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Solid Phase Synthesis of Nucleobase and Ribose Modified Inosine Nucleoside Analogues

Giorgia Oliviero^a, Jussara Amato^a, Stefano D'Errico^a, Nicola Borbone^a, Gennaro Piccialli^a & Luciano Mayol^a

^a Dipartimento di Chimica delle Sostanze Naturali , Università di Napoli Federico II , Napoli, Italy Published online: 05 Dec 2007.

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SOLID PHASE SYNTHESIS OF NUCLEOBASE AND RIBOSE MODIFIED INOSINE NUCLEOSIDE ANALOGUES

Giorgia Oliviero, Jussara Amato, Stefano D'Errico, Nicola Borbone,

Gennaro Piccialli, and Luciano Mayol Dipartimento di Chimica delle Sostanze Naturali, Università di Napoli Federico II, Napoli, Italy

□ The synthesis and the use of new N-1-dinitrophenyl-inosine based solid support is reported. The support, which binds the nucleoside by a 5 '-O-monomethoxytrityl function, reacting with Nnucleophiles allowed the synthesis of a small library of N-1 alkylated inosine and AICAR derivatives. Moreover, the obtained supports, after the cleavage of the 2'-3' ribose bond, furnished a set of new N-1 alkylated-2'-3'-secoinosine derivatives in high yields.

Keywords N-1-Dinitrophenyl-inosine based solid support; N-nucleophiles; 2'-3'-seconucleosides

Nucleosides are biomolecules possessing a pivotal role in the metabolism. In fact, they are involved, as tri-phosphate derivatives, in the nucleic acid replications and in a very wide number of interactions with enzymes, structural proteins, and nucleic acids. Furthermore, nucleosides are involved with a broad array of biological targets of therapeutic importance and a number of their derivatives exhibit antineoplastic,^[1] antibiotic,^[2] and antiviral properties.^[3] A variety of solid phase combinatorial strategies have been reported for the preparation of nucleoside and small oligonucleotide analogues libraries.^[4] In an effort to enlarge the nucleoside chemical reactivity on the solid phase, and, thus, the number of accessible structurally diverse analogues, we report here the new acid labile nucleoside functionalized support 2, which binds the N-1-dinitrophenyl-inosine derivative 1 through the 5'-O-ribose position. These support has been employed in the solid phase synthesis of N-1 substituted inosine **4a-e**, the related 2'-, 3'seconucleoside derivatives 6a-e and the 5-aminoimidazole-4-carboxamide riboside (AICAR) 8. The solid phase strategy is based on our previous studies on the C-2 reactivity of N-1-dinitrophenyl-2'-deoxyinosine towards Nnucleophiles^[5,6] to obtain N-1 substituted inosine and AICAR derivatives.

Address correspondence to Giorgia Oliviero, Dipartimento di Chimica delle Sostanze Naturali, Università di Napoli Federico II, via D. Montesano 49, Napoli I-80131, Italy. E-mail: golivier@unina.it



SCHEME 1 i) 2 or **3** (1.5 eq.) in pyridine (1.5 mL/250 mg of resin), DMAP (0.2 eq.), 24 hours r.t; **ii**: R_1 -NH₂/DMF (38.0 eq), 8 hours 50°C; **iii**) TFA 2% solution in DCM; **iv**: EDA/DMF (1:1, w/w) 8 hours 50°C; **v**: NaIO₄ (10 eq.) in DMF/H₂O (1:1,v/v), 12 hours, 60°C; resin washings and treatment with NaBH₄ (20 eq.) in EtOH, 2 hours, r.t.

The reported reaction mechanism indicates that when a strong electronwithdrawing group (such as the 2,4-dinitrophenyl or the nitro group^[7]) is attached to the N-1 atom of the hypoxanthine ring, the C-2 carbon become electrophilic enough to react with amino nucleophiles (R_1 -NH₂) leading to R_1 -N-1 substituted inosine derivatives by a fast opening and re-closure of the six terms purine cycle.

Support **2** was obtained by reaction of the commercially available polystyrenemonomethoxytrityl chloride (MMTCl) with the 1-(2,4-dinitrophenyl)-inosine^[8] **1** (Scheme 1). The structure and the loading of the support **2** (1.2–1.3 meq/g) was confirmed analyzing, by ¹H NMR and quantitative UV experiments, the released inosine **1** by treatment with 2% TFA in DCM. The reaction of support **2** (100 mg, 0.13 mmol) with N-nucleophiles (5.0 mmol, R₁-NH₂, Table 1 entry **a–e**) in DMF (8 hours, at 50°C) gave supports **3a–e**. The reaction of **2** with ethylenediamine (Table 1, entry **f**) furnished, as expected,^[9] the support **7** bearing AICAR in almost quantitative yields. The structures of the supports **3a–e** and **7** were ascertained by HPLC, ¹H NMR, and MS analyses of the corresponding detached

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TABLE

				¹ H NMR ^b			¹ H NMR ^b
Entry	$\mathbf{R_{l}}$ -NH $_{2}$	4a–e and 8 Yield ^{<i>a</i>} (%)	H-2; H-9; H-1′	R1 moiety	6a–e Yield ^{c} (%)	H-2; H-9; H-1'	R ₂ moiety
5	NH ⁵	4a , (98)	8.41; 8.36; 6.02	4.12; 1.76; 1.40; 0.98	6a (85)	8.30; 8.26; 6.04	4.00; 1.75; 1.38; 0.96
q		4 b , (96)	8.42; 8.26; 6.01	4.19; 3.82	6b (85)	8.28; 8.24; 6.04	4.20; 3.83
c	НО	4c , (97)	8.41; 8.32; 6.02	4.20; 3.60; 1.98	6c (84)	8.31; 8.26; 6.03	4.21; 3.60; 1.98
q	но Су он	4d, (98)	8.40; 8.35; 6.02	4.12; 3.56 1.81; 1.59; 1.42	6d (82)	4.21; 3.60; 1.98	4.11; 3.55; 1.79; 1.58; 1.43
e	HO-HA	4e , (90)	8.38; 8.32; 6.00	3.98 (2CH ₂ OH); 3.92 (CH)	6e (75)	8.29; 8.04; 6.05	4.02 (2CH ₂ OH) 3.95 (CH)
f		8 (98)	8.04; 5.66		N.T.	N.T.	

"Starting from resin 2. $^{b}400$ MHz, (CD₃OD) significative protons at ppm. ^cStarting from resin 3.

crude materials **4a–e** and **8**. The product yields and the ¹H NMR selected data are reported in Table 1. The second goal of this work was aimed to combining the set of the N-1 alkylations of the supports **3a–e** with the 2'-3'-oxidative cleavage of the ribose to obtain the related 2'-3'-seconucleoside derivatives.^[10] In a typical reaction the support **3a–e** (100 mg) was left in contact with a solution of NaIO₄ (1.3 mmol) in DMF/H₂O (1:1,v/v) and shaken for 12 hours at 60°C. The resulting support was treated with NaBH₄ (2.6 mmol) in EtOH and shaken for 2.0 hours at room temperature. After washings, the resins **5a–e** were analyzed by detachment of the nucleosidic material by TFA treatment. HPLC analyses indicated that the 2'-3'-secoinosine derivatives **6a–e** were obtained in 75–85% yields. The structures of **6a–e** were confirmed by ¹H NMR (Table 1) and MS analyses.

In conclusion, we have reported the synthesis of the new N-1dinitrophenyl-inosine based solid support **2**, which allowed the synthesis of small libraries of N-1 alkylated inosine derivatives **4a–e** and N-1 alkylated 2'-3'-secoinosine derivatives **6a–e** in good yields. Further studies are currently in progress in this direction to obtain new series of modified nucleoside analogues.

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