Reaction of Imidoyl and Amidinoyl Isothiocyanates with Some *C*-Acid Salts

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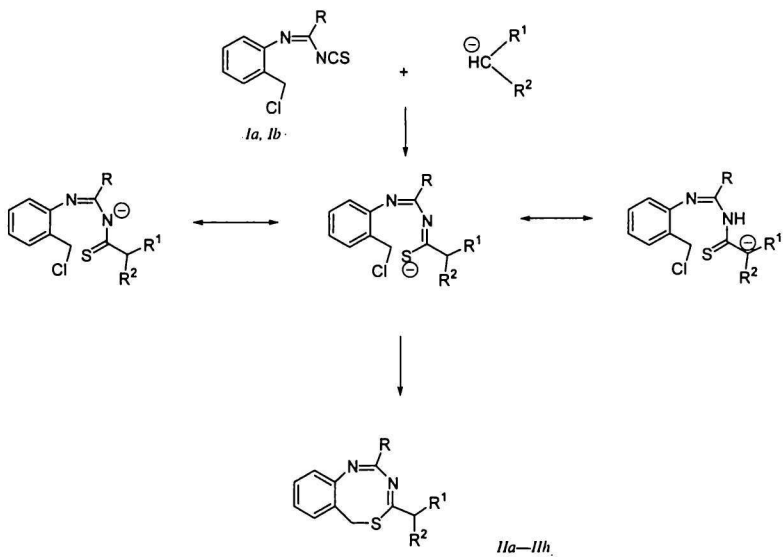
Some 2,4-disubstituted 6*H*-benzo[*g*][5,1,3]thiadiazocines were prepared by addition of *C*-acid salts to corresponding imidoyl and amidinoyl isothiocyanates. IR and ^{1}H NMR spectra of the synthesized compounds are presented.

The effects of benzodiazepines and benzodiazocines on the central nervous system are well known. In order to tune the psychotropic effects of benzodiazepines, a range of derivatives has been synthesized, such that carried a variety of substituents on both rings, and/or another fused heterocyclic (O, S, N) ring of 7 or 8 members [1].

Synthetic methods leading to benzodiazines, benzodiazepines, and benzodiazocines mostly start from anilines, carrying a carboxyl group in position 2. Such structural prerequisite allows closing of fused 6-, 7-, or 8-membered rings after extending the amine or carboxylic end, or both of them.

We have found that the above approach worked well also for 2-phenyl-6*H*-benzo[*g*][5,1,3]thiadiazocines, accessible from starting imidoyl isothiocyanates [2—4].



Ia	R = piperidino	
Ib	R = phenyl	
IIa	R = piperidino	$R^1 = R^2 = CO_2C_2H_5$
IIb	R = piperidino	$R^1 = CO_2C_2H_5$, $R^2 = COCH_3$
IIc	R = piperidino	$R^1 = R^2 = COCH_3$
IId	R = piperidino	$R^1 = CN$, $R^2 = CO_2CH_3$
IIe	R = phenyl	$R^1 = R^2 = CO_2C_2H_5$
IIf	R = phenyl	$R^1 = CO_2C_2H_5$, $R^2 = COCH_3$
IIg	R = phenyl	$R^1 = R^2 = COCH_3$
IIh	R = phenyl	$R^1 = CN$, $R^2 = CO_2CH_3$

Scheme 1

Table 1. Characterization of the Prepared Compounds *IIa*—*IIh*

Compound	Formula	w_i(calc.)/% w_i(found)/%				Yield	M.p.
	M_r	C	H	N	S	%	°C
IIa	$C_{20}H_{25}N_3O_4S$	59.54	6.24	10.41	7.95	32	147—152
	403.5	59.50	6.13	10.48	7.88		
IIb	$C_{20}H_{25}N_3O_3S$	61.99	6.50	10.84	8.27	35	174—180
	387.5	61.80	6.46	10.79	8.14		
IIc	$C_{19}H_{23}N_3O_2S$	63.84	6.48	11.75	8.95	45	115—118
	357.5	63.80	6.35	11.72	8.89		
IId	$C_{18}H_{20}N_4O_2S$	60.65	5.66	15.72	8.99	43	228—231
	356.4	60.62	5.59	15.65	9.03		
IIe	$C_{22}H_{22}N_2O_4S$	64.37	5.40	6.82	12.80	41	155—157
	410.5	64.30	5.32	6.76	12.68		
IIf	$C_{21}H_{20}N_2O_3S$	66.30	5.30	7.36	8.43	30	103—108
	380.5	66.23	5.28	7.34	8.40		
IIg	$C_{20}H_{18}N_2O_2S$	68.55	5.18	7.99	9.15	38	151—154
	350.4	68.39	5.16	7.95	9.10		
IIh	$C_{19}H_{15}N_3O_2S$	65.31	4.33	12.03	9.18	33	123—126
	349.4	65.15	4.30	11.98	9.15		

Table 2. IR Spectral Data of Compounds *IIa*—*IIh*

Compound	$\tilde{\nu}$/cm^{-1}			
	ν(C—O—C)	ν(C=O)	ν(C—H_{alif})	ν(C—H_{arom})
IIa	1120	1730	2853	3061
	1148		2934	
	1161			
IIb	1100	1718	2853	3061
	1121		2934	
	1146			
IIc		1701	2855	3059
		1718	2936	
		1734		
IId	1119	1707	2853	3063
	1142	1718	2932	
	1161	1734		
IIe	1026	1713	2936	3063
	1047		2982	
	1182			
IIf	1014	1772	2936	3061
	1045		2980	
	1184			
IIg		1701	2936	3063
		1734	3003	
		1774		
IIh	1026	1718	2932	3134
	1097		2978	
	1196			

Although the low intrinsic solubility of such benzothiadiazocines hampered the testing, it could be alleviated by introducing a hydrophilic carboxylic function in the side chain.

The starting isothiocyanates *Ia* (*N*-(2-chloromethylphenyl)benzimidoyl isothiocyanate) and *Ib* (*N*-(2-chloromethylphenyl)-*N'*,*N'*-pentamethyleneformamidinoyl isothiocyanate) have been already described [2, 3].

Freshly prepared isothiocyanates *Ia* and *Ib* were converted to thioamides by treatment with sodium salts of *C*-acids, such as acetoacetate, cyanoacetate, malonic esters or acetylacetone. Alkyl, aryl, and acyl isothiocyanates are known to undergo such reactions [5]. *Barnikow* and *Kunzek* have described reactions of *N*-alkyl- and *N*-arylbenzimidoyl isothiocyanates with salts of α,β-dicarbonyl compounds [6], and in several cases also isolated unstable salts of thioamides. Upon

Table 3. ^{1}H NMR Data of Compounds *IIa—IIh*

Compound	δ_i
IIa	1.28 (t, 6H, 2 × CH_3CH_2), 1.45—1.90 (m, 6H,H_{pip}), 3.50—4.10 (m, 4H, H_{pip}), 4.25 (q, 4H, 2 × CH_2CH_3), 4.75 (s, 1H, CH), 3.37 (d, 1H, SCH_2), 4.51 (d, 1H, SCH_2), 7.00—8.12 (m, 4H, H_{arom})
IIb	1.39 (t, 3H, CH_3CH_2), 1.57—1.90 (m, 6H, H_{pip}), 2.57 (s, 3H, CH_3CO), 3.75—4.12 (m, 4H, H_{pip}), 4.40 (q, 2H, CH_3CH_2), 4.55 (s, 1H, CH), 3.45 (d, 1H, SCH_2), 4.98 (d, 1H, SCH_2), 6.80—8.00 (m, 4H, H_{arom})
IIc	1.37—1.75 (m, 6H, H_{pip}), 1.80 (s, 6H, 2 × CH_3CO), 3.34—3.61 (m, 4H, H_{pip}), 4.00 (s, 1H, CH), 3.38 (d, 1H, SCH_2), 4.51 (d, 1H, SCH_2), 7.00—7.70 (m, 4H, H_{arom})
IId	1.40—1.88 (m, 6H, H_{pip}), 3.37—3.75 (m, 4H, H_{pip}), 3.95 (s, 3H, CH_3O), 4.22 (s, 1H, CH), 3.51 (d, 1H, SCH_2), 4.51 (d, 1H, SCH_2), 6.75—8.10 (m, 4H, H_{arom})
IIe	1.17 (t, 6H, 2 × CH_3CH_2), 4.14 (q, 4H, 2× CH_3CH_2), 4.52 (s, 1H, CH), 3.39 (d, 1H, SCH_2), 4.63 (d, 1H, SCH_2), 6.75—8.13 (m, 9H, H_{arom})
IIf	1.23 (t, 3H, CH_3CH_2), 1.89 (s, 3H, CH_3CO), 4.20 (s, 1H, CH), 3.52 (d, 1H, SCH_2), 4.77 (m, 1H, SCH_2; 2H, CH_3CH_2), 6.88—8.25 (m, 9H, H_{arom})
IIg	1.75 (s, 6H, 2× CH_3CO), 3.43 (s, 1H, CH), 3.39 (d, 1H, SCH_2), 4.66 (d, 1H, SCH_2), 7.00—8.20 (m, 9H, H_{arom})
IIh	3.21 (s, 3H, CH_3O), 4.22 (s, 1H, CH), 3.32 (d, 1H, SCH_2), 5.37 (d, 1H, SCH_2), 7.00—8.38 (m, 9H, H_{arom})

pip – piperidine.

acidification the liberated thioamides spontaneously cyclized to the corresponding pyrimidinethiones, splitting off a molecule of alcohol.

Abraham and *Barnikow* investigated similar reaction in the formamidinoyl isothiocyanates [7]. They have found that of all *C*-acids only the sodium salt of ethyl cyanoacetate afforded well-defined products, namely formamidinoyl thioamides. These amides, however, failed to cyclize.

In our hands both isothiocyanates *Ia* and *Ib* underwent a reaction with salts of *C*-acids already at laboratory temperature involving the cyclization as well. In no instance the intermediary salts of thioamides or free thioamides themselves could be isolated; the former by evaporating to dryness, the latter by extraction with a weak aqueous acid. The products were found to be the corresponding derivatives of 6*H*-benzo[*g*][5,1,3]thiadiazocines *IIa—IIh*. In their IR spectra there was a typical band of ester or ketone carbonyl group introduced by the *C*-acid (Scheme 1, Tables 1 and 2).

The ^{1}H NMR spectra (Table 3) displayed apart from protons of aliphatic CH_3 and CH_2 groups also two characteristic doublets, the first at higher δ values (4.51—5.37), the other at δ values (3.32—3.52) corresponding to SCH_2 protons of the thiodiazocine ring and the singlet at δ = 3.43—4.75, belonging to the remaining proton of the *C*-acid.

EXPERIMENTAL

IR spectra were recorded on a Philips PU 9800 FTIR instrument using the KBr technique. ^{1}H NMR spectra were taken on a Tesla BS 587A spectrometer (80 MHz) in $CDCl_3$ using tetramethylsilane as internal standard.

The starting compounds were prepared according to the literature:

N-(2-chloromethylphenyl)-*N*,*N*′-pentamethylene-formamidinoyl isothiocyanate [2], and *N*-(2-chloromethylphenyl)benzimidoyl isothiocyanate [3].

2,4-Disubstituted 6*H*-Benzo[*g*][5,1,3]-thiadiazocines *IIa—IIh*

To a solution of sodium ethanolate prepared from sodium (0.46 g; 0.02 mol) and absolute ethanol (10 cm^3), the corresponding reagent (0.02 mol; ethyl malonate, ethyl acetoacetate, acetylacetone or methyl cyanoacetate) was added.

The mixture of the prepared corresponding sodium salt and the isothiocyanate *Ia* or *Ib* in absolute ethanol (100 cm^3) was stirred at room temperature for 24 h, then refluxed for 1 h. A precipitate of product and NaCl was filtered off, dissolved in chloroform (20 cm^3) and extracted with water. Organic layer was dried, purified with charcoal, filtered and concentrated to the dryness. The residue was crystallized from methanol.

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