The Radziszewski Oxidation of Cycloalkylidene-α-(thiazol-2-yl)acetonitriles: A New Approach Toward Spirooxiranes

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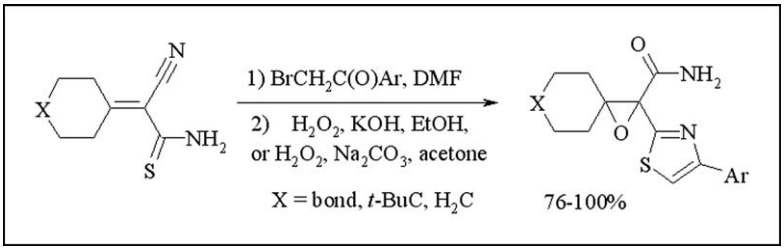

Upon treatment with H_2O_2/KOH in EtOH or with Na_2CO_3/H_2O_2 in acetone, cycloalkylidene-α-(4-arylthiazol-2-yl)acetonitriles afforded 2-(4-arylthiazol-2-yl)-1-oxaspiro[2.5]octane-2-carboxamides and 2-(4-arylthiazol-2-yl)-1-oxaspiro[2.4]heptane-2-carboxamides in excellent yields (76–100%).

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INTRODUCTION

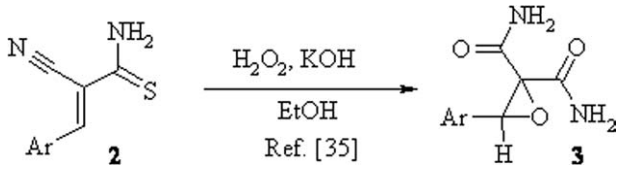
Oxiranes were found to belong to one of the most promising classes of heterocyclic compounds. As they are versatile, highly reactive, and chemically flexible reagents, a considerable attention has been devoted to both the methods of epoxidation and reactions of oxiranes (for recent reviews on the methods of epoxidation and chemical transformations of oxiranes see, *e.g.*, [1–6]). Spirooxiranes (or 1-oxaspiro[2.*n*]alkanes) are of special interest because their biological profile and specific reactions, in some cases, could be vastly different from those reported for other oxiranes [2,7]. A couple of naturally occurred spirooxiranes have been reported to possess fungicidal, phytotoxic, insecticidal, and cytotoxic activity [1,8].

An evident approach to the simpliest 1-oxaspiro[2.*n*]alkanes is based on the rather uneffective two-step halohydrine procedure [9]. Spirooxiranes could also be obtained from cycloalkanones upon treatment with a couple of sulfur ylides (*e.g.*, by Corey-Chaykowski reaction, for reviews see [10]), diazoalkanes [2,11], organolithium compounds [12], by Darzens reaction [13], *etc*.

However, less is known about methods of direct epoxidation of 1-methylenecycloalkanes leading to spirooxiranes, probably because of a heightened tendency toward cleavage of spirooxirane moiety in acidic media, even under mild conditions. The direct epoxidation of 1-methylenecycloalkanes to spirooxiranes has been successfully accomplished with only a few epoxidizing agents such as dioxiranes [14] (for reviews on the dioxirane epoxidation see [15]), monoperphtalic acid [16], *p*-nitroperbenzoic acid [17], *m*-chloroperbenzoic acid (MCPBA)–$NaHCO_3$ system [18], or Oxone® ($2KHSO_5 \times KHSO_4 \times K_2SO_4$)–cyclohexanone–phosphate buffer [19]. Noteworthy that organic peroxy acids could be used for epoxidation of methylenecycloalkanones, but reaction is frequently accomplished with low ratio of exo/endo enantiomers [2] and often complicated by side reactions such as acid-promoted oxirane ring cleavage and rearrangements [2,6,7,20]. For instance, the epoxidation of methylenecyclopropanes with MCPBA is accompanied by rearrangement resulted in formation of cyclobutanones as sole products [21]. When camphene and 1-methylenecycloalkanones were treated with $MeCO_3H$, corresponding aldehydes derived from Meinwald-type rearrangement and glycol monoacetates were obtained along with minor amounts of desired 1-oxaspiro [2.*n*]alkanes [2,22].

Both isomerization and ring opening can be avoided in nonacidic media; thus, a successful epoxidation with $MeCO_3H$ can be achieved in a buffered reaction media upon mild conditions only [23]. Another procedure to effect the epoxidation of methylenecycloalkanes uses peroxycarboximidic acids (RC(=NH)OOH) easily generated *in situ* from H_2O_2 and RC≡N, usually in a slightly alkaline medium. This method is known as Payne epoxidation [24] (for more recent developments

Scheme 1



see also [25]) and could be considered as a development of the classical Radziszewski method of oxidative hydrolysis of nitriles.

The absence of an acid is the major advantage of the Payne epoxidation as only neutral amides are formed as by-products. In contrast with peroxy acids, peroxycarboximidic acids appear to be milder reagents and those substrates containing carbonyl groups tend not to react to give Baeyer-Villiger by-products [24c]. However, the literature contains only a few reports on the epoxidation of methylenecycloalkanes effected by peroxycarboximidic acids. Thus, 1-oxaspiro[2.*n*]alkanes were obtained from corresponding alkenes upon treatment with $PhC{\equiv}N/H_2O_2/NaHCO_3$ [24c] or $Cl_3CC{\equiv}N/H_2O_2$ in the presence of K_2HPO_4 [2,23c]. Tsuno and Sugiyama have reported that 5-cycloalkylidene Meldrum's acids easily react with H_2O_2 in acetonitrile to afford spirooxiranes in good yields [26]. Finally, ethyl cycloalkylidenecyanoacetates reacted with H_2O_2 in the presence of sodium tungstate to give 2-ethoxycarbonyl-1-oxaspiro[2.*n*]alkane-2-carboxamides [27] because of specific behavior of unsaturated nitriles under Radziszewski reaction conditions.

At the end of 19th century, Radziszewski described an original method for preparation of amides by treatment of nitriles with alkaline hydrogen peroxide [28]. This reaction became a standard route for synthesis of amides from nitriles, and many variations of this procedure have been subsequently reported (for instance, see [29]; the Radziszewski reaction has been reviewed [30]).

In 1932, Murray and Cloke [31] have found that α,β-unsaturated nitriles undergo the double C=C bond epoxidation under Radziszewski conditions, along with expected transformation of cyano group into amide moiety. The mechanism of epoxidation remained unclear until mid-1950s when Payne has suggested and proved [24a,32] that initial formation of peroxycarboximidic acids from unsaturated nitriles and H_2O_2 takes place, following the intramolecular epoxidation. Since that time some modifications and extensions of the method have been described [33]. Apart from its synthetic potential and usability, epoxidation of unsaturated nitriles under Radziszewski conditions is of considerable interest in the light of recent data on the biological activity of 2,3-epoxy amides [1].

Our interests in the chemistry of cyanothioacetamide (**1**) [34] prompted us to investigate the oxidation of unsaturated nitriles derived from compound **1**. Recently, we showed that oxidation of arylmethylene cyanothioacetamides (**2**) under Radziszewski conditions proceeds with involvement of both conjugated cyano group and thioamide moiety giving rise to 3-aryl-2,2-oxiranedicarboxamides (**3**) [35] (Scheme 1).

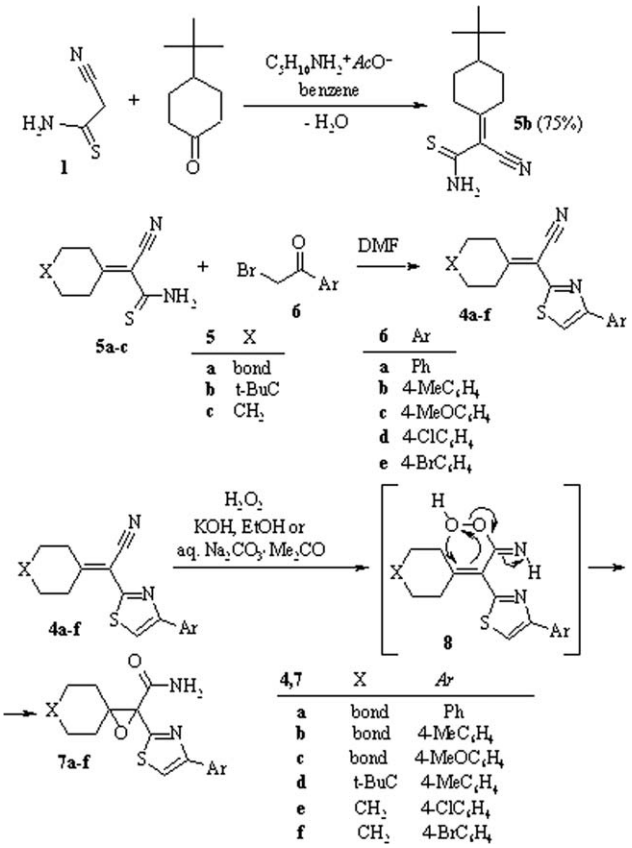
Encouraged with these results, we decided to extend this method to cycloalkylidene-α-(4-arylthiazol-2-yl)acetonitriles, which are seemed to be a good starting point for the synthesis of 1-oxaspiro[2.*n*]alkane derivatives.

RESULTS AND DISCUSSION

Cycloalkylidene-α-(4-arylthiazol-2-yl)acetonitriles (**4a–f**) were obtained from easily available 2-cyano-2-cycloalkylideneethanethioamides (**5a–c**) [36] and α-bromo ketones **6a–e** *via* modified Hantzsch procedure, as shown in Scheme 2.

Starting 2-(4-*tert*-butylcyclohexylidene)-2-cyanoethanethioamide (**5b**) was prepared by Knoevenagel condensation of cyanothioacetamide **1** with 4-*tert*-butylcyclohexanone.

Scheme 2



We found that unsaturated nitriles **4** could be easily converted into spiroepoxyamides **7** upon short-time treatment with alkaline H_2O_2 solution in EtOH (method A, yields 76–90%). It is strongly believed that the reaction proceeds through the formation of peroxycarboximidic intermediate **8**, following the intramolecular epoxidation.

Murray and Cloke [31] had shown that unsaturated nitriles could be successfully oxidized by means of H_2O_2 in the presence Na_2CO_3 as a catalyst in acetonic solution. The Na_2CO_3/acetone system appears to be more efficient than KOH/EtOH because it gives a better yields (up to quantitative) and has a better solvability; the last factor plays a role in the case of certain unsaturated nitriles, which are hardly soluble in aqueous EtOH. The specific and superior action of the system Na_2CO_3–H_2O_2 could be explained by a weaker and milder basic nature of Na_2CO_3 than KOH and by a new potent oxidant formation *in situ*, sodium carbonate sesquiperhydrate $2Na_2CO_3 \times 3H_2O_2$, also referred as ''sodium percarbonate'' (SPC). The chemistry of SPC has been reviewed [37]. Although SPC has proved to be readily available, cheap, and effective oxidant, only a few reports on the Radziszewski nitrile hydrolysis [31,38,39] or Payne epoxidation [40] with SPC are known to date. Therefore, we attempted to repeat the oxidation of unsaturated nitriles **4** with Na_2CO_3–H_2O_2 in acetonic solution (method B). Comparing the methods A and B, one can note that method B is preferable over the method A because of higher yields (almost quantitative), milder conditions, and shortened reaction time.

All the obtained compounds **7a–f** are colorless crystalline solids, easily soluble in hot EtOH, acetone, DMSO, or DMF, and insoluble in water, hydrocarbons, benzene, or CCl_4. The structures of spiroepoxyamides **7** were supported by the spectral data and microanalysis analysis data as well. Thus, the IR spectra of **7** revealed the lack of conjugated —C≡N group; instead, broad and intensive bands corresponding to $C(O)NH_2$ moiety appeared at ν = 3405–3380 (N—H) and 1683–1655 (C=O) cm^{-1}. The ^{1}H-NMR spectra revealed signals of $C(O)NH_2$ protons as two broadened peaks at δ 7.60–7.30 ppm and sharp characteristic singlets at δ 7.95–7.66 ppm corresponding to thiazole C(5)H protons.

In conclusion, we have developed a simple and convenient method to obtain new spirooxiranes, 1-oxaspiro[2.5]octane-2-carboxamide and 1-oxaspiro[2.4]heptane-2-carboxamide derivatives, based on the Radziszewski oxidation of cycloalkylidene acetonitriles by means of H_2O_2/KOH in EtOH or SPC in acetonic solution.

EXPERIMENTAL

Melting points were measured on a Kofler hot-stage apparatus. Elemental analyses for C, H, and N were conducted using a Perkin–Elmer C, H, and N analyzer; their results were found to be in good agreement with the calculated values (±0.2%). IR spectra were recorded on an IKS-29 spectrophotometer in Nujol mulls. The ^{1}H-NMR spectra were performed on Bruker Avance II 400 (399.97 MHz) spectrometer in DMSO-d_6 solutions with Me_4Si as the internal standard. The ^{13}C-NMR spectra were performed on Bruker Avance DRX 500 (125.771 MHz) spectrometer in $CDCl_3$. The purity of all obtained compounds was checked by TLC on Silufol® UV 254 plates (sorbent—Silpearl, large-pore silica gel after Pitra with luminescent indicator for UV 254 on the aluminum foil, binder—starch) in the acetone–heptane (1:1) system; spots were visualized with iodine vapors and UV light. Cyanothioacetamide (**1**) was prepared by known procedure [41]. Unsaturated thioamides **5a,b** were obtained from cyanothioacetamide (**1**) and cycloalkanones by slightly modified Knoevenagel procedure described by Elgemeie *et al*. [36].

2-Cyano-2-cyclopentylideneethanethioamide (5a). A 500-mL one-necked round-bottom flask equipped with the Dean-Stark trap and a reflux condenser was charged with 20.0 mL (0.226 mol) of cyclopentanone, 20.0 g (0.2 mol) of cyanothioacetamide (**1**), 150 mL of benzene, 0.7 mL (7 mmol) of piperidine, and 0.5 mL (8.7 mmol) of AcOH. The reaction mixture was heated under reflux until no more water separated in the Dean-Stark trap (about 4 h). Benzene was removed *in vacuo* to give 40–45 mL of red viscous syrup. It was treated with 100 mL of boiling ether, filtered through a paper filter, and left to stand in refrigerator overnight. The product was filtered off and washed subsequently with cold ether, H_2O, and cold ether to give 19.2 g (58%) of pure thioamide **5a** as yellow crystalline solid, mp 115–118°C (ether) (Ref. [36]: 108°C); IR and ^{1}H-NMR spectra were found to be in agreement with those reported in Ref. [36]. Anal. Calcd. for $C_8H_{10}N_2S$ (166.25): C, 57.80; H, 6.06; N, 16.85; Found: C, 58.03; H, 6.10; N, 16.74.

2-(4-*tert*-Butylcyclohexylidene)-2-cyanoethanethioamide (5b). This compound was prepared as follows: a 250-mL one-necked round-bottom flask equipped with the Dean-Stark trap and a reflux condenser was charged with 15.4 g (0.1 mol) of 4-(*tert*-butyl)cyclohexanone (purchased from Acros), 10.0 g (0.1 mol) of cyanothioacetamide (**1**) [41], 100 mL of benzene, 0.2 mL (2 mmol) of piperidine, and 2.0 mL (35 mmol) of AcOH. The reaction mixture was heated to reflux whereupon the required amount of liberated water (about 2.0 mL) was collected in the Dean-Stark trap, which usually takes 4–5 h. Thereafter, benzene was removed *in vacuo*, and a deep-yellow oily residue was treated with 100–120 mL of boiling ether. After cooling to ambient temperature, a yellow crystalline solid began to separate. The mixture was allowed to stand overnight, and then the product was filtered off and washed subsequently with cold ether, H_2O, and cold ether to give 17.7 g (75%) of pure thioamide **5b** as yellow powder, mp 134–136°C (ether); ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 10.31 and 9.67 (both br s, 2H, $C(S)NH_2$), 2.69–1.13 (m, 9H, $(CH_2CH_2)_2CH$), 0.83 (s, 9H, *t*-C_4H_9) ppm; ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 194.10, 160.80, 116.39, 110.54, 46.83, 40.55, 40.48, 40.38, 40.31, 40.22, 40.16, 40.15, 40.05, 39.98, 39.89, 39.72, 39.55, 34.06, 32.64, 31.37, 28.52, 28.14, 27.85. Anal. Calcd. for $C_{13}H_{20}N_2S$ (236.38): C, 66.06; H, 8.53; N, 11.85; Found: C, 66.20; H, 8.55; N, 11.86.

2-Cyano-2-cyclohexylideneethanethioamide (5c). A solution of 15.0 g (0.15 mol) of cyanothioacetamide (**1**), 16.0 mL (0.155 mol) of cyclohexanone, 0.6 mL (6 mmol) of piperidine,

and 0.5 mL (8.7 mmol) of AcOH was heated under reflux for 6 h in a Dean-Stark apparatus. Benzene was removed *in vacuo*, and the residue was treated with 100 mL of boiling ether and left to stand at ambient temperature. When no crystals appeared after cooling, crystallization was induced by the addition of a seed crystal or scratching with glass rod. A mixture was left to stand in refrigerator overnight, and yellow crystalline product was filtered off and washed subsequently with cold ether, cold EtOH, and cold ether to give 18.9 g (70%) of pure thioamide **5c**, mp 133–135°C (ether) (Ref. [36]: 119°C); IR and ^{1}H-NMR spectra were found to be in agreement with those reported in Ref. [36].

(4-Arylthiazol-2-yl)cycloalkylideneacetonitriles 4a–f. General procedure. 2-Cyano-2-cycloalkylideneethanethioamide **5a–c** (6 mmol) and corresponding α-bromo ketone **6a–e** (6 mmol) were dissolved in minimal amounts of DMF (2–3 mL). The mixture was gently refluxed for 2–3 min, cooled, diluted with EtOH, and left to stand overnight (for **6c–e**—diluted with cold EtOH and kept in freezer (+4°C) for 3 h). The precipitate formed was filtered off, washed with 50% aq. EtOH and twice with cold EtOH. The obtained compounds **4a–f** were pure enough for analytical purposes and are suitable for use without further purification.

Cyclopentylidene-2-(4-phenylthiazol-2-yl)acetonitrile (4a). This compound was obtained from 1.00 g (6 mmol) of 2-cyano-2-cyclopentylideneethanethioamide **5a** and 1.20 g (6 mmol) of α-bromoacetophenone **6a** as beige crystals, yield 1.57 g (98%), mp 148–150°C (EtOH); IR (nujol): ν = 2214 (C≡N), 1605 (C=C) cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.12 (s, 1H, thiazolyl C(5)H), 7.96 (br d, 2H, J = 7.6 Hz, phenyl C(2)H, C(6)H), 7.40 (m, 3H, phenyl C(3)H-C(5)H), 2.95 and 2.83 (2 m, 4H, cyclopent. C(2)H$_2$, C(5)H$_2$), and 1.93–1.82 (m, 4H, cyclopent. C(3)H$_2$, C(4)H$_2$) ppm. Anal. Calcd. for $C_{16}H_{14}N_2S$ (266.37): C, 72.15; H, 5.30; N, 10.52; Found: C, 72.25; H, 5.29; N, 10.54.

Cyclopentylidene-2-[4-(4-methylphenyl)thiazol-2-yl]acetonitirile (4b). This compound was obtained from 1.00 g (6 mmol) of **5a** and 1.28 g (6 mmol) of 2-bromo-1-(4-methylphenyl)ethanone **6b** as beige crystals, yield 1.62 g (96%), mp 161–161.5°C (EtOH); IR (nujol): ν = 2218 (C≡N), 1605 (C=C) cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.83 (s, 1H, thiazolyl C(5)H), 7.81 (br d, 2H, J = 8.0 Hz, arom. C(2)H, C(6)H), 7.19 (br d, 2H, J = 8.0 Hz, arom. C(3)H, C(5)H), 3.04 and 2.87 (2 m, 4H, cyclopent. C(2)H$_2$, C(5)H$_2$), 2.39 (s, 3H, CH$_3$), and 1.99–1.87 (m, 4H, cyclopent. C(3)H$_2$, C(4)H$_2$) ppm. Anal. Calcd. for $C_{17}H_{16}N_2S$ (280.39): C, 72.82; H, 5.75; N, 9.99; Found: C, 72.93; H, 5.75; N, 10.01.

Cyclopentylidene-2-[4-(4-methoxyphenyl)thiazol-2-yl]acetonitirile (4c). This compound was obtained from 0.50 g (3 mmol) of **5a** and 0.69 g (3 mmol) of 2-bromo-1-(4-methoxyphenyl)ethanone **6c** as beige crystalline solid, yield 0.83 g (93%), mp 133–134.5°C (AcOEt); IR (nujol): ν = 2210 (C≡N), 1610 (C=C) cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 7.86 (br d, 2H, J = 8.7 Hz, arom. C(2)H, C(6)H), 7.75 (s, 1H, thiazolyl C(5)H), 6.92 (br d, 2H, J = 8.7 Hz, arom. C(3)H, C(5)H), 3.83 (s, 3H, OCH$_3$), 3.03 and 2.87 (2 m, 4H, cyclopent. C(2)H$_2$, C(5)H$_2$), and 1.98–1.89 (m, 4H, cyclopent. C(3)H$_2$, C(4)H$_2$) ppm. Anal. Calcd. for $C_{17}H_{16}N_2OS$ (296.39): C, 68.89; H, 5.44; N, 9.45; Found: C, 68.95; H, 5.42; N, 9.43.

(4-*tert*-Butylcyclohexylidene)-2-[4-(4-methylphenyl)thiazol-2-yl]acetonitirile (4d). This compound was obtained from 1.40 g (6 mmol) of **5b** and 1.28 g (6 mmol) of 2-bromo-1-(4-methylphenyl)ethanone **6b** as beige crystalline solid, yield 1.68 g (80%), mp 95–96.5°C (EtOH); IR (nujol): ν = 2220 (C≡N), 1603 (C=C) cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 7.85 (s, 1H, thiazolyl C(5)H), 7.78 (br d, 2H, J = 7.8 Hz, arom. C(2)H, C(6)H), 7.19 (br d, 2H, J = 7.8 Hz, arom. C(3)H, C(5)H), 2.38 (s, 3H, ArCH$_3$), 2.45–2.30, 2.20–2.04, and 1.43–1.25 (3 m, 9H, (CH$_2$)$_2$CH(CH$_2$)$_2$), and 0.91 (s, 9H, *t*-C$_4$H$_9$) ppm. Anal. Calcd. for $C_{22}H_{26}N_2S$ (350.53): C, 75.38; H, 7.48; N, 7.99; Found: C, 75.50; H, 7.47; N, 8.02.

2-[4-(4-Chlorophenyl)thiazol-2-yl]cyclohexylideneacetonitrile (4e). This compound was obtained from 1.08 g (6 mmol) of **5c** and 1.40 g (6 mmol) of 2-bromo-1-(4-chlorophenyl)ethanone **6d** as yellow needles, yield 1.50 g (80%), mp 93–94°C (EtOH); IR (nujol): ν = 2211 (C≡N), 1605 (C=C) cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.34 (s, 1H, thiazolyl C(5)H), 7.98 (br d, 2H, J = 8.5 Hz, arom. C(2)H, C(6)H), 7.53 (br d, 2H, J = 8.5 Hz, arom. C(3)H, C(5)H), 2.97 and 2.70 (both m, each 2H, cycloalk. H$_2$C─C=), and 1.78–1.63 (m, 6H, cycloalk.) ppm. Anal. Calcd. for $C_{17}H_{15}ClN_2S$ (314.84): C, 64.86; H, 4.80; N, 8.90; Found: C, 64.97; H, 4.79; N, 8.92.

2-[4-(4-Bromophenyl)thiazol-2-yl]cyclohexylideneacetonitrile (4f). This compound was obtained from 1.08 g (6 mmol) of **5c** and 1.67 g (6 mmol) of 2-bromo-1-(4-bromophenyl)ethanone **6e** as sand-colored crystals, yield 1.57 g (73%), mp 103–104°C (EtOH) (Ref. [42]: 100–101°C); IR and ^{1}H-NMR spectra were found to be identical with the one described in Ref. [42]. Anal. Calcd. for $C_{17}H_{15}BrN_2S$ (359.29): C, 56.83; H, 4.21; N, 7.80; Found: C, 56.90; H, 4.21; N, 7.82.

2-(4-Arylthiazol-2-yl)-1-oxaspiro[2.*n*]alkane-2-carboxamides (7a–f). General procedure.

Method A. A suspension of finely powdered cycloalkylideneacetonitrile **4a–f** (2 mmol) in 8–10 mL of EtOH was stirred at room temperature while 0.5 mL (0.9 mmol) of 10% aqueous KOH and an excess of 32% aqueous H_2O_2 (1.9 mL, 20 mmol) were subsequently added dropwise. The mixture was slowly heated under vigorous stirring until exothermic reaction was initiated and whereupon a clear, almost colorless solution formed (Oxygen is extremely evolved). The mixture was stirred at room temperature for 1 h and then was kept in freezer at +4°C for 2 h. A colorless crystalline solid was filtered off and washed with cold 50% aq. EtOH to afford pure oxaspiro[2.*n*]cycloalkane-2-carboxamides **7a–f**. For analytical purposes, compounds were recrystallized from appropriate solvents.

Method B. A 25-mL beaker was charged with corresponding cycloalkylideneacetonitrile **4** (2 mmol) and 10 mL of acetone. To a clear solution formed, an aqueous 10% Na_2CO_3 solution (0.4 mL, 0.4 mmol) and an excess of 32% aq. H_2O_2 (1.0 mL, 10 mmol) were subsequently added (the colorless precipitate of SPC may form at first). The mixture was gently refluxed under vigorous stirring for 5–7 min, allowed to cool, and thereafter treated with ice-cold water (10 mL). The white crystalline solid was filtered off and washed with a plenty of water and cold 50% aq. EtOH to give pure oxaspiro[2.*n*]cycloalkane-2-carboxamides **7**.

2-(4-Phenylthiazol-2-yl)-1-oxaspiro[2.4]heptane-2-carboxamide (7a). This compound was obtained as colorless crystals, yield 76% (method A), mp 165–166.5°C (EtOH); IR (nujol): ν = 3380 ($NH_{2\ amide}$), 1655 ($C{=}O_{amide}$) cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 7.92 (br d, 2H, J = 7.4 Hz, arom. C(2)H, C(6)H), 7.81 (s, 1H, thiazolyl C(5)H), 7.59 (br s, 1H, CONH$_2$), 7.40–7.28 (m, 3H of arom. C(3)H–C(5)H and 1H of CONH$_2$ overlapped), and 2.03–1.66 (m, 8H, (CH$_2$)$_4$) ppm.

Anal. Calcd. for $C_{16}H_{16}N_2O_2S$ (300.38): C, 63.98; H, 5.37; N, 9.33; Found: C, 64.09; H, 5.38; N, 9.35.

2-[4-(4-Methylphenyl)thiazol-2-yl]-1-oxaspiro[2.4]heptane-2-carboxamide (7b). This compound was obtained as colorless crystals, yield 81% (method A) or 95% (method B), mp 174–175°C (dec.) (EtOH/acetone = 1:1); IR (nujol): ν = 3400 ($NH_{2\ amide}$), 1660 ($C{=}O_{amide}$) cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 7.80 (d, 2H, J = 8.0 Hz, arom. C(2)H, C(6)H), 7.73 (s, 1H, thiazolyl C(5)H), 7.59 and 7.39 (2 br s, 2H, $CONH_2$), 7.19 (d, 2H, J = 8.0 Hz, arom. C(3)H, C(5)H), and 2.38–1.70 (m, 8H, $(CH_2)_4$) ppm. Anal. Calcd. for $C_{17}H_{18}N_2O_2S$ (314.41): C, 64.94; H, 5.77; N, 8.91; Found: C, 64.99; H, 5.77; N, 8.91.

2-[4-(4-Methoxyphenyl)thiazol-2-yl]-1-oxaspiro[2.4]heptane-2-carboxamide (7c). This compound was obtained as colorless crystals, yield 76% (method A), mp 161–162°C (EtOH/acetone = 1:1); IR (nujol): ν = 3380 ($NH_{2\ amide}$), 1655 ($C{=}O_{amide}$) cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 7.82 (d, 2H, J = 8.7 Hz, arom. C(2)H, C(6)H), 7.66 (s, 1H, thiazolyl C(5)H), 7.56 and 7.41 (2 br s, 2H, $CONH_2$), 6.89 (d, 2H, J = 8.7 Hz, arom. C(3)H, C(5)H), 3.80 (s, 3H, OMe), and 1.98–1.64 (m, 8H, $(CH_2)_4$) ppm. Anal. Calcd. for $C_{17}H_{18}N_2O_3S$ (330.41): C, 61.80; H, 5.49; N, 8.48; Found: C, 61.92; H, 5.50; N, 8.47.

6-*tert*-Butyl-2-[4-(4-methylphenyl)thiazol-2-yl]-1-oxaspiro[2.5]octane-2-carboxamide (7d). This compound was obtained as white powder, yield 84% (method A) or ~100% (method B), mp 185–187°C (EtOH); IR (nujol): ν = 3405 ($NH_{2\ amide}$), 1683 ($C{=}O_{amide}$) cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 7.80 (d, 2H, J = 8.0 Hz, arom. C(2)H, C(6)H), 7.73 (s, 1H, thiazolyl C(5)H), 7.56 and 7.30 (2 br s, 2H, $CONH_2$), 7.18 (d, 2H, J = 8.0 Hz, arom. C(3)H, C(5)H), 2.37 (s, 3H, $ArCH_3$), 1.86–1.11 (m, 9H, $(CH_2)_2CH(CH_2)_2$), and 0.87 (s, 9H, t-C_4H_9) ppm. Anal. Calcd. for $C_{22}H_{28}N_2O_2S$ (384.54): C, 68.72; H, 7.34; N, 7.28; Found: C, 68.81; H, 7.35; N, 7.30.

2-[4-(4-Chlorophenyl)thiazol-2-yl]-1-oxaspiro[2.5]octane-2-carboxamide (7e). This compound was obtained as colorless crystals, yield 84% (method A) or 97% (method B), mp 181–182°C (EtOH/acetone = 1:1); IR (nujol): ν = 3365 ($NH_{2\ amide}$), 1645 ($C{=}O_{amide}$) cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 7.96 (m, 3 H, signals overlapped: d, 2 H, Ar, J = 8.5 Hz, and s, thiazolyl C(5)H), 7.60 (br s, 1 H, $CONH_2$), 7.39 (m, 3 H, signals overlapped: d, 2 H, Ar, J = 8.5 Hz, and s, 1 H, $CONH_2$), 1.75 (m, 4 H, 2 CH_2), and 1.51 (m, 6 H, $(CH_2)_3$) ppm. Anal. Calcd. for $C_{17}H_{17}ClN_2O_2S$ (348.85): C, 58.53; H, 4.91; N, 8.03; Found: 58.60; H, 4.90; N, 8.05.

2-[4-(4-Bromophenyl)thiazol-2-yl]-1-oxaspiro[2.5]octane-2-carboxamide (7f). This compound was obtained as colorless crystals, yield 90% (method A) or ~100% (method B), mp 211–213°C (EtOH/acetone = 1:1); IR (nujol): ν = 3375 ($NH_{2\ amide}$), 1630 ($C{=}O_{amide}$) cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 7.95 (s, 1 H, thiazolyl C(5)H), 7.89 (d, 2 H, arom. C(2)H, C(6)H, J = 8.5 Hz), 7.58 (br s, 1 H, $CONH_2$), 7.52 (d, 2 H, arom. C(3)H, C(5)H, J = 8.5 Hz), 7.35 (br s, 1 H, $CONH_2$), 1.74 (m, 4 H, 2 CH_2), and 1.50 (m, 6 H, $(CH_2)_3$) ppm. Anal. Calcd. for $C_{17}H_{17}BrN_2O_2S$ (393.31): C, 51.92; H, 4.36; N, 7.12; Found: C, 52.00; H, 4.35; N, 7.10.

REFERENCES AND NOTES

[1] Dryuk, V. G.; Kartsev, V. G.; Voitsekhovskaya, M. A. Oxiranes—Synthesis and Biological Activity. Mechanism, Associative and Steric Effects of Alkene Peroxide Epoxidation; Bogorodsky Pechatnik: Moscow, 1999; p 528 (in Russian).

[2] Kas'yan, L. I.; Seferova, M. F.; Okovitiy, S. I. Alicyclic Epoxy Compounds. Methods of Synthesis; Dnepropetrovsky National University Publishing Office: Dnepropetrovsk, 2003; p 208 (in Russian).

[3] Padwa, A.; Murphree, S. S. ARKIVOC 2006, 3, 6.

[4] Gorzinsky-Smith, J. Synthesis 1984, 629, and references cited therein.

[5] Salomatina, O. V.; Yarovaya, O. I.; Barkhash, V. A. Russ J Org Chem 2005, 41, 155.

[6] Kas'yan, L. I.; Kas'yan, A. O.; Okovitiy, S. I.; Tarabara, I. N. Alicyclic Epoxy Compounds. The Reactivity; Dnepropetrovsky National University Publishing Office: Dnepropetrovsk, 2003; p 516 (in Russian).

[7] The chemistry of spirooxiranes has been reviewed recently: Kas'yan, L. I.; Kas'yan, A. O.; Tarabara, I. N. Russ J Org Chem 2001, 37, 1361.

[8] For review on the naturally occurred spirooxiranes see: Jarvis, B. B.; Mazzola, E. P. Acc Chem Res 1982, 15, 388.

[9] Traynham, Y. G.; Pascual, O. S. Tetrahedron 1959, 7, 165.

[10] For reviews on the Corey-Chaykowski oxirane synthesis see: (a) Aubé J. In Comprehensive Organic Synthesis; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 1, p 819; (b) Gololobov, Y. G.; Nesmeyanov, A. N.; Lysenko, V. P.; Boldeskul, I. E. Tetrahedron 1987, 43, 2609.

[11] (a) Kohler, E. P.; Tishler, M.; Potter, H.; Thompson, H. T. J Am Chem Soc 1939, 61, 1057; (b) Gutsche, C. D. In Organic Reactions; Adams, R., Ed.; Wiley: New York, 1954; Vol. 8, p 364; (c) Okaev, E. V.; Zvonok, A. M. Chem Heterocycl Compd 1995, 31, 249.

[12] For instance see: (a) Tarhouni, R.; Kirschleger, B.; Rambaud, M.; Villieras, J. Tetrahedron Lett 1984, 25, 835; (b) Einhorn, C.; Allavena, C.; Luche, J. L. J Chem Soc Chem Commun 1988, 333.

[13] (a) Newman, M. S.; Magerlein, B. J. In Organic Reactions; Adams, R., Ed.; Wiley: New York, 1949; Vol. 5, pp 413–440; (b) Ballester, M. Chem Rev 1955, 55, 283; (c) Rosen, T. In Comprehensive Organic Synthesis; Heathcock, C. H., Ed.; Pergamon Press: Oxford, UK, 1991; Vol. 2, pp 409–439; (d) Aggarwal, V. K.; Badine, D. M.; Moorthie, V. A. In Aziridines and Epoxides in Organic Synthesis; Yudin, A. K., Ed.; Wiley-VCH Verlag: Weinheim, 2006; p 1.

[14] (a) Adam, W.; Hadjiarapoglou, L.; Jäger, V.; Seidel, B. Tetrahedron Lett 1989, 30, 4223; (b) Adam, W.; Hadjiarapoglou, L.; Nestler, B. Tetrahedron Lett 1990, 31, 331; (c) Adam, W.; Hadjiarapoglou, L. Chem Ber 1990, 123, 2077; (d) Adam, W.; Hadjiarapoglou, L.; Smerz, A. Chem Ber 1991, 124, 227.

[15] (a) Adam, W.; Curci, R.; Edwards, J. O. Acc Chem Res 1989, 22, 205; (b) Adam, W.; Hadjiarapoglou, L.; Curci, R.; Mello, R. In Organic Peroxides; Ando, W., Ed.; Wiley: West Sussex, UK, 1992; p 195.

[16] Cope, A. C.; Burton, P. E. J Am Chem Soc 1960, 82, 5439.

[17] Sevin, A.; Dense, O. Bull Chim Soc Fr 1974, 5/6 (Part 2), 963.

[18] (a) Knorr, R.; Freudenreich, J.; von Roman, Th.; Mehlstaeubl, J.; Boehrer, P. Tetrahedron 1993, 49, 8837; (b) Fringuelli, F.; Germani, R.; Pizzo, F.; Savelli, G. Tetrahedron Lett 1989, 30, 1427.

[19] Brodfuehrer, P. R.; Sattleberg, S. T. R. U.S. Pat. 6,353,122 (2002); Available at: http://ep.espacenet.com/.

[20] Schwartz, L. H.; Feil, M.; Kascheres, A. J.; Kaufmann, K.; Levine, A. M. Tetrahedron Lett 1967, 39, 3785.

[21] Crandall, J. K.; Conover, W. W. J Org Chem 1978, 43, 3533.

[22] (a) Endo, A.; Saito, M.; Ogura, T.; Fusezaki, Y. Nihon Kagaku Zasshi 1965, 86, 426; (b) Endo, A.; Okada, Y.; Fusezaki, Y.; Saito, M. Nihon Kagaku Zasshi 1965, 86, 108; (c) Endo, A.; Saito,

M.; Takahashi, M.; Nagata, K.; Fusezaki, Y. Nihon Kagaku Zasshi 1965, 86, 1304; (d) Endo, A.; Saito, M.; Fusezaki, Y. Nihon Kagaku Zasshi 1964, 85, 593; (e) Endo, A.; Saito, M.; Wada, Y.; Fusezaki, Y. Nihon Kagaku Zasshi 1964, 85, 797.

[23] (a) Paquette, L. A.; Underiner, T. L.; Gallucci, J. C. J Org Chem 1992, 57, 86; (b) Kas'yan, L. I.; Batog, A. E.; Seferova, M. F.; Tomalak, N. V.; Batrak, T. A.; Levashova, G. B.; Dryuk, V. G. Soviet Union Pat. 1,643,540 (1991); Available at: http://ep.espacenet.com; (c) Kas'yan, L. I.; Seferova, M. F.; Gorb, L. G.; Kozina, M. P.; Dryuk, V. G. Russ J Org Chem 1989, 25, 1131.

[24] (a) Payne, G. B.; Williams, P. H. J Org Chem 1961, 26, 651; (b) Payne, G. B.; Deming, P. H.; Williams, P. H. J Org Chem 1961, 26, 659; (c) Payne, G. B. Tetrahedron 1962, 18, 763; (d) Payne, G. B.; Deming, P. H. U.S. Pat. 3,053,856 (1962); Available at: http://ep.espacenet.com.

[25] (a) McIsaac, J. E., Jr.; Ball, R. E.; Behrman, E. J. J Org Chem 1971, 36, 3048; (b) Arias, L. A.; Adkins, S.; Nagel, C. J.; Bach, R. D. J Org Chem 1983, 48, 888; (c) Bachmann, C.; Gesson, J. P.; Renoux, B.; Tranoy, I. Tetrahedron Lett 1998, 39, 379; (d) Frank, W. C. Tetrahedron Asymmetry 1998, 9, 3745; (e) Laus, G. J Chem Soc Perkin Trans 2 2001, 864; (f) von Holleben, M. L. A.; Livotto, P. R.; Schuch, C. M. J Braz Chem Soc 2001, 12, 42; (g) Shi, Y. U.S. Pat. 6,369,245 (2002); Available at: http://ep.espacenet.com.

[26] (a) Tsuno, T.; Sugiyama, K. Heterocycles 1990, 31, 1591; (b) Tsuno, T.; Sugiyama, K.; Ago, H. Heterocycles 1994, 38, 2631.

[27] Igarashi, M.; Midorikawa, H. J Org Chem 1963, 28, 3088.

[28] Radziszewski, B. Ber Deutsch Chem Ges 1885, 18, 355.

[29] For further developments and extensions of the Radziszewski oxidative nitrile hydrolysis see: (a) Deinert, J. J Prakt Chem 1895, 52, 431; (b) Friedlander, P.; Weisberg, J. Ber Deutsch Chem Ges 1895, 28, 1838; (c) Rupe, H.; von Majewski, K. Ber Deutsch Chem Ges 1900, 33, 3401; (d) Dubsky, J. V. J Prakt Chem 1916, 93, 137; (e) Bogert, M. T.; Hand, W. F. J Am Chem Soc 1902, 24, 1031; (f) Keiser, E. H.; McMaster, L. Am Chem J 1913, 49, 81; (g) McMaster, L.; Langreck, F. B. J Am Chem Soc 1917, 39, 103; (h) Knowles, E. C.; Cloke, J. B. J Am Chem Soc 1932, 54, 2028; (i) McMaster, L.; Noller, C. R. J Indian Chem Soc 1935, 12, 652; Chem Abstr 1936, 30, 1736; (j) Wiberg, K. B. J Am Chem Soc 1953, 75, 3961; (k) Payne, G. B. J Org Chem 1961, 26, 668; (l) Zhdanov, Yu. A.; Alekseev, Yu. E.; Kurdanov, H. A.; Guterman, G. E. Russ J Gen Chem 1972, 42, 481 (In Russian); (m) Eastmond, G. C.; Paprotny, J.; Steiner, A.; Swanson, L. New J Chem 2001, 25, 379; (n) Burakova, E. A.; Burchak, O. N.; Chibiryaev, A. M. Russ Chem Bull Int Ed 2002, 51, 1829; (o) Piazza, G.; Pamukcu, R. U.S. Pat. 6,479,520 (2002); Available at: http://ep.espacenet.com/; (p) Brauer, H. D.; Eilers, B.; Lange, A. J Chem Soc Perkin Trans 2 2002, 1288; (q) Ren, Z.; Cao, W.; Chen, J.; Lu, Y.; Wu, D. J Heterocycl Chem 2007, 44, 999.

[30] Zilberman, E. N. Reactions of Nitriles; Khimia: Moscow, 1972; p 74 (in Russian).

[31] Murray, J. V.; Cloke, J. B. J Am Chem Soc 1934, 56, 2749.

[32] Payne, G. B. J Org Chem 1961, 26, 663.

[33] (a) Kornfeld, E. C.; Fornefeld, E. J.; Kline, G. B.; Mann, M. J.; Morrison, D. E.; Jones, R. G.; Woodward, R. B. J Am Chem Soc 1956, 78, 3087; (b) Igarashi, M.; Midorikawa, H. Bull Chem Soc Jpn 1961, 34, 1543; (c) Sakurai, A.; Igarashi, M.; Midorikawa, H. Bull Chem Soc Jpn 1965, 38, 1030.

[34] For review on the chemistry of cyanothioacetamide see: Litvinov, V. P. Russ Chem Rev 1999, 68, 737.

[35] Dotsenko, V. V.; Krivokolysko, S. G.; Rusanov, E. B.; Gutov, A. V.; Litvinov, V. P. Russ Chem Bull Int Ed 2007, 56, 1470.

[36] Elgemeie, G. E. H.; Regaila, H. A.; Shehata, N. J Chem Soc Perkin Trans 1 1990, 1267.

[37] For reviews on the SPC chemistry see: (a) McKillop, A.; Sanderson, W. R. Tetrahedron 1995, 51, 6145; (b) McKillop, A.; Sanderson, W. R. J Chem Soc Perkin Trans 1 2000, 471; (c) Jones, C. W. Applications of Hydrogen Peroxide and Derivatives; The Royal Society of Chemistry: Cambridge, UK, 1999; p 282.

[38] Boulouard, M.; Rault, S.; Dallemagne, P.; Alsaidi, A.; Robba, M. J Heterocycl Chem 1996, 33, 87.

[39] Kabalka, G. W.; Deshpande, S. M.; Wadgaonkar, P. P.; Chatla, N. Synth Commun 1990, 20, 1445.

[40] Ando, T.; Cork, D. G.; Kimura, T. Chem Lett 1986, 665.

[41] Howard, E. G. U.S. Pat. 2,733,260 (1956); Available at: http://ep.espacenet.com/.

[42] Dyachenko, A. D.; Desenko, S. M.; Dyachenko, V. D. Kharkov Univer Bull Chem Ser 2006, 549, 46 (in Russian).