N-Acyl and *N*-sulfonyl derivatives of thiazolidines

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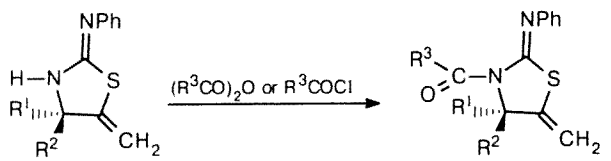
The major reaction center in the reaction of 4,4-dialkyl-5-methylene-2-phenyliminothiazolidines with acid chlorides or anhydrides and with arenesulfonyl chlorides is the nitrogen atom at position 3 of the ring.

Key words: thiazoline-thiazolidine tautomerism; ^{1}H NMR spectra.

A tautomeric amine-imine equilibrium is observed for 2-aminothiazolines and 2-iminothiazolidines.[1–3] Alkylation of these compounds with alkyl halides affords 3-alkyl-2-iminothiazolidines,[4] whereas acylation produces, depending on the amount of acylating agent, 2-acylaminothiazolines or *N*,*N*′-diacyliminothiazolidines.[5]

We have studied reactions of 4,4-dialkyl-5-methylene-2-phenyliminothiazolidines (**1a,b**) with anhydrides and chlorides of aliphatic and aromatic acids (Scheme 1).

Scheme 1

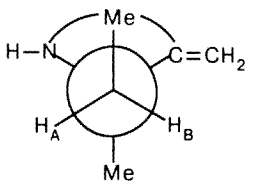


1a,b **2a–g**

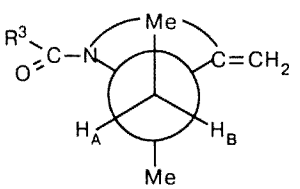
1a, **2a–d**: $R^1 = R^2 = Me$; **2a**: $R^3 = Me$;
2b: $R^3 = Et$; **2c**: $R^3 = Ph$; **2d**: $R^3 = C_6H_4COOH$-*o*;
1b, **2e–g**: $R^1 = Me$, $R^2 = Et$; **2e**: $R^3 = Me$;
2f: $R^3 = Et$; **2g**: $R^3 = C_6H_4COOH$-*o*

Based on the data of ^{1}H NMR spectroscopy and the results of quantum-chemical calculations, we concluded that thiazoline tautomers of compounds **1a,b** and **2a–f** are absent. In compounds **2e,f**, the geminal methylene protons of the ethyl groups are nonequivalent. In the initial thiazoline **1b**, these protons are equivalent and, therefore, in this case, the asymmetry of the chiral C(4) center affects only slightly the magnetic environment of the methylene protons (conformation **A**).

The introduction of a carbonyl group, which exhibits magnetic anisotropy, affects the proton (H_A) located in proximity to this group, which is the cause of the inequivalence of the geminal methylene protons (conformation **B**). Previously, this effect of the carbonyl and sulfo groups was observed for amido and sulfamido



A



B

ketones under conditions of limited conformational freedom due to the formation of an intramolecular hydrogen bond.[6,7]

Therefore, the data on chemical shifts of methyl groups of compounds **2a–d** and the nonequivalence of the methylene protons of the ethyl groups of compounds **2e,f** indicate that substitution occurs at the endocyclic nitrogen atom, and the products have thiazolidine structures.

The presence of the amido group at the endocyclic nitrogen atom of the heterocycle was additionally supported by the results of quantum-chemical calculations of the energy minima of the initial compound **1a**, its isomer (**3a**), and isomeric *N*-acetyl derivatives (**2e** and **4a**). Calculations were carried out on an IBM computer using the ATOM program. The energy minima calculated for these structures are given below.

These values indicate that for both the initial compounds and the *N*-acetylation products, the thiazolidine (amidothiazolidine) form is thermodynamically more favorable.

As part of our continuing studies, we attempted to find out whether the steric factor is the governing factor for this type of reactions.

For this purpose, the IR and ^{1}H NMR spectra of the products of the reaction of thiazolidine **1b** with arenesulfonyl chlorides (Scheme 2) were studied.

The IR spectra of compounds **5a–d** show absorption bands corresponding to vibrations of the sulfonyl group, whereas the absorption bands corresponding to the NH group disappear. The bands at 1640 and 1670 cm^{-1} were assigned to vibrations of the exocyclic C=N bond.

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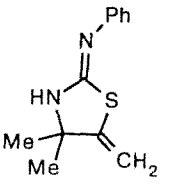
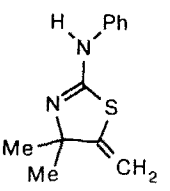
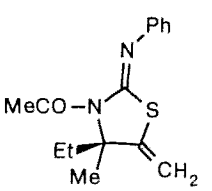
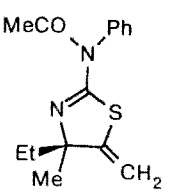
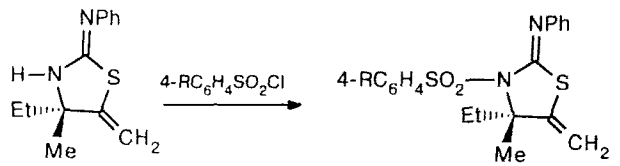
Compound				
	1a	**3a**	**2e**	**4a**
E_{min} /kJ mol^{-1}	34.494	44.462	32.844	51.869

Scheme 2



1b **5a—d**

5a: R = H; **5b**: R = Me; **5c**: R = Br; **5d**: R = NHCOMe

The ^{1}H NMR spectra also indicate that the sulfonyl group is attached to the nitrogen atom at position 3 of the ring. The ^{1}H NMR spectra of compounds **5a—d** show a multiplet signal of nonequivalent methylene protons ($CH_3—CH_AH_B—$) in the region of methylene protons of the ethyl group, instead of the quartet observed for the initial compound. This may also be a result of the effect of the magnetically anisotropic SO_2 group on one of the methylene protons, as was observed in the case of acyl derivatives **2e,f.**

Experimental

The ^{1}H NMR spectra were recorded on a Tesla-487 C instrument. The IR spectra were obtained on an UR-20 instrument. Melting points were measured on a Boetius microscope table (4 °C min^{-1}).

Synthesis of 3-R-4,4-dialkyl-5-methylene-2-phenyliminothiazolidines (2a—g) (general procedure). Acid anhydride or chloride (0.01 mol) was added dropwise with stirring to a solution of 4,4-dialkyl-5-methylene-2-phenyliminothiazolidines **1a** or **1b** (0.01 mol, obtained from the corresponding 1,1-dialkylpropargylamines and phenyl isothiocyanate according to the known procedure[8]) in anhydrous dioxane (10 mL). Then the reaction mixture was heated at 60—70 °C for 4—5 h. The cooled mixture was poured onto ice (100 g), stirred, and neutralized with a NaOH solution. The crystals that formed were filtered off, washed with water twice, dried, and recrystallized from hexane.

3-Acetyl-4,4-dimethyl-5-methylene-2-phenyliminothiazolidine (2a). Yield 2.39 g (92%), m.p. 114 °C. Found (%): C, 64.52; H, 6.10; N, 10.70; S, 12.40. $C_{14}H_{16}N_2OS$. Calculated (%): C, 64.61; H, 6.15; N, 10.76; S, 12.30. IR, ν/cm^{-1}: 880 (=CH_2); 1700 (C=O); 1610 (C=N); 1500, 1595 (N—Ar). ^{1}H NMR (CCl_4), δ: 1.12 (s, 6 H, 2 Me); 1.86 (s, 3 H, COMe); 4.86 (d, 1 H, =CH, J = 1.0 Hz); 4.96 (d, 1 H, =CH); 7.0—7.6 (m, 5 H, Ph).

4,4-Dimethyl-5-methylene-2-phenylimino-3-propionylthiazolidine (2b). The yield was 2.35 g (86%), m.p. 116 °C. Found (%): C, 65.51; H, 6.56; N, 12.08; S, 11.15. $C_{15}H_{18}N_2OS$. Calculated (%): C, 65.69; H, 6.44; N, 12.19; S, 11.67. IR, ν/cm^{-1}: 870 (=CH_2); 1705 (C=O); 1610 (C=N); 1500, 1600 (N—Ar). ^{1}H NMR (CCl_4), δ: 0.88 (t, 3 H, $\underline{Me}CH_2CO$, J = 7.0 Hz); 1.10 (s, 6 H, 2 Me); 2.04 (q, 2 H, $\underline{CH_2}CO$); 4.82 (d, 1 H, =CH, J = 1.0 Hz); 4.92 (d, 1 H, =CH); 7.0—7.5 (m, 5 H, Ph).

3-Benzoyl-4,4-dimethyl-5-methylene-2-phenyliminothiazolidine (2c). The yield was 2.89 g (90%), m.p. 135 °C. Found (%): C, 70.63; H, 5.45; N, 8.58; S, 9.81. $C_{19}H_{18}N_2OS$. Calculated (%): C, 70.80; H, 5.59; N, 8.73; S, 9.93. IR, ν/cm^{-1}: 880 (=CH_2); 1680 (C=O); 1630 (C=N); 1500, 1590 (N—Ar). ^{1}H NMR (CD_3CN), δ: 1.08 (s, 6 H, Me); 5.02 (d, 1 H, =CH, J = 1.0 Hz); 5.08 (d, 1 H, =CH); 7.0—7.5 (m, 10 H, Ph).

3-(2-Carboxybenzoyl)-4,4-dimethyl-5-methylene-2-phenyliminothiazolidine (2d). The yield was 3.18 g (87%), m.p. 145 °C. Found (%): C, 65.41; H, 4.80; N, 7.56; S, 8.65. $C_{20}H_{18}N_2O_3S$. Calculated (%); C, 65.57; H, 4.95; N, 7.65; S, 8.74. IR, ν/cm^{-1}: 860, 1635 (=CH_2); 1710 (C=O); 1620 (C=N); 1510, 1600 (N—Ar); 2500, 3000 (COOH). ^{1}H NMR (CD_3CN), δ: 1.46 (s, 6 H, 2 Me); 5.24 (d, 1 H, =CH, J = 1.0 Hz); 5.36 (d, 1 H, =CH); 7.2—7.6 (m, 9 H, Ar).

3-Acetyl-4-ethyl-4-methyl-5-methylene-2-phenyliminothiazolidine (2e). The yield was 2.00 g (73%), m.p. 85 °C. Found (%): C, 65.45; H, 6.44; N, 10.21; S, 11.50. $C_{15}H_{18}N_2OS$. Calculated (%): C, 65.69; H, 6.56; N, 10.15; S, 11.67. IR, ν/cm^{-1}: 865 (=CH_2); 1700 (C=O); 1610 (C=N); 1500, 1595 (N—Ar). ^{1}H NMR (CCl_4), δ: 0.56 (t, 3 H, $\underline{Me}CH_2$, J = 7.0 Hz); 1.08 (s, 3 H, Me); 1.50 (m, 2 H, $MeC\underline{H_A}\underline{H_B}$); 1.82 (s, 3 H, COMe); 4.80 (d, 1 H, =CH, J = 1.0 Hz); 5.04 (d, 1 H, =CH); 7.0—7.5 (m, 5 H, Ph).

4-Ethyl-4-methyl-5-methylene-2-phenylimino-3-propionylthiazolidine (2f). The yield was 1.55 g (54%), m.p. 105 °C. Found (%): C, 66.51; H, 6.75; N, 9.65; S, 11.02. $C_{16}H_{20}N_2OS$. Calculated (%); C, 66.66; H, 6.94; N, 9.72; S, 11.11. IR, ν/cm^{-1}: 870 (=CH_2); 1700 (C=O); 1605 (C=N); 1500, 1595 (N—Ar). ^{1}H NMR (CCl_4), δ: 0.56 (t, 3 H, $\underline{Me}CH_2$, J = 7.0 Hz); 0.94 (t, 3 H, $\underline{Me}CH_2CO$, J = 7.0 Hz), 1.08 (s, 3 H, Me); 1.46 (m, 2 H, $MeC\underline{H_A}\underline{H_B}$); 2.04 (q, 2 H, $\underline{CH_2}CO$); 4.80 (d, 1 H, =CH, J = 1.0 Hz); 5.04 (d, 1 H, =CH); 7.0—7.5 (m, 5 H, Ph).

3-(2-Carboxybenzoyl)-4-ethyl-4-methyl-5-methylene-2-phenyliminothiazolidine (2g). The yield was 2.85 g (75%), m.p. 133 °C. Found (%): C, 66.15; H, 5.11; N, 7.25; S, 8.31. $C_{21}H_{20}N_2O_3S$. Calculated (%): C, 66.31; H, 5.26; N, 7.36; S, 8.42. IR, ν/cm^{-1}: 860, 1630 (=CH_2); 1710 (C=O); 1665 (C=N); 1510, 1600 (N—Ar); 2600, 3000 (COOH).

^{1}H NMR (CD_3CN), δ: 0.84 (t, 3 H, $\underline{Me}CH_2$, J = 7.0 Hz); 1.50 (s, 3 H, Me); 1.74 (m, 2 H, $MeC\underline{H_A}\underline{H_B}$); 5.3 (s, 2 H, CH_2); 7.0—7.5 and 8.0 (both m, 9 H, Ar).

Synthesis of 4-ethyl-4-methyl-5-methylene-2-phenylimino-3-R-sulfonylthiazolidines (5a—d) (general procedure). Arenesulfonyl chloride (0.01 mol) was added to a solution of 4-ethyl-4-methyl-5-methylene-2-phenyliminothiazolidine **(1b)** (0.01 mol) in anhydrous pyridine (10 mL). The mixture was heated with stirring at 40—50 °C for 5—6 h, cooled, and poured into a mixture of dilute hydrochloric acid with ice. The crystals that formed were filtered off, dried, and recrystallized from hexane.

3-Benzenesulfonyl-4-ethyl-4-methyl-5-methylene-2-phenyliminothiazolidine (5a). The yield was 2.23 g (60%), m.p. 55 °C. Found (%): C, 61.17; H, 5.24; N, 7.40; S, 17.01. $C_{19}H_{20}N_2O_2S_2$. Calculated (%): C, 61.29; H, 5.24; N, 7.52; S, 17.20. IR, ν/cm^{-1}: 865, 1620 (=CH_2); 1370, 1185 (SO_2); 1650 (C=N); 700, 1500 (N—Ar). ^{1}H NMR (CCl_4), δ: 0.60 (t, 3 H, $\underline{Me}CH_2$, J = 7.0 Hz); 1.50 (m, 2 H, $MeC\underline{H_A}\underline{H_B}$); 1.14 (s, 3 H, Me); 4.92 (d, 1 H, CH, J = 1.0 Hz); 4.84 (d, 1 H, =CH); 7.04—7.94 (m, 10 H, Ar).

4-Ethyl-4-methyl-5-methylene-2-phenylimino-3-*p*-toluenesulfonylthiazolidine (5b). The yield was 2.23 g (58%), m.p. 102 °C. Found (%): C, 62.12; H, 5.54; N, 7.02; S, 16.44. $C_{20}H_{22}N_2O_2S_2$. Calculated (%): C, 62.17; H, 5.70; N, 7.25; S, 16.58. IR, ν/cm^{-1}: 830, 1620 (=CH_2); 1185, 1360 (SO_2); 1640 (C=N); 700, 1500 (N—Ar). ^{1}H NMR (CCl_4), δ: 0.58 (t, 3 H, $\underline{Me}CH_2$, J = 7.0 Hz); 1.14 (s, 3 H, Me); 1.50 (m, 2 H, $MeC\underline{H_A}\underline{H_B}$); 2.28 (s, 3 H, $\underline{Me}Ph$); 4.80 (d, 1 H, =CH); 4.88 (d, 1 H, =CH, J = 1.0 Hz); 7.0—7.8 (m, 9 H, Ar).

3-*p*-Bromobenzenesulfonyl-4-ethyl-4-methyl-5-methylene-2-phenyliminothiazolidine (5c). The yield was 2.16 g (48%), m.p. 162 °C. Found (%): C, 50.41; H, 4.05; N, 6.01; S, 14.07. $C_{19}H_{19}N_2BrO_2S_2$. Calculated (%): C, 50.55; H, 4.21; N, 6.20; S, 14.19. IR, ν/cm^{-1}: 830 (=CH_2); 1170, 1335 (SO_2); 1640 (C=N); 1480, 1580 (N—Ar). ^{1}H NMR (CCl_4), δ: 0.62 (t, 3 H, $\underline{Me}CH_2$, J = 7.0 Hz); 1.16 (s, 3 H, Me); 1.50 (m, 2 H, $MeC\underline{H_A}\underline{H_B}$); 4.82 (d, 1 H, CH, J = 1.0 Hz); 4.92 (d, 1 H, =CH); 7.10—8.0 (m, 9 H, Ar).

3-(*p*-Acetamido)benzenesulfonyl-4-ethyl-4-methyl-5-methylene-2-phenyliminothiazolidine (5d). The yield was 2.23 g (52%), m.p. 180 °C. Found (%): C, 58.60; H, 5.21; N, 9.63; S, 14.75. $C_{21}H_{23}N_3O_3S_2$. Calculated (%): C, 58.74; H, 5.36; N, 9.79; S, 14.91. IR, ν/cm^{-1}: 840 (=CH_2); 1180, 1325 (SO_2); 1605 (C=N); 1500, 1550 (N—Ar). ^{1}H NMR (CD_3CN), δ: 0.52 (t, 3 H, $\underline{Me}CH_2$, J = 7.0 Hz); 1.12 (s, 3 H, Me); 1.48 (m, 2 H, $MeC\underline{H_A}\underline{H_B}$); 1.98 (s, 3 H, MeCO); 4.92 (d, 1 H, =CH); 5.0 (d, 1 H, =CH, J = 1.0 Hz); 7.1—7.6 (m, 5 H, N—Ar); 7.62 (d, 2 H, H—Ar, J = 8.0 Hz); 7.8 (d, 2 H, H—Ar).

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