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# 8-Bromination of 2,6,9-trisubstituted purines with pyridinium tribromide

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ABSTRACT

2,6,9-Trisubstituted purines are brominated in high yields using pyridinium tribromide as the brominating reagent. This procedure works excellently for electron-rich purines having electron-donating substituents at the 2- and 6-positions. The use of pyridinium tribromide, a crystalline alternative to elemental bromine, improves the bromination procedure for this type of substrate as the reagent is easy to handle and the work-up and purification procedures are simplified.


Purines (Fig. 1) are found naturally in compounds key to life such as ATP, DNA (adenosine and guanosine), and NAD.[1] The biological importance of naturally occurring purines has led to an interest in studies of the biological activity of synthetically modified purines.[2] Examples include protein kinase inhibitors,[3,4] adenosine receptor modulators,[5] adenylation enzyme inhibitors,[6] and fructose bisphosphatase inhibitors.[7]

The bioactivity of purines has spurred efforts in developing methods to control selectively the substitution pattern of the purine ring system.[8] Purines are commonly substituted at the 2-, 6-, 8-, and 9-positions (see Fig. 1).[8,9] While purines with either amino or chloro substituents at the 2- and/or 6-positions are commercially available, the 8-position generally needs to be activated to affect substitution. Except for a few recent examples of direct C—H activation,[10,11] the 8-position is commonly activated by halogenation followed by nucleophilic aromatic substitution[12] or palladium-catalyzed cross-coupling. Examples of the latter include Sonogashira,[13] Suzuki[14,15] and Stille[12,16] type couplings to introduce alkynyl, aryl, and alkenyl substituents, respectively.

Commonly, $Br_2$[12] and NBS[17,18] are used as reagents for the 8-bromination of purines. The use of sodium monobromoisocyanurate[19] and 1,3-dibromo-5,5-dimethyl hydantoin[20] have also been reported for the bromination of nucleobases including adenosine. An excess of the brominating reagent is often used, and as elemental bromine is toxic and corrosive it becomes inconvenient to work with. In this Letter, we evaluate pyridinium tribromide as a brominating reagent for a range of purine derivatives. Pyridinium tribromide ($PyrBr_3$) has been utilized for the bromination of indoles[21] and other aryl compounds,[22,23] the α-position of ketones[24–26] and also alkenes.[27,28] It is a solid which can be weighed in air and is easily handled. In solution, $PyrBr_3$ is in equilibrium with pyridinium bromide and $Br_2$ (Scheme 1) and the distribution is reported to be dependent on the polarity of the solvent.[29] Both $PyrBr_3$ and $Br_2$ act as brominating agents.

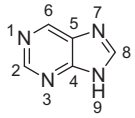
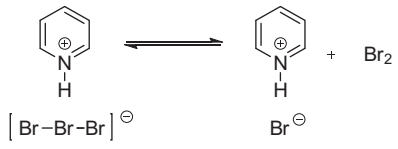



**Figure 1.** Purine core structure with atom numbering.




**Scheme 1.** Pyridinium tribromide ($PyrBr_3$) in equilibrium with bromine and pyridinium bromide.

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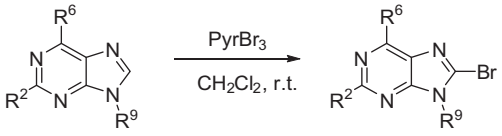
In an ongoing study of 2,6,8,9-tetrasubstituted purines we needed a protocol that would allow selective bromination at the 8-position of purines in the presence of aromatic substituents. We turned first to the commonly used methods for purine derivatives. In our model reaction, bromination of **1a** (Table 1, entry 1) using NBS in acetonitrile at room temperature[30] resulted in only a 25% isolated yield of **2a**; *para*-bromination of the phenyl also occurred in trace amounts according to $^1$H NMR spectroscopy. Reaction of purine **1a** with $Br_2$ in NaOAc/HOAc buffer in THF/MeOH[12,31] resulted in a 30% yield of **2a**. However, when **1a** was treated with $PyrBr_3$ in $CH_2Cl_2$ at room temperature for 5 h, **2a** was isolated in 93% yield (Table 1, entry 1).[32] In addition to the higher yield, the workup, and purification of the $PyrBr_3$ reactions are more convenient than for reactions involving elemental $Br_2$.

These results encouraged us to explore the scope of $PyrBr_3$ as a brominating reagent for the 8-bromination of purines. The results are summarized in Table 1. Initially, we wanted to investigate if the method was applicable to purines lacking substituents at the 9-position. This is of interest since it allows insertion of bromine early in a reaction sequence and paves the way for subsequent diversification. Treating 6-chloropurine (**1b**) and 2-amino-6-chloropurine (**1c**) with $PyrBr_3$ in $CH_2Cl_2$ did not result in any or only a trace amount of bromination (entries 2 and 3). Since these compounds are largely insoluble in $CH_2Cl_2$, the reactions were also run in DMF, but without success (results not shown). Bromination of **1d** in DMF gave the product in 38% yield (entry 4). Although **1d** was poorly soluble in $CH_2Cl_2$, **2d** was obtained in 46% isolated yield after 55 h at room temperature (entry 5). Therefore, compounds lacking a substituent at the 9-position did not react or provided unsatisfactory yields.

Next, we introduced substituents at the 9-position. Bromination of purines not substituted at the 2-position (**1e–h**) was unsuccessful using $PyrBr_3$ in $CH_2Cl_2$ at room temperature (entries 6–9). The bromination of 9-benzyladenine (**1f**) was also performed in DMF at both room temperature and 60 °C, but no product was observed. Lewis acids (TMS-triflate and $BBr_3$) have been reported to increase the rate of bromination reactions on similar substrates,[20] but failed to result in more than a trace amount of brominated material (as observed by LCMS) in this case.

2,6-Diaminopurines (**1i**,**j** and **1l**,**m**) were brominated in high yields (80–91%) with $PyrBr_3$ in $CH_2Cl_2$ at room temperature (entries 10, 11, 13, and 14). 2,6-Diaminopurine **1k** has poor solubility in $CH_2Cl_2$, but can be brominated in DMF, although with a significantly lower yield (27%, entry 12) compared to the bromination of electron-rich purines soluble in $CH_2Cl_2$ (**1i**,**j** and **1l**,**m**). When a *tert*-butyloxycarbamoyl group was introduced at the C2 position (entry 15) as in **1n**, treatment with $PyrBr_3$ gave **2n** in 36% isolated yield. The conversion was however not complete after 3 h and the protecting group was partially cleaved under these conditions. For 9-substituted 2,6-diaminopurines (**1i** and **1a**), changing the solvent to DMF resulted in lower yields (entries 16 and 17) compared to $CH_2Cl_2$ (entries 10 and 1). In addition, acetonitrile as the solvent resulted in a comparable yield to reactions in $CH_2Cl_2$, but the reaction was slower (entry 18).

**Table 1**
8-Bromination of purines using $PyrBr_3$




**1** **2**

| Entry | Substrate[a] | $R^6$ | $R^2$ | $R^9$ | Solvent | Time (h) | Product | Yield[b] (%) |
|---|---|---|---|---|---|---|---|---|
| 1 | **1a** | $N(Me)_2$ | $NH_2$ | Phenethyl | $CH_2Cl_2$ | 5 | **2a** | 93 |
| 2 | **1b** | Cl | H | H | $CH_2Cl_2$ | 24 | **2b** | nr[c] |
| 3 | **1c** | Cl | $NH_2$ | H | $CH_2Cl_2$ | o.n[d] | **2c** | Trace[e] |
| 4 | **1d** | $N(Me)_2$ | $NH_2$ | H | DMF | 6 | **2d** | 38 |
| 5 | **1d** | $N(Me)_2$ | $NH_2$ | H | $CH_2Cl_2$ | 55 | **2d** | 46 |
| 6 | **1e** | $NH_2$ | H | Bn | $CH_2Cl_2$ | 48 | **2e** | nr |
| 7 | **1f** | Cl | H | Bn | $CH_2Cl_2$ | o.n | **2f** | nr |
| 8 | **1g** | OMe | H | Bn | $CH_2Cl_2$ | o.n | **2g** | nr |
| 9 | **1h** | $N(Me)_2$ | H | Bn | $CH_2Cl_2$ | o.n | **2h** | Trace |
| 10 | **1i** | $N(Me)_2$ | $NH_2$ | Bn | $CH_2Cl_2$ | 3 | **2i** | 90 |
| 11 | **1j** | NHBn | $NH_2$ | Bn | $CH_2Cl_2$ | 3 | **2j** | 87 |
| 12 | **1k** | $NH_2$ | $NH_2$ | Bn | DMF | 5 | **2k** | 27 |
| 13 | **1l** | $N(Me)_2$ | $NH_2$ | *i*-Bu | $CH_2Cl_2$ | 2.5 | **2l** | 80 |
| 14 | **1m** | $N(Me)_2$ | NHBn | Phenethyl | $CH_2Cl_2$ | 1 | **2m** | 91 |
| 15 | **1n** | NHBn | NHBoc | Bn | $CH_2Cl_2$ | 3 | **2n** | 36 |
| 16 | **1i** | $N(Me)_2$ | $NH_2$ | Bn | DMF | 3 | **2i** | 47 |
| 17 | **1a** | $N(Me)_2$ | $NH_2$ | Phenethyl | DMF | 3 | **2a** | 59 |
| 18 | **1i** | $N(Me)_2$ | $NH_2$ | Bn | MeCN | o.n | **2i** | 80 |
| 19 | **1o** | OMe | $NH_2$ | Bn | $CH_2Cl_2$ | o.n | **2o** | 37 |
| 20 | **1o** | OMe | $NH_2$ | Bn | $CH_2Cl_2$ | o.n | **2o** | 43[f] |
| 21 | **1p** | Cl | $NH_2$ | Bn | $CH_2Cl_2$ | 16 | **2p** | nr |
| 22 | **1i** | $N(Me)_2$ | $NH_2$ | Bn | $CH_2Cl_2$ | 4 | **2i** | 93[g] |

[a] Protocols for brominations, synthesis of non-commercially available starting materials, and data from product characterization are available in the Supporting Information.
[b] Isolated yield.
[c] nr = no reaction, that is, only starting material was observed by LCMS and/or TLC.
[d] o.n = overnight.
[e] Only a trace amount of the product was observed by LCMS.
[f] 3 equiv of $PyrBr_3$ were used.
[g] Polymer supported $PyrBr_3$ was used.

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When 2-amino-6-methoxypurine (**1o**) was treated with $PyrBr_3$, **2o** was isolated in 37% yield (entry 19). Increasing the equivalents of $PyrBr_3$ did not affect the yield of **2o** (entry 20). No bromination occurred on 2-amino-9-benzyl-6-chloropurine (**1p**), indicating that an electron-withdrawing substituent at the 6-position was not tolerated (entry 21). Furthermore, comparison of entry 8 with 11, and entry 9 with 12 clearly shows that the C2 amino group is necessary for bromination to occur under these conditions.

$PyrBr_3$ is also commercially available on a polymer support. The use of the polymer-supported reagent for the bromination of **1i** worked as equally well as the solution phase reaction; **2i** was isolated in 93% yield (entry 22). In addition, the solution phase reaction could be scaled up to 0.5 g without any decrease in the yield or purity.

In conclusion, we have presented a procedure for the 8-bromination of 2,6,9-trisubstituted purines using $PyrBr_3$, a crystalline alternative to elemental bromine. The reactions of electron-rich purine derivatives are typically completed in one to five hours and the products are isolated in high yields after column chromatography. Other aromatic substituents that are present on the substrate are not brominated under these conditions. The reaction is limited to purines with electron-donating substituents at the 2- and 6-postions. We are currently utilizing this method for the bromination of 2,6,9-trisubstituted purines to obtain a library of highly functionalized biologically active purines.

## Acknowledgements

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.03.084.

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32. *Experimental procedure:* 2-Amino-6-dimethylamino-9-(2-phenethyl)-purine (**1a**, 560 mg, 1.98 mmol, 1.0 equiv) was dissolved in dry $CH_2Cl_2$ (36 ml) in oven-dried glassware under nitrogen. The nitrogen flow was temporarily removed and $PyrBr_3$ (761 mg, 2.38 mmol, 1.2 equiv) was added in one portion and the reaction mixture was stirred at room temperature for 5 h. The reaction was quenched with 10% aq $Na_2S_2O_3$ and the pH was adjusted to approx. 10 with 15% NaOH (aq). The phases were separated and the aqueous phase was extracted with $CH_2Cl_2$ ($3 \times 30$ ml). The organic phases were pooled, washed with brine (90 ml), dried over $Na_2SO_4$ and filtered. The solvent was removed under reduced pressure and the residue purified by automated flash column chromatography (1% MeOH in $CHCl_3$). 2-Amino-8-bromo-6-dimethylamino-9-(2-phenethyl)-purine (**2a**) was isolated as an off white solid (662 mg, 93%). $^1$H NMR (DMSO-$d_6$): 7.32–7.19 (m, 3H), 7.15–7.09 (m, 2H), 5.99 (s, 2H), 4.17 (t, *J* 7.4 Hz, 2H), 3.29 (br s, 6H), 3.01 (t, *J* 7.4 Hz, 2H); $^{13}$C NMR (DMSO-$d_6$): 159.4, 153.6, 153.5, 137.6, 128.7, 128.5, 126.6, 120.3, 113.9, 44.5, 37.6, 34.4; HRMS *m/z* $[M+H]^+$ calculated for $C_{15}H_{18}BrN_6$: 361.0776. Found: 361.0783.