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Mendeleev Commun., 1993, **3**(**4**), 151–153

Mendeleev Communications

Intramolecular Cyclization in 4-Azido-5-ethoxycarbonyl-2-(2′-hydroxyphenyl)pyrimidine: Synthesis and Properties of 3-Ethoxy-6-(2′-hydroxyphenyl)isoxazolo[3,4-*d*]pyrimidine

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The title azide in the solid state or in DMSO solution cyclizes thermally to isoxazolo[3,4-*d*]pyrimidine **2**, which can either further rearrange to isoxazolone **3** or be transformed to hydroxylamine **5** or sulfoximine **7** on interaction with water or upon dilution of its DMSO solution by water, respectively; the tetrazolo tautomer **1T** yields the acrylate **6**.

Thermal intramolecular cyclizations of aromatic and heteroaromatic azides with α,β-unsaturated *ortho* substituents (NO_2, N=NPh, COMe, COPh, HCO, *etc.*) are the subjects of considerable synthetic and mechanistic interest.[1,2] In contrast, *o*-azidobenzoates on thermolysis fail to produce 3-alkoxy-2,1-benzisoxazoles.[3] There is also no information, to our knowledge, on annelation of the 3-alkoxy-2,1-isoxazole cycle by this method and on heteroaromatic rings.[4] However, in the *p*-benzoquinone series, thermal azide cyclizations onto an adjacent ester grouping are known.[5] Recently[6] we have reported an unexpected dark solid-phase transformation of azide **1A** to hydroxylamine **5** at room temperature (r.t.) and postulated that this conversion involves the initial formation of isoxazole **2** as an intermediate.

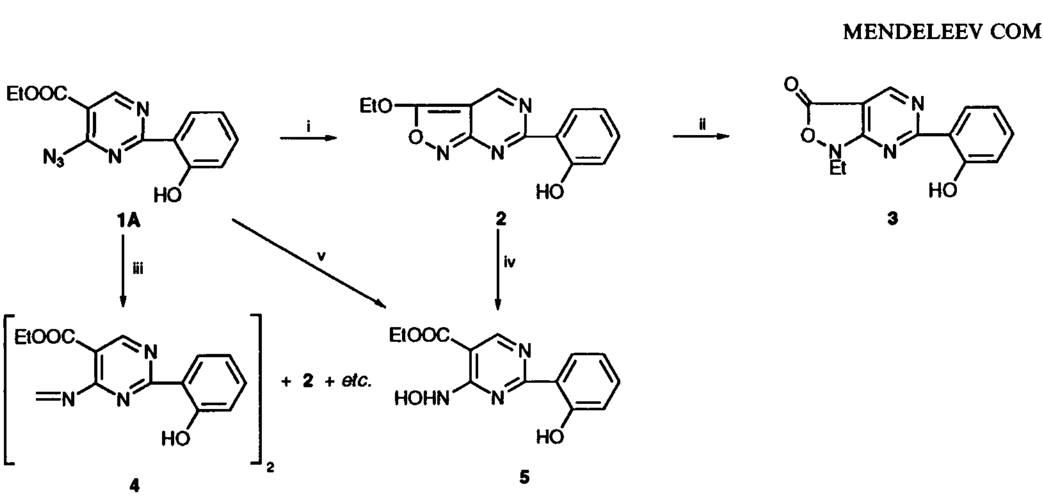
We now report the preparation of isoxazole **2** by thermolysis of *o*-azidoester **1A** and some results of investigations on the thermal behaviour of **1A** and **2** in both the solid state and solution.

On heating azide **1A** in the solid state, isoxazole **2**[†] was isolated from the reaction mixture by column chromatography (SiO_2 40/100, eluent $CHCl_3$) and identified by spectral evidence (Scheme 1). More prolonged heating of **1A** led to formation of isoxazolone **3**[‡], *i.e.* thermal isomerization **2**→**3** was observed in the solid state.[7] On short-term heating in a melt, azide **1A** undergoes partial decomposition with formation of isoxazole **2**, azopyrimidine **4**[§], and other unidentified products (Scheme 1).

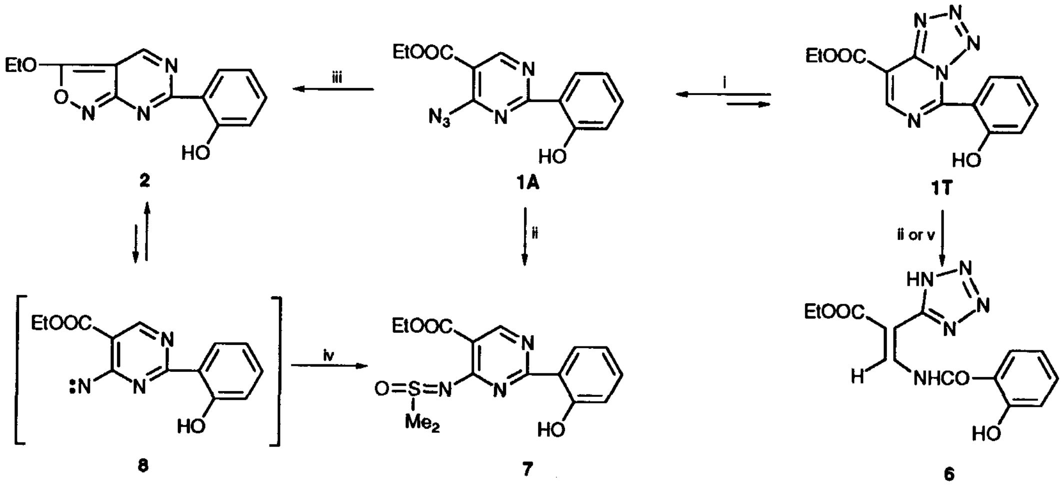
[†] **2**: yellow crystals m.p. 153–155 °C; ^{1}H NMR (400.13 MHz, [^{2}H$_6$]DMSO, 30 °C) δ 1.31 (t. 3H, Me), 4.27 (q, 2H CH_2), 6.94 (dm, 1H, 3′-H), 6.97 (m, 1H, 5′-H), 7.42 (m, 1H, 4′-H), 8.25 (dd, 1h, 6′-H), 8.80 (s, 1H, 4-H), 10.87 (s, 1H, 2′-OH); ^{13}C NMR (100.61 MHz, [^{2}H$_6$]DMSO, 30 °C) δ 13.99 (CH_3), 60.58 (CH_2, $^{1}J_{CH}$ 148.1 Hz), 113.15 (C-3a, $^{2}J_{C^{3a}-H^{4}}$ 5.5 Hz), 117.70 (C-3′), 117.99 (C-1′), 118.91 (C–5′), 129.01 (C–6′), 133.54 (C–4′), 156.44 (C-4, $^{1}J_{CH}$ 184.1 Hz), 160.52 (C-2′), 162.49 (C-7a, $^{3}J_{C^{7a}-H^{4}}$ 6.1 Hz), 163.84 (C-3, $^{3}J_{C^{3}-H^{4}}$ 3.0 Hz, $^{3}J_{C^{3}-H(CH_2)}$ 3.0 Hz), 164.05 (C-6, $^{3}J_{C^{6}-H^{4}}$ 11.4, $^{3}J_{C^{6}-H^{6'}}$ 4.3 Hz); HRMS *m*/*z* (M^+) (Found: 257.0796. Calc. for $C_{13}H_{11}N_3O_3$: 257.0800).

[‡] **3** m.p. 177–179 °C; ^{1}H NMR (400.13 MHz, $CDCl_3$, 27 °C) δ 1.41 (t, 3H, CH_3), 4.14 (q, 2H, CH_2), 6.95 (m, 1H, 5′-H), 7.01 (dd, 1H, 3′-H), 7.44 (m, 1H, 4′-H), 8.44 (dd, 1H, 6′-H), 8.98 (s, 1H, 4-H), 12.92 (s, 1H, 2′-OH); ^{13}C NMR (100.61 MHz, $CDCl_3$, 27 °C) δ 11.83 (CH_3), 45.39 (CH_2, $^{1}J_{CH}$ 141.6 Hz), 99.82 (C-3a, $^{2}J_{C^{3a}-H^{4}}$ 7.2 Hz), 117.61 (C-1′), 118.44 (C-3′), 119.30 (C-5′), 130.09 (C-6′), 135.23 (C-4′), 154.78 (C-4, $^{1}J_{CH}$ 188.7 Hz), 161.86 (C-2′), 162.48 (C-3, $^{3}J_{C^{3}-H^{4}}$ < 1.5 Hz), 165.72 (C-7a), 168.70 (C-6, $^{3}J_{C^{6}-H^{4}}$ 10.9, $^{3}J_{C^{6}-H^{6'}}$ 4.3 Hz); IR (KBr) ν/cm^{-1} 1772 (CO), 1601, 1560, 1491, 1468, 1421, 1356, 1317, 1298, 1202, 1151; HRMS *m*/*z* (M^+) (Found: 257.0808. Calc. for $C_{13}H_{11}N_3O_3$: 257.0800).

[§] **4** m.p. 192–194 °C; ^{1}H NMR (400.13 MHz, $CDCl_3$, 30 °C) δ 1.31 (t, 3H, Me), 4.42 (q, 2H, CH_2), 6.97 (m, 1H, 5′-H), 7.05 (dd, 1H, 3′-H), 7.45 (m, 1H, 4′-H), 8.55 (dd, 1H, 6′-H), 9.42 (s, 1H, 6-H), 12.38 (s, 1H, 2′-OH); ^{13}C NMR (100.61 MHz, $CDCl_3$, 30 °C) δ 14.06 (CH_3), 62.44 (CH_2, $^{1}J_{CH}$ 148.8 Hz), 114.68 (C-5, $^{2}J_{C^{5}-H^{6}}$ 6.0 Hz), 117.75 (C-1′), 118.39 (C-3′), 119.47 (C-5′), 130.31 (C-6′), 135.12 (C-4′), 159.97 (C-6, $^{1}J_{CH}$ 187.5 Hz), 161.47 (C-2′), 162.15 (COO, $^{3}J_{C-H^{6}}$ 3.0, $^{3}J_{C-H(CH_2)}$ 3.0 Hz), 167.59 (C-2, $^{3}J_{C^{2}-H^{6}}$ 11.3, $^{3}J_{C^{2}-H^{6'}}$ 4.1 Hz), 167.72 (C-4); IR (KBr) ν/cm^{-1} 3549, 3477, 3416, 2922, 1728(CO), 1618, 1591, 1579, 1535, 1431, 1279, 1194, 1163, 823, 733; HRMS *m*/*z* (M^+) (Found: 514.1604. Calc. for $C_{26}H_{22}N_6O_6$: 514.1601).



Scheme 1 *Reagents and conditions*: i, solid state, *ca.* 110 °C, 1 h, 65%; ii, (analogous to i); iii, liquid phase, *ca.* 130 °C, *ca.* 90 s; iv, H_2O, reflux, *ca.* 3 h, 100%; v, (analogous to iv).



Scheme 2 *Reagents and conditions*: i, see ref. 6; ii, solution DMSO–H_2O, *ca.* 110 °C, *ca.* 2 h; iii, dried DMSO, *ca.* 110 °C, *ca.* 1.5 h; iv, addition of DMSO solution of **2** in H_2O, r.t., *ca.* 5 min; v, undried DMSO, Na_2CO_3 (2 mol), *ca.* 100 °C, 1.5 h

On boiling the reaction mixture in water under heterogeneous conditions, both isoxazole **2** and azide **1A** are converted into hydroxylamine **5** (Scheme 1). Contrary to this, under homogeneous conditions in an H_2O–DMSO (dimethyl sulfoxide) solution the tautomeric mixture **1A**$\rightleftarrows$**1T** is transformed into the acrylate **6** (identical to that obtained in ref. 6), and sulfoximine **7**[¶] (Scheme 2) in the ratio 1:5, respectively (^{1}H NMR spectrum).

The unexpected formation of sulfoximine **7** instead of hydroxylamine **5** indicates that the reaction of isoxazole **2** with water is completely suppressed by the competing interaction of isoxazole **2** with DMSO, which is confirmed by the following experimental data. The thermolysis of azide **1A** in dry DMSO quantitatively gives **2** (^{1}H NMR spectrum). However, when this solution was poured into water at room temperature, sulfoximine **7** quantitatively precipitated from it. The surprising mild conditions of formation of the latter indicate the intermediate formation of nitrene **8** in this reaction. The specific solvation of isoxazole **2** by water molecules seems toweaken its N–O bond, facilitating the equilibrium or its shift towards singlet nitrene **8** which is effectively intercepted by the lone electron pair on the S atom in DMSO[8] to form sulfoximine **7**.

An interesting observation is the smooth transformation of isoxazole **2** into hydroxylamine **5** in $CHCl_3$ solution at room temperature in the presence of SiO_2 (TLC, Silufol UV-254).

It has also been found that in the one-pot synthesis of sulfoximine **7** from 4-chloro-5-ethoxycarbonyl-2-(2′-hydroxyphenyl)pyrimidine and NaN_3 in dry DMSO, the acrylate **6** was also unexpectedly formed. If the reaction is conducted with two moles of NaN_3 and/or undried DMSO, the yield of **6** considerably increases, *i.e.* the observed increase of the rate of covalent hydration of tetrazole **1T** seems to be due to the catalytic activity of NaN_3 or the bases in the DMSO solution. The latter fact is confirmed by the virtually complete transformation **1A**→**6** in these conditions in the presence of Na_2CO_3 (Scheme 2); compound **7** was not formed (TLC, Silufol UV-254).

Thus, the results of synthesis of compounds **2**, **5** and **6** experimentally support the mechanism which we have earlier suggested[6] for the transformation of azide **1A** into hydroxylamine **5** and acrylate **6** with intermediate formation of isoxazole **2** and tetrazole **1T**, respectively.

We are continuing to explore the scope and mechanistic details of the above intramolecular cyclizations.

We are grateful to the Soros Cultural Initiative Foundation for financial support.

[¶] **7** m.p. 181–183 °C; ^{1}H NMR (200.13 MHz, $CDCl_3$, 27 °C) δ 1.36 (t, 3H, Me), 3.47 (s, 6H, Me_2S), 4.33 (q, 2H, CH_2), 6.90 (m, 1H, 5′-H), 6.98 (dd, 1H, 3′-H), 7.36 (m, 1H, 4′-H), 8.28 (dd, 1H, 6′-H), 8.88 (s, 1H, 6-H), 13.25 (s, 1H, 2′-OH); ^{13}C NMR (100.61 MHz, $CDCl_3$, 27 °C) δ 14.15 (CH_3), 42.81 (Me_2S, $^1J_{CH}$ 140.2 Hz), 60.93 (CH_2, $^1J_{CH}$ 147.9 Hz), 112.49 (C-5, $^2J_{C^5-H^6}$ 5.3 Hz), 118.07 (C-3′), 118.23 (C-1′), 118.94 (C-5′), 129.23 (C-6′), 133.62 (C-4′), 157.41 (C-6, $^1J_{CH}$ 183.9 Hz), 161.28 (C-2′)., 163.19 (C-4, $^3J_{C^4-H^6}$ 6.2 Hz), 163.78 (COO, $^3J_{C\text{-}H^6} = {}^3J_{C\text{-}H(CH_2)}$ 3.2 Hz), 165.19 (C-2, $^3J_{C^2-H^6}$ 12.2, $^3J_{C^2-H^{6'}}$ 5.0 Hz); IR (KBr) ν/cm^{-1} 1730 (CO), 1576, 1406, 1281, 1255, 1196, 1124, 1038, 1024; HRMS *m*/*z* (M^+) (Found: 335.0933. Calc. for $C_{15}H_{17}N_3O_4S$: 335.0940).

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Received: Moscow, 18th March 1993
Cambridge, 14th April 1993; Com. 3/01704D