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SYNTHESES OF SOME 1-(α-HYDROXYBENZYL)THIENO[3,4-*b*]-INDOLIZINE DERIVATIVES AND THEIR UNEXPECTED CONDENSATION REACTIONS[1]

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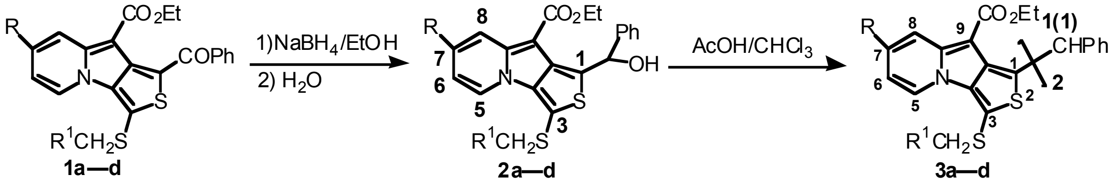
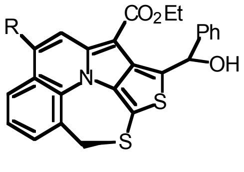
Abstract - Some ethyl 3-(benzyl or methylthio)-1-(α-hydroxybenzyl)-thieno[3,4-*b*]indolizine-9-carboxylates were prepared by the reduction of the corresponding 1-benzoyl derivatives with sodium borohydride. These compounds were considerably unstable and their treatment with acetic acid afforded the unexpected condensation products.

We recently reported the preparation of various ethyl 3-(arylmethylthio)thieno[3,4-*b*]indolizine-9-carboxylate derivatives whose NMR spectra showed an considerable high-field shifts of the pyridine ring protons due to the intramolecular π-π interaction between the thieno[3,4-*b*]indolizine and the aryl rings.[2] We also disclosed that the more crowded *gauche* conformation in relation to the sulfide spacer is more stable than the sterically more favorable anti one in the MOPAC MO calculations.[2c] However, the differences of the formation energies between these conformers are always small and the *anti* conformers often appeared in the crystal states. In our preliminary attempts to develop a new type of chiral auxiliary using the *gauche* conformation stabilized by the intramolecular π-π stacking, we interested in the introduction of an asymmetric center into these molecules, because our reported compounds are racemic and not separable to each enantiomer by usual methods even though their conformations were fixed. In this communication we report smooth reductions of some ethyl 1-benzoyl-3-(benzyl or methylthio)thieno[3,4-*b*]-indolizine-9-carboxylates with sodium borohydride and the unexpected condensation reactions of the resulting 1-(α-hydroxybenzyl) derivatives to the corresponding bis[3-(benzyl or methylthio)thieno[3,4-*b*]indolizin-1-yl]phenylmethanes.

The title compounds, ethyl 1-(α-hydroxybenzyl)thieno[3,4-*b*]indolizine-9-carboxylates (**2a**—**d**)[3] having a benzylthio or a methylthio group at the 3-position, were readily prepared in good yields by the treatment of the corresponding ethyl 1-benzoylthieno[3,4-*b*]indolizine-9-carboxylate (**1a**—**d**)[2a,b,4] with 0.3 molar amount of sodium borohydride in refluxing ethanol for 0.5—1 h (see Scheme 1): **2a**, 99%, mp 115—117 °C, ν(OH) 3385, ν(CO) 1643 cm^{-1}; **2b**, 97%, mp 127–129 °C, ν(OH) 3451, ν(CO) 1669 cm^{-1}; **2c**, 85%, mp 139–141 °C, ν(OH) 3418, ν(CO) 1620 cm^{-1}; **2d**, 93%, mp 165–166 °C, ν(OH) 3360, ν(CO) 1626 cm^{-1}.

These products (**2a**—**d**) were unstable, in particular, in the chloroform solution, and decomposed gradually. When compound (**2b**) was separated by column chromatography on silica gel or **2c** was recrystallized from chloroform-ether, a quite different type of compound (**3b**) or (**3c**) were obtained, respectively. However, these transformations were little reproducible and similar treatment of derivatives (**2a**,**b**) did not provide any significant products at all. In considering the function of silica gel as an acidic catalyst and the compositions ($C_{35}H_{30}N_2O_4S_4$ and $C_{49}H_{42}N_2O_4S_4$, see later) of **3b**,**c**, we examined the reactions of **2a**—**d** with some acids. The reactions of **2a**—**d** with strong acids such as trifluoroacetic acid and methanesulfonic acid gave only tarry materials, but those with 4 equimolar amounts of acetic acid in chloroform at room temperature for 1 day afforded the corresponding products (**3a**—**d**),[3] respectively (Scheme 1): **3a**, 40%, mp 114–116 °C, ν(CO) 1663 cm^{-1}; **3b**, 51%, mp 235–237 °C, ν(CO) 1669 cm^{-1}; **3c**, 25%, mp 189–191 °C, ν(CO) 1671 cm^{-1}; **3d**, 54%, mp 159–161 °C, ν(CO) 1661 cm^{-1}.





2'a,c (*gauche*)

Prod.	React.	R	R1	Yield (%)
2a	**1a**	H	Ph	99
2b	**1b**	H	H	97
2c	**1c**	Me	Ph	85
2d	**1d**	Me	H	93

Prod.	React.	R	R1	Yield (%)
3a	**2a**	H	Ph	40
3b	**2b**	H	H	51
3c	**2c**	Me	Ph	25
3d	**2d**	Me	H	54

Scheme 1

The elemental analyses of **2a**—**d** were in accord with our initially expected structures and the IR and ^{1}H NMR spectra (Table 1) of **2a**—**d** were clearly exhibited a new hydroxyl signal at 3360—3451 cm^{-1} and δ5.75—5.87. On the other hand, the IR and ^{1}H NMR spectra (Table 1) of **3a**—**d** did not show any hydroxyl signal, and the ^{1}H NMR spectra exhibited the presence of two magnetically equivalent 3-(benzyl or methylthio)-9-(ethoxycarbonyl)thieno[3,4-*b*]indolizin-1-yl moieties in the comparison with the peak area of the 1(1)-proton singlet appeared at δ7.65—

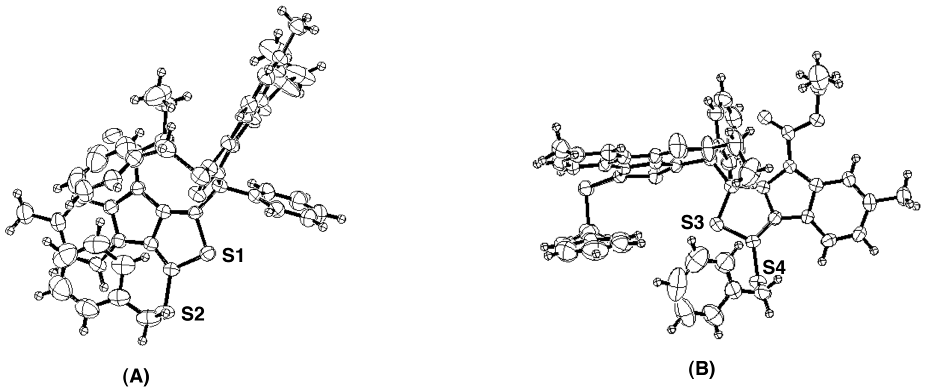
Table 1. ^{1}H NMR Spectral Data of Thieno[3,4-*b*]indolizine-9-carboxylates (**2a**—**d**) and (**3a**—**d**)[a]

No	C-5	C-6	C-7	C-8	C-1(1)	OH	R^1	□$_{5\text{-H}}$	□$_{6\text{-H}}$	□$_{7\text{-H}}$	□$_{8\text{-H}}$
2a	8.77	6.39	b)	8.07	6.68	5.85	3.89 6.8-7.8	0.35	0.22	-----	0.04
2b[c]	9.12	6.61	b)	8.11	6.61	5.81	2.38	0.00	0.00	-----	0.00
2c	9.63	6.22	2.33	7.82	6.53	5.87	3.86 6.8-7.7	0.40	0.33	0.07	0.11
2d[d]	9.03	6.55	2.40	7.93	6.59	5.75	2.40	0.00	0.00	0.00	0.00
3a	8.80	6.36	b)	8.21	7.79	-----	3.89 6.7-7.5	0.33	0.23	-----	0.06
3b[e]	9.13	6.59	b)	8.27	7.80	-----	2.41	0.00	0.00	-----	0.00
3c	8.66	6.22	2.31	8.00	7.65	-----	3.87 6.8-7.5	0.37	0.23	0.08	0.10
3d[f]	9.03	6.45	2.39	8.10	7.71	-----	2.39	0.00	0.00	0.00	0.00

a) □ ($CDCl_3$). b) Overlapped with phenyl proton signals. c) Standard to **2a**. d) Standard to **2c**.

e) Standard to **3a**. f) Standard to **3c**.

7.80. Furthermore, the elemental analyses of **3a**—**d** were consistent with the compositions that each one molecule of water and benzaldehyde was eliminated from two molecules of **2a**—**d**. Therefore, compounds (**3a**—**d**) should be the acid-catalyzed condensation products between two molecules of 1-(□-hydroxybenzyl) derivatives (**2a**—**d**). The structures of compounds (**3a**—**d**) were finally confirmed by the X-Ray analysis[5] of compound (**3c**) and the ORTEP drawings[6] are shown in Figure 1. Very interestingly, **3c** in the crystal state exhibited two different types of *gauche* conformations in trelation of the sulfide spacer, in which one *gauche* form (**A**) has intramolecular □□□ interaction and the other (**B**) has not it. This crystal structure is not consistent with the structure in the solution state showed by its ^{1}H NMR spectrum, because the two thieno[3,4-*b*]indolizine moieties in the latter are magnetically equivalent. Maybe, this phenomenon may due to the small energy difference between these conformers.[2b.c]



(A) (B)

Figure 1. ORTEP drawings of **3c**

As expected by their structures, considerable high-field shifts (□ 0.22—0.40 ppm) for the 5- and 6-protons of 3-benzyllthio derivatives (**2a**,**c**) and (**3a**,**c**) were observed in comparison with those of 3-methylthio derivatives (**2b**,**d**) and (**3b**,**d**). These values are comparable to those of 1-

arylcarbonyl-3-(benzylthio)thieno[3,4-*b*]indolizine derivatives reported by us[2] and the predominance of the gauche conformation such as **2'a**,**c** (see Scheme 1) stabilized by the intramolecular □□□ interactions in such molecules was suggested. Interestingly, both 3-benzylthio derivatives (**2a**,**c**) and (**3a**,**c**) exhibited the photochromism under the exposure to fluorescent or sun light.

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5. Crystallography of **3c:** A single crystal (0.44 x 0.68 x 0.56 mm) grown from $CHCl_3$–hexane was used for the unit-cell determinations and the data collection by Rigaku AFC5S four-circle diffractometer with graphite-monochromated Mo$K_{□}$ radiation (□=0.71069 Å). Crystal data of these compounds are as follows: **3c**: $C_{49}H_{42}N_2O_4S_4$; M=851.12; triclinic, space group $P\bar{1}$ (#2), Z=2 with a=11.458 (2) Å, b=18.169 (3) Å, c=10.983 (2) Å, □=101.60 (1), □=99.11° (2), □=72.99° (1); V=2129.6 (7) Å^3, and $D_{calc.}$=1.327 g/cm^3. All calculation were performed using the teXsan program.[7] The structure was solved by a direct method (SIR).[8] The non-hydrogen atoms were refined anisotropically, and the hydrogen atoms were refined isotropically. The final R- and R_w-factors after full-matrix least-squares refinements were 0.059 and 0.048 for 5269 (I>2. observed reflections), respectively.

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