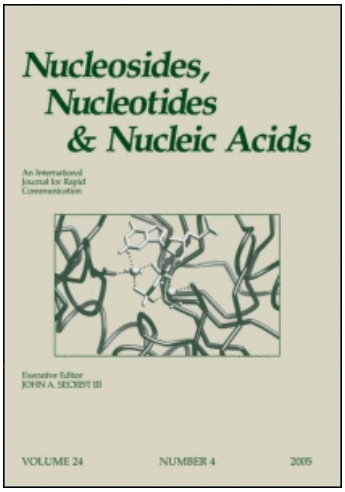

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SOLID PHASE SYNTHESIS OF NUCLEOBASE AND RIBOSE MODIFIED INOSINE NUCLEOSIDE ANALOGUES

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 N-nucleophiles 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 N-nucleophiles[5,6] to obtain N-1 substituted inosine and AICAR derivatives.

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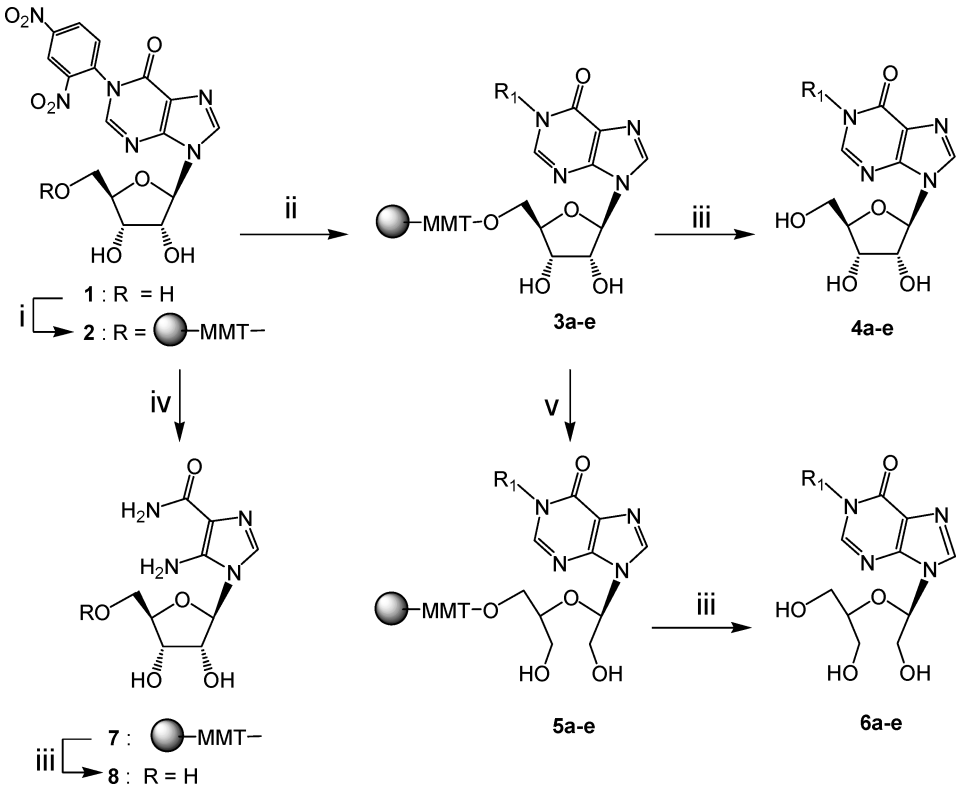
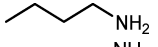
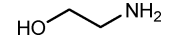
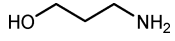
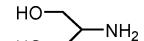
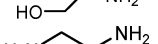


SCHEME 1 **i)** **2** or **3** (1.5 eq.) in pyridine (1.5 mL/250 mg of resin), DMAP (0.2 eq.), 24 hours r.t; **ii**: R_1-NH_2/DMF (38.0 eq), 8 hours 50°C; **iii**) TFA 2% solution in DCM; **iv**: EDA/DMF (1:1, w/w) 8 hours 50°C; **v**: $NaIO_4$ (10 eq.) in DMF/H_2O (1:1,v/v), 12 hours, 60°C; resin washings and treatment with $NaBH_4$ (20 eq.) in EtOH, 2 hours, r.t.

The reported reaction mechanism indicates that when a strong electron-withdrawing 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-NH_2) 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 ^{1}H 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, R_1-NH_2, 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, ^{1}H NMR, and MS analyses of the corresponding detached

TABLE 1 Reactions of the support **2** products **4**, **6**, and **8**. N.T: not tested.

			^{1}H NMR[b]			^{1}H NMR[b]	
Entry	R_1-NH_2	**4a–e** and **8** Yield[a] (%)	H-2; H-9; H-1′	R_1 moiety	**6a–e** Yield[c] (%)	H-2; H-9; H-1′	R_2 moiety
a		**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
b		**4b,** (96)	8.42; 8.26; 6.01	4.19; 3.82	**6b** (85)	8.28; 8.24; 6.04	4.20; 3.83
c		**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
d		**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		**4e,** (90)	8.38; 8.32; 6.00	3.98 ($2CH_2OH$); 3.92 (CH)	**6e** (75)	8.29; 8.04; 6.05	4.02 ($2CH_2OH$) 3.95 (CH)
f		**8** (98)	8.04; 5.66		N.T.	N.T.	

[a]Starting from resin **2**.
[b]400 MHz, (CD_3OD) significative protons at ppm.
[c]Starting from resin **3.**

crude materials **4a–e** and **8**. The product yields and the ^{1}H 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 $NaIO_4$ (1.3 mmol) in DMF/H_2O (1:1,v/v) and shaken for 12 hours at 60°C. The resulting support was treated with $NaBH_4$ (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 ^{1}H NMR (Table 1) and MS analyses.

In conclusion, we have reported the synthesis of the new N-1-dinitrophenyl-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.

REFERENCES

1. a) Miura, S.; Izuta, S. *Current Drug Targets* **2004,** 5, 191–195; b) Parker, W.B.; Secrist, J.A.; Waud, W.R. *Current Opinion in Investigational Drugs* **2004**, 5, 592–596; c) Szafraniec, S.I.; Stachnick, K.J.; Skierski, J.S. *Acta Pol. Pharm.* **2004**, 61, 297–306.
2. a) Lagoja, I.M. *Chem. Biodiv.* **2005**, 2, 1–50; b) Kimura K.; Bugg, T.D.H. *Nat. Prod. Rep.* **2003**, 20, 252–273; c) Rachakonda, S.; Cartee, L. *Curr. Med. Chem.* **2004,** 11, 775–793.
3. (a) Chu, C.K., Ed. In *Antiviral Nucleosides*; Elsevier, New York; 2003; b) Simons, C.; Wu, Q.; Htar, T.T. *Curr. Top. Med. Chem.* **2005**, 5, 1191–1203; c) De Clercq, E.; Neyts, J. *Rev. Med. Virol.* **2004**, 14, 289–300.
4. For example see: a) Epple, R.; Kudirka, R.; Greenberg, W.A. *J. Comb. Chem.* **2003**, 5, 292–310; b) Ding, Y.; Habib, Q.; Shaw, S.Z.; Li, D.Y.; Abt, J.W.; Hong, Z.; An, H. *J. Comb. Chem.* **2003**, 5, 851–859; c) Rodenko, B.; Wanner, M.J.; Koomen, G.-J. *J. Chem. Soc., Perkin Trans.* 1 **2002**, 1247–1252; d) Roland, A.; Xiao, Y.; Jin, Y.; Iyer, R.P. *Tetrahedron Lett.* **2001**, 42, 3669–3672.
5. De Napoli, L.; Messere, A.; Montesarchio, D.; Piccialli, G. *J. Org. Chem.* **1995**, 60, 2251–2253.
6. De Napoli, L.; Messere, A.; Montesarchio, D.; Piccialli, G.; Varra, M. *J. Chem. Soc., Perkin Trans.* 1 **1997**, 2079–2082.
7. Ariza, X.; Bou, V.; Villarasa, J. *J. Am. Chem. Soc.* **1995**, 117, 3665–3673.
8. Galeone, A.; Mayol, L.; Oliviero, G.; Piccialli, G.; Varra, M. *Eur. J. Org. Chem.* **2002**, 4234–4238.
9. De Napoli, L.; Messere, A.; Montesarchio, D.; Piccialli, G.; Varra, M. *J. Chem. Soc., Perkin Trans.* 1 **1997**, 2079-2082.
10. For example see: Kumar, A., Walker, R.T. *Tetrahedron* **1990**, 46, 3101–3110.