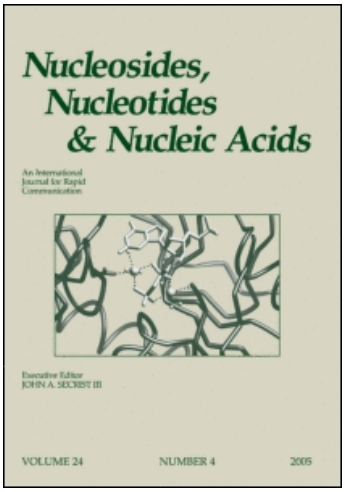

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New Fluorescent Nucleoside Derivatives -5-Alkynylated 2-Deoxyuridines

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NEW FLUORESCENT NUCLEOSIDE DERIVATIVES – 5-ALKYNYLATED 2'-DEOXYURIDINES

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ABSTRACT: Four fluorescent nucleosides, 5-(4-pyrenylethynyl)-, 5-(1-pyrenylbutadiynyl)-, 5-(3-perylenylethynyl)-, and 5-[4-(2-benzoxazolyl)phenylethynyl]-2'-deoxyuridines, were synthesized.

It is known that attaching an alkyn-1-yl group to the 5-position of dUTP does not considerably impair the substrate properties of the triphosphate in the DNA polymerase reaction[1] and even additionally stabilizes nucleic acid complexes.[2] We have been synthesizing fluorescent nucleoside derivatives in which the nucleic base is π-conjugated with a fluorophore and which can be introduced into oligonucleotides. Carbon-carbon triple-bond-containing spacers are suitable to conjugate (at least, in the excited state) the π-electron systems of a fluorophore and a nucleic base and to vary their spectral properties in that way. Thus, in the case of 5-(1-pyrenylethynyl)-2'-deoxyuridine,[3] the first nucleoside derivative of this type, the pyrene absorbance and emission maxima exhibited bathochromic shifts by ca. 60 and 30 nm, respectively. Here we report a synthesis of a number of conjugates of this type, some other 5-alkynyl-2'-deoxyuridines. Chromophores based on polycyclic aromatic hydrocarbons (pyrene, perylene) or a heterocyclic compound (2-phenylbenzoxazole) were attached to the 5-position of deoxyuridine through an ethynyl or butadiynyl linker.

As an approach, we used the Pd(0)-catalyzed Heck–Sonogashira coupling of the 5-iodonucleoside derivatives **1** with terminal alkynes **2a-d** in the conditions adapted for nucleosides[4] (Scheme 1).

Among the alkynes used, only the perylene derivative **2c** had been known.[5] Pyrene **4** was converted, according to the published procedures,[6] to its 4-acetyl derivative **5**. This compound, through the Vilsmeier–Haak–Arnold transformation to aldehyde **6** and the alkali-induced elimination (the Bodendorf method[7]) yielded the desired alkyne **2a** (Scheme 2).

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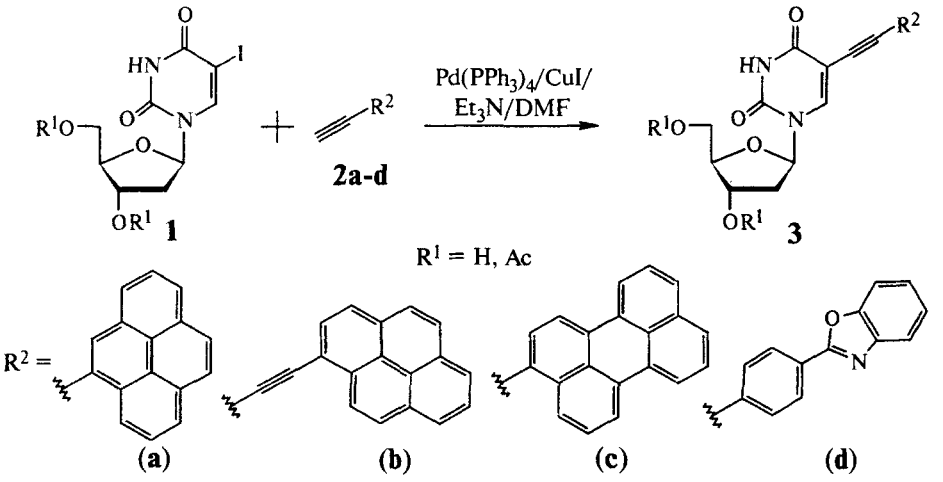
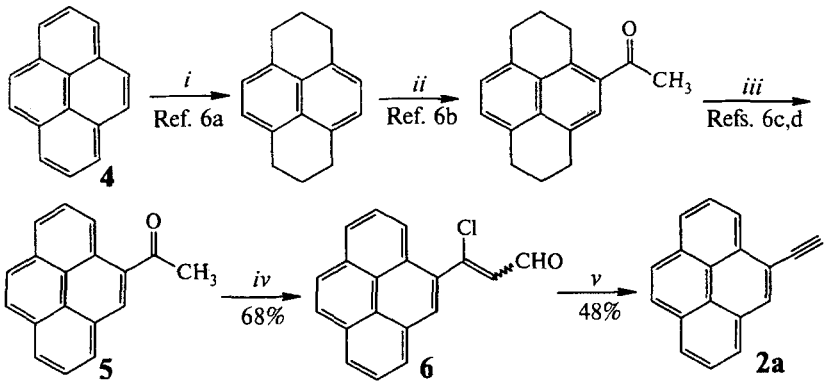


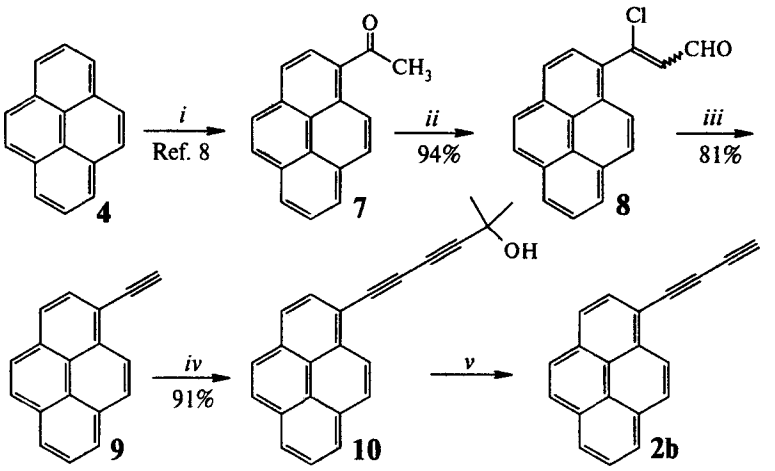
Scheme 1



Reagents: (*i*) Na/*i*-$C_5H_{11}OH$; (*ii*) $Ac_2O/AlCl_3/CH_2Cl_2$; (*iii*) DDQ/C_6H_6; (*iv*) 1. $POCl_3$/DMF, 2. OH^-; (*v*) KOH/dioxane

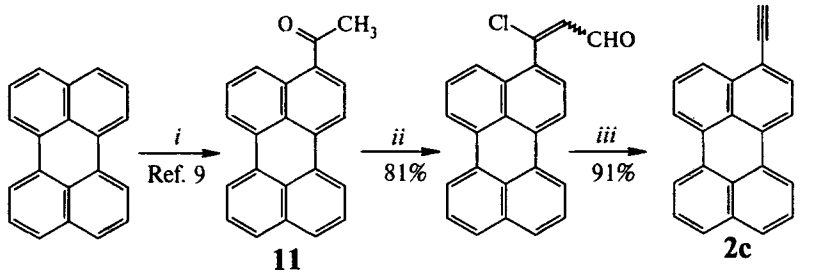
Scheme 2

In a similar way, 1-acetylpyrene **7** gave the acroleine derivative **8** and alkyne **9** (Scheme 3). The alkyne chain was extended using the Cadiot–Chodkiewicz cross-coupling with a protected bromoacetylene to give **10** followed by the alkaline deprotection. The resulting rather labile diyne **2b** after chromatographic purification was directly, without evaporation, reacted with **1** (R^1 = Ac) to give 5-(1-pyrenylbuta-diynyl)-3,5-*O*-diacetyl-2′-deoxyuridine **3** (R^1 = Ac, R^2 = 1-pyrenylethynyl), overall yield 68% from **10**.



Reagents: (*i*) $Ac_2O/AlCl_3/CH_2Cl_2$; (*ii*) 1. $POCl_3$/DMF, 2. OH^-; (*iii*) KOH/dioxane; (*iv*) $BrC{\equiv}CC(CH_3)_2OH/NH_2OH/n\text{-}C_4H_9NH_2/CuCl$/DMF; (*v*) KOH/dibenzo-18-crown-6

Scheme 3



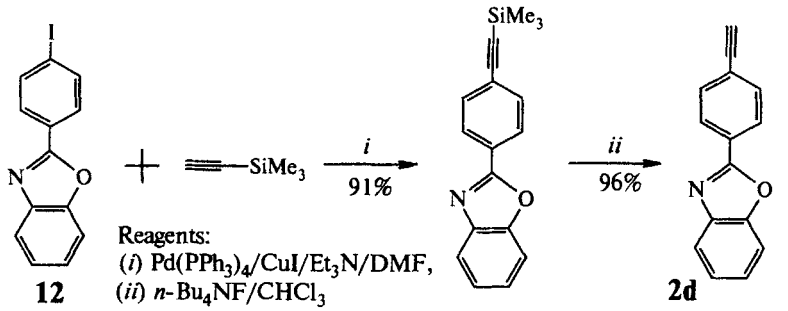
Reagents: (*i*) $Ac_2O/AlCl_3/CH_2Cl_2$; (*ii*) 1. $POCl_3$/DMF, 2. OH^-; (*iii*) KOH/dioxane

Scheme 4

3-Ethynylperylene **2c** was prepared likewise from the 3-acetyl derivative **11** using the Bodendorf method, which proved more convenient in this case than the published procedure[5] (Scheme 4).

Alkyne **2d** was synthesized starting from 2-(4-iodophenyl)benzoxazole **12**[10] through its coupling with trimethylsilylacetylene and the fluoride-mediated desilylation (Scheme 5).

Alkynes **2a-d** were coupled with iodonucleosides **1** to give alkynylated derivatives **3** in 65–85% yields. The desired *O*-nonprotected nucleosides **3** (R^1 = H) were poorly soluble in most organic solvents, which complicated their isolation from the reaction mixture. On the contrary, the protected derivatives **3** (R = Ac) were easily purified by column chromatography on silica gel and then deacylated by 25% aq. NH_3/MeOH to



Scheme 5

afford **3** (R = H) in an almost quantitative yield (the experimental conditions were similar to those earlier described for 5-(1-pyrenylethynyl)-2′-deoxyuridine[3]).

The attachment of a nucleoside-ethynyl grouping to the polycyclic or heterocyclic chromophore produced a considerable bathochromic shift of the absorbtion and emission maxima accompanied by an increase in absorbance.

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