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REGIOSELECTIVE CONTROL OF ALLYLLITHIUMS OF SOME HETEROCYCLES: α vs γ CONDENSATION WITH ALDEHYDES.

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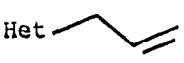
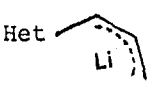
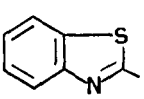
Summary: A procedure for directing the condensation of allyllithiums of benzothiazole, benzoxazole and pyrimidine such as 2 with aldehydes to the α or γ position is described.Erythro diasteroselection is observed in the α regioisomers.

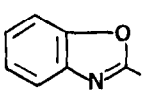
There is considerable current interest in the synthetic application of stabilized allylic carbanions.[1]The control of α vs γ substitution in such anions depends upon the complex interplay between the nature of the stabilizing group, charge delocalisation, steric effects, solvation, the type of electrophile, and the counterion.[2] The development of a methodology to control the regiochemistry with a predictable value is highly desirable from both practical and theoretical viewpoints.

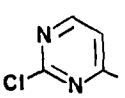
Of the numerous stabilized allylic anions much frequently used, those with a heterocyclic ring as the stabilizing group have not much been studied.[3] As part of a study concerning the reactions of metalloalkylbenzoazoles[4], we report here on the condensation of lithioallyl heterocycles 2 with aldehydes.





1a Het =  (BT) 2a

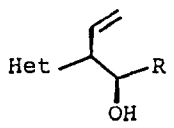
1b Het =  (BO) 2b

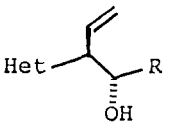
1c Het =  (CPy) 2c

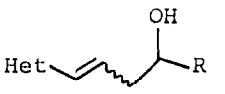
We have found that the α or γ regioselectivity markedly depends upon the experimental conditions in terms of temperature and reaction times.

Lithiation of 1a,[5] carried out using LDA/THF at -78°C, gave 2a. Addition of benzaldehyde to the brown solution of 2a followed after 20 min by quenching with aqueous NH_4Cl afforded almost quantitative yield of the

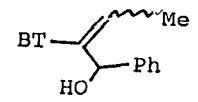
erythro and threo homoallylic alcohols 3a and 4a (3a/4a: 67/33).

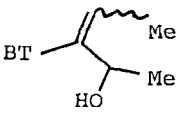


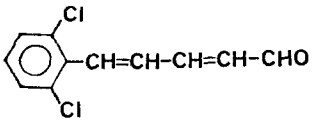




3a	R= Ph; Het= BT	4a	5:R=2,6-$Cl_2C_6H_3$;Het=BT
3b	R=2,6-$Cl_2C_6H_3$;Het=BT	4b	6:R= Ph; Het= BT
3c	R= Me; Het= BT		9:R=2,6-$Cl_2C_6H_3$;Het=BO
3d	R=2,6-$Cl_2C_6H_3$;Het=BO	4d	10: R= Ph; Het= CPy
3e	R= Ph; Het= CPy	4e	

7 

8 

11 

Under the same experimental conditions the reaction of 2a with 2,6-dichlorobenzaldehyde led to the diastereomeric alcohols 3b and 4b with high erythrodiastereoselectivity (3b/4b : 89/11). Similarly, treatment of 2a with acetaldehyde furnished almost exclusively the erythro alcohol 3c.

In sharp contrast, the reaction of 2a with 2,6-dichlorobenzaldehyde carried out at -78°C for 30 min and then at RT for 2h before quenching with aqueous NH_4Cl afforded quantitative yield of the regioisomer 5. Under the same conditions treatment of 2a with benzaldehyde led to the isomer 6 (65%) together with allylic alcohol 7 (32%), while the reaction of 2a with acetaldehyde led mainly to the allylic alcohol 8.

Table Reaction of allyllithiums 2 with aldehydes

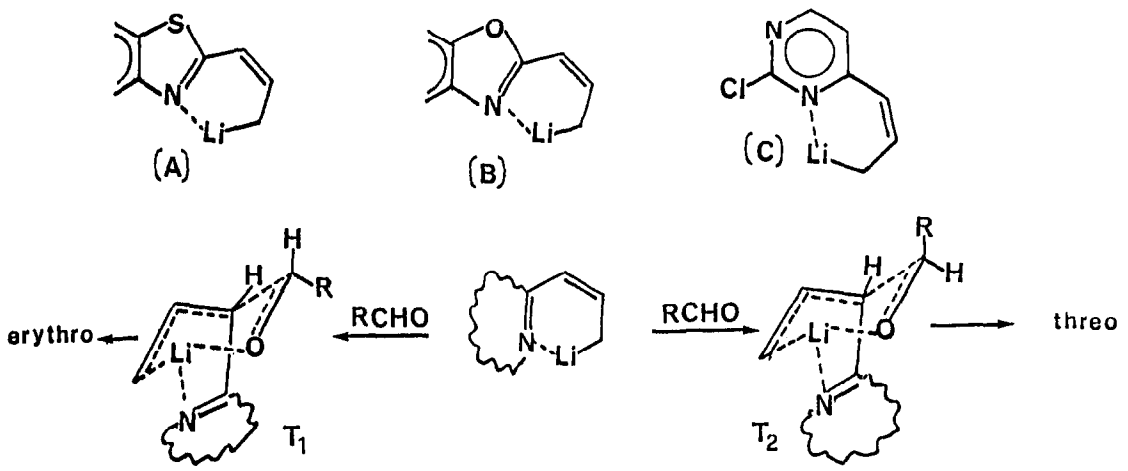
allyllithium	RCHO	Reaction Products	global yield (%)
2a[a]	PhCHO	3a (67%) 4a (33%)	>95%
2a[b]	"	6 (65%) 7 (32%)	>95%
2a[a]	2,6-$Cl_2C_6H_3$	3b (89%) 4b (11%)	90%
2a[b]	"	5	>95%
2a[a]	CH_3CHO	3c (100%)	>95%
2a[b]	"	8	56%
2b[a]	2,6-$Cl_2C_6H_3$	3d (44%) 4d (10%) 9 (8%)	62%
2b[b]	"	9 (100%)	>95%
2c[a]	PhCHO	3e (63%) 4e (37%)	84%
2c[b]	"	10 (100%)	74%

a) Reaction quenched with NH_4Cl at -78°C soon after mixing the reactants. b) Reaction quenched after 2h or 3h at RT.

Reactions of lithiated species of benzoxazole and chloropyrimidine 2b and 2c, readily available from 1b[6] and 1c[7] respectively, with

aldehydes gave results very similar to those obtained with 2a. Indeed, the reaction of 2b with 2,6-dichlorobenzaldehyde at -78°C (20 min) and immediate quenching with NH_4Cl gave a mixture of the α regioisomers 3d(44%) and 4d (10%) [3d/4d:82/18] and the isomer 9 (8%), while quenching after 3h at room temperature furnished quantitative yield of 9.

Finally the reaction of 2c with PhCHO led to the α regioisomers 3e and 4e (3e/4e:67/33) upon quenching soon after mixing the reactants at -78° and to the regioisomer 10 on quenching with NH_4Cl after 3h at RT.



A plausible rationalisation for the α or γ regioselectivity observed in the condensation of 2 with aldehydes might be that intramolecularly chelated forms (A), (B) and (C) add to the aldehyde with allylic rearrangement to give the α regioisomers that then at longer reaction times isomerize to the thermodinamically preferred γ isomers. Allylic alcohol 7 and 8 may arise from the isomerisation of the α regioisomers 3a and 3c respectively. The erythro diastereoselection in the α regioisomers might be explained by assuming that the chelated species (A)[or (B) or(C)] adds to the aldehyde with rearrangement via a chairlike transition state. Transition state T_1, that leads to the erythro product, is more stable than T_2, in which the R group sets axial.

The here described condensation is of interest from the synthetic viewpoint as the unsaturated hydroxybenzoazoles prepared this way represent suitable precursors of unsaturated carbonyls upon deblocking of the heterocyclic ring. Indeed, we have found that deblocking of 5, following the literature procedure[9], gives the unsaturated aldehyde 11[10] in very good yield. Fur-

ther applications and the counterion effect on the regio- and stereo-selectivity will be reported in due course.

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References and Notes:

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5) E. Epifani, S. Florio and G. Ingrosso, Tetrahedron, 40, 4527 (1984).
6) F. Babudri, S. Florio and L. Ronzini, Tetrahedron, 42, 3905 (1986).
7) 1c was prepared by addition of allylmagnesium bromide to 2-chloropyrimidine and dehydrogenation with DDQ. Unpublished results.
8) A typical experimental procedure is described for the reaction of 1a with PhCHO. 2-Allylbenzothiazole 1a (0.6 g, 3.42 mmol) in THF (20 ml) was added to a cooled (-78°), stirred solution of LDA [4.1 mmol, prepared from n-BuLi (2.4 M in hexane, 1.7 ml) and diisopropylamine (4.1 mmol) in THF (20 ml)] under nitrogen. The resulting mixture was kept at -78° for 20 min; then a solution of PhCHO (0.436 g, 4.1 mmol) in THF (10 ml) was added dropwise. Immediate quenching with NH_4Cl, extraction with ether (3x25 ml) and usual workup gave the α regioisomers 3a and 4a, which were separated by column chromatography and characterised by IR and ^1H NMR spectroscopy (Varian EM 360 A and Varian XL-200). New compounds had the following data. 3a, oil, IR (neat) 3165 cm^{-1} (OH). ^1H NMR ($CDCl_3$, D_2O): δ 4.09 (dd, 1H, J 3.74 Hz, J 8.65 Hz), 5.02-5.3 (m, 2H), 5.44 (d, 1H, J 3.74 Hz), 6.1-6.3 (m, 1H), 7.2-8.2 (m, 9H). 4a, m.p. 119-121° (ether-petrol), IR (nujol) 3280 cm^{-1} (OH). ^1H NMR ($CDCl_3$, D_2O): δ 4.07-4.16 (m, 1H), 5.0-5.2 (m, 2H), 5.17 (d, 1H, J 7.61 Hz), 5,8-6.1 (m, 1H), 7.2-8.1 (m, 9H). 3b, m.p. 138-139°C (ether-petrol); IR (nujol) 3250 cm^{-1} (OH). ^1H NMR ($CDCl_3$, D_2O): δ 4.9-5.5 (m, 3H), 5.6-6.3 (m, 2H) [6.2 (d, 1H, J 10 Hz)] 7.2-8.3 (m, 7H). 4b, oil. ^1H NMR ($CDCl_3$, D_2O): δ 4.7-5.0 (m, 1H), 5.3-5.68 (m, 2H), 6.08 (d, 1H, J 10 Hz), 6.3-6.8 (m, 1H), 7.2-8.2 (m,7H). 3c, oil. ^1H NMR ($CDCl_3$, D_2O): δ 1.27 (d, 3H, J 6.4 Hz), 3.72-4.03 (m, 1H), 4.15-4.85 (m, 1H), 5.25-5.65 (m, 2H), 5.95-6.35 (m, 1H), 7.43-8.35 (m, 4H). 3d, m.p. 142-143°C (ether-petrol); IR (nujol) 3253 cm^{-1} (OH). ^1H NMR ($CDCl_3$,D_2O): δ 4.77-5.12(m, 3H), 5.8-6.0 (m, 1H), 6.11 (d, 1H, J 10.4 Hz), 7.1-7.7 (m, 7H). 4d, oil, IR (neat) 3248 cm^{-1} (OH); ^1H NMR ($CDCl_3$, D_2O): δ 4.6-4.9 (m, 1H), 5.3-5.7 (m, 2H), 5.95 (d, 1H, J 10.0 Hz), 6.2-7.0 (m, 1H), 7.0-8.0 (m, 7H). 3e, oil, IR (neat) 3400 cm^{-1} (OH) ^1H NMR ($CDCl_3$, D_2O): δ 3.5-3.85 (m, 1H), 4.9-5.5 (m, 3H), 5.9-6.4 (m, 1H), 7.0 (d, 1H, J 5 Hz), 7.32 (s, 5H), 6.5 (d, 1H, J 5 Hz). 4e, oil, IR (neat) 3380 cm^{-1} (OH); ^1H NMR ($CDCl_3$, D_2O): δ 3.75 (dd, 1H, J 7.90 Hz, J 8.75 Hz), 4.85-5.07 (m, 2H), 5.95 (d, 1H, J 7.90 Hz), 5.80-6.0 (m 1H) 7.11 (d, 1H, J 5.0 Hz), 7.25 (s, 5H), 8.45 (d, 1H, J 5.0Hz). 5, oil, ^1H NMR ($CDCl_3$,D_2O): δ 2.65-3.4 (m, 2H), 5.6-5.92 (m, 1H), 6.7-8.2 (m, 9H). 6, oil. ^1H NMR ($CDCl_3$ D_2O): δ 2.7-2.82 (m, 2H), 4.86-5.02 (m, 1H), 6.66-6.84 (m, 2H), 7.15-8.0 (m, 9H). 7, m.p. 118-120°C (ether-petrol), ^1H NMR ($CDCl_3$, D_2O): δ 2.07 (d, 3H, J 7.14 Hz), 6.05 (s, 1H), 6.72 (q, 1H, J 7.14 Hz), 7.2-7.95 (m, 9H). 8, oil, ^1H NMR ($CDCl_3$, D_2O): δ 1.55 (d, 3H, J 7.0 Hz), 1.95 (d, 3H, J 8.0 Hz), 5.12 (q, 1H, J 7.0 Hz), 6.53 (q, 1H, J 8.0 Hz), 7.25-8.3 (m, 4H). 9, oil, IR (neat) 3340 cm^{-1} (OH). ^1H NMR ($CDCl_3$, D_2O): δ 2.55-3.6 (m, 2H), 5.5-6.0 (m, 1H), 6.3-6.8 (m, 1H), 6.9-7.8 (m, 8H). 10, oil, IR (neat) 3380 cm^{-1} (OH). ^1H NMR ($CDCl_3$, D_2O): δ 2.6-2.8 (m, 2H), 4.8-4.92 (m, 1H), 6.4 (d, 1H, J 15.75 Hz), 7.0-7.4 (m, 7H), 8.32 (d, 1H, J 5.15 Hz).
9) H. Chikashita, S. Ikegami, T. Okumura, K. Itoh, Synthesis, 375 (1986).
10) m.p. 95-96°C (ether-petrol). IR (nujol) 1691 (C=O), 1630 cm^{-1} (C=C). ^1H NMR ($CDCl_3$):δ 6.2-6.7 (m,2H), 7.1-7.8 (m, 5H), 9.87 (d, 1H, J 8 Hz).

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