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DIASTEREOSELECTIVE ALDOL CONDENSATION OF 2-METALLOALKYL-BENZOTHYAZOLES.

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Abstract.- 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-i.

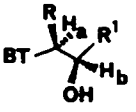
2-Lithiomethylbenzothiazole 1a, readily available by lithiation of 2-methylbenzothiazole 1a under proper conditions [1,2], cleanly adds to carbonyl compounds affording vinyl benzothiazoles probably via dehydration of the aldol intermediate.[1]

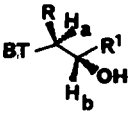
It has recently been reported that the reaction of 1a with carbonyls can be stopped at the aldol stage.[3] This prompted us to disclose our results[4] on the diastereoselective aldol type reaction of some 2-metalloalkylbenzothiazoles also in view of the fact that no stereoselective aldol condensation of 2-alkylbenzothiazoles have been reported so far.

Lithiation of 2-alkylbenzothiazoles 1b-d with n-buthyllithium at -78°C followed by addition of a number of aldehydes gave after work-up quite good yields of the diastereomeric β-hydroxyalkylbenzothiazoles 3-4, which were easily separated by column chromatography and characterized by IR and ^{1}H-NMR spectroscopy. Aldols 3 and 4 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

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

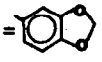
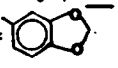
No aldol reaction took place when the LDA/HMPA combination was used for the lithiation step both in the case of 1b and 1c. This could tentatively be explained by the complexation of lithium by HMPA in such a way that the metal cannot participate in the stabilisation of the aldolate in a chair-like conformation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

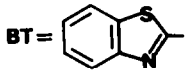




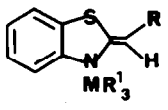
1a: R = H
1b: R = Me
1c: R = Et
1d: R = Ph

2a: R = H; M = Li
2b: R = Me; M = Li
2c: R = Et; M = Li
2d: R = Ph; M = Li
2e: R=Me;M=$SiMe_3$
2f: R=Et;M=$SiMe_3$
2g: R=Ph;M=$SiMe_3$
2h: R=Me;M=$SnCl_3$
2i: R=Et;M=$SnCl_3$

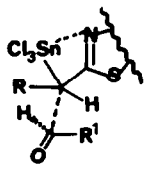
3a: R = Me; R^1 = Ph 4a
3b: R = Et; R^1 = Ph 4b
3c: R = R^1 = Ph 4c
3d: R =Me; R^1 =p ClC_6H_4 4d
3e: R =Me; R^1 =2,6$Cl_2C_6H_3$ 4e
3f: R = Me; R^1 =  4f
3g: R = Me; R^1 =  4g
3h:R=Me; R^1 =Pr^i 4h
3i: R =Et; R^1 = pClC_6H_4 4i
3k: R = Et; R^1 = 

BT= 

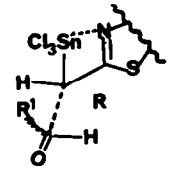
Looking for higher diastereoselection we investigated the aldol reaction of some other 2-metalloalkylbenzothiazoles. We prepared the trimethylsilylalkylbenzothiazoles 2e-g according to the Corey's procedure from 1b, 1c and 1d with trimethylsilylchloride.[7] We could prove by ^{1}H-NMR that indeed the silyl derivatives 2e-g 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 2e-g were unreactive towards unactivated benzaldehyde.



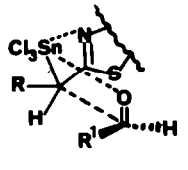
(A): M=Si; R^1=Me
(B): M=Sn; R^1=Cl



(K)



(L)



(M)

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

BF_3 Et_2O or $TiCl_4$ with poor diastereoselectivity. Knowing that the enol silyl ethers of certain ketones give α-trichlorostannyl ketones,[8] upon treatment with $SnCl_4$, we attempted preparation of the stannyl derivatives of the abovementioned 2-alkylbenzothiazoles. We examined the reaction of the silyl derivative 2e and $SnCl_4$ in CH_2Cl_2. Instantaneous reaction occurred on mixing 2e with $SnCl_4$ at low temperature, yielding the stannyl derivative 2h. Attempts to purify 2h failed, but the chemical shift of the methine proton and the absence in the ^{1}H-NMR spectrum of the vinylic proton of the trichlorostannyl aza-enolate (B) are compatible with the formulated structure 2h.

The reaction of 2h with benzaldehyde produced the erythro adduct 3a as the main aldol product.

It was worthy noting that again the threo isomer slightly prevailed when benzaldehyde preteated with $SnCl_4$ was added to 2e. Possibly the Mukajiama aldol condensation of 2e with the $SnCl_4$ activated benzaldehyde occurs.[9]

The erythro isomer 3b forms with high yield in the reaction between benzaldehyde and the stannylpropylbenzothiazole 2i, prepared from 2f via transmetallation with $SnCl_4$. Similarly 2i reacted with piperonal and p-chlorobenzaldehyde to give exclusively the erythro isomers 3k and 3i 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-R^1 interactions.

Thus we have found a suitable procedure for the diastereoselective aldol condensation of 2-alkylbenzothiazoles. When 2-lithioalkylbenzothiazoles derived from 1b-c 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 3 and 4 are suitable starting materials for the preparation of vinylbenzothiazoles of Z and E configuration, which could be used for the stereospecific synthesis of α,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-metalloalkylbenzothiazoles (M-BT) 2a-k with aldehydes.

Entry	M-BT	Solvent	Aldehyde[j]	3+4 Yield %	3/4 Ratio %	Temp. °C
1	2b[a]	THF	a_1	88	42/58	-78
2	"	"	"	80	"	-12
3	"	Et_2O	"	78	54/56	-78
4	"	THF	a_2	77	55/45	"
5	"	"	a_3	86	56/44	"
6	"	"	a_4	86	33/67	"
7	"	"	a_5	84	34/66	"
8	"	"	a_6	62	38/62	"
9	2c[a]	"	a_1	83	43/57	"
10	"	Et_2O	"		54/46[g]	"
11	2b[b]	THF	"	90	19/81	"
12	2c[b]	"	"	68	28/72	"
13	2d[b]	"	"	80	20/80	"
14	2e[c]	CH_2Cl_2	"		62/38[g]	
15	2e[d]	"	"		50/50[g]	"
16	2f[d]	"	"		55/45[g]	"
17	"	"	a_2		62/38[g]	"
18	2h[e]	"	a_1	58[i]	72/28	"
19	2h[f]	"	"		38/62[g]	"
20	2l[e]	"	"	89[i]	80/20	"
21	"	"	a_4	86	>98	"
22	"	"	a_2	84	>98	"

[a] n-BuLi was used as the lithiating agent. [b] LDA was used for the lithiation. [c] $TiCl_4$ was added to 2e before PhCHO. [d] BF_3 Et_2O added before PhCHO. [e] $SnCl_4$ added to the silyl derivative before the aldehyde. [f] $SnCl_4$ added to the aldehyde. [g] ratio determined on the diastereomeric mixture by TLC or ^{1}H-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

^{1}H-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.

Materials. Tetrahydrofuran (THF) and diethyl ether from commercial sources (RS, Carlo Erba) were purified by distillation (twice) from sodium wire in a N_2 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.

Reaction of 2-lithioalkylbenzothiazoles 2b-d with aldehydes. General procedure. The reaction of 1b with benzaldehyde is described as an example. An hexane solution of 2.4 N n-BuLi (1.12 ml, 2.7 mmol) was added dropwise to a stirred THF (or ether) solution of 1b (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 NH_4Cl solution. Extraction with ether (3 x 20 ml), drying over Na_2SO_4 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 1-phenyl-2-(2-benzothiazolyl)propan-1-ol 3a. The second eluted component was the threo isomer 4a. Spectral data are reported below and yields are given in the Table. When LDA was used as the lithiating agent the solution of 1b (1 mole) in THF was added to the LDA solution (1.1 mole) prepared from n-BuLi (hexane) and diisopropylamine in THF. Then the benzaldehyde was added as above.

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

The 2-lithioethylbenzothiazole 2b (1.84 mmol) was generated as above. To the stirred solution of 2b (1.84 mmol) a slight excess of Me_3SiCl (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 2e was dissolved in 20 ml of CH_2Cl_2 Then benzaldehyde (2.21 mmol) pretreated with $BF_3 \cdot Et_2O$ (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 1:1 3a:4a ratio was obtained as indicated by TLC and ^{1}H-NMR. A slight erythro selection was observed when titanium tetrachloride was used instead of BF_3 Et_2O. Similarly, 2-trimethylsilylpropylbenzothiazole 2f, prepared from 1c as 2e, was reacted with benzaldehyde and p-chlorobenzaldehyde pretreated with $BF_3 \cdot Et_2O$.

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 CH_2Cl_2 prepared as above a solution of $SnCl_4$ (2.1 mmol) in 5 ml of CH_2Cl_2 was added at -78°C. After about 30 min the p-chlorobenzaldehyde (2.02 mmol) in 5 ml of CH_2Cl_2 was added and then the reaction mixture was allowed to warm to room temperature. The reaction was quenched with NH_4Cl after 10 h and worked up as usual.

Aldols 3 and 4 (physical data. ^{1}H-NMR Spectra were recorded in $CDCl_3$ and a few drops of D_2O):

1-Phenyl-2-(2-benzothiazolyl)-propan-1-ol. Erythro isomer 3a. m.p. 86-87°C; IR (CH_2Cl_2): 3420 (OH) cm^{-1}; ^{1}H-NMR: δ 1.1 (d, 3H), 3.2 (m, 1H), 5.2 (d, 1H, J 3 Hz), 6.9-8.0 (m, 9H).
Threo isomer 4a. m.p. 123-124°C (EtOH); IR (CH_2Cl_2): 3400 (OH) cm^{-1}; ^{1}H-NMR: 1.2 (d, 3H), 3.4 (m, 1H), 4.8 (d, 1H,J 7 Hz), 6.9-8.0 (m, 9H).

1-Phenyl-2-(2-benzothiazolyl)butan-1-ol. Erythro isomer 3b. m.p. 100-101°C; IR (nujol): 3500-3160 br b (OH) cm^{-1}; ^{1}H-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 4b. m.p. 132-133°C; IR (nujol): 3500-3100 br b (OH) cm^{-1}; ^{1}H-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).

1,2-Diphenyl-2-(2-benzothiazolyl)ethanol. Erythro isomer 3c. ^{1}H-NMR:δ 4.6 (d, 1H, J 5 Hz), 5.7 (d, 1H, J 5 Hz), 6.9-8.1 (m, 14H).
Threo isomer 4c. m.p. 150-151°C (EtOH); IR (CH_2Cl_2): 3400 (OH) cm^{-1}; ^{1}H-NMR: δ 4.45 (d, 1H, J 8 Hz), 5.4 (d, 1H, J 8 Hz), 6.9-8.1 (m, 14H).

1-p-Chlorophenyl-2-(2-benzothiazolyl)propan-1-ol. Erythro isomer 3d. m.p. 95-96°C; IR (nujol) 3600-3100 br b (OH) cm^{-1}; ^{1}H-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 4d. m.p. 97-99°C; IR (nujol) 3600-3100 br b (OH) cm^{-1} ^{1}H-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).

1-(2,6-Dichlorophenyl)-2-(2-benzothiazolyl)propan-1-ol. Erythro isomer 3e. Oil IR (neat) 3700-3100 br b (OH) cm^{-1}; ^{1}H-NMR δ 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).
Threo isomer 4e. m.p.117-119°C; IR (nujol) 3700-3100 br b (OH) cm^{-1}; ^{1}H-NMR: δ 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).

1-(3,4-Methylenedioxyphenyl)-2-(2-benzothiazolyl)propan-1-ol. Erythro isomer 3f. Oil; IR (neat) 3660-3100 br b (OH) cm^{-1}; ^{1}H-NMR: δ 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).
Threo isomer 4f. m.p. 114-117°C; IR (nujol) 3460-3070 br b (OH); ^{1}H-NMR: δ 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-Furyl)-2-(2-benzothiazolyl)propan-1-ol. Erythro isomer 3g. Oil; IR (neat 3600-3100 br b (OH) cm^{-1}; ^{1}H-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}; ^{1}H-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 3h. Oil; IR (neat

3650-3100 br b (OH) cm^{-1}; ^{1}H-NMR: δ 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).
Threo isomer 4h, m.p. 56-58°C; IR (nujol) 3500-3100 br b (OH) cm^{-1}; ^{1}H-NMR: δ 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).

1-p-Chlorophenyl-2-(2-benzothiazolyl)butan-1-ol. Erythro isomer 3i. m.p. 101-102°C; IR (nujol) 3500-3100 br b (OH) cm^{-1}; ^{1}H-NMR: δ 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).
Threo isomer 4i. m.p. 140-141°C; IR (nujol) 3500-3080 br b (OH) cm^{-1} ^{1}H-NMR: δ 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).
1-(3,4-Methylenedioxyphenyl)-2-(2-benzothiazolyl)butan-1-ol. Erythro isomer 3k. Oil; IR (CH_2Cl_2) 3400 (OH) cm^{-1}; ^{1}H-NMR: δ 0.9-1.3 (m, 3H), 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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