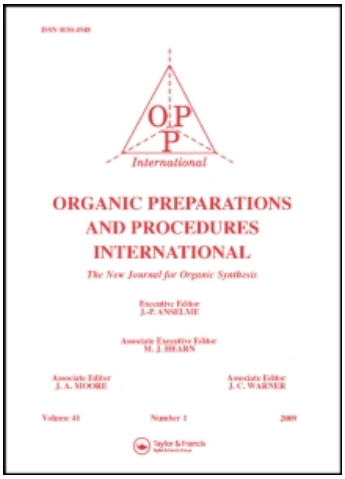

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PREPARATION OF IMIDAZO[2,1-b]THIAZOLES AND THIAZOLO[3,2-a]-BENZIMIDAZOLES USING S-ETHENYLSULFILIMINES

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PREPARATION OF IMIDAZO[2,1-b]THIAZOLES AND THIAZOLO[3,2-a]-BENZIMIDAZOLES USING S-ETHENYLSULFILIMINES†

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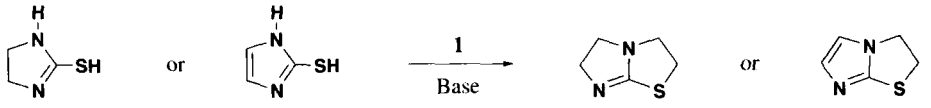
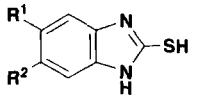
We have been developing the use of S-ethenylsulfilimines (**1**) as a building block for ring construction. Previous papers reported the efficient preparation of cyclopropanes[1] and 2-substituted oxazolines[2] by the reaction of active methylene compounds and amides with **1**, respectively. The present paper describes the elaboration of thiaza five-membered ring upon imidazoles and imidazolines to generate thiazolo[2,1-b]imidazoles and imidazo[3,2-a]benzoimidazoles. Thiazolo[2,1-b]imidazole derivatives have previously been obtained by the reaction of 2-mercaptoimidazoline with 1,2-dihaloethane,[3] cyclization of 1-(2-hydroxyethyl)-2-mercaptoimidazoline with 6N HCl,[4] cyclization of 2-(2-haloethyl)iminothiazoline (from 2-methylthio-2-thiazoline hydroiodide and 2-aminoethanol)[5] and by cyclization of 2-imino-3-(2-chloroethyl)thiazoline (from isothiocyanates and di-(2-haloethyl)amine).[6] Thiazolo[3,2-a]benzimidazole derivatives have been obtained by reaction of 2-mercaptobenzimidazoles with 1,2-dihaloethanes[7] and by cyclization of 1-(2-haloethyl)-2-mercaptobenzimidazoles.[8]

2-Mercaptoimidazoline (**2a**), 2-mercaptoimidazole (**2b**), and 2-mercaptobenzimidazoles (**4a-4e**) were selected as cyclic Michael donors toward **1** in a manner similar to our synthesis of 2-substituted oxazolines using **1**.[1] The reaction was allowed to proceed at room temperature for long

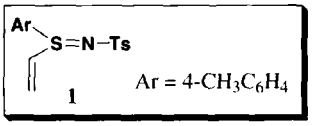


2a **2b** **3a** **3b**



4a: $R^1 = R^2 = H$,
4b: $R^1 = MeO$, $R^2 = H$,
4c: $R^1 = NO_2$, $R^2 = H$,
4d: $R^1 = R^2 = Me$,
4e: $R^1 = R^2 = C$

5a: $R^1 = R^2 = H$,
5b: $R^1 = MeO$, $R^2 = H$,
5b': $R^1 = H$, $R^2 = MeO$,
5c: $R^1 = NO_2$, $R^2 = H$,
5c': $R^1 = H$, $R^2 = NO_2$,
5d: $R^1 = R^2 = Me$,
5e: $R^1 = R^2 = Cl$



1 Ar = 4-$CH_3C_6H_4$

time or for shorter time at room temperature followed by warming at 40-45° in the presence of sodium hydride in 1,2-dimethoxyethane (DME) (See Table 1).

Higher yields were obtained with **2a**, **2b**, **4a**, **4b** and **4e**. The yields of imidazo[2,1-b]thiazole derivatives (**3a**, **3b**) and thiazolo[3,2-a]benzimidazole derivatives (**5a**, **5d** and **5e**) are superior to those in literature syntheses. In the case of the reaction of **1** with **4b** and **4c**, two cyclization products **5b** and **5b'** (from **4c**), and **5c** and **5c'** (from **4c**) were obtained, respectively. The higher ratios of **5b'** to **5b** and of **5c** to **5c'** were inversely proportional to the temperature, presumably due to the stability of the intermediate anion formed by proton transfer, thus leading to the higher selectivity is observed at lower temperature.

Table 1. Imidazo[2,1-b]thiazoles **3** and Thiazolo[3,2-a]-benzimidazoles **5** from Cyclic Michael Donors (**2** and **4**) and **1**[a]

Michael donor	Temp/Time °C / h		mp (°C)	Product Yield (%)	Ratio (%)[b]
2-Mercapto-imidazoline (**2a**)	rt/15 → 40/1	**3a**	oil	90	
2-Mercapto-imidazole (**2b**)	rt/15 → 40/1	**3b**	oil	80	
2-Mercapto-benzimidazole (**4a**)	rt/15 → 45/1	**5a**	111.5-112.5 (108-109)[c]	90	
5-Methoxyl-2-mercaptobenz-imidazole (**4b**)	rt/15 →45/1	**5b**	105-110	83[d]	46
		5b'			54
5-Methoxyl-2-mercaptobenz-imidazole (**4b**)	rt / 72	**5b**	106-110	84	30
		5b'			70
5-Nitro-2-mercaptobenzimidazole (**4c**)	rt/15 → 45/1	**5c**	230-231 (229-230)[e]	28	66
		5c'	209-210[f]	14	34
5-Nitro-2-mercaptobenzimidazole (**4c**)	rt / 72	**5c**	230-231 (229-230)[e]	74	88
		5c'	209-210	10	12
5,6-Dimethyl-2-mercaptobenz-imidazole (**4d**)	rt/15 → 45/1	**5d**	186-187 (167-168)[c]	85	
5,6-Dichloro-2-mercaptobenz-imidazole (**4e**)	rt/15 → 45/1	**5e**	181.0-182.5	91	

a) Solvent: Dry 1,2-dimethoxyethane. Molar ratio of NaH to **2**: 1.0. Molar ratio of **2** to **1**: 1.0. b) Composition of the mixtures was determined by ^{1}H NMR. c) Ref. No. 7a. d) As a mixture. e) Ref. No. 8. f) Ref. No. 7b.

In comparison with the other methods, the present method has the merits that the ring products could be obtained under mild conditions by a simple procedure and thereby the selective preparation is possible, moreover the yields of the products **3**s are higher than those by the literature methods.

EXPERIMENTAL SECTION

All melting points are uncorrected. The IR spectra were determined on a Shimadzu FTIR-8100A spectrophotometer and ^{1}H-NMR spectra on a JEOL JNM-GSX270 spectrometer using TMS as an internal standard in $CDCl_3$ unless otherwise noted. Mass spectral data were obtained on a JEOL JMS-AX505W. 4,5-Dimethyl- and 4,5-dichloro-1,2-diaminobenzenes, 2-mercaptoimidazoline, 2-mercaptoimidazole and 2-mercaptobenzimidazoles except for **4c, 4d** and **4e** were reagents of Tokyo Kasei Kogyo Co., Ltd. The benzimidazole **4c** and 2-(2-amino-4-nitroanilino)ethanol were reagents of Aldrich Chemical Company Inc. S-Ethenyl-S-(4-methylphenyl)-N-tosylsulfilimine **1** was prepared by the reported method.[9,10]

Preparation of 5,6-Substituted-2-mercaptobenzimidazole (4d and **4e).**- Compounds **4d** and **4e** were prepared by literature procedure.[11] Thus, to a stirred solution of 10.0 mmol of the corresponding 4,5-disubstituted-1,2-diaminobenzene in 40 mL of ethanol was added 11.0 mmol of KOH in 5 mL of H_2O, and followed by 11 mmol of carbon disulfide (below 5°). After refluxing for 3 hr, the reaction solution was treated with activated carbon. The decolorized solution was neutralized with 50% aqueous acetic acid. The precipitated solid (**4d** and **4e**) was collected and recrystallized from EtOH.

5,6-Dimethyl-2-mercaptobenzimidazole (4d): 62% yield, mp 303-304° (dec.) (EtOH), *lit.*[12] 328° (dec.) (EtOH). ^{1}H NMR (DMSO-d_6): δ 2.23 (s, 3H + 3H), 3.33 (s, 1H), 6.93 (s, 1H +1H), 12.32 (s, 1H).

5,6-Dichloro-2-mercaptobenzimidazole (4e): 60% yield, mp 350-354° (EtOH), *lit.*[13] 355° (AcOH). ^{1}H NMR (DMSO-d_6): δ 3.34 (s, 1H), 7.32 (s, 1H + 1H)), 12.80 (s, 1H).

General Procedure of Imidazo[2,1-b]thiazoles (3) and Thiazolo[3,2-a]-benzimidazoles (5). *Procedure A.*- In 20 mL of dry DME were dissolved 1.0 mmol of ESI **1** and 1.0 mmol of Michael donor (**2**), and then to the solution was added 1.0 mmol of sodium hydride. After stirring at room temperature for 15 hrs followed by heating at 40-45° for 1 hr, the solvent was removed by distillation *in vacuo*. The resulting residue was extracted with 20 mL of ether. The ethereal extract was evaporated to give an oil or solid residue of **3** and **5**. The solid residues were purified by recrystallization and the oil residues (**3a** and **3b**) were purified by fractional precipitation during cooling their THF solution. The isomeric mixtures of **4b** and **4b'**, and **4c** and **4c'** were separated by column chromatography on silica gel (Wako gel C300) with ethyl acetate as eluent. The structures of the products except for **4c** were confirmed by IR, NMR and mass spectra.

Procedure B.- In 20 mL of dry DME were dissolved 1.0 mmol of **1** and 1.0 mmol of Michael donor (**4b** and **4d**). and then to the solution was added a 1.0 mmol of sodium hydride. After stirring at room temperature for 72 hr, the precipitate was removed by suction filtration. The filtrate was evaporated *in vacuo* and the resulting residue was worked up in a manner similar to that of *procedure A*.

2,3,5,6-Tetrahydroimidazo[2,1-b]thiazole (3a): 90% yield. ^{1}H-NMR: δ 3.18 (t, 2H, *J* = 8.1 Hz), 3.19 (t, 2H, *J* = 6.6 Hz), 3.57 (t, 2H, *J* = 6.6 Hz), 4.11 (t, 2H, *J* = 8.1 Hz). Picrate of **3a** (EtOH): mp 178-179°, *lit.*[3b] 173.5-174.6°.

2,3,-Dihydroimidazo[2,1-b]thiazole (3b): 80% yield. ^{1}H-NMR: δ 3.81 (t, 3H, *J* = 7.2 Hz), 4.15 (t, 2H, *J* = 7.2 Hz), 6.95 (s, 1H), 7.00 (s, 1H). Picrate of **3c** (EtOH): mp 183-185°, *lit.*[3b] 182-184°.

2,3-Dihydrothiazolo[3,2-a]benzimidazole (5a): 90% yield, mp. 111.5-112.5° (EtOH), *lit.*[7a] 108-109° (from EtOH). ^{1}H-NMR: δ 3.99 (t, 2H, *J* = 7.2 Hz), 4.30 (t, 2H, *J* = 7.2 Hz), 7.14 (m, 3H), 7.59 (m, 1H).

Mixture of 2,3-Dihydro-6-methoxythiazolo[3,2-a]benzimidazole (5b) and 2,3-Dihydro-7-methoxythiazolo[3,2-a]benzimidazole (5b'): The separation of **5b** and **5b'** from the their mixture was not successful. The ^{1}H-NMR data of each compound in the mixture are as follows: for **5b**, δ 3.84 (s, 3H), 3.91 (t, 2H, *J* = 7.3 Hz), 4.27 (t, 2H, *J* = 7.3 Hz), 6.81 (dd, 1H, *J* = 2.4 and 8.8 Hz), 7.08 (d, 1H, *J* = 8.8 Hz), 7.14 (d, 1H, *J* = 2.4 Hz); for **5b'**, δ 3.84 (s, 3H), 3.91 (t, 2H, *J* = 7.3 Hz), 4.25 (t, 2H, *J* = 7.3 Hz), 6.71 (d, 1H, *J* = 2.4 Hz), 6.82 (dd, 1H, *J* = 2.4 and 8.8 Hz), 7.48 (d, 1H, *J* = 8.8 Hz). HRMS (20eV) (M^+) of the mixture: Calcd. for $C_{10}H_{10}N_2OS$: 206.0512. Found: 206.0510.

2,3-Dihydro-6-nitrothiazolo[3,2-a]benzimidazole (5c): mp 230-231° (EtOH) *lit.*[8] 229-230°. ^{1}H-NMR: δ 4.02 (t, 2H, *J* = 7.3 Hz), 4.40 (t, 2H, *J* = 7.3 Hz), 7.25 (d, 1H, *J* = 8.8 Hz), 8.16 (dd, 1H, *J* = 2.0 and 8.8 Hz), 8.50 (d, 1H, *J* = 2.0 Hz).

An authentic sample of **5c,** was prepared in 82% yield by the literature method.[8] mp. 231-233° (EtOH), *lit.*[8] 229-230°, ^{1}H-NMR: δ 4.02 (t, 2H, *J* = 7.3 Hz), 4.40 (t, 2H, *J* = 7.3 Hz), 7.25 (d, 1H, *J* = 8.8 Hz), 8.16 (dd, 1H, *J* = 2.0 and 8.8 Hz), 8.50 (d, 1H, *J* = 2.0 Hz).

2,3-Dihydro-7-nitrothiazolo[3,2-a]benzimidazole (5c'): mp 209-210° (EtOH), *lit.*[7b] 175°. ^{1}H-NMR: δ 4.04 (t, 2H, *J* = 7.3 Hz), 4.42 (t, 2H, *J* = 7.3 Hz), 7.63 (d, 1H, *J* = 8.8 Hz), 8.15 (dd, 1H, *J* = 8.8 and 2.0 Hz), 8.16 (d, 1H, *J* = 2.0 Hz). MS (M^+): 221 (100%). HRMS (M^+): Calcd. for $C_9H_7N_3O_2S$: 221.0253, found: 221.0247.

2,3-Dihydro-6,7-dimethylthiazolo[3,2-a]benzimidazole (5d): 85% yield, mp.198.5-199.5° (EtOH), *lit.*[7a] 167-168° (EtOH). ^{1}H-NMR: δ 2.34 (s, 6H), 3.89 (t, 2H, *J* = 7.3 Hz), 4.21 (t, 2H, *J* = 7.3 Hz). 6.96 (s, 1H), 7.36 (s,1H). HRMS (M^+): Calcd. for $C_{11}H_{12}N_2S$: 204.0733, found: 204.0727.

2,3-Dihydro-6,7-dichlorothiazolo[3,2-a]benzimidazole (5e): 91% yield, mp. 209-210° (EtOH), ^{1}H-NMR: δ 3.96 (t, 2H, *J* = 7.3 Hz), 4.28 (t, 2H, *J* = 7.3 Hz), 7.30 (s, 1H), 7.67 (s.1H). HRMS (M^+): Calcd. for $C_9H_6Cl_2N_2$-S: 243.9691, found: 243.9690.

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