropionamide (**1c**) as a colorless solid, mp 277-281° (dec); ^{1}H nmr (DMSO-d_6): δ 1.18 (s, 9H), 7.09 (d, J = 2.5 Hz, 1H), 10.8 (br s, 1H), 11.8 (br s, 1H), 11.9 (br s, 1H); ^{13}C nmr (DMSO-d_6): δ 26.3, 39.7, 89.5, 101.9, 119.6, 147.1, 147.3, 156.0, 180.9; ir (potassium bromide pellet): ν 3225, 1680, 1652, 1613, 1571, 1242, 1175, 938 cm^{-1}; uv (ethanol): λ max 292 nm (ε 12,800), 224 nm (ε 14,000); ms: (fd) m/z 314, 312 (M^+).

Anal. Calcd. for $C_{11}H_{13}BrN_4O_2$: C, 42.19; H, 4.18; N, 17.89. Found: C, 41.77; H, 4.10; N, 17.58.

REFERENCES AND NOTES

[1] A. J. Cocuzza, *Tetrahedron Letters*, **29**, 4061 (1988).

[2] E. C. Taylor, D. G. Kuhnt, C. Shih, S. M. Rinzel, G. B. Grindey, J. Barredo, M. Jannatipour and R. G. Moran, *J. Med. Chem.*, **35**, 4450 (1992).

[3] E. C. Taylor, D. G. Kuhnt, C. Shih and G. B. Grindey, U.S. Patent 4,996,206 (1991); *Chem. Abstr.*, **115**, 183951w (1991).

[4] J. F. Gerster, B. C. Hinshaw, R. K. Robins and L. B. Townsend, *J. Heterocyclic Chem.*, **6**, 207 (1969).

[5] For example, the most commonly used chlorination procedure involves heating of the 4-hydroxy compounds with phosphorus oxychloride; J. Davoll, *J. Chem. Soc.*, 131 (1960). The corresponding 4-alkoxypyrrolo-[2,3-*d*]pyrimidines, on the other hand, have usually been prepared by reaction of the 4-chloro derivatives with alkali alkoxides. Both the 4-chloro and 4-alkoxy derivatives can be converted back to the 4-hydroxy compounds by displacement of the alkoxy substituent with sodium or potassium hydroxide under vigorous conditions or by dealkylation with, for example, sodium thiocresylate/HMPA; F. Seela and H.-D. Kehne, *Leibigs Ann. Chem.*, 137 (1983).

[6] This experiment was carried out under the general conditions used for the iodination of silylated **1c** as described in the experimental section. The silylation step (one equivalent of BSA) provided a mixture of about 20% of disilylated **4c** and 25% of unreacted **1c**, with the remainder being a roughly equal mixture of the two possible monosilylation products by nmr analysis. About 16% of **1c** was recovered unreacted after exposure of this mixture to 1.2 equivalents of NIS in addition to **2e** and the 5,6-diiodo derivative.

[7] References 2 and 3.

[8] The assignment of the 6.37 and 6.92 signals to protons at C-5 and C-6, respectively, in **1c** could be anticipated from the published nmr analysis of 4-chloropyrrolo[2,3-*d*]pyrimidine and its C-5 and C-6 halogenated derivatives as described in reference 4. Additionally, the iodination (without silylation) of **1a**, which possessed nmr peaks at δ 6.36 and 6.95, (DMF-d_7) assigned to H-5 and H-6, respectively, gave a minor product with an apparent singlet at δ 6.57 (DMF-d_7), attributed to H-5 of the 6-iodo isomer of **2a**, in addition to **2a** itself (H-6, δ 7.17) and the 5,6-diiodide; T. M. Wilson, Lilly Research Laboratories, unpublished observations. Thus monohalogenation of the 4(3*H*)-oxopyrrolo[2,3-*d*]pyrimidines at C-5 or C-6 causes a downfield shift of about 0.2 ppm of the surviving pyrrole ring proton but does not change the relative positions of the shifts of these protons (as compared to the parent compound) and the assignments for the pyrrole positions in the 4(3*H*)-oxo series are relatively as predicted by the preceding study of the 4-chloro analogs.

[9] J. Davoll, cited in reference 5.

[10] R. A. West and L. J. Beauchamp, *J. Org. Chem.*, **26**, 3809 (1961).

[11] In the case of IC1, 2.4 equivalents of imidazole was added prior to addition of the halogenating agents.

[12] In all cases reaction was complete in < 16 hours (overnight); halogenations of **1c** required 1.5 hours.