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New 4-amino-5-*H*-2,3-dihydroisothiazole-1,1-dioxides from sugar α-aminonitriles using the CSIC reaction

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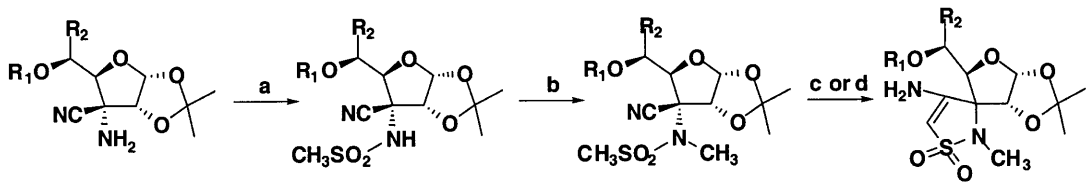
Abstract—4-Amino-5-*H*-2,3-dihydroisothiazole-1,1-dioxide ring was attached to a monosaccharide ring system by carbanion-mediated sulfonate intramolecular cyclisation (CSIC) of either secondary or tertiary aminonitrilesulfonamide carbohydrate derivatives using NaH, Cs_2CO_3 or BuLi as a base. These new bicyclic systems were used as glycone precursors of aza analogues of TSAO RT inhibitors. We report the first synthesis of an aza analogue of TSAO-m^{3}T.

Carbanion-mediated sulfonate intramolecular cyclisation (CSIC) was first reported by Gómez de las Heras in 1988.[1] Since then, this reaction has been used extensively to synthesise various sulfonates from cyanohydrins[2–4] and to sulfonamides from aminonitriles.[4–8] Also, Camarasa used the CSIC reaction for



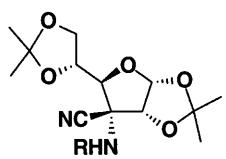
1a:R$_1$,R$_2$=C(CH$_3$)$_2$OCH$_2$
2a:R$_1$=Tr ; R$_2$=H
3:R$_1$=Bn ; R$_2$=H
4:R$_1$=Bz ; R$_2$=H

5:R$_1$,R$_2$=C(CH$_3$)$_2$OCH$_2$ (80%)
6:R$_1$=Tr ; R$_2$=H (92%)
7:R$_1$=Bn ; R$_2$=H (98%)
8:R$_1$=Bz ; R$_2$=H (98%)

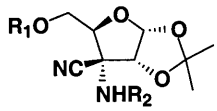
9:R$_1$,R$_2$=C(CH$_3$)$_2$OCH$_2$ (95%)
10:R$_1$=Tr ; R$_2$=H (98%)
11:R$_1$=Bn ; R$_2$=H (96%)
12:R$_1$=Bz ; R$_2$=H (98%)

13:R$_1$,R$_2$=C(CH$_3$)$_2$OCH$_2$(40%[d])
14:R$_1$=Tr ; R$_2$=H (61%[c];90%[d])
15:R$_1$=Bn ; R$_2$=H (35%[c];33%[d])
16:R$_1$=Bz ; R$_2$=H (25%[d])

Scheme 1. (a) CH_3SO_2Cl, DMAP–pyridine; (b) CH_3-I, K_2CO_3, acetone; (c) NaH, acetonitrile; (d) Cs_2CO_3, acetonitrile.



1a : R=H (80%)
1b : R=CH$_3$ (50%)
1c : R=C$_8$H$_{17}$ (73%)
1d : R=Bn (98%)



2a : R$_1$=Tr ; R$_2$=H (98%)
2b : R$_1$=Tr ; R$_2$=CH$_3$ (60%)
2c : R$_1$=Tr ; R$_2$= C$_8$H$_{17}$ (83%)
2d : R$_1$=Tr ; R$_2$=Bn (86%)
3 : R$_1$=Bn ; R$_2$=H (70%)
4 : R$_1$=Bz ; R$_2$=H (82%)

Keywords: α-aminonitriles; CSIC reaction; 4-amino-5-*H*-2,3-dihydroisothiazole-1,1-dioxide ring; TSAO.
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the synthesis of 3′-spiro-5″-(4″-amino-1″,2″-oxathiol-2″,2″-dioxide) nucleosides (TSAO nucleosides), which represents a particular type of specific HIV-1 RT inhibitor.[9] Marco-Contelles widely studied the scope and limitations of the CSIC reaction using derivatives of aldehydes and ketone.[5–8] He demonstrated that the central nitrogen atom of aminonitrilesulfonamides would have to be fully substituted in order for the CSIC reaction to proceed, otherwise the amino nitrogen would be removed to give insoluble sodium salts of the alkylsulfonamidonitriles. Whatever the initial sulfonate or sulfonamide, the carbanion is generated by the removal of a proton from the methylene neighbouring the SO_2 group with non-nucleophilic bases such as DBU, NaH and Cs_2CO_3.

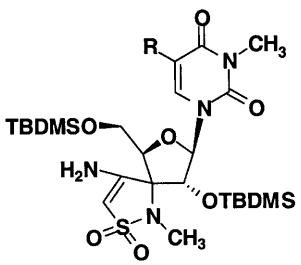
Recently, we have reported the stereoselective synthesis of the D-allose (**1a–d**) and D-ribose (**2a–d**, **3** and **4**) α-aminonitriles from the corresponding uloses using titanium(IV) isopropoxide as a mild Lewis acid catalyst and TMSiCN as a cyanating agent.[10]

We now report the derivatisation of these α-aminonitriles using the CSIC reaction to obtain novel monosaccharides possessing a 4-amino-5-*H*-2,3-dihydroisothiazole-1,1-dioxide ring system at position 3 of the furanose ring. As a first approach, we restricted the cyclisation study to *N*-H and *N*-Me sulfonamide derivatives. Compounds **1a**, **2a**, **3** and **4** were reacted with methanesulfonyl chloride to give the sulfonamides **5**, **6**, **7** and **8**, respectively (Scheme 1). *N*-Methylation was performed using MeI and K_2CO_3 in acetone or acetonitrile to give **9–12**, which were cyclised with either NaH or Cs_2CO_3 to give the target monosaccharide derivatives **13–14**, respectively, in good yields (Scheme 1).[11]

It is notable that under similar basic CSIC reaction conditions no reaction was observed with the sulfonamides **5–8**. This lack of reactivity would be explained by the removal of the acidic hydrogen atom from the nitrogen atom of the sulfonamide group to give the corresponding insoluble salt.[8] Alternatively, an excess of butyl lithium was used with the objective of generating the lithium salt which would be expected to be sufficiently soluble to undergo a second attack of the base leading to the carbanion required for the cyclisation (Scheme 2).[12] However, no CSIC reaction was observed for the benzoylated derivative **8** and the initial compound was not finally recovered.

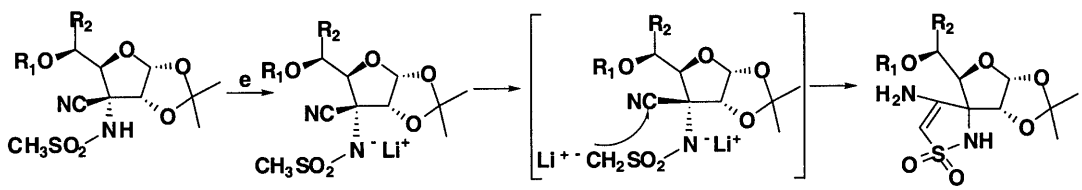
These interesting results showed that a fully substituted central nitrogen atom, in the sugar aminonitrilesulfonamides studied, is not necessary for the CSIC reaction to take place if an alkyl lithium is used as base.

Over the last decade, extensive structure–activity relationship studies on TSAO derivatives have been conducted.[2,9,13,14] In order to prepared aza analogues of these non-nucleoside RT inhibitors, we first synthesised the thymine and uracil α-aminonitrilesulfonamide nucleoside derivatives. CSIC reaction of the key nucleoside intermediates gave [3-*N*-methyl-1-[2′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-β-D-ribofuranosyl]thymine]-3′-spiro-3″-(4″-amino-5-*H*-2″-methyl-2″,3″-dihydroisothiazole-1″,1″-dioxide) (**21**) and [3-*N*-methyl-1-[2′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-β-D-ribofuranosyl]-uracil]-3′-spiro-3″-(4″-amino-5-*H*-2″-methyl-2″,3″-dihydroisothiazole-1″,1″-dioxide) (**22**), which are the first aza analogues of TSAO-m^3-T and TSAO-m^3-U.[15]



21 : R = CH_3
22 : R = H

In conclusion, we have demonstrated that sugar α-aminonitriles are important key intermediates for the synthesis of systems in which a 3-(4-amino-5-*H*-2-methyl-2,3-dihydroisothiazole-1,1-dioxide) ring is attached to a furanose ring using the CSIC reaction. The preliminary results reported herein proved that cyclisation could be achieved from a secondary sulfonamide group using alkyllithium as a base. This strategy appears to provide convenient access to a new range of aza analogues of TSAO nucleosides (ATSAOs). Studies in this direction are in progress.



5:R_1,R_2=$C(CH_3)_2OCH_2$
6:R_1=Tr ; R_2=H
7:R_1=Bn ; R_2=H
8:R_1=Bz ; R_2=H

17:R_1,R_2=$C(CH_3)_2OCH_2$ (60%)
18:R_1=Tr ; R_2=H (98%)
19:R_1=Bn ; R_2=H (98%)
20:R_1=Bz ; R_2=H (0%)

Scheme 2. (e) BuLi–THF.

Acknowledgements

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11. *Spectroscopic values* for **14**: ^{1}H NMR ($CDCl_3$) δ 7.46–7.25 (m, 15H, H trityl), 5.84 (d, 1H, $J_{1,2}=4.0$ Hz, H-1), 5.43 (s, 1H, H-5′), 4.60 (d, 1H, H-2), 4.52 (t, 1H, $J_{4,5}=5.0$ Hz, H-4), 4.38 (s, 2H, NH_2), 3.40 (d, H, H-5), 2.77 (s, 3H, CH_3-N), 1.64 (s, 3H, CH_3), 1.34 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ 151.9 (1C, C-4′), 143.2 (3C, C ipso), 128.5, 127.8, 127.1 (15C, trityl), 113.0 (1C, CH_3CCH_3), 103.4 (1C, C-1), 93.2 (1C, C-5′), 87.4 (1C, C trityl), 84.2 (1C, C-2), 74.8 (1C, C-4), 70.4 (1C, C-3), 60.9 (1C, C-5), 26.4 (1C, CH_3-N), 26.0 (1C, CH_3), 25.8 (1C, CH_3).
12. *Spectroscopic values* for **18**: ^{1}H NMR ($CDCl_3$) δ 7.40–7.23 (m, 15H, H trityl), 5.86 (d, 1H, $J_{1,2}=4.0$ Hz, H-1), 5.22 (s, 1H, H-5′), 4.85 (s, 1H, NH), 4.48 (d, 1H, H-2), 4.46 (s, 2H, NH_2), 4.00 (t, 1H, $J_{4,5}=5.0$ Hz, H-4), 3.48 (d, 2H, H-5), 1.51 (s, 3H, CH_3), 1.31 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ 152.1 (1C, C-4′), 143.3 (3C, C ipso), 128.6, 127.9, 127.2 (15C, trityl), 113.5 (1C, CH_3CCH_3), 103.7 (1C, C-1), 94.1 (1C, C-5′), 87.6 (1C, C trityl), 81.8 (1C, C-2), 79.3 (1C, C-4), 69.3 (1C, C-3), 60.5 (1C, C-5), 26.4 (1C, CH_3), 26.1 (1C, CH_3).
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15. *Spectroscopic values* for **21**: ^{1}H NMR ($CDCl_3$) δ 7.08 (s, 1H-6), 5.66 (s, 1H, NH_2), 5.40 (s, 1H, H-5″), 5.03 (d, 1H, $J_{1',2'}=6.5$ Hz, H-2′), 4.86 (d, 1H, H-1′), 4.22 (t, 1H, $J_{4',5'}=5.0$ Hz, H-4′), 3.95 (d, 2H, H-5′), 3.33 (s, 3H, CH_3-N_{th}), 2.90 (s, 3H, CH_3-NSO_2), 1.98 (s, 3H, CH_{3th}), 0.89 (s, 9H, *tert*-$But_{5'}$), 0.80 (s, 9H, *tert*-$But_{2'}$), 0.12 (s, 3H, CH_3), 0.08 (s, 6H, $2CH_3$), −0.02 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ 163.0 (1C, C-4), 153.0 (1C, C-4″), 150.9 (1C, C-2), 138.7 (1C, C-6), 111.1 (1C, C-5), 99.5 (1C, C-5″), 90.1 (1C, C-1′), 79.3 (1C, C4′), 74.4 (1C, C-2′), 69.4 (1C, C-3′), 61.7 (1C, C-5′), 27.9 (1C, CH_3-N_{th}), 26.6 (1C, CH_3-NSO_2), 25.9, 25.4 (6C, *tert*-But), 18.4, 18.0 (2C, *tert*-But), −4.7 (1C, CH_3Si), −5.2 (2C, CH_3Si), −5.9 (1C, CH_3Si).