Novel Transformation of Aralkylsulfinates to Their Aldehydes and Its Mechanistic Study

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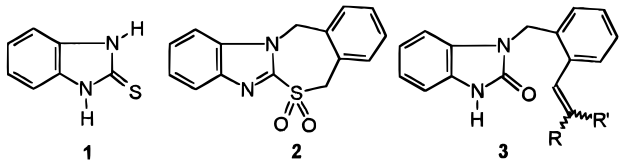
Received July 12, 1995 (Revised Manuscript Received October 25, 1995)

Recently we reported an efficient method for the synthesis of 1-(*o*-vinylbenzyl)benzimidazolin-2-ones **3** from benzimidazoline-2-thione (**1**) by way of 5*H*,13*H*-benzo[5,6][1,3]thiazepino[4,3-*a*]benzimidazole 6,6-dioxide (**2**).[1]



1 **2** **3**

As part of our studies on the synthesis of new functionalized benzimidazolin-2-ones which have received much attention due to their potential biological activities such as antiulcer,[2,3] neureoleptic,[4] antihistaminic,[5] antihypertensive,[6] and antiallergic[7] activities. Compound **2** dissolved in a mixture of THF and MeOH was treated with an excess amount of *n*-BuLi at −78 °C under nitrogen atmosphere, warmed to room temperature, and quenched with a few drops of water to afford lithium [[2-(2-methoxybenzimidazol-1-yl)methyl]benzyl]sulfinate (**4a**). Similar treatment of **2** with sodium methoxide in a mixture of THF and MeOH (10:1) at room temperature gave a sodium salt **4b** (Scheme 1). The formation of a sulfinate functionality with the ring opening of **2** was determined on the basis of characteristic IR bands at 1000−1050 and 980−990 cm^{-1} due to the sulfinate (S(O)−O) group and the conversion of sodium [[2-(2-ethoxybenzimidazol-1-yl)methyl]benzyl]sulfinate (**4c**) to methyl sulfone **5** by treatment with MeI in THF at room temperature.

The sulfinates **4** were excessively hygroscopic, regardless of metallic ion species. Although the salts were recrystallized from a mixture of CH_2Cl_2 and *n*-hexane, it was unsuccessful to obtain pure crystalline solids. TLC (silica gel, EtOAc:*n*-hexane = 1:2) showed that compound **4a** and **4b** were slowly converted to a new compound (R_f = 0.73, EtOAc:*n*-hexane = 1:2), and identified to be 1-(2-formylbenzyl)-2-methoxybenzimidazole (**6a**) even during the quenching process. However, the conversion of **4** to **6** was completed in a few minutes in water at reflux.

Table 1. Yields and Mps of 2-Alkoxy-1-(2-formylbenzyl)benzimidazoles (6)

		yield,[a] %		
compound	R	path A	path B	mp, °C
6a	Me	59	61	140−141
6b	Et	22	62	124−125.5
6c	*n*-Pr	54	63	135−136
6d	*n*-Bu	49	50	107−108
6e	*n*-pent		62	105−107
6f	benzyl	28		liquid
6g	*i*-Pr	26		143−144
6h	cyclohexyl	24		105−107

[a] Isolated yields. Path A: *n*-BuLi, THF−ROH (10:1); path B: RONa, THF.

Similarly the reactions of **2** with various sodium alkoxides in THF afforded the corresponding sodium [[2-(2-alkoxybenzimidazol-1-yl)methyl]benzyl]sulfinates **4**, which, without purification, were directly converted to the corresponding 2-alkoxy-1-(2-formylbenzyl)benzimidazoles (**6**) by heating the aqueous solution of **4**. However, the reaction of **2** with ^{t}BuOK in THF gave 1-(2-formylbenzyl)benzimidazolin-2-one (**7**) instead. Compound **7** was conceived to be formed by solvolysis of **6** (R = ^{t}Bu). The yields of **6** obtained *via* two different routes and their melting points are listed in Table 1.

The presence of a formyl group of **6** was also confirmed by the formation of 1,3-thioxolane **8** in 98% yield from the reaction of **6c** with ethanedithiol in the presence of $BF_3{\cdot}OEt_2$.

The reactions of **2** with sodium alkanethiolates in THF at room temperature, followed by water quenching afforded 2-(alkylthio)-1-(2-formylbenzyl)benzimidazoles (**9a**, R = Et, 32%; **9b**, R = *n*-Pr, 32%). Treatment of **2** with $NaBH_4$ in THF at room temperature, followed by the same workup procedure described above, gave 1-(2-formylbenzyl)benzimidazole (**10**) in 59% yield.

In order to test the generality of the conversion ($CH_2SO_2^- \rightarrow$ CHO), readily available benzylsulfinates[8] were subjected to the same conditions as in the conversions of **4**. Benzaldehyde and its derivatives such as *m*-chlorobenzaldehyde, *o*-tolualdehyde, and *p*-anisaldehyde were obtained in 29, 28, 19, and 21% yields, respectively.

For the mechanistic determination, an oxygen atom of the sulfone group of compound **2** was labeled with ^{18}O by a series of reactions.[9] Comparing mass spectral data of compound **10** obtained individually from labeled and nonlabeled compound **2**, the former showed 4.51% and the latter 1.77% of *m*/*z* ($M^+ + 2$) values.

This result clearly indicates that ^{18}O within a SO_2 group of compound **2** is incorporated into the formyl group. This observation can be rationalized by an intramolecular nucleophilic attack of an oxy anion of a sulfinate ion at the benzylic carbon atom with concomitant bond cleavage between the benzylic carbon and sulfur atoms to form an ion **11a** which undergoes delocalization of electrons to form **11b** with a negative charge on the electronegative oxygen atom (Scheme 2). One may also conceive a radical mechanism to give a radical pair **12** which then undergoes recombination to form **11**. The latter view is based on the transformation of benzylic selenoxides to aldehydes[10] and the racemization of ben-

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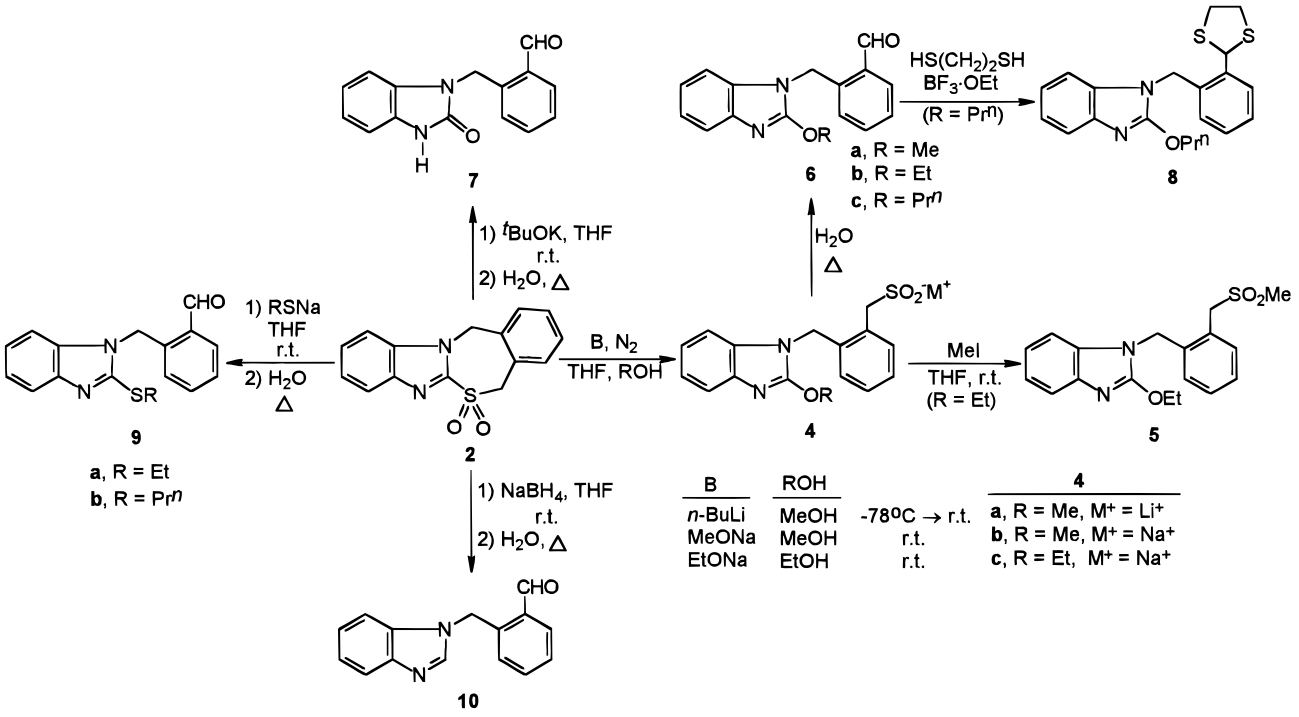
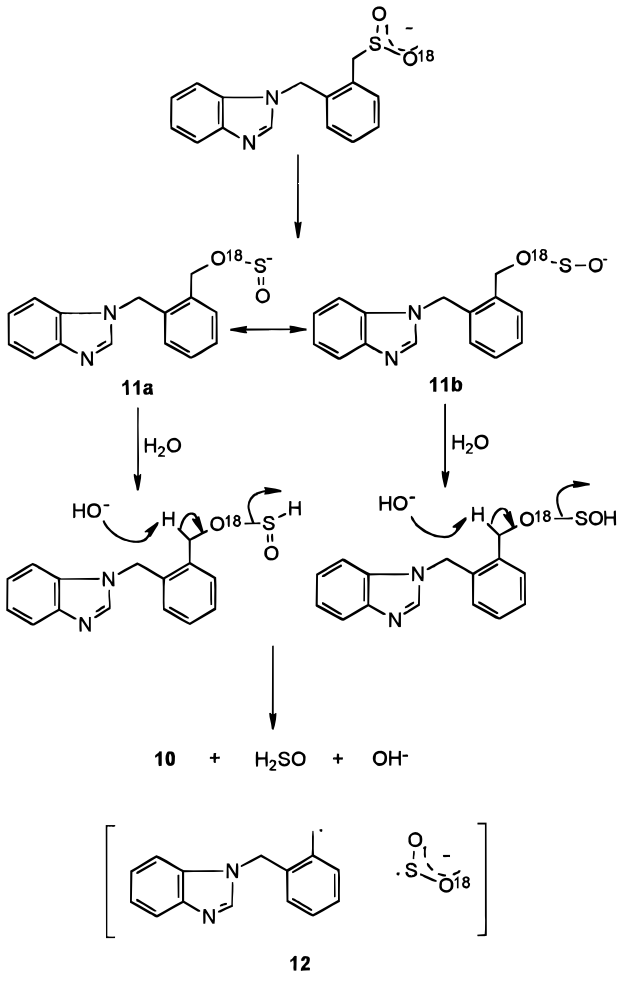
Scheme 1



Scheme 2



zylic sulfoxides.[11] Protonation of **11** in the presence of water was followed by base-catalyzed elimination of H_2SO to give **10**. A similar type of mechanism has been proposed for the formation of aldehydes by the thermal decomposition of sulfones by way of [α-(methylthio)-benzyl]benzenesulfinate.[12]

In conclusion, we have found a new transformation involving a sulfinate functionality in which a formyl group is formed *via* an intramolecular rearrangement of aralkylsulfinates. This transformation is expected to be a useful method for not only direct synthesis of aldehydes from alkylsulfinates but also introducing various functionalities at the *ortho* position of benzyl group of 1-benzylbenzimidazole and 1-benzylbenzimidazolin-2-one which might be biologically important.

Experimental Section

The ^{1}H NMR spectra were recorded at 80 or 200 MHz in $CDCl_3$ solution containing Me_4Si as an internal standard. IR spectra were recorded in KBr or thin films on KBr plates. Mass spectra were obtained by electron impact at 70 eV. Elemental analyses were determined by the Korea Basic Science Center. Column chromatography was performed using silica gel (70−230 mesh, Merck).

General Procedure for the Preparation of 2-Alkoxy-1-(2-formylbenzyl)benzimidazoles (6). (a) To a solution of **2** (0.3 mmol) in a mixture of THF (5 mL) and ROH (0.5 mL) at −78 °C under nitrogen atmosphere was added an excess amount of *n*-BuLi (10 M in *n*-hexane, 12 equiv). The mixture was stirred for 15 h at room temperature, followed by quenching with a few drops of water. After removal of the solvent *in vacuo*, the residue was washed with CH_2Cl_2 to give hygroscopic lithium [2-[(2-alkoxybenzimidazol-1-yl)methyl]benzyl]sulfinates **4** as white solids. A solution of lithium salts of **4** in water (10 mL) was heated at reflux for 20 min, and the mixture was extracted with EtOAc (50 mL). The extracts were dried over $MgSO_4$. Removal of the solvent *in vacuo* gave a residue, which was chromatographed on silica gel (2 × 10 cm). Elution with CH_2Cl_2, followed by a mixture of *n*-hexane and EtOAc (1:5, 100 mL) gave white solids **6**, which were recrystallized from a mixture of CH_2Cl_2 and *n*-hexane. Yields and melting points of **6a**−**h** are summarized in Table 1. (b) To a solution of **2** (0.3 mmol) in dried THF (10

(11) Oae, S. *Organic Chemistry of Sulfur*; Oae, S., Ed.; Plenum Press: New York, 1977; Ch. 8, pp 389, 397.

(12) Belen'kii, L. I. *Chemistry of Organosulfur Compounds*; Belen'kii, L. I., Ed.; Ellis Horwood, Ltd.: New York, 1990; Ch. 9, p 217.

mL) was added an excess amount of sodium alkoxide (5 equiv). The mixture was stirred for 4 h at room temperature under nitrogen atmosphere, followed by quenching with a few drops of water. After removal of the solvent, the residue was worked up as in (a) to give white sodium salts of **4**, which were recrystallized from a mixture of CH_2Cl_2 and *n*-hexane. Yields and melting points of compounds **6a**−**f** are summarized in Table 1.

Preparation of 2-(*n*-Propoxy)-1-[2-(thiolanyl)benzyl]-benzimidazole (8). To a solution of 2-(*n*-propoxy)-1-(2-formylbenzyl)benzimidazole (**6c**) (60 mg, 0.204 mmol) in dried CH_2Cl_2 (10 mL) was added 1,2-ethanedithiol (33 mg, 0.350 mmol), followed by addition of boron trifluoride diethyl etherate (33 mg, 0.210 mmol). The mixture was stirred for 5 h at room temperature and quenched with water (100 mL). After removal of the solvent *in vacuo*, the aqueous solution was extracted with CH_2Cl_2 (100 mL), which was dried over $MgSO_4$. Removal of the solvent *in vacuo* gave a residue which was chromatographed on silica gel column (2 × 10 cm). Elution with a mixture of *n*-hexane and EtOAc (1:2, 90 mL) gave **8** (67 mg, 98%): mp 85−86 °C (CH_2Cl_2−*n*-hexane); ^{1}H NMR δ 0.97 (t, 3H, J = 7.0 Hz), 1.63−2.06 (m, 2H, CH_2), 3.20−3.69 (m, 4H, $2SCH_2$), 4.53 (t, 2H, J = 7.0 Hz), 5.40 (s, 2H), 5.99 (s, 1H), 6.74−7.88 (m, 8H); IR (KBr) 3055, 2960, 2920, 1590, 1533, 1467, 1450, 742 cm^{-1}; MS (*m*/*z*) 370 (M^+). Anal. Calcd for $C_{20}H_{22}N_2OS_2$: C, 64.83; H, 5.98; N, 7.56; S, 17.30. Found: C, 64.79; H, 6.01; N, 7.49; S, 17.44.

General Procedure for the Preparation of 1-(*o*-Formylbenzyl)-2-(alkylthio)benzimidazole (9). To a solution of **2** (0.5 mmol) in dried THF (10 mL) at room temperature under nitrogen atmosphere was added sodium alkanethiolate (3 equiv). The mixture was stirred for 15 h at room temperature, followed by quenching with water (50 mL). After the reaction mixture was washed with EtOAc (100 mL), the aqueous solution was heated at reflux to give white solids, which were extracted with CH_2Cl_2 (100 mL). Drying of CH_2Cl_2 solution over $MgSO_4$, followed by removal of the solvent *in vacuo*, gave a residue, which was chromatographed on silica gel column (2 × 10 cm). Elution with a mixture of *n*-hexane and CH_2Cl_2 gave a small amount of thiol. Elution next with a mixture of *n*-hexane and EtOAc (1:1, 100 mL) gave **9** as a white solid, which was recrystallized from a mixture of CH_2Cl_2 and *n*-hexane.

2-(Ethylthio)-1-(*o*-formylbenzyl)benzimidazole (9a): yield 32%, mp 138−139 °C (CH_2Cl_2−*n*-hexane), ^{1}H NMR δ 1.43 (t, 3H, J = 7.0 Hz), 3.40 (q, 2H, J = 7.0 Hz), 5.84 (s, 2H), 6.60−6.70 (m, 1H, ArH), 7.11−8.09 (m, 7H), 10.23 (s, 1H); IR (neat) 2878, 2700, 1696 cm^{-1}; MS (*m*/*z*) 296 (M^+). Anal. Calcd for $C_{17}H_{16}N_2OS$: C, 68.89; H, 5.44; N, 9.45; S, 10.82. Found: C, 68.72; H, 5.41; N, 9.40; S, 10.69.

1-(*o*-Formylbenzyl)-2-(*n*-propylthio)benzimidazole (9b): yield 32%; mp 129−130 °C (CH_2Cl_2−*n*-hexane), ^{1}H NMR δ 1.00 (t, 3H, J = 7.0 Hz), 1.62−2.16 (m, 2H, J = 7.0 Hz), 3.03 (t, 2H, J = 7.0 Hz), 5.77 (s, 2H), 6.58−8.07 (m, 8H), 10.16 (s, 1H); IR (neat) 2878, 2805, 2700, 1688 cm^{-1}; MS (*m*/*z*) 310 (M^+). Anal. Calcd for $C_{18}H_{18}N_2OS$: C, 69.65; H, 5.85; N, 9.02; S, 10.33. Found: C, 69.51; H, 5.75; N, 9.06; S, 10.21.

Preparation of 1-(*o*-Formylbenzyl)benzimidazole (10). A mixture of **2** (88 mg, 0.309 mmol) and $NaBH_4$ (23 mg, 0.618 mmol) in dried THF (10 mL) was stirred for 2 h at room temperature. Evaporation of the solvent, followed by addition of *n*-hexane (50 mL) gave a white solid which was filtered. The white solid was dissolved in water (15 mL), and the solution was heated for 30 min at reflux. The reaction mixture was extracted with CH_2Cl_2 (50 mL x 3), which was dried over $MgSO_4$. Removal of the solvent *in vacuo* gave a residue which was chromatographed on silica gel column (2 × 10 cm). Elution with a mixture of *n*-hexane and EtOAc (1:1, 80 mL) gave **10** (43 mg, 59%): mp 152−153 °C (CH_2Cl_2−*n*-hexane); ^{1}H NMR δ 5.90 (s, 2H), 6.77−6.91 (m, 1H), 7.30−8.07 (m, 8H), 10.17 (s, 1H); IR (neat) 2875, 2754, 1688 cm^{-1}; MS (*m*/*z*) 236 (M^+). Anal. Calcd for $C_{15}H_{12}N_2O$: C, 76.25; H, 5.12; N, 11.86. Found: C, 76.28; H, 4.94; N, 11.75.

Preparation of Mono ^{18}O-Labeled 2. (a) 5*H*,13*H*-Benzo[5,6][1,3]thiazepino[4,3-*a*]benzimidazole 6-Oxide. To a solution of 5*H*,13*H*-benzo[5,6][1,3]thiazepino[4,3-*a*]benzimidazole[1] (228 mg, 0.904 mmol) in CH_3CN (20 mL) was added dropwise a solution of MCPBA (187 mg, 1.08 mmol) in ethyl ether (20 mL) for 20 min at room temperature. The mixture was stirred for 2 days at room temperature and quenched with water (100 mL), which was extracted with EtOAc (150 mL). Drying of the extract over $MgSO_4$, followed by evaporation of the solvent, gave the title compound (216 mg, 89%): mp 203−205 °C (EtOH); ^{1}H NMR δ 4.91 (s, 2H), 5.59 (s, 2H), 7.22−8.30 (m, 8H); IR (KBr) 1060 cm^{-1}. Anal. Calcd for $C_{15}H_{12}N_2OS$: C, 67.14; H, 4.51; N, 10.44; S, 11.95. Found: C, 67.07; H, 4.49; N, 10.38; S, 12.06. **(b) ^{18}O-Labeled 5*H*,13*H*-Benzo[5,6][1,3]thiazepino[4,3-*a*]benzimidazole 6-Oxide.** According to the literature procedure,[4] $H_2{}^{18}O$ (10 atom %, 2 g) was added to 5*H*,13*H*-benzo[5,6][1,3]thiazepino[4,3-*a*]benzimidazole 6-oxide (546 mg, 2.02 mmol) in *p*-dioxane (15 mL). Hydrogen chloride gas was bubbled into the solution for 24 h during which time the solution was maintained at 80 °C. Chloroform (50 mL) was added to the reaction mixture cooled at room temperature, and then the water layer was removed by using a pipette. The chloroform layer was dried over $MgSO_4$. Evaporation of the solvent gave a residue which was recrystallized from EtOH to give the title compound (228 mg, 42%). **(c) Mono ^{18}O-Labeled 2.** The ^{18}O-labeled sulfoxide (228 mg, 0.850 mmol) in dried CH_3CN (10 mL) was treated with MCPBA (297 mg) in dried ethyl ether (15 mL). Yield of the title compound: 186 mg (77%).

^{18}O-Labeled 10. ^{18}O-labeled **2** (186 mg, 0.654 mmol) in dried THF (10 mL) was treated with $NaBH_4$ (37 mg, 0.981 mmol) for 4 h at room temperature. Workup as described in the preparation of **9** gave the title compound which was recrystallized as described to give pure compound (57 mg, 37%).

Mass Spectroscopy of 10 and ^{18}O-Labeled 10. MS (*m*/*z*) of **10**: 236 (M^+, 100%), 238 ($M^+ + 2$, 1.77%). MS (*m*/*z*) of ^{18}O-labeled **10**: 236 (M^+, 100%), 238 ($M^+ + 2$, 4.51%).

Acknowledgment. The authors are grateful for the financial support by the Center for Biofunctional Molecules (C.B.M.).

Supporting Information Available: Copies of ^{1}H NMR, IR, mass spectra, and elemental analyses of **6a**−**h** and **7** (2 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS. See any current masthead page for ordering information.

JO951247V