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Hydrazinolysis of Dimethyl 2-Bromo-1-(thietan-3-yl)-1*H*-imidazole-4,5-dicarboxylates

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Abstract—Alkylation of dimethyl 2-bromo-1*H*-imidazole-4,5-dicarboxylate with 2-chloromethylthiirane gave dimethyl 2-bromo-1-(thietan-3-yl)-1*H*-imidazole-4,5-dicarboxylate which was oxidized to dimethyl 2-bromo-1-(1-oxo-λ^4-thietan-3-yl)- and 2-bromo-1-(1,1-dioxo-λ^6-thietan-3-yl)-1*H*-imidazole-4,5-dicarboxylates. Reactions of the resulting thietanyl-substituted imidazoledicarboxylates with hydrazine afforded 2-bromo-1-(thietan-3-yl)-, 2-bromo-1-(1-oxo-λ^4-thietan-3-yl)-, and 2-bromo-1-(1,1-dioxo-λ^6-thietan-3-yl)-1*H*-imidazole-4,5-dicarbohydrazides and the corresponding 1-(thietanyl)-substituted 2-bromoimidazo[4,5-*d*]pyridazine-4,7(5*H*,6*H*)-diones.

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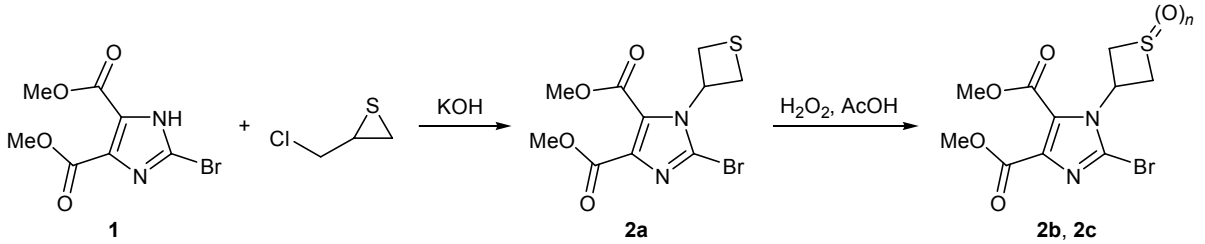
Imidazole-4,5-dicarboxylic acid derivatives affect glycolysis parameters [1] and activity of *N*-methyl-D-aspartic acid receptors [2] and were patented as antiviral agents [3] and protease inhibitors [4]. 1-Methyl-1*H*-imidazole-4,5-dicarbohydrazide was reported to inhibit monoamine oxidase [5], while imidazo[4,5-*d*]-pyridazine-4,7(5*H*,6*H*)-diones that may be regarded as cyclic imidazole-4,5-dicarboxylic acid hydrazides inhibit dipeptidyl peptidase IV and were proposed for the treatment of type II diabetes [6].

With the goal of obtaining new potential biologically active compounds in the present work we studied hydrazinolysis of dimethyl 2-bromo-1-(thietan-3-yl)-1*H*-imidazole-4,5-dicarboxylates. Dimethyl 2-bromo-1-(thietan-3-yl)-1*H*-imidazole-4,5-dicarboxylate (**2a**) was synthesized by alkylation of dimethyl 2-bromo-1*H*-imidazole-4,5-dicarboxylate (**1**) with 2-chloromethylthiirane in aqueous medium in the presence of potassium hydroxide, which was accompanied by thiirane–thietane rearrangement [7] (Scheme 1). The yield of **2a** was as poor as 16%, and we failed to improve it by varying the reaction temperature toward higher or lower values. Change of the solvent nature and the use of phase-transfer catalysis inhibited the thiirane–thietane rearrangement. It should be noted that about 50% of initial compound **1** was recovered from the reaction mixture.

By oxidation of ester **2a** with 2 equiv of hydrogen peroxide in glacial acetic acid we obtained sulfoxide **2b**, and the reaction of **2a** with 5 equiv of hydrogen peroxide produced sulfone **2c** (Scheme 1); the yields of **2b** and **2c** were 80% and 85%, respectively.

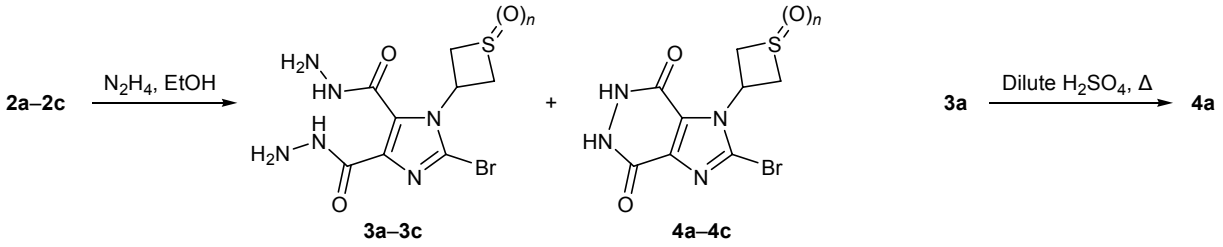
The ^{1}H NMR spectra of **2a**–**2c** characteristically displayed signals from protons in the thietanyl substituents [8] and singlets from methoxy protons. Ester **2b** was formed as a mixture of *cis* and *trans* isomers with respect to the thietane 1-oxide ring. Signals from two protons of the CH_2SCH_2 fragment of the *cis* isomer

Scheme 1.



n = 1 (**b**), 2 (**c**).

Scheme 2.



n = 0 (**a**), 1 (**b**), 2 (**c**).

appeared at δ 3.47–3.52 ppm, and signals from the two other protons were overlapped by the signal from both SCH_2 groups of the *trans* isomer at δ 4.14–4.20 ppm. The NCH proton of the *cis* isomer (major) resonated at δ 6.54–6.61 ppm, and the corresponding signal of the minor *trans* isomer was located at δ 5.08–5.16 ppm. The ratio of the *cis* and *trans* isomers was estimated at 6:1 from the intensities of the methyl proton singlets.

The ^{13}C NMR spectra of esters **2a**–**2c** contained signals from carbon atoms in the imidazole ring and ester groups. Carbon signals of the thietane ring in **2a** were observed at δ_C 33.70 (SCH_2) and 53.40 ppm (NCH); the thietane dioxide ring in **2c** gave signals at δ_C 70.14 (SCH_2) and 39.01 ppm (NCH). In the spectrum of **2b**, the *cis* isomer was characterized by signals of the thietane oxide ring at δ_C 54.50 (SCH_2) and 52.46 ppm (NCH), and signals of the *trans* isomer were located at δ_C 58.76 (SCH_2) and 41.69 ppm (NCH); these data were consistent with those reported in [8].

The structure of compounds **2a**–**2c** was also confirmed by IR spectra. Sulfoxide **2b** displayed an absorption band at 1060 cm^{-1} due to stretching vibrations of the S=O group, and in the IR spectrum of **2c** absorption bands at 1136 and 1324 cm^{-1} due to symmetric and antisymmetric stretching vibrations of the SO_2 group were present.

It is known that the reaction of dimethyl 1*H*-imidazole-4,5-dicarboxylate with hydrazine yields the corresponding dihydrazide [9]. As shown previously [10], dimethyl 1-methyl-1*H*-imidazole-4,5-dicarboxylate reacts with hydrazine to give a mixture of the dihydrazide and cyclic hydrazide, 1-methyl-1*H*-imidazo[4,5-*d*]pyridazine-4,7(5*H*,6*H*)-dione. By heating ester **2a** with hydrazine in boiling ethanol we obtained a mixture of dihydrazide **3a** and thietanyl-substituted imidazo[4,5-*d*]pyridazine-4,7(5*H*,6*H*)-dione **4a** (Scheme 2), which were separated due to their different solubilities in ethanol. The yields of **3a** and **4a** were 27% and 39%, respectively. Variation of the amounts of the reactants and reaction time neither improved the yield nor changed the product ratio. Cyclic hydrazide **4a** was also synthesized in 50% yield by heating dihydrazide **3a** in dilute sulfuric acid (Scheme 2; cf. [10]).

Esters **2b** and **2c** reacted with hydrazine in a similar way (Scheme 2). Dihydrazides **3b** and **3c** were isolated in 39 and 30% yield, respectively, by crystallization of the product mixture from water. The ability of dihydrazides **3a**–**3c** to undergo transformation into cyclic hydrazides **4a**–**4c** was utilized to isolate substituted imidazo[4,5-*d*]pyridazine-4,7(5*H*,6*H*)-diones **4b** and **4c**. The latter were obtained in 45 and 51% yield, respectively, by keeping the product mixtures in dilute mineral acids.

The ^1H NMR spectra of dihydrazides **3a**–**3c** contained signals from protons of the thietanyl substituent, a broadened singlet from NH_2 groups at δ 4.55–4.86 ppm, and two NH singlets at δ 9.80–9.93 and 11.11–11.54 ppm. Cyclic hydrazides **4a**–**4c** showed in the ^1H NMR spectra a broadened signal due to two NH protons in the region δ 11.40–12.40 ppm and signals of the thietanyl substituent. In the spectrum of **4b**, protons in the thietane oxide fragment of the *cis* isomer resonated at δ 3.45–3.50, 4.24–4.29 (CH_2SCH_2) and 6.36–6.43 ppm (NCH), and those of the *trans* isomer, at δ 4.14–4.16, 4.48–4.50 (CH_2SCH_2) and 5.13–5.23 ppm (NCH). The *cis*/*trans* ratio was estimated at 7:1 from the intensities of the NCH signals.

The structure of **3a**–**3c** and **4a**–**4c** was also confirmed by their IR spectra which contained absorption bands due to stretching vibrations of the S=O (**3b**, **4b**) and SO_2 groups (**3c**, **4c**), as well as broadened N–H stretching vibration bands in the regions 3100–3400 (**3a**–**3c**) and 2700–3300 cm^{-1} (**4a**–**4c**).

EXPERIMENTAL

The ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance III spectrometer at 500 and 125 MHz, respectively; the chemical shifts were determined

relative to the residual proton and carbon signals of the deuterated solvents. The IR spectra were recorded in KBr on an Infralyum FT-02 instrument. Analytical TLC was performed on Sorbfil plates using butan-1-ol–acetic acid–water (4 : 1 : 2, **2a**–**2c**) and dioxane–ethanol (1 : 1; **3a**–**3c**, **4a**–**4c**) as eluents; development with iodine vapor. Initial ester **1** was synthesized according to the procedure described in [11].

Dimethyl 2-bromo-1-(thietan-3-yl)-1*H*-imidazole-4,5-dicarboxylate (2a). 2-Chloromethylthiirane, 0.85 g (7.8 mmol), was added to a solution of 0.44 g (7.8 mmol) of potassium hydroxide and 1.7 g (6.5 mmol) of ester **1** in 30 mL of water, and the mixture was stirred for 30 min at 55–60°C. The mixture was cooled, and the precipitate was filtered off and washed with a solution of KOH and water. Yield 0.36 g (16%), mp 156–158°C (from EtOH), R_f 0.70. IR spectrum, ν, cm^{-1}: 1729 (C=O), 1560 (C=N). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 3.31–3.40 m (2H, (CH_2SCH_2), 3.86 s and 3.99 s (3H each, OCH_3), 4.12–4.21 m (2H, CH_2SCH_2), 5.88–6.02 m (1H, NCH). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 33.70 (SCH_2), 52.35 and 52.75 (OCH_3), 53.40 (NCH), 122.14 (C^2), 128.58 (C^4, C^5), 160.41 and 161.35 (C=O). Found, %: C 35.91; H 3.24; N 8.41. $C_{10}H_{11}BrN_2O_4S$. Calculated, %: C 35.82; H 3.28; N 8.36.

Dimethyl 2-bromo-1-(1-oxo-λ⁴-thietan- 3-yl)-1*H*-imidazole-4,5-dicarboxylate (2b). A solution of 1.0 g (3 mmol) of ester **2a** and 0.55 g (6 mmol) of a 37% solution of hydrogen peroxide in 50 mL of glacial acetic acid was stirred for 1.5 h at 30°C. The solution was cooled to 10°C, neutralized with concentrated aqueous ammonia to pH 7–8, and extracted with chloroform. The extract was evaporated, the residue was ground with diethyl ether, and the precipitate was filtered off and washed with diethyl ether. Yield 0.85 g (80%), mp 132–134°C (from hexane–benzene), R_f 0.50. IR spectrum, ν, cm^{-1}: 1724 (C=O), 1544 (C=N), 1060 (S=O). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 3.47–3.52 m (2H, CH_2SCH_2, *cis*), 3.90 s and 3.95 s (3H each, OCH_3, *cis*), 3.89 s and 4.00 s (3H each, OCH_3, *trans*), 4.14–4.20 m (6H, CH_2SCH_2, *cis*, *trans*), 5.08–5.16 m (1H, NCH, *trans*), 6.54–6.61 m (1H, NCH, *cis*). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 41.69 (NCH, *trans*), 52.46 (NCH, *cis*), 52.78 and 53.55 (OCH_3), 54.50 (SCH_2, *cis*), 58.76 (SCH_2, *trans*), 124.33 (C^2), 126.61 (C^5), 138.54 (C^4), 160.40 and 161.70 (C=O). Found, %: C 34.28; H 3.09; N 8.09. $C_{10}H_{11}BrN_2O_5S$. Calculated, %: C 34.19; H 3.13; N 7.98.

Dimethyl 2-bromo-1-(1,1-dioxo-λ⁶-thietan-3-yl)-1*H*-imidazole-4,5-dicarboxylate (2c). A solution of 1.0 g (3 mmol) of ester **2a** and 1.38 g (15 mmol) of a 37% solution of hydrogen peroxide in 20 mL of glacial acetic acid was heated for 2 h at 60–70°C. The mixture was cooled to 10°C and neutralized with concentrated aqueous ammonia to pH 7–8. The precipitate was filtered off and washed with water. Yield 0.93 g (85%), mp 180–182°C (from EtOH), R_f 0.56. IR spectrum, ν, cm^{-1}: 1732 (C=O), 1551 (C=N), 1324, 1136 (SO_2). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 3.84 s and 3.94 s (3H each, OCH_3), 4.44–4.49 m and 4.94–4.99 m (2H each, CH_2SCH_2), 5.64–5.71 m (1H, NCH). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 39.01 (NCH), 52.82 and 53.93 (OCH_3), 70.14 (SCH_2), 124.07 (C^2), 127.51 (C^5), 137.72 (C^4), 160.02 and 161.37 (C=O). Found, %: C 32.87; H 2.96; N 7.56. $C_{10}H_{11}BrN_2O_6S$. Calculated, %: C 32.70; H 3.00; N 7.63.

2-Bromo-1-(thietan-3-yl)-1*H*-imidazole-4,5-dicarbohydrazide (3a) and 2-bromo-1-(thietan-3-yl)-imidazo[4,5-*d*]pyridazine-4,7(5*H*,6*H*)-dione (4a). *a*. A solution of 1.0 g (3.0 mmol) of ester **2a** and 1.75 g (30.0 mmol) of a 55% solution of hydrazine in 50 mL of ethanol was heated for 2 h under reflux. The mixture was left to stand for 24 h at 8–10°C, and the precipitate was filtered off and washed with ethanol. The product mixture, 0.75 g, was treated with 50 mL of ethanol, the mixture was heated under reflux, and the undissolved material (compound **4a**) was filtered off and washed with ethanol. The filtrate was cooled, and the precipitate of **3a** was filtered off and washed with ethanol.

Compound **3a**. Yield 0.27 g (27%), mp 205–207°C (from EtOH), R_f 0.54. IR spectrum, ν, cm^{-1}: 3400–3100 (NH), 1659 (C=O), 1575 (C=N). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 3.32–3.36 m and 4.22–4.26 m (2H each, CH_2SCH_2), 6.26–6.30 m (1H, NCH), 4.55 s and 4.69 s (2H each, NH_2) 9.80 s and 11.11 s (1H each, NH). Found, %: C 28.71; H 3.24; N 24.77. $C_8H_{11}BrN_6O_2S$. Calculated, %: C 28.66; H 3.28; N 25.07.

Compound **4a**. Yield 0.35 g (39%), mp >250°C (decomp.), R_f 0.36. IR spectrum, ν, cm^{-1}: 3300–2700 (NH), 1659 (C=O), 1567 (C=N). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 3.32–3.37 m and 4.32–4.36 m (2H each, CH_2SCH_2), 6.05–6.12 m (1H, NCH), 11.80 br.s (2H, NH). Found, %: C 31.73; H 2.29; N 18.56. $C_8H_7BrN_4O_2S$. Calculated, %: C 31.68; H 2.31; N 18.48.

b. A solution of 0.27 g (0.8 mmol) of compound **IIIa** in 10 mL of 10% sulfuric acid was heated for 15 min under reflux. The mixture was cooled, and the

precipitate was filtered off and washed with water. Yield 0.12 g (50%).

2-Bromo-1-(1-oxo-λ^4-thietan-3-yl)-1*H*-imidazole-4,5-dicarbohydrazide (3b). A solution of 1.0 g (2.8 mmol) of ester **2b** and 1.6 g (28 mmol) of a 55% solution of hydrazine in 30 mL of ethanol was heated for 2 h under reflux. The mixture was cooled, and the precipitate was filtered off and washed with ethanol. The resulting mixture of compounds **3b** and **4b**, 0.83 g, was treated with 5 mL of water, the mixture was heated under reflux, the solution was cooled, and the precipitate of **3b** was filtered off and washed with ethanol. Yield 0.38 g (39%), mp 202–203°C (from water), R_f 0.40. IR spectrum, ν, cm^{-1}: 3400–3100 (NH), 1641 (C=O), 1573 (C=N), 1032 (S=O). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 3.39–3.45 m and 4.16–4.20 m (2H each, CH_2SCH_2), 6.45–6.52 m (1H, NCH), 4.67 br.s (4H, NH_2), 9.89 s and 11.54 s (1H each, NH). Found, %: C 27.55; H 3.16; N 24.16. $C_8H_{11}BrN_6O_3S$. Calculated, %: C 27.35; H 3.13; N 23.93.

2-Bromo-1-(1-oxo-λ^4-thietan-3-yl)-1*H*-imidazo[4,5-*d*]pyridazine-4,7(5*H*,6*H*)-dione (4b). A solution of 0.83 g of mixture **3b**/**4b** (isolated as described above in the synthesis of **3b**) in 20 mL of 10% aqueous HCl was left to stand for 24 h at room temperature. The precipitate was filtered off and washed with water and ethanol. Yield 0.4 g (45%), mp >250°C (decomp.), R_f 0.12. IR spectrum, ν, cm^{-1}: 3300–2700 (NH), 1667 (C=O), 1570 (C=N), 1020 (S=O). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 3.45–3.50 m (2H, CH_2SCH_2, *cis*), 4.14–4.16 m (2H, CH_2SCH_2, *trans*), 4.24–4.29 m (2H, CH_2SCH_2, *cis*), 4.48–4.50 m (2H, CH_2SCH_2, *trans*), 5.13–5.23 m (1H, NCH, *trans*), 6.36–6.43 m (1H, NCH, *cis*), 11.40–12.40 br.s (2H, NH). Found, %: C 30.21; H 2.21; N 17.67. $C_8H_7BrN_4O_3S$. Calculated, %: C 30.09; H 2.19; N 17.55.

2-Bromo-1-(1,1-dioxo-λ^6-thietan-3-yl)-1*H*-imidazole-4,5-dicarbohydrazide (3c). A solution of 1.0 g (2.7 mmol) of ester **2c** and 3.14 g (54 mmol) of a 55% solution of hydrazine in 60 mL of ethanol was heated for 2 h under reflux and was then left to stand for 24 h at 8–10°C. The precipitate was filtered off and washed with ethanol. The resulting mixture of compounds **3c** and **4c**, 0.57 g, was dissolved in 40 mL of boiling water, the solution was cooled, and the precipitate of **3c** was filtered off and washed with ethanol. Yield 0.3 g (30%), mp 218–220°C (from water), R_f 0.48. IR spectrum, ν, cm^{-1}: 3400–3100 (NH), 1669 (C=O), 1553 (C=N), 1325, 1148 (SO_2). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 4.56–4.61 m and 5.08–5.13 m (2H each, CH_2SCH_2), 5.84–5.91 m (1H, NCH), 4.86 br.s (4H, NH_2), 9.93 s and 11.47 s (1H each, NH). Found, %: C 26.37; H 2.97; N 23.17. $C_8H_{11}BrN_6O_4S$. Calculated, %: C 26.16; H 3.00; N 22.89.

2-Bromo-1-(1,1-dioxo-λ^6-thietan-3-yl)-1*H*-imidazo[4,5-*d*]pyridazine-4,7(5*H*,6*H*)-dione (4c). A solution of 0.57 g of mixture **3c**/**4c** (isolated as described above in the synthesis of **3c**) in 25 mL of 10% H_2SO_4 was heated for 15 min under reflux. After cooling, the precipitate was filtered off and washed with water and ethanol. Yield 0.46 g (51%), mp >290°C (decomp.), R_f 0.26. IR spectrum, ν, cm^{-1}: 3300–2700 (NH), 1659 (C=O), 1560 (C=N), 1332, 1154 (SO_2). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 4.56–4.60 m and 5.18–5.23 m (2H each, CH_2SCH_2), 5.54–5.61 m (1H, NCH), 11.40–12.40 br.s (2H, NH). Found, %: C 28.77; H 2.11; N 16.88. $C_8H_7BrN_4O_4S$. Calculated, %: C 28.66; H 2.09; N 16.72.

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