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SYNTHESIS OF 2,3-DISUBSTITUTED THIAZOLIDIN-4-ONES CONTAINING THE STERICALLY HINDERED 4-HYDROXY-3,5-DI(*tert*-BUTYL)PHENYL GROUPING

M. A. Silin, V. I. Kelarev, and V. Abu-Ammar

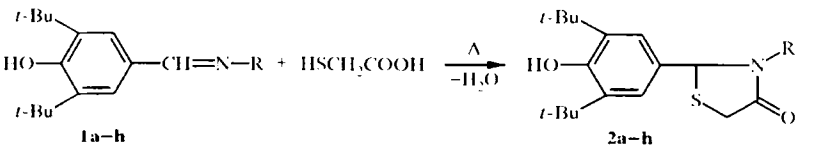
A series of 2,3-disubstituted thiazolidin-4-ones containing 4-hydroxy-3,5-di(tert-butyl)phenyl groups has been synthesized. For preparation of these sterically hindered compounds the condensation of thioglycolic acid with azomethines – derivatives of 4-hydroxy-3,5-di(tert-butyl)benzaldehyde was used.

Keywords: azomethines, thiazolidine, thioglycolic acid, phenols, condensation.

In continuation of investigations on the synthesis of five-membered nitrogen-containing heterocycles with shielded phenolic substituents [1-3] we report in the present work the preparation of 2,3-disubstituted thiazolidin-4-ones containing 4-hydroxy-3,5-di(*tert*-butyl)phenyl substituents.

There are only some examples of thiazolidine derivatives with sterically hindered hydroxyl substituents in the literature [4]. However compounds of this type are promising as potentially biologically active substances and also as stabilizers for polymeric materials, hydrocarbon fuel, and lubricating oils [5].

Azomethines may serve as convenient synthons in the synthesis of thiazolidin-4-ones [6,7]. Starting materials used in the present work were N-[4-hydroxy-3,5-di(*tert*-butyl)benzylidene]amines **1a-h** which are the products of condensation of 4-hydroxy-3,5-di(*tert*-butyl)-benzaldehyde with various amines. 2-[4-Hydroxy-3,5-di(*tert*-butyl)phenyl]-3-R-thiazolidin-4-ones **2a-h** were formed by the interaction of azomethines **1a-h** with thioglycolic acid. The best yields of compounds **2a-h** (Table 1) were achieved on boiling (8-10 h) the reactants in benzene or dioxane at a molar ratio of azomethine **1** : thioglycolic acid equal to 1 : 2 to 1 : 2.5.



1, 2 a R = C_6H_{11}, **b** R = $PhCH_2$, **c** R = 4-MeC_6H_4, **d** R = 4-HOC_6H_4, **e** R = 2-naphthyl, **f** R = 2-pyridyl, **g** R = 2,2,6,6-tetramethyl-4-piperidyl, **h** R = 2-thiazolyl

α,ω-Bis{2-[4-hydroxy-3,5-di(*tert*-butyl)phenyl]-4-oxo-3-thiazolidinyl}alkanes (**4a,b**) were synthesized under analogous conditions from N,N'-bis[4-hydroxy-3,5-di(*tert*-butyl)benzylidene]-ethylenediamine (**3a**) and -hexamethylenediamine (**3b**) and thioglycolic acid (molar ratio 1 : 4 to 1 : 5).

I. M. Gubkin Russian State University for Petroleum and Gas, Moscow 117917. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 2, pp. 256-260, February, 2000. Original article submitted March 5, 1999.

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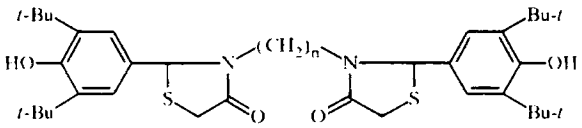

4a,b

a n = 2, b n = 6

On heating of 4-hydroxy-3,5-di(*tert*-butyl)benzaldehyde 4-phenylthiosemicarbazone (**5**) with an excess of thioglycolic acid in benzene 2-[4-hydroxy-3,5-di(*tert*-butyl)phenyl]-3-(3-phenylthioureido)thiazolidin-4-one (**6**) was obtained in 82% yield. At the same time the interaction of thiosemicarbazone **5** with chloroacetic acid and sodium acetate in acetic acid (boiling for 2 h) leads to azine **7** in 84% yield.

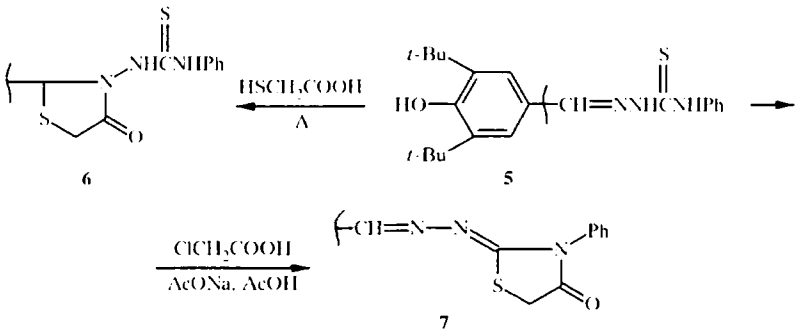

TABLE 1. Characteristics of 2,3-Disubstituted Thiazolidin-4-ones

Compound	Empirical formula	Found, % / Calculated, %			mp, °C*	R_f (solvent system)	Yield, %
		C	H	N			
2a	$C_{23}H_{31}NO_2S$	71.44 / 71.60	9.87 / 9.78	3.21 / 3.34	Oil	0.84 (a)	77
2b	$C_{24}H_{33}NO_2S$	69.71 / 69.80	8.43 / 8.59	4.02 / 3.88	73-74	0.57 (a)	83
2c	$C_{25}H_{35}NO_2S$	69.92 / 69.80	8.68 / 8.59	3.72 / 3.88	51-52.5	0.74 (b)	80
2d	$C_{25}H_{35}NO_3S$	69.26 / 69.17	7.35 / 7.27	3.37 / 3.51	132-133	0.63 (b)	75
2e	$C_{27}H_{39}NO_2S$	75.02 / 74.83	7.04 / 7.16	3.33 / 3.23	128-129	0.48 (a)	81
2f	$C_{22}H_{28}N_2O_2S$	68.88 / 68.75	7.17 / 7.29	7.44 / 7.29	75-76	0.51 (b)	88
2g	$C_{24}H_{32}N_2O_2S$	70.13 / 69.95	9.31 / 9.42	6.45 / 6.28	165-167	0.74 (a)	78
2h	$C_{26}H_{36}N_2O_2S_2$	61.39 / 61.54	6.75 / 6.67	7.06 / 7.18	136-138	0.58 (b)	74
4a	$C_{46}H_{72}N_2O_4S_2$	66.11 / 66.23	8.56 / 8.44	4.70 / 4.54	154-155	0.55 (a)	63
4b	$C_{50}H_{80}N_2O_4S_2$	69.10 / 68.97	8.51 / 8.62	4.16 / 4.02	125-126	0.71 (a)	56
6	$C_{31}H_{43}N_3O_2S_2$	62.91 / 63.02	6.89 / 6.78	9.31 / 9.19	185-187	0.67 (b)	82
7	$C_{31}H_{29}N_3O_2S_2$	68.21 / 68.08	6.53 / 6.85	10.11 / 9.93	103-105	0.44 (a)	84

* Compounds **2b,c,e,4b**, and **7** were recrystallized from benzene–hexane; **2d,f,h,4a** and **6** from aqueous ethanol; **2g** from aqueous dioxane.

TABLE 2. ^{1}H NMR Spectral Characteristics of the Compounds Synthesized

Compound	Chemical shift, δ, ppm*					
	t-Bu (br. s)	OH (s)	H arom. (s)	thiazolidin-4-one		other protons
				2-H (s)	5-H (s)	
2a	1.58 (18H)	5.05 (1H)	7.18 (2H)	3.90 (1H)	4.35 (2H)	1.08 (3H, t, CH_3); 1.22-1.44 (12H, m, CH_2); 3.30 (2H, t, CH_2N)
2b	1.62 (18H)	4.84 (1H)	7.30 (2H)	3.62 (1H)	4.40 (2H)	3.51 (2H, s, $CH_2C_6H_5$); 6.92-7.16 (5H, m, C_6H_5)
2c	1.50 (18H)	5.14 (1H)	7.15 (2H)	3.38 (1H)	4.26 (2H)	2.52 (3H, s, CH_3); 6.74-7.02 (4H, m, H arom.)
2d	1.73 (18H)	4.92 (1H)	7.21 (2H)	3.47 (1H)	4.53 (2H)	5.82 (1H, br, HO); 6.84-7.10 (4H, m, H arom.)
2e	1.54 (18H)	5.07 (1H)	7.43 (2H)	3.55 (1H)	4.23 (2H)	6.80-7.20 (7H, m, H arom.)
2f	1.60 (18H)	4.95 (1H)	7.20 (2H)	3.44 (1H)	4.31 (2H)	7.47-7.74 (4H, m, H arom.)
2g	1.52 (18H)	5.21 (1H)	7.23 (2H)	3.52 (1H)	4.28 (2H)	1.25 (24H, br. s, CH_3); 2.10-2.38 (5H, m, CH_2, CH); 6.20 (1H, br, NH)
2h	1.67 (18H)	5.08 (1H)	7.22 (2H)	3.42 (1H)	4.42 (2H)	6.72 (1H, d, 5-H thiazole, $J_{5,4}$ = 3.2 Hz); 7.45 (1H, d, 4-H thiazole)
4a	1.62 (36H)	4.90 (2H)	7.18 (4H)	3.50 (2H)	4.35 (4H)	4.04 (4H, t, CH_2N)
4b	1.54 (36H)	5.16 (2H)	7.27 (4H)	3.64 (2H)	4.42 (4H)	1.74-2.29 (8H, m, CH_2); 3.87 (4H, t, CH_2N)
6	1.55 (18H)	5.00 (1H)	7.32 (2H)	3.39 (1H)	4.37 (2H)	6.09 (1H, br, HN); 6.38 (1H, br, NH); 6.90-7.10 (5H, m, C_6H_5)
7	1.70 (18H)	5.15 (1H)	7.27 (2H)		4.30 (2H)	6.72 (1H, s, CH=N); 7.04-7.14 (5H, m, C_6H_5)

* The spectra of compounds **2a,2g,4a,b** were recorded in $CDCl_3$ and of the remaining compounds in DMSO-d_6.

The characteristics of the synthesized disubstituted thiazolidin-4-ones **2a-h,4a,b,6**, and **7** are given in Table 1. The composition and structure of these compounds were confirmed by the results of elemental analysis, IR spectral data, ^{1}H NMR spectra, and mass spectroscopy. Absorption bands of various intensity were observed in the IR spectra corresponding to the vibrations of the thiazolidine ring and of discrete fragments of it [8] at 1450-1460, 1425-1440 (scissor vibrations of CH_2), 1280-1290, 1070-1080 (ν ring), 1160-1175 and 995-1005 cm^{-1}. The intense absorption maxima at 1720-1755 cm^{-1} are characteristic of carbonyl group vibrations in thiazolidinones [8,9].

Absorption was also observed in the spectra of all the compounds considered being due to the sterically hindered phenol fragment: a fairly narrow band at 3635-3665 cm^{-1} characteristic of shielded phenolic hydroxyl [10], two medium intensity bands at 1220-1260 cm^{-1} corresponding to the deformation vibrations of the *tert*-butyl groups, and also bands at 870-885 and 820-835 cm^{-1} (out-of-plane deformation vibrations of the C–H bond of tetrasubstituted benzene ring).

Signals of hydroxyl group protons in the ^{1}H NMR spectra (Table 2) of the synthesized compounds appeared as singlets at 4.84-5.21 ppm, which is characteristic of sterically hindered phenols [10]. Signals of the *tert*-butyl substituent protons were observed as broadened singlets at 1.50-1.73 ppm. The singlet signals at 7.15-7.43 ppm correspond to the two magnetically equivalent protons of the hydroxyaryl fragments [2,3]. The 2-H proton of the thiazolidine ring was displayed as a singlet at 3.38-3.84 ppm. Singlet signals at 4.24-4.53 ppm with an intensity of two proton units must be assigned to the protons at position 5 of the thiazolidine ring.

Peaks were present in the mass spectra of the synthesized thiazolidin-4-ones for the molecular ions M^+, the intensity of which was 3-24% of maximum. The most intense peak in the mass spectra of the majority of the synthesized compounds was the peak of *m/z* 57 characteristic of the *tert*-butyl cation $[t\text{-Bu}]^+$. Peaks for $[M\text{-}15]^+$

ions, arising by elimination of CH_3 radical from the molecular ion, had a lower intensity (37-52%). Peaks for [M-43] ions had a relatively low intensity and are formed from the sequential fission of CH_3 radical and C_2H_4 molecule from the molecular ion. This is characteristic of derivatives of 2,6-di(*tert*-butyl)phenol [12].

EXPERIMENTAL

The IR spectra were taken on a Bruker IFS 48 instrument in KBr disks or in thin films. The ^1H NMR spectra were recorded on a Bruker WP 250 (250 MHz) spectrometer, internal standard was TMS. The mass spectra were obtained on a Finnigan MAT INCOS-50 spectrometer with energy of the ionizing electrons 70 eV, by direct insertion of the sample into the ion source. A check on the progress of reactions and the purity of the obtained compounds was carried out by TLC on Al_2O_3 Brockmann activity grade III in the solvent systems a) benzene–methanol, 30 : 1, b) CCl_4–acetone, 15 : 1. Visualization was with iodine vapor.

The initial compounds **1b-f and 3a,b** were obtained by the procedure [13]. Compounds **1a,g,h** were synthesized previously.

2-[4-Hydroxy-3,5-di(*tert*-butyl)phenyl]-3-R-thiazolidin-4-ones (2a-h). Mixture of azomethine **1a-h** (10 mmol) and freshly distilled thioglycolic acid (1.84 g, 20 mmol) in anhydrous benzene (70 ml) was boiled with stirring for 10 h, then evaporated to dryness under reduced pressure. The residue was washed with 5% $NaHCO_3$ solution (2 × 30 ml), dried in vacuum over P_2O_5, and either crystallized from an appropriate solvent (see Table 1), or chromatographed on column with alumina (90 × 5.0 cm) (when obtaining compound **2a**), eluting with benzene–methanol, 10 : 1.

α,ω-Bis{2-[4-hydroxy-3,5-di(*tert*-butyl)phenyl]-4-hydroxy-3-thiazolidinyl}alkanes (4a,b) were synthesized analogously from bisazomethine **3a,b** (10 mmol) and freshly distilled thioglycolic acid (4.14 g, 45 mmol). The products were isolated and purified by column chromatography on Al_2O_3 (column 90 x 5.0 cm, eluent benzene–hexane–methanol, 15 : 5 : 1).

2-[4-Hydroxy-3,5-di(*tert*-butyl)phenyl]-3-(3-phenylureido)thiazolidin-4-one (6) was synthesized analogously from 4-phenylthiosemicarbazide **5**.

N-[4-Hydroxy-3,5-di(*tert*-butyl)benzylidene]-N'-(4-oxo-3-phenyl-2-thiazolidinylidene)azine (8). Mixture of 4-phenylthiosemicarbazide **5** (2.17 g, 5.7 mmol), chloroacetic acid (0.54 g, 5.7 mmol), and sodium acetate (0.94 g, 11.4 mmol) in acetic acid (50 ml) was boiled with stirring for 2 h. The reaction mixture was cooled to 20°C and ice water (70 ml) added to it. The solid which separated was filtered off, washed on the filter with water, dried, and crystallized from hexane–benzene, 2 : 1.

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