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Researches on Thiazolobenzodiazepines: Behavior of Tetrahydro-1,5-benzodiazepine-thiones with Aromatic α-Haloketones

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ABSTRACT: *A number of 1-substituted 4H,5H,6H-[1,3]thiazolo[3,2-a][1,5]benzodiazepinium-11-bromides and S-(2-oxo-2-phenyl-X-(p)-ethyl)-3-(2-methyl-1H-benzimidazol-1-yl) propane (or butane) thioate hydrobromides were obtained by direct reaction of the 5-acetyl(or formyl, or anilinocarbonyl)-substituted tetrahydro-1,5-benzodiazepine-2-thiones with aromatic α-bromoketones. 2-[(1-Acetyl-2(or 3)-methyl-2,3-dihydro-1H-1,5-benzodiazepin-4-yl) sulfanyl]-1-phenylethanones as intermediates of the formation of thiazolo [3,2-a][1,5]benzodiazepine and N-substituted 2-methyl-1H-benzimidazole derivatives have been synthesized. Semiempirical AM1 calculations of a mechanism and energetic parameters for the heptatomic nucleus rearrangement to benzimidazole ring are presented.* © 2008 Wiley Periodicals, Inc. Heteroatom Chem 19:72–81, 2008; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20414

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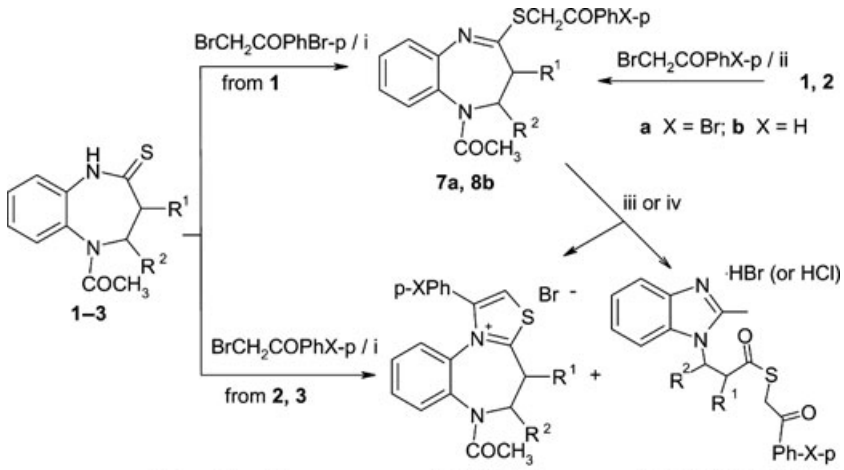
INTRODUCTION

In recent years, a great effort has been made in the benzodiazepine area to develop new members of this family by the fusion of heterocyclic rings to different faces of the heptatomic moiety [1,2]. For this purpose, the reactivity of C=S bond of 1,4- and 1,5-benzodiazepine derivatives was tested as a tool for a differentiated cyclofunctionalization of the seven-membered ring [2,3–5]. In the previous report, we have described the synthesis of thiazolo[1,5]benzodiazepine derivatives via the direct reaction of thiolactams with bromoacetaldehyde diethyl acetal [6]. To extend our study of these compounds, an analogous synthetic route was examined with aromatic α-halogen ketones. We present in this paper the preparation of new tricyclic thiazolobenzodiazepine and benzimidazole derivatives from variously substituted 1,5-benzodiazepine-2-thiones.

RESULTS AND DISCUSSION

The synthesis was based on the formation of the thiazole ring by condensation–cyclization of an appropriate thiolactam **1–6** [6,7] with 1.5 equivalent excess of the 2,4′-dibromoacetophenone or 2-bromoacetophenone in refluxing dry butan-2-one.



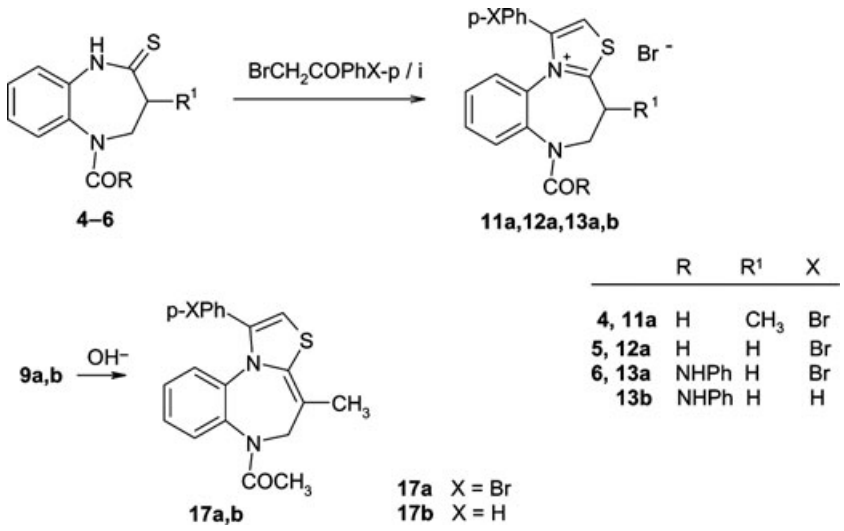
	R^1	R^2	X
1, 7a	H	CH_3	Br
2, 8b	CH_3	H	H
2, 9a, 14a	CH_3	H	Br
9b, 14b	CH_3	H	H
3, 10a, 15a	H	H	Br
10b, 15b	H	H	H
16a	H	CH_3	Br

SCHEME 1

The reaction sequence followed for the synthesis of tricyclic derivatives is illustrated in Scheme 1.

Thus, by cycloaddition of the haloketones to thiolactams **2, 3**, carrying N_5-acetyl substituent, the corresponding thiazolobenzodiazepinium bromides **9a,b** and **10a,b**, and unexpected hydrobromides of the benzimidazole derivatives **14a,b** and **15a,b** as a result of the concurrent reactions were obtained. The same reaction carried out on N_5-formyl or N_5-anilinocarbonylsubstituted thiolactams **4, 5**, and **6** afforded the corresponding tricyclic derivatives **11a, 12a**, and **13a,b** in 32%–46% yields, and the corresponding benzimidazole derivatives could not be separated (Scheme 2). The formation of the mixture of tricyclic compounds **9a,b, 10a,b** in 31%–48% yields and benzimidazole derivatives **14a,b** and **15a,b** in 32%–46% yields (Table 1) suggests that energetically two direct reactions are possible in this cyclization process.

S-Alkyl derivative **7a** was isolated only in the case of the thermal cyclization reaction of thiolactam **1** with 2,4′-dibromoacetophenone in 92% yield as hydrobromide (practically insoluble in butan-2-one) which then was converted into the corresponding base. It is noteworthy to note that S-alkylation could take place in the primary step in the course



	R	R^1	X
4, 11a	H	CH_3	Br
5, 12a	H	H	Br
6, 13a	NHPh	H	Br
13b	NHPh	H	H

SCHEME 2

TABLE 1 Characterization of **7a, 8b, 9–10a,b, 11a, 12a, 13–15a,b, 16a** and Elemental Analysis Data[a]

	Yield[b] (%)	*mp (°C)*[c]	*Molecular Formula (Molecular Weight)*	*Found (Calcd.)*		
				C	*H*	*N*
7a•HBr	92	171–173	$C_{20}H_{20}Br_2N_2O_2S$ (512.28)	46.67 (46.89)	3.86 (3.94)	5.61 (5.47)
7a	67	117–119	$C_{20}H_{19}BrN_2O_2S$ (431.36)	55.83 (55.69)	4.41 (4.44)	6.72 (6.49)
8b	65	133–135	$C_{20}H_{20}N_2O_2S$ (352.46)	68.32 (68.16)	5.56 (5.72)	7.61 (7.95)
9a	42	252–254	$C_{20}H_{18}Br_2N_2OS$ (494.26)	48.77 (48.60)	3.59 (3.67)	5.85 (5.67)
9b	48	255–257	$C_{20}H_{19}BrN_2OS$ (415.36)	57.54 (57.84)	4.57 (4.61)	6.59 (6.74)
10a	31	207–209	$C_{19}H_{16}Br_2N_2OS$ (480.23)	47.38 (47.52)	3.43 (3.36)	5.97 (5.83)
10b	29	134–136	$C_{19}H_{17}BrN_2OS$ (401.33)	56.51 (56.86)	4.36 (4.27)	6.79 (6.98)
11a	46	261–263	$C_{19}H_{16}Br_2N_2OS$ (480.23)	47.75 (47.52)	3.40 (3.36)	5.98 (5.83)
12a	32	242–243	$C_{18}H_{14}Br_2N_2OS$ (466.21)	46.13 (46.37)	3.20 (3.03)	5.85 (6.01)
13a	35	242–244	$C_{26}H_{23}Br_2N_3OS$ (585.37)	53.59 (53.35)	3.89 (3.96)	7.24 (7.18)
13b	32	210–212	$C_{26}H_{24}BrN_3OS$ (506.47)	61.48 (61.66)	4.89 (4.78)	8.21 (8.30)
14a	34	142–144	$C_{20}H_{20}Br_2N_2O_2S$ (512.28)	46.67 (46.89)	3.82 (3.94)	5.61 (5.47)
14b	46	176–177	$C_{20}H_{21}BrN_2O_2S$ (433.38)	55.29 (55.43)	4.96 (4.88)	6.21 (6.46)
15a (base)	38	89–91	$C_{19}H_{17}BrN_2O_2S$ (417.33)	54.59 (54.68)	3.91 (4.11)	6.83 (6.71)
15b	47	95–97	$C_{19}H_{19}BrN_2O_2S$ (419.35)	54.69 (54.42)	4.51 (4.57)	6.52 (6.68)
16a	50	121–123	$C_{20}H_{20}BrClN_2O_2S$ (467.82)	51.17 (51.35)	4.27 (4.31)	6.15 (5.99)

[a]Satisfactory microanalyses were obtained: C ± 0.35; H ± 0.17; N ± 0.34.
[b]Yields of purified products.
[c]Crystallization solvent: **10a,b** (MeOH-diethyl ether), base of **15a** (diethyl ether), **15b** (CH_2Cl_2-diethyl ether).

of the cyclization. This fact was stated when the reaction between tetrahydro-1,5-benzodiazepine-2-thiones and bromoacetaldehyde diethyl acetal was studied [6].

The cyclization reaction was monitored by the TLC analysis. Thus, at the beginning of the reaction, the formation of S-alkyl derivative ($R_f \sim 0.7$) in the reaction mixture was observed in all experiments. During the course of the reaction when the starting thiolactam ($R_f \sim 0.6$) and S-alkyl derivative were no longer detectable, the presence of two products at $R_f \sim 0.3$ (benzimidazole compound) and tricyclic compound at the start point of TLC was observed. The single products were separated on account of their different solubilities in butan-2-one or by dry column vacuum chromatography. For example, purification by chromatography (silica gel) of the crude reaction mixture obtained from the reaction of **3** with 2,4′-dibromoacetophenone furnished compound **15a** as a base. The excess of 1.5 equivalent of aromatic halogen ketone was needed in this reaction. When this reaction was repeated using less ketone (1.0 equivalent), the cyclic thiolactam was not fully consumed. However, after the addition of 2.0 equivalents of ketone to the reaction mixture, some of this reagent remained unreacted and the purification of products mixture became complicated. Attempts to optimize the cyclization conditions were not successful. When this reaction was performed in the more polar anhydrous ethanol, the condensation proceeded more quickly. However, the isolation of the reaction products under these conditions was rather intricate. But the reaction of **2** with 2,4′-dibromoacetophenone performed in the benzene/dichloroethane mixture stimulated the formation of tricyclic compound **9a** in 92% yield, whereas in experiments with other thiolactams such result was not achieved.

TABLE 2 IR and ^{1}H NMR Data of **7a, 8b, 9–10a,b, 11a, 12a, 13–15a,b**, and **16a**

	IR, ν (cm^{-1})	*^{1}H NMR δ (ppm), J (Hz)*
7a	1698, 1652	1.18 (d, 3H, $J=6.3$, CH_3), 1.73 (s, 3H, CH_3), 2.30–2.41 (m, 2H, 3-CH_2), 4.28 and 4.74 (AB-q, 2H, $J=16.0$, 4-CH_2), 5.38 (m, 1H, CH), 6.98 (dd, 1H, $J=1.4$, 7.9, H-6), 7.07 (dd, 1H, $J=1.5$, 7.7, H-9), 7.14 (dt, 1H, $J=1.5$, 7.7, H-8), 7.35 (dt, 1H, $J=1.6$, 7.8, H-7), 7.63 (m, 2H, H-3′,5′), 7.93 (m, 2H, H-2′,6′)
8b	1702, 1659	1.27 (d, 3H, $J=6.9$, CH_3), 1.80 (s, 3H, CH_3), 2.99 (m, 1H, CH), 3.56 (dd, 1H, $J=6.0$, 12.7, CH_2), 4.35 and 4.70 (AB-q, 2H, $J=16.1$, 4-CH_2), 4.73 (dd, 1H, $J=12.9$, 12.8, CH_2), 6.95 (bd, 1H, H-6), 7.06–7.13 (m, 2H, H-8,9), 7.30 (m, 1H, H-7), 7.48 (m, 2H, H-3′,5′), 7.59 (m, 1H, H-4′), 8.04 (m, 2H, H-2′,6′)
9a	1675	Two rotamers in a ratio of 68:32. 1.67 (d, 3H, $J=6.5$, 4-CH_3), [1.68 (d, 3H, $J=6.5$, 4-CH_3)], 2.04 (s, 3H, 6-CH_3), [2.28 (s, 3H, 6-CH_3)], 3.48–3.61 (m, 1H, CH), 3.89 (dd, 1H, $J=6.3$, 12.5, 5-CH_2), [4.24–4.38 (m, 2H, 5-CH_2)], 4.66 (dd, 1H, $J=12.5$, 12.6, 5-CH_2), 7.01–7.78 (m, 8H, arom), 8.41 (s, 1H, H-2), [8.412 (s, 1H, H-2)]
9b	1672	Two rotamers in a ratio of 70:30. 1.68 (d, 3H, $J=6.6$, 4-CH_3), [1.69 (bd, 3H, 4-CH_3)], 2.05 (s, 3H, 6-CH_3), [2.30 (s, 3H, 6-CH_3)], 3.47–3.61 (m, 1H, CH), 3.90 (dd, 1H, $J=6.6$, 12.7, 5-CH_2), [4.28–4.42 (m, 2H, 5-CH_2)], 4.67 (dd, 1H, $J=12.6$, 12.7, 5-CH_2), 6.98–7.79 (m, 9H, arom), 8.38 (s, 1H, H-2), [8.382 (s, 1H, H-2)]
10a	1674	Two rotamers in a ratio of 70:30. 2.08 (s, 3H, 6-CH_3), [2.32 (s, 3H, 6-CH_3)], 3.15–3.27, 3.85–3.92, 4.01–4.08, 4.25–4.32, 4.66–4.79, 4.95–5.05 (m each, 4H, 4-CH_2, 5-CH_2), 7.05–7.83 (m, 8H, arom), 8.40 (s, 1H, H-2), [8.402 (s, 1H, H-2)]
10b	1670	Two rotamers in a ratio of 70:30. 2.05 (s, 3H, 6-CH_3), [2.30 (s, 3H, 6-CH_3)], 3.13–3.25, 3.81–3.88, 3.98–4.05, 4.22–4.29, 4.64–5.03 (m, each, 4H, 4-CH_2, 5-CH_2), 6.98–7.78 (m, 9H, arom), 8.32 (s, 1H, H-2)
11a	1666	Two rotamers in a ratio of 60:40. [1.68 (d, 3H, $J=6.6$, 4-CH_3)], 1.71 (d, 3H, $J=6.7$, 4-CH_3), [3.67 (m, 1H, CH)], 3.74 (m, 1H, CH), 3.91 (ddd, 1H, $J=0.9$, 5.9, 12.5, 5-CH_2), [4.22–4.40 (m, 2H, 5-CH_2)], 4.53 (ddd, 1H, $J=0.7$, 12.4, 12.6, 5-CH_2), 7.04–7.76 (m, 8H, arom), [8.32 (s, 1H, 6-CH)] 8.39 (s, 1H, H-2), [8.41 (s, 1H, H-2)], 8.49 (dd, 1H, $J=0.7$, 0.9, 6-CH)
12a	1682, 1666	Two rotamers in a ratio of 65:35. 3.30–3.47, 3.89–3.96, 4.04–4.15, 4.22–4.29, 4.62–4.72, 4.78–4.88 (m each, 4H, 4-CH_2, 5-CH_2), 7.08–7.81 (m, 8H, arom), [8.38 (s, 1H, 6-CH)], 8.39 (s, 1H, H-2), [8.40 (s, 1H, H-2)], 8.54 (s, 1H, 6-CH)
13a	3230, 3182, 1662	3.15–3.25 and 3.95–4.02 (m, each, 2H, 4-CH_2), 4.06–4.13 and 4.75–4.85 (m, each, 2H, 5-CH_2), 7.02–7.80 (m, 13H, arom), 8.35 (s, 1H, H-2)
13b	3223, 3180, 1661	3.14–3.26 (m, 1H, 4-CH_2), 3.96–4.12 (m, 2H, 4-CH_2, 5-CH_2), 4.75–4.88 (m, 1H, 5-CH_2), 7.00–7.79 (m, 14H, arom), 8.28 (s, 1H, H-2)
14a	2800–2525, 1697, 1677	1.47 (d, 3H, $J=7.0$, CH_3), 3.02 (s, 3H, 2′-CH_3), 3.53 (m, 1H, CH), 4.23 and 4.29 (AB-q, 2H, $J=16.9$, SCH_2), 4.46 (dd, 1H, $J=5.0$, 14.7, CH_2), 4.65 (dd, 1H, $J=10.0$, 14.7, CH_2), 7.46–7.56 (m, 2H, H-5′,6′), 7.58-7.62 (m, 1H, H-7′), 7.62 (m, 2H, H-3″,5″), 7.80 (m, 2H, H-2″,6″), 7.86–7.90 (m, 1H, H-4′)
14b	2800–2530, 1694, 1667	1.48 (d, 3H, $J=7.0$, CH_3), 3.02 (s, 3H, 2′-CH_3), 3.54 (m, 1H, CH), 4.27 and 4.33 (AB-q, 2H, $J=16.9$, SCH_2), 4.45 (dd, 1H, $J=5.1$, 14.8, CH_2), 4.66 (dd, 1H, $J=10.0$, 14.7, CH_2), 7.44–7.55 (m, 4H, H-5′,6′,3″,5″), 7.60 (m, 1H, H-4″), 7.64 (m, 1H, H-7′), 7.86 (m, 1H, H-4′), 7.92 (m, 2H, H-2″,6″)
15a	1680	2.61 (s, 3H, 2′-CH_3), 3.13 (t, 2H, $J=6.9$, CH_2), 4.32 (s, 2H, SCH_2), 4.45 (t, 2H, $J=6.9$, NCH_2), 7.21–7.32 (m, 3H, H-5′,6′,7′), 7.64 (m, 2H, H-3″,5″), 7.67–7.70 (bm, 1H, H-4′), 7.81 (m, 2H, H-2″,6″)
15b	2800–2525, 1691, 1681	3.09 (s, 3H, 2′-CH_3), 3.41 (br t, 2H, CH_2), 4.37 (s, 2H, SCH_2), 4.78 (br t, 2H, NCH_2), 7.42–7.54 (m, 4H, H-5′,6′,3″,5″), 7.61 (m, 1H, H-4″), 7.69 (m, 1H, H-7′), 7.86 (m, 1H, H-4′), 7.93 (m, 2H, H-2″,6″)
16a	2800–2530, 1698, 1670	1.83 (d, 3H, $J=7.0$, CH_3), 3.09 (s, 3H, 2′-CH_3), 3.28 (dd, 1H, $J=3.6$, 16.2, CH_2), 3.72 (dd, 1H, $J=10.2$, 16.2, CH_2), 4.18 and 4.36 (AB-q, 2H, $J=17.0$, SCH_2), 5.22 (m, 1H, CH), 7.49–7.55 (m, 2H, H-5′,6′), 7.62 (m, 2H, H-3″,5″), 7.63–7.69 (m, 1H, H-7′), 7.80 (m, 2H, H-2″,6″), 8.01 (m, 1H, H-4′)

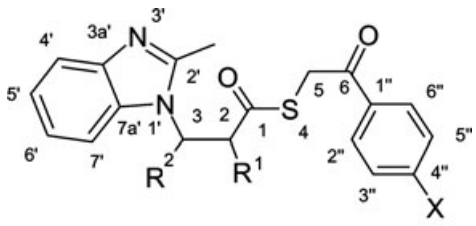
The structure of the studied compounds was investigated using IR and ^{1}H, ^{13}C NMR spectra (Tables 2 and 3). The assignment of the resonances in the NMR spectra was based on the chemical shift theory, signal intensity arguments, and multiplicities and comparison with structurally related compounds, as well as APT, NOE, COSY, ^{1}H-^{13}C 2D NMR experiments for some compounds. For ease of description of ^{13}C NMR spectra of compounds **14a,b, 15a,b**, and **16a**, we have used arbitrary numbering of atoms (Scheme 3).

^{1}H NMR spectra of **9a,b, 10a,b, 11a, 12a**, and **13a,b** showed singlets between 8.28 and 8.41 ppm, attributable to proton of thiazole nucleus shifted to such low fields due to the presence of a positive charge on the nitrogen atom. The spectra of **9a,b,**

TABLE 3 ^{13}C NMR Data of Compounds **7a, 8b, 9–10a,b, 12a, 13b, 14–15a,b**, and **16a**

	^{13}C NMR δ (ppm)
7a	18.73 (2-CH_3), 22.94 (1-CH_3), 37.19 (4-CH_2), 40.70 (C-3), 58.95 (C-2), 124.86 (CH), 125.17 (CH), 128.71 (C-4′), 129.13 (CH), 129.75 (C-9a), 129.96 (C-2′,6′), 130.04 (CH), 131.95 (C-3′,5′), 134.72 (C-1′), 146.51 (C-5a), 170.00 (1-CO or C-4), 170.44 (C-4 or 1-CO), 192.83 (4-CO)
8b	13.16 (3-CH_3), 22.62 (1-CH_3), 37.16 (4-CH_2), 37.73 (C-3), 59.38 (C-2), 124.70 (CH), 124.89 (CH), 128.38 (CH, C-2′,6′), 128.60 (C-3′,5′), 128.89 (CH), 131.47 (C-9a), 133.35 (C-4′), 136.21 (C-1′), 146.15 (C-5a), 170.66 (1-CO), 175.48 (C-4), 193.78 (4-CO)
9a	14.72 (4-CH_3), 23.12 (6-CH_3), 36.20 (4-C), 58.88 (5-C), 122.86, 127.66, 129.10, 130.95, 132.30, 132.80 (2CH), 133.46, 133.66 (2CH), 133.86, 133.98, 137.13, 149.16 (C-1), 172.34 (6-CO), 181.48 (C-3a)
9b	14.77 (4-CH_3), 23.11 (6-CH_3), 36.18 (4-C), 58.81 (5-C), 122.44, 128.61, 129.17, 130.37 (2CH), 130.77, 131.01 (2CH), 132.17, 132.18, 133.81, 134.08, 137.07, 150.24 (C-1), 172.21 (6-CO), 181.22 (C-3a)
10a	23.30 (6-CH_3), 28.61 (4-C), 52.33 (5-C), 123.59, 127.77, 129.09, 130.99, 132.33, 132.54, 132.69 (2CH), 133.44, 133.65 (2CH), 134.00, 136.77, 148.68 (C-1), 172.57 (6-CO), 175.63 (C-3a)
10b	[22.40 (6-CH_3)], 23.30 (6-CH_3), 28.68 (4-C), [29.39 (4-C)], 52.32 (5-C), [54.4 (5-C)], 123.12, 128.71, 129.15, 130.22, 130.41 (2CH), 130.96 (2CH), 132.18, 132.41, 133.89, 134.10, 136.68, 149.80 (C-1), 172.59 (6-CO), 175.24 (C-3a)
12a	27.93 (C-4), [28.78 (C-4)], 50.72 (C-5), [53.45 (C-5)], 123.40, 123.57, 126.49, 126.50, 127.82, 127.89, 128.67, 129.29, 130.55, 131.04, 131.12, 132.29, 132.70 (2CH), [132.75 (2CH)], 133.49, [133.49 (2CH)], 133.55 (2CH), 133.76, 134.20, 134.54, 135.03, 135.44, 149.03 (C-1), 164.60 (C-6), [165.35 (C-6)], [174.72 (C-3a)], 175.60 (C-3a)
13b	29.41 (C-4), 53.4 (C-5), 122.65, 122.88 (2CH), 125.20, 128.55, 128.68, 129.69 (2CH), 130.24 (2CH), 130.39, 130.99 (2CH), 132.01, 132.84, 133.91, 135.63, 136.97, 139.61, 149.99 (C-1), 157.25 (6-CO), 175.08 (C-3a)
14a	12.00 (2-CH_3), 16.30 (CH_3), 36.99 (SCH_2), 46.66 (CH), 47.18 (NCH_2), 111.41, 115.30, 126.27, 126.62, 129.34, 129.85 (C-2″,6″), 129.94, 130.93, 132.19 (C-3″,5″), 133.78 (C-1″), 150.58 (C-2′), 190.50 (CO), 199.09 (SCO)
14b	11.99 (2-CH_3), 16.30 (CH_3), 37.07 (SCH_2), 46.69 (CH), 47.20 (CH_2), 111.56, 115.11, 126.21, 126.54, 128.30 (C-2″,6″), 128.81 (C-3″,5″), 129.81 (C-3a′ or C-7a′), 130.93 (C-3a′ or C-7a′), 133.94 (C-4″), 135.02 (C-1″), 150.53 (C-2′), 191.42 (CO), 199.13 (SCO)
15a	13.80 (2-CH_3), 36.44 (SCH_2), 39.18 (CH_2), 42.62 (CH_2), 108.86 (C-7′), 119.26 (C-4′), 122.16 (C-5′ or C-6′), 122.30 (C-5′ or C-6′), 129.21 (C-4″), 129.86 (C-2″,6″), 132.16 (C-3″,5″), 134.00 (C-1″), 134.43 (C-7a′), 142.62 (C-3a′), 151.30 (C-2′), 191.52 (CO), 194.81 (SCO)
15b	12.00 (2-CH_3), 37.15 (SCH_2), 40.52 (CH_2), 41.11 (CH_2), 111.29, 115.38, 126.25, 126.58, 128.38 (C-2″,6″), 128.88 (C-3″,5″), 130.06 (C-3a′ or C-7a′), 130.68 (C-3a′ or C-7a′), 134.05 (C-4″), 135.08 (C-1″), 150.69 (C-2′), 191.69 (CO), 194.56 (SCO)
16a	12.44 (2-CH_3), 19.43 (CH_3), 37.08 (SCH_2), 46.72 (CH), 50.33 (CH_2), 112.44, 116.08, 126.03, 126.34, 129.05, 129.42, 129.86 (C-2″,6″), 130.79, 132.22 (C-3″,5″), 133.74 (C-1″), 150.28 (C-2′), 190.59 (CO), 194.12 (SCO)

10a,b, 11a, and **12a** showed the presence of two forms exhibiting double sets of signals due to rotational isomers of the exocyclic amide bond. ^{13}C NMR signals are consistent with the proposed structure. Compounds **14a,b, 15a,b**, and **16a** exhibited resonances in their ^{1}H and ^{13}C NMR spectra assigned to derivatives bearing N-alkyl substituted benzimidazole nucleus (as neutral or protonated form) [8,9]. The presence of $CHR^2CHR^1COSCH_2COPh$ fragment



14a,b, 15a,b, 16a

SCHEME 3

was confirmed as follows: ^{1}H NMR spectra exhibited two triplets of CH_2CH_2 group and singlets of SCH_2 group at 4.32 and 4.37 ppm for **15a,b**. In the spectra of **14a,b, 16a**, there were observed ABX patterns for CHR^2CHR^1 (R^2, R^1 = H or Me) fragment and AB-signals at 4.18–4.36 ppm, $J = 16.9$ Hz for CH_2 group. The methylene SCH_2 group exhibited nonequivalence of their protons due to the chiral center at the alkanoic chain. The expected multiplet signals for carbonyl-substituted phenyl protons were also observed. Moreover, in ^{13}C NMR spectra, the resonances at 190.50–191.69, 194.12–199.19, and about 37 ppm were assigned to CO, SCO, SCH_2 (sharp triplet, $J = 140$ Hz) groups, respectively.

An alternative synthetic pathway was tried for compound **7a** (Scheme 1). Compounds **7a** and **8b** were synthesized under basic conditions. The reaction of thiolactams **1** and **2** with 2,4′-dibromoacetophenone or 2-bromoacetophenone in the presence of the potassium carbonate in butan-2-one at room temperature afforded S-alkylated 1,5-benzodiazepine derivatives **7a** and **8b** in 65%–67%

yields. The IR spectra of compounds **7a** and **8b** exhibited two CO stretching absorption bands at 1698–1702 (CO) and 1652–1659 (CON acyclic) cm^{-1}. In the ^1H NMR spectra, protons of CH_2S group appeared between 4.28 and 4.74 ppm. Moreover, in the ^{13}C NMR spectra, the C-4, C-5a resonances are mainly influenced by replacement of thiolactam functionality with N=C—S and shifted about 34 ppm (upfield) and about 11 ppm (downfield), respectively, with respect to precursors **1** and **2** [7]. The presence of CO aromatic group was confirmed by the resonances between 192.8 and 193.8 ppm as well as SCH_2 between 37.16 and 37.19 ppm (sharp triplet with $J_{C\text{-}H} = 139.9$ Hz). Brief heating of **7a** with an excess of concentrated hydrochloric acid in butan-2-one gave N-substituted benzimidazole derivative **16a**, carrying the thiolic acid fragment, whereas cyclization to tricyclic compound does not occurred. The heating of **8b** with 1 equivalent of 40% aqueous hydrobromic acid solution afforded **9b** and **14b** in 43% and 40% yields, respectively. Under these conditions, compound **7a** remained unchanged. Generally, 3*H*- and 2,3-dihydro-1*H*-1,5-benzodiazepine derivatives undergo decomposition or isomerization to benzimidazole derivatives if they are heated for some time and especially in an acidic medium [10]. An analogous transformation into 2-methylbenzimidazole derivatives was also observed in the group of N_5-acetyl substituted 1,5-benzodiazepin-2-ones when acylation or bromination reactions were performed in the presence of concentrated sulfuric acid [11,12]. The formation of five-membered ring is rationalized on the basis of acid hydrolysis of the amide or N=C bond of the starting 1,5-benzodiazepine derivative and followed cyclization with the loss of water. So, the results of studied cyclization reactions between thiolactams **1–6** and aromatic halogen ketones confirmed the formation of S-alkylated intermediates of **7a** and **8b** type and their transformation into the tricyclic thiazole and benzimidazole derivatives under the reaction conditions. The presence of N_5-acetyl substituent is favorable for the formation of benzimidazole derivatives. On the other hand, the formation of benzimidazole derivatives was not observed at the construction of thiazolobenzodiazepine system from 1,5-benzodiazepine-2-thiones and aliphatic α-halogen ketones (e.g., chloroacetone) [7].

According to Scheme 2, the bromides **9a,b** may be in turn converted into the thiazolobenzodiazepines **17a,b** of enamine structure by treatment with potassium hydroxide in water–methanol solution at room temperature. However, since compounds **17a,b** are relatively unstable their formation has been evidenced only by ^1H NMR spectroscopy. The signals of the thiazole nucleus were shifted upfield at 6.05–6.07 ppm (2-CH) with respect to those 8.38–8.41 ppm in the bromides **9a,b**. Furthermore, the 4-methyl group protons signals appear as doublet-doublets at 1.57–1.59 ppm ($^4J = 1.0$ Hz). All other resonance patterns agree with the proposed of base structure, as well as ^{13}C NMR spectral data.

Starting thiolactams **1, 4–6**, and **2** were prepared according to the procedure previously described by us [6,7]. Compound **3** was synthesized by acylation of 1,3,4,5-tetrahydro-2*H*-1,5-benzodiazepine-2-thione [13].

To get an exhaustive insight about the reactivity of benzodiazepinethiones toward different α-halogenketones, the theoretical study was carried out. The N_5-acetyl-3-methylsubstituted thiolactam **2**, bromoacetone (A), and 2-bromoacetophenone (B) were selected as model compounds for the calculations. For the reaction of **2** with aliphatic (A) and aromatic (B), α-bromoketones two stepwise reaction pathways I and II were proposed (see Fig. 1).

The first step for both reaction pathways includes an electrophilic attack of bromoketones to sulfur atom of thiolactam **2**, leading to the formation of the intermediate of **8b** type. The second step of the pathway I comprises the cyclization reaction of the intermediate promoted by an electrophilic attack of S-substituent C=O group carbon atom on the diazepine nucleus N_1-nitrogen and formation of the tricyclic system with the elimination of water. The second step of the pathway II consists of an acidic hydrolysis of the intermediate C=N bond promoted by nucleophilic displacement at carbon atom and subsequent rearrangement of the molecule. Both steps of the proposed mechanism were computationally studied. The AM1 semiempirical study of the potential energy surface (PES) for complete model allowed to locate intermediates for the first step of the reaction and transition state (TS) structures for the second steps of pathways I and II. The energy profiles for the stationary points of the reaction pathways I and II are shown in Fig. 1. The geometries of the transition states and intermediates are displaced in Figs. 2 and 3.

The first step of an addition reaction is thermodynamically favorable for compound **2**, reaction with the bromoacetone (123.1 kcal/mol) and, particularly, with the 2-bromoacetophenone (294.3 kcal/mol). The energetic values obtained for the second steps allow us to explain experimental observations. Activation energies (E_a) of the reaction of **2** with aromatic bromoketone (B) for pathways I and II via transition states (TS-p,h and TS-p,c) are equal to 42.1 kcal/mol. It correlates with the experiment showing that two products (compounds **9b** and **14b** from **8b**) could be formed. The formation

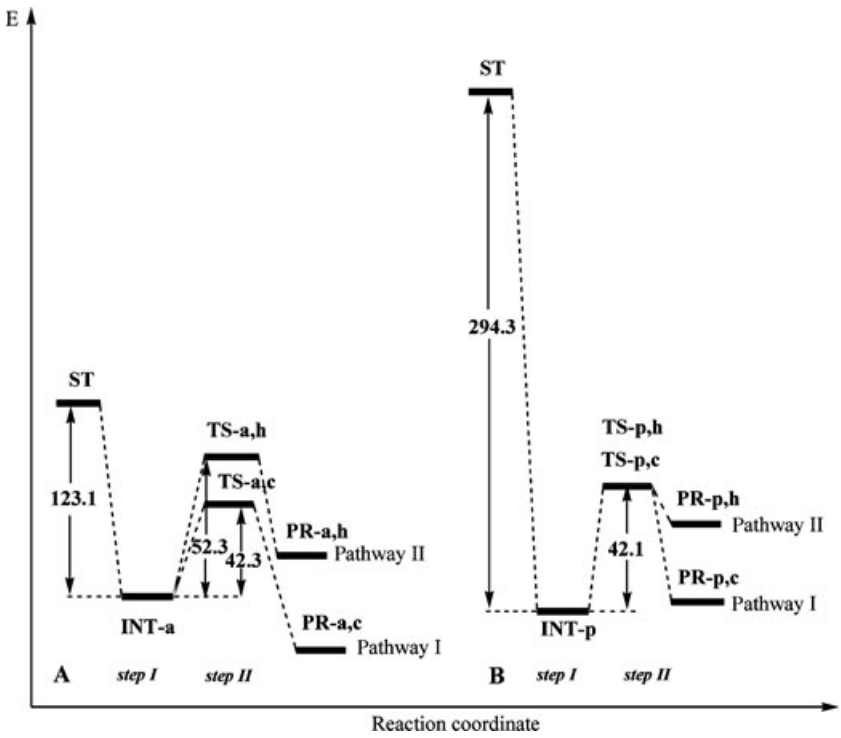


FIGURE 1 Energy profiles (kcal/mol) for stationary points of the corresponding pathways I and II of **2** reactions with bromoacetone (A) and 2-bromoacetophenone (B). ST: starting species, TS: transition states, INT: reaction intermediates, PR: reaction products.

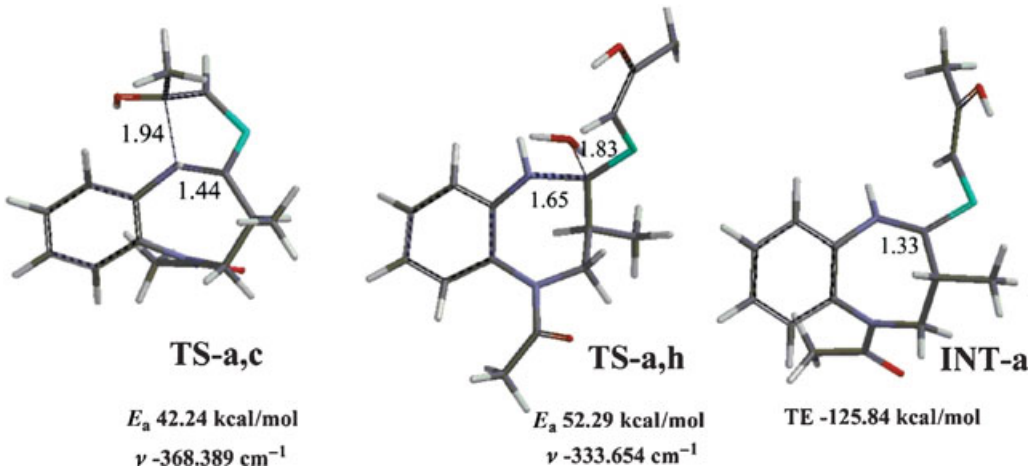


FIGURE 2 TS structures, their activation energies (E_a) in kcal/mol and unique imaginary frequency (ν) in cm^{-1}; intermediate structure INT-a with total energy (TE) in kcal/mol for **2** reaction with bromoacetone (A).

of transition states (TS-a,c and TS-a,h) for the pathways I and II in the reaction of **2** with aliphatic bromoketone (A) is 42.3 /and 52.3 kcal/mol, respectively. It is in an agreement with the experimental results that the reaction of **2** with chloroacetone afforded only tricyclic thiazolobenzodiazepine derivative [7]. For the TS structures associated with the cyclization process (pathway I) of haloketones A and B, the lengths of the forming N—C bond are 1.94 and 1.88 Å at the TS-a,c and TS-p,c, respectively. For the TS associated with the hydrolysis process (pathway II), the lengths of the forming C—O bond and breaking N—C bond are 1.83 and 1.65 Å at the TS-a,h with bromoketone A and 1.73 and 1.55 Å at TS-p,h with

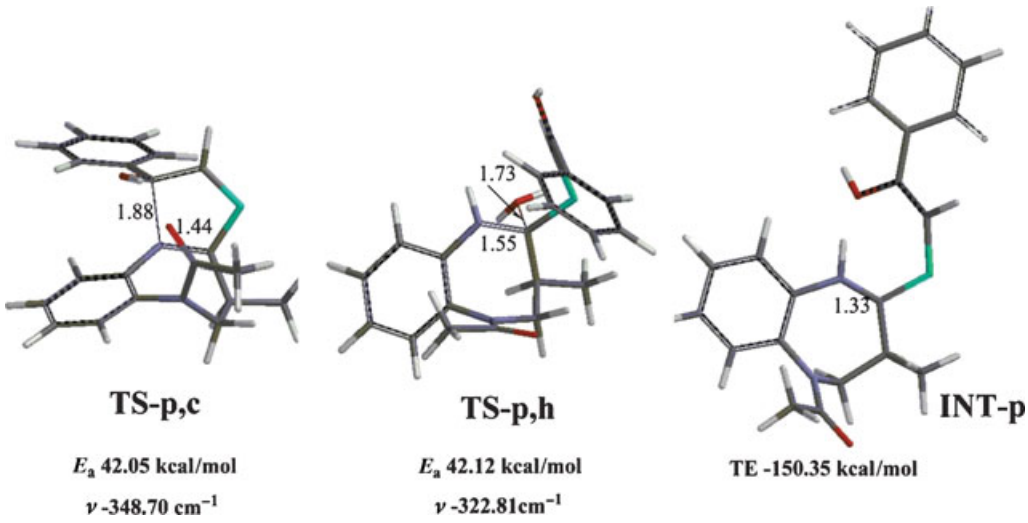


FIGURE 3 TS structures, their activation energies (E_a) in kcal/mol and unique imaginary frequency (ν) in cm^{-1}; intermediate structure INT-a with total energy (TE) in kcal/mol for **2** reaction with bromoacetophenone (B).

bromoketone B, respectively. Analysis of the atomic motion along vibrational frequencies indicates that transition states of cyclization (TS-a,c and TS-p,c) are mainly associated with the motion of the N and C atoms along the C—N bond formation and the transition states of the hydrolysis reaction (TS-a,h and TS-p,h) are mainly associated with the motion of the atoms along the breaking C—N bond and forming C—O bond.

EXPERIMENTAL

Melting points were determined by the capillary method on a PTP (Thermopribor) apparatus and are uncorrected. The IR spectra (KBr) were taken on a PerkinElmer spectrum GX FT-IR spectrometer. The ^{1}H and ^{13}C NMR spectra were recorded on a Varian Unity Inova 300 spectrometer (300 MHz) in deuteriochloroform (compounds **7a, 8b, 14–15a,b, 16a**) or in deuteriomethanol (compounds **9–10a,b, 11a, 12a, 13a,b**). The chemical shifts are referenced to tetramethylsilane (δ ^{1}H = 0) and the solvent signal deuteriochloroform (δ ^{13}C = 77.0 ppm), and deuteriomethanol (δ ^{13}C = 49.0 ppm). NMR peaks corresponding to the minor isomer of compounds **9–10a,b** and **11a** are given in square brackets. Data on the mass spectra obtained using a Waters (Micromas) ZQ 2000 spectrometer. Elemental analysis for C, H, and N was performed on the microelemental analyzer (Labopribor). Ascending TLC was carried out on Merck precoated silica gel aluminum rolls ($60F_{254}$) with chloroform-ethyl acetate-methanol (14:7:1) as the eluent and was visualized with UV light. Dry column vacuum chromatography was performed with silica gel Chemapol L 5/40 mesh. All calculations were carried out using GAMESS program package. An extensive characterization of PES was carried out using AM1 method to ensure that all relevant stationary points were located and properly characterized. The stationary points were characterized by frequency calculations to verify that the transition states have one and only one imaginary frequency.

*Synthesis of 1-PhX-(p)-4-R^1-5-R^2-6-acetyl-(**9a,b, 10a,b**) and 1-PhX-(p)-4-R^1-6-R (**11a, 12a, 13a,b**) 4H,5H,6H-[1,3]thiazolo[3,2-a][1,5]benzodiazepin-11-ium Bromides and S-[2-(4-Bromophenyl)-2-oxoethyl]- or S-(2-Oxo-2-phenylethyl)-2-methyl-(**14a,b**), and S-[2-(4-Bromophenylethyl)-2-oxoethyl]- or S-(2-Oxo-2-phenylethyl)-(**15a,b**), 3-(2-Methyl-1H-benzimidazol-1-yl)propanethioate Hydrobromides and 2-[(1-Acetyl-2-methyl-2,3-dihydro-1H-1,5-benzodiazepin-4-yl)sulfanyl]-1-(4-bromophenyl)ethanone (**7a**)*

General Procedure. To a stirred solution of the appropriate benzodiazepinethione derivative **1–6** (5.0 mmol) in 50–80 mL of dry butan-2-one, 2,4′-dibromoacetophenone or bromoacetophenone (7.5 mmol) was added. The mixture was refluxed for 1–3 h (reaction time in each case was determined by TLC monitoring). The resulting precipitate was collected by filtration of the warm reaction mixture. The solid was recrystallized from anhydrous

methanol and diethyl ether mixture to give **9a,b, 11a, 12a**, and **13a,b** as a colorless amorphous powders. The preceding filtrate was allowed to stand overnight in a refrigerator. After cooling, the formed precipitate was collected by filtration and crystallized from dichloromethane/diethyl ether mixture to give hydrobromides of **14a,b** as white crystals.

In the case of thiolactam **3** reaction with dibromo- or bromoacetophenone, no precipitate in the warm reaction mixture was formed. To a cooled in a refrigerator reaction mixture, the diethyl ether (5 mL) was added in portions. The fractional crystallization gave **10a,b** and **15b**. After separation of **10a**, the deeply colored filtrate was concentrated by evaporation. Subjection of the residue to dry column vacuum chromatography using the dichlorethane/ethyl acetate system for gradient elution gave the base of **15a** as a colorless solid. MS *m/z* (%): 417.1, 419.1 $(M + H)^+$.

In the case of 1.17 g (5 mmol) of thiolactam **1** reaction with 2.08 g (7.5 mmol) of 2,4′-dibromoacetophenone, the reaction mixture was refluxed for 45 min. The formed precipitate was collected by filtration and washed with diethyl ether (20 mL) to give 1.98 g of hydrobromide of **7a**. The solid was suspended in 100 mL of dry chloroform, and a solution of ammonia in chloroform dropwise was added till precipitation of ammonium bromide was watched. The insoluble material was removed by filtration. The addition of ammonia solution to the filtrate and filtration procedures were repeated. The filtrate was concentrated, and residue was crystallized from diethyl ether/hexane mixture to give the base of **7a** (1.33 g, 83%), mp 116°C–119°C.

*Synthesis of 2-[(1-Acetyl-2-methyl-2,3-dihydro-1H-1,5-benzodiazepin-4-yl)sulfanyl]-1-(4-bromophenyl)ethanone (**7a**) and 2-[(1-Acetyl-3-methyl-2,3-dihydro-1H-1,5-benzodiazepin-4-yl)sulfanyl]-1-phenylethanone (**8b**)*

A mixture of thiolactam **1** or **2** (3 mmol), 2,4′-dibromoacetophenone or 2-bromoacetophenone (3 mmol), and 2.07 g (15 mmol) of potassium carbonate in 50 mL of butan-2-one was stirred for 2 h at room temperature. It was filtered, and the filtrate was evaporated. The residue was dissolved in *tert*-butylmethyl ether (100 mL), washed with water, dried, and concentrated. A solid residue was crystallized from diethyl ether to yield **7a** and **8b** as a slightly yellow powder. Mixed sample of **7a** with authentic compound did not show depression of the melting point.

*Preparation of 6-Acetyl-4-methyl-1-phenyl-4H,5H,6H-[1,3]thiazolo[3,2-a][1,5]benzodiazepin-11-ium bromide (**9b**) and 3-(2-Oxo-2-phenylethyl)2-methyl-3-(2-methyl-1H-benzimidazol-1-yl)propanethioate Hydrobromide (**14b**) from **8b***

A mixture of 0.35 g (1.0 mmol) of **8b** and 0.2 g (1.0 mmol) of 40% aqueous hydrobromic acid in 30 mL of butan-2-one was heated at reflux for 15 min. After cooling to room temperature, the precipitated product was filtered and purified by crystallization to give 0.18 g (43%) of **9b**, mp 251°C–253°C. The preceding filtrate was allowed to stand overnight in a refrigerator, and diethyl ether was added till the solution becomes turbid. The solid compound obtained was separated by filtration and purified by crystallization to give 0.17 g (40%) of **14b**, mp 176°C–177°C. Mixed samples of **9b** and **14b** with authentic compounds did not show depression of the melting point.

The treatment of 0.43 g (1.0 mmol) of **7a** with 0.2 g (1.0 mmol) of 40% aqueous hydrobromic acid under the same reaction conditions as for **8b** yielded 0.31 g (70%) of hydrobromide **7a**, mp 170°C–172°C. Mixed sample of **7a**•HBr with authentic compound did not show depression of the melting point.

*S-[2-(4-Bromophenyl)-2-oxoethyl]-3-(2-methyl-1H-benzimidazol-1-yl)butanethioate Hydrochloride (**16a**)*

To a solution of 0.43 g (1.0 mmol) of **7a** in 40 mL of butan-2-one, 0.5 g (5.0 mmol) of conc. hydrochloric acid was added and the mixture was heated at reflux for 5 min. After cooling, diethyl ether was added. The formed precipitate was filtered off and recrystallized from dichloromethane/diethyl ether mixture to give 0.23 g (50%) of hydrochloride **16a**.

*Preparation of 6-Acetyl-1-(4-bromophenyl)-4-methyl-5,6-dihydro[1,3]thiazolo[3,2-a][1,5]benzodiazepine (**17a**) and 6-Acetyl-4-methyl-1-phenyl-5,6-dihydro[1,3]thiazolo[3,2-a][1,5]benzodiazepine (**17b**)*

Compound **9a** or **9b** (1.0 mmol) was dissolved in 30 mL of water and 2 mL of methanol. To a stirred solution, 0.17 g (3.0 mmol) of potassium hydroxide was added. The formed precipitate was filtered to give a solid of thiazolobenzodiazepine **17a** or **17b**. The ^{1}H NMR spectrum was recorded immediately.

17a. IR (cm^{-1}): 1663. ^{1}H NMR ($CDCl_3$) δ: 1.57 (bs, 3H, 4-CH_3), 2.04 (s, 3H, 6-CH_3), 3.51 (d, 1H, $J = 16.9$, 5-CH_2), 5.39 (d, 1H, $J = 16.9$, 5-CH_2), 6.07 (s, 1H, H-2), 6.67–7.23 (m, 8H, arom). ^{13}C NMR

($CDCl_3$) δ: 19.19 (4-CH_3), 22.18 (6-CH_3), 49.31 (5-C), 99.70 (C), 104.27 (CH), 121.50 (C), 124.65 (CH), 125.80 (CH), 127.75 (2CH), 128.17 (CH), 128.49 (CH), 131.49 (C), 131.82 (2CH), 136.69 (C), 136.89 (C), 139.03 (C), 142.63 (C), 169.30 (CO) ppm.

17b. IR (cm^{-1}): 1667. ^1H NMR ($CDCl_3$) δ: 1.59 (dd, 3H, $J = 1.0$, 1.0, 4-CH_3), 2.07 (s, 3H, 6-CH_3), 3.53 (bd, 1H, $J = 16.9$, 5-CH_2), 5.41 (bd, 1H, $J = 16.9$, 5-CH_2), 6.05 (s, 1H, H-2), 6.63–7.36 (m, 9H, arom). ^{13}C NMR ($CDCl_3$) δ: 19.23 (4-CH_3), 22.25 (6-CH_3), 49.40 (5-C), 99.24 (C), 103.33 (CH), 124.86 (CH), 125.56 (CH), 126.38 (2CH), 127.79 (CH), 127.97 (CH), 128.37 (CH), 128.43 (C), 128.60 (2CH), 132.63 (C), 136.93 (C), 140.20 (C), 142.90 (C), 169.35 (CO) ppm.

*5-Acetyl-1,3,4,5-tetrahydro-2H-1,5-benzodiazepine-2-thione (**3**)*

A solution of 1.78 g (10.0 mmol) of 1,3,4,5-tetrahydro-2*H*-1,5-benzodiazepine-2-thione [13] in 50 mL of dry chloroform and acetic anhydride (1.5 mL, 15.0 mmol) was refluxed for 6 h. After cooling, the organic solution was washed with 0.1 M hydrochloric acid solution (2 × 20 mL), 5% aqueous sodium hydrogencarbonate solution (40 mL) and water, dried, and concentrated. A solid residue was purified by recrystallization from ethyl acetate to give **3** (1.4 g, 64%), mp 163°C–165°C. IR (cm^{-1}): 3153, 1659. ^1H NMR ($CDCl_3$) δ: 1.83 (s, 3H, 5-CH_3), 2.85–3.16 (b m, 2H, 3-CH_2), 3.52–3.68 (b m, 1H, 4-CH_2), 4.90–5.10 (b m, 1H, 4-CH_2), 7.20–7.46 (m, 4H, arom), 10.20 (b s, 1H, NH). ^{13}C NMR ($CDCl_3$) δ: 22.92 (5-CH_3), 41.46 (C-3), 50.51 (C-4), 122.60, 127.73, 129.37, 129.95, 134.38, 135.97, 170.64 (5-CO), 205.00 (C-2) ppm.

Anal. Calcd for $C_{11}H_{12}N_2OS$ (220.29): C, 59.98; H, 5.49; N, 12.72. Found: C, 59.90; H, 5.56; N, 12.61.

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