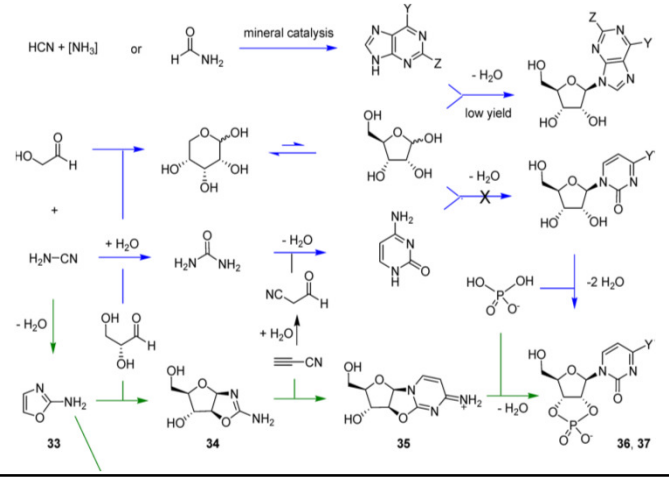
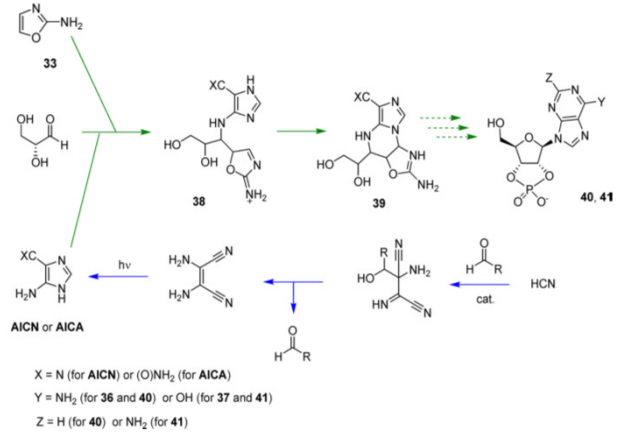
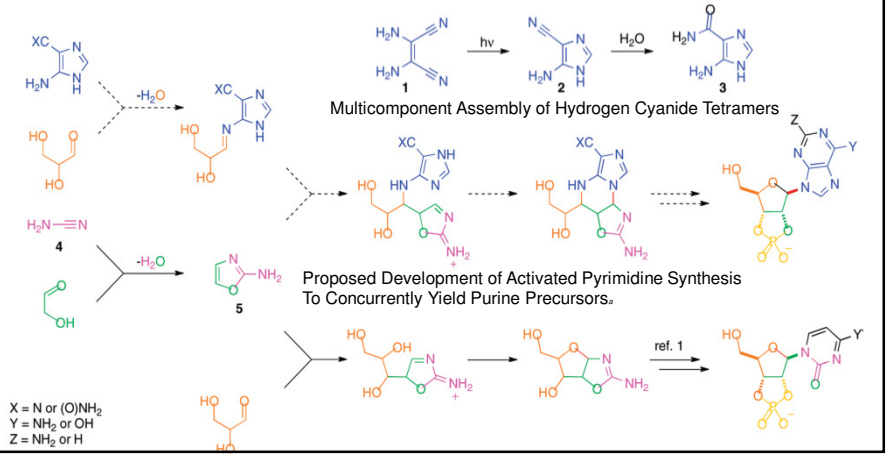
Modular vs. systems synthesis



Modular vs. systems synthesis

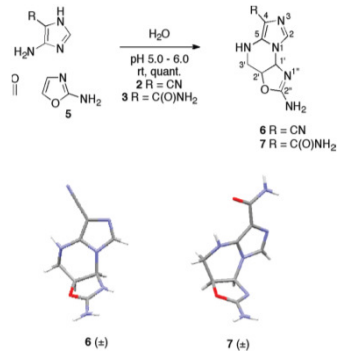


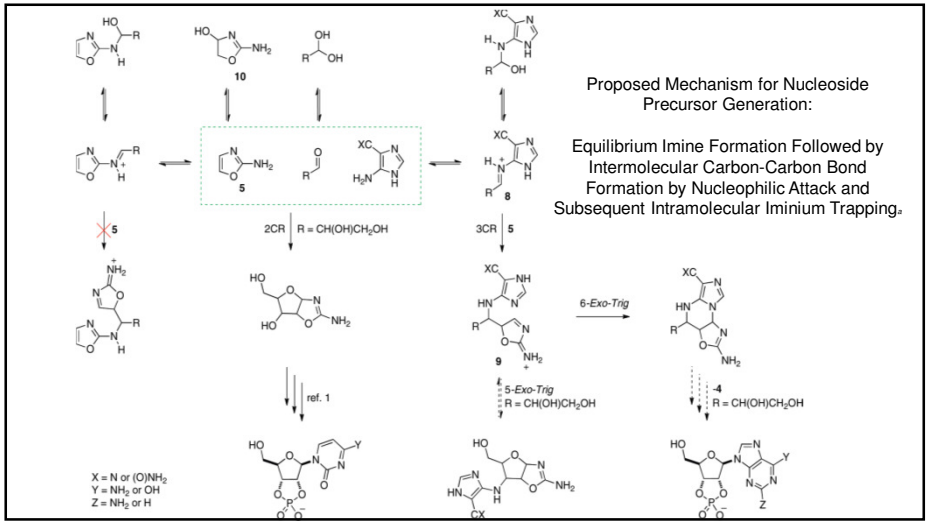
Cyanosulfidic chemistry



Cyanosulfidic chemistry

One-Pot Multicomponent Assembly of *rac*-Tetrahydroimidazo[1,3]-2-aminooxazolo[1,2]-pyrimidines **6** and **7**

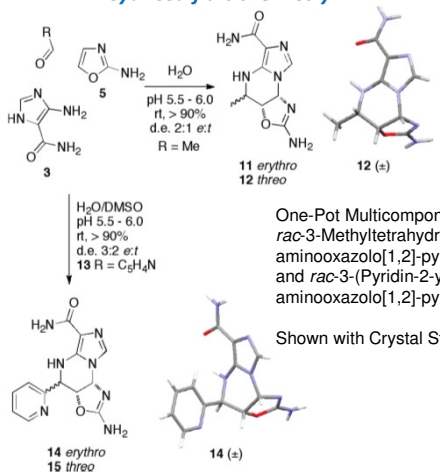




Proposed Mechanism for Nucleoside Precursor Generation:

Equilibrium Imine Formation Followed by Intermolecular Carbon-Carbon Bond Formation by Nucleophilic Attack and Subsequent Intramolecular Iminium Trapping.

Cyanosulfidic chemistry

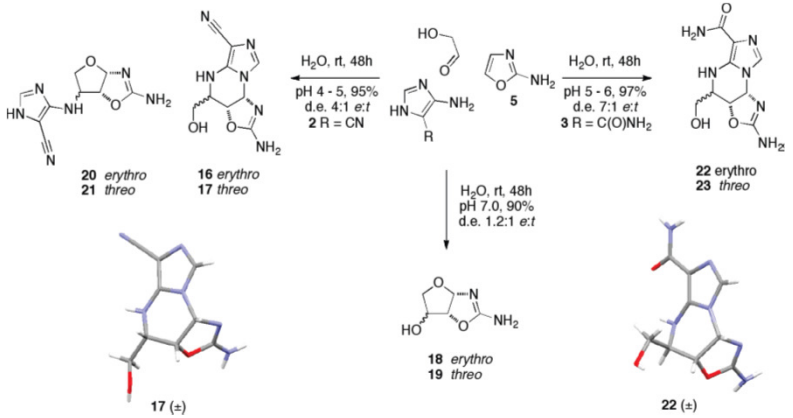


One-Pot Multicomponent Assembly of *rac*-3-Methyltetrahydroimidazo[1,3]-2-aminooxazolo[1,2]-pyrimidines **11** and **12** and *rac*-3-(Pyridin-2-yl)tetrahydroimidazo[1,3]-2-aminooxazolo[1,2]-pyrimidines **14** and **15**,

Shown with Crystal Structures of **12** and **14**

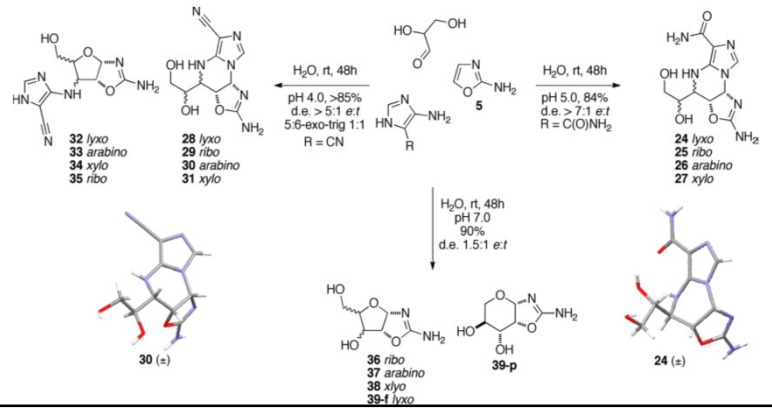
Cyanosulfidic chemistry

One-pot multicomponent assembly of *rac*-3-(Hydroxymethyl)tetrahydroimidazo[1,3]-2-aminooxazolo[1,2]-pyrimidines from glycolaldehyde, AICN **2** or AICA **3**, and 2AO **5**, with crystal structures of **17** and **22**



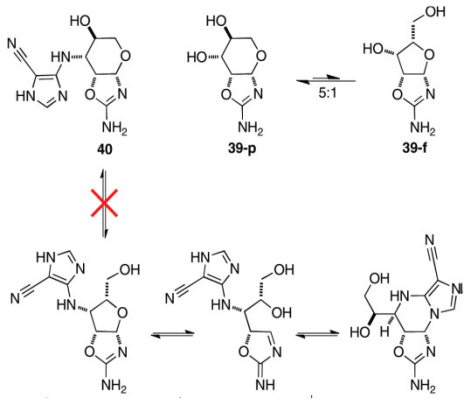
Cyanosulfidic chemistry

One-pot multicomponent [3*R*,4*R*]-selective assembly of *rac*-3-(Dihydroxyethyl)tetrahydroimidazo-2-aminooxazolopyrimidines from glyceraldehyde with crystal structures of **24** and **30**



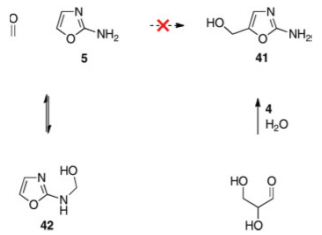
Cyanosulfidic chemistry

pH-controlled isomerization of **32** to **28** in water after 3 days at room temperature



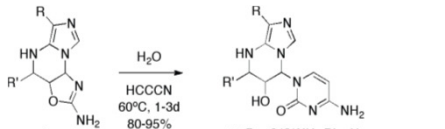
Cyanosulfidic chemistry

potential hydroxymethylation of 2-Aminooxazole **5**



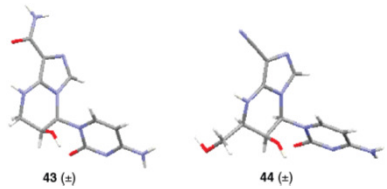
Cyanosulfidic chemistry

cyanovinylation of tetrahydroimidazo[1,3]-2-aminooxazolo[1,2]-pyrimidines with unbuffered aqueous cyanoacetylene



6
17 *threo*
21 *erythro*
24 *lyxo*
30 *arabino*

43 R = C(O)NH_2 R' = H
44 R = CN R' = CH_2OH
45 R = C(O)NH_2 R' = CH_2OH
46 R = CN R' = CH(OH)CH_2OH
47 R = C(O)NH_2 R' = CH(OH)CH_2OH

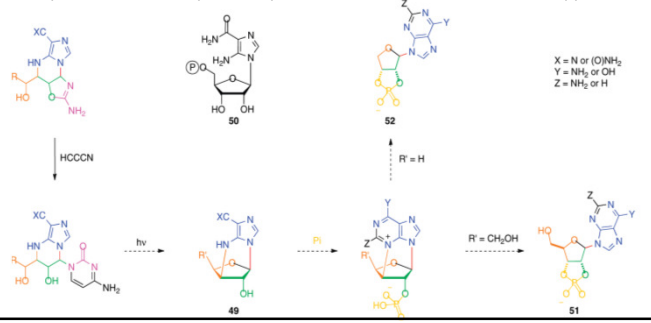


43 (±)

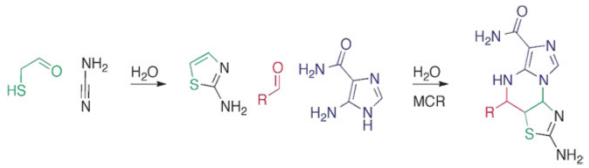
44 (±)

Cyanosulfidic chemistry

beta-Ribofuranosyl-pyrimidine nucleotide assembly and potential stepwise, regioselective beta-ribofuranosyl-purine assembly
Pathway via the intermediacy of tetrahydroimidazo[1′,3′]-2′′-aminooxazolo[1′,2′]-pyrimidinesa

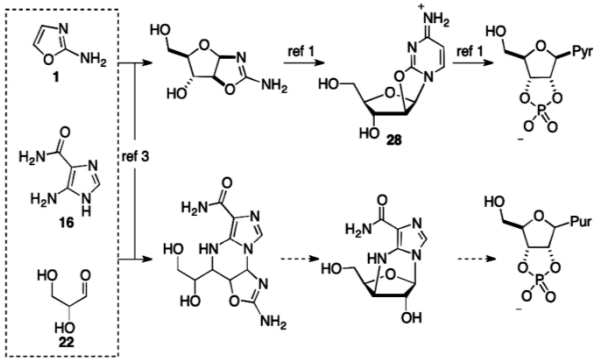


Prebiotic synthesis of deoxyribonucleosides



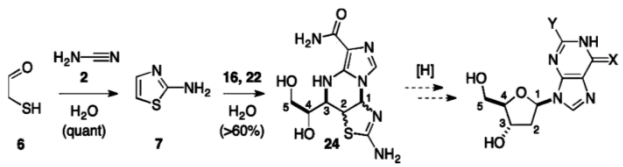
Prebiotic synthesis of deoxyribonucleosides

proposed multicomponent ribonucleotide syntheses

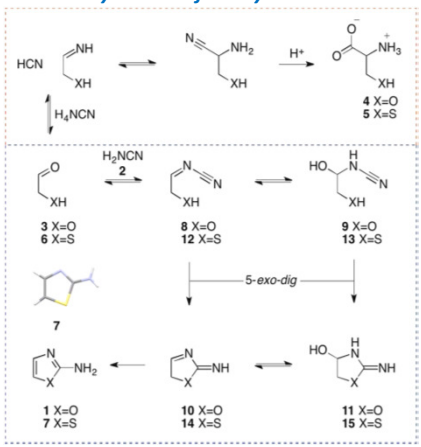


Prebiotic synthesis of deoxyribonucleosides

proposed multicomponent deoxyribonucleotide syntheses



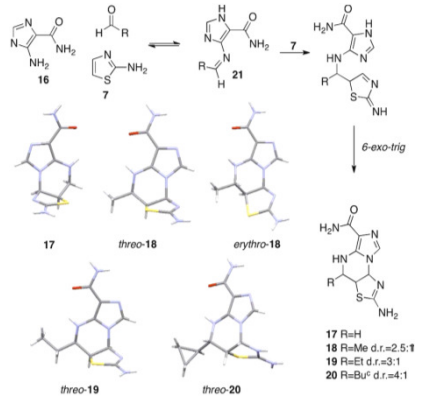
Prebiotic synthesis of deoxyribonucleosides



Strecker-Type Synthesis of Amino Acids (Red Box) and Azole Synthesis in Water (Blue Box)

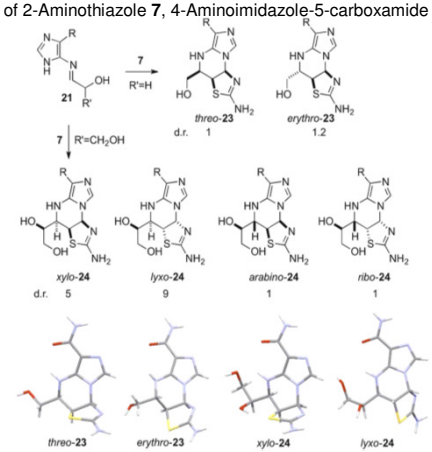
Prebiotic synthesis of deoxyribonucleosides

Three-Comp. Reaction of 2-Aminothiazole **7**, 5-Amino-imidazole-4-carboxamide **16**, and Various Aliphatic Aldehydes



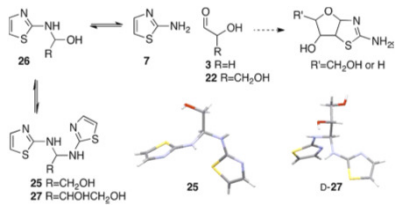
Prebiotic synthesis of deoxyribonucleosides

Three-Component Reaction of 2-Aminothiazole **7**, 4-Aminoimidazole-5-carboxamide **16**, and Glyceraldehyde **22**



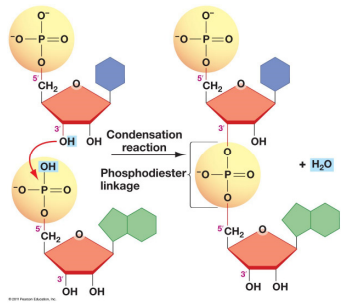
Prebiotic synthesis of deoxyribonucleosides

Crystallization of Bis-(2-aminothiazole)-aminals of Glycolaldehyde **3** and D-Glyceraldehyde **22** from Water at pH 7

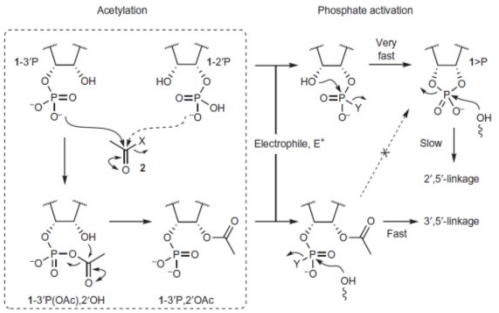


Nucleotide polymerization

Regioselective formation of 3'-5' phosphodiester bonds between nucleotides

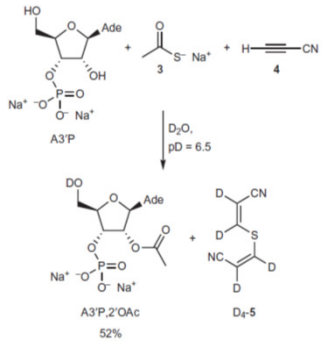


Regioselective ribonucleotide ligation



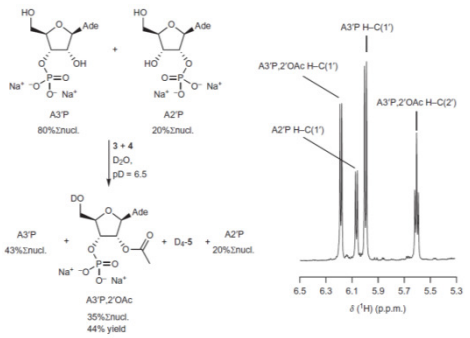
Protection of the 2'-OH group of **1**-3'P facilitates rapid template-directed 3',5'-ligation after electrophilic phosphate activation. The 3'-OH group of **1**-2'P is protected to a lesser extent, such that **1**>P is the major product of phosphate activation and slow template-directed 2',5' -ligation follows.
X = leaving group, Y = leaving group generated by electrophilic activation of phosphate oxygen with or without a subsequent nucleophilic displacement

Regioselective ribonucleotide ligation

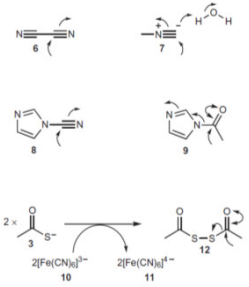


Treatment of A3'P (100 mM) with sodium thioacetate 3 (100 mM) and cyanoacetylene 4 (200 mM) in D_2O at neutral pD for 24 hours results in selective acetylation of the 2-OH group. Curly arrows indicate electrophilic activation/acetylation steps. Yields were judged by ^1H NMR integration. Ade = N9-linked adenine.

Regioselective ribonucleotide ligation



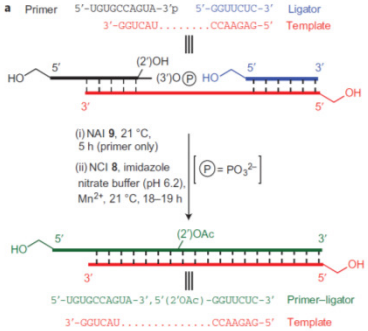
Treatment of A3'P (80 mM) and A2'P (20 mM) as given before results in the exclusive 2-acetylation of the former nucleotide. Partial ^1H NMR spectrum of the reaction products.



Additional electrophiles 6–8 shown to drive the acetylation of ribonucleotides with thioacetate 3. Direct acetylation with 9 is also possible, as is oxidative activation of 3 with errycanide 10 to afford ferrocyanide 11 and a dimeric acetylating agent 12. Curly arrows indicate electrophilic activation/acetylation steps.

Regioselective ribonucleotide ligation

Chemoselective acetylation of 39P-oligoribonucleotides expedites templated ligation



Sequences and reaction conditions employed for acetylation (i) and subsequent templated ligation (ii). The acetylation mixture contained 80 mM primer and 50 mM NAI 9; the ligation mixture contained 4 mM primer from the acetylation reaction, 25 mM template, 30 mM ligator, 200 mM imidazole nitrate buffer (pH 6.2), 10 mM $MnCl_2$ and 100 mM NCI 8. Ligation conditions were based on those reported previously for the conversion of A3'P into A>P (ref. 35) and for the ligation of oligomers with 5P and 2,3-diol termini.