REACTION OF *O*-ALKYL-*N*-SUBSTITUTED IMINOTHIOCARBONATES WITH BROMOACETYL BROMIDE. A GENERAL METHOD FOR THE SYNTHESIS OF 3-SUBSTITUTED 1,3-THIAZOLIDINE-2,4-DIONES

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Reaction of sodium salts of *O*-methyl-*N*-substituted iminothiocarbonates with bromoacetyl bromide represents a new general method for preparation of 3-substituted 1,3-thiazolidine-2,4-diones in good yields and high purity. The structure of the synthesized products has been confirmed by ^{1}H NMR, ^{13}C NMR, IR and mass spectroscopy as well as by independent synthesis.

Key words: Isothiocyanates; Iminothiocarbonates; 1,3-Thiazolidine-2,4-diones.

In our previous communication[1] we studied the reaction of sodium salts of *N*-(9-acridinyl)-iminothiocarbonates with alkyl bromoacetates which proceeded under formation of the corresponding spiro[dihydroacridine-9(10*H*),4′-thiazolines]. The unusual course of this reaction prompted us to investigate the analogous reaction with bromoacetyl bromide. As starting compounds we used 9-isothiocyanatoacridines **1a**–**1c** which on addition of sodium methoxide afforded sodium salts of *O*-methyl-*N*-(9-acridinyl)iminothiocarbonates[2] **2a**–**2c**. In principle, reaction of these salts with bromoacetyl bromide can afford two structural isomers: thiazolidines **4a**–**4c** or oxathiolanes **5a**–**5c** (Scheme 1), provided that the sulfur atom in compounds **2** is preferentially alkylated (in accord with the literature[3]) and not acylated (the acyl carbon atom is a harder acid). Intramolecular cyclization of the intermediates **3a**–**3c**, involving the imine nitrogen and proceeding with simultaneous loss of methyl bromide, leads to thiazolidinediones **4a**–**4c**, whereas analogous cyclization, involving the methoxy oxygen, affords the isomeric 2-imino-1,3-oxathiolan-5-ones **5a**–**5c**.

Proton NMR, ^{13}C NMR and mass spectra have unequivocally shown that the reaction affords exclusively the corresponding thiazolidine-2,4-diones **4a**–**4c** in high yields and purity. These compounds were also synthesized by Turkevich[4] by reaction of 9-chloro-

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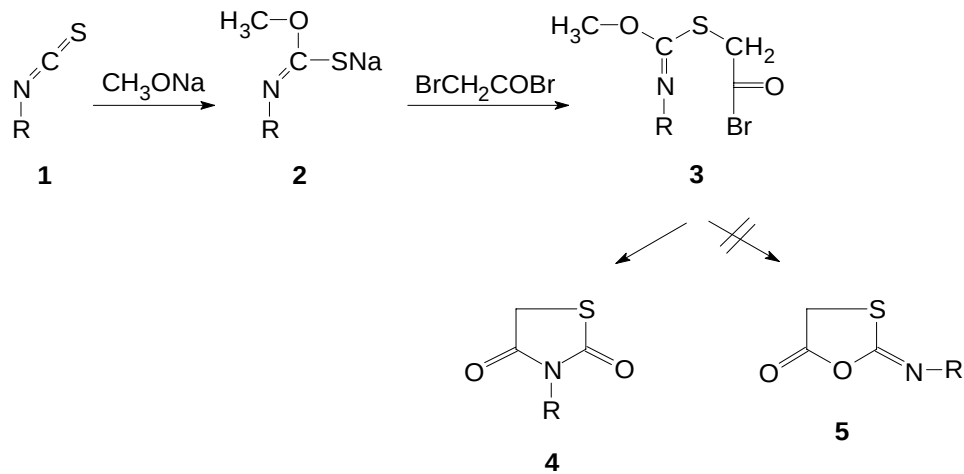
acridines with potassium salt of 1,3-thiazolidine-2,4-dione. The published melting points differed substantially from our values and therefore we tried to exclude the possibility of a different crystalline modification. However, crystallization of compound **4a** from aqueous ethanol (as described in ref.[4]) did not change the melting point of our compound. It seems thus that the higher melting point of our compound is due to its higher purity. This, together with good yields and relatively facile preparation of the starting reactants, led us to extend the method to the synthesis of various types of *N*-substituted 1,3-thiazolidine-2,4-diones. Although there are many methods of preparation of such derivatives, no one is generally applicable (cf. refs[5–10]).

As starting compounds for all the types of derivatives served the corresponding alkyl, arylalkyl and aryl isothiocyanates, mostly commercially available. In this manner we prepared ten products of which the 3-(1-naphthyl) derivative **4j** was synthesized for



1-5	R	1-5	R
a	9-acridinyl	**f**	4-methoxyphenyl
b	2-chloro-9-acridinyl	**g**	4-bromophenyl
c	4-methyl-9-acridinyl	**h**	4-chlorophenyl
d	methyl	**i**	1-naphthyl
e	phenyl	**j**	1-naphthylmethyl

SCHEME 1

the first time. The structure of derivative **4g** has been confirmed also by an independent synthesis: reaction of the corresponding amine with carbon disulfide gave 3-(4-bromophenyl)-1,3-thiazolidine-2-thion-4-one which on reaction with mesitylnitrile oxide was converted into the dioxo derivative **4g**.

EXPERIMENTAL

Spectral measurements. Proton NMR spectra were measured on a Tesla BS 587 spectrometer (Tesla Brno, 80 MHz) in deuteriochloroform (compounds **4b**–**4j**) or in deuteriochloroform–hexadeuteriodimethyl sulfoxide (5 : 1) (compound **4a**) with tetramethylsilane as internal standard, ^{13}C NMR spectra were taken on a Tesla BS 567 instrument (Tesla Brno, 25 MHz) in deuteriochloroform (**4c**–**4e**, **4g**–**4j**) or in deuteriochloroform–hexadeuteriodimethyl sulfoxide (**4b**, **4f**), again with tetramethylsilane as standard. Compound **4a** was measured in hexadeuteriodimethyl sulfoxide and the signals were referenced to the solvent peak at 39.39 ppm. The chemical shifts are given in ppm (δ-scale). Infrared spectra were recorded on a Specord 75 IR instrument (Zeiss, Jena) in chloroform. Elemental analyses were performed on a Perkin–Elmer CHN 2400 analyzer, mass spectra were taken on an SSQ 710 Finnigan spectrometer (direct inlet, E_e = 70 eV, T = 150 °C, I_e = 200 μA).

Chemicals. Methyl and ethyl isothiocyanate were commercial products (Aldrich). 4-Methoxyphenyl, 4-bromophenyl and 4-chlorophenyl isothiocyanates were prepared by the thiophosgene method according to the literature[11–12]. Analogously were synthesized also 1-naphthyl isothiocyanate[13] and 1-naphthylmethyl isothiocyanate[14]. 9-Isothiocyanatoacridine and 4-methyl-9-isothiocyanatoacridine were obtained by reflux of the corresponding substituted 9-chloroacridines with AgSCN in toluene[15]. 2-Chloro-9-isothiocyanatoacridine was obtained by reaction of 2,9-dichloroacridine with KSCN at room temperature in a mixture of dichloromethane and water in the presence of tetrabutylammonium iodide[16].

General Procedure for Preparation of 3-Substituted 1,3-Thiazolidine-2,4-diones **4a**–**4j**

Solid sodium methoxide (1.62 g, 30 mmol) was added in portions to a stirred solution of isothiocyanate **1** (10 mmol) in anhydrous ether (30 ml). The reaction was monitored by TLC (benzene–acetone 5 : 2). The precipitate was filtered off, washed with ether and dried at room temperature. The obtained sodium salt of *O*-methyl-*N*-substituted iminothiocarbonate **2** (10 mmol) was suspended under nitrogen in dichloromethane (25 ml) and a solution of bromoacetyl bromide (1.31 ml, 15 mmol) in dichloromethane (10 ml) was slowly added under stirring. After stirring overnight, the solid was collected on filter and washed with small amount of dichloromethane. The filtrate was concentrated, the oily residue was mixed with small amount of ether and the obtained crystals were crystallized from an appropriate solvent (charcoal).

3-(9-Acridinyl)-1,3-thiazolidine-2,4-dione (**4a**): m.p. 230–233 °C (chloroform–hexane), reported[4] m.p. 138–140 °C (ethanol–water); yield 85%. IR spectrum: 1 768, 1 713, 1 692 (C=O). ^{1}H NMR spectrum: 4.59 s, 2 H (CH_2); 7.54–7.97 m, 6 H (ArH); 8.32 m, 2 H (ArH). ^{13}C NMR spectrum: 171.53 (2-C=O); 171.20 (4-C=O); 35.40 (5-CH_2); 122.67 (C-1′,8′); 127.69 (C-2′,7′); 130.92 (C-3′,6′); 129.28 (C-4′,5′); 135.36 (C-9′); 122.67 (C-8′a,9′a); 148.61 (C-4′a,10′a). Mass spectrum, *m/z* (%): 294 (100) [$M^{+\bullet}$] 220 (50) [$M^{+\bullet}$ – $SCOCH_2$].

3-(2-Chloro-9-acridinyl)-1,3-thiazolidine-2,4-dione (**4b**): m.p. 241–244 °C (chloroform–hexane), reported[4] m.p. 182–185 °C (ethanol–water); yield 82%. IR spectrum: 1 765, 1 692 (C=O). ^{1}H NMR spectrum: 4.44 s, 2 H (CH_2); 7.62–7.95 m, 5 H (ArH); 8.23–8.43 m, 2 H (ArH). ^{13}C NMR spectrum: 169.80 (2- and 4-C=O); 34.53 (5-CH_2); 120.30 (C-1′); 133.59 (C-2′); 131.65 (C-3′); 130.94 (C-4′);

129.26 (C-5′); 130.68 (C-6′); 128.10 (C-7′); 121.65 (C-8′); 134.19 (C-9′); 122.92 and 123.10 (C-8′a,9′a); 146.58 (C-4′a); 148.41 (C-10′a).

3-(4-Methyl-9-acridinyl)-1,3-thiazolidine-2,4-dione (**4c**): m.p. 180–184 °C (chloroform–hexane), reported[4] m.p. 195–197 °C (ethanol–water); yield 78%. IR spectrum: 1 765, 1 700 (C=O). ^{1}H NMR spectrum: 4.39 s, 2 H (CH_2); 7.48–7.92 m, 6 H (ArH); 8.39 m, 1 H (ArH); 2.97 s, 3 H (CH_3). ^{13}C NMR spectrum: 169.80 (2-C=O); 169.95 (4-C=O); 34.60 (5-CH_2); 119.71 (C-1′); 128.00 and 128.07 (C-2′,7′); 130.38 and 130.46 and 130.53 (C-3′,5′,6′); 138.26 (C-4′); 121.65 (C-8′); 135.24 (C-9′); 122.84 and 123.22 (C-8′a,9′a); 148.23 and 148.53 (C-4′a,10′a); 18.70 (CH_3).

3-Methyl-1,3-thiazolidine-2,4-dione (**4d**): m.p. 33–35 °C (ether), reported[17] m.p. 36–39 °C; yield 68%. IR spectrum: 1 745, 1 682, 1 674 (C=O). ^{1}H NMR spectrum: 3.99 s, 2 H (CH_2); 3.11 s, 3 H (CH_3). ^{13}C NMR spectrum: 171.74 (2-C=O); 171.48 (4-C=O); 33.82 (5-CH_2); 27.92 (CH_3).

3-Phenyl-1,3-thiazolidine-2,4-dione (**4e**): m.p. 143–145 °C (chloroform–hexane), reported[18] m.p. 143–145 °C; yield 82%. IR spectrum: 1 763, 1 702, 1 680 (C=O). ^{1}H NMR spectrum: 4.11 s, 2 H (CH_2); 7.15–7.67 m, 5 H (ArH). ^{13}C NMR spectrum: 170.88 (2-C=O); 170.59 (4-C=O); 33.78 (5-CH_2); 132.89 (C-1 of phenyl); 127.25 (2 × C-2 of phenyl); 129.41 (2 × C-3 of phenyl); 129.26 (C-4 of phenyl). Mass spectrum, *m/z* (%): 193 (69) [$M^{+\bullet}$], 119 (100) [C_6H_5NCO], 91 (30) [C_6H_5N], 74 (24) [SCH_2CO].

3-(4-Methoxyphenyl)-1,3-thiazolidine-2,4-dione (**4f**): m.p. 164–165 °C (chloroform–ether), reported[19] m.p. 166 °C; yield 87%. IR spectrum: 1 762, 1 692 1 684 (C=O). ^{1}H NMR spectrum: 4.09 s, 2 H (CH_2); 6.92–7.24 m, 4 H (ArH); 3.83 s, 3 H (CH_3O). ^{13}C NMR spectrum: 170.55 (2-C=O); 170.06 (4-C=O); 32.96 (5-CH_2); 124.71 (C-1 of phenyl); 127.73 (2 × C-2 of phenyl); 113.70 (2 × C-3 of phenyl); 158.98 (C-4 of phenyl); 54.61 (CH_3O).

3-(4-Bromophenyl)-1,3-thiazolidine-2,4-dione (**4g**): m.p. 160–163 °C (chloroform–ether), reported[20] m.p. 163 °C; yield 81%. IR spectrum: 1 764, 1 707, 1 688 (C=O). ^{1}H NMR spectrum: 4.11 s, 2 H (CH_2); 7.16 m, 2 H (ArH); 7.61 m, 2 H (ArH). ^{13}C NMR spectrum: 170.51 (2-C=O); 170.14 (4-C=O); 33.78 (5-CH_2); 131.73 (C-1 of phenyl); 128.78 (2 × C-2 of phenyl); 132.62 (2 × C-3 of phenyl); 123.29 (C-4 of phenyl).

3-(4-Chlorophenyl)-1,3-thiazolidine-2,4-dione (**4h**): m.p. 142–145 °C (chloroform–ether), reported[19] m.p. 145 °C; yield 74%. IR spectrum: 1 760, 1 708, 1 683 (C=O). ^{1}H NMR spectrum: 4.12 s, 2 H (CH_2); 7.22 m, 2 H (ArH); 7.46 m, 2 H (ArH). ^{13}C NMR spectrum: 170.62 (2-C=O); 170.25 (4-C=O); 33.78 (5-CH_2); 131.21 (C-1 of phenyl); 128.56 (2 × C-2 of phenyl); 129.68 (2 × C-3 of phenyl); 135.31 (C-4 of phenyl).

3-(1-Naphthyl)-1,3-thiazolidine-2,4-dione (**4i**): m.p. 154–156 °C (chloroform–ether), reported[21] m.p. 194 °C; yield 71%. IR spectrum: 1 761, 1 684, 1 679 (C=O). ^{1}H NMR spectrum: 4.12, 4.16 split signal, 2 H (CH_2); 7.22–7.64 m, 5 H (ArH); 7.82–8.02 m, 2 H (ArH). ^{13}C NMR spectrum: 170.70 (2- and 4-C=O); 34.08 (5-CH_2); 134.49 (C-1′); 121.54, 125.38, 126.73, 126.73, 127.51, 128.74, 130.50 (CH carbons); 129.45, 129.56 (quaternary carbons).

3-(1-Naphthylmethyl)-1,3-thiazolidine-2,4-dione (**4j**): m.p. 84–86 °C (chloroform–hexane); yield 75%. For $C_{14}H_{11}NO_2S$ (257.3) calculated: 65.35% C, 4.31% H, 5.44% N; found: 65.18% C, 4.20% H, 5.41% N. IR spectrum: 1 757, 1 695, 1 687 (C=O). ^{1}H NMR spectrum: 3.90 s, 2 H (CH_2); 7.29–7.65 m, 4 H (ArH); 7.75–7.91 m, 2 H (ArH); 8.23 m, 1 H (ArH); 5.22 s, 2 H ($ArCH_2$). ^{13}C NMR spectrum: 171.56 (2-C=O); 171.26 (4-C=O); 43.11 ($ArCH_2$); 33.63 (5-CH_2); 133.86, 131.28, 130.12 (quaternary carbons); 123.40, 125.19, 125.91, 126.69, 126.72, 127.58, 128.78, 129.00 (CH carbons).

Alternative Synthesis of 3-(4-Bromophenyl)-1,3-thiazolidine-2,4-dione (**4g**)

A solution of mesitylnitrile oxide[22] (322 mg, 2 mmol) in anhydrous acetonitrile (20 ml) was added dropwise under nitrogen to a stirred solution of 3-(4-bromophenyl)-1,3-thiazolidine-2-thion-4-one[23]

(288 mg, 1 mmol) in anhydrous acetonitrile (40 ml). The reaction mixture was stirred at room temperature for 1 h and the solvent was evaporated. The residue was washed with hexane (50 ml), dried and crystallized from chloroform–ether. The melting point and physicochemical data of the product were identical with those of the compound prepared from 4-bromophenyl isothiocyanate (vide supra).

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