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Efficient microwave-assisted solid phase coupling of nucleosides, small library generation, and mild conditions for release of nucleoside derivatives

Hanumantharao Paritala [a], Yuta Suzuki [b], Kate S. Carroll [a,*]

[a] Department of Chemistry, The Scripps Research Institute, 130 Scripps Way, Jupiter, FL 33458, USA
[b] Department of Chemistry, University of Michigan, Ann Arbor, MI 48109, USA

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ABSTRACT

Nucleosides are essential bio-molecules that participate in a wide array of biological processes involved in maintaining physiologic homeostasis. Recent efforts geared toward the synthesis of nucleoside analogues and development of nucleoside combinatorial libraries using solid phase synthesis have contributed invaluable information toward drug design and development. These studies have provided information concerning the structural requirements of substrate binding pockets of enzymes and evaluation of enzyme kinetics. However, the synthesis of nucleosides and its corresponding analogues remains a challenging and time consuming process. Herein, we report an efficient, microwave assisted solid phase coupling of nucleosides, combinatorial chemistry on the coupled nucleosides to generate small library, and mild cleavage conditions to release nucleoside derivatives from its solid support. We anticipate these findings will accelerate the development of synthetic methods or combinatorial library design of nucleoside analogues in similar settings.

Introduction

Nucleosides and its derivatives are important components and hold key roles in numerous biological processes and signal transduction. These bio-molecules are utilized as genomic building blocks, enzyme substrates, and cellular energy sources.[1] Additionally, nucleoside analogues have been successfully utilized in anticancer, -bacterial, and—viral therapeutics.[2] In this context, the synthesis and testing of bio-mimetic nucleoside derivatives has emerged as a widely used approach in drug discovery campaigns. The design of nucleoside analogues and combinatorial libraries using solid phase based techniques has garnered large momentum due to the importance of their therapeutic applications.[3] However, the synthesis of nucleosides remains a challenge due to long reaction times, harsh cleavage conditions, and poor product yields.[4] Redwan et al. recently reported a novel solid phase strategy that enables the synthesis of structurally different 5-*O*-[*N*-(acyl)-sulfamoyl] adenosines from a protected ribo-purine starting material. This approach applied cleavage conditions using trifluoroacetic acid (TFA) and ammonium formate, which resulted in poor yields of the nucleoside derivatives.[5] In a separate study, Caroline et al. reported the synthesis of solid phase poly-phosphorylated nucleoside analogues with decent yields and mild cleaving conditions, but extremely slow reaction times.[6] Therefore, we have explored microwave assisted solid phase nucleoside synthesis in order to optimize reaction conditions and to create a platform to perform combinatorial chemistry on solid phase nucleosides. Herein, we describe an efficient microwave assisted solid phase coupling of nucleosides, small chemical library generation on the resin bound nucleosides, and the mild cleavage conditions to release the nucleoside derivatives from its resin support.

Results and discussion

For the synthesis of the adenosine scaffold, we initially used an existing protocol developed for generating inosine and uridine analogues[3a]. This procedure required purification after formation of the benzylidene intermediate **4**, gave low yields of the scaffold (10–25%), and was insufficient for further solid phase synthesis of adenosine analogues. Collectively, this synthetic procedure was time consuming and required 8–10 days to achieve the final product. Optimization of the reported literation conditions would result in a facile synthesis of nucleoside derivatives with improved yield and decreased reaction times. The following key factors were included during the development of our approach: (1) employ microwave conditions to enhance reaction rates, and (2) utilize mild reaction conditions (Scheme 1). Generation of the poly styrene bound nucleoside scaffold started with the synthesis of Aldehyde 2 as previously reported[3a], and activated by the formation of dimethylacetal **3**. Compound **3** was immediately converted into benzylidene **4** via transacetylation to prevent reversion back to compound **2**. The acetal forming reaction produced a mixture of diastereomers due to non-selective formation of the acetal

* Corresponding author. Tel.: +1 561 228 2460; fax: +1 561 228 2919.
E-mail address: kcarroll@scripps.edu (K.S. Carroll).

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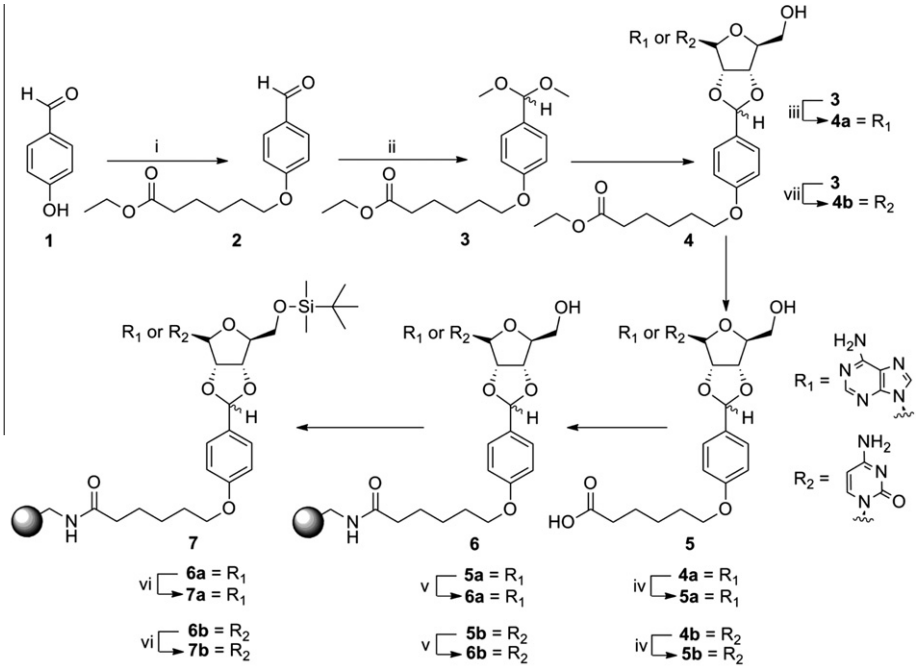
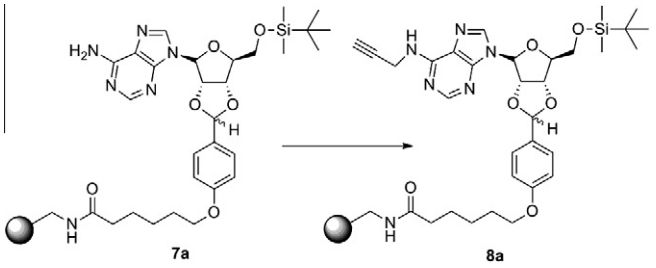


Conditions: (i) Ethyl 6-bromohexanoate, K_2CO_3, DMF, microwave 150°C (ii) Trimethylorthoformate, *p*-toluenesulfonicacid, MeOH, microwave 60 °C (iii) adenosine, *p*-toluenesulfonicacid, dimethylformamide, microwave 130 °C (iv) NaOH, MeOH, H_2O, microwave 100 °C (v) aminomethylated polystyrene HL, *O*-Benzotriazole-*N,N,N′,N′*-tetramethyl-uronium-hexafluoro-phosphate (HBTU), *N,N*-Diisopropylethylamine, DMF, microwave 60 °C (vi) *tert*-butyldimethylsilyl chloride, imidazole, microwave 40 °C (vii) cytidine, *p*-toluenesulfonicacid, dimethylformamide, microwave 130 °C.

Scheme 1. Synthesis of solid-supported nucleoside derivatives.

Table 1
Optimization of reaction conditions for alkylation of aromatic amine on the nucleosides



S. No	Microwave temperature (°C)	Time (min)	Equivalents of propargylbromide	Equivalents of base (DIEA)[b]	Yield[a] (%)
1	80	10	1	1	0
2	100	15	1	1	0
3	150	10	1	1	45
4	150	15	2	2	90

[a] % yield was determined by NMR using alanine as an internal standard.
[b] *N,N*-Diisopropylethylamine.

carbon.[7] Compound **4** was hydrolyzed to the carboxylic acid **5** with 48% overall yield in four steps. Finally, compound **5** was coupled to aminomethyl resin using *O*-(Benzotriazol-1-yl)-*N,N,N′,N′*-tetramethyluroniumtetrafluoroborate (HBTU) activation to obtain the corresponding solid phase nucleoside scaffolds **6**. When compared to solution chemistry, MW irradiation provides an overall higher yield and shorter reaction times.

Using the resin bound nucleosides **6** as platform we started exploring possible chemistry on the aromatic amine and 5′-hydroxyl functionalities to construct four member library of resin bound nucleosides. In order to achieve this 5′-hydroxyl group of the resin bound nucleosides **6** was protected by using *tert*-butyldimethylsilyl chloride and imidazole with quantitative yields and this protection allowed us to selectively explore the alkylation reactions on the aromatic amine of **7**. We have tested variety of conditions to install propargyl group on the aromatic amine as shown in Table 1. The ideal conditions to conduct this reaction using microwave are achieved by using two equivalents of propargylbromide and two equivalents of *N,N*-diisopropylethylamine at 150 °C with reasonable yields. Using the alkyne functional group on **8** we have