Reaction of 1,3-diethyl-4,5-dihydroxyimidazolidin-2-one with 1,3-dimethylsulfamide at a high pressure

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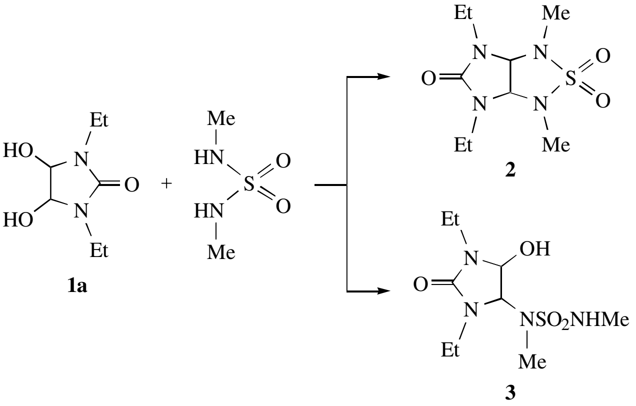
The title reaction under conditions of a solvent phase transition was found to afford *N*-(1,3-diethyl-5-hydroxy-2-oxo-4-imidazolidinyl)-*N*,*N*′-dimethylsulfamide along with expected 2,4-dimethyl-6,8-diethyl-3-thia-2,4,6,8-tetraazabicyclo[3.3.0]octan-7-one 3,3-dioxide.

Previously,[1,2] the reactions of 1,3-dialkyl-4,5-dihydroxyimidazolidin-2-ones **1** with sulfamides at ordinary pressures were examined. Depending on pH, the condensation of **1** with sulfamide resulted in 4,4′-sulfonyldiiminobis(1,3-dialkylimidazolidin-2-ones)[1] or 6,8-dialkyl-3-thia-2,4,6,8-tetraazabicyclo-[3.3.0]octan-7-one 3,3-dioxides,[2] and the condensation with 1,3-dimethylsulfamide, in 2,4,6,8-tetraalkyl-3-thia-2,4,6,8-tetraazabicyclo[3.3.0]octan-7-one 3,3-dioxides.[2] In the latter case, 2,4-dimethyl-6,8-diethyl-3-thia-2,4,6,8-tetraazabicyclo[3.3.0]-octan-7-one 3,3-dioxide **2** was formed in 8% yield. Other sulfamides such as 1,3-diethylsulfamide did not react with **1**.

In this work, we examined the condensation of 1,3-diethyl-4,5-dihydroxyimidazolidin-2-one **1a** with 1,3-dimethylsulfamide at a high pressure,[†] which resulted in bicyclic compound **2** and *N*-(1,3-diethyl-5-hydroxy-2-oxo-4-imidazolidinyl)-*N*,*N*′-dimethylsulfamide **3** (Scheme 1).



Scheme 1 Reagents and conditions are specified in Table 1.

The reaction conditions given in Table 1 (except for nos. 1, 5 and 8) correspond to the liquid–solid phase transition[3] of the solvent; this phase transition considerably accelerates a number of organic reactions.[4] It can be seen that maximum yields of bicyclic product **2** were observed in acetone and acetic acid at 1000 MPa (nos. 3 and 4). A comparison between experiment nos. 5 and 6 indicates that under conditions of the repeatedly

Table 1 Reaction conditions and product yields.

No.	*t*/h	pH or acid added	*T*/°C	*p*/MPa	Solvent	Yield (%)		Note
						2	**3**	
1	16	1–2	12	1000	H_2O	2	—	
2	16		12	1000	AcOH	5	traces	
3	5		80	1000	AcOH	8	traces	traces of **4**[a]
4	16	1 drop of conc. HCl	12	1000	Me_2CO	12	2	traces of **4**
5	4.5	2 drops of AcOH	80	1000	Me_2CO	—	4	traces of **4**
6	4.5[b]	2 drops of AcOH	19	1000	Me_2CO	traces	33.5	
7	5	2 drops of AcOH	80	1000	dioxane	traces	11	
8	4.5	2 drops of AcOH	100	1000	dioxane	—	traces	**4**[c]
9	4.5[b]	2 drops of AcOH	40	700	dioxane	—	7.5	**4**

[a] 1,3-Diethyl-2,4-dioxoimidazolidine **4** was detected by TLC ($R_f = 0.69$ in chloroform–methanol, 9:1, visualisation by an alkaline solution of sodium nitroprusside). [b] The pressure was produced and released 5 min after; nine 10 min cycles were performed; then, the reaction system was held at the specified pressure for 3 h. [c] Dimethylsulfamide degradation or condensation products.

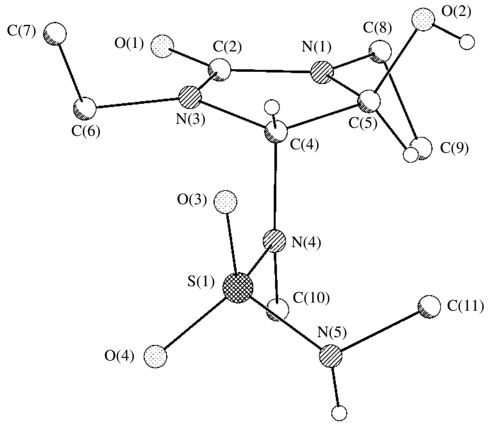


Figure 1 The general view of **3**. The methyl and ethyl hydrogen atoms are omitted for clarity. The important bond lengths (Å): S(1)–O(3) 1.431(2), S(1)–O(4) 1.435(2), S(1)–N(5) 1.620(2), S(1)–N(4) 1.643(2), O(1)–C(2) 1.240(3), N(3)–C(2) 1.371(3), N(3)–C(4) 1.449(3), N(3)–C(6) 1.460(3), O(2)–C(5) 1.411(3), C(2)–N(1) 1.355(3), N(1)–C(5) 1.441(3), N(1)–C(8) 1.459(3), N(4)–C(4) 1.460(3), N(4)–C(10) 1.472(3), N(5)–C(11) 1.466(3); bond angles (°): O(3)–S(1)–O(4) 120.3(1), O(3)–S(1)–N(5) 108.4(1), O(4)–S(1)–N(5) 105.9(1), O(3)–S(1)–N(4) 105.7(1), O(4)–S(1)–N(4) 108.8(1), N(5)–S(1)–N(4) 107.2(1), C(2)–N(3)–C(4) 111.0(2), O(1)–C(2)–N(1) 125.0(2), O(1)–C(2)–N(3) 126.1(2), N(1)–C(2)–N(3) 108.9(2), C(2)–N(1)–C(5) 112.9(2), C(4)–N(4)–C(10) 118.2(2), C(4)–N(4)–S(1) 121.6(1), C(10)–N(4)–S(1) 118.0(2), N(1)–C(5)–C(4) 102.4(2), C(11)–N(5)–S(1) 117.8(2), N(3)–C(4)–N(4) 112.9(2).

[†] High-pressure experiments were performed on a plunger-cylinder unit in 1.6 cm^3 Teflon ampoules. The concentrations of 1,3-diethyl-4,5-dihydroxyimidazolidin-2-one **1a** and 1,3-dimethylsulfamide were 1.26 mmol ml^{-1} for each reactant. ^{1}H NMR spectra were measured on a Bruker AM 300 spectrometer. Chemical shifts were measured with reference to residual protons of the [$^2H_6$]DMSO solvent (δ 2.50 ppm).

2: yield 12%, the properties are consistent with published data.[2]

Racemate (4*S*,5*S*; 4*R*,5*R*) **3**: yield 33.5%, mp 149–151 °C. ^{1}H NMR ([$^2H_6$]DMSO) δ: 1.02 (t, 3H, Me, *J* 7.15 Hz), 1.05 (t, 3H, Me, *J* 7.15 Hz), 2.41 (s, 3H, NMe), 2.48 (s, 3H, NMe), 2.81–2.95 (m, 1H, NCH_2), 2.98–3.12 (m, 1H, NCH_2), 3.21–3.33 (m, 1H, NCH_2), 3.33–3.45 (m, 1H, NCH_2), 4.87 (d, 1H, CH, *J* 6.60 Hz), 4.99 (s, 1H, CH), 6.44 (d, 1H, OH, *J* 7.15 Hz), 7.31 (d, 1H, NH, *J* 4.95).

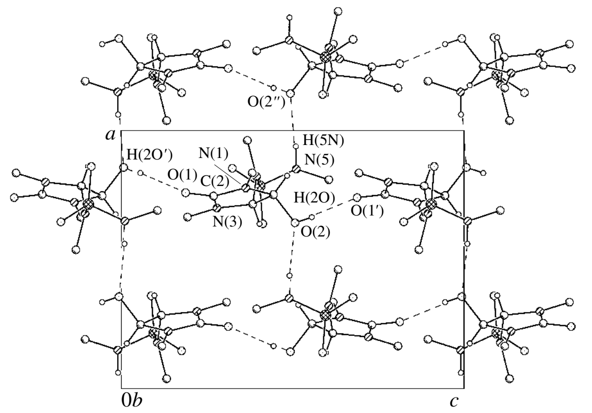


Figure 2 The formation of a three-dimensional H-bonded network in **3**. The ethyl groups are omitted for clarity. The parameters of the H-bonds: O(2)–H(2O)···O(1′) (–0.5 + *x*, –*y*, 0.5 + *z*) [O(2)···O(1′) 2.638(2) Å, H(2O)···O(1′) 1.79 Å, O(2)–H(2O)–O(1′) 174°]; N(5)–H(5N)···O(2″) (0.5 + *x*, –0.5 – *y*, 1 – *z*) [N(5)···O(2″) 2.029(2) Å, H(5N)···O(2″) 2.03 Å, N(5)–H(5N)–O(2″) 175°].

performed phase transition the yield of product **3** increased by a factor higher than eight, although the temperature was decreased by a factor of four. An increase in the temperature up to 80–100 °C resulted in a considerable decrease in the yields of compounds **2** and **3** in a liquid phase (experiment nos. 5 and 8). Thus, the experimental data obtained at high pressures demonstrated that bicyclic product **2** was formed under phase transitions of the solvents (acetic acid, acetone and dioxane). Under these conditions, probable intermediate **3** can be isolated in considerable amounts.

To study the stereochemistry of compound **3**, a single crystal of **3** obtained by crystallisation from acetone was examined by X-ray diffraction analysis.‡ It was found that, as in previously studied 4,5-dihydroxyimidazolidin-2-ones,[5,6] substituents at C(4) and C(5) atoms occupy *trans* positions [the N(4)–C(5)–C(4)–O(2) torsion angle is 130.2°], and hence only two enantiomers can exist (Figure 1). Note that the crystallisation of **3** results in the spontaneous resolution of enantiomers (space group $P2_12_12_1$). Thus, the above synthetic procedure provides an opportunity to prepare enantiomerically pure crystals of this compound. It was found that the examined single crystal of **3** exhibited the 4*S*, 5*S* absolute configuration.

An imidazolidine ring is characterised by a flat chair conformation with the C(4) atom shifted by 0.17 Å. An analysis of the molecular geometry of **3** showed that the N(3)–C(2) bond [1.371(3) Å] in an imidazolidine ring is somewhat longer than the N(1)–C(2) bond [1.355(3) Å]; the sums of valence angles at N(3) and N(1) atoms are equal to 359.4(2) and 360.0(2)°, respectively. It is likely that this elongation of the N(3)–C(2) bond resulted from the participation of the O(1) atom in the formation of an intermolecular hydrogen bond [O···O 2.638(2) Å] with the hydroxyl group (Figure 2). This hydrogen bond can decrease a contribution from the lone electron pair of the O(1) atom in the pseudo-*cis* position to the N(3)–C(2) bond [the pseudo-torsion angle N(3)–C(2)–O(1)–H(2O′) is 46°].

In contrast to N(5), the N(4) atom is flat [the sums of the valence angles at N(4) and N(5) are 357.8(2) and 347.1(2)°, respectively]. It is likely that the observed flattening of the N(4) atom results from the conjugation of the lone electron pair of the N(4) atom with the anti-periplanar S(1)–O(3) bond, as follows from the torsion angle C(10)–N(4)–S(1)–O(3) of 170.2°.

In addition to the above O–H···O bonds, intermolecular hydrogen bonds of the type N–H···O (Figure 2), which join the molecules in spirals oriented along the axes *c* and *a*, respectively, and result in a three-dimensional hydrogen-bonded framework, also occur in the crystal.

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‡ *Crystallographic data for* **3**: crystals of $C_9H_{20}N_4O_4S$ are orthorhombic at 110 K, space group $P2_12_12_1$, $a = 9.833(2)$ Å, $b = 10.073(1)$ Å, $c = 13.060(2)$ Å, $V = 1293.6(3)(2)$ Å^3, $Z = 4$, $M = 280.35$, $d_{\text{calc}} = 1.439$ g cm^{-3}, μ(MoKα) = 2.65 cm^{-1}, $F(000) = 600$. Intensities of 8476 reflections were measured with a Smart 1000 CCD diffractometer at 110 K [λ(MoKa) = 0.71072 Å, ω-scans with a step of 0.3° in ω and 10 s per frame exposure, $2\theta < 58°$], and 3325 independent reflections ($R_{\text{int}} = 0.0319$) were used in the further refinement. The absorption correction was carried out semi-empirically from equivalents using the Sadabs program. The structure was solved by a direct method and refined by the full-matrix least-squares technique against F^2 in the anisotropic–isotropic approximation. Hydrogen atoms were located from the Fourier synthesis and refined in the isotropic approximation. The absolute configuration of the C(4) and C(5) atoms in **3** was confirmed by estimating the Flack absolute parameter, which, in the case of *S* configuration for both atoms, has a value close to zero with rather small e.s.d. 0.00(9). The refinement converged to $wR_2 = 0.1253$ and GOF = 1.000 for all independent reflections [$R_1 = 0.0500$ was calculated against F for 2742 observed reflections with $I > 2\sigma(I)$]. The number of the refined parameters was 244 (the ratio of the refined parameters for observed reflections was more than 11). All calculations were performed using the SHELXTL PLUS 5.0 program on IBM PC AT. Atomic coordinates, bond lengths, bond angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). For details, see ‘Notice to Authors’, *Mendeleev Commun.*, Issue 1, 2001. Any request to the CCDC for data should quote the full literature citation and the reference number 1135/84.