H_3C_ϵ), 2.4 (m, Met: H_2C_γ), 2.48 (s, (5Me)Th: H_3C), 2.78 (t, Histam: H_2C_β), 3.49 (t, Histam: H_2C_α), 3.90 (dd, Met: HC_α), 6.78 (dd, (5Me)Th: H^4), 6.83 (s, Histam: H^5), 7.23 (d, (5Me)Th: H^3), 7.55 (d, Histam: H^2), 8.26 (s, (5Me)Th: H^{im}).

Optical rotation: $\alpha^{20} = -8.13°$ L mol^{-1} dm^{-1} (concentration independent).

Data Collection and Structure Determination of (5Me)-Th-Met-Histam. Crystallization of (5Me)Th-Met-Histam was achieved from a solution of about 2 g in a mixture of methanol (5 mL), diethyl ether (10 mL), and hexane (5 mL) placed at 4 °C.

X-ray data were collected for a transparent plate-shaped [0.1 × 0.2 × 0.5 mm] crystal, glued on top of a glass fiber. Crystal data and numerical results of the structure determination have been collected in Table I. Cell parameters were derived from the SET4 setting angles of 25 reflections [6° < θ < 12°]. Data were corrected for L_p and averaged [$R_{av} = 0.04$]. The structure was solved by direct methods [SHELXS-86][18] and refined by full-matrix least-squares [SHELX-76].[19] All non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms (except for H[N3] that was located from a difference map and its position refined) were introduced on calculated positions and refined with fixed geometry, C–H = 0.98 Å, with two common isotropic thermal parameters. Reflection 001 was omitted from the final refinement cycles. Final coordinates are listed in Table II. Neutral scattering factors were obtained from ref 20 and corrected for anomalous dispersion.[21] The programs PLUTON and PLATON[22] were used for geometrical calculations and illustrations.

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Registry No. BOC-Met-OH, 2488-15-5; H-Histam·2HCl, 56-92-8; BOC-Met-Histam, 124780-96-7; H-Met-Histam·2TFA, 124780-95-6; H-Met-Histam·2HCl, 134781-03-6; (5Me)Th-Met-Histam, 134757-70-3; (5Me)Th-Met-Histam·TFA, 134929-64-9; 5-methyl-2-thiophenecarbaldehyde, 13679-70-4.

Supplementary Material Available: An ORTEP figure (50% probability), H bond network plot, H atom coordinates, anisotropic thermal parameters, bond distances and angles, and NMR spectra of BOC-Met-OH (^{1}H), BOC-Met-Histam (^{1}H), H-Met-Histam·2TFA (^{1}H, ^{19}F), H-Met-Histam·2HCl (^{1}H), and TFA-salt derived (5Me)Th-Met-Histam (^{1}H, ^{19}F) (14 pages); tables of structure factors (25 pages). Ordering information is given on any current masthead page.

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Highly Regioselective Bromination Reactions of Polymethylpyrimidines

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4,5-Dimethyl- and 4,5,6-trimethyl-substituted pyrimidines are brominated at C5-Me with NBS in CCl_4 and at C4(6)-Me with bromine in acetic acid to give the corresponding bromomethyl derivatives in a high yield. The remaining methyl group(s) can also be brominated with high regioselectivity. The 2-methylthio substituent is not oxidized under these conditions.

Introduction

Direct bromination of polymethylbenzenes has been widely used in the synthesis of bromomethyl derivatives.[1] By contrast, a few efficient preparations of bromomethyl-substituted azaaromatic compounds via direct bromination have been reported because overbromination is a major problem. In fact, many successful preparations of tribromomethyl-substituted pyridines,[2] pyrimidines,[3] quinolines,[4] quinoxalines,[4] phenanthridines,[4] and phenanthrolines[5] from the corresponding methyl derivatives are known. Bromination of *o*-dimethyl-substituted pyridines, pyrazine, pyrimidine, and 1,2,4-triazine is of synthetic value for the preparation of the corresponding bis(dibromomethyl) derivatives.[6] These results are in contrast to numerous unsuccessful attempts to improve the low-yield synthesis of 2,6-bis(bromomethyl)pyridine by bromination of 2,6-dimethylpyridine under a variety of experimental conditions.[1,7] The direct bromination of only one methyl group of the latter pyridine[7a] or its 3,5-isomer[8] was also inefficient. Interestingly, however, regioselective brominations of 2,3-dimethylpyridine[9] and 3,4-dimethylpyridine[8] with 1 equiv of NBS have been reported to give mainly a 3-(bromomethyl)-substituted product in both cases, albeit in a low overall yield. A similar regioselectivity was observed in the reaction of 4,6-dichloro-2,5-dimethylpyrimidine with NBS,[10] which gave a 5-(bromomethyl)-pyrimidine. Of related interest is opposite regioselectivity of the bromination reaction of ethyl 6-hydroxy-2,5-dimethyl-4-pyrimidinecarboxylate with bromine in acetic

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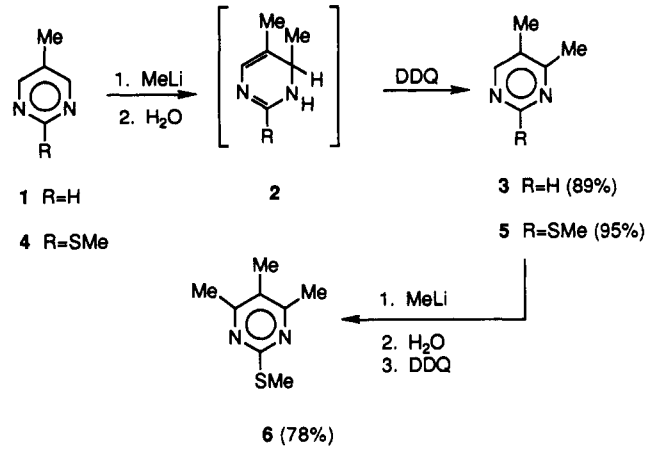
Scheme I



acid to give a 2-tribromomethyl derivative in a high yield.[3] These limited examples suggest that ring nitrogen atoms play a pivotal role in regioselective brominations of methyl substituents with the two reagents. While the methyl group located meta to the ring nitrogen is brominated selectively with NBS, the ortho methyl group undergoes selective bromination with Br_2/AcOH.

In this paper, we report on bromination reactions of dimethylpyrimidines **3** and **5** and a sterically congested trimethylpyrimidine **6**. It was hoped that selective introductions of bromine atoms at benzylic positions of these pyrimidines would provide invaluable intermediates for a facile modification of the pyrimidine ring. The 2-(methylthio)pyrimidines **5** and **6** are included in this study because additional synthetic manipulations are possible with the use of a rich chemistry of the methylthio group.[11]

Results and Discussion

A new efficient synthesis of pyrimidines **3**, **5**, and **6** is given in Scheme I. The approach is based on the addition reaction of methyllithium with a formal C=N double bond of a pyrimidine ring followed by dehydrogenation of the resultant dihydropyrimidine **2**, without isolation, by treatment with DDQ.[12] This method is vastly superior to other reported preparations of **3**,[13] **5**,[14] and **6**[15] because of its simplicity and high efficiency.

The bromination reactions were conveniently monitored by TLC. The reaction of **3** with NBS (Scheme II) gave a rather unstable 5-(bromomethyl)pyrimidine **8** and a stable 5-(dibromomethyl)pyrimidine **7** as a major and minor product, respectively. The NMR spectrum of the mixture was consistent with absolute regioselectivity of the bromination reaction. A rapid chromatographic separation gave pure samples of both products which were fully characterized by NMR, including NOE experiments to establish the bromination site, and by MS. Treatment of **3** with Br_2/AcOH produced unstable 4-(bromomethyl)-pyrimidine **9** as the major product and stable 4-(dibromomethyl)pyrimidine **10**, which were rapidly separated and characterized in a manner similar to that described above. Again, the NMR spectrum of a crude mixture indicated the absence of isomeric products obtained in the reaction with NBS.

As with **3**, the opposite high regioselectivities with similar ratios of bromomethyl- to dibromomethyl-substituted products were observed in the respective reactions of **5** with NBS and bromine. Interestingly, a careful analysis of crude product mixtures revealed the absence of sulfoxides or sulfones (vide infra) that might result from oxidation of the sulfur atom in **5** or products derived from **5**.[16] A high stability of all products **11**–**14** was also an unexpected gratification of these studies. The stability of bromomethyl derivatives **12** and **13** permitted the synthesis of 4,5-bis-(bromomethyl)pyrimidine **16**. The same product **16** was obtained in the reaction of **12** with Br_2/AcOH and in the reaction of **13** with NBS.

In addition to NMR experiments the structures of several brominated products and, therefore, regioselectivities of the bromination reactions were also determined independently by transformations of these products into known derivatives. Thus, DMSO-mediated oxidation of **12** in the presence of $NaHCO_3$ furnished known aldehyde **15**.[17] Interestingly, treatment of **12** with DMSO in the absence of $NaHCO_3$ and followed by aqueous workup gave known alcohol[14] **18a**, additionally characterized as a crystalline ester **18b**. This result can be explained in terms of hydrolysis of the intermediate oxysulfonium ion.[18] On the other hand, the treatment of bromide **13** with DMSO gave aldehyde **17** even in the absence of $NaHCO_3$. Apparently, the intermediate oxysulfonium ion derived from **13** undergoes fragmentation mediated by intramolecular proton transfer to the adjacent ring nitrogen. Such intramolecular proton transfer is not possible for the ion derived from **12**. The two types of oxygenation reactions are nicely summarized in the reaction of bis(bromomethyl) derivative **16** with DMSO in the absence of $NaHCO_3$ which produced a hydroxy aldehyde **19a**. Product **19a** has been obtained previously[19a] by using an independent chemistry and suggested to exist in an equilibrium with hemiacetal **19b**.[19b] In this work the two forms of **19** were observed in $CDCl_3$ solution by high-field NMR in the ratio of **19a**:**19b** of 1:3. Complete chemical shift assignments for protons of **19a** and **19b** were made.

The bromination reactions of **6** followed the patterns of those regioselectivity observed with **3** and **5** to give the corresponding bromomethyl derivatives in high yields[16] (Scheme III). Of interest are highly efficient reactions of **20** with NBS and **22** with Br_2/AcOH to give tris(bromomethyl)pyrimidine **23**. A virtual lack of the formation of dibromomethyl derivatives is apparently due to steric hindrance in **23**. This suggestion is consistent with the results of the bromination reaction of a nonhindered methylpyrimidine **24** with Br_2/AcOH, which gave dibromomethyl and bromomethyl derivatives **25** and **26** as major products (Scheme IV). Electrophilic bromination of the pyrimidine ring[20] is also a competing reaction as evidenced by isolation of the minor product **27**. When the reaction

(11) Brown, D. J. *The Pyrimidines. Supplement II*; Interscience: New York, 1985; p 280.
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(15) Kreutzberger, A.; Tesch, U.-H. *J. Heterocycl. Chem.* **1977**, *14*, 1197.
(16) Methyl group signals characteristic of methyl sulfoxides (δ 3.0) and methyl sulfones (δ 3.4) were absent from the ^1H NMR spectra of crude products of the reactions of **5** and **6** with either NBS or Br_2/AcOH. On the other hand, the spectra of the crude mixtures from the NBS-mediated bromination of **5** and **6** gave a minor signal at δ 5.1 in both cases, suggesting bromination of SMe to give SCH_2Br. These products could not be isolated in an analytically pure form.
(17) Benneche, T.; Undheim, K. *Acta Chem. Scand.* **1982**, *B36*, 529.
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(19) (a) Shadbolt, R. S.; Ulbricht, T. L. V. *J. Chem. Soc. C* **1968**, 1203. (b) Hemiacetal **19b** is an analogue of pyridoxal (vitamin B6): Harris, S. A.; Heyl, D.; Folkers, K. *J. Am. Chem. Soc.* **1944**, *66*, 2088.
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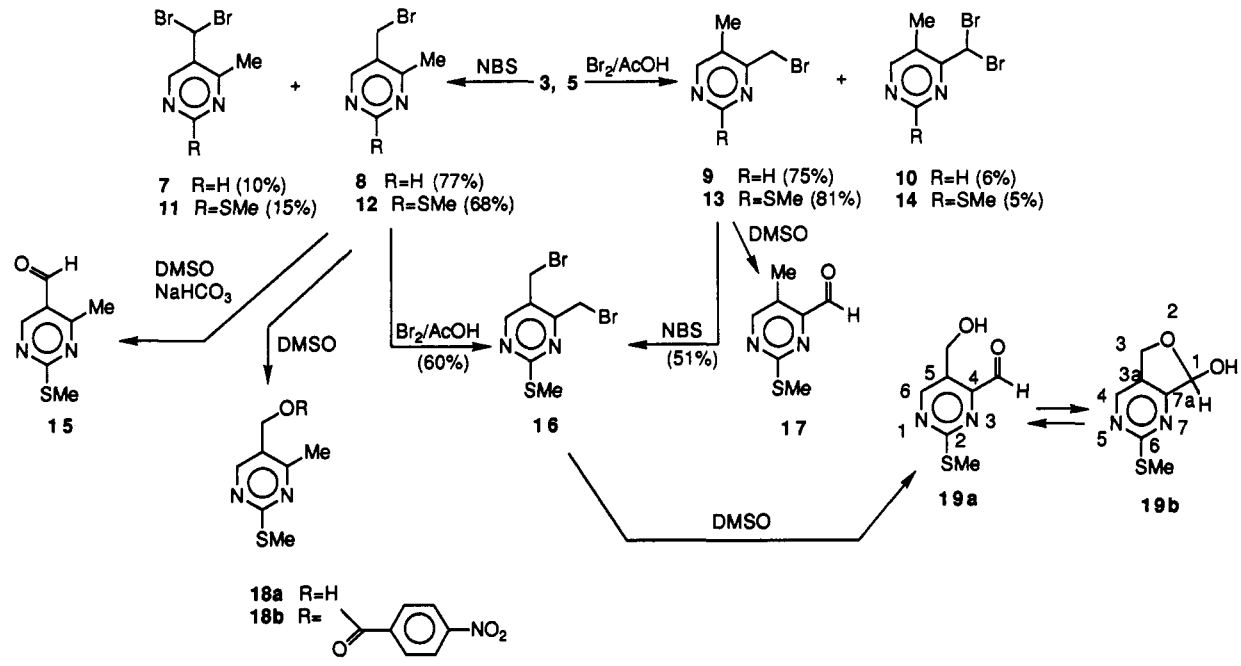
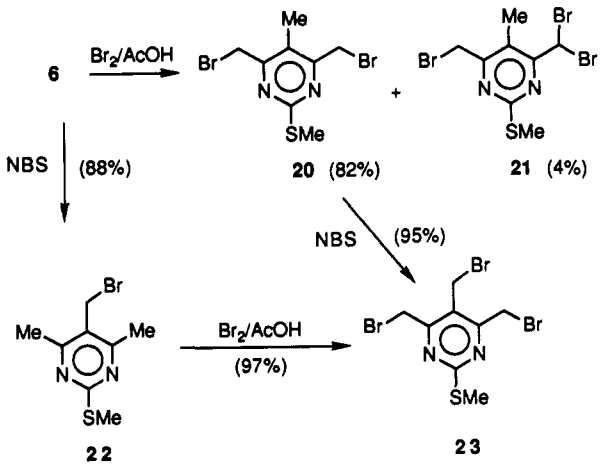
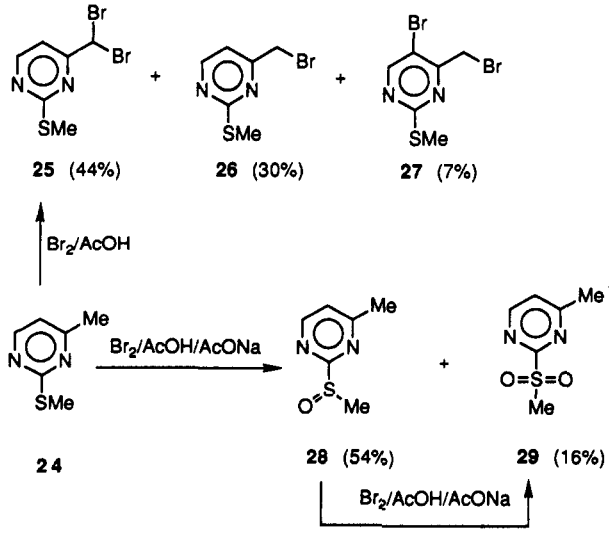
Scheme II



Scheme III

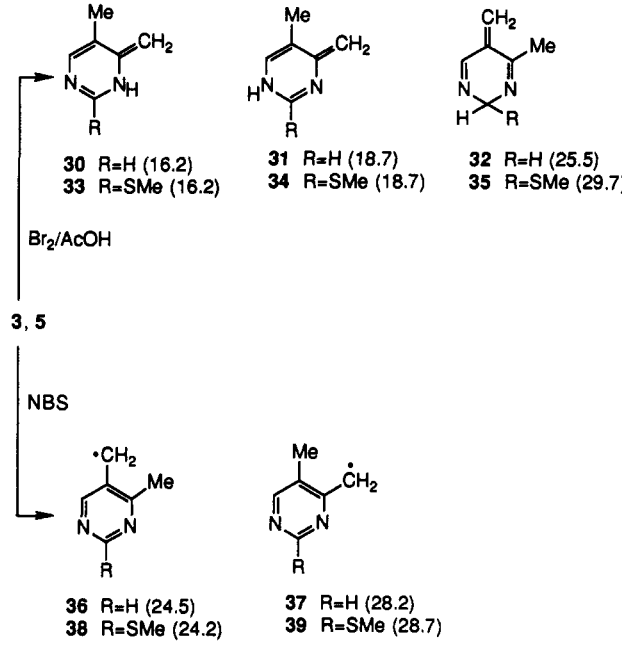


Scheme IV



was conducted in the presence of sodium acetate, sulfoxide **28** and sulfone **29** were produced and the benzylic and ring brominations were suppressed.[21] Treatment of **28** with Br_2 gave **29** as the sole product.

Scheme V. Destabilization Energies (kcal/mol) Calculated by the AMPAC Method for Possible Intermediates 30–39 in the Bromination Reactions of 3 and 5



All these results strongly suggest that benzylic bromination of 4-methylpyrimidines with Br_2 in AcOH involves protonation of the pyrimidine ring.[22] This protonation is suppressed in a mixture of AcOH with AcONa, which is less acidic than AcOH itself, and with pyrimidines containing strongly electronegative sulfinyl or sulfonyl groups.[23]

(21) ^1H NMR spectrum of crude products gave a small singlet at δ 4.60 characteristic of 4-CH_2Br. This bromination occurred in a yield <3%.

(22) Riand, J.; Chenon, M. T.; Lumbroso-Bader, N. *J. Am. Chem. Soc.* **1977**, *99*, 6838.

(23) For example, pK_a of 0.59 for 2-(methylthio)pyrimidine is reduced to <−3 upon oxidation to either 2-(methylsulfinyl)pyrimidine or 2-(methylsulfonyl)pyrimidine: Brown, D. J.; Ford, P. W. *J. Chem. Soc. C* **1967**, 568.

It is likely that protonation of one of the nitrogen atoms is followed by deprotonation of the 4-methyl group to give methide-type intermediate products such as **30**, **31** or **33**, **34** derived from **3** and **5**, respectively (Scheme V). Electrophilic addition of bromine to such intermediate products would furnish the observed bromomethyl derivatives. Since bromination of a 5-methyl group does not occur with Br_2/AcOH, the corresponding intermediate products **32** and **35** apparently are not formed. As can be seen from Scheme V, the theoretical calculations of the destabilization energies of the discussed possible intermediate products are fully consistent with the observed regioselectivity.

Bromination of the 5-methyl group occurs under conditions which are typical for free-radical reactions. Free radicals **36** and **38** are the suggested intermediates in the respective reactions of **3** and **5**. The results of similar calculations on two possible sets of free radicals **36**, **37** and **38**, **39** derived from **3** and **5**, respectively, are fully consistent with the intermediary of **36** and **38** in these reactions. Regardless of the mechanism, the introduction of a second bromine atom into a bromomethyl group would be sterically inhibited in the presence of an ortho substituent, as observed.

Experimental Section

The reported yields of all new compounds are for analytically pure samples obtained by separation on a chromatotron (silica gel, hexanes/CH_2Cl_2, unless stated otherwise). Solid samples were additionally crystallized from hexanes or hexanes/CH_2Cl_2. Melting points are uncorrected. Molecular ion peaks were observed in the mass spectra of all new compounds. Unless stated otherwise, the ^1H NMR spectra were run at 60 MHz in $CDCl_3$ with Me_4Si as internal reference.

In the preparation of **3**, **5**, and **24** the respective pyrimidines **1** (Aldrich), **4**,[24] and 2-(methylthio)pyrimidine[25] were reacted with MeLi (Aldrich), and then the mixtures were treated with DDQ by using a general procedure.[12] A similar treatment of **5** gave **6**. Crude products were distilled on a Kugelrohr (80–120 °C (10 mmHg)) to give **3** (yield 89%), **5** (95%), **6** (78%), and **24** (86%), the spectra of which were identical with those reported (**3**,[13] **5**,[14] **6**,[15] **24**[26]).

The MO calculations were carried out with the program AMPAC 1.00 (QCPE Program 506, Indiana University) running on either a MicroVAX II or a VAXstation 3100. All MO calculations were performed using the unrestricted Hartree-Fock version of the Schrödinger equation and the Austin Model 1 quantum mechanical model method.[27] Structures for **3**, **5**, and **30–35** were generated with the program MACROMODEL 2.5 (provided by Professor C. Still, Columbia University). The MACROMODEL output files were edited to AMPAC data files in internal coordinates. Data files for radicals **36–39** were produced from AMPAC data files for **3** or **5**. All subsequent MO calculations were conducted with geometry optimization for bond lengths, bond angles, and dihedral angles.

Bromination of 5-Methylpyrimidines with NBS: General Procedure. A solution of a 5-methylpyrimidine (5.0 mmol), a catalytic amount of benzoyl peroxide (0.01 g), and NBS (1.1 g, 6.2 mmol) in CCl_4 (75 mL) in a Pyrex flask was heated under reflux and irradiated with a long-wavelength UV lamp for 40 min. Then the mixture was filtered, and the solution containing products was washed with a 10% solution of $NaHCO_3$ and concentrated on a rotary evaporator. Products were separated by chromatography.

Bromination of 4-Methyl- and 4,6-Dimethylpyrimidines with Bromine in Acetic Acid: General Procedure. A solution of a 4-methylpyrimidine (1.5 mmol) and bromine (0.26 g, 1.6 mmol) in AcOH (2 mL) was heated at 80 °C for 2 h. The amounts of Br_2 and AcOH were doubled for 4,6-dimethylpyrimidines. Then the mixture was cooled and treated with ether. The resultant precipitate was filtered and treated with 10% $NaHCO_3$. Products were isolated by extraction of the aqueous mixture with ether, concentration of the ether, and chromatography. The given yields for **25–27** (**24** + 1.07 equiv of Br_2) are based on consumed **24**.

5-(Dibromomethyl)-4-methylpyrimidine (7): yield 10%; an oil; ^1H NMR δ 2.66 (s, 4-Me), 6.85 (s, $CHBr_2$), 9.00 (s, 2-H and 6-H). Anal. Calcd for $C_6H_6Br_2N_2$: C, 27.09; H, 2.27; Br, 60.09; N, 10.54. Found: C, 27.25; H, 2.22; Br, 59.80; N, 10.40.

5-(Bromomethyl)-4-methylpyrimidine (8): yield 77%; an unstable yellow oil darkening on standing; ^1H NMR δ 2.65 (s, Me), 4.49 (s, CH_2), 8.62 (s, H-6), 9.05 (s, 2-H); HRMS m/z (M^+) calcd 187.9773, obsd 187.9764.

4-(Bromomethyl)-5-methylpyrimidine (9): yield 75%; an unstable yellow oil quickly darkening on standing; ^1H NMR δ 2.41 (s, Me), 4.47 (s, CH_2), 8.47 (s, 6-H), 8.93 (s, 2-H); HRMS m/z (M^+) calcd 187.9773, obsd 187.9780.

4-(Dibromomethyl)-5-methylpyrimidine (10): yield 6%; mp 103–104 °C; ^1H NMR δ 2.50 (s, Me), 6.72 (s, $CHBr_2$), 8.59 (s, 6-H), 9.12 (s, 2-H). Anal. Calcd for $C_6H_6Br_2N_2$: C, 27.09; H, 2.27; N, 10.54. Found: C, 27.10; H, 2.28; N, 10.50.

5-(Dibromomethyl)-4-methyl-2-(methylthio)pyrimidine (11): yield 15%; an oil; ^1H NMR δ 2.55 and 2.58 (2s, 4-Me and SMe), 6.67 (s, $CHBr_2$), 8.70 (s, 6-H). Anal. Calcd for $C_7H_8Br_2N_2S$: C, 26.94; H, 2.58; Br, 51.22; N, 8.97. Found: C, 27.05; H, 2.53; Br, 51.00; N, 8.91.

5-(Bromomethyl)-4-methyl-2-(methylthio)pyrimidine (12): yield 68%; mp 54–56 °C; ^1H NMR δ 2.50 and 2.53 (2s, 4-Me and SMe), 4.33 (s, CH_2Br), 8.23 (s, 6-H). Anal. Calcd for $C_7H_9N_2OS$: C, 36.06; H, 3.89; Br, 34.27; N, 12.01. Found: C, 35.99; H, 3.92; Br, 34.08; N, 11.86.

4-(Bromomethyl)-5-methyl-2-(methylthio)pyrimidine (13): yield 81%; mp 71–72 °C; ^1H NMR δ 2.30 (s, 5-Me), 2.57 (s, SMe), 4.33 (s, CH_2Br), 8.25 (s, 6-H). Anal. Calcd for $C_7H_9BrN_2S$: C, 36.06; H, 3.89; Br, 34.27; N, 12.01. Found: C, 36.18; H, 3.88; Br, 34.16; N, 11.92.

4-(Dibromomethyl)-5-methyl-2-(methylthio)pyrimidine (14): yield 5%; mp 80–81 °C; ^1H NMR δ 2.45 (s, 5-Me), 2.63 (s, SMe), 6.67 (s, $CHBr_2$), 8.40 (s, 6-H). Bromination of **5** with 2 equiv of Br_2 under otherwise identical conditions gave **14** in a 57% yield. Anal. Calcd for $C_7H_8Br_2N_2S$: C, 26.94; H, 2.58; Br, 51.22; N, 8.97. Found: C, 27.01; H, 2.57; Br, 51.09; N, 9.05.

4,5-Bis(bromomethyl)-2-(methylthio)pyrimidine (16): yield 60% (**12** + Br_2), 51% (**13** + NBS); an unstable yellow oil darkening on standing; ^1H NMR δ 2.63 (s, SMe), 4.57 and 4.61 (2s, 4-CH_2Br and 5-CH_2Br), 8.57 (s, 6-H). Anal. Calcd for $C_7H_8Br_2N_2S$: C, 26.94; H, 2.58; Br, 51.22; N, 8.97. Found: C, 27.30; H, 2.66; Br, 50.91; N, 8.90.

4,6-Bis(bromomethyl)-5-methyl-2-(methylthio)pyrimidine (20): yield 82%; mp 124–125 °C; ^1H NMR δ 2.38 and 2.58 (2s, 5-Me and SMe), 4.45 (s, 4-CH_2Br and 6-CH_2Br). Anal. Calcd for $C_8H_{10}Br_2N_2S$: C, 29.47; H, 3.09; Br, 49.02; N, 8.59. Found: C, 29.53; H, 3.04; Br, 48.85; N, 8.49.

4-(Bromomethyl)-6-(dibromomethyl)-5-methyl-2-(methylthio)pyrimidine (21): yield 4%; mp 102–103 °C; ^1H NMR δ 2.49 and 2.62 (2s, 5-Me and SMe), 4.45 (s, CH_2Br), 6.71 (s, $CHBr_2$). Anal. Calcd for $C_8H_9Br_3N_2S$: C, 23.73; H, 2.24; Br, 59.20; N, 6.92. Found: C, 23.75; H, 2.22; Br, 59.02; N, 6.85.

5-(Bromomethyl)-4,6-dimethyl-2-(methylthio)pyrimidine (22): yield 88%; mp 70–71 °C; ^1H NMR δ 2.53 (s, 4-Me and 6-Me), 2.56 (s, SMe), 4.48 (s, CH_2Br). Anal. Calcd for $C_8H_{11}BrN_2S$: C, 38.87; H, 4.49; Br, 32.33; N, 11.33. Found: C, 38.97; H, 4.46; Br, 32.22; N, 11.41.

4,5,6-Tris(bromomethyl)-2-(methylthio)pyrimidine (23): yield 95% (**20** + NBS), 97% (**22** + Br_2); mp 105–107 °C; ^1H NMR δ 2.58 (s, Me), 4.51 (s, 4-CH_2Br and 6-CH_2Br), 4.71 (s, 5-CH_2Br). Anal. Calcd for $C_8H_9Br_3N_2S$: C, 23.73; H, 2.24; Br, 59.20; N, 6.92. Found: C, 23.62; H, 2.19; Br, 59.00; N, 6.81.

4-(Dibromomethyl)-2-(methylthio)pyrimidine (25): yield 44%; an oil; ^1H NMR δ 2.57 (s, Me), 6.37 (s, $CHBr_2$), 7.32 (d, J = 5 Hz, 5-H), 8.53 (d, J = 5 Hz, 6-H). Anal. Calcd for $C_6H_6Br_2N_2S$: C, 24.18; H, 2.03; N, 9.40. Found: C, 24.49; H, 2.12; N, 9.23.

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4-(Bromomethyl)-2-(methylthio)pyrimidine (26): yield 30%; an unstable oil; ^{1}H NMR δ 2.62 (s, Me), 4.40 (s, CH_2Br), 7.17 (d, J = 5 Hz, 5-H), 8.58 (d, J = 5 Hz, 6-H); HRMS m/z (M^+) calcd 217.9514, obsd 217.9521.

5-Bromo-4-(bromomethyl)-2-(methylthio)pyrimidine (27): yield 7%; mp 62-64 °C; ^{1}H NMR δ 2.60 (s, Me), 4.53 (s, CH_2Br), 8.63 (s, 6-H). Anal. Calcd for $C_6H_6Br_2N_2S$: C, 24.18; H, 2.03; N, 9.40. Found: C, 24.27; H, 2.02; N, 9.48.

Oxidation of 24 with Br_2 in AcOH-AcONa. A solution of **24** (0.33 g, 2.36 mmol) and sodium acetate (3.8 g) in acetic acid (8 mL) was heated at 70 °C and treated dropwise within 1 h with a solution of bromine (1.23 g, 7.67 mmol) in acetic acid (7 mL). After an additional 10 min the mixture was cooled, diluted with water (10 mL), neutralized with solid $NaHCO_3$, and then extracted with $CHCl_3$ (6 × 10 mL).[21] Chromatography on silica gel (CH_2Cl_2-AcOEt (8:2)) gave sulfone[28] **29** (0.065 g, 16%), which was eluted first, and sulfoxide **28** (0.20 g, 54%). Treatment of **28** with bromine under the same conditions gave **29**.

4-Methyl-2-(methylsulfinyl)pyrimidine (28): an oil; ^{1}H NMR δ 2.70 (s, 4-Me), 3.00 (s, S(O)Me), 7.42 (d, J = 5 Hz, 5-H), 8.82 (d, J = 5 Hz, 6-H). Anal. Calcd for $C_6H_8N_2OS$: C, 46.13; H, 5.16; N, 17.94. Found: C, 45.77; H, 5.19; N, 17.65.

4-Methyl-2-(methylsulfonyl)pyrimidine (29): mp 38-40 °C; ^{1}H NMR δ 2.73 (s, 4-Me), 3.42 (s, SO_2Me), 7.58 (d, J = 5 Hz, 5-H), 8.88 (d, J = 5 Hz, 6-H). Anal. Calcd for $C_6H_8N_2O_2S$: C, 41.84; H, 4.68; N, 16.27. Found: C, 41.54; H, 4.60; N, 15.98.

Reactions of (Bromomethyl)pyrimidines 12, 13, and 16 with DMSO. A solution of **12**, **13**, or **16** (1 mmol) in anhydrous DMSO (2 mL) was allowed to stand at 23 °C for 24 h and then treated with water (1 mL). The mixture was extracted with ether (5 × 10 mL), and the extract was dried (Na_2SO_4) and concentrated. The oxidation of **12** in the presence of $NaHCO_3$[18] (0.5 g) was conducted in a similar manner. Crude products were purified by chromatography.

4-Methyl-2-(methylthio)-5-pyrimidinecarbaldehyde (15): yield 63%; mp 67-69 °C (lit.[17] mp 63-64 °C); ^{1}H NMR spectrum was identical with that reported.[17]

5-Methyl-2-(methylthio)-4-pyrimidinecarbaldehyde (17): yield 78%; mp 56-57 °C; ^{1}H NMR δ 2.45 (s, 5-Me), 2.60 (s, SMe), 8.75 (s, 6-H), 9.93 (s, CHO); IR (neat) ν 1719 (C=O) cm^{-1}. Anal. Calcd for $C_7H_8N_2OS$: C, 49.98; H, 4.79; N, 16.66. Found: C, 50.07; H, 4.79; N, 16.58.

5-(Hydroxymethyl)-4-methyl-2-(methylthio)pyrimidine (18a): yield 36%; an oil; ^{1}H NMR δ 2.48 (s, 4-Me), 2.57 (s, SMe), 3.70 (br s, OH), 4.67 (s, CH_2), 8.38 (s, 6-H). Compound **18a** was transformed into a crystalline *p*-nitrobenzoyl derivative **18b** as described:[14] mp 149-150 °C (lit.[14] mp 148.5-149.5 °C).

5-(Hydroxymethyl)-2-(methylthio)-4-pyrimidinecarbaldehyde (19a) and 6-(Methylthio)-1,3-dihydrofuro[3,4-*d*]pyrimidin-1-ol (19b): yield 74%; mp 136-137 °C (lit.[19] mp 135-136 °C); IR (KBr) ν 3283 (OH) cm^{-1}; no C=O absorption; IR ($CHCl_3$) ν 1735 (C=O) cm^{-1}. The two forms exist in $CDCl_3$ solution in the ratio **19a**:**19b** = 1:3. ^{1}H NMR (400 Hz) for **19a**: δ 2.65 (s, SMe), 3.00 (t, J = 6 Hz, OH), 4.84 (d, J = 6 Hz, 5-CH_2), 8.80 (s, 6-H), 10.04 (s, CHO). ^{1}H NMR (400 Hz) for **19b**: δ 2.61 (s, SMe), 3.51 (d, J = 6 Hz, OH), 5.05 and 5.26 (2d, J = 13 Hz, 3a-CH_2), 6.33 (s, 7a-CH), 8.56 (s, 4-H).

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Regioselective Functionalization of *N*-Phthaloyl-Substituted Amino Acid and Peptide Derivatives

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The free-radical reactions of a range of amino acid derivatives with *N*-bromosuccinimide are described. The products and relative rates of these reactions indicate that the α-position of an *N*-phthaloyl-substituted α-amino acid derivative is much less reactive than that of a corresponding *N*-acyl amino acid derivative toward hydrogen atom transfer. This is attributed to the proactive effects of acylamino and carboxyl substituents, in contrast to the counteractive effects of phthalimido and carboxyl groups. The reactions exemplify procedures for the regiocontrolled functionalization of amino acid and peptide derivatives.

Introduction

Hydrogen atom transfer reactions of *N*-acyl α-amino acid derivatives generally favor formation of α-carbon-centered radicals.[1] These radicals are resonance stabilized by the combined action of an electron-releasing amido substituent and an electron-withdrawing carboxy substituent, and they may be classified as captodative,[2] merostabilized,[3] or push-pull-stabilized[4] radicals. Amido-, carboxy-substituted radicals have been identified in proteins upon irradiation[5] and are thought to be intermediates in the photoalkylation[6] and carboxylation[7] of peptides.

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