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[4,5]-Bicyclic sydnone imines

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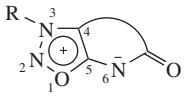
Lithiation of N^6-(α-haloacyl)-3-isopropylsydnone imines at 4-position followed by treatment with sulfur affords the 4-lithiosulfanyl derivatives whose intramolecular cyclization leads to [4,5]-bicyclic sydnone imines.

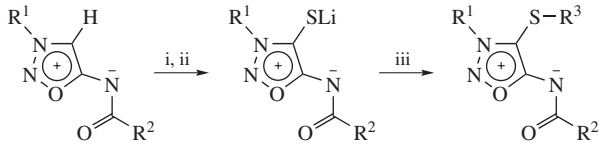
Sydnone imines[1,2] are the most well-studied representatives of mesoionic heterocyclic compounds. They show a broad spectrum of biological activity; sydnone imines were found to be effective exogenous donors of nitrogen oxide (NO).[1–3] However, only few polycyclic representatives condensed with a 3,4-edge of a ring were reported.[4–6]

The purpose of this study was working out a new synthetic way for bicyclic sydnone imines **1** condensed at 4,5-edge.



1

Earlier we showed that 4-lithiated sydnone imines easily reacted with sulfur to form the corresponding lithium thiolates **2**.[7] The *in situ* treatment of these thiolates with alkyl halides gives the corresponding sulfides **3** (Scheme 1).



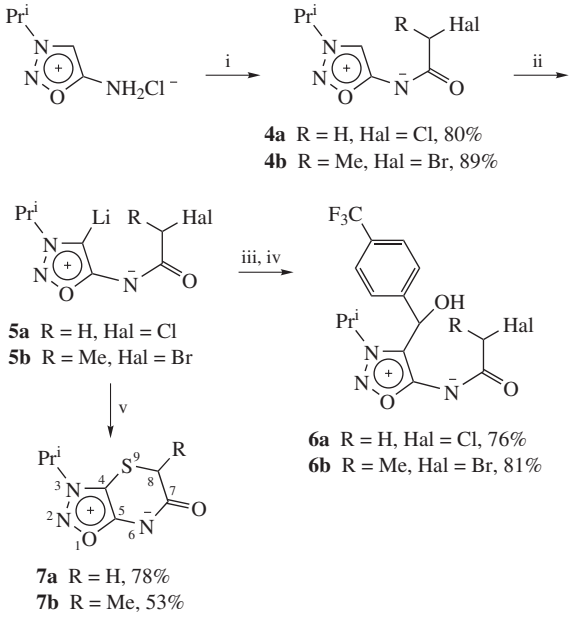
2 **3**

Scheme 1 *Reagents and conditions*: i, BuLi, THF, –90 °C, 30 min; ii, S_8, THF, –90 → +20 °C, 30 min; iii, R^3X, THF, 20 °C, 2–24 h.

We assumed that intramolecular nucleophilic substitution with the formation of a bicyclic product would be possible by using a sydnone imine with halogen atom at α-position of N^6-acyl group. The required N^6-α-halogenacyl derivatives **4a**,**b** were obtained by acylation of sydnone imine hydrochlorides with α-haloacyl chlorides (Scheme 2).

Lithiation of compounds **4a**,**b** having active halogen atom with BuLi to afford derivatives **5a**,**b** proceeded cleanly (Scheme 2). This was proved by treatment of organolithium compounds **5a**,**b** with 4-trifluoromethylbenzaldehyde, which gave the corresponding secondary alcohols in high yields.

Treatment of lithium derivatives **5a**,**b** with elementary sulfur led to lithium thiolates which spontaneously cyclized into bicyclic sydnone imines **7a**,**b**† at room temperature (see Scheme 2).



4a R = H, Hal = Cl, 80%
4b R = Me, Hal = Br, 89%

5a R = H, Hal = Cl
5b R = Me, Hal = Br

6a R = H, Hal = Cl, 76%
6b R = Me, Hal = Br, 81%

7a R = H, 78%
7b R = Me, 53%

Scheme 2 *Reagents and conditions*: i, RCH(Hal)C(O)Cl, Et_3N, CH_2Cl_2, –30 °C, 60 min; ii, BuLi, THF, –90 °C, 30 min; iii, 4-$CF_3C_6H_4CHO$, THF, –90 → +20 °C, 30 min; iv, H^+; v, S_8, THF, –90 → +20 °C, 30 min.

† *Standard procedure. n*-Butyllithium solution in hexane (2.1 mmol) was added to sydnone imine (2.0 mmol) in dry THF (50 ml) at –90 °C. The solution was stirred at –90 °C for 30 min, then 2.2 mmol of powdered sulfur was added. The resulting mixture was stirred at –90 °C for 15 min, heated up at a bath to room temperature. The mixture was stirred for additional 4 h to complete the reaction (TLC control) and quenched with water (1 ml). The solvent was evaporated under reduced pressure, the residue was dissolved in dichloromethane (50 ml) and the solution was filtered through a layer of Al_2O_3. The solvent was evaporated, the residue was purified by chromatography (column with SiO_2, eluent chloroform–ethyl acetate, 5:1). The product was crystallized from isopropyl alcohol–hexane mixture.

For **7a**: yield 78%, mp 125–127 °C. IR (KBr pellet, ν/cm^{-1}): 2922 (m), 2853 (m), 1653 (s), 1572 (vs), 1458 (vs), 1377 (m), 1343 (w), 1259 (w), 1188 (vw), 1172 (vw), 1128 (w), 1101 (vw), 1066 (vw), 1050 (vw). ^{1}H NMR ($CDCl_3$) δ: 1.44 (d, 3H, CH*Me*, J_{AB} 6.83 Hz), 1.64 (d, 6H, *Me*$_2$CH, J_{AB} 6.54 Hz), 3.56 (q, 1H, C*H*Me, J_{AB} 6.83 Hz), 4.75 (sp, 1H, Me$_2$C*H*, J_{AB} 6.54 Hz). ^{13}C NMR ($CDCl_3$) δ: 18.06, 20.47, 20.52, 36.59, 57.75, 102.56, 171.44, 172.10.

For **7b**: yield 53%, mp 115–117 °C. IR (KBr pellet, ν/cm^{-1}): 2928 (m), 2849 (m), 1650 (s), 1575 (vs), 1454 (s), 1375 (m), 1340 (w), 1255 (w), 1186 (w), 1170 (w), 1154 (vw), 1131 (w), 1105 (vw), 1083 (vw), 1068 (vw), 1048 (vw). ^{1}H NMR ($CDCl_3$) δ: 1.44 (d, 3H, CH*Me*, J_{AB} 6.83 Hz), 1.64 (d, 6H, *Me*$_2$CH, J_{AB} 6.54 Hz), 3.56 (q, 1H, C*H*Me, J_{AB} 6.83 Hz), 4.75 (sp, 1H, Me$_2$C*H*, J_{AB} 6.54 Hz). ^{13}C NMR ($CDCl_3$) δ: 18.06, 20.47, 20.52, 36.59, 57.75, 102.56, 171.44, 172.10.

For detailed synthetic procedures and characteristics of compounds **4a**,**b** and **6a**,**b**, see Online Supplementary Materials.

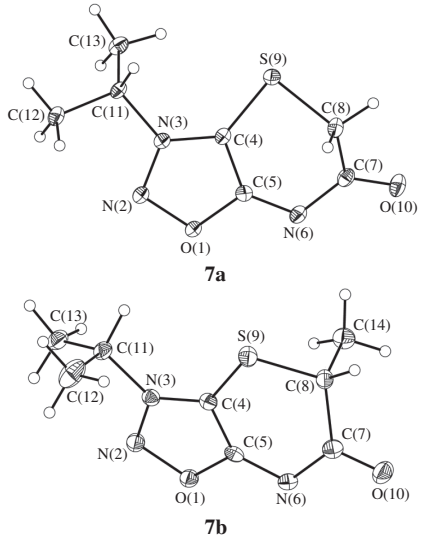


Figure 1 General view of sydnone imines **7a** and **7b** in representation of non-hydrogen atoms by thermal ellipsoids (p = 50%); the second independent molecule of product **7a** is not shown. Selected bond lengths (Å) for **7a** and **7b**, respectively, are: O(1)–N(2) 1.3975(13)/1.3918(15) and 1.3903(19), O(1)–C(5) 1.3674(14)/1.3668(16) and 1.366(2), N(2)–N(3) 1.3182(14)/1.3201(15) and 1.319(2), N(3)–C(4) 1.3397(14)/1.3403(15) and 1.331(2), C(4)–C(5) 1.3949(16)/1.3949(17) and 1.387(2), C(4)–S(9) 1.7230(12)/1.7231(13) and 1.7263(17), C(5)–N(6) 1.3053(15)/1.3055(17) and 1.305(2), N(6)–C(7) 1.3780(16)/1.3719(18) and 1.372(2), C(7)–O(10) 1.2201(15)/1.2253(15) and 1.217(2), C(7)–C(8) 1.5312(17)/1.5345(19) and 1.543(2), C(8)–S(9) 1.8271(12)/1.8282(13) and 1.8341(17).

The nomenclature of condensed cyclic compounds appears to be not quite convenient for such bicyclic sydnone imines because of the exocyclic nitrogen atom N^6, which is a part of the mesoionic fragment and the second cycle at the same time. We have suggested easier nomenclature (Scheme 2) by describing the second cycle as a linker between N^6 and C^4 positions of the mesoionic fragment. According to such nomenclature the mesoionic nature of these compounds is emphasized and usual numeration for sydnone imines is saved. So compound **7a** should be named as 3-isopropyl-7-oxo-9-thia[4,6-propano]sydnone imine, and **7b** as 3-isopropyl-8-methyl-7-oxo-9-thia[4,6-propano]sydnone imine.

The structures of these two bicyclic sydnone imines (**7a** and **7b**) were clarified by single-crystal X-ray diffraction analysis[‡] (Figure 1). According to it the molecular geometries of these compounds are very close: the largest difference in bond lengths between **7a** and **7b** is less than 0.01 Å. Geometrical parameters of mesoionic core are very similar to those of earlier described 3-isopropyl-4-methylsulfanyl-N^6-benzoylsydnone imine;[8] the largest difference of ~0.02 Å was observed for the bond C(4)–C(5) that belongs to only one (mesoionic) heterocyclic moiety. In all cases, mesoionic cycle is planar within 0.01 Å as expected. The second cycle adopts a distorted half chair conformation [the atom C(8) deviates by 0.60(1)–0.83(1) Å from the plane of the others having a mean deviation of 0.04(1)–0.06(1) Å]; note that the largest deviation of the atom C(8) was observed for the second independent molecule of the sydnone imine **7a**, which together with some minor discrepancies in positions of the methyl groups is the most pronounced difference between the two independent molecules in a crystal.

In conclusion, the study performed has extended the range of valuable and promising sydnone imines.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2014.11.027.

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‡ *Crystallographic data*.

Crystals of **7a** ($C_7H_9N_3O_2S$, M = 199.23) are triclinic, space group $P\bar{1}$, at 100 K: a = 9.1443(6), b = 9.6390(6) and c = 10.4539(6) Å, α = 87.4420(10)°, β = 74.0010(10)°, γ = 77.7110(10)°, V = 865.34(9) Å^3, Z = 4 (Z' = 2), d_{calc} = 1.529 g cm^{-3}, μ(MoKα) = 3.43 cm^{-1}, F(000) = 416.

Crystals of **7b** ($C_8H_{11}N_3O_2S$, M = 213.26) are orthorhombic, space group $P2_12_12_1$, at 100 K: a = 6.1696(6), b = 8.1555(8) and c = 19.6390(19) Å, V = 988.16(17) Å^3, Z = 4 (Z' = 1), d_{calc} = 1.433 g cm^{-3}, μ(MoKα) = = 3.05 cm^{-1}, F(000) = 448.

Intensities of 11083 and 6469 reflections for **7a** and **7b**, respectively, were measured with a BrukerAPEX2 DUO CCD diffractometer [λ(MoKα) = = 0.71072 Å, ω-scans, $2\theta < 60°$ and 58°]; 5039 and 2628 independent reflections [R_{int} = 0.0217 and 0.0234] were used in further refinement for **7a** and **7b**, respectively. The structures were solved by direct method and refined by the full-matrix least-squares technique against F^2 in the anisotropic–isotropic approximation. The H(C) atom positions were calculated, and they were refined in the isotropic approximation using a riding model. For **7a**, the refinement converged to wR_2 = 0.0873 and GOF = 1.008 for all the independent reflections [R_1 = 0.0325 was calculated against F for 4300 observed reflections with $I > 2\sigma(I)$]. For **7b**, the refinement converged to wR_2 = 0.0686 and GOF = 1.002 for all the independent reflections [R_1 = 0.0339 was calculated against F for 2502 observed reflections with $I > 2\sigma(I)$]. All calculations were performed using SHELXTL PLUS 5.0.[9]

CCDC 985517 and 985518 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk. For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2014.