

A General Approach to the Synthesis of 5-S-functionalized Pyrimidine Nucleosides and their Analogues

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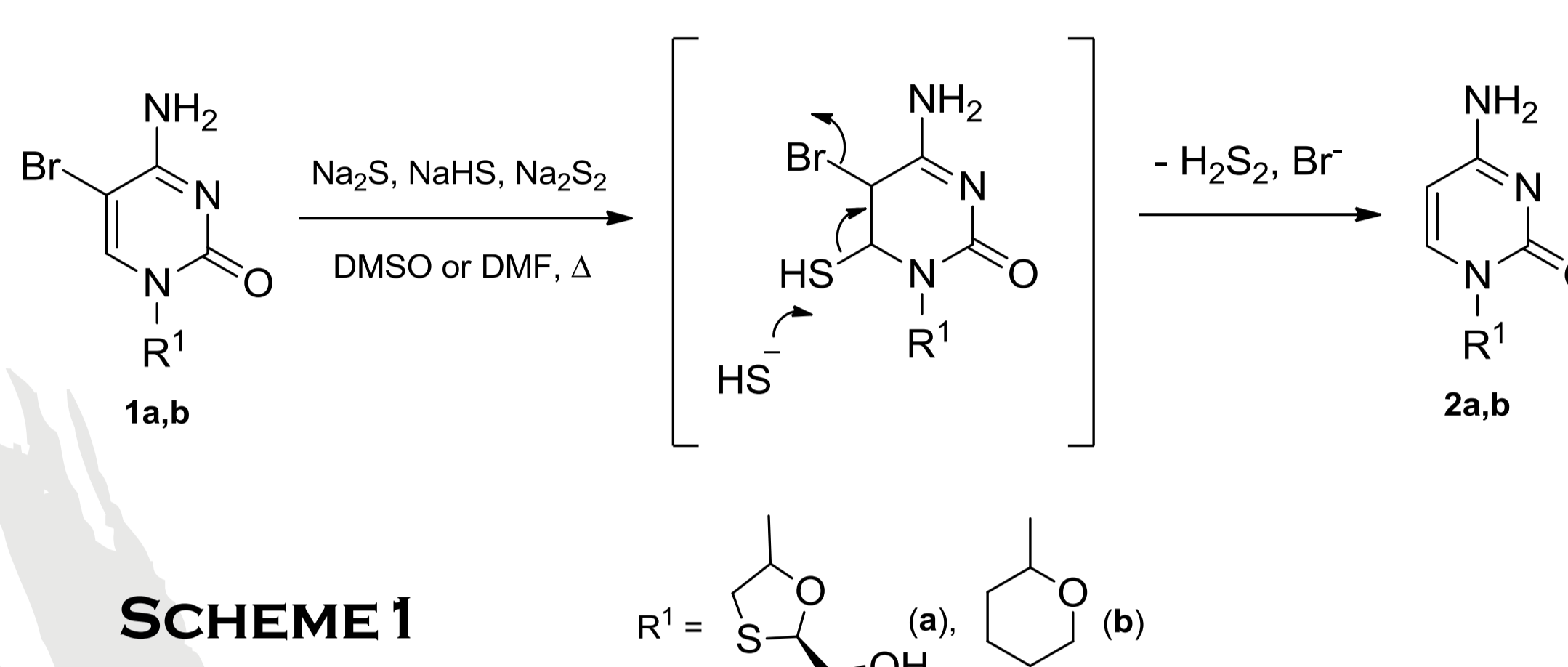
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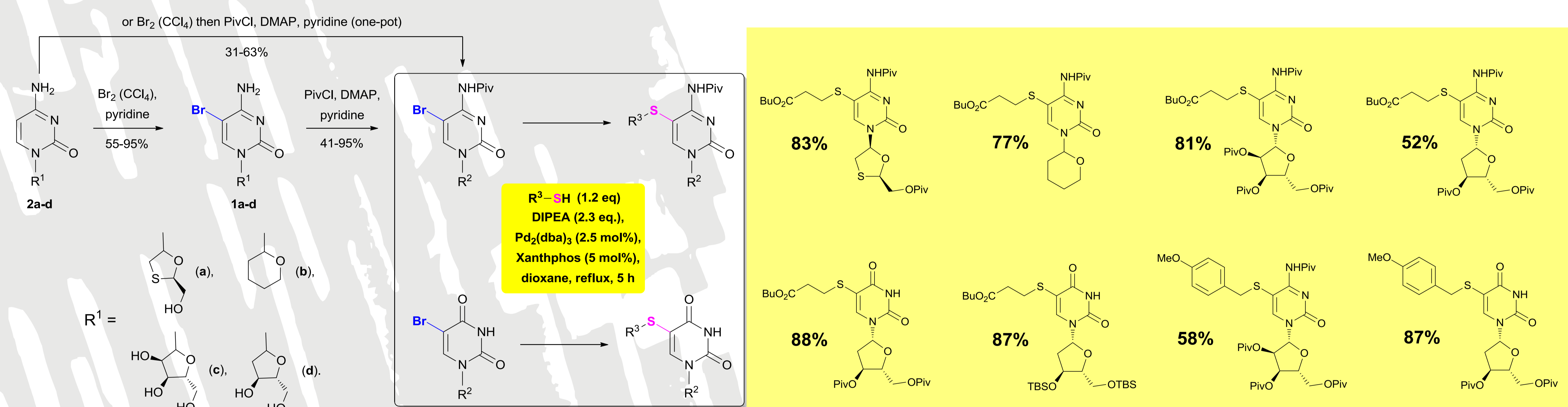
Introduction

Nucleosides and their analogues are important substances owing to their broad medical use. Structural modifications of these molecules are of great practical importance, making it possible to expand the number of compounds with anti-tumour or antiviral activity, and/or to adjust pharmacological properties of the parent compounds.¹ One of the modifications of substantial interest is the introduction of S-functionality into a nucleobase ring. For instance, double-stranded RNAs modified at the 5-position by selective thiolation of some cytosine bases have shown high activity against HIV-1 in human cells and against DNA polymerases of DNA and RNA tumours.²

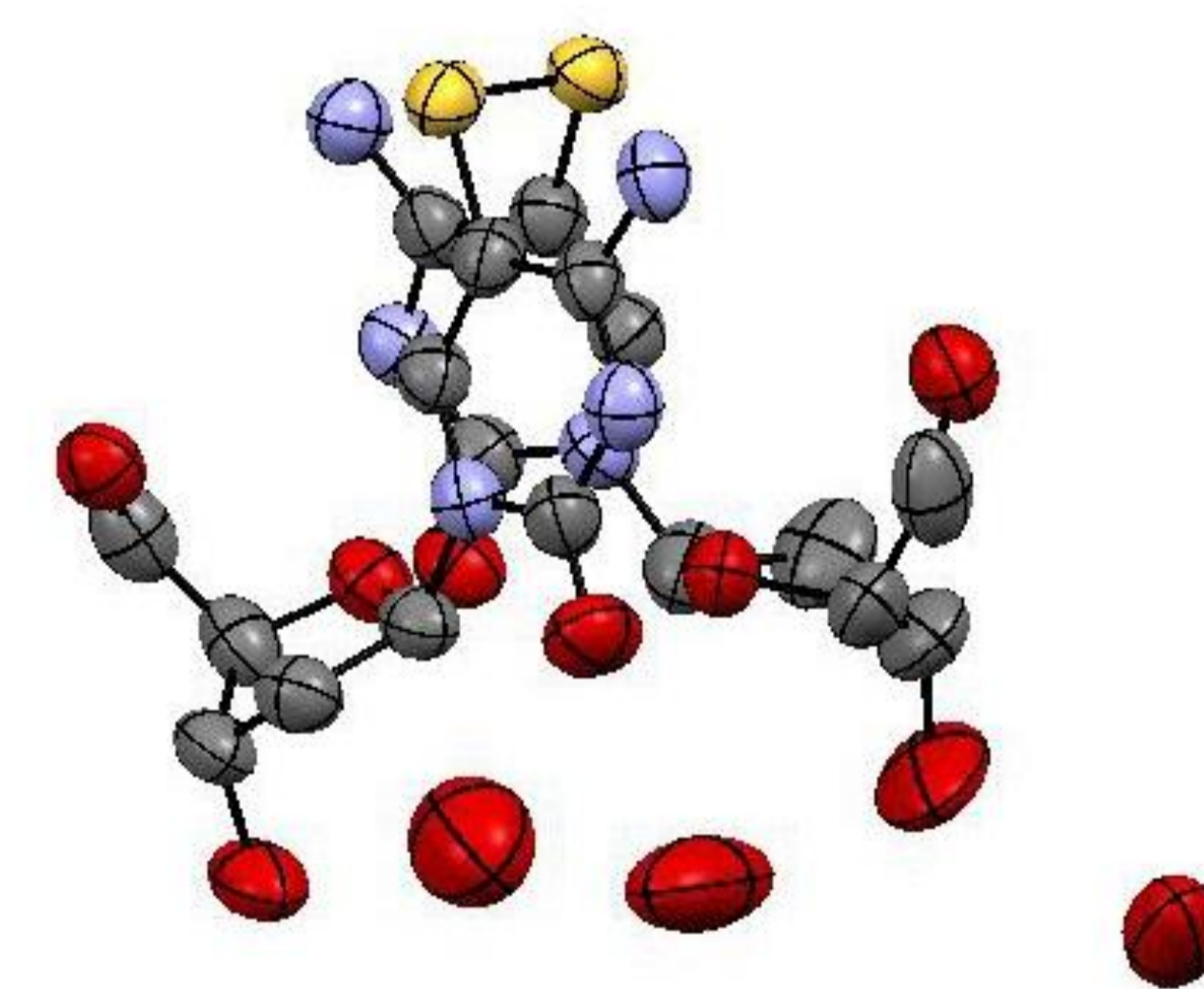
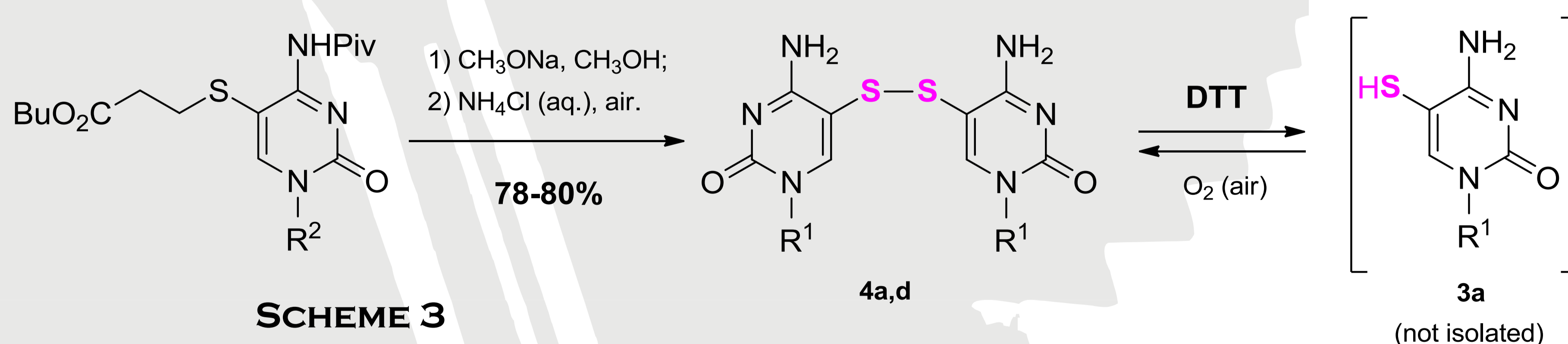
5-Mercaptopyrimidine nucleosides have been prepared by a number of methods, including reactions of 5-halogenated pyrimidine derivatives with sulphur nucleophiles,³ the addition of the electrophilic sulphur species (CISCN) to the double bond of the pyrimidine base,⁴ and palladium-mediated substitution in 5-mercupyrimidine derivatives.⁵ However, most of these methods often require harsh conditions and gave low yields of the desired compounds. Thus, for example, reaction of 5-bromocytosine derivatives **1a,b** with several sulphur nucleophiles³ (e.g. Na₂S, NaSH and Na₂S₂) gave products of reductive debromination **2a,b** rather than the desired substitution reaction (Scheme 1). Therefore, a new and general approach furnishing 5-mercupyrimidine derivatives under mild conditions is required.



Here we present a general and efficient approach for the introduction of S-functionality to the C-5 position of cytosine and uracil nucleosides and their analogues. The key step is a palladium-catalyzed C-S coupling of the corresponding 5-bromo nucleoside derivative and alkyl thiols.⁶ A number of protected natural uracil and cytosine nucleotides as well as their unnatural analogs have been successfully modified using this approach (Scheme 2).



The butyl 3-mercaptopropionate coupling products were further converted to the corresponding disulphides, the stable precursors of 5-mercupyrimidine nucleosides, using one-pot deprotection protocol (Scheme 3). 5-Mercaptopyrimidine nucleosides **3** are unstable to oxidation with air and can be generated from stable disulphides **4** by their reduction *in situ* with dithiothreitol (DTT) (Scheme 3).³ Thus, a colourless solution of disulphide **4a** in DMSO gave a bright yellow solution of the corresponding 5-mercupyrimidine derivative **3a** when treated with an excess of DTT.



Molecular structure of 2'-deoxycytidine disulphide (**4d**) hydrate (hydrogens are omitted for clarity; displacement parameters are drawn at the 50% probability level).

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