Chemistry of Heterocyclic Compounds, Vol. 34, No. 4, 1998

SYNTHESIS OF HETEROCYCLES FROM PRODUCTS OF THE ANION ARYLATION OF UNSATURATED COMPOUNDS. 3.* 2-ARYLIMINO-5-ARYLMETHYL-4-THIAZOLIDONES

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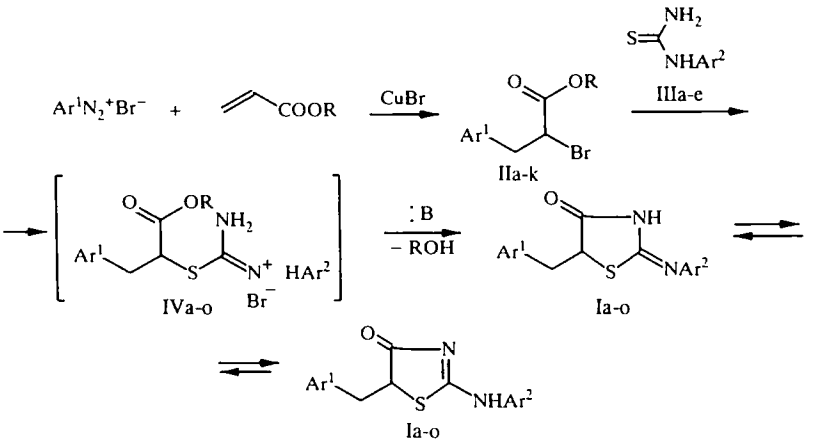
The reaction of esters of 3-aryl-2-bromopropionic acids with N-arylthioureas gives 2-arylimino-5-arylmethyl-4-thiazolidones, which exist in solution as (E) and (Z) isomers of the imino form.

The methods for synthesis of 4-thiazolidones and their properties have been studied rather extensively [2, 3], in particular, due to the biological activity of many of these compounds [3]. The 5-arylidene derivatives are most available. The methods for the preparation of 5-alkyl and 5-aryl derivatives of 4-thiazolidone involve use of not readily available starting materials or multiple steps. These reactions are often carried out under vigorous conditions and accompanied by ring opening or isomer formation [2]. Thus, 2-phenylimino-5-phenyl-4-thiazolidone was obtained in only about 25% yield in the reaction of 2-phenylimino-5-phenyl-4-thiazolidone with N-phenylthiourea [4].



$Ar^1 = C_6H_4R^1$, $Ar^2 = C_6H_4R^2$; IIa-d R = Me, a R^1 = Me-*m*, b R^1 = Me-*p*, c $R^1 = NO_2$-*m*, d R^1 = Br-*p*, e-h R = Et, e R^1 = OMe-*p*, f $R^1 = NO_2$-*o*, g $R^1 = NO_2$-*m*; h R^1 = Me-*o*; i-k R = Bu, i R^1 = H, j R^1 = Me-*p*, k $R^1 = NO_2$-*o*; IIIa R^2 = H, b R^2 = Me-*o*, c R^2 = Me-*m*, d R^2 = Cl-*p*, e R^2 = Br-*p*; Ia-f R^2 = H, a R^1 = H, b R^2 = Me-*o*, c R^1 = Me-*m*, d R^1 = Me-*p*, j R^1 = Br-*p*, f $R^1 = NO_2$-*m*, g $R^1 = NO_2$-*m*, R^2 = Me-*o*, h-i R^2 = Me-*m*, h R^1 = Me-*o*, i $R^1 = NO_2$-*m*, j-m R^2 = Cl-*p*, j R^1 = OMe-*p*, k R^1 = Br-*p*, l $R^1 = NO_2$-*o*, m $R^1 = NO_2$-*m*, n, o R^2 = Br-*p*, n R^1 = OMe-*p*, o $R^1 = NO_2$-*o*

We propose a new approach to the synthesis of heterocyclic compounds using bifunctional products of anion arylation of unsaturated compounds using arenediazonium salts [1, 5]. In the present communication, we describe a simple method for the synthesis of 2-arylimino-5-arylmethyl-4-thiazolidones (I) involving the reaction of esters of 3-aryl-2-bromopropionic acid

*For Communication 2, see [1].

I. Franko Lvov State University, Lvov 290602, Ukraine. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 4, pp. 555-559, April, 1998. Original article submitted June 30, 1997; revision submitted January 27, 1998.

 0009-3122/98/3404-0492$20.00

TABLE 1. Indices of Esters of 3-Aryl-2-bromopropionic Acids IIa-IIj

Compound	Chemical formula	Found, % / Calculated, % C	Found, % / Calculated, % H	bp, °C (2 mm Hg)	n^{20}_D /mp, °C	Yield, %
IIa	$C_{11}H_{13}BrO_2$	51.21 51,38	5,03 5,10	124...126	1,5402	36
IIb	$C_{11}H_{13}BrO_2$	51.13 51,38	4,92 5,10	130...131	1,5393	38
IIc	$C_{10}H_{10}BrNO_4$	41.75 41,69	3.47 3,50		101...102	46
IId	$C_{10}H_{10}Br_2O_2$	37.54 37,30	3.22 3,13	150...153	1,5778	44
IIe	$C_{12}H_{15}BrO_3$	49.90 50,19	5,18 5,27	136...138	1,5335	47
IIf	$C_{11}H_{12}BrNO_4$	43.97 43,73	4.15 4,00	164...167	1,5530	36
IIg	$C_{11}H_{12}BrNO_4$	43.61 43,73	3.96 4,00	170...175	55...56	40
IIi	$C_{13}H_{17}BrO_2$	54.46 54,75	5.97 6,01	141...143	1,5208	35
IIj	$C_{14}H_{19}BrO_2$	56.11 56,20	6.28 6,40	145...146	1,5172	43
IIk	$C_{13}H_{16}BrNO_4$	47.44 47,29	5.00 4,88	183...186	1,5383	34

TABLE 2. Indices of 2-Arylimino-5-arylmethyl-4-thiazolidones

Compound	Chemical formula	Found, % / Calculated, % C	Found, % / Calculated, % H	Found, % / Calculated, % N	mp, °C	Yield, %
Ia	$C_{15}H_{14}N_2OS$	67.85 68,06	4.92 5,00	9.78 9,92	184...185	70
Ib	$C_{17}H_{16}N_2OS$	68.60 68,89	5.42 5,44	9.33 9,45	157...158	59
Ic	$C_{17}H_{15}N_2OS$	68.78 68,89	5.29 5,44	9.30 9,45	140...141	74
Id	$C_{17}H_{16}N_2OS$	68.59 68,89	5.37 5,44	9,23 9,45	162...163	62
Ie	$C_{15}H_{13}BrN_2OS$	53.32 53,20	3.68 3,63	7.69 7,75	183...185	73
If	$C_{15}H_{13}N_3O_3S$	58.55 58,70	3.89 4,00	12.96 12,84	185...186	71
Ig	$C_{17}H_{15}N_3O_3S$	59.87 59,81	4.32 4,43	12,10 12,31	147...149	65
Ih	$C_{18}H_{18}N_2OS$	69.48 69,65	5.83 5,84	8.88 9,02	159...160	75
Ii	$C_{17}H_{15}N_3O_3S$	59.54 59,84	4.35 4,43	12.29 12,31	161...163	60
Ij	$C_{17}H_{15}ClN_2O_2S$	58.75 58,87	4.26 4,36	8.15 8,08	178...179	64
Ik	$C_{15}H_{12}BrClN_2OS$	48.40 48,57	3.03 3,06	6.81 7,08	196...197	61
Il	$C_{15}H_{12}ClN_3O_3S$	53.30 53,12	3.29 3,34	11.52 11,61	150...151	75
Im	$C_{15}H_{12}ClN_3O_3S$	53.01 53,12	3.17 3,34	11.46 11,61	174...175	61
In	$C_{17}H_{15}BrN_2O_2S$	52.27 52,18	3.95 3,86	7.03 7,16	199...200	67
Io	$C_{15}H_{12}BrN_3O_3S$	47.41 47,30	2.93 2,98	10.21 10,34	154...156	47

(IIa-IIk) with N-arylthioureas (IIIa-IIIe). Esters IIa-IIk were synthesized by the reaction arenediazonium bromides with acrylate esters in the presence of CuBr [1, 6]. The physical indices of new esters IIa-IIg and IIi-IIk are given in Table 1.

The alkylation of thioureas IIIa-IIIe by esters IIa-IIk gave the corresponding thiouronium salts IVa-IVo, which cyclize to give substituted 4-thiazolidones Ia-Io. We also found that the iodine analogs of esters IIa-IIk obtained by the iodoarylation of acrylates [7] react similarly with arylthioureas, while esters of α-chlorohydrocinnamic acids do not participate readily in this

TABLE 3. PMR Spectra of 2-Arylimino-5-arylmethyl-4-thiazolidones, δ, ppm*

Compound	CH_2		CH, d.d	Me or OMe (R^1, R^2) 3H, s	H_{arom} in Ar^1, m- and p-H_{arom} in Ar^2, m‡	o-H_{arom} in Ar^2, 2H		NH, br. s
	1H, d.d	1H, d.d†				(E) isomer, d	(Z) isomer, d	
Ia	2,99	3,42	4,73	–	7,14 (1H, *p*-H); 7,28 (7H)	6,92	7,66	11,07
Ib	2,92	3,50	4,68	2,30	7,16...7,60 (7H)	6,95	7,70	11,20
Ic	2,94	3,40	4,68	2,27	7,05...7,18 (5H), 7,34 (2H, *m*-H)	6,93	7,67	
Id	2,90	3,37	4,65	2,25	7,10...7,50 (7H)	6,90	7,65	
Ie	3,00	3,36	4,69	–	7,12 (1H, *p*-H), 7,20 (2H), 7,33 (2H), 7,47 (2H)	6,91	7,64	
If	3,30	3,44	4,82	–	7,15 (1H, *p*-H), 7,36 (2H, *m*-H), 7,61 (2H), 8,13 (2H)	6,92	7,74	11,13
Ig	3,31	3,42	4,80	1,95(*E*) 2,01(*Z*)	7,04 (1H, *p*-H), 7,16 (2H, *m*-H), 7,63 (2H), 8,11 (2H)	6,76	7,63	10,65 11,69
Ih	2,91	3,48	4,66	2,28 br. s (6H)	6,97 (1H, *p*-H), 7,13 (5H)	6,75	7,50	11,40
Ij	3,23	3,43	4,81	2,27	6,94 (1H, *p*-H), 7,10...7,75 (3H), 8,14 (2H)	6,70	7,67	
Ik	2,93	3,40	4,68	3,70	6,88...7,50 (6H)	6,80	7,70	11,23
Il	3,01	3,38	4,75	–	7,10...7,57 (6H)	6,88	7,68	11,24
Im	3,26	3,82	4,76	–	7,30...7,80 (5H), 8,01 (1H)	6,92	–	
In	3,25	3,51	4,85	–	7,35 d (1H, *m*-H), 7,42 d (1H, *m*-H), 7,57...7,72 (2H), 8,12 (2H)	6,88	–	11,28
Io	2,88	3,35	4,61	3,71	6,88...7,80 (6H)	6,83	–	
Ip	3,28	3,83	4,78	–	7,54 (4H), 7,69 (1H), 8,03 (1H)	6,88	7,65	11,34

*Coupling constants of the protons of the CH_2CH fragment for similar compounds given in our previous work [1].

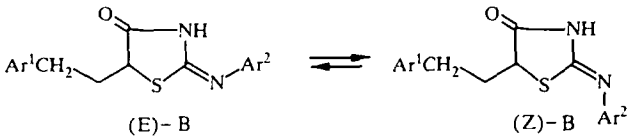
†This signal for most compounds is poorly resolved.

‡Centers are given for narrow multiplets.

reaction. This aspect was studied in greater detail in our previous work [1]. Going from methyl ester IIc to ethyl ester IIg, from methyl ester IIb to butyl ester IIj, and from ethyl ester IIf to butyl ester IIk has no significant effect on the yield of the corresponding products I. The indices of these products are given in Table 2.

Two tautomeric forms are possible for substituted thiazolidones Ia-Io. 2-Arylamino-4-thiazolidones exist in the crystalline state in the amino form (A) with a marked contribution of resonance ionic imino structures [8, 9]. A shift in the tautomeric equilibrium toward the imino form (B) should be expected for Ia-Io in solution [10-12].

Examination of the PMR spectra of thiazolidones Ia-Io (Table 3) shows doublets at 6.7-6.95 and 7.5-7.7 ppm in all the spectra, which were assigned to the *ortho*-protons of the Ar^2 substituent of the *syn*(E) and *anti*(Z) isomers of imino form (B), respectively [12].



The multiplets for the *para*-protons of the arylimino fragment NAr^2 are seen at 6.90-7.15 ppm. The NH group proton is seen as a broad singlet in the vicinity of 11.00 ppm. This signal is not sufficiently distinct for all products Ia-Io and its intensity is not reproducible [13, 14].

Thus, thiazolidones Ia-Io exist in solution as an equilibrium mixture of (E) and (Z) isomers of the imino form. The isomerization probably occurs through an inversion mechanism [11, 15]. The signal intensities in the PMR spectra indicate that the (E) and (Z) isomers are present in approximately equal amounts except for IVg, for which the equilibrium is shifted toward the (E) isomer as a result of the methyl group in the *ortho* position of substituent Ar^2.

EXPERIMENTAL

The PMR spectra were taken on a Varian VXR-300 at 300 MHz for Ia, Ic, Ie-Ig, Im, and Io and a Bruker WP-100SY spectrometer at 100 MHz for Ib, Id, Ih-Il, and In for solutions in DMSO-d_6 with HMDS as the internal standard.

Esters IIa-IIk were prepared according to our previous procedure [1]. The indices of these products are given in Table 1. Ester IIh described in our previous work [1] was obtained in 30% yield using a two-fold excess of 2-methylphenyldiazonium bromide, mp 60°C. Esters IIc, IIg, and IIh were recrystallized from ethanol.

5-(R^1-Benzyl)-2-(R^2-phenyl)imino-4-thiazolidones (Ia-Io).

5-Benzyl-2-phenylimino-4-thiazolidone (Ia). A sample of 2.85 g (0.01 mole) butyl 3-phenyl-2-bromopropionate IIi was added to a solution of 1.52 g (0.01 mole) N-phenylthiourea IIIa and 1 ml pyridine in 10 ml ethanol. The mixture was heated at reflux for 3 h. After cooling, the precipitate formed was filtered off and crystallized from ethanol. Products Ib-Io were obtained analogously.

This work was carried out with the partial support of the International Soros Science Education Program (ISSEP), Grant No. APU 053075.

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