Available online at www.sciencedirect.com

ScienceDirect

Mendeleev Commun., 2018, **28**, 300–302

Mendeleev Communications

Novel reactions of ninhydrin oxime with mercaptoalkanoic acids

Lev Yu. Ukhin,*[a] Lyudmila G. Kuz'mina,[b] Danil V. Alexeenko,[a] Lyudmila V. Belousova,[a] Eugenii N. Shepelenko,[c] Vitaly A. Podshibyakin[a] and Anatolii S. Morkovnik[a]

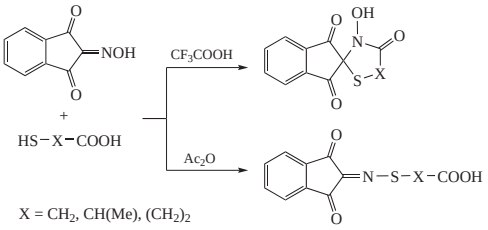
[a] *Institute of Physical and Organic Chemistry, Southern Federal University, 344090 Rostov-on-Don, Russian Federation. E-mail: lyukhin@ipoc.sfedu.ru*

[b] *N. S. Kurnakov Institute of General and Inorganic Chemistry, Russian Academy of Sciences, 119991 Moscow, Russian Federation. E-mail: kuzmina@igic.ras.ru*

[c] *Southern Scientific Center, Russian Academy of Sciences, 344006 Rostov-on-Don, Russian Federation. E-mail: dubon@ipoc.sfedu.ru*

DOI: 10.1016/j.mencom.2018.05.024

Ninhydrin oxime and mercaptoalkanoic acids in the presence of trifluoroacetic acid form 2,2′-spiranes incorporating indane-1,3-dione and 3-hydroxy-1,3-thiazolidin-4-one or 3-hydroxy-tetrahydro-1,3-thiazin-4-one moieties. On heating in acetic anhydride, the same reactants undergo replacement of oxime hydroxy group by sulfur thus affording thiooxime-containing alkanoic acids.

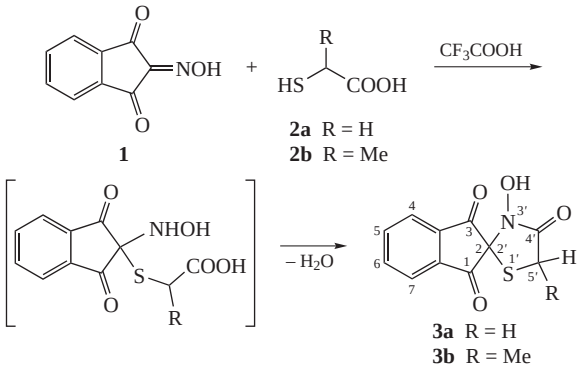


Thiazole and its derivatives play an important role in many biological processes. Thiazole ring is one of the components of vitamin B_1, and thiazolidine ring is a part of penicillin. One of the synthetic routes for such structures is 1,2-cycloaddition of mercapto carboxylic acids to oximes followed by lactamization.

In contrast with azomethines, oximes are less susceptible of addition reactions due to occurrence of the internal conjugation $\ddot{O}-\vec{N}=\vec{C}$, resulting in the high thermodynamic stability of oximes.[1] However, they can undergo cyclocondensation with α-mercapto carboxylic acids to form of 2-substituted 3-hydroxy-1,3-thiazolidin-4-ones.[2–4]

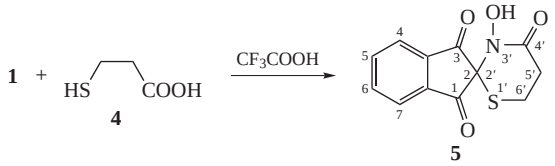
The charge distribution calculations in ninhydrin 2-oxime molecule **1** (B3LYP6-311G** method) have shown that the oxime carbon can serve as an electrophilic centre only in N-protonated form (quantum chemical data for model reactions are given in Online Supplementary Materials). This observation supports a need of acidic catalysis to promote the reaction.

We have found that oxime **1** reacts smoothly with α-mercapto carboxylic acids **2a**,**b** (Scheme 1) in CF_3COOH to form spiranes **3a**,**b** of indane-1,3-dione type containing spiro-fused 3-hydroxy-1,3-thiazolidin-4-one moiety.



Scheme 1

Oxime **1** also reacted smoothly with 3-mercaptopropionic acid **4** in a similar manner giving spirane **5** with 3-hydroxytetrahydro-1,3-thiazinone moiety (Scheme 2).†



Scheme 2

Due to the presence of the C(O)N(OH) structural fragment in the cycle, compounds **3a**,**b**, and **5** may be regarded as cyclic hydroxamic acids. Note that recently unique anticancer activity of some hydroxamic acids was reported.[5] Unfortunately, the described reaction is not of a general character. We failed to carry out it with camphor, isatin and phenanthrenequinone oximes. A spirane

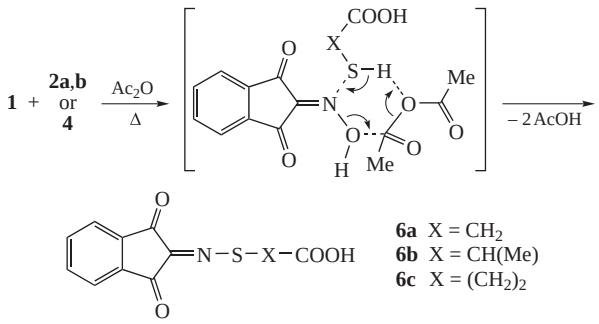
† *General procedure for synthesis of spiro derivatives* **3a**,**b**, **5** *and carboxylic acids* **6a**–**c**. The reactions were carried out with ninhydrin oxime **1** (0.35 g, 2 mmol) and a small excess of mercaptoalkanoic acids **2a**,**b**, **4**. Spiranes **3a**,**b**, **5** were formed in the presence of CF_3COOH, and carboxylic thiooxime derivatives **6a**–**c** in Ac_2O (1.5 ml). Compound **3a** was obtained at room temperature (12 h). The other spiranes and all acids were synthesized under brief heating. Detailed synthetic procedures are given in Online Supplementary Materials.

*3′-Hydroxy-4′*H*-spiro[indene-2,2′-1′,3′-thiazolidine]-1,3,4′-trione* **3a**. Colourless crystals (0.24 g), mp 220–222 °C (Pr^iOH). IR (ATR, ν/cm^{-1}): 3138 (br., OH), 1761 (m), 1748 (m), 1724 (s), 1698 (s, CO), 1591 (m), 1499 (m, arom.). ^{1}H NMR (600 MHz, DMSO-d_6) δ: 3.85 (s, 2H, $C^{5'}H_2$), 8.11 (m, 4H, C^4H, C^5H, C^6H, C^7H), 10.58 (s, 1H, OH). ^{13}C NMR (150 MHz, DMSO-d_6) δ: 28.82 ($C^{5'}$), 67.76 ($C^{2'}$), 124.71 (C^5), 124.71 (C^6), 138.50 (C^4), 138.50 (C^7), 139.85 (C^{3a}), 139.85 (C^{7a}), 168.20 ($C^{4'}$), 194.21 (C^1), 194.21 (C^3). MS (EI, 70 eV), *m*/*z* (%): 249 (10) [M^+], 232 (17) [M−OH], 204 (35), 190 (2), 177 (4), 158 (64), 149 (9), 132 (12), 121 (9), 102 (56), 90 (5), 76 (100), 63 (5), 50 (62). Found (%): C, 52.89; H, 3.11; S, 12.98. Calc. for $C_{11}H_7NO_4S$ (%): C, 53.01; H, 2.87; S, 12.86.

in which one fragment, 3-hydroxy-1,3-thiazolidin-4-one, analogous to compound **3a**, was reported,[6] however it was obtained in a different way.

We have also demonstrated that short heating a mixture of oxime **1**, mercapto carboxylic acids **2a**,**b** or **4** and Ac_2O initiates an exothermic reaction leading to earlier unknown 1,3-indanedione thiooxime carboxylic acids **6a**–**c** (Scheme 3).‡ The reaction of oxime **1** with 3-mercaptopropionic acid **4** proceeds most smoothly. The reactions with **2a** and **2b** are less robust and are sensitive to overheating.

In contrast with oximes, their sulfur analogues are less studied (see review[7]). Thiooximes with the SH-function have not been isolated up to now, however, they were detected in solutions at low temperatures.[8,9]



Scheme 3

*3'-Hydroxy-5'-methyl-4'*H*-spiro[indene-2,2'-1',3'-thiazolidine]-1,3,4'-trione* **3b**. Colourless crystals (0.28 g), mp 183–185 °C (EtOH). IR (ATR, ν/cm^{-1}): 3118 (br., OH), 1763 (m), 1746 (m), 1728 (s), 1665 (s, CO), 1589 (m), 1499 (m, arom). ^{1}H NMR (600 MHz, $CDCl_3$) δ: 1.73 (d, 3H, Me, J 7.2 Hz), 4.20 (q, 1H, C$^{5'}$H, J 7.2 Hz), 7.94–7.97 (m, 2H, H_{arom}), 8.05–8.08 (m, 2H, H_{arom}). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 20.17 (Me), 39.26 (C$^{5'}$), 66.94 (C$^{2'}$), 124.66 (C^5), 124.66 (C^6), 137.25 (C^4), 137.26 (C^7), 139.98 (C^{3a}), 140.05 (C^{7a}), 171.86 (C$^{4'}$), 192.45 (C^1), 192.57 (C^3). MS (EI, 70 eV), m/z (%): 263 (38) [M$^+$], 246 (37) [M – OH], 218 (80), 200 (3), 185 (19), 174 (27), 158 (100), 147 (12), 134 (9), 121 (11), 90 (6), 60 (34), 50 (34).

*3'-Hydroxy-2',3',5',6'-tetrahydro-4'*H*-spiro[indene-2,2'-1',3'-thiazine]-1,3,4'-trione* **5**. Colourless crystals (0.28 g), mp 201–203 °C (Pr^iOH, 35 ml). IR (ATR, ν/cm^{-1}): 3095 (br., OH), 1761 (m), 1747 (m), 1720 (s, CO), 1634 (s), 1589 (m, arom). ^{1}H NMR (600 MHz, $CDCl_3$) δ: 3.14 [t, 2H, C(C$^{5'}$)H, J 6.0 Hz], 3.21 [t, 2H, C(C$^{6'}$)H, J 6.0 Hz], 7.91–7.94 (m, 2H, CH_{arom}), 8.02–8.05 (m, 2H, CH_{arom}), 8.34 (br.s, 1H, OH). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 23.83 (C$^{5'}$), 35.07 (C$^{6'}$), 69.51 (C$^{2'}$), 124.73 (C^5), 124.73 (C^6), 137.00 (C^4), 137.00 (C^7), 138.52 (C^{3a}), 138.52 (C^{7a}), 169.91 (C$^{4'}$), 190.62 (C^1), 190.62 (C^3). MS (EI, 70 eV), m/z (%): 263 (16) [M$^+$], 246 (5) [M – OH], 190 (3), 177 (3), 158 (29), 149 (8), 132 (6), 121 (5), 102 (25), 90 (3), 76 (28), 60 (8), 55 (100).

‡ *2-[(1,3-Dioxoindan-2-ylidenamino)sulfanyl]acetic acid* **6a**. Orange crystals (0.19 g), mp 170–172 °C (MeOH). IR (Nujol, ν/cm^{-1}): 3171 (br., OH), 1729 (s), 1694 (s, CO), 1590 (m), 1554 (m, arom). ^{1}H NMR (600 MHz, DMSO-d_6) δ: 4.18 (s, 2H, CH_2), 7.94 (s, 4H, H_{Ar}), 12.98 (s, 1H, OH). ^{13}C NMR (150 MHz, DMSO-d_6) δ: 45.11 (C$^{3'}$), 123.56 (C^5 or C^6), 123.79 (C^5 or C^6), 136.12 (C^4 or C^7), 136.23 (C^4 or C^7), 140.32 (C^{3a}), 140.88 (C^{7a}), 153.02 (C^2), 169.70 (C$^{4'}$), 182.10 (C^3), 183.51 (C^1). Found (%): C, 52.85; H, 3.18; S, 12.43. Calc. for $C_{11}H_7NO_4S$ (%): C, 53.01; H, 2.87; S, 12.86.

2-[(1,3-Dioxoindan-2-ylidenamino)sulfanyl]propionic acid **6b**. Orange crystals (0.19 g), mp 122–125 °C (MeCN, 3 ml). IR (Nujol, ν/cm^{-1}): 3423 (s, OH), 2049 (w, H_2O), 1724 (s), 1714 (s), 1693 (s, CO), 1657 (w), 1639 (w), 1589 (m), 1568 (w), 1545 (s). ^{1}H NMR (600 MHz, DMSO-d_6) δ: 1.55 (d, 3H, Me, J 6.0 Hz), 4.23 (q, 1H, CH, J 6.0 Hz), 7.91–7.93 (m, 4H, H_{arom}). ^{13}C NMR (150 MHz, DMSO-d_6) δ: 15.87 (Me), 51.18 (CH), 123.56 (C^5 or C^6), 123.76 (C^5 or C^6), 136.11 (C^4 or C^7), 136.23 (C^4 or C^7), 140.27 (C^{3a} or C^{7a}), 140.95 (C^{3a} or C^{7a}), 152.78 (C^2), 172.12 (C$^{4'}$), 182.16 (C^1 or C^3), 183.59 (C^1 or C^3). MS (El, 70 Ev), m/z (%): 263 (25) [M$^+$], 218 (3), 190 (49), 158 (82), 132 (17), 104 (100), 90 (3), 76 (77), 59 (26), 50 (31).

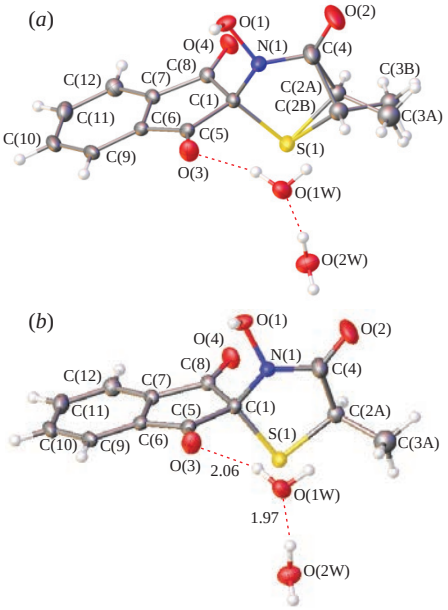


Figure 1 (*a*) Disordered molecules of compound **3b** and (*b*) only major component of the disordered system.

The structures of compounds **3b**, **5**, **6b** and **6c** were estimated by single crystal X-ray diffraction (XRD).§

Molecular structure of compound **3b** is shown in Figure 1. The 5-membered heterocycle of the molecule is disordered over two positions [see Figure 1(*a*)]. The compound crystallizes in hydrated form.

The 5-membered heterocycle adopts a non-planar conformation that cannot be described within the canonic presentations.The conformation of the 6-membered heterocycle in the molecule of compound **5** (Figure 2) may be described as a flattened boat; the

3-[(1,3-Dioxoindan-2-ylidenamino)sulfanyl]propionic acid **6c**. Orange crystals, mp 190–192 °C (MeOH). IR (Nujol, ν/cm^{-1}): 3140 (br., OH), 1736 (s), 1692 (s, CO), 1593 (m), 1548 (s, arom.) ^{1}H NMR (600 MHz, DMSO-d_6) δ: 2.77–2.80 (t, 2H, CH_2, J 6.0 Hz), 3.39–3.41 (t, 2H, CH_2, J 6.0 Hz), 7.90–7.93 (m, 4H, H_{Ar}), 12.43 (br.s, 1H, OH). ^{13}C NMR (150 MHz, DMSO-d_6) δ: 32.82 (C$^{4'}$), 37.58 (C$^{3'}$), 123.48 (C^5 or C^6), 123.74 (C^6 or C^5), 136.04 (C^7 or C^4), 136.14 (C^4 or C^7), 140.36 (C^{3a} or C^{7a}), 140.67 (C^{7a} or C^{3a}), 152.89 (C^2), 172.61 (C$^{5'}$), 182.17 (C^1 or C^3), 183.47 (C^3 or C^1). MS (El, 70 eV), m/z (%): 263 (16) [M$^+$], 190 (5), 177 (3), 158 (60), 132 (15), 104 (100), 76 (78), 59 (11), 50 (35).

§ *XRD analysis.* A SMART-APEX-II diffractometer was used for measurements [graphite monochromated MoKα radiation (λ = 0.71073 Å), ω-scan technique]. Structure reduction was performed using SAINT program.[10(a)] Structures were solved by direct methods and refined by least squares in the anisotropic approximation for non-hydrogen atoms. Hydrogen atoms were placed at the calculated positions and refined using riding model. In structure **3b**, a disorder of a C(2)–C(3) fragment was established [C(2A)–C(3A) and C(2B)–C(3B)] with the ratio of occupations equal to 0.78 : 0.22. In all the calculations, SHELXTL-Plus and OLEX-2 software was used.[10(b)–(d)]

Crystal data for **3b**. $C_{12}H_{13}NO_6S$ (M = 299.29), triclinic, space group $P\bar{1}$ (no. 2), a = 6.9224(5), b = 7.9368(6) and c = 12.4529(10) Å, α = = 92.1970(10)°, β = 105.0570(10)°, γ = 92.6220(10)°, V = 659.11(9) Å^3, Z = 2, T = 150 K, μ(MoKα) = 0.271 mm^{-1}, d_{calc} = 1.508 g cm^{-3}, 6349 reflections measured (5.14° ⩽ 2θ ⩽ 55.98°), 3078 unique (R_{int} = 0.0199, R_σ = 0.0311) which were used in all calculations. The final R_1 = 0.0411 [$I > 2\sigma(I)$] and wR_2 = 0.0983 (all data).

Crystal data for **5**. $C_{12}H_9NO_4S$ (M = 263.26), triclinic, space group $P\bar{1}$ (no. 2), a = 7.3102(4), b = 7.8948(4) and c = 9.9952(5) Å, α = = 75.5540(10)°, β = 82.4400(10)°, γ = 84.4820(10)°, V = 552.55(5) Å^3, Z = 2, T = 170 K, μ(MoKα) = 0.299 mm^{-1}, d_{calc} = 1.582 g cm^{-3}, 5847 reflections measured (4.24° ⩽ 2θ ⩽ 58°), 2926 unique (R_{int} = 0.0128, R_σ = 0.0184) which were used in all calculations. The final R_1 = 0.0320 [$I > 2\sigma(I)$] and wR_2 = 0.0867 (all data).

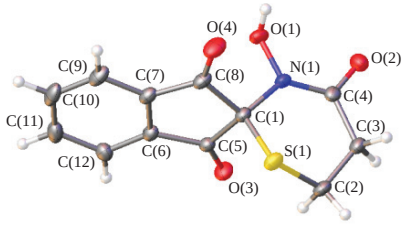


Figure 2 Molecular structure of compound **5**; atomic thermal displacement parameters are given at 50% probability level.

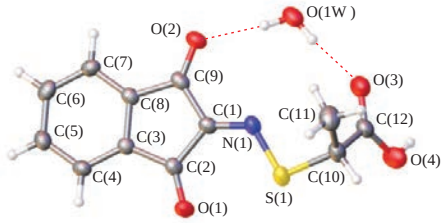


Figure 3 Molecular structure of compound **6b**; atomic thermal displacement parameters are given at 50% probability level.

C(1)N(1)C(3)C(2) atoms are in the same plane within 0.01 Å and the C(4) and S(1) atoms are displaced from this plane in the same side by 0.15 and 0.91 Å, respectively. Fused benzene and 5-membered cycles form a planar system.

According to the XRD analysis, the molecule of compound **6b** represents an aqua solvate with the equal proportion of the components of crystal unit cell (Figure 3). The fused bicycle is also planar.

The molecular structure of compound **6c** is shown in Figure 4. The carboxyl group is disordered over two rotationally related positions with their equal occupations. In the molecule of **6c**, the fused bicycle is planar.

In summary, the described spiranes and their possible analogues are attractive because their molecules are composed of two components exhibiting pharmacophore properties in other compounds. Furthermore, carboxylic acids with thiooxime fragments that

Crystal data for **6b**. $C_{12}H_{11}NO_5S$ (M = 281.28), monoclinic, space group $P2_1/c$ (no. 14), a = 12.130(3), b = 7.0236(14) and c = 15.352(3) Å, β = 110.478(3)°, V = 1225.2(4) Å^3, Z = 4, T = 150 K, μ(MoKα) = = 0.280 mm^{-1}, d_{calc} = 1.525 g cm^{-3}, 10555 reflections measured (5.54° ⩽ ⩽ 2θ ⩽ 56°), 2926 (R_{int} = 0.0686, R_σ = 0.0698) which were used in all calculations. The final R_1 = 0.0756 [$I > 2\sigma(I)$] and wR_2 = 0.1984 (all data).

Crystal data for **6c**. $C_{12}H_9NO_4S$ (M = 263.26), monoclinic, space group $P2_1/n$ (no. 14), a = 4.8835(3), b = 16.6935(10) and c = 14.7413(8) Å, β = 99.4930(10)°, V = 1185.29(12) Å^3, Z = 4, T = 150 K, μ(MoKα) = = 0.278 mm^{-1}, d_{calc} = 1.475 g cm^{-3}, 12975 reflections measured (5.6° ⩽ 2θ ⩽ ⩽ 58°), 3151 (R_{int} = 0.0442, R_σ = 0.0402) which were used in all calculations. The final R_1 = 0.0462 [$I > 2\sigma(I)$] and wR_2 = 0.1174 (all data).

CCDC 1539329, 1539332, 1550366 and 1541086 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 more details, see Online Supplementary Materials.

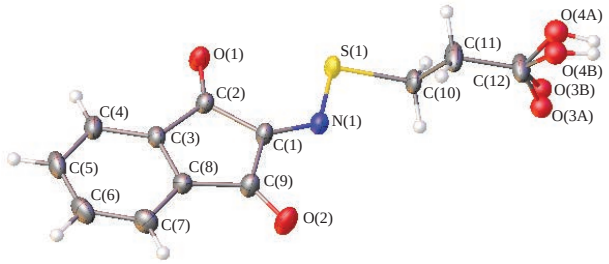


Figure 4 Molecular structure of compound **6c**; atomic thermal displacement parameters are given at 50% probability level; carboxyl group is disordered over two positions that correspond to two rotamers about the C(11)–C(12) bond.

are so far *terra incognita*, are of interest as a potential bioactive compounds. A widening of their assortment and study of bioactivity are underway.

This work was supported by the Ministry of Education and Science of the Russian Federation (base part of a state task for scientific activity of Southern Federal University, no. 4.5821.2017/8.9). The authors are grateful to the 'Molecular Spectroscopy' Center of the Institute of Physical and Organic Chemistry of Southern Federal University, Rostov-on-Don.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2018.05.024.

References

1 C. K. Ingold, *Structure and Mechanism in Organic Chemistry*, Cornell University Press, Ithaca, NY, 1969.
2 H. Priewe and K. Pirner, *Patent DE 946140*, 1956.
3 R. A. Mane and D. B. Ingle, *Indian J. Chem., Sect. B*, 1983, **22**, 690.
4 M. A. Berghot, D. S. Badawy and E. B. Moad, *Rev. Roum. Chim.*, 1995, **40**, 377.
5 A. V. Aksenov, A. N. Smirnov, I. V. Magedov, M. R. Reisenauer, N. A. Aksenov, I. V. Aksenova, A. L. Pendleton, G. Nguyen, R. K. Johnston, M. Rubin, A. De Carvalho, R. Kiss, V. Mathieu, F. Lefranc, J. Correa, D. A. Cavazos, A. J. Brenner, B. A. Bryan, S. Rogelj, A. Kornienko and L. V. Frolova, *J. Med. Chem.*, 2015, **58**, 2206.
6 Z. A. Hozien, A. A. O. Sarhan and O. S. Mohamed, *Heterocycl. Commun.*, 1999, **5**, 269.
7 *Gmelin Handbook of Inorganic and Organometallic Chemistry*, 8th edn., Springer-Verlag, Berlin, Heidelberg, 1994, pp. 96–99.
8 D. H. R. Barton, P. D. Magnus and S. I. Pennanen, *J. Chem. Soc., Chem. Commun.*, 1974, 1007.
9 C. Brown, B. T. Grayson and R. F. Hudson, *J. Chem. Soc., Chem. Commun.*, 1974, 1007.
10 (*a*) *SAINT, v. 6.02A*, Bruker AXS, Madison, WI, 2001; (*b*) *SHELX-TL-Plus, v. 5.10*, Bruker AXS, Madison, WI, 2001; (*c*) *SAINT, v. 6.02A*, Bruker AXS, Madison, WI, 2001; (*d*) O. V. Dolomanov, L. J. Bourhis, R. J. Gildea, J. A. K. Howard and H. Puschmann, *J. Appl. Crystallogr.*, 2009, **42**, 339.

Received: 20th October 2017; Com. 17/5378