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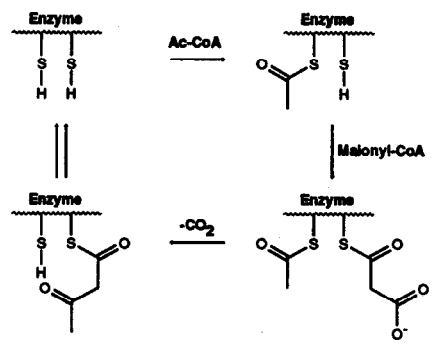
Efficient Claisen-type Condensation between Acyl Units Bound to a Molecular Template

Sengen Sun and Paul Harrison*

Department of Chemistry, McMaster University, 1280 Main Street West, Hamilton, Ontario, Canada L8S 4M1

Abstract: Acylation of 3,4,7,8-tetramethylglycoluril[1] (1) provides the monoacyl derivative 3 which can be acylated further with LDA and acyl chlorides. The resulting symmetric or asymmetric diacyl derivatives 4 undergo efficient base-catalyzed acyl transfer to provide 2-(acylacyl)glycolurils *5,6*. Thus, 1 acts as a template to allow facile condensations between acyl units.

The goal of this work is to develop a biomimetic and synthetically useful method for formation of polyketides. The biosynthesis of both polyketides and fatty acids proceeds by head to tail condensation of acyl units in a formal Claisen condensation.[2] In the early stages of such a biosynthetic scheme, the 3-ketoacyl synthase is acylated at two distinct sulfhydryl groups, first by acetyl-CoA, then by malonyl-CoA (Scheme 1).[2] The carbon-carbon bond-forming reaction then occurs by an 'intramolecular' decarboxylative condensation to give β-ketobutanoyl-synthase. Repetitive condensation with further malonyl groups leads to long carbon chains.



Scheme 1

Consideration of these facts led us to propose a process in which two acyl moieties would be sequentially attached to a bifunctional template, thus promoting an intramolecular acyl transfer upon deprotonation. Such a process would allow further acylation and repetition of the condensation reaction. Scott[3] has investigated a similar system, using catechol as a template: catechol acetate malonate undergoes decarboxylation to afford acetoacetyl catechol in 30% yield.

The desire for higher yields in order to gain synthetic utility led us to investigate the template **1**. The choice of template was based on consideration of the chiral oxazolidinone method of Evans,[4] which has been used extensively in synthesis of putative functional oligoketides for biosynthetic studies.[5] This approach, which involves an intermolecular condensation of the two carbonyl moieties, leads to polyketides which are grown in the opposite sense to that occurring in nature.[6] Further, the concept that a six-membered ring in the transition state for the acyl transfer could enhance the efficiency of the process suggested **1** as a viable template.[7]

Compound **1** is produced from condensation of two equivalents of *N*-methylurea with butane-2,3-dione (51%, recryst.).[8] Acylation with acyl anhydrides **2a-c** (150 °C bath temp., neat, 24 h) affords the monoacyl derivatives **3a-c**,[8,9] with minimal formation of diacyl species[10] (Scheme 2) (for yields, see Table 1). The second acylation to give **4a-c** is accomplished by treatment of **3a-c** with LDA (THF, 0 °C) followed by addition of acyl chloride.

Table 1: Yields and Isomer Ratios for the Formation and Rearrangement of Acylated Templates.

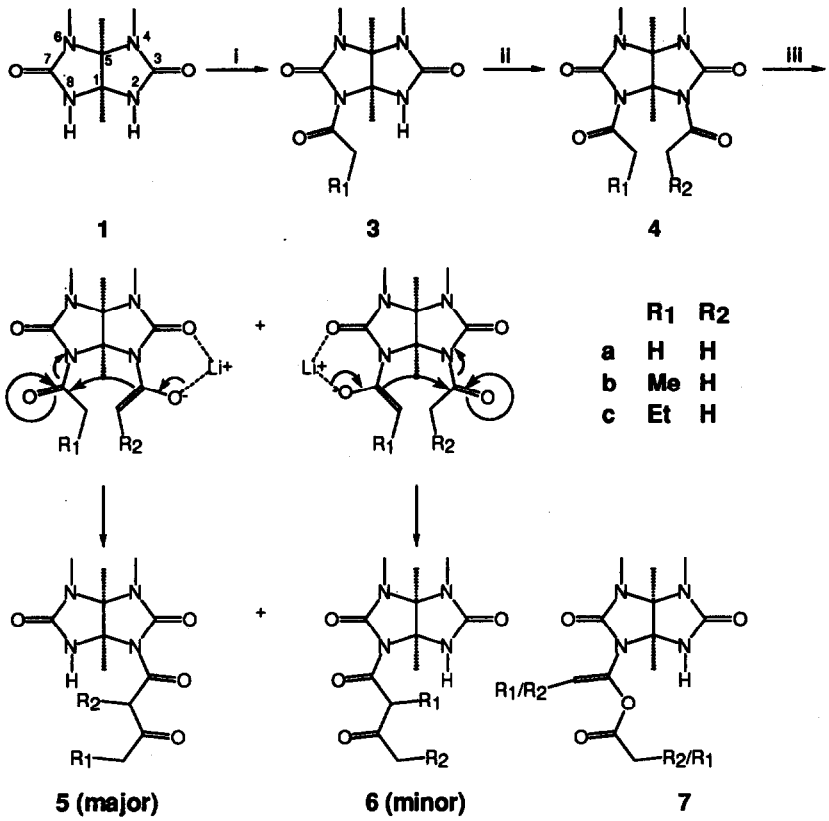
Compound	R_1	R_2	% Yields[1]		Base for	% Yield[1,2]	Ratio[3]
			3	4	4->5+6	5+6	5 : 6
a	H	H	89	78	*t*-BuOLi	93	-
b	CH_3	H	83	54	*t*-BuOLi	81	83:17
c	C_2H_5	H	70	61	*t*-BuOLi	88	81:19
a	H	H	89	78	LDA	43	-

Table Notes: 1. All yields are for products after purification by column chromatography. 2. Yields of isolated material prior to chromatography, which was pure by TLC and NMR, were somewhat higher. 3. Determined by proton NMR.

Initial attempts to effect rearrangement of **4a** used LDA as base (THF, -78 to 0 °C). Although the desired product **5a** was isolated,[11] the yield was poor (ca. 40%). In contrast, the use of lithium *tert*-butoxide[12] as base results in efficient rearrangement, giving **5a-c** and **6a-c** as sole detectable products in each case. For the diacetyl compound, **5a=6a** and a single product is obtained. To determine the regiochemical preference for this reaction, **4b** and **4c** were converted to mixtures **5b**, **6b** and **5c**, **6c** respectively. The ratio **5:6** was determined by NMR in each case; the results are shown in Table 1.

The yield for formation of template **1** is moderate; however, the reagents are readily available and large quantities are easily prepared.[13] The template fulfills the requirement for selective introduction of one acyl group at a time, thus allowing formation of asymmetric derivatives such as **4b** and **4c**.

Rearrangement of the diacylated template (**4a-c**) proceeds almost quantitatively under relatively mild conditions, and with reasonable regioselectivity in the asymmetric cases (**b** and **c**). The base prefers to deprotonate the (lower pK_a and less hindered) acetyl group and the propanoyl or butanoyl group acts as the electrophile.[14] In these cases, the side product is exclusively the result of acetylation of the propanoyl and butanoyl moieties: no product resulting from combination of two acetyl groups (ie **5a**) or two propanoyl or butanoyl groups is observed. These results suggest that this reaction proceeds by an intramolecular mechanism, which could involve a cyclic six-membered transition state, as indicated in Scheme 2.



Reagents: I. $(R_1CH_2CO)_2O$ [2a-c], 150 °C, neat
OR LDA, R_1CH_2COCl, THF;
II. LDA, R_2CH_2COCl, THF; III. *t*-BuOLi, THF

Scheme 2

We were unable to detect any *O*-acyl enol ether (**7a-c**), or monoacylated template **3** which could result from hydrolysis thereof. The absence of *O*-acylation could be explained by chelation of the lithium counter-ion in the putative intermediate enolate, as indicated in Scheme 2. Chelation in the oxazolidinones of Evans is well-documented, and is an important factor in the efficient stereocontrol involved in this methodology.[4] Such chelation effects in the enolate derived from **4** would prevent intramolecular attack by the oxygen atom on the adjacent acyl group.

The results of further experiments to test the intramolecularity of this process and to develop a decarboxylative approach to enolate generation from a malonyl group, as well as further chemical transformations of the product will be reported in due course.

Acknowledgments:

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References and Notes:

1. In IUPAC nomenclature, 1 is 1,4,5,6-tetramethyl-2,4,6,8-tetra-azabicyclo[3.3.0]octane-3,7-dione; other common names for this compound are 3,4,7,8-tetramethylglycoluril, and 3,4,7,8-tetramethylperhydroimidazo[4,5-d]imidazol-2,5-dione.
2. For recent reviews of polyketide biosynthesis, see: Robinson, J.A. *Phil. Trans.: Biol. Sci.* **1991**, *332*, 107-114. Simpson, T.J. *Annu. Rep. Prog. Chem., B*, **1988**, *85*, 321-351.
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6. In the synthetic process, the 'starter' unit for the biosynthesis is the last unit to be attached.
7. For a discussion of energetics of intramolecular reactions and enzyme catalysis, see: Page, M.I. *Phil. Trans.: Biol. Sci.* **1991**, *332*, 149-156.
8. Biltz, H. *Chem. Berichte* **1907**, *40*, 4806-4816.
9. All new compounds were analyzed by ^{1}H and ^{13}C NMR, IR and either elemental analysis or high-resolution MS.
10. The diacetyl, dipropanoyl and dibutanoyl compounds were isolated in yields of <1, 9 and 5%, respectively, from the reaction mixtures.
11. In addition to spectral data, compound **5a** was also characterized by reduction to the β-hydroxyacyl compound, in which the four carbon atoms were shown to be contiguous by ^{1}H NMR.
12. Lithium *tert*-butoxide (1.1 eq.) was added to **4a-c** in THF at 0 °C. The reaction was complete within 20 min. Addition of solid NH_4HCO_3 as quench, followed by filtration and evaporation gives a mixture of **5a-c** and **6a-c**, which could be purified further if necessary by flash chromatography.
13. Although ethane-1,2-dial gives a similar derivative, the two extra methyl groups reduce the polarity of all the compounds in this series. This effect facilitates chromatographic purification at each step.
14. 2,4,6,8-tetraacetyl-2,4,6,8-tetra-azabicyclo[3.3.0]octane-3,7-dione is an efficient acylating agent for alcohols, thiols and primary amines: Hase, C.; Kuhling, D. *Liebigs Ann. Chem.*, **1975**, 95-102. Tice, C.M.; Ganem, B. *J. Org. Chem.*, **1983**, *48*, 2106-2108.

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