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Thiazole *C*-nucleosides. V. Remote group participation operating in the reactions of diastereomeric 2-(2′-deoxypent-1′-enopyranosyl)thiazole derivatives

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Summary – The supposed interplay of remote group participation and anomeric, allylic and stereodirecting effects exerted by different groups are invoked to explain the formation of a new stereocenter in unsaturated thiazole *C*-nucleosides **5** and **6**.

remote group participation / thiazole *C*-nucleoside / conformation

The stereocontrolled creation of new stereogenic centers at sites far from existing stereocenters is a challenging problem in synthetic organic chemistry. Herein I would like to report a unique case in which the assumed interplay of remote group participation and anomeric, allylic and stereodirecting effects exerted by different groups controls the formation of a new stereocenter in an unequivocal fashion.

During the course of studies aimed at new thiazole *C*-nucleosides [1, 2], it has been observed that the unsaturated thiazole derivatives **1** and **2** easily undergo Lewis acid-mediated nucleophilic substitution reactions giving 3′-substituted products in a regio- and stereochemically controlled way (fig 1). Thus, diastereomers **1** and **2** reacted with trimethylsilyl azide in the presence of boron trifluoride etherate to afford enantiomers

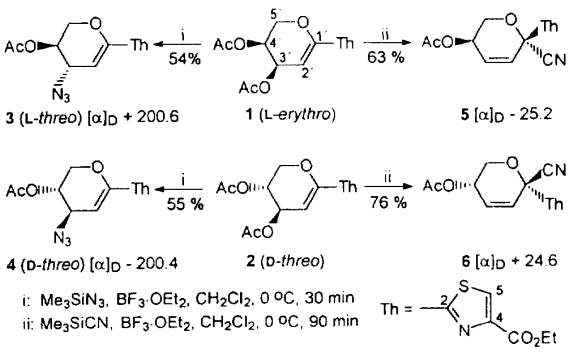

Fig 1

3 and **4**, respectively, in convincing optical purities [2]. Various *C*-, *N*-, *O*-, *S*-, and *H*-nucleophiles displayed similar behavior yielding 3′,4′ *trans*-configured (D- or L-*threo*) products.

A notable exception is represented by trimethylsilyl cyanide. In this particular case a single C-1′-substituted product **6** was formed from **2** [2]. Surprisingly, when the same reaction was carried out with compound **1**, **5** was exclusively formed with UV, IR, ^{1}H and ^{13}C NMR spectra that were superimposable on those of **6** and with nearly the same optical rotation power, but of opposite sign, as **6**. Clearly, **5** and **6** are enantiomers.

The enantiomers **5** and **6** were subjected to thorough NMR analysis (the general structure for compound **6**, except for the exact stereochemistry at C-1′, was reported earlier [2]). The coupling constant $^3J_{H-3',H-4'}$ = 5.5 Hz indicated the preponderance of the $^oH_5$ (L) conformer in the case of compound **5** (the following comments also hold for the energetically equivalent ^5H_o (D) conformation of compound **6**). This is in line with the findings of various groups [3–16], who reported coupling constants in the range 5.5 to 6.5 Hz for peracylated 3-deoxypent-2-enopyranoses and 3-deoxyhex-2-enopyranoses in conformations ($^oH_5$ (L) and ^5H_o (D) for pentopyranoses; ^5H_o (D), $^oH_5$ (D), depending on the C-4 (C-4′) configuration, for hexopyranoses) where the torsional angle between the pertinent protons (H-3 and H-4 or H-3′ and H-4′, respectively) is a small value, and 1.3 to 2.7 Hz for the corresponding equilibrium conformations where the same angle is larger. Intermediate values have also been reported [4, 5, 9, 12, 13, 17] indicating the presence of conformational equilibria.

Model calculations performed with a PC model 4.0 [18] using the Haasnoot equations [19] also corroborated this fact. Namely, for the conformation $^{O}H_5$ (L) a coupling constant of 4.8 Hz was obtained, which corresponds to the torsional angle 41°, while for the $^{5}H_o$ (L) conformer this value should be 2.8 Hz (torsional angle 78°; see bonds in bold in the projections along the C-3′ ... C-4′ axis, fig 2; conformational drawings and Newman projections are shown for enantiomer **5** only). As the extreme values of these coupling constants in the two conformers are not known with absolute certainty for similar systems, the exact position of the $^{O}H_5$ (L) $\rightleftarrows$ $^{5}H_o$ (L) equilibrium cannot be determined. However, supported by calculations and literature evidence, we have good reason to assume that this equilibrium is largely shifted to the $^{O}H_5$ (L) **5** and $^{5}H_o$ (D) **6** conformers, respectively.

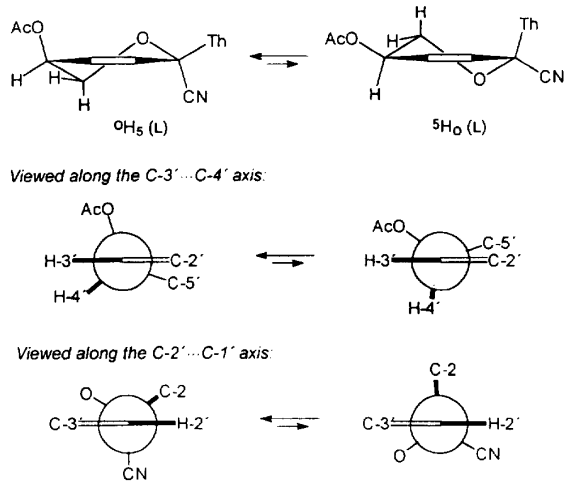

Fig 2

The favorable arrangement of the protons concerned in the $^{O}H_5$ (L) conformation also accounts for the observed allyl coupling $^{4}J_{H-2',H-4'}$ (0.9 Hz).

Although Bonin *et al* [20] have reported the determination of the anomeric configuration of 1-cyano $\Delta^{2,3}$-unsaturated pyranoses by means of the $^{1}J_{C-1,H-1}$ coupling constants, this was not applicable in the case of **5** and **6** due to the lack of H-1′. An indirect proof for the above conformational prevalence and the C-1′ configuration was also provided by heteronuclear coupling constants. $^{3}J_{C-2,H-2'}$ (8.2 Hz) and $^{3}J_{CN,H-2'}$ (0 Hz) for compound **5** are only consistent with conformer $^{O}H_5$ (L), because in this case the C-2 atom of the thiazole ring and the H-2′ proton of the sugar moiety are nearly coplanar, while the cyano group is nearly perpendicular to the latter (see the bonds in bold in the projections along the C-2′ ... C-1′ axis; in the $^{5}H_o$ (L) conformer this situation is reversed). In this conformer, the thiazole ring is quasi-equatorial; a similar situation has also been observed with (3′-deoxy-hex-2′-enopyranosyl)purines [9].

The above-mentioned homo- and heteronuclear coupling constants for **5** (and analogously for **6**) and the other proof (*vide infra*) are only compatible with the depicted configurations at C-1′.

The stereoselective formation of **3** and **4** can be explained in terms of neighboring group participation [21–23]. Thus, for example, in the case of compound **1** (and analogously with compound **2**), carbocation **I** was formed upon the action of boron trifluoride etherate (fig 3), which reacted with the majority of nucleophiles according to *path a* to give derivatives **7** through carbocation **II** with the neighboring group participation of the adjacent 4′-acetoxy group [1, 2]. In the case of *path b*, leading to C-1′-substituted derivatives of type **8** (if Nu′ = CN, **5** and its diastereomer), carbocation **III** would allow the formation of diastereomers. The unequivocal formation of enantiomers **5** and **6**, however, questions this simplified reaction path.

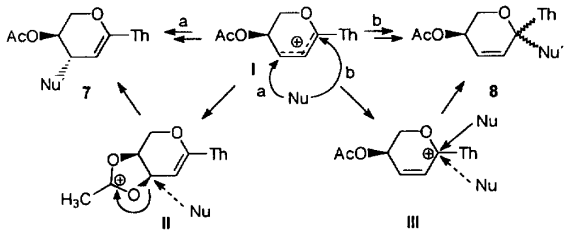

Fig 3

The exclusive formation of **5** and **6** from **1** and **2**, respectively, necessitates the assumption that the stereochemical outcome of the reaction, as in the case of **3** and **4** [2], is independent of the configuration of the C-3′ substituent and is determined by the C-4′ acetoxy grouping. Thus, being of opposite configuration in the starting materials **1** and **2**, the acetoxy substituent forms a cyclic structure (**III** → **IV** in the case of **1**, and analogously with its enantiomer; fig 4), in which the arriving cyanide nucleophile attacks from the opposite side to the originally present 4′-substituent. This remote group participation clearly accounts for the exclusive formation of a single diastereomer.

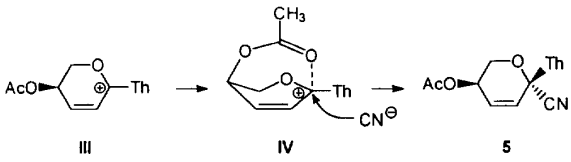

Fig 4

There may be a single intermediate (**I–IV**) for both the azides (**3**, **4**) and the nitriles (**5**, **6**). This intermediate is attacked at either C-3′ ($N_3^{\ominus}$) or C-1′ ($CN^{\ominus}$) to give the corresponding products. According to Pearson's principle, soft *C*-nucleophiles should react at the soft C-3′ center of the above carbocations and not at the harder C-1′ [24]. The apparent discrepancy between the supposedly soft character of C-3′ in **I–IV** and the observed binding of cyanide at the anomeric center may be explained in kinetic terms [24]. If the rate of the reaction at C-1′ is sufficiently greater than at C-3′

exclusive formation of **5** and **6** can be expected. It is known that peracetylated hexopyranoid glycals react with trimethylsilyl cyanide under Lewis acid catalysis to give 2,3-unsaturated glycosyl cyanides. Isomeric 3-*C*-cyanohex-1-enopyranosyl derivatives have not been detected even after prolonged reaction times and at elevated temperatures and so there was no thermodynamic equilibration [12, 24]. Analogously, it may be assumed that compounds **5** and **6** have also been formed in a kinetic reaction. In the case of azides **3** and **4**, a possible [3,3] sigmatropic rearrangement cannot be excluded, *ie* a rapid attack of **I**–**IV** at C-1′ followed by a slower rearrangement to C-3′ products.

The above remote group participation merits further discussion. The interaction of a substituent with an adjacent atom bearing a leaving group is generally termed as neighboring group participation [21–23]. The widespread occurrence of simple (as in **A**) and complex (as in **B**) neighboring groups [23] resulting in the formation of different ring systems (**V**–**VIII**) is well documented (fig 5). The term 'neighboring' is usually reserved for contiguous centers (in cations **V** and **VI**–**VIII** ($n = 0$), respectively), involving three- (**V** (typically Z = sulfur, iodine, and bromine) and **VII** ($n = 0$)) and five-membered rings (rarely six-membered) (**VI**–**VIII** ($n = 0, 1$; A = oxygen, nitrogen *etc*)). Little is known about other cases (non-contiguous centers ($n > 0$), larger, seven- or eight-membered rings). The reason is probably the sporadic occurrence and less spectacular consequences than in the case of classical neighboring groups, which dramatically increase the rate and/or unequivocally influence the stereochemical outcome of reactions [25].

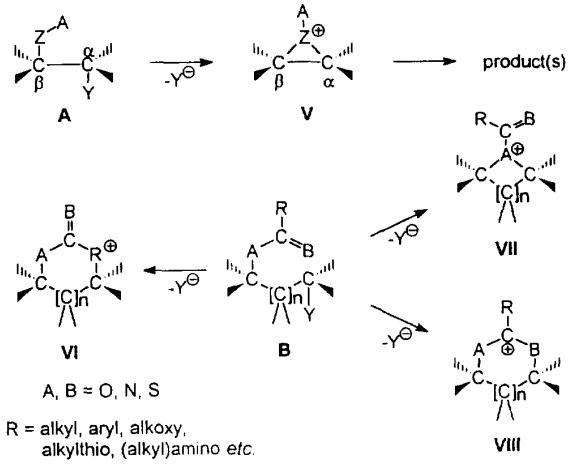

Fig 5

Scrutinizing some reactions of various peracylated pyranoid glycals with *C*- [11–14, 20, 24, 26, 27], *N*- [8–10, 16, 17, 28–30], and *O*-nucleophiles [3–6, 31, 32], I have found some evident and several latent instances in which phenomena similar to the above observations have been experienced. Ferrier and Sankey [4, 5] were the first to report that the product distribution of allylic rearrangement reactions of peracylated hexo- or pentopyranoid 2-hydroxyglycals markedly differs by the anomer ratios of the formed hex- (or pent-) 2-enopyranoses. Thus, for example, in the reaction of 2,3,4,6-tetra-*O*-acetyl-2-hydroxy-D-glucal, the α- and β-2,3-unsaturated products are present at equilibrium in the ratio 3.4:1, whereas from 2,3,4-tri-*O*-acetyl-2-hydroxy-D-xylal this ratio is 0.34:1, and in the rearrangement products of 2,3,4,6-tetra-*O*-acetyl-2-hydroxy-D-galactal no detectable β-2,3-unsaturated compound is produced. These facts evidently show the influence of 4′-acetoxy configuration on the product distribution. Later, Fuertes *et al* [28] reported an even more interesting case. By allowing 3,4-di-*O*-acetyl-D-xylal to react with benzotriazole or its 5,6-dimethyl derivative in the presence of trifluoroacetic acid, 1-(4-*O*-acetyl-2,3-dideoxy-D-*glycero*-pent-2-enopyranosyl)benzotriazoles were obtained. In the same reaction 3,4-di-*O*-acetyl-L-arabinal (epimeric at C-4 with the D-xylal derivative) afforded compounds with identical pairwise spectral and physical data except for the optical rotations, which had the same absolute values but opposite signs. These data suggest the presence of enantiomers. This was indeed proved by repeated experiments by the same workers in a careful ^{1}H NMR study establishing that in these products the configuration is β-D and β-L, respectively [10]. Several less clear cases leading to anomeric product mixtures have been described indicating preferred entrance of nucleophiles from the side opposite to the original 4-acyloxy group [6, 11, 13, 27, 29, 32].

Saturated pyranose derivatives were also suspected for stereodirecting effect by distant acyloxy substituents but no conclusive results have been obtained so far [33–36]. An interesting example is represented by the interaction of remote acyloxy or acylamino groups with mercury atoms supposed to form six-membered rings in the Ferrier carbocyclic ring transformation reactions of 6-deoxyhex-5-enopyranoses [37], although this assumption was later questioned [38, 39]. Saturated furanoses seem to be better candidates for such an interaction. Participating groups at C-3 or C-5 exert directing effect on the entering nucleophile; β-2′-deoxyribonucleosides [40–42], β-2′-deoxy-*C*-glycosides [43], α-glycosides [44] and substituted tetrahydrofurans [45] can all be obtained in good stereoselectivities. Remote group participation was also postulated in some acyclic asymmetric induction reactions [46, 47]. However, the expression 'remote' in these cases is misleading (with respect to our present approach) because in these transformations the assumed cyclic structures are usually five-membered, which clearly places this phenomenon among the classical neighboring group participation reactions.

A closer look at the favored conformation ($^{\circ}H_5$ (L)) of compound **5** might reveal some deeper reasons for the preferred formation of this substance. The 4′-acetoxy group is in quasi- axial orientation which is favored by *ca* 0.8 kcal/mol over the quasi-equatorial position (allylic effect) [5]. There is no data on whether the cyano group exerts a similar effect or not; if it does, this gives further stabilization to the conformation in question (in the solid state this group is preferentially quasi-axially oriented [48]). Moreover, in this conformation the group is stabilized by the anomeric effect which was estimated to be 1.9–2.4 kcal/mol for the cyano group [49]. The role of the thiazole group needs further clarification. Besides

the preference of bulky heterocycles for quasi-equatorial orientation in similar systems [9], there is some evidence that this group might play a role in directing the stereochemical course of the reactions of compounds **1** and **2**, respectively. The reaction of peracylated pento- or hexopyranoid glycals with trimethylsilyl cyanide in the presence of boron trifluoride etherate [12, 24] or diethylaluminium cyanide at room temperature [20, 26] invariably leads to anomeric mixtures of pent-2- or hex-2-enopyranosyl cyanides, independently of the configuration of 4-acyloxy group. The reaction of 3,4,6-tri-*O*-acetyl-D-glucal with diethylaluminium cyanide in boiling benzene afforded 98% α-anomer [14].

In conclusion, the supposed interplay of the stereodirecting effect of the thiazole ring, the remote group participation and the allylic effect of the acetoxy group in carbocation **IV** might assist the pseudo-axial attack of cyanide nucleophile, thus resulting in the exclusive formation of compound **5** (and analogously for its enantiomer **6**), which is further stabilized by the anomeric effect of the cyano group. Therefore, the intermediate carbocation **IV** probably has a product-like conformation.

Experimental section

For general procedures see the previous papers in this series [1, 2]. The starting compounds **1** and **2** were prepared according to the described procedures from the corresponding thioamides [1], with the exception that for dehydration step; 2 equiv of trifluoroacetic anhydride and 4 equiv of pyridine were used in contrast with the previously described 1 and 2 equiv, respectively. Without these surplus reagents the transformation was not complete.

Ethyl 2-[(5'S)-acetyloxy-(2'S)-cyano-5',6'-dihydro-2'H-pyran-2'-yl]thiazole-4-carboxylate **5**

Compound **1** (1.777 g; 5.0 mmol) in anhydrous dichloromethane (20 mL) was allowed to react with trimethylsilyl cyanide (1.00 mL; 7.5 mmol) in the presence of boron trifluoride etherate (0.9 mL; 5.5 mmol) at 0°C for 90 min. The reaction mixture was diluted with dichloromethane, washed with sat $NaHCO_3$ solution, water, and brine. Drying ($MgSO_4$), evaporation, and chromatography (toluene/diethyl ether 95:5) afforded the syrupy product (1.01 g; 63%). $[\alpha]_D = -25.2$ (*c* 2.26; chloroform). The UV, ^1H, ^{13}C NMR, and EI-MS data were reported previously [2]. FAB-MS (glycerol): 323 ($[M + H]^+$, 17%). The previously described 0.9 Hz coupling in the pattern of H-2' proton was erroneously described as $^4J_{H-3',H-5'e}$; this should read $^4J_{H-2',H-4'}$. The best separation of the signals in the proton spectrum was obtained in C_6D_6, although the crucial couplings $^3J_{H-3',H-4'}$ and $^4J_{H-2',H-4'}$ had the same values in $CDCl_3$ (the heteronuclear couplings were obtained in this solvent).

Ethyl 2-[(5'R)-acetyloxy-(2'R)-cyano-5',6'-dihydro-2'H-pyran-2'-yl]thiazole-4-carboxylate **6**

This compound was prepared analogously as **5** from enose **2** in 78% yield. $[\alpha]_D = +24.6$ (*c* 2.28; chloroform). The UV, IR, ^1H, ^{13}C NMR, and EI-MS spectral parameters of this substance were identical to those of compound **5**.

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