Synthesis of 3-(4-chlorophenyl)oxirane-2,2-dicarboxamide

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Oxidation of (*E*)-3-(4-chlorophenyl)-2-cyanoprop-2-enethioamide with hydrogen peroxide or the H_2O_2—KOH system gave 3-(4-chlorophenyl)oxirane-2,2-dicarboxamide. This compound was also obtained by an independent "one pot" synthesis from *p*-chlorobenzaldehyde and 2-cyanoacetamide through *in situ* oxidation of their adduct (*E*)-3-(4-chlorophenyl)-2-cyanoprop-2-eneamide with the H_2O_2—KOH system. The structure of 3-(4-chlorophenyl)oxirane-2,2-dicarboxamide was confirmed by X-ray diffraction and spectroscopic data.

Key words: arylmethylidene(cyano)thioacetamides, oxidation, the Radziszewski reaction, 3-(4-chlorophenyl)oxirane-2,2-dicarboxamide, X-ray diffraction analysis.

It is known that oxidation of thioamides gives, depending on the structures of the substrate and the oxidant, the corresponding amides,[1,2] benzothiazole[1,3] or thiadiazole derivatives,[4] nitriles,[1,5] and thioamide *S*-oxides.[6] Proceeding further in our investigations of the chemistry of cyanothioacetamide,[7] we studied peroxidation of arylmethylidene(cyano)thioacetamides. These easily accessible compounds are of interest because of the presence of several oxidizable fragments: the thioamide group, the cyano group, and the activated double bond. In addition, the vicinity of the cyano and thioamide groups allows oxidative closure of an isothiazole ring, which has been illustrated[8,9] with a number of cyclic cyanothioacetamide derivatives, 3-cyanopyridine-2(1*H*)-thiones, as examples.

We found that oxidation of (*E*)-3-(4-chlorophenyl)-2-cyanoprop-2-enethioamide (**1**) with an excess of 30% H_2O_2 in hot EtOH both in the presence (method *A*) and in the absence of an alkali (method *B*) is a non-regioselective process that involves both the functional groups and the double bond and leads to earlier unknown 3-(4-chlorophenyl)oxirane-2,2-dicarboxamide (**2**) (Scheme 1). The structure of compound **2** was confirmed by X-ray diffraction and spectroscopic data and an independent synthesis from (*E*)-3-(4-chlorophenyl)-2-cyanoacrylamide (**3**). For the latter reaction, we developed a convenient "one pot" synthesis *via* the Knoevenagel condensation of aldehyde **4** with 2-cyanoacetamide (**5**) followed by the *in situ* Radziszewski oxidation[10,11] of the resulting cyanoacrylamide **3** (method *C*) (see Scheme 1). It should be noted that methods *A* and *B* provide comparable results (the yields of compound **2** are low (23—29%)), while method *C* is simpler and more efficient.

The ^{1}H NMR spectrum of diamide **2** shows a singlet at δ 4.27 for the sole proton of the oxirane ring, which is characteristic of the oxirane protons in 2,3-epoxy dicarboxylic acid derivatives: 2-alkoxycarbonyl-2-cyanooxiranes (δ 4.11—4.50)[12] and 2,2-dicyanooxiranes (δ 4.48—5.20).[12—14] At the same time, the signal for the olefinic proton in the starting thioamide **1** appears at δ 8.10.[15] In addition, the spectrum of compound **2** contains a quadruplet for the protons of the aryl substituent and two broadened singlets for the protons of the diastereotopic carbamoyl groups. The IR spectrum of compound **2** shows no absorption bands due to the cyano group but contains bands at 3450, 3370, and 3150 cm^{-1} (NH_2 stretching vibrations) and a broadened band at 1675 cm^{-1} (C=O).

X-ray diffraction analysis unambiguously proved the structure of compound **2**, which crystallizes in a centrosymmetric space group. The general view of its molecule is shown in Fig. 1 (for selected geometrical parameters, see the figure caption). The angle between the planes of the phenyl and oxirane rings is 121.2°; the carbamoyl

† Deceased.

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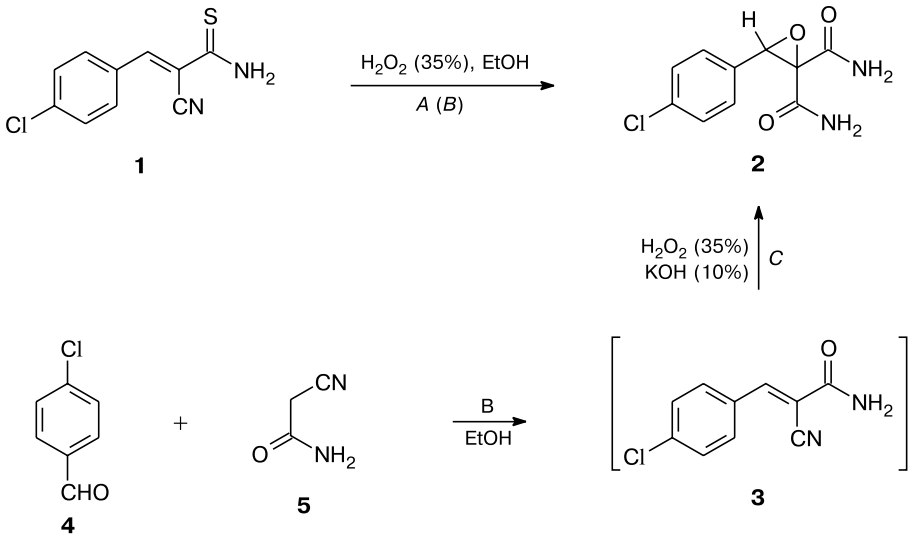
Scheme 1



B is morpholine

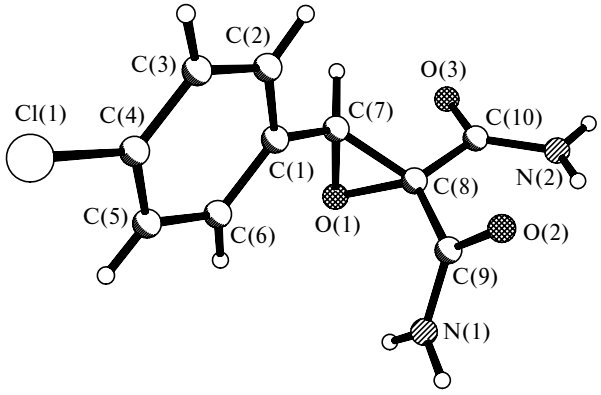


Fig. 1. General view of structure **2**. Selected bond lengths: C(7)—C(8) 1.483(3) Å, C(7)—O(1) 1.445(2) Å, C(8)—O(1) 1.439(2) Å, C(8)—C(9) 1.501(3) Å, C(8)—C(10) 1.524(3) Å, C(9)—N(1) 1.312(3) Å, and C(10)—N(2) 1.320(3) Å; and bond angles: O(1)—C(7)—C(8) 58.9(1)°, O(1)—C(8)—C(7) 59.2(1)°, and C(8)—O(1)—C(7) 61.9(1)°.

C(9)N(1)O(2) and C(10)N(2)O(3) groups make angles of 120.6° and 83.4°, respectively, with the oxirane ring. The C(9)—N(1) (1.312(3) Å) and C(10)—N(2) bonds (1.320(3) Å) are substantially shorter than a standard single C—N bond (1.45 Å) because of strong conjugation of the lone electron pairs of the N atoms with the π-systems of the carbonyl groups. In the crystal, a branched system of NH···O hydrogen bonds was detected; their selected parameters are given in Table 1.

In conclusion, it should be noted that 2,3-epoxy amides show antiinflammatory and hypotensive effects,[16] inhibit calcium-activated neutral thiol protease,[17] and can act as tranquillizers, antibiotics, and peptide hydrolase inhibitors.[18] The reactions described in the present work and the properties of the products will be a subject of our future investigations.

Table 1. Selected geometrical parameters of the hydrogen bonds in the crystal of compound **2**

D—H···A	*d*/Å			D—H—A angle /deg
	D—H	H···A	D···A	
N(1)—H(3)···O(1)$^{\#1}$	0.94(3)	2.16(3)	2.952(2)	141(2)
N(1)—H(9)···O(2)$^{\#2}$	0.92(3)	1.98(3)	2.896(3)	171(3)
N(2)—H(5)···O(3)$^{\#3}$	0.86(3)	2.11(3)	2.934(3)	161(3)
N(2)—H(6)···O(2)$^{\#4}$	0.86(3)	2.43(3)	3.031(3)	127(2)

Note. The symmetry operation codes for generation of equivalent atoms are $^{\#1}$ $-x-1/2, y-1/2, z$; $^{\#2}$ $-x+1/2, y-1/2, z$; $^{\#3}$ $-x, -y+1, -z+1$; and $^{\#4}$ $x+1/2, -y+1/2, -z+1$.

Experimental

^{1}H NMR spectra were recorded on a Varian Gemini 200 instrument (200 MHz) in DMSO-d_6 with Me_4Si as the internal standard. IR spectra were recorded on an IKS-29 spectrophotometer (in Nujol). Elemental analysis was carried out on a Perkin—Elmer C,H,N-Analyser instrument. The purity of the compounds obtained was checked by TLC on Silufol UV 254 plates in acetone—heptane (1 : 1). Spots were visualized in the iodine vapor or under UV light. Melting points were determined on a Kofler hot stage and are given uncorrected. (*E*)-3-(4-Chlorophenyl)-2-cyanoprop-2-enethioamide (**1**) was prepared according to a known procedure.[15]

3-(4-Chlorophenyl)oxirane-2,2-dicarboxamide (2). Method *A*. 35% Hydrogen peroxide (d = 1.1 g cm^{-3}; 4 mL,

45 mmol) was added at 0 °C to a suspension of thioamide **1** (1 g, 4.5 mmol) in EtOH (5 mL). Then 10% KOH (2.5 mL, 4.5 mmol) was added dropwise with cooling and stirring. The observed exothermic reaction was accompanied by dissolution of thioamide **1** and evolution of oxygen. After the reaction was completed, the mixture was filtered through a paper filter and kept at ~20 °C for several days. The colorless crystalline precipitate that formed was filtered off, washed with EtOH, and recrystallized from EtOH—Me_2CO (1 : 1). The yield was 29%, m.p. 225—227 °C. The crystals obtained were used for X-ray diffraction analysis. Found (%): C, 50.29; H, 3.76; N, 11.60. $C_{10}H_9ClN_2O_3$. Calculated (%): C, 49.91; H, 3.77; N, 11.64. IR, ν/cm^{-1}: 3450, 3370, 3150 (2 NH_2); 1675 (C=O). ^1H NMR, δ: 4.27 (s, 1 H, CH, oxirane); 7.36 (q, 4 H, 4-ClC_6H_4, ^2J = 8.5 Hz); 7.40, 7.58 (both br.s, 2 H each, 2 C(O)NH_2).

Method *B*. 35% Hydrogen peroxide (2 mL, 2.26 mmol) was added to a suspension of thioamide **1** (0.5 g, 2.25 mmol) in EtOH (5 mL) and the mixture was brought to boiling. The observed exothermic reaction was accompanied by dissolution of thioamide **1** and evolution of oxygen. On reflux with stirring for 3 min, the dark red solution turned pale yellow. The reaction mixture was kept for 5 days. The white resinous precipitate that formed was treated with EtOH and filtered off. The yield of compound **2** was 23%, colorless crystals, m.p. 223—225 °C. On recrystallization from Me_2CO, m.p. 225—227 °C. The product was identical with that obtained according to method *A*.

Method *C*. Three drops of morpholine were added to a mixture of 2-cyanoacetamide **5** (0.5 g, 6 mmol) and 4-chlorobenzaldehyde **4** (0.84 g, 6 mmol) in EtOH (8 mL). The mixture was brought to boiling and then stirred at ~50 °C for 3 min to give a suspension of (*E*)-3-(4-chlorophenyl)-2-cyanoacrylamide **3** as colorless crystals. 35% Addition of H_2O_2 (5 mL, 57 mmol) and 10% KOH (0.5 mL, 0.9 mmol) to the suspension initiated a highly exothermic reaction resulting in a pale yellow solution. The mixture was kept at ~20 °C for 24 h and colorless crystals of oxiranedicarboxamide **2** were filtered off and washed with EtOH. The yield was 60%, m.p. 225—227 °C. In terms of spectroscopic characteristics, the product was identical with those obtained according to methods *A* and *B*.

X-ray diffraction analysis of compound **2** was carried out at ~20 °C for a single crystal (0.26×0.21×0.19 mm) on an Enraf—Nonius CAD-4 automatic four-circle diffractometer (λ-CuK_α radiation, graphite monochromator, ω/2θ scan mode, $\theta_{max} = 65°$, sphere segment $-1 \le h \le 9$, $-1 \le k \le 8$, $-1 \le l \le 45$). The total number of reflections was 2373. Crystals of compound **2** are orthorhombic: a = 7.693(2) Å, b = 7.390(2) Å, c = 38.641(7) Å, V = 2196.7(9) Å^3, Z = 8, d_{calc} = 1.552 g cm^{-3}, μ = 4.759 cm^{-1}, $F(000)$ = 1056, space group *Pbca* (No. 61). The structure was solved by the direct method and refined by the least-squares method in the full-matrix anisotropic approximation with the SHELXS97 and SHELXL97 programs.[19,20] In refinement, 1751 independent reflections were used (1525 reflections with $I > 2\sigma(I)$); the number of parameters refined was 182; the number of reflections per parameter was 8.4; the weighting scheme was $\omega = 1/[\sigma^2(F_0^2) + (0.0640P)^2 + 0.933P]$, where $P = (F_0^2 + 2F_c^2)/3$; max. (mean) shift/esd in the final cycle was 0.018 (0.002). Calculations were corrected for anomalous scattering; PSI scan semiempirical absorption correction was applied (T_{min} = 0.32, T_{max} = 0.46). All hydrogen atoms were objectively located from the electron density difference map and refined isotropically. At the final step of refinement, an isotropic extinction correction was applied (extinction coefficient 0.0026(3)). Final residuals were $R_1(F^2)$ = 0.0393 and $R_w(F^2)$ = 0.1081, GOF = 1.035 for reflections with $I > 2\sigma(I)$ and $R_1(F)$ = 0.0477 and $R_w(F^2)$ = 0.1144, GOF = 1.035 for all reflections. The residual electron densities in the final refinement cycle were 0.20 and −0.26 *e* Å^{-3}. Comprehensive X-ray diffraction data for compound **2** have been deposited with the Cambridge Crystallographic Data Center (CCDC 605743).

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