Leaving-Group Directed S_NAr Reactions of 2,6-Disubstituted Purines

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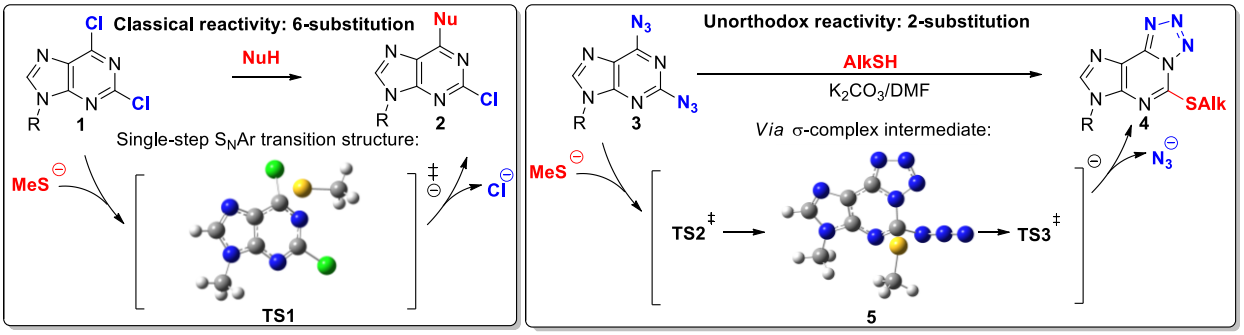
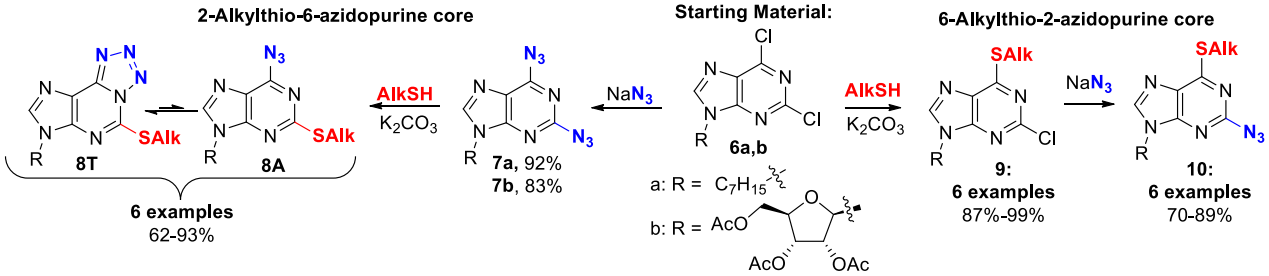
In the well-developed area of purine chemistry there persists a rule of thumb that 6th position shows elevated reactivity in purines having leaving groups at positions 2 and 6 of the heterocycle. However, it has been reported by Novosjolova *et al.* that this reactivity may be switched in 2,6-diazidopurine derivatives[1]. In our present work, 2,6-disubstituted purine reactivity trends are explored by DFT methods and the utility of these reactions is demonstrated by the synthesis of 6/2-azido-2/6-alkylthio-purine derivatives.

For DFT calculations, the substitution at 2,6-dichloropurine **1** was chosen as an example of the ordinary behaviour of purine system in S_NAr reactions. It was shown that 6-substitution *via* transition structure **TS1** is favoured over analogous transition structures towards 2-substitution. In the 2,6-diazidopurine **3**, calculations were based on the most populated azide-tetrazole tautomeric forms of 2,6-diazidopurine. The obtained results indicate that the origin of the unusual reactivity arises due to the stabilization of the intermediate complex **5** and transition structures **TS2** and **TS3** by the tetrazolo system.



Both the classical and unusual reactivity trends have been employed for an efficient synthesis of azidopurine-alkylthiole conjugates **8** and **10** in good to excellent yields. The developed methods may find a use in medicinal and biological chemistry.



Literature:

[1] I. Novosjolova, I., Ē. Bizdēna, M. Turks, Tetrahedron Lett. 2013, 54, 6557.