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Communication

Bromination of Pyrimidines: A Simple Inexpensive Method

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Although the introduction of halogens into the pyrimidine ring has been accomplished numerous times, the methods usually involve either specialised reagents or very aggressive conditions. This communication paper describes the introduction of bromine into position 5 of the pyrimidine ring using common inorganic salts at room temperature. An evaluation of the substituents required for successful reaction is provided.

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The introduction of halogens into the pyrimidine ring, especially at position 5, has been accomplished by numerous investigators.[1a] All four of the halogens can be introduced into a variety of pyrimidines, with F being the most difficult. In reality, chlorinations and brominations have been the subject of the majority of such investigations. Interest in having a halogen in position 5 remains high as this provides a vehicle for the introduction of other functional groups via replacement of the halogen.

Typically, chlorinations are accomplished using Cl_2, $SOCl_2$, or *N*-chlorosuccinimide ranging from room temperature to 100°C.[1b] Brominations likewise proceed via Br_2 or *N*-bromosuccinimide (NBS), again ranging from room temperature to 100°C.[1c] The majority of iodinations usually involve I_2.[1d]

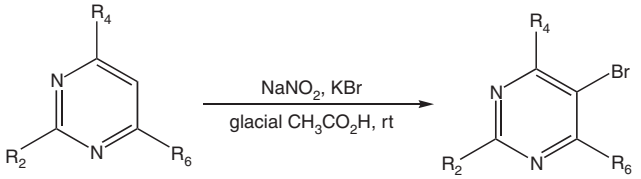
Recently, we began a series of experiments designed to achieve replacement of an amino group by a halogen. Thus, a series of 2-aminopyrimidines bearing other groups at positions 4 and 6 was treated with sodium nitrite and a potassium salt, KX (X = F, Cl, Br, I). Although no reaction occurred with KF, each of the other salts led to mixtures of 2-halo and 2,5-dihalo products. This introduction of halogen into position 5 was quite unexpected under these reaction conditions. Consequently, we focussed our efforts on examining this observation further by carrying out reactions of pyrimidines without an amino group. The results were inconsistent except in the case of bromination. Herein, we report on the results of this investigation.

In order to understand the requirements for a successful bromination at position 5 of the pyrimidine ring, we chose a series of compounds that offered a variety of substituents, especially at positions 4 and 6. Table 1 contains a group of six pyrimidines that possess both activating and deactivating groups at these two locations.

We opted to use glacial acetic acid as the sole solvent, both for the ability to dissolve the relatively non-polar pyrimidines and to provide the weakly acidic environment required to initiate reaction with $NaNO_2$.

It is clear that at least one activating group (e.g. MeO, NMe_2) is necessary at one of the positions surrounding C-5 to accomplish the bromination process (compounds **1**, **3**, **5**, **7**). The presence of a mild deactivating group, Cl (as in pyrimidines **3**, **5**), did not preclude the reaction from occurring. Even hydrogen (as in pyrimidine **7**) did not affect the outcome. However, if C-5 was surrounded by two chlorine atoms (see pyrimidine **9**) or even one chlorine and a hydrogen atom (see pyrimidine **10**), depriving C-5 of the presence of an activating group, no reaction occurred. The higher yield of compound **4** might suggest a radical process that is not constrained as it would be in an ionic process. However, based on the lack of α-halogenation of compound **1**, this possibility is less likely.

Table 1. Bromination of selected pyrimidines



Compound no.	R_2	R_4	R_6	Product	Percentage yield (isolated)
1	OCH_3	OCH_3	CH_3	**2**[2]	69
3	OCH_3	OCH_3	Cl	**4**[3]	96
5	Cl	$N(CH_3)_2$	Cl	**6**[A]	45
7	OCH_3	OCH_3	H	**8**[4]	68
9	Cl	Cl	Cl	NR[B]	
10	Cl	Cl	H	NR	

[A]See Experimental section for characterisation of this compound.
[B]NR: no reaction.

A review of the literature failed to uncover any prior use of sodium nitrite and a bromide salt as a method for bromination. As our experience with the C-5 position of pyrimidines suggested an electrophilic process, we initially considered this to be the pathway for bromination. However, it was hard to rationalize the oxidation of the bromine anion to a bromine cation. The formation of the active brominating agent will have to be examined further.

However, in an effort to further define a possible pathway for the observed reactions, compound **1** was treated with Br_2 in glacial acetic acid. Analysis of the reaction mixture by gas chromatography–mass spectrometry (GC-MS) showed that compound **2** was, indeed, formed and isolated in a yield of 85 %. Consequently, formation of Br_2 from $NaNO_2$ and KBr is a viable possibility for the actual brominating agent. Further investigation of this observation is warranted and will be pursued.

We conclude from these experiments that any pyrimidine containing at least one activating group adjacent to C-5 will provide a 5-bromopyrimidine. Thus, this process represents a novel approach to C-5 bromination under quite mild conditions and without the use of either specialized brominating agents, e.g. NBS, or harsh and toxic reagents, e.g. Br_2.

Experimental

All chemicals used in these reactions were obtained commercially. ^{1}H and ^{13}C NMR spectra for compound **6** were obtained in [D3]chloroform on an Agilent (Varian) Mercury-300 or Inova 500 instrument and a high-resolution mass spectrum (HRMS) for compound **8** (see Supplementary Material) was obtained on a Waters GCT mass spectrometer, coupled to an Agilent 7890 GC instrument (with appropriate software that factors in relevant isotope ratios and masses). Reactions were followed using the same instrument employing the following conditions: GC oven temperature raised from 40°C to 300°C in 6.5 min and held at 300°C for 3.5 min; column was an MS-5, 10-m, 0.1-μm inside diameter (ID), 0.1-μm film thickness; flow rate of 1 mL min^{-1} and an ionization energy of 70 eV for the mass spectrometer. Because the known compounds (**2**, mp 76–77°C;[2] **4**, mp 97–98°C;[3] and **8**, mp 63–64°C[4]) have been adequately described in the literature and the chemistry involved here does not materially change the structures of the starting pyrimidines, GC-MS spectra were used to confirm the expected product formation. This confirmation included purity of the product, reasonable retention times compared with starting material, and predictable ion fragmentation. In addition, melting points of isolated products were obtained and were consistent with the reported values.

Typical Experimental Procedure for Bromination

The pyrimidine (~1 mmol) was dissolved in glacial acetic acid (~5 mL), and solid $NaNO_2$ (~2 mmol) and solid KBr (~2 mmol) were added all at once. An immediate evolution of brown fumes was observed and the mixture was stirred at room temperature (rt) overnight. Progress of the reaction was followed by GC-MS analysis. In those cases where the reaction was incomplete, as observed by the presence of starting pyrimidine, additional $NaNO_2$ was added and gentle heating applied (~50°C) for up to 1 h until no starting material was observed by GC-MS analysis. Workup consisted of evaporation of the acetic acid (in a fume hood at atmospheric pressure) followed by suspension of the residue in Et_2O (~20 mL). This was passed through a short bed of silica gel (60–100 mesh), and eluted with Et_2O until the effluent showed no UV absorption. Evaporation of the Et_2O led to pure product.

5-Bromo-2,6-dichloro-4-dimethylaminopyrimidine **6**: mp 96–98°C. δ_H 3.254 ($(CH_3)_2$). δ_C 41.617 (N–CH_3), 99.470 (C_5–Br), 156.423 (C_6–N), 161.474 (C_4–Cl), 163.351 (C_2–Cl). *m*/*z* (HRMS) 270.9090. Calc. 270.9098. See Supplementary Material for complete NMR and MS.

Supplementary Material

^{1}H NMR, ^{13}C NMR, and HRMS spectra of compound **6** are available on the Journal's website.

References

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