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From α,α-Disubstituted α-Aminonitriles to Heterocycles: Synthesis of Derivatives of 4-Amino-2,3-dihydroisothiazole 1,1-Dioxide, a New Heterocyclic Ring System

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Abstract: The synthesis of derivatives of 4-amino-2,3-dihydroisothiazole 1,1-dioxide (**8-10**, **12**, **15**, **16**), a new heterocyclic ring system, from α,α-disubstituted α-aminonitriles, is described. © 1997 Elsevier Science Ltd.

For years we have been interested in the synthesis and chemical utility of α-aminonitriles.[1] These may be prepared[2] readily by the Strecker reaction and are valuable intermediates for the synthesis of amines, aminoalcohols and aminoacids.[3,4]

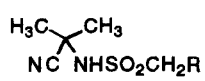
To our knowledge the synthesis of heterocycles from α,α-disubstituted α-aminonitriles has not been reported. These compounds are particularly well functionalized since nucleophilic attack of the amino group and subsequent nucleophilic attack to the cyano moiety would yield heterocyclic systems.[5] Derivatives of 4-amino-5*H*-1,2-oxathiole 2,2-dioxide have been obtained *via* an aldol-type cycloaddition of *O*-methylsulphonyl cyanohydrins.[6] This chemistry has been mostly limited at present to sugar and nucleoside derivatives.[7,8] Attempts to produce 4-amino-2,3-dihydroisothiazole 1,1-dioxides from ketone sugars has not been successful due to difficulties encountered in the preparation of the required aminonitriles.[9] We have implemented this "aldol-type" strategy using active methylene containing sulphonamides[10] and in this paper we disclose some preliminary results for the synthesis of the new 4-amino-2,3-dihydroisothiazole 1,1-dioxide system.

Beginning with 2-amino-2-methylpropanenitrile (**1**),[11] readily obtained from acetone in 84% yield, the methyl **2**[12] (65% yield), ethyl **3**[12] (25% not optimized) and benzyl **4**[12] (47%) sulphonamides were produced under standard conditions (sulphonyl chloride, triethylamine, methylene chloride). Attempts to cyclize these compounds proved unsuccessful presumably due to preferential deprotonation of the nitrogen atom. We thus decided to protect each sulphonamide as their *N*-benzyl derivatives. From **2** the intermediates **5**[13] (60%), **6**[12] (11%, not optimized) and **7**[12] (64%) were obtained by treatment with the appropriate benzyl halides and K_2CO_3 in refluxing acetonitrile.[12] Similarly, compounds **3** and **4** gave the derivatives **11**, and **13** or **14**,[12] respectively.

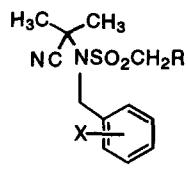
The treatment of **5** with sodium hydride in acetonitrile resulted in a rapid reaction giving compound **8** in 65% yield. The ^1H and ^{13}C NMR spectra and good elemental analysis confirmed the 2-benzyl-4-amino-2,3-dihydroisothiazole 1,1,-dioxide structure. Compound **8** showed in the ^1H NMR (DMSO) spectrum signals at δ 1.22 [a singlet for six protons (CH_3CCH_3)], 4.18 [a singlet for two protons ($NCH_2C_6H_5$)], 5.16 [a singlet for one proton (H5)], 6.42 (a broad singlet for two protons corresponding to NH_2) and 7.50-7.28 (multiplet for five aromatic protons). In the ^{13}C NMR spectrum we observed also signals for C4 (160.2 ppm), aromatic carbons (138.7, 126.9, 128.1, 128.0 ppm), C5 (85.8 ppm), C3 (63.3 ppm), $NCH_2C_6H_5$ (41.3 ppm), CH_3CCH_3 (23.8 ppm). Compounds **6** and **7** cyclized similarly to give **9**[12] (43%) and **10** (43%),[13] respectively. Product **12**[13] (46% overall yield from aminonitrile **3**) was prepared without isolation of the intermediate **11**. The more activated benzylsulphonamide derivatives **13** and **14** afforded **15** (75%) and **16** (47%), respectively, when acetonitrile solutions of these products were treated with 0.2 mol.equiv of DBU.

In summary, we have reported a simple and short strategy for the synthesis of 4-amino-2,3-dihydroisothiazole 1,1-dioxides based upon α-sulphonyl carbanion mediated ring closure using α,α-

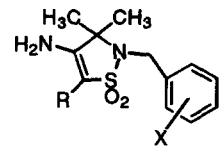
disubstituted α-aminonitriles as starting materials. These results pave the way for a more detailed study of this approach. We are currently studying the use of other ketones (chiral or racemic) and chiral Strecker synthesis for the preparation of the α-aminonitriles. This shall be published in due course.



2 R= H
3 R= CH_3
4 R= C_6H_5



5 R, X= H
6 R= H, X= *p*-Cl
7 R= H, X= *m*-Cl
11 R= CH_3, X= H
13 R= C_6H_5, X= H
14 R= C_6H_5, X= *m*-Cl



8 R, X= H
9 R= H, X= *p*-Cl
10 R= H, X= *m*-Cl
12 R= CH_3, X= H
15 R= C_6H_5, X= H
16 R= C_6H_5, X= *m*-Cl

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12. All new compounds showed good spectroscopic and analytical data.
13. Selected spectroscopic values: **5**: ^{1}H NMR ($CDCl_3$) δ 7.41-7.30 (m, 5 H), 4.62 (s, 2 H, NCH_2Ar), 3.07 (s, 3 H, SO_2CH_3), 1.34 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 137.4, 128.7, 127.8, 127.2 (Ph), 120.8 (CN), 55.4 (CH_3CCH_3), 50.7 (SO_2CH_3), 41.3 (NCH_2Ar), 29.1 (CH_3CCH_3). **10**: ^{1}H NMR (DMSO) δ 7.47-7.30 (m, 4 H), 6.47 (br s, 2 H, NH_2), 5.17 (s, 1 H, H5), 4.21 (s, 2 H, NCH_2Ar), 1.23 (s, 6 H); ^{13}C NMR (DMSO) δ 160.3 (C4), 141.6 (C3'), 132.8 (C1'), 129.8, 127.6, 126.8, 126.5 (C2',4',5',6'), 85.6 (C5), 63.4 (C3), 40.7 (NCH_2Ar), 23.8 (CH_3CCH_3). **12**: ^{1}H NMR (DMSO) 7.48-7.20 (m, 5 H), 5.97 (br s, 2 H, NH_2), 4.21 (s, 2 H, NCH_2Ar), 1.71 (s, 3 H, C5-CH_3), 1.19 (s, 6 H); ^{13}C NMR (DMSO) δ 153.5 (C4), 138.7, 128.0, 127.9, 126.9 (Ph), 91.6 (C5), 62.1 (C3), 41.3 (NCH_2Ar), 29.9 (CH_3CCH_3), 5.1 (C5-CH_3).

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