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### Original Citation

Ochocinska, Agata, Bethel, Paul and Sweeney, Joseph B. (2013) Catalytic Synthesis of Riboside-Amino Acid Hybrids. *Synlett*, 24 (16). pp. 2170-2172. ISSN 0936-5214

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# Catalytic Synthesis of Riboside-Amino Acid Hybrids

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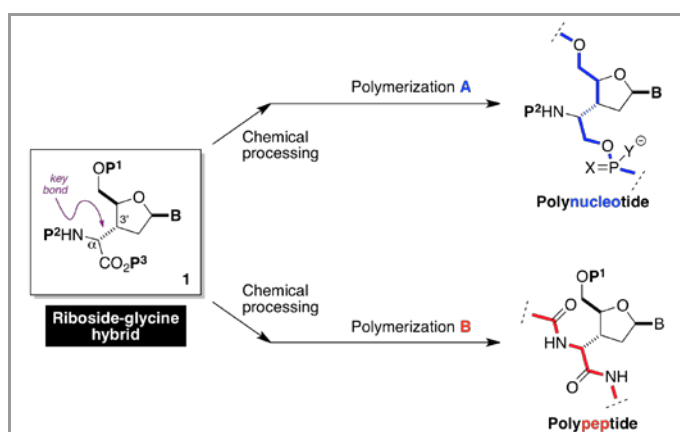
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**Received:** The date will be inserted once the manuscript is accepted.

**Abstract:** The catalytic synthesis of 3-(2'-glycinoyl)ribose derivatives under mild conditions is described. The key reaction involves silver-catalyzed condensation of isocyanoacetates with 3-ketoriboses.

**Key words:** Catalytic, non-coded amino acids, hybrid peptides, ribonucleoproteins, asymmetric synthesis.

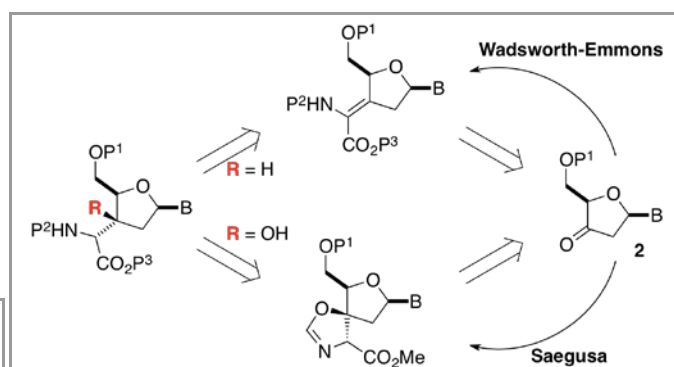
Processes involving nucleic acids and proteins dominate the chemistry of biological systems, and synthetic molecules combining the structural features of these two biopolymer classes possess privileged biological properties. As testament to the intrinsic challenge of carrying out synthetic manipulation of nucleosides, there are few methods which are reported to deliver hybrid molecules containing riboside and peptide-like characteristics. Those methods which have been described often feature lynchpin attachment through C-X bonds rather than C-C bonds.<sup>1</sup> As part of a program of research directed towards the preparation and analysis of riboside-glycine hybrids **1**, we have investigated catalytic methods to create C-C bonds between riboses and glycine anion equivalents and we here describe the preliminary data from these studies.



**Scheme 1.** Riboside-glycine hybrids: ambident polymerization monomers.

Our target was a riboside-amino acid hybrid which allowed for dual-polymerization strategies; thus monomers **1** could (after appropriate chemical processing) function as building blocks for either synthetic oligonucleotide synthesis (via automated phosphoramidite

technology, path A, Scheme 1), or synthetic oligopeptides (path B). The key synthetic challenge to deliver monomers was construction of the 3'-C $\alpha$  C-C bond highlighted; our studies commenced with preparation and reactions of 3'-ketoribosides **2**. We envisaged that olefination with an apposite 2-aminophosphonate (or equivalent reagent), followed by directed reduction would yield our desired ribosyl glycines (Scheme 2). Thus, 3'-ketouridine and thymines **2a** and **2b** were prepared and reacted with a range of phosphorus-based carbonyl olefination reagents, but after an exhaustive study of a diverse range of reactions, we concluded that such methodology would not efficiently deliver the desired target products.

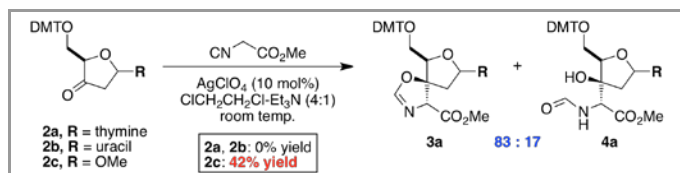


**Scheme 2.** Ribosylglycine synthesis: strategy.

We therefore turned our attention away from olefination strategies and towards the methodology of Saegusa,<sup>ii,iii</sup> envisaging Lewis acid-catalyzed reaction of isocyanoacetates with ketoribosides<sup>iv</sup> as an alternative method to ultimately deliver the target hybrids (Scheme 2). This method not only offered an attractive option of a catalytic rather than stoichiometric process, but also allowed the delivery of a conformation controller in the form of the 3'-hydroxy motif. However, given that ketones are often unpredictable electrophiles in isocyano aldol reactions,<sup>3</sup> this was a challenging ambition.

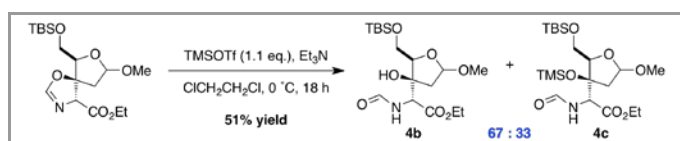
Reactions of ketoribosides **2a** and **2b** with isocyanoacetate in the presence of substoichiometric Ag(I) salts delivered small amounts of the desired targets, but the product mixture was complex and dominated by depyrimidinated products. After significant at-

tempts to optimize the process, we turned to ribose (rather than riboside) substrates and were gratified to observe that 5-DMT-protected 3-keto deoxyribose **2c** delivered a mixture of oxazoline **3a**<sup>v,vi</sup> and the hydrolyzed analogue **4a**<sup>vii</sup> in 42% combined yield upon reaction with AgClO<sub>4</sub> at room temperature (Scheme 3).



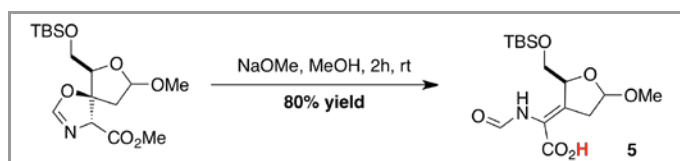
**Scheme 3.** First-pass ribosylglycine synthesis.

After a lengthy screening process, the best results were obtained by reaction of 5-TBS-protected substrates, in the presence of molecular sieves, which suppressed the *in situ* oxazoline hydrolysis process seen in the initial reactions (Table). Conditions which deliver the hydrolyzed product exclusively have not, to date, been identified, and subsequent oxazoline hydrolysis has also proved challenging; best results have so far been obtained by reaction with TMSOTf, which furnishes a separable mixture of alcohol **4b** and silylated analogue **4c** (Scheme 4).



**Scheme 4.** Ribosylloxazoline hydrolysis.

An alternative hydrolysis protocol delivers the dehydrated amino acid **5** (presumably via an  $\alpha$ -lactone intermediate), which represents an excellent entry point to our 3-deoxy targets.



**Scheme 5.** Oxazoline hydrolysis: elimination via  $\beta$ -lactone.

In conclusion, we have described here the preparation of structurally-unique ribose-glycine hybrids using catalytic C-C bond-forming methodology. As is often the case with non-natural carbohydrates, the reactivity

profiles of these new substances are not well-understood and we are currently engaged in a rigorous study which will map the reactivity boundaries of these compounds.

### Acknowledgment

We gratefully acknowledge the support of AstraZeneca and EPSRC (CASE studentship to AMO), the Royal Society and EPSRC for provision of an Industry Fellowship to JBS.

### References

- (1) See, for instance: van der Heden van Noort, G. J.; van Delft, P.; Meeuwenoord, N. J.; Overkleeft, H. S.; van der Marel, G. A. Filippov, D. V. *Chem. Commun.* **2012**, 48, 8093-8095; Moyle, P. M.; Muir, T. W. *J. Am. Chem. Soc.* **2010**, *132*, 15878-15880; van der Heden van Noort, G. J.; van Delft, P.; van der Horst, M. G.; Overkleeft, H. S.; van der Marel, G. A. Filippov, D. V. *J. Am. Chem. Soc.* **2010**, *132*, 5236-5240.
- (2) Saegusa, T.; Ito, Y.; Kinoshita, H.; Tomita, S. *J. Org. Chem.* **1971**, *36*, 3316; Ito, Y.; Sawamura, M.; Hayashi, T. *J. Am. Chem. Soc.* **1986**, *108*, 6405-6406.
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- (5) Stereochemistry tentatively assigned by analogy with reported nucleophilic addition reactions of 3-ketoriboses.
- (6) **3a**:  $\delta_H$  (250 MHz, CDCl<sub>3</sub>) 2.00 (1H, dd, J 4.7, 14.5), 2.37 (1H, dd, J 5.0, 14.5), 3.18 (1H, dd, J 7.3, 10.0), 3.3 (1H, s), 3.54 (1H, dd, J 5.2, 10.0), 3.79 (6H, s), 3.80 (3H, s), 4.19 (1H, dd, J 5.2, 7.3), 4.96 (1H, d, J 2.5), 5.07 (1H, dd, J 4.7, 5.0), 6.74 (1H, d, J 2.5), 6.80-6.85 (4H, m), 7.15-7.41 (8H, m);  $\delta_C$  (62.5 MHz, CDCl<sub>3</sub>) 43.0, 52.6, 55.2, 55.8, 60.9, 70.8, 81.4, 87.0, 92.0, 103.8, 113-144.3, 155.8, 158.5, 169.9.
- (7) **4a**:  $\delta_H$  (250 MHz, CDCl<sub>3</sub>) 2.00 (1H, dd, J 4.7, 14.5), 2.37 (1H, dd, J 5.0, 14.5), 3.18 (1H, dd, J 7.3, 10.0), 3.3 (1H, s), 3.54 (1H, dd, J 5.2, 10.0), 3.79 (6H, s), 3.80 (3H, s), 4.19 (1H, dd, J 5.2, 7.3), 4.96 (1H, d, J 2.5), 5.07 (1H, dd, J 4.7, 5.0), 6.74 (1H, d, J 2.5), 6.80-6.85 (4H, m), 7.15-7.41 (8H, m);  $\delta_C$  (62.5 MHz, CDCl<sub>3</sub>) 45.4, 52.6, 53.5, 55.1, 56.7, 64.4, 80.6, 84.6, 86.9, 104.3, 113.2-158.6, 160.8, 169.3.

**Table.** Ribosyl glycine synthesis: optimization.

Entry	P	R (Product)	3 : 4	Yield (%)
1	DMT	Me ( <b>3a/4a</b> )	90 : 10	21
2	DMT	Me ( <b>3a/4a</b> )	83 : 17	42 <sup>a</sup>
3	DMT	Me ( <b>3a/4a</b> )	>95 : 5	50 <sup>b</sup>
4	TBS	Me ( <b>3b/4b</b> )	>95 : 5	63 <sup>b</sup>
5	TBS	Et ( <b>3c/4c</b> )	>95 : 5	64 <sup>b</sup>
6	TBS	<sup>t</sup> Bu ( <b>3d/4d</b> )	>95 : 5	42 <sup>b</sup>

<sup>a</sup> Reaction carried out in presence of excess Et<sub>3</sub>N; <sup>b</sup> Reaction carried out in presence of 4Å molecular sieves