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2-ACETYLTHIAZOLE AS A THREE-CARBON HOMOLOGATING REAGENT OF ALDEHYDES. APPLICATION TOWARD THE SYNTHESIS OF AMINO HEXOSES FROM L-SERINAL

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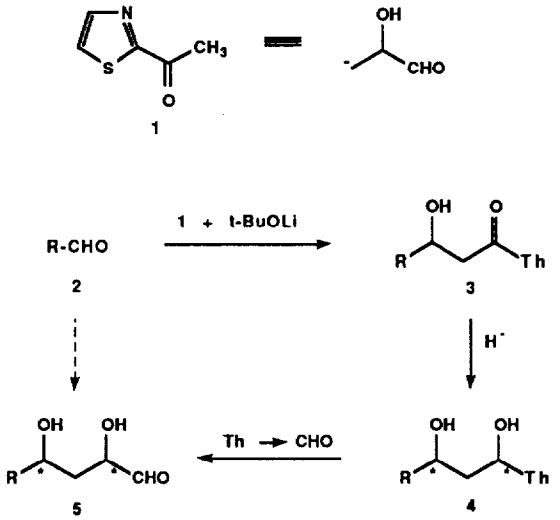
Summary. 2-Acetylthiazole (1) serves as a source of the α-hydroxypropanal β-anion synthon for the conversion of aldehydes into *syn* and *anti* α,γ-dihydroxy homologues with three-more carbon atoms via a sequence consisting of : i) aldol condensation of the lithium enolate derived from 1; ii) reduction of the hydroxy ketone; iii) thiazole to formyl unmasking. The methodology is employed for the conversion of L-serinal into amino sugars.

In recent reports from this laboratory we have demonstrated the synthetic utility of 2-substituted thiazoles as effective equivalents to aldehyde synthons in stereoselective methodologies directed toward the synthesis of long-chain 1,2-polyhydroxylated compounds (Thiazole Route).[1] Several advantages arise from the use of thiazoles as auxiliaries since the thiazole ring combines high stability to a wide range of reaction conditions with facile conversion to the unmasked aldehyde. We would like to introduce here a newcomer to this family of synthetic auxiliaries, namely 2-acetylthiazole (2-ATT) (1), which acts as a three-carbon homologating reagent of aldehydes via a sequence consisting of aldol condensation, stereoselective carbonyl reduction, thiazole-to-formyl conversion. Since the overal operation



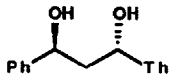
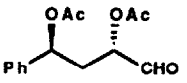
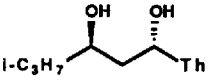
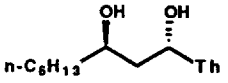
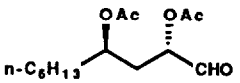
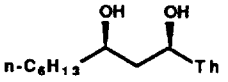
Scheme I

transforms aldehydes into α,γ-dihydroxy homologues with three-more carbon atoms, this corresponds to using 2-acetylthiazole (1) as the α-hydroxypropanal β-anion equivalent (d^3-synthon)[2] (Scheme I). The stereocontrolled

assembly of 1,3-diol fragments is an important issue in methodologies directed toward the synthesis of polyene and polyol macrolide antibiotics.[3] This is conveniently carried out by stereoselective hydroxyl-directed hydride reduction[4] of β-hydroxy ketones which in turn are readily available from various routes,[5] mainly aldol condensation[6] and cycloadditive strategies.[7] However, none of the methods reported deals with the construction of 1,3-diol units bearing a protected α-functionality, such as a formyl group, which may be used in further synthetic elaborations. The methodology presented here employing 2-ATT as an aldehyde synthon equivalent provides an entry to diastereoselective α,γ-dihydroxybutanal units.

2-Acetylthiazole (1) was readily prepared in multigram quantities from either 2-lithiothiazole and ethyl acetate[8] (-78° C, Et_2O, 90 %) or from 2-trimethylsilylthiazole and acetyl chloride as described.[9] The aldol condensation of the lithium enolate derived from 1 with aldehydes **2a-c** occurred smoothly at -40° C in THF to give the corresponding β-hydroxy ketones **3a-c** in fair yields after chromatography[10] (Table). The enolate generation was a

Table

Aldehyde **2**	Aldol Condn[a] **2** ⟶ **3**, yield %	Reduction[a,b] **3** ⟶ **4** ds, yield %	**CHO** Unmasking[a,c] **4** ⟶ **5**, yield %
a; R = Ph	(**3a**), 54	TETAB  **a**-(**4a**), 95, 90	 **a**-(**5a**), 74
b; R = i-C_3H_7	(**3b**), 58	TETAB  **a**-(**4b**), 95, 90	
c; R = n-C_6H_{13}	(**3c**), 55	TETAB  **a**-(**4c**), 96, 85	 **a**-(**5c**), 68
		DIBAL  **a**-(**4c**), 80, 88	

[a] Yields refer to chromatographically pure isolated products. Th = 2-Thiazolyl. [b] Reducing Agents : **TETAB** ($(Me_4NBH(OAC)_3$) in MeCN / $MeCO_2H$ at -35°C; **DIBAL** (i-Bu_2AlH) in THF at -70°C. [c] i) Ac_2O, Py; ii) ref 1b .

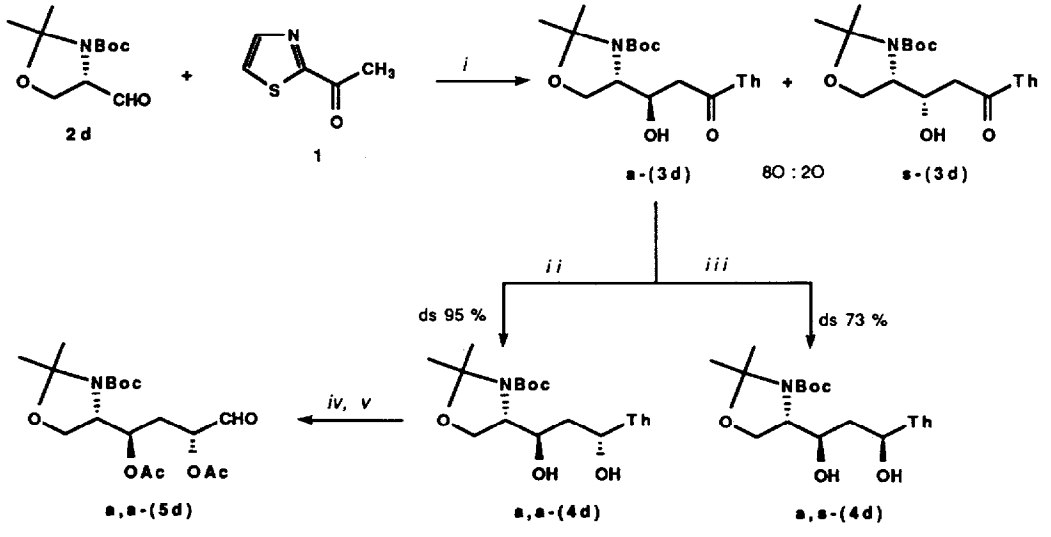
rather crucial step in this reaction because of the competing deprotonation of the thiazole ring. This was controlled by kinetic generation of the enolate in the presence of the aldehyde using lithium *t*-butoxide as a base.[11] A representative procedure follows:

Aldol condensation. To a solution of *t*-butanol (108 g, 14.6 mmol) in 20 mL of anhydrous THF is added *n* butyllithium (14.6 mmol) under argon atmosphere at room temperature. The solution is cooled to -40 °C and a mixture of aldehyde **2** (12.2 mmol) and 2-ATT (**1**) (14.6 mmol) in 25 mL of THF is added dropwise. After stirring at -40 °C for ca. 1 h, the reaction mixture is quenched by addition of a saturated aqueous solution of ammonium chloride or 3 % HCl and then extracted several times with diethyl ether. The combined extracts are dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue is purified by column chromatography on silica gel to give the desired aldol.

The reduction of the hydroxy ketones **3a-c** with the Evans borohydride[4a] $Me_4NBH(OAC)_3$ in a 1:1 mixture of $MeCN/MeCO_2H$ as described, afforded the 1,3-diols *anti*-(**4a-c**) with high diastereoselection[12] and chemical yield. On the other hand using chelating aluminum hydride reducing agents,[4] such as DIBAL or $LiAlH_4$ in the presence of LiI, converted **3c** into the 1,3-diol *syn*-(**4c**) as the principal product.[12] Similar arguments as those employed to explain the *anti*- and *syn*-selectivity in the reduction of β-hydroxy ketones with the above hydride releasing reagents,[4] can be extended to the present cases. Interestingly enough, these hydroxyl-directed reductions tolerate the presence of the thiazole ring although this might interfere through its heteroatoms. As the final step of the sequence, the thiazole-to-formyl conversion was carried out by our well established one-pot method[1b] consisting of three consecutive operations, i.e. *N*-methylation, reduction, hydrolysis. Thus, the α,γ-dihydroxyalkylthiazoles *anti*-(**4a**) and *anti*-(**4c**) protected as their diacetyl derivatives were transformed into the corresponding aldehydes *anti*-(**5a**) and *anti*-(**5c**) in ca. 70 % overal yields. Hence, a thiazole-mediated sequence for the conversion of aldehydes into α,γ-dihydroxy higher homologues appears to be at hand.

The methodology was extended to N-Boc L-serinal acetonide (**2d**), i.e. a chiral α-amino aldehyde[13] of increasing synthetic importance[14] for its ready availability and configurational stability . The aldol condensation of

Scheme II



Th = 2-thiazolyl; Boc = t-butoxycarbonyl. ***Reagents and Conditions :*** *i)* t-BuOLi, THF, - 40 °C; *ii)* $Me_4NBH(OAc)_3$, MeCN / $MeCO_2H$, -35 °C; *iii)* DIBAL, THF, -70 °C; *iv)* Ac_2O, Py; *v)* CHO-unmasking (ref. 1)

2d with the lithium enolate derived from 2-ATT (**1**) as described above produced a mixture of two diastereomeric aldols **3d** with a *syn : anti* ratio of 2O : 8O (Scheme II). The assigned configuration to the major aldol *anti*-(**3d**) is in agreement with earlier observations on the addition of other organometallic reagents[15] to the aldehyde (**2d**) under non-chelating conditions and is that expected on the basis of the Felkin-Anh open-chain model for diastereoselection.[16] After chromatographic separation of individual isomers, the reduction of the major product *anti*-(**3d**) with $Me_4NBH(OAc)_3$ afforded essentially the amino 1,3-diol *anti,anti*-(**4d**) (ds 95 %) whereas the reduction with DIBAL gave the isomer *anti,syn*-(**4d**) (ds 73 %) as main product. Finally, the thiazole-to-formyl unmasking of the diacetyl derivative of *anti,anti*-(**4d**) gave the protected amino hexose *anti,anti*-(**5d**) in good isolated yield.[17] This shows an application of 2-ATT as a d^3-synthon in a new stereocontrolled route to amino hexoses from amino aldehydes. Work is in progress to investigate the scope of this approach as well as the synthetic utility of **1** in general.

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