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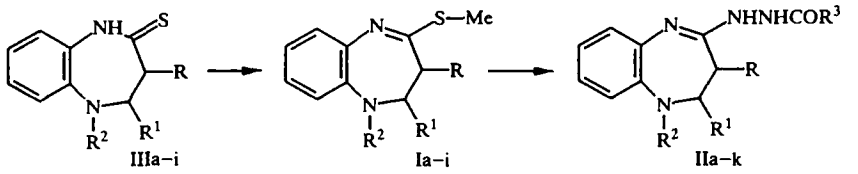
SYNTHESIS AND MILD CONVERSION OF 1,5-BENZODIAZEPINE IMINOTHIOETHERS INTO HYDRAZIDES

B. Puodžiūnaitė, L. Kosychova, R. Jančienė, and Z. Stumbrevičiūtė

4-Methylthio-2,3-dihydro-1H-1,5-benzodiazepine derivatives were prepared by alkylation of tetrahydro-1H-1,5-benzodiazepine-2-thiones with iodomethane or dimethyl sulfate in the presence of base or using phase-transfer catalysis. The desired 4-acyl-hydrazino-2,3-dihydro-1H-1,5-benzodiazepines resulted from the reaction of iminothioethers with hydrazides.

In connection with several projects on the synthesis of new annelated tricyclic 1,5-benzodiazepines, a clean and efficient method for the preparation of 4-hydrazino-2,3-dihydro-1H-1,5-benzodiazepines is needed. Since tetrahydro-1H-1,5-benzodiazepine-2-thiones [1] show insufficient reactivity towards some nucleophiles, it is important to transform them to a more reactive form, e.g., to the corresponding iminothioethers [2-4].



	R	R^1	R^2		R	R^1	R^2	R^3
I, IIIa	H	H	H	IIa	H	H	H	Me
b	Me	H	H	b	Me	H	H	Me
c	H	Me	H	c	H	Me	H	Me
d	H	H	Me	d	H	H	Me	Me
e	Me	H	Me	e	Me	H	Me	Me
f	H	Me	Me	f	H	Me	Me	Me
g	H	H	CH_2Ph	g	H	H	CH_2Ph	Me
h	Me	H	CH_2Ph	h	Me	H	CH_2Ph	Me
i	H	Me	CH_2Ph	i	H	Me	CH_2Ph	Ph
				j	H	Me	Me	Ph
				k	Me	H	CH_2Ph	Ph

In the present study, methods for the synthesis of novel 4-methylthio-2,3-dihydro-1H-1,5-benzodiazepines Ia-i and their conversion into N-substituted hydrazides IIa-k were developed.

The precursors (thiolactams IIIa-i) were previously described by us [1]. The treatment of thiolactams IIIc, f with iodomethane in the presence of potassium carbonate at ambient temperature [2] afforded thioethers Ic, f (Method A). The ^1H NMR spectra indicated a characteristic singlet for $S-CH_3$ proton signals of iminothioethers at 2.35-2.53 ppm (Table 1), while $N-CH_3$ proton signals of tetrahydro-1,5-benzodiazepine-2-thione derivatives were observed at 3.66-3.77 ppm [3, 5, 6]. Consequently, the reaction product has structure I, but not the structure of N-methyl thiolactams. TLC monitoring of the

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TABLE 1. ^{1}H NMR Data for Compounds Ia-i

Compound	δ, ppm, J, Hz ($CDCl_3$)
Ia	2,41 (3H, s, CH_3); 2,65 (2H, m, CH_2CS); 3,59 (2H, m, CH_2N); 6,51...7,27 (4H, m, Ar)
Ib	1,10 (3H, d, CH_3C); 2,35 (3H, s, CH_3S); 2,89 (1H, m, CH); 2,90...3,31 (2H, m, CH_2); 3,74 (1H, bs, NH); 6,39...7,36 (4H, m, Ar)
Ic	1,23 (3H, d, CH_3C); 2,15...2,50 (2H, m, CH_2); 2,43 (3H, s, CH_3S); 3,09 (1H, bs, NH); 3,99 (1H, m, CH); 6,55...7,25 (4H, m, Ar)
Id	2,44 (2H, m, CH_2CS); 2,47 (3H, s, CH_3S); 2,71 (3H, s, CH_3N); 3,52 (2H, m, CH_2N); 6,82...7,40 (4H, m, Ar)
Ie	1,13 (3H, d, CH_3C); 2,43 (3H, s, CH_3S); 2,70...3,57 (3H, m, CH_2CH); 2,72 (3H, s, CH_3N); 6,71...7,21 (4H, m, Ar)
If	1,09 (3H, d, CH_3C); 2,19 (1H, d. d, ^2J = 13,4, ^3J = 8,2, C<u>H</u>H); 2,41 (1H, d. d, ^3J = 6,1, C<u>H</u>H); 2,46 (3H, s, CH_3S); 2,72 (3H, s, CH_3N); 3,89 (1H, m, CH); 6,80...7,21 (4H, m, Ar)
Ig	2,45 (2H, m, CH_2CS); 2,48 (3H, s, CH_3); 3,42 (2H, m, CH_2N); 4,21 (2H, s, $C\underline{H}_2Ar$); 6,83...7,34 (9H, m, Ar)
Ih	1,07 (3H, d, CH_3C); 2,47 (3H, s, CH_2S); 2,87...3,50 (3H, m, CH_2CH); 4,08 and 4,40 (2H, AB-q, J = 14,0, $C\underline{H}_2Ar$); 6,79...7,25 (9H, m, Ar)
Ii	1,01 (3H, d, CH_3C); 2,10...2,47 (2H, m, CH_2S); 2,53 (3H, s, CH_3S); 3,88 (1H, m, CH); 4,21 and 4,24 (2H, AB-q, J = 14,2, CH_2N); 6,85...7,40 (9H, m, Ar)

preparation of products I showed that desulfuration of iminothioethers I leading to the formation of the corresponding tetrahydro-1,5-benzodiazepin-2-ones under reaction conditions also took place (TLC analysis with authentic samples).

Iminothioethers Ie, h were obtained from IIIe, h by alkylation with iodomethane in the presence of potassium hydrocarbonate in polar solvents (Method B). The reaction was also accompanied by the formation of desulfuration products. Thiolactam IIIb can also be S-alkylated with dimethyl sulfate using the described procedure [7] (Method C). Compound Ib was isolated as an oil and proved to be less stable than other methylthio derivatives I.

The phase-transfer catalyzed alkylation of compounds IIIa, d, g, i with an excess of iodomethane in 40% aqueous potassium hydroxide/chlorobenzene or benzene at room temperature led to the desired iminothioethers Ia, d, g, i (Method D) [3]. Control of the reaction time by TLC analysis led to minimum formation of desulfurated product. Iminothioethers Ia-i were converted to the 4-acylhydrazino derivatives IIa-k by condensation with an excess of acetyl or benzoylhydrazines under relatively mild conditions.

The ^{1}H NMR spectra of acetylhydrazino derivatives IIa-h show two singlets for the methyl protons of the acetyl group with Δδ 0.10-0.18 ppm. This indicates that these compounds exist in the solution form at 35°C as a mixture of Z- and E-isomers in the ratio 40:60 to 60:40. The ratio of isomers varies depending on the nature of R and R^1.

EXPERIMENTAL

^{1}H NMR spectra were measured on a Hitachi R-22 spectrometer operating at 90 MHz (35°C) with HMDS as an internal reference, and chemical shifts were expressed as δ (ppm). TLC was performed on Silufol UV-254 silica gel plates in the system benzene–methanol (v/v, 6:1). For column chromatography, silica gel Chemapol L 40/100 was used.

1,2-Dimethyl-4-methylthio-2,3-dihydro-1H-1,5-benzodiazepine (If). (Procedure A). To a solution of 2.84 g (13.7 mmol) of thiolactam IIIf in tetrahydrofuran (60 ml), 3.9 g (28 mmol) of potassium carbonate and 1.74 ml (28 mmol) of iodomethane were added. The mixture was stirred at room temperature until the starting material (R_f 0.,65) was consumed as evidenced by TLC analysis. The formation of 4,5-dimethyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-2-one (R_f 0.30) was also observed. The mixture was filtered and the filtrate was evaporated *in vacuo*. The resultant thick residue was dissolved in 20 ml of methanol and diluted with 40 ml of water. The suspension formed was made basic with 1 N sodium hydroxide and the resulting precipitate was filtered off. Recrystallization of the solid from ethanol gave 2.3 g (76%) of If as white needles, m.p. 48-50°C. Found, %: N 12.85. $C_{12}H_{16}N_2S$. Calculated, %: N 12.71.

2-Methyl-4-methylthio-2,3-dihydro-1H-1,5-benzodiazepine (Ic) was obtained following the above procedure from the reaction of compound IIIc with iodomethane. The thick oily residue was treated with ethyl ether. After long standing in the refrigerator (−18°C), pale yellow crystalline compound Ic precipitated (62%), m.p. 85-87°C. Found, %: N 13.44. $C_{11}H_{14}N_2S$. Calculated, %: N 13.58.

TABLE 2. Experimental Data for Compounds IIa-k

Compound	Molecular formula	Found, % / Calculated, %			M.p. (°C)	^{1}H NMR δ, ppm (DMSO-D$_6$)	Yield (%)
		C	H	N			
IIa	$C_{11}H_{14}N_4O$	60,67 60,53	6,27 6,46	25,45 25,67	200...201	1,92 and 2,06 (3H, bs, CH_3); 2,35 (2H, bs, CH_2C=); 3,47 (2H, bs, CH_2N); 5,28 (1H, bs, N<u>H</u>CH_2); 6,56...7,05 (4H, m, Ar); 8,10 and 9,60 (2H, bs, NHNH)	66
IIb	$C_{12}H_{16}N_4O$	61,85 62,05	6,67 6,94	24,25 24,12	155...156	1,04 (3H, d, C<u>H</u>$_3$CH); 1,92 and 2,08 (3H, s, CH_3CO); 2,57 (1H, m, CH); 2,92...3,37 (2H, m, CH_2); 5,25 (1H, bs, N<u>H</u>CH); 6,58 ...7,05 (4H,m,Ar); 8,04 and 9,62 (2H, bs, NHNH	75
IIc	$C_{12}H_{16}N_4O$	61,90 62,05	7,14 6,94	24,31 24,12	171...172	1,14 (3H, d, C<u>H</u>$_3$CH); 1,99...2,55 (2H, m, CH_2); 3,74 (1H, m, CH); 4,90 (1H, bs, N<u>H</u>CH_2); 6,67...6,99 (4H, m, Ar); 8,17 and 9,55 (2H, bs, NHNH)	80
IId	$C_{12}H_{16}N_4O$	62,33 62,05	7,20 6,94	23,96 24,12	162...164	1,89 and 2,07 (3H, s, CH_3CO); 2,17...2,47 (2H, m, CH_2C=); 2,69 (3H, s, CH_3N); 3,05...3,35 (2H, m, CH_2N); 6,75...7,10 (4H, m, Ar); 8,26 and 9,49 (2H, bs, NHNH)	45
IIe	$C_{13}H_{18}N_4O$	63,22 63,39	7,22 7,36	22,47 22,74	170...171	1,01 (3H, d, C<u>H</u>$_3$CH); 1,89 and 2,07 (3H, s, CH_3CO); 2,34...3,24 (3H, m, CH_2CH); 2,69 (3H, s, CH_3N); 6,84...7,03 (4H, m, Ar); 8,16; 8,24 and 9,55 (2H, bs, NHNH)	72
IIf	$C_{13}H_{18}N_4O$	63,61 63,39	7,48 7,36	22,69 22,74	190...193	1,09 (3H, d, C<u>H</u>$_3$CH); 1,86 and 2,03 (3H, s, CH_3CO); 1,95...2,55 (2H, m, CH_2); 2,69 (3H, s, CH_3N); 3,43 (1H, m, CH); 6,77...7,07 (4H, m, Ar); 8,19; 8,28; 9,48 and 9,58 (2H, bs, NHNH)	82
IIg	$C_{18}H_{20}N_4O$	69,89 70,10	6,36 6.54	17,96 18.17	142...144	1,90 and 2,04 (3H, s, CH_3CO); 2,20...2,44 (2H, m, CH_2C=); 3,15...3,37 (2H, m, CH_2N); 4,26 (2H, s, C<u>H</u>$_2$Ph); 6,83...7,36 (9H, m, Ar); 8,34; 9,53 and 9,64 (2H, bs, NHNH)	94
IIh	$C_{19}H_{22}N_4O$	70,61 70,78	7,00 6,88	17,25 17,35	169...171	0,95 (3H, d, C<u>H</u>$_3$CH); 1,95 and 2,05 (3H, s, CH_3CO); 2,34...2,57 (1H, m, CH); 2,79...3,22 (2H, m, CH_2N); 4,09 and 4,36 (2H, AB-q, C<u>H</u>$_2$Ph); 6,82...7,34 (9H, m, Ar); 8,29 and 9,58 (2H, bs, NHNH	74
IIi	$C_{24}H_{24}N_4O$	74,82 74,98	6,41 6,29	14,59 14,57	210...212	1,08 (3H, d, CH_3); 1,85...2,35 (2H, m, CH_2); 3,80 (1H, m, CH); 4,35 (2H, s, CH_2N); 6,88...8,04 (14H, m, Ar); 8,54 and 10,17 (2H, bs, NHNH)	85
IIj	$C_{18}H_{20}N_4O$	70,18 70,10	6,72 6,54	18,33 18,17	160...161	1,04 (3H, d, C<u>H</u>$_3$CH); 1,89...2,35 (2H, m, CH_2); 2,71 (3H, s, CH_3N); 3,60 (1H, m, CH); 6,87...7,98 (9H, m, Ar); 9,71 (2H, bs, NHNH)	71
IIk	$C_{24}H_{24}N_4O$	74,66 74,98	6,26 6,29	14,87 14,57	165...167	1,03 (3H, d, CH_3); 2,90...3,65 (3H, m, CH_2CH); 4,14 and 4,39 (2H, AB-q, CH_2N); 6,89...8,02 (14H, m, Ar); 8,53 and 10,08 (2H, bs, NHNH)	67

^{1}H NMR spectrum of the crude residue of product Ic indicated the presence of 1,2-dimethyl derivative If formed by competing alkylation at the diazepine ring nitrogen.

1-Benzyl-3-methyl-4-methylthio-2,3-dihydro-1H-1,5-benzodiazepine (Ih). (Procedure B). To a suspension of 1.13 g (4 mmol) of thiolactam IIIh in acetone (50 ml), 2.0 g (20 mmol) of potassium hydrocarbonate was added and the mixture was stirred at room temperature for 2 h. After that a solution of 1.25 ml (20 mmol) of iodomethane in methanol (10 ml) was added dropwise. The reaction mixture was warmed to 30°C and stirred overnight at room temperature. TLC analysis did not indicate completion of the reaction (IIIh, R_f 0.85) and also the formation of the corresponding desulfurated product (R_f 0.34) was observed. The mixture was filtered. The solvent and excess of iodomethane were evaporated. The oily residue was dissolved in a small volume of benzene and subjected to column chromatography (silica gel) using benzene–hexane mixture (9:1) as eluent. Removal of the solvent from the eluate afforded a thick oil, which was kept *in vacuo* over phosphorus pentoxide overnight at room temperature. The nearly pure compound Ih (0.6g, 51%) was obtained as a pale yellow oil, R_f 0.95. Found, %: N 9.21. $C_{18}H_{20}N_2S$. Calculated, %: N 9.45.

1,3-Dimethyl-4-methylthio-2,3-dihydro-1H-1,5-benzodiazepine (Ie) was obtained following a procedure identical to that described above from the reaction of thiolactam IIIe with iodomethane. Compound Ie (65%) was obtained as a yellow oil, R_f 0.97. Found, %: N 12.36. $C_{12}H_{16}N_2S$. Calculated, %: N 12.71.

3-Methyl-4-methylthio-2,3-dihydro-1H-1,5-benzodiazepine (Ib). (Procedure C). To a stirred solution of IIIb (1.1 g, 5.8 mmol) in dry dioxane (40 ml), a solution of 1.93 g (34 mmol) of potassium hydroxide in dry methanol (10 ml) and dimethyl sulfate (1.7 ml, 17.5 mmol) in methanol (5 ml) was added in four portions during 1 h. The mixture was stirred overnight at room temperature, diluted with methanol, and filtered. The filtrate was concentrated to ca. 25 ml and water was added. The oil formed was extracted with ethyl ether and dried. Removal of the solvent gave an oily residue, which was dissolved in a small volume of benzene and chromatographed on a silica gel column. The fraction was collected by eluting with benzene–hexane (9:1). After removing the solvent and drying the residue *in vacuo* 0.49 g (42%) of Ib as a pale yellow oil, R_f 0.87, was obtained. Found, %: N 13.31. $C_{11}H_{14}N_2S$. Calculated, %: N 13.58. Compound Ib was also obtained according to method D in 82% yield.

4-Methylthio-2,3-dihydro-1H-1,5-benzodiazepine (Ia). (Procedure D). To a solution of thiolactam IIIa (0.89 g, 5 mmol) in 50 ml of chlorobenzene or benzene, 1.48 g (6.5 mmol) of benzyltriethylammonium chloride and 1.25 ml (20 mmol) of iodomethane were added. The obtained suspension was stirred at room temperature for 1.5-2 h until TLC analysis indicated the completion of the reaction. The mixture was filtered, and filtrate was diluted with chloroform (100 ml) and water (100 ml). The organic layer was separated and the aqueous phase extracted with chloroform. The combined organic phases were washed with water (until neutral), dried (Na_2SO_4), and evaporated to dryness *in vacuo*.

The thick oily residues obtained (compounds Ia, Id, and Ig) were purified by column chromatography following a procedure identical to that described for method B. The fraction eluted with benzene gave the pure compound Ia (0.58 g, 61%) as a yellow oil, R_f 0.81. Found, %: N 14.71. $C_{10}H_{12}N_2S$. Calculated, %: N 14.57. Compounds Id, g, i were obtained similarly.

1-Methyl-4-methylthio-2,3-dihydro-1H-1,5-benzodiazepine (Id). From the eluate, after removal of the solvent, iminothioether Id (0.55 g, 55%) was obtained as an oil, R_f 0.85. Found, %: N 13.83. $C_{11}H_{14}N_2S$. Calculated, %: N 13.58.

1-Benzyl-4-methylthio-2,3-dihydro-1H-1,5-benzodiazepine (Ig). From the eluate (benzene–hexane, 9:1), after removal of the solvent, compound Ig (1.1 g, 78%) was obtained as an oil, R_f 0.91. Found, %: N 10.21. $C_{17}H_{18}N_2S$. Calculated, %: N 9.92.

1-Benzyl-2-methyl-4-methylthio-2,3-dihydro-1H-1,5-benzodiazepine (Ii). The semisolid residue was triturated with ethyl acetate–ethyl ether (1:5) to give white crystalline compound Ii (1.27 g, 85%), m.p. 38-40°C. Found, %: N 9.48. $C_{18}H_{20}N_2S$. Calculated, %: N 9.45.

1-R^2-2-R^1-3-R-4-(2'-acylhydrazino)-2,3-dihydro-1H-1,5-benzodiazepines (IIa-k). General procedure. A solution of 5 mmol of a suitable methylthio derivative (Ia-i) and 9 mmol of acetyl- or benzoylhydrazine in anhydrous ethanol (40 ml) was refluxed for 1 h (for the preparation of compound IIi 15 min and for compound IIIb 5 h). After that the reaction mixture was stirred overnight at room temperature. The resulting precipitate was separated by filtration. After crystallization from ethanol pure compounds IIa-k were obtained as white solids. The experimental data for compounds IIa-k are presented in Table 2.

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