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New and Unexpected Developments of the Carbanion-mediated Sulfonate (Sulfonamide) Intramolecular Cyclization Reaction (CSIC Reaction)

José L. Marco*, S. T. Ingate and Pilar Manzano

Instituto de Química Orgánica General, Consejo Superior de Investigaciones Científicas (CSIC), C/Juan de la Cierva 3, 28006-Madrid, Spain

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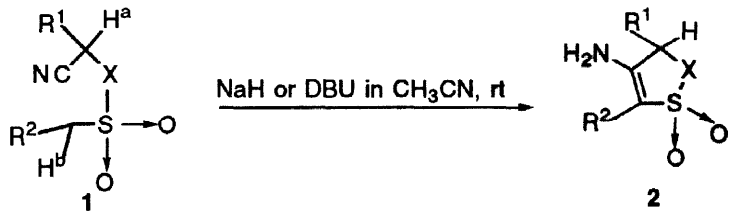
Abstract.- The Carbanion-mediated Sulfonate (Sulfonamide) Intramolecular Cyclization reaction (CSIC reaction) on conveniently functionalized cyanoalkylsulfonates and cyanoalkylsulfonamides derived from aldehydes is possible and gives the new heterocyclic ring systems 5-alkyl-5*H*-4-amino-1,2-oxathiole-2,2-dioxide and 5-alkyl-5*H*-4-amino-3-cyano-2,3-dihydroisothiazole-1,1-dioxide in good yield.

Keywords: Aldol reaction/ Amino nitriles/ Cyanohydrins

In 1988 Gómez de la Heras published the first report [1] on the Carbanion-mediated Sulfonate Intramolecular Cyclization reaction (CSIC reaction) with nitriles as the carbonyl component of this aldol type ring closure [2]. In subsequent communications from this group, this process was successfully applied to other ketones from sugars [3], nucleosides [4] or to adamantanone [5]. Quinuclidine derivatives have been also tested [6]. However, in spite of the large mass of results in this area [1, 3-6], no attention has been directed to the analysis and scope of the CSIC reaction with nitriles; furthermore, the potentially rich reactivity of the 4-amino-1,2-oxathiole-2,2-dioxides has been also almost unexplored [7-9].

Scheme 1



1 **2**

1a-f X = O
3a-j X = NR^3

2a-f X = O
4i and **4j** only when R^2 = CN; X = NR^3

In this communication we report that the CSIC reaction on conveniently functionalized cyanosulfonates and cyanosulfonamides obtained from aldehydes is possible and affords the corresponding new heterocycles 5-alkyl-5*H*-4-amino-1,2-oxathiole-2,2-dioxide (**2b-f**) and 5-alkyl-5*H*-4-amino-3-cyano-2,3-dihydroisothiazole 1,1-dioxide (**4i, j**) in good yield (Scheme 1).

A literature search for such reactivity in sulfonyl derivatives of aldehydecyanohydrins showed no precedent. Not surprisingly [10], treatment of compound **1a** [11] (R^1= Ph, R^2= H; Scheme 1) with base did not afford the cyclized product. We decided therefore to investigate derivatives with a simple alkyl residue next to the carbon

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bearing H^a. In accordance with this, when we turned our attention to cyanoalkylsulfonate derivative **1b** (R^1= Me, R^2= H; Scheme 1), the reaction with sodium hydride or DBU gave heterocycle **2b** in 50% yield. Other analogues (**1c**: R^1, R^2= Me; **1d**: R^1= Et, R^2= H; **1e**: R^1= Et, R^2= Me; **1f**: R^1= Et, R^2= Ph; Scheme 1), under the same experimental conditions, afforded products **2c-f** in varying yields (**2c**: 58%, **2d**: 61%, **2e**: 84%, **2f**: 91%) [12]. With this promising results we attempted similar CSIC reactions using the precursors **3a-h** (X= NR^3) [11] (**a**: R^1, R^2, R^3= H; **b**: R^1, R^2= H, R^3= Bn; **c**: R^1= Et, R^2, R^3= H; **d**: R^1= Et, R^2= Me, R^3= H; **e**: R^1= Et, R^2= H, R^3= Bn; **f**: R^1= Et, R^2= Me, R^3= Bn; **g**: R^1= Et, R^2= Ph, R^3= Me; **h**: R^1= Et, R^2, R^3= Me). To our great surprise no ring closure took place, and no reliable side product could be isolated. This showed us that the selective deprotonation of H^b in products **1b-f** (X= O) is a consequence of a favorable balance of the different electronic interactions in the oxygen intermediates **1** respect to the analogous nitrogen substituted intermediates **3**. Independently of this effect, we hypothesized that increasing the acidity of H^b, by incorporating electron-withdrawing substituents (R^2= CN) in compounds **3**, would favour the cyclization. Indeed, this was the case. The reaction of intermediates **3i** and **3j** gave compounds **4i** and **4j**. The cyclic structures were readily confirmed by spectroscopy. Compound **4i** showed in the ^1H NMR and ^{13}C NMR spectra signals for H-3 (4.12 ppm), NH_2 (7.62 ppm), C-3 (65.0 ppm), C-4 (164.5 ppm) and C-5 (80.1 ppm), respectively.

In summary, we have reported for the first time the successful CSIC reaction of cyanoalkylsulfonates and cyanoalkylsulfonamides derived from aldehydes. Some structural limitations have been observed: for the cyanohydrins, only aliphatic aldehydes, and for the aliphatic α-aminonitriles, only cyanomethylenesulfonamides give the CSIC reaction. This is a new and unexpected development of this reaction that expands the synthetic scope, interest and usefulness of the CSIC reaction [13].

Acknowledgments

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[11] Compounds 1 and 3 have been prepared by standard methodologies. Experimental details will be reported elsewhere. All new compounds showed excellent analytical and spectroscopic data.

Selected spectroscopic data. **2c**: ^1H NMR (200 MHz, DMSO) δ 1.44 (d, 3 H, CH_3-5), 1.73 (s, 3 H, CH_3-3), 5.03 (q, 1 H, H-5), 6.28 (br s, 2 H, NH_2); ^{13}C NMR (75 MHz, DMSO) δ 5.4 (CH_3-3), 19.5 (CH_3-5), 77.4 (C-5), 90.8 (C-3), 151.1 (C-4); IR (KBr) υ 1685 (C=CNH_2); 1295, 1150 (SO_2) cm^{-1}. **4j**: ^1H NMR (200 MHz, acetone) δ 0.92, 1.14 [2xd, 2x3 H, (CH_3)$_2$CH], 2.35 [m, 1 H, CH(CH_3)$_2$], 2.80 (s, 3 H, CH_3N), 4.04 (d, 1 H, H-3), 7.50 (br s, 2 H, NH_2); ^{13}C NMR (50 MHz, acetone) δ 15.5, 20.4 [2xCH(CH_3)], 33.0 (N-CH_3), 36.4 [CH(CH_3)$_2$], 71.0 (C-3), 80.1 (C-5), 111.4 (CN), 164.7 (C-4); IR (KBr) υ 3380, 3235 (NH), 2200 (CN), 1670, 1615 (NCC=CNH_2), 1285, 1150 (SO_2) cm^{-1}
[12] In a typical experiment, to a solution of **1e** (0.51 g, 2.89 mmol) in CH_3CN (10 mL) was added slowly NaH (0.14 g, 3.47 mmol; 60% dispersion in oil), the reaction was stirred at rt for 20 min. Water (20 mL) was added and the mixture was extracted with dichloromethane (3 x 25 mL), the organic solvent was dried (Na_2SO_4) and was evaporated to give a residue that was purified by column chromatography (40:1-20:1 CH_2Cl_2: MeOH) to yield **2e** (0.429 g, 84%) as a colourless solid (mp. 89-90 °C, CH_2Cl_2:hexane). The ^1H NMR and ^{13}C NMR spectra of compound **2e** show signals for H-3 (5.40 ppm), H-5 (a quartet at 5.12 ppm), NH_2 (6.67 ppm) and C-3 (84.3 ppm), C-4 (157.8 ppm), C-5 (78.1 ppm), respectively.
[13] The resulting products are CHAO-like compounds [7,8] and are being subjected to antiviral pharmacological screening [4].