DIASTEREOSELECTIVE ALDOL CONDENSATION OF 2-METALLOALKYL-BENZOTHYAZOLES.

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<u>Abstract.</u> - 2-Metalloalkylbenzothiazoles 2, readily available from 2-alkylbenzothiazoles 1, undergo aldol reaction to give aldols 3 and 4. Low to satisfactory threo diastereoselection was observed with 2-lithio- and 2-trimethylsilyl derivatives 2b-d and 2e-g. High to excellent erythrostereoselection occurs with 2-stannylalkylbenzothiazoles 2h-1.

2-Lithiomethylbenzothiazole <u>la</u>, readily available by lithiation of 2-methylbenzothiazole <u>la</u> under proper conditions ^{1,2}, cleanly adds to carbonyl compounds affording vinyl benzothiazoles probably via dehydration of the aldol intermediate.¹

It has recently been reported that the reaction of <u>la</u> with carbonyls can be stopped at the aldol stage.³ This prompted us to disclose our results⁴ on the diastereoselective aldol type reaction of some 2-metalloalkylbenzothiazoles also in view of the fact that no stereoselective aldol condensation of 2-alkylbenzothiazoles have been reported so far. Lithiation of 2-alkylbenzothiazoles <u>lb-d</u> with <u>n</u>-buthyllithium at -78°C followed by addition of a number of aldehydes gave after work-up quite good yields of the diastereomeric β -hydroxyalkylbenzothiazoles <u>3-4</u>, which were easily separated by column chromatography and characterized by IR and ¹H-NMR spectroscopy. Aldols <u>3</u> and <u>4</u> were assigned the erythro and threo configuration respectively on the basis of the coupling constants between the hydrogens Ha and Hb. As can be seen from the Table there was no or rather poor diastereoselection with a slight preference of the threo or the erythro isomer depending upon the solvent, the benzothiazole and the aldehyde.⁴ A

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satisfactory threodiastereoselection could be achieved by using lithium diiso_ propylamide (LDA) as the lithiating agent (entries 11, 12, 13).

No aldol reaction took place when the LDA/HMPA combination was used for the lithiation step both in the case of <u>1b</u> and <u>1c</u>. This could tentatively be explained by the complexation of lithium by HMPA in such a way that the metal cannot participate in the stabilisation of the aldolate in a chair-like conformation according to the Heathcock, Dubois and House cyclic transition state model.⁵ Yet no reaction occurred when using lithium hexamethyldisilylazide (LHMDS).⁶



Looking for higher diastereoselection we investigated the aldol reaction of some other 2-metalloalkylbenzothiazoles. We prepared the trimethylsilylalkylbenzothiazoles <u>2e-g</u> according to the Corey's procedure from <u>1b</u>, <u>1c</u> and <u>1d</u> with trimethylsilylchloride.⁷ We could prove by ¹H-NMR that indeed the silyl derivatives <u>2e-g</u> have the trimethylsilyl group bonded at the alkyl group in the 2-position of the heterocyclic ring as no signal of the vinylic proton of the aza-silylderivative (A) could be observed. Silyl derivatives <u>2e-g</u> were unreactive towards unactivated benzaldehyde.



However, we found that 2e and 2f condense with benzaldehyde in the presence of

BF₃ Et₂O or TiCl₄ with poor diastereoselectivity. Knowing that the enol silyl ethers of certain ketones give α -trichlorostannyl ketones,⁸ upon treatment with SnCl₄, we attempted preparation of the stannyl derivatives of the abovementioned 2-alkylbenzothiazoles. We examined the reaction of the silyl derivative <u>2e</u> and SnCl₄ in CH₂Cl₂. Instantaneous reaction occurred on mixing <u>2e</u> with SnCl₄ at low temperature, yielding the stannyl derivative <u>2h</u>. Attempts to purify <u>2h</u> failed, but the chemical shift of the methine proton and the absence in the ¹H-NMR spectrum of the vinylic proton of the trichlorostannyl aza-enolate (B) are compatible with the formulated structure <u>2h</u>.

The reaction of $\underline{2h}$ with benzaldehyde produced the erythro adduct $\underline{3a}$ as the main aldol product.

It was worthy noting that again the three isomer slightly prevailed when benzaldehyde preteated with $SnCl_4$ was added to <u>2e</u>. Possibly the Mukajiama aldol condensation of <u>2e</u> with the $SnCl_4$ activated benzaldehyde occurs.⁹

The erythro isomer <u>3b</u> forms with high yield in the reaction between benzaldehyde and the stannylpropylbenzothiazole <u>2i</u>, prepared from <u>2f</u> via transmetallation with $SnCl_4$. Similarly <u>2i</u> reacted with piperonal and p-chlorobenzaldehyde to give exclusively the erythro isomers <u>3k</u> and <u>3i</u> respectively. It is interesting to note that the reaction of tin enolates with aldehydes proceeds with threodiastereoselection.¹⁰

The high erythro stereoselection observed in the aldol reaction of stannyl derivatives 2h-i might be rationalised by assuming that the reaction proceeds via an acyclic transition state. Taking into account that internal chelation provides stabilisation, transition states K,L,M, all leading to the erythro aldol, minimize the R-R¹ interactions.

Thus we have found a suitable procedure for the diastereoselective aldol condensation of 2-alkylbenzothiazoles. When 2-lithioalkylbenzothiazoles derived from <u>1b-c</u> upon treatment with LDA are used the aldol reaction proceeds with a satisfactory threostereoselection, whereas an almost exclusive erythrodiastereoselection occurs with 2-stannylalkylbenzothiazoles. This is of particular importance from the synthetic viewpoint as both the threo and the erythro aldols <u>3</u> and <u>4</u> are suitable starting materials for the preparation of vinylbenzothiazoles of Z and E configuration, which could be used for the stereospecific synthesis of \prec , β -unsaturated carbonyls.¹ Moreover, the stereoselective aldol reaction described in this paper could be exploited for the preparation of deoxysugars. Work is in progress to this end.

Table.	Reaction	of	2-metalloal	kvlhen	zothiazoles	(M-BTT)	2a-k with	aldehvdes.
Tante.	reaction	OL.	2-metalloal	LVATOGII	ZUCHITAZUIES	(11-01)	Za-r will	I aluenvues.

Entry	M-BT	Solvent	Aldehyde ^j	<u>3+4</u> Yield %	3/4 Ratio	Temp.	
1	<u>2b</u> a	THF	a ₁	88	42/58	-78	
2	11	11	**	80	"	-12	
3		Et_2O	11	78	54/56	-78	
4	**	THĒ	a ₂	77	55/45	11	
5		11	ลวี	86	56/44	11	
6	11	**	a	86	33/67	**	
7	11	11	aç	84	34/66	**	
8		11	ac	62	38/62	11	
9	$2c^{a}$	11	a1	83	43/57	11	
10	TT I	Et ₂ 0	" 1		54/469	11	
11	2b ^b	THÉ		90	19/81	11	
12	2cb		"	68	28/72	11	
13	$\overline{2d}$ b	**	"	80	20/80	**	
14	2ec	CHaCla	**		62/389		
15	$\frac{1}{2e}d$	"22	**		50/509	**	
16	27d	11	**		55/459	"	
17	- - -	н	an		62/389	11	
18	_{2h} e		~ a1	58İ	72/28		
19	<u>26</u> f	11		50	38/629	**	
20	<u>21</u> e		11	ggi	80/20	"	
21	~	**	а.	86	>98	"	
22	"	"	a2	84	>98	"	

^a n-BuLi was used as the lithiating agent.^b LDA was used for the lithiation. ^c TiCl₄ was added to <u>2e</u> before PhCHO. ^d BF₃ Et₂O added before PhCHO. ^e SnCl₄ added to the silyl derivative before the aldehyde. ^f SnCl₄ added to the aldehyde. ^g ratio determined on the diastereomeric mixture by TLC or ¹H-NMR. ⁱ yield calculated on converted starting material. ^j: $a_1 =$ PhCHO; $a_2 =$ p-Cl-benzaldehyde; $a_3 = 2,6$ -dichlorobenzaldehyde; $a_4 =$ piperonal; $a_5 = 2$ -furaldehyde; $a_6 =$ isobutyraldehyde.

EXPERIMENTAL

¹H-NMR spectra were recorded on a Varian EM-360A instrument and chemical shifts are expressed in values relative to Me_4Si as an internal standard. The infrared spectra were recorded on a Perkin-Elmer 681 spectrophotometer. Melting points were determined on a Electrothermal apparatus and are uncorrected. Column chromatography was carried out by using 70-230 mesh silica gel from Merck.

<u>Materials.</u> Tetrahydrofuran (THF) and diethyl ether from commercial sources (RS, Carlo Erba) were purified by distillation (twice) from sodium wire in a N₂ atmosphere. 2-Ethyl-, 2-n-propyl- and 2-benzyl-benzothiazole were prepared as reported.¹¹ All other chemicals were commercial grade and were purified by distillation or crystallisation prior to use. Petroleum ether refers to the 40-70°C boiling fraction.

<u>Reaction of 2-lithioalkylbenzothiazoles</u> <u>2b-d</u> with aldehydes. General procedure. The reaction of <u>1b</u> with benzaldehyde is described as an example. An hexane solution of 2.4 N <u>n</u>-BuLi (1.12 ml, 2.7 mmol) was added dropwise to a stirred THF (or ether) solution of <u>1b</u> (0.4 g, 2.45 mmol) in 20 ml THF at -78° C under a nitrogen atmosphere. After 20 min the THF (or ether) solution of benzaldehyde (0.29 g, 2.7 mmol) in 5 ml THF was added. After 30 min at -78° C the reaction mixture was warmed to room temperature and quenched with a saturated NH₄Cl solution. Extraction with ether (3 x 20 ml), drying over Na₂SO₄ and removal of the solvent under reduced pressure left a residue that was column chromatographed on silica gel, using petroleum ether-ether 8:2 as the eluant. The first eluted compound was the <u>1-phenyl-2-(2-benzothiazolyl)propan-1-ol</u> <u>3a</u>. The second eluted component was the threo isomer <u>4a</u>. Spectral data are reported below and yields are given in the Table. When LDA was used as the lithiating agent the solution of <u>1b</u> (1 mole) in THF was added to the LDA solution (1.1 mole) prepared from <u>n</u>-BuLi (hexane) and di-isopropylamine in THF. Then the benzaldehyde was added as above.

Reaction of 2-trimethylsilylalkylbenzothiazoles 2e-f with aldehydes.

The 2-lithioethylbenzothiazole <u>2b</u> (1.84 mmol) was generated as above. To the stirred solution of <u>2b</u> (1.84 mmol) a slight excess of Me₃SiCl (2.21 mmol) in 3 ml of THF was added. After 20 min at -78 °C the solution was warmed to room temperature and the solvent (THF) removed under reduced pressure. The resulting yellow silyl derivative <u>2e</u> was dissolved in 20 ml of CH₂Cl₂ Then benzaldehyde (2.21 mmol) pretreated with BF₃·Et₂O (2.21 mmol) was added at -78° C. The resulting solution was warmed to room temperature after 30 min and worked up as above. A 1:l <u>3a</u>:4a ratio was obtained as indicated by TLC and ¹H-NMR. A slight erythro selection was observed when titanium tetrachloride was used instead of BF₃ Et₂O. Similarly, 2-trime-thylsilylpropylbenzothiazole <u>2f</u>, prepared from <u>1c</u> as <u>2e</u>, was reacted with benzaldehyde and p-chlorobenzaldehyde pretreated with BF₃·Et₂O.

Reaction of 2-trichlorostannylalkylbenzothiazoles 2h-i with aldehydes. General procedure. The reaction of 2i with p-chlorobenzaldehyde is described as an example. To a solution of 2f (1.84 mmol) in 20 ml of CH₂Cl₂ prepared as above a solution of SnCl₄ (2.1 mmol) in 5 ml of CH₂Cl₂ was added at -78° C. After about 30 min the p-chlorobenzaldehyde (2.02 mmol) in 5 ml of CH₂Cl₂ was added and then the reaction mixture was allowed to warm to room temperature. The reaction was quenched with NH₄Cl after 10 h and worked up as usual.

Aldols <u>3</u> and <u>4</u> (physical data. ¹H-NMR Spectra were recorded in CDCl₃ and a few drops of $D_{2}O$):

<u>1-Phenyl-2-(2-benzothiazolyl)-propan-1-ol</u>. Erythro isomer <u>3a</u>. m.p. 86-87°C; IR (CH₂Cl₂): 3420 (OH) cm⁻¹; ¹H-NMR: § 1.1 (d, 3H), 3.2 (m, 1H), 5.2 (d, 1H, J 3 Hz), 6.9-8.0 (m, 9H). Three isomer <u>4a</u>. m.p. 123-124°C (EtOH); IR (CH₂Cl₂): 3400 (OH) cm⁻¹; ¹H-NMR: 1.2 (d, 3H), 3.4 (m, 1H), 4.8 (d, 1H,J 7 Hz), 6.9-8.0 (m, 9H).

<u>1-Phenyl-2-(2-benzothiazolyl)butan-1-ol</u>. Erythro isomer <u>3b</u>. m.p. 100-101°C; IR (nujol): 3500-3160 br b (OH) cm⁻¹; ¹H-NMR: δ 0.8 (t, 3H, J 7 Hz), 1.7-2.3 (m, 2H), 3.2-3.6 (m, 1H), 5.2 (d, 1H,J 4.4 Hz), 7.2-8.2 (m, 9H). Threo isomer <u>4b</u>. m.p. 132-133°C; IR (nujol): 3500-3100 br b (OH) cm⁻¹; ¹H-NMR: δ 0.9 (t, 3H, J 7 Hz), 1.6-2.2 (m, 2H), 3.2-3.6 (m, 1H), 5.15 (d, 1H, J 6.4 Hz), 7.2-8.2 (m, 9H).

<u>1,2-Diphenyl-2-(2-benzothiazolyl)ethanol</u>. Erythro isomer <u>3c</u>. ¹H-NMR: δ 4.6 (d, 1H, J 5 Hz), 5.7 (d, 1H, J 5 Hz), 6.9-8.1 (m, 14H). Threo isomer <u>4c</u>. m.p. 150-151°C (EtOH); IR (CH₂Cl₂): 3400 (OH) cm⁻¹; ¹H-NMR: δ 4.45 (d, 1H, J 8 Hz), 5.4 (d, 1H, J 8 Hz), 6.9-8.1 (m, 14H).

<u>1-p-Chlorophenyl-2-(2-benzothiazolyl)propan-1-ol</u> Erythro isomer <u>3d</u>. m.p. 95-96°C; IR (nujol) 3600-3100 br b (OH) cm⁻¹; ¹H-NMR: δ 1.32 (d, 3H, J 6.5 Hz), 3.35-3.75 (m, 1H), 4.8 (br s, 1H), 5.3 (d, 1H, J 3.5 Hz), 7.3-8.15 (m, 8H). Threo isomer <u>4d</u>. m.p. 97-99°C; IR (nujol) 3600-3100 br b (OH) cm⁻¹ ¹H-NMR: δ 1.3 (d, 3H, J 7 Hz), 3.25-3.8 (m, 1H), 4.65 (s, 1H), 4.95 (d, 1H, J 7.8 Hz), 7.3-8.2 (m, 8H).

 $\frac{1-(2,6-\text{Dichlorophenyl})-2-(2-\text{benzothiazolyl})\text{propan-1-ol. Erythro isomer } \underline{3e}. \text{ Oil IR (neat) } 3700-3100 \text{ br b (OH) cm}^{-1}; \ 1H-NMR \ \delta \ 1.75 \ (d, \ 3H, \ J \ 7 \ Hz), \\ 4.05-4.55 \ (m, \ 1H), \ 5.8 \ (d, \ 1H, \ J \ 8.8 \ Hz), \ 7.1-8.1 \ (m, \ 7H). \\ \text{Three isomer } \underline{4e}. \ m.p.117-119^{\circ}\text{C}; \ IR \ (nujol) \ 3700-3100 \ \text{br b (OH) cm}^{-1}; \\ 1H-NMR: \ \delta \ 1.32 \ (d, \ 3H, \ J \ 7 \ Hz), \ 4.1-4.6 \ (m, \ 1H), \ 5.95 \ (d, \ 1H, \ J \ 9.76 \ Hz), \\ 7.3-8.2 \ (m, \ 7H). \\ \end{array}$

 $\frac{1-(3,4-\text{Methylenedioxyphenyl})-2-(2-\text{benzothiazolyl})\text{propan-1-ol}. Erythro isomer }{\underline{3f}. 0il; IR (neat) 3660-3100 br b (OH) cm^{-1}; ^{1}H-NMR: $$1.36 (d, J 7 Hz, 3H), 3.3-3.8 (m, 1H), 5.27 (d, 1H, J 3.8 Hz), 6.0 (s, 2H), 6.8-8.2 (m, 7H). Three isomer <math>\underline{4f}.$ m.p. 114-117°C; IR (nujol) 3460-3070 br b (OH); 1 -H-NMR: \$\$1.26 (d, 3H, J 7 Hz), 3.3-3.8 (m, 1H), 4.92 (d, 1H, J 8.4 Hz), 6.0 (s, 2H), 6.8-8.2 (m, 7H).

1-(2-Fury1)-2-(2-benzothiazoly1)propan-1-ol. Erythro isomer 3q. Oil; IR (neat 3600-3100 br b (OH) cm⁻¹; ¹H-NMR: δ 1.4 (d, 3H, J 7 Hz), 3.4-4.0 (m, 1H), 5.3 (d, 1H, J 4 Hz), 6.4 (m, 2H), 7.3-8.2 (m, 5H). Threo isomer 4g. Oil; IR (neat) 3600-3100 br b (OH) cm⁻¹; ¹H-NMR: δ 1.35 (d, 3H, J 7 Hz), 3.6-4.1 (m, 1H), 5.05 (d, 1H, J 7.2 Hz), 6.25-6.35 (m, 2H), 7.3-8.15 (m, 5H).

2-(2-Benzothiazolyl)-4-methylpentan-3-ol. Erythro isomer <u>3h</u>. Oil; IR (neat

3650-3100 br b (OH) cm⁻¹; ¹H-NMR: \S 1.0 (d, 6H, J 6.5 Hz), 1.45 (d, 3H, J 7 Hz), 1.5-2.0 (m, 1H), 3.4-4.1 (m, 2H), 7.3-8.2 (m, 4H). Three isomer <u>4h</u>. m.p. 56-58°C; IR (nujel) 3500-3100 br b (OH) cm⁻¹; ¹H-NMR: \S 0.9-1.15 (m, 6H), 1.45 (d, 3H, J 7 Hz), 1.5-2.1 (m, 1H), 3.3-3.9 (m, 2H), 7.4-8.2 (m, 4H).

<u>1-p-Chlorophenyl-2-(2-benzothiazolyl)butan-1-ol</u>. Erythro isomer <u>3i</u>. m.p. 101-102°C; IR (nujol) 3500-3100 br b (OH) cm⁻¹; <u>1</u>H-NMR: **3** 0.85 (t, 3H, J 7 Hz), 1.6-2.2 (m, 2H), 3.2-3.6 (m, 1H), 5.22 (d, 1H. J 4.4 Hz), 7.3-8.2 (m, 8H). Three isomer <u>41</u>. m.p. $140-141^{\circ}$ C; IR (nujol) 3500-3080 br b (OH) cm⁻¹ ¹H-NMR: **5** 0.9 (t, 3H, J 7 Hz), 1.6-2.1 (m, 2H), 3.2-3.6 (m, 1H), 5.12 (d, 1H, J 6.2 Hz), 7.3-8.2 (m, 8H). $\frac{1-(3,4-Methylenedioxyphenyl)-2-(2-benzothiazolyl)butan-1-ol. Erythro isomer$ <u>3k</u>. Oil; IR (CH₂Cl₂) <u>3400 (OH) cm⁻¹; 1</u>H-NMR:**5**0.9-1.3 (m,<u>3H</u>), 1.8 (m, 2H), 3.15 (m, 1H), 5.0 (d, J 4 Hz, 1H), 6.6-8.0 (m, 9H).

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