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First tandem nucleophilic addition–electrophilic amination reaction of Eschenmoser's salts: synthesis of cyclic and spiro-fused hydrazonium salts

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Abstract—A series of cyclic and spiro-fused hydrazonium salts was prepared by tandem nucleophilic addition–electrophilic amination reactions. The method presented makes use of Eschenmoser's salt or benzotriazole aminals and 2-hydroxylamino-4,5-dihydroimidazolium-*O*-sulfonate. The products structures were determined by X-ray analysis.

1. Introduction

Quaternary ammonium salts (QACs) are found in various commercial products including antiseptics and sanitizers,[1–3] fungicides,[4] crop protection agents,[5] cosmetics,[5] and dental composites.[6] They are also widely used within specialized areas such as fabric softeners and hair conditioners as well as in organic synthesis for phase transfer catalysis.[7] Recently, a number of research programs have been aimed at obtaining QACs with anticancer,[8–10] bronchodilating[11], and analgesic[12,13] activity.

Unfortunately, most QACs available today suffer from disadvantages limiting their use, such as microbial resistance phenomena, poor compatibility with other materials, and poor biodegradation under practical sewage plant conditions.[14] Therefore there is a need for the preparation of new compounds with novel chemical structures incorporating new molecular parameters such as heteroatoms, chemical functions, and aromatic rings.

Following our interest in the chemistry of imidazoline compounds with potential medicinal interest,[15–18] we have now developed a new and efficient method for the synthesis of novel bicyclic imidazo[2,1-*c*][1,2,4]triazole derivatives having a quaternary hydrazonium moiety, employing a tandem nucleophilic addition–electrophilic amination approach.

2. Results and discussion

The starting material for the synthesis of the title compounds was 2-hydroxylamino-4,5-dihydroimidazolium-*O*-sulfonate (**1**), which upon treatment with triethylamine gives triethylaminium 2-hydroxylimino-imidazolidine-*O*-sulfonate (**1a**) (Fig. 1).[15] Due to the presence of an electron withdrawing sulfate group at the exocyclic nitrogen atom, compound **1** is susceptible to proton abstraction, and the exocyclic nitrogen atom of **1a** can react as an electrophile.

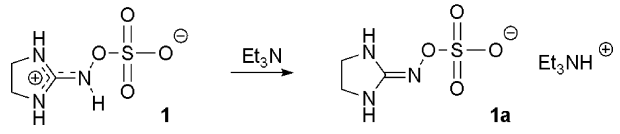

Figure 1.

In the present work, the reaction of **1a** with Eschenmoser's salt **2** in a 2:1 molar ratio carried out in anhydrous DMF at ambient temperature for 12 h afforded 2,2-dimethyl-3,5,6,7-tetrahydro-2*H*-imidazo[2,1-*c*][1,2,4]triazol-2-ium 2-hydroxyliminoimidazolidine-*O*-sulfonate (**4**) in 64% yield (Scheme 1). The reaction can be envisaged

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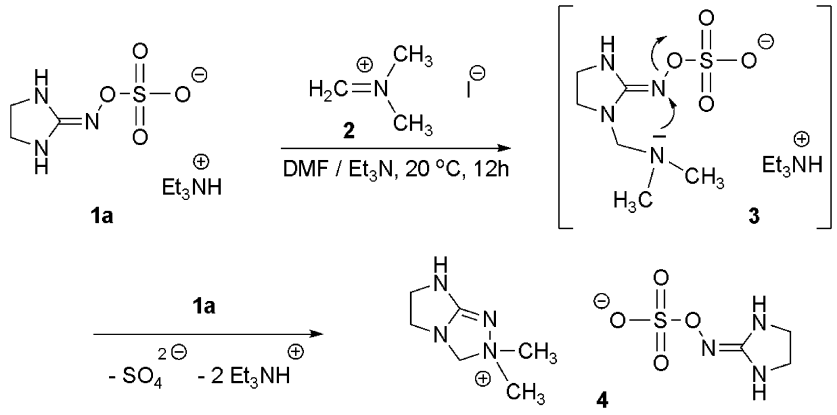


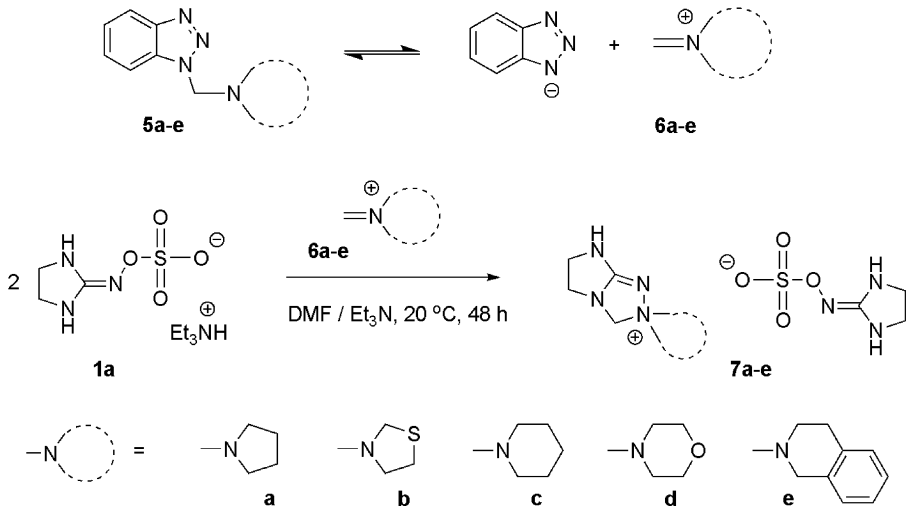
Scheme 1.

to proceed via an initial Mannich-type reaction between the Eschenmoser's salt **2** and the nitrogen nucleophile affording aminal **3**, followed by electrophilic amination of the tertiary amine, which gave rise to the formation of the quaternary 1,2,4-triazolium salt **4**. Our attempts to isolate the intermediate Mannich base **3** by intercepting and analyzing the reaction mixture at different stages during the course of the reaction were unsuccessful showing that aminal **3** is very reactive toward intramolecular electrophilic amination.

Once it was established that the imidazo[2,1-*c*][1,2,4]triazol-2-ium salt can be obtained, we examined the possibility of an alternative approach using the well known benzotriazole aminals[19] to serve as Eschenmoser salt precursors. As shown in Scheme 2, 1-(α-aminoalkyl)benzotriazoles **5a**–**e** exist in solution in equilibrium with benzotriazolyl anion and immonium cation **6a**–**e**. The cation adds at the nucleophilic imidazoline nitrogen atom of **1a** to form a Mannich-type base, which then undergoes intramolecular electrophilic amination giving rise to the formation of the corresponding spiro-fused hydrazonium salts **7a**–**e** in 44–68% yield. It is worth noting that the thiazolidine and tetrahydroisoquinoline compounds **7b** and **7e** were obtained as a 1:1 mixture of enantiomers at the spirocenter.

The structures of **4** and **7a**–**e** were in accord with ^{1}H, ^{13}C, and 2D NMR spectroscopic data as illustrated for the representative example **4**. The four proton singlet at δ 3.22 ppm was assigned to the CH_2CH_2 moiety of the 2-substituted imidazolidine ring of the anion. The methylene protons of the 1,2-disubstituted imidazoline give two triplets at δ 3.37 and 3.79 ppm with a J value of 7 Hz, this assignment being confirmed by HMBC correlation of these protons with the quaternary C-2 carbon at δ 170.2 ppm. The two protons of the methylene group flanked by two nitrogen atoms appeared as a singlet at δ 4.76 ppm. These protons show a HSQC correlation with a carbon signal appearing at δ 80.2 ppm and HMBC correlations with signals observed at δ 46.3, 55.2, and 170.2 ppm corresponding, respectively, to the CH_2 group, the *N*-methyl groups, and C-2 of the imidazoline ring (Supplementary data).

The structure of the spiro-fused compound **7a** was confirmed by a single crystal X-ray analysis (Fig. 2, Supplementary data).[20] The fused bicyclic system of the



Scheme 2.

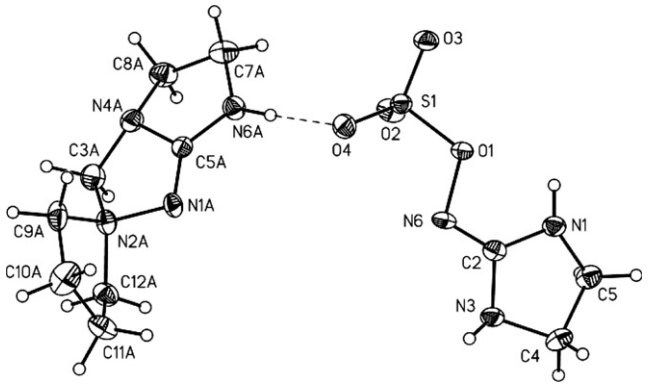


Figure 2. ORTEP representation of salt **7a**.

quaternary cation is flattened but not planar, with the absolute values of the endocyclic torsion angles not exceeding 30°. The imidazolidine fragment adopts a conformation, which is intermediate between an envelope and a half-chair whereas the other fused five-membered ring has an envelope form with C3A as the flap. The nitrogen atom at the fusion of the rings (N4A) has hybridization, which is intermediate between sp^2 and sp^3 (the sum of the valence angles is 335°). The length of the N–C bond at the fusion of the two rings, 1.384 Å, points to only weak conjugation of the N4A p orbital with the amidine (N1A, C5A, N6A) π-system.

Summing up, the results described herein suggest that the tandem nucleophilic addition–electrophilic amination reaction of Eschenmoser's-type salts provides a useful method for the synthesis of variously substituted cyclic and spiro-fused hydrazonium salts. Presently, we are investigating the scope of this interesting cyclization based on the reaction of iminium salts with amidines bearing an electron withdrawing group at the N^2 nitrogen atom.

3. Typical experimental procedure

To a suspension of 2-hydroxylamino-4,5-dihydro-imidazolium-*O*-sulfonate (**1**, 1.81 g, 10 mmol) and Eschenmoser's salt (**2**, 5 mmol) or the corresponding benzotriazole aminal (**6a–e**, 5 mmol) in dry DMF (8 mL) was added Et_3N (2.8 mL, 20 mmol) with stirring. The reaction mixture was heated at 50 °C for 5–10 min and then left at ambient temperature for 12 h. The solid that precipitated was separated by suction, washed with MeOH, and purified by crystallization from DMF. In the case of **7b**, the solvent was evaporated under reduced pressure and the oily residue was treated with MeOH to give the crude product that was purified by crystallization from DMF/MeOH.

3.1. 2,2-Dimethyl-3,5,6,7-tetrahydro-2*H*-imidazo[2,1-*c*][1,2, 4]triazol-2-ium 2-hydroxyliminoimidazolidine-*O*-sulfonate (4)

Yield 64%; ^{1}H NMR (DMSO, 500 MHz) $\delta = 3.22$ (s, 4H, CH_2), 3.32 (s, 6H, CH_3), 3.37 (t, 2H, CH_2, $J = 7$ Hz), 3.79 (t, 2H, CH_2, $J = 7$ Hz), 4.76 (s, 2H, CH_2), 5.85 (br s, 2H, NH), 7.89 (br s, 1H, NH); ^{13}C NMR (DMSO, 125 MHz) $\delta = 43.1$, 46.7, 48.5, 55.2, 80.2, 163.3, 170.2; IR cm^{-1} 1055, 1217, 1261, 1673, 3228, 3402; mp: 109–114 °C; Anal. Calcd for $C_9H_{19}N_7O_4S$: C, 33.64; H, 5.96; N, 30.51. Found: C, 33.32; H, 6.23; N, 30.13.

3.2. 3,5,6,7-Tetrahydrospiro[imidazo[2,1-*c*][1,2,4]triazole-2,1′-pyrrolidin]-1′-ium 2-hydroxyliminoimidazolidine-*O*-sulfonate (7a)

Yield 68%; ^{1}H NMR (DMSO, 200 MHz) $\delta = 2.00$–2.16 (m, 4H, CH_2), 3.20 (s, 4H, CH_2), 3.35 (t, 2H, CH_2), 3.55–3.84 (m, 6H, CH_2), 4.81 (s, 2H, CH_2), 5.54 (br s, 1H, NH), 5.82 (br s, 1H, NH), 7.87 (br s, 1H, NH); ^{13}C NMR (DMSO, 50 MHz) $\delta = 21.7$, 42.7, 46.4, 48.1, 66.1, 77.2, 162.9, 169.9; IR cm^{-1} 1049, 1199, 1264, 1672, 3213, 3313; mp: 193–196 °C; Anal. Calcd for $C_{11}H_{21}N_7O_4S$: C, 38.03; H, 6.09; N, 28.22. Found: C, 37.74; H, 6.39; N, 27.93.

3.3. 3,5,6,7-Tetrahydrospiro[imidazo[2,1-*c*][1,2,4]triazole-2,3′-thiazolidin]-2-ium 2-hydroxyliminoimidazolidine-*O*-sulfonate (7b)

Yield 44%; ^{1}H NMR (DMSO, 500 MHz) $\delta = 3.25$–3.30 (m, 2H, CH_2), 3.37–3.42 (m, 2H, CH_2), 3.83 (t, 2H, CH_2), 3.90–3.98 (m, 1H, CH_2), 4.01–4.09 (m, 1H, CH_2), 4.65 (d, 1H, CH_2, $J = 9.8$ Hz), 4.94 (d, 1H, CH_2, $J = 9.8$ Hz), 4.95–4.99 (m, 2H, CH_2), 7.20 (br s, 2H, NH), 8.05 (br s, 1H, NH); ^{13}C NMR (DMSO, 125 MHz) $\delta =$ IR cm^{-1} 1059, 1246, 1654, 3296; mp: 161–163 °C; Anal. Calcd for $C_{10}H_{19}N_7O_4S_2$: C, 32.87; H, 5.24; N, 26.83. Found: C, 32.55; H, 5.60; N, 26.52.

3.4. 3,5,6,7-Tetrahydrospiro[imidazo[2,1-*c*][1,2,4]triazole-2, 1′-piperidin]-1′-ium 2-hydroxyliminoimidazolidine-*O*-sulfonate (7c)

Yield 55%; ^{1}H NMR (DMSO, 200 MHz) $\delta = 1.40$–2.03 (m, 6H, CH_2), 3.20 (s, 4H, CH_2), 3.35 (t, 2H, CH_2), 3.40–3.70 (m, 4H, CH_2), 3.79 (t, 2H, CH_2), 4.74 (s, 2H, CH_2), 5.61 (br s, 1H, NH), 5.86 (br s, 1H, NH), 7.91 (br s, 1H, NH); ^{13}C NMR (DMSO, 50 MHz) $\delta = 20.9$, 21.4, 42.6, 42.8, 46.3, 48.1, 63.3, 78.6, 162.9, 169.6; IR cm^{-1} 1053, 1208, 1255, 1652, 3236, 3342; mp: 187–190 °C; Anal. Calcd for $C_{12}H_{23}N_7O_4S$: C, 39.88; H, 6.41; N, 27.13. Found: C, 39.71; H, 6.56; N, 27.06.

3.5. 3,5,6,7-Tetrahydrospiro[imidazo[2,1-*c*][1,2,4]triazole-2,4′-morpholin]-2-ium 2-hydroxyliminoimidazolidine-*O*-sulfonate (7d)

Yield 61%; ^{1}H NMR (DMSO, 200 MHz) $\delta = 3.20$ (s, 4H, CH_2), 3.30–3.56 (m, 4H, CH_2), 3.70–4.06 (m, 8H, CH_2), 4.82 (s, 2H, CH_2), 5.62 (br s, 1H, NH), 5.86 (br s, 1H, NH), 8.02 (br s, 1H, NH); ^{13}C NMR (DMSO, 125 MHz) $\delta = 43.2$, 46.7, 48.6, 62.5, 62.7, 79.9, 163.3, 170.3; IR cm^{-1} 1057, 1201, 1260, 1648, 3180, 3325; mp: 187–190 °C; Anal. Calcd for $C_{11}H_{21}N_7O_5S$: C, 36.36; H, 5.82; N, 26.98. Found: C, 36.12; H, 6.17; N, 27.00.

3.6. 3,3′,4′,5,6,7-Hexahydro-1′*H*-spiro[imidazo[2,1-*c*][1,2,4]triazole-2,2′-isoquinolin]-2-ium 2-hydroxyliminoimidazolidine-*O*-sulfonate (7e)

Yield 49%; ^{1}H NMR (DMSO, 500 MHz) $\delta = 3.08$–3.14 (m, 1H, CH_2), 3.19 (s, 4H, CH_2), 3.26–3.31 (m, 1H, CH_2), 3.42 (t, 2H, CH_2, $J = 7.3$ Hz), 3.83 (t, 2H, CH_2, $J = 7.3$ Hz), 3.93–3.98 (m, 2H, CH_2), 4.69 (d, 1H, CH_2, $J = 15.1$ Hz), 4.84 (d, 1H, CH_2, $J = 6.3$ Hz), 4.93 (d, 1H, CH_2, $J = 6.3$ Hz), 4.99 (d, 1H, CH_2, $J = 15.1$ Hz), 5.62 (br s, 1H, NH), 5.88 (br s, 1H, NH), 7.18–7.20 (m, 1H, CH), 7.25–7.32 (m, 3H, CH), 7.95 (br s, 1H, NH); IR cm^{-1} 1060, 1220, 1258, 1667, 3319; mp: 189–190 °C; Anal. Calcd for $C_{16}H_{23}N_7O_4S$: C, 46.93; H, 5.66; N, 23.95. Found: C, 46.68; H, 5.99; N, 23.82.

Supplementary data

Crystallographic data for the structure **7a**; 2D NMR HSQC and HMBC spectra of **4**. Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tetlet.2007.08.127.

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20. X-ray crystallographic determination of compound **7a**. *Crystal data* for $C_{11}H_{21}N_7O_4S$: monoclinic, space group $P2_1/n$, $a = 9.6312(11)$, $b = 9.7876(11)$, $c = 16.889(2)$ Å, $V = 1526.6(3)$ Å^3, $Z = 4$, $\lambda = 0.71073$ Å, $R_1 = 0.0353$, $wR_2 = 0.0773$ for 2850 independent reflections with $I > 2\sigma(I)$.