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The Pixyl (Px) Group: A Novel Photocleavable Protecting Group for Primary Alcohols

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Abstract: The 9-phenylxanthyl (pixyl or Px) moiety has been investigated as a potential photocleavable protecting group for primary alcohols. Alcohols **2a-e** were protected in good yield by treatment with 9-chloro-9-phenylxanthene in dry pyridine at room temperature. Irradiation of the alcohol derivatives in neutral aqueous acetonitrile regenerates **2a-e** and the 9-phenylxanthyl alcohol.

With the emergence of new synthetic techniques such as oligonucleotide synthesis via combinatorial chemistry,[1,2] novel protecting groups for primary alcohols are in high demand, especially groups that are more selective, and that are easily removed without the complication of side reactions. Trityl and methoxy-substituted trityl functionalities have been extensively used as protecting groups of primary hydroxyl groups in sugar, nucleoside, and steroid chemistry.[1,3] The 9-phenylxanthen-9-yl (pixyl or Px) group has also been widely used to protect the 5'-OH of nucleosides,[1,2,4,5] however the moderate acid conditions required for cleavage also partially cleave the 2'-tetrahydropyranyl (THP) protecting group, an undesirable complication in oligoribonucleotide synthesis.[6]

An alternative approach is the use of photodeprotecting groups, including 2-nitrobenzyl and related groups, benzyloxycarbonyl, phenacyl groups and others.[7,8] Many of these groups, however, form reactive byproducts upon irradiation which may hinder the efficiency of the deprotection step. Fodor and coworkers have combined solid-phase synthesis, photolithography and photolabile protecting groups to achieve light-directed, spatially addressable synthesis of oligonucleotide arrays.[9,10] A recent report suggests that the protecting group presently employed in this process exhibits similar problems with reactive byproducts.[11] With the importance of this new synthetic technique and its applications in DNA sequencing by hybridization, there is an urgent need to develop novel photocleavable protecting groups.

We focused our attention on the pixyl group which possesses a highly rigid and planar backbone. This rigidity results in an increased stability of the pixyl carbocation over other similar groups currently in use such as

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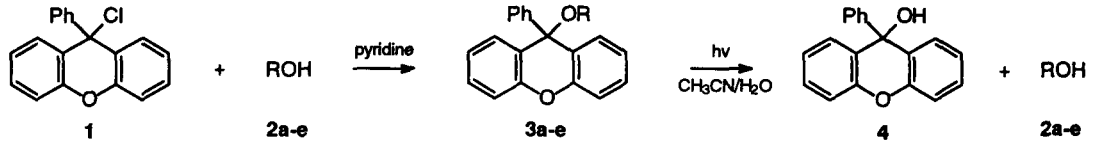
dimethoxytrityl. 9-Phenylxanthen-9-ol **4** has been previously shown to undergo photochemically induced heterolytic carbon-oxygen bond cleavage to generate the 9-phenylxanthyl cation in neutral aqueous solution.[12] This result persuaded us that the pixyl group has potential as a photocleavable protecting group for primary alcohols.

In order to investigate the pixyl group as a potential photodeprotecting group we have protected five primary alcohols representing different functionalities (**2a-e** in Table). Among these was the nucleoside thymidine to extend the utility of the pixyl group to nucleoside chemistry. Following the general procedure for treatment of nucleosides with **1**,[1] the corresponding pixyl derivatives **3a-e** were obtained in fair yields (Table). Each of the derivatives has been isolated as a pure crystalline solid, but yields have not yet been optimized.



1 **2a-e** **3a-e** **4** **2a-e**

Photoreactions of **3** (0.2mM) as shown in the Table were carried out in neutral aqueous acetonitrile by irradiation with low-pressure mercury lamps in quartz photolysis tubes. Complete removal of the pixyl group was achieved in times that varied from 13 min to 110 min depending on the wavelength used for irradiation (254 or 300nm) with yields of recovered alcohol in the upper 90% range. Optimal results were obtained when the photolysis solution was comprised of the maximum percentage of water that solubility would allow, usually on the order of 4:6 v/v CH_3CN:H_2O. In each case, the primary photoproducts were the starting primary alcohol and 9-phenylxanthen-9-ol, as determined by GC or HPLC analysis. Control experiments determined that no thermal degradation was occurring. 9-Phenylxanthen-9-ol undergoes some secondary photochemistry, although this does not affect recovery of the starting alcohol. The Table below summarizes the protection and deprotection results obtained for each experiment.

In summary, we have examined the pixyl group as an effective photocleavable protecting group for primary alcohols. The photodeprotection readily proceeds in aqueous acetonitrile at wavelengths of 254 or 300nm. The results described here suggest that the pixyl group could be an effective protecting group for the combinatorial synthesis of oligoribonucleotides.

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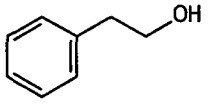
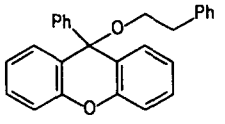
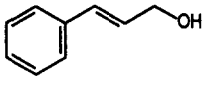
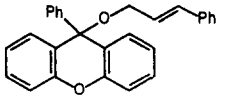
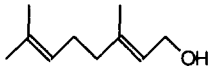
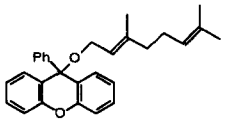
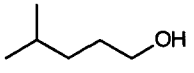
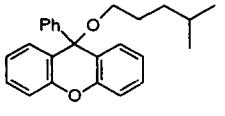
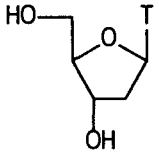
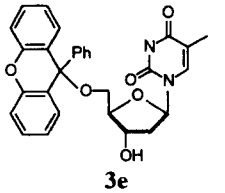
Table. Alcohols Protected with the Pixyl Group

Primary Alcohol	Protection (% yield)	Deprotection[D] (% yield)	Derivative
 **2a**	65[A]	97	 **3a**
 **2b**	74[A]	90[E]	 **3b**
 **2c**	67[B]	78	 **3c**
 **2d**	69[B]	89	 **3d**
 **2e**	66[C]	83	 **3e**

[A]Isolated yield after recrystallization from hexane. [B]Isolated yield after column chromatography (CH_2Cl_2 on alumina). [C]Isolated yield after crystallization from benzene. [D]Photolysis conditions: **3a**, T_{hv} = 13min, λ= 254nm, by GC analysis; **3b**, T_{hv}= 30min, λ= 300nm, by HPLC analysis; **3c**, T_{hv} = 13min, λ= 254nm, by GC analysis; **3d**, T_{hv} = 14 min, λ= 254nm, by GC analysis; **3e**, T_{hv} = 110min, λ= 300nm, by HPLC analysis. [E]Yield measured for disappearance of ether since cinnamyl alcohol undergoes secondary photochemistry at 254, 300nm.

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