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Biomimetic self-condensation of malonates mediated by nucleosides

Qi Ji,[†] Howard J. Williams,[*] Charles A. Roessner and A. Ian Scott[✠]

Center for Biological NMR, Department of Chemistry, Texas A&M University, College Station, TX 77843, USA

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Abstract—Nucleoside mediated Claisen condensation of malonates has been achieved under biomimetic weak acid conditions, pH 3 or 4, 0.15 M NaCl, and 0.125 M Mg^{2+}. The result illustrates the catalyzing property of end-nucleosides of t-RNA in the RNA world.

It has been suggested that the most primitive organisms used RNA's rather than proteinaceous enzymes as catalysts for their metabolic pathways.[1,2] Molecular mechanisms were proposed by Scott for carbon–carbon bond forming processes (Fig. 1) in the RNA world leading to the lipids necessary for the membranes.[3] However, to our knowledge, no self Claisen condensation of nucleoside malonates has been reported. In this work, self-condensation of nucleoside malonates has been explored.

Previous attempts to observe Claisen condensation using solutions of adenosine malonate or deoxyadenosine malonate under various conditions were unsuccessful.[4] As the active amino group of adenosine might interfere with the condensation and accelerate the hydrolysis of adenosine malonate, nucleoside malonates with lower polarity (**5a** and **5b**, Fig. 2) were used in the condensation experiments.

The nucleoside malonates were synthesized from the corresponding nucleosides as shown in Figure 2. Separation of the 2′- and 3′-isomers of the nucleoside malonates was not possible because they immediately reisomerized in solvents. NMR spectra confirmed that the malonyl groups of nucleoside malonates were switching between the 2′- and 3′-OH of the nucleosides.

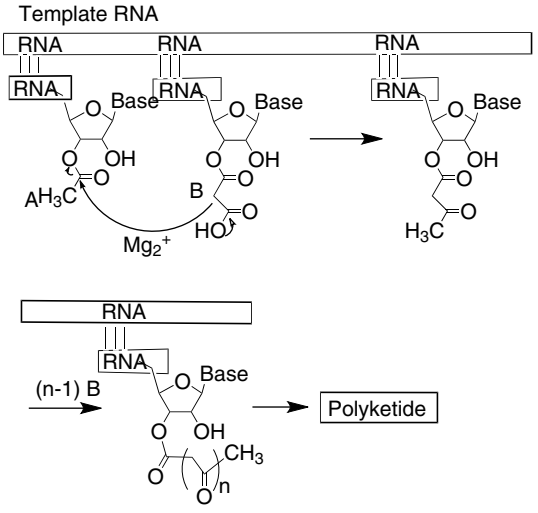

Figure 1. Mechanisms proposed for polyketide biosynthesis in the RNA world.

A series of condensation experiments were carried out in aqueous solution under acidic condition, as shown in Table 1 and Figure 3. For some experiments, we added Poly-U or Poly-A to see if the polynucleotides had some template effect[4,5] for the condensation. For most experiments, Mg^{2+} was used as a catalyst. All the experiments were carried out in 0.15 M NaCl solution, which is similar in concentration to sea water. After 30 h incubation at 37 °C, the reaction mixture was analyzed by TLC ($CHCl_3/CH_3OH = 2:1$) to separate the products.

As seen from Table 1, in the presence of Mg^{2+} (entries 1, 2, 5 and 6), the nucleoside malonates were converted into the corresponding 1,3-acetonedicarboxylic acid

* Corresponding author. Tel.: +1 979 845 4040; fax: +1 979 845 5992; e-mail: williams@cbnmr.chem.tamu.edu
† Present address: Section of Molecular Genetics and Microbiology, School of Biological Sciences, University of Texas at Austin, Austin, TX 78712, USA.
✠ Deceased April 18, 2007.

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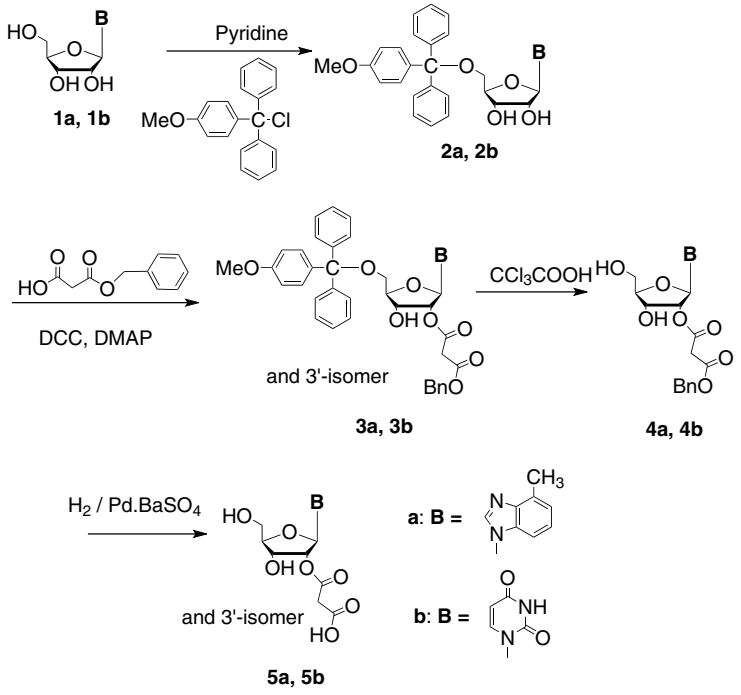

Figure 2. Synthesis of nucleoside 2′- and 3′-malonates.

Table 1. Conditions for condensation experiments

Entry	Substrate	Template	Condition	Product	Yield (%)
1	**5a** (50 mM)	Poly-U (50 mM U)	0.15 M NaCl, 0.125 M $MgCl_2$, pH 4	**6a**	93
2	**5a** (50 mM)	None	0.15 M NaCl, 0.125 M $MgCl_2$, pH 4	**6a**	90
3	**5a** (50 mM)	Poly-U (50 mM U)	0.15 M NaCl, pH 4	None	
4	**5a** (50 mM)	None	0.15 M NaCl, pH 4	None	
5	**5b** (50 mM)	Poly-A (25 mM A)	0.15 M NaCl, 0.125 M $MgCl_2$, pH 3	**6b**	86
6	**5b** (50 mM)	None	0.15 M NaCl, 0.125 M $MgCl_2$, pH 3	**6b**	87
7	**5b** (50 mM)	Poly-A (25 mM A)	0.15 M NaCl, pH 3	None	
8	**5b** (50 mM)	None	0.15 M NaCl, pH 3	None	

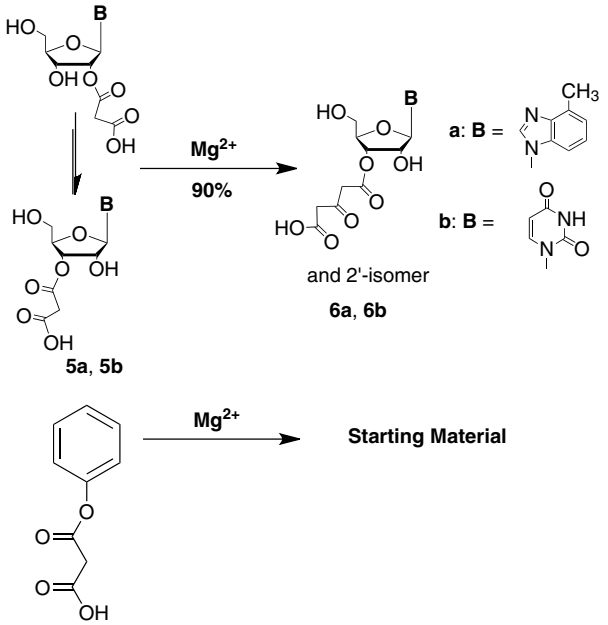

Figure 3. Decarboxylative Claisen condensation of nucleoside 2′- and 3′-malonates.

esters in yields of around 90% (Figure 3). No template effects were observed in our experiment. Magnesium cation, as a catalyst,[6] was essential for successful condensation (entries 3, 4, 7 and 8). Generally, Claisen condensations of malonate oxyesters happen only under basic and harsher conditions. As a control experiment, mono-benzylmalonate (Aldrich) was incubated under the same reaction conditions and was unchanged after 30 h as indicated by a ^{13}C spectrum of ether reaction mixture extract. Our successful condensation experiment under acidic and mild conditions (aqueous solution, no enzyme, no imidazole and body temperature) may suggest that the malonate moiety can be highly activated by linking to nucleosides and therefore can easily undergo a biomimetic decarboxylative Claisen condensation.

Although some examples of biomimetic self Claisen condensation of malonate esters had been reported,[7–14] all used thioesters or amides as substrates, with the exception of Scott[13,14] in which malonate catechol esters or monobenzyl malonates were used as substrates. Our results are the first to show that malonate can be activated simply by binding to nucleoside, and will pro-

vide us to further understand the function of the end-nucleosides of t-RNA.

Acknowledgements

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Supplementary data

Supplementary data includes synthetic procedures, characterization and spectral data for compounds **2a**–**6a**, **3b**–**6b** and ^{13}C spectra of mono-benzylmalonate from Aldrich (lower trace) and from an ether extract of a 30 h incubation (upper trace). Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.09.036.

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