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Ethynyl-equipped spirobenzopyrans as promising photochromic markers for nucleic acid fragments

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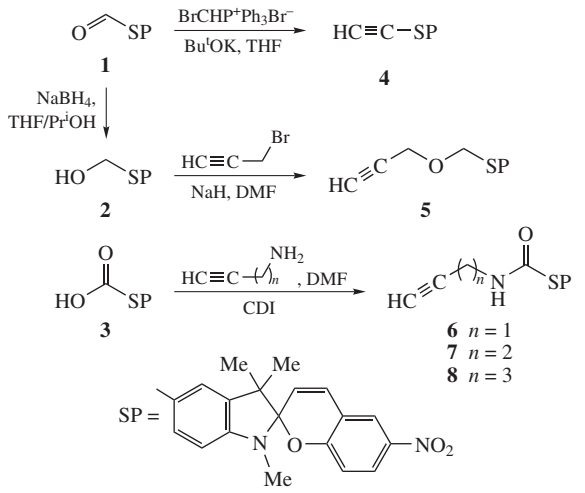
New photochromic markers for nucleic acid fragments, 6′-nitro-substituted spirobenzopyrans equipped with ethynyl group through the appropriate linkers, were subjected to the Sonogashira coupling with model 5-iodo-1,3-dimethyluracil.

The use of nucleic acids as building blocks for constructing self-assembling functional objects is of considerable current interest. Thus, sensors, diagnosticums, therapeutic agents and catalytic systems prepared *in vivo* based on nucleic acids are the most attractive test materials.[1] The photocontrol of the local sections of nucleic acids can ensure the complete control of a process with their participation. This effect is of paramount applied importance in the development of methods for the photochemical control of recognition and interaction processes in the nucleic acid–nucleic acid or peptide–nucleic acid systems.[2] Thus, application of chromophore, fluorescent and radioactive substituents of functionalized nucleic acids and nucleosides makes it possible to follow the participation of nucleic acids in biological processes.[3] Modified nucleosides serve as the antiviral, antitumorigenic or antibacterial agents in medicine.[4–7] Labeling of nucleic acids and their fragments with photochromic and photosensitive moieties was noted.[8]

Here, we make a contribution to nucleic acid technology by modification of nucleoside fragments with photochromic spirobenzopyranes.

Reactions outlined in Schemes 1 and 2 were chosen as the strategy of the synthesis.† The strategy is based on the Sonogashira cross-coupling between terminal acetylene component and halogen-substituted nucleic bases or nucleosides, which was successfully demonstrated for both deoxyribonucleosides[4,7,9,10] and ribonucleosides.[4,7,11]



Scheme 1

For the implementation of this approach, a number of acetylene derivatives **4–8** of spiropyrans (SP) with various spacers were prepared. The spacer variation was necessary to optimize the arrangement of a photochrome and a nucleoside base; the photochromic marker should exert a minimum or maximum effect on the complementary interaction of nucleic acid bases (Watson–Crick or Hoogsteen pairs) in one or another state. Furthermore, one should consider that the spatial geometry of a functional nucleoside can determine the choice of phosphorylation procedure (enzymatic method, which is more convenient than chemical one, can be sometimes ineffective).

Acetylene derivative **4** was obtained in one-pot by the Wittig olefination of formyl precursor **1** with ylide generated from (bromomethyl)triphenylphosphonium bromide, followed by HBr elimination from the intermediate bromoolefin. The propargyloxymethyl derivative of spiropyran **5** was prepared in a moderate yield by alkylation of the corresponding hydroxymethyl precursor **2** with propargyl bromide. Alkynes **6–8** were accessed by amidation of spiropyran carboxylic acid **3** with homologous commercially available aminoalkynes $HC{\equiv}C(CH_2)_nNH_2$. The following reagent systems were tested: (i) isobutyl chloroformate/*N*-methylmorpholine/DMAP in THF, (ii) CDI in DMF, and (iii) DCC in THF and DMF. Systems (i) and (ii) gave the best results in terms of the conversion of starting compound **3** and the yields of the target product and by-products; however, the simpler method (ii) was of our choice.

The starting spiropyran precursors **1** and **3** were synthesized as described previously.[12,13]

The applicability of our strategy (Scheme 2) was tested during coupling of acetylene spiropyran **4** with 5-iodo-1,3-dimethyluracil **9** as model reaction. Under the Sonogashira conditions, we obtained product **10** in a high yield. The homocoupling dimer **11** was isolated in insignificant amounts. Important to note, bicyclic compounds of type **12** reported previously[4,6,7,11] were not detected.

The approach developed can be applied to nucleosides and other classes of photochromic compounds. The photochromic behavior of the synthesized compounds will be reported elsewhere.

As a result, we obtained the new derivatives of spiropyrans (photochromic markers) equipped with terminal acetylene moieties

† For synthetic procedures and characteristics of the products, see Online Supplementary Materials.

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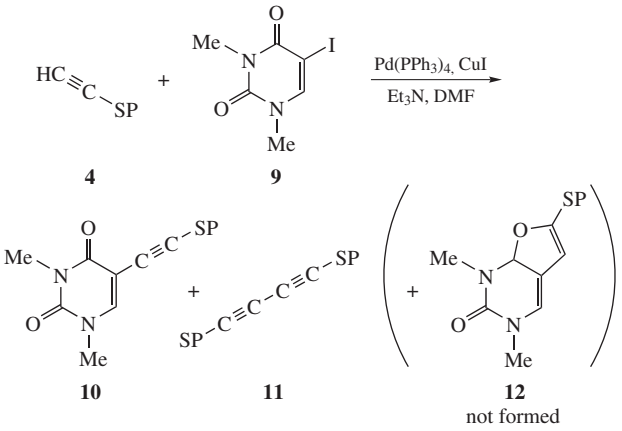

Scheme 2

through a number of spacers. Their model Sonogashira coupling with 5-iodo-1,3-dimethyluracil can open a gateway to a new procedure of marking nucleic acids with photosensitive units.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2013.05.008.

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