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Solid-phase synthesis (SPS) of substituted uracils via Oxone® cleavage methodology

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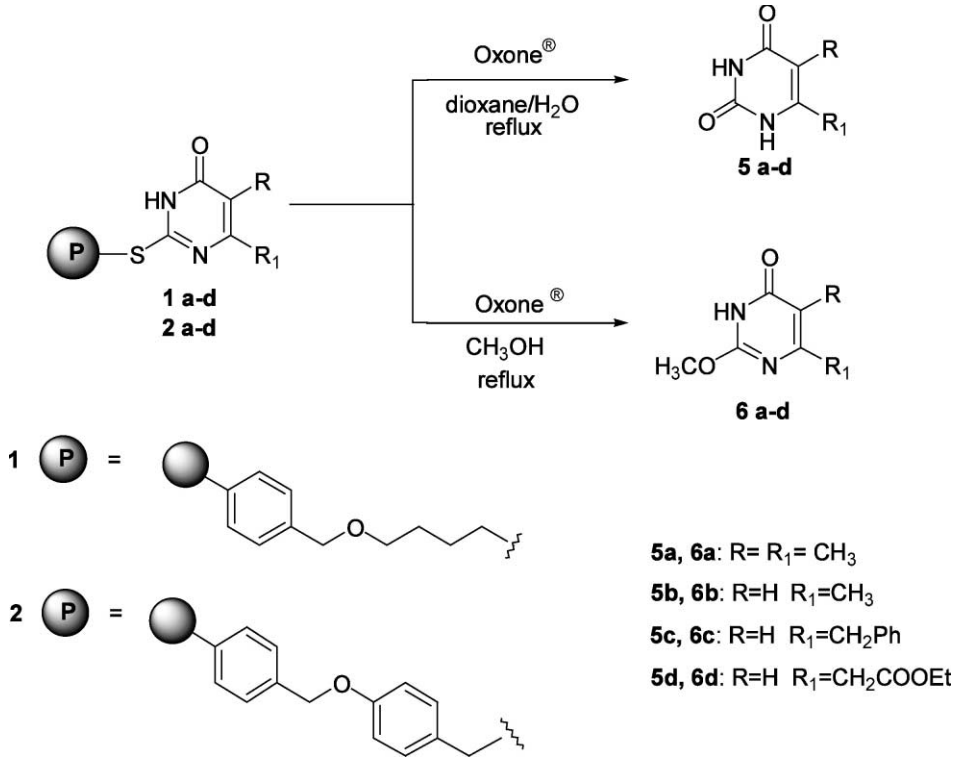
Abstract—An original and highly efficient Oxone® cleavage methodology for the solid-phase synthesis of substituted uracils has been developed. An example of application of this methodology to the solid-phase synthesis of uridine derivatives is also reported.

Based on the growing interest in solid-phase approaches to the synthesis of compound families and taking into account the wide range of biological activities demonstrated by uracil derivatives,[1–9] our efforts were directed toward the development of a solid phase methodology for obtaining substituted uracils.



Scheme 1.

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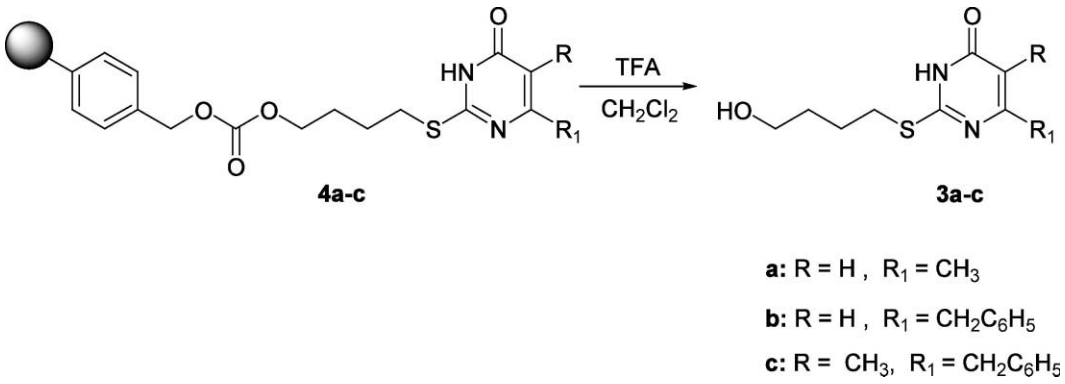


Scheme 2.

In the past we focused our attention on an assembly strategy performed in solution,[10] which gave access to 5,6-disubstituted uracil compounds possessing interesting biological activities. Although this methodology provides a simple route to the target molecules, the purification of these compounds is sometimes tedious and limits their potential interest as intermediates in the synthesis of more complex molecules. A solid-phase approach to the synthesis of the target uracil derivatives would allow to avoid the purification step and to produce a large number of biologically interesting compounds by means of combinatorial techniques. The polymer-bound pyrimidinone nucleus **1**, **2** (Scheme 1) could in principle be easily derivatized, coupled with sugars, or transformed into a polycyclic compound, before being cleaved from the solid support.[11–13]

In a previous note,[2] we reported a successful solid-phase synthesis of pyrimidinones **3a–c** (Scheme 2), where the pyrimidinone system was anchored to the solid support (Merrifield resin) through a carbonate moiety (see compound **4**), which could be selectively cleaved to afford the target compounds in good yield and purity. As expected, we noticed that such a tetramethylene spacer was able to create a 'chemical distance' between the pyrimidinone nucleus and the polymer backbone and to confer more 'solution like' properties and better solvent compatibility to the resin. Moreover, it was of potential utility for the NMR analysis of the polymer-bound compounds.[14,15]

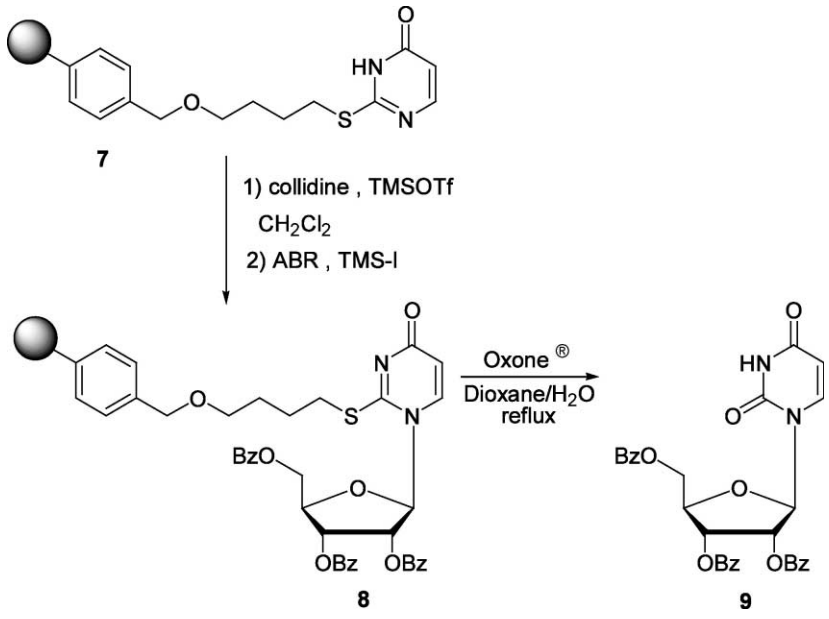
Based on these findings, the aim of the present work was the solid-phase synthesis of different uracils by cleavage of the thioether bond. However, in order to avoid the formation of undesired products in the cleavage reaction, we decided to anchor the spacer to the solid support through a more stable ether moiety instead of the carbonate group. Accordingly, compounds **1c–d** and **2a–d** (Scheme 1) were synthesized following a procedure already described by us for the preparation of compounds **1a**,**b**.[16]

It is well known that *n*-alkyl thioethers are difficult to be cleaved and hence have not been extensively used as protecting groups; as a result, the most important issue to be addressed was the identification of a suitable cleavage methodology. Some common methods of thioether cleavage, such as reduction with sodium/ammonia, acid catalyzed hydrolysis, or reaction with heavy metal ion followed by treatment with hydrogen sulfide,[17] proved to be unsuccessful in our case, since no uracil compound could be isolated from the reaction mixture. Attempts to cleave the thioether function by iodotrimethylsilane, which is commonly used in the *O*-demethylation of alkoxypyrimidines[18] and has proven by us to be an effective reagent for the *S*-demethylation of 2-methyl-4(3*H*)-pyrimidinones,[19] or by oxidation of the sulfide group to sulfoxide, followed by Pummerer reaction,[20] failed as well.[21]

Finally, we found that Oxone® (potassium peroxymonosulfate), an efficient and selective oxidizing agent,[23] was a suitable reagent for the cleavage of polymer-bound compounds **1**, **2**. Thus, swelling resin **1** in a solution of dioxane/water (6/1), followed by refluxing for 12 h in the presence of 3 molar equivalents of Oxone®, the desired products **5a–d** were obtained (Scheme 1). In order to drive reaction to completion, the cleavage step was repeated twice under the same experimental conditions to give highly pure substituted uracils **5a–d** in 78–98% yield (Table 1). When methanol was used as solvent for the cleavage reaction, the corresponding 2-methoxy derivatives **6a–d** were obtained in 67–95% yield.

Table 1. Uracil derivatives obtained with Oxone® cleavage methodology using dioxane/H_2O (compounds **5 a–d**) or methanol (compounds **6 a–d**) as solvents

Compd	R	R′	Yield (%)	
			From **1**	From **2**
5a	CH_3	CH_3	83	78
5b	CH_3	H	98	95
5c	CH_2Ph	H	85	70
5d	CH_2COOEt	H	78	65
6a	CH_3	CH_3	72	70
6b	CH_3	H	95	96
6c	CH_2Ph	H	77	73
6d	CH_2COOEt	H	67	56



Scheme 3.

This original and highly efficient cleavage procedure was also applied to the Wang resin supported pyrimidinones **2** to afford compounds **5** and **6** in comparable yields (Scheme 1, Table 1).

The same procedure has been also applied to the parallel synthesis of a small library of 12 uracil derivatives using a Syncore® organic synthesizer at 200 rpm; substituted uracils (6-methyl; 6-benzyl; 6-trifluoromethyl; 6-ethyl; 6-isopropyl; 6-*tert*-butyl; 6-chloromethyl; 6-adamantyl; 5-ethyl-6-methyl; 5-chloro-6-methyl; 5-fluoro-6-methyl; ethyl 6-acetate) have been obtained in yields ranging from 20 to 40%.

In order to point out its synthetic flexibility, the Oxone® cleavage methodology was also used for the releasing of a nucleoside analog from the solid support (Scheme 3). Thus, in the search of an original approach for solid-phase synthesis of nucleosides, compound **8** was synthesized starting from resin **7** and β-D-ribofuranose-1-acetate-2,3,5-tribenzoate (ABR), using a one-pot approach.[24] Subsequent treatment of **8** with Oxone® provided **9** in 40% yield. In a typical experiment, the resin **7** was swelled for 30 min in dichloromethane, then collidine was added and the mixture was treated with trimethylsilyl trifluoromethanesulfonate at 0°C. After stirring for 48 h at room temperature, ABR was added. The mixture was cooled to 0°C, treated with iodotrimethylsilane and then stirred for additional 48 h. Treatment of **8** with Oxone® for 12 h afforded compound **9**.

In conclusion, an original, efficient and mild procedure for the cleavage of polymer-bound pyrimidinones, anchored to the resin through an alkyl thioether spacer, has been developed, allowing for the very convenient preparation of uracil compounds, never prepared before using a solid-phase approach.

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