HETEROCYCLES, Vol. 62, 2004, pp. 815 - 819
Received, 23rd July, 2003, Accepted, 8th September, 2003, Published online, 27th October, 2003

REGIOSELECTIVE SYNTHESIS OF 6- AND 7-SUBSTITUTED THIAZOLO[3,2-*a*]BENZIMIDAZOLE DERIVATIVES USING CRYSTALLIZATION INDUCED REGIOISOMERIZATION

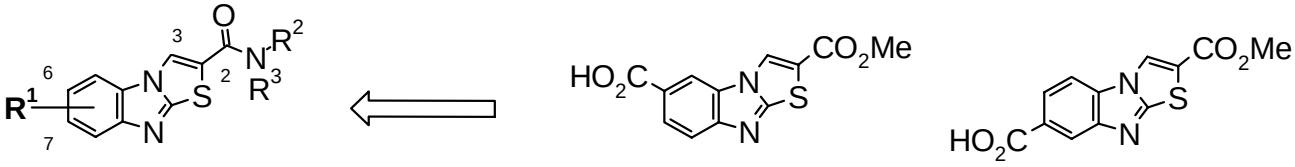
Satoshi Hayashibe*, Takashi Kamikubo, Shin-ichi Tsukamoto, and Shuichi Sakamoto

Institute for Drug Discovery Research, Yamanouchi Pharmaceutical Co. Ltd., 21 Miyukigaoka, Tsukuba-shi, Ibaraki 350-8585, Japan

Abstract – An efficient regioselective synthesis of 2-methoxycarbonyl-thiazolo[3,2-*a*]benzimidazole-6-carboxylic acid (**2**) and 2-methoxycarbonyl-thiazolo[3,2-*a*]benzimidazole-7-carboxylic acid (**3**) have been developed.

INTRODUCTION

The chemistry and biological activity of thiazolo[3,2-*a*]benzimidazole derivatives have been studied for several years.[1] Recently our laboratories discovered that the derivatives of thiazolo[3,2-*a*]-benzimidazole-2-carboxamide are good analogues of the metabotropic glutamate receptor ligands, especially the 6- or 7-substituted derivatives (**1**), which have higher activity.[2] A regioselective, efficient synthetic method for 6- and 7-carboxyl thiazolo[3,2-*a*]benzimidazole-2-carboxylic acid esters (**2**, **3**), useful intermediates for the synthesis of **1**, has been developed (Figure 1).



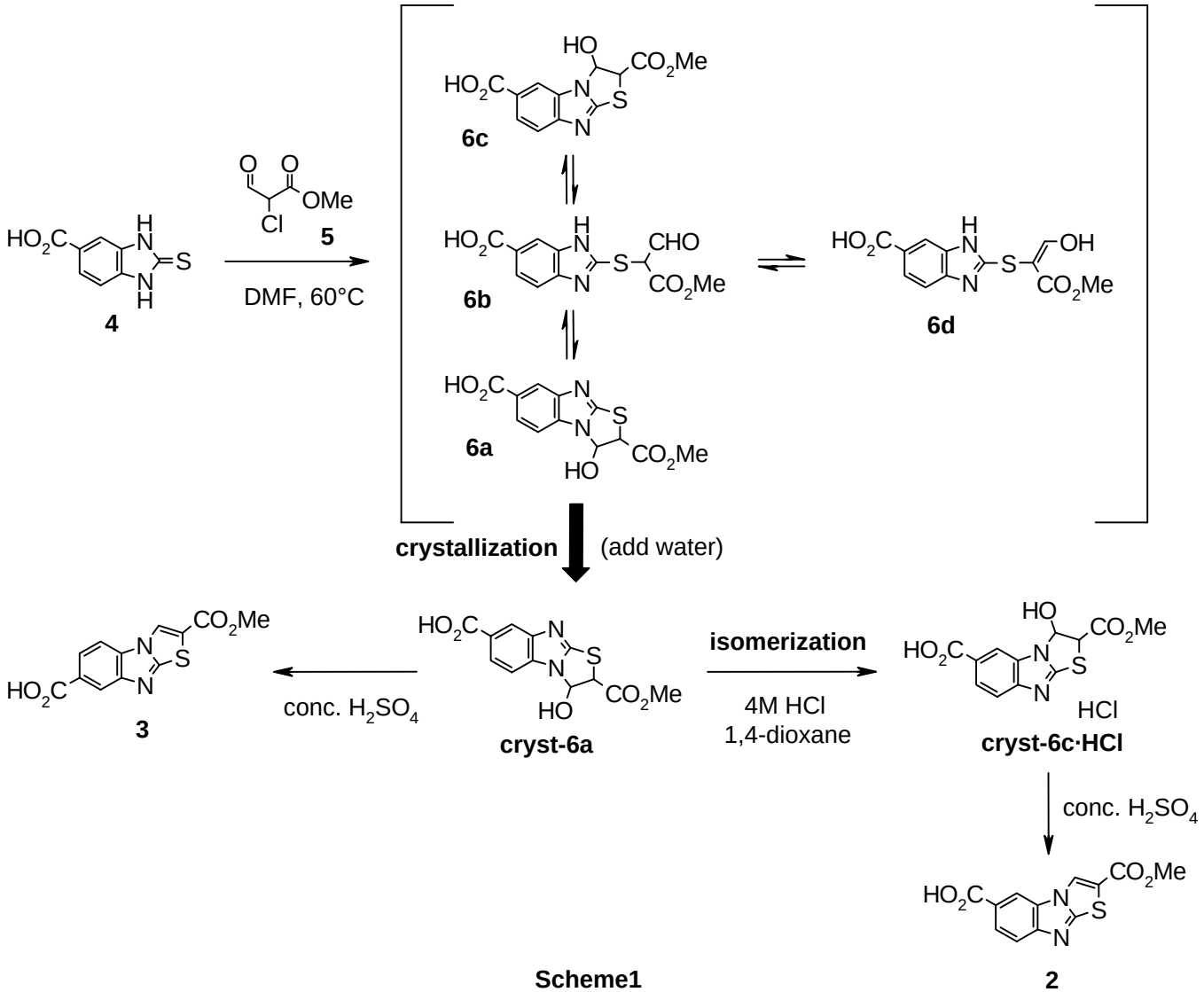
1 **2** **3**

Figure 1

† Dedicated to Prof. Leo A. Paquette on the occasion of his 70th birthday.

RESULTS AND DISCUSSION

2-Mercaptobenzimidazole (**4**) and methyl formylchloroacetate (**5**)[3] were heated in 2-butanone and the resulting precipitates, *S*-alkylated mercaptobenzimidazole, were collected. A subsequent dehydration using conc. H_2SO_4 gave a mixture of 6-carboxylthiazolo[3,2-*a*]benzimidazole (**2**) and the 7-substituted regioisomer (**3**), in a 2:1 ratio. When the solvent 2-butanone was replaced with DMF and the reaction solution diluted slowly with water, pale green precipitates (**cryst-6a**) were formed. The precipitates were treated with conc. H_2SO_4 to afford 7-carboxylic acid (**3**) in good yield, without the formation of the 6-isomer (**2**). When **cryst-6a** was suspended in a solution of 4M HCl/1,4-dioxane at room temperature for 2 days light gray precipitates (**cryst-6c·HCl**) were produced, which was treated with conc. H_2SO_4 to afford the 6-carboxylic acid (**2**) selectively. The position of carboxyl substituents in **2** and **3** was determined by NOE experiments[4] (Scheme 1).



Scheme1

The ^{1}H-NMR spectrum of the crystallized *S*-alkylated intermediates (**cryst-6a** or **cryst-6c·HCl**) in DMSO-d_6, showed in both cases complex signals resulting from 5 isomers, proposed to be **cis-6a**, **trans-6a**, **cis-6c**, **trans-6c** and the enol form **6d**. The signals resulting from **6b** were not detected. The ratio of **cis-6a**/**6c**:**trans-6a**/**6c**:**6d** was approximately 1:2:2 in the case of **cryst-6c·HCl**. This was determined by the signals of H-2 on **cis-6a**/**6c** (5.81 ppm, d, J = 5.4 Hz), **trans-6a**/**6c** (5.04 ppm, d, J = 1.2 Hz) and H_{vinyl} on **6d** (8.55 ppm, s). The ratio of **6a**:**6c** could not be clearly appreciated.[5] **Cryst-6a** and **cryst-6c·HCl** were recrystallized from DMSO-water to afford only **cryst-6a** in both cases similarly in the case of aqueous-DMF system. It is proposed that **6** is in equilibrium in DMF as described above and **cryst-6a** is essentially removed from the aqueous-DMF system by virtue of its insolubility, driving the equilibrium through **6c**, **6d** to **6b**, then **6a** to **cryst-6a**. On the contrary, **cryst-6c·HCl** is insoluble to 1,4-dioxane and removed from the 4M HCl/1,4-dioxane system, driving the equilibrium. It is also proposed that there is no equilibrium between **6a** and **6c** in the subsequent dehydration reaction using conc. H_2SO_4 because of the fast reaction rate. In our preliminary experiments, dehydration reactions of **cryst-6c·HCl** using trifluoroacetic acid or acetic acid gave a mixture of **2** and **3**.

In conclusion, we have established an efficient synthesis of 2-methoxycarbonylthiazolo[3,2-*a*]-benzimidazole-6-carboxylic acid (**2**) and 2-methoxycarbonylthiazolo[3,2-*a*]benzimidazole-7-carboxylic acid (**3**) using crystallization-induced isomerization. These mono protected dicarboxylic acids could easily be converted to **1** and will be useful synthetic intermediates for a variety of carbon substituted thiazolo[3,2-*a*]benzimidazoles.

EXPERIMENTAL

Melting points were determined with a Yanaco MP-3 melting point apparatus and are uncorrected. IR spectra were recorded with a Horiba FT-720 spectrophotometer. The ^{1}H-NMR spectra were recorded on a JEOL EX400 spectrometer in DMSO-d_6. MS spectra were recorded with a Hitachi M-80 or JEOL JMS-DX300 spectrometer.

3-Hydroxy-2-methoxycarbonyl-2,3-dihydrothiazolo[3,2-*a*]benzimidazole-7-carboxylic acid (cryst-6a)

A solution of 2-mercaptobenzimidazole-4-carboxylic acid (**4**) (162 g, 0.835 mol) and methyl formylchloroacetate (**5**)[3] (137 g, 1.00 mol) in DMF (550 mL) was heated at 60°C for 12 h. The solution was then cooled to rt and water (3 L) was added slowly. The resulting precipitates were collected by filtration. The precipitates were washed with water, 1,4-dioxane and EtOAc to afford **cryst-6a** (211 g, 86 %) as pale green crystals. mp>190°C (decomp) (recrystallized from DMSO-water); IR (KBr, cm^{-1})

2947, 2856, 1732, 1685, 1439, 1346, 1302, 1248, 1182, 1107; Anal. Calcd for $C_{12}H_{10}N_2O_5S.2H_2O$: C 48.38, H 3.52, N 9.40, S 10.76. Found: C 48.16, H 3.41, N 9.51, S 10.60; MS (FAB) *m/z* 295 $(M+1)^+$.

3-Hydroxy-2-methoxycarbonyl-2,3-dihydrothiazolo[3,2-*a*]benzimidazole-6-carboxylic acid hydrochloride (cryst-6c·HCl)

Cryst-6a (210 g, 0.714 mol) was suspended in 1,4-dioxane (2 L) and a 4M HCl solution of 1,4-dioxane (535 mL) was added. The suspension was stirred at rt for 2 days and the precipitates were collected by filtration. The precipitates were washed with 1,4-dioxane and dried to afford **cryst-6c·HCl** (283 g, quantitative) as grey crystals. mp>185 °C (decomp); IR (KBr, cm^{-1}) 3162, 2958, 1732, 1697, 1523, 1437, 1408, 1296, 1180, 1105; Anal. Calcd for $C_{12}H_{10}N_2O_5S$·HCl: C 43.58, H 3.35, N 8.47, S 9.70. Found: C 43.69, H 3.71, N 8.25, S 9.45; MS (FAB) *m/z* 295 $(M+1)^+$.

2-Methoxycarbonylthiazolo[3,2-*a*]benzimidazole-6-carboxylic acid (2)

Cryst-6c·HCl (11.8 g, 0.040 mol) was dissolved in conc. H_2SO_4 (5 g) and heated at 60°C for 1 h. The reaction solution was poured onto crushed ice and the resulting precipitates were collected by filtration. The precipitates were washed with water and acetone to afford **2** (8.89 g, 81 %) as pale green crystals. mp 270-271°C (recrystallized from DMSO-water); IR (KBr, cm^{-1}) 3086, 1712, 1618, 1574, 1477, 1435, 1346, 1304, 1259, 1066; ^{1}H-NMR δ 3.92 (3H, s), 7.78 (1H, d, *J* = 8.4 Hz), 8.01(1H, dd, *J* = 8.4, 1.6 Hz), 8.86 (1H, d, *J* = 1.6 Hz), 9.53 (1H, s) ppm; Anal. Calcd for $C_{12}H_8N_2O_4S·0.2H_2O$: C 51.50, H 3.03, N 10.01, S 11.46, Found: C 51.44, H 3.32, N 9.89, S 11.44; MS (FAB) *m/z* 277 $(M+1)^+$.

2-Methoxycarbonylthiazolo[3,2-*a*]benzimidazole-7-carboxylic acid (3)

3 was synthesized from **cryst-6a** as light gray crystals**,** by the same procedure as for **2** in 74 % yield. mp 282-283 °C (recrystallized from DMSO-water); IR (KBr, cm^{-1}) 3082, 1716, 1672, 1614, 1568, 1477, 1437, 1302, 1232, 1072; ^{1}H-NMR δ 3.92 (3H, s), 7.94 (1H, dd, *J* = 8.8, 1.2 Hz), 8.22 (1H, d, *J* = 8.8 Hz), 8.26 (1H, d, *J* = 1.2 Hz), 9.46 (1H, s), 12.98 (1H, s) ppm; Anal. Calcd for $C_{12}H_8N_2O_4S$: C 52.17, H 2.92, N 10.14, S 11.61, Found: C 51.87, H 3.00, N 10.05, S 11.56; MS (FAB) *m/z* 277 $(M+1)^+$.

REFERENCES AND NOTES

1. P. N. Preston, M. F. G. Stevens, and G. Tennant, *Heterocyclic Compounds*, 1981, Vol. 40, part 2, pp. 84-219, A. Chimirri, S. Grasso, G. Romeo, and M. Zappala, *Heterocycles*, 1988, **27**, 1975, M. Z. A. Badr, A. M. Mahmoud, S. A. Mahgoub, and Z. A. Hozien, *Bull. Chem. Soc. Jpn.*, 1988, **61**, 1339, V. M. Dianov, S. V. Sibiryak, R. F. Sadykov, Y. V. Strokin, and S. F. Khaibullina, *Khim-Farm. Zh.*, 1991, **25**, 40, A. A. O. Sarhan, H. A. H. EL-Sherief, and A. M. Mahmoud, *Tetrahedron*, 1996, **52**,

10485, A. A. O. Sarhan, H. A. H. EL-Sherief, and A. M. Mahmoud, *J. Chem. Res. (S)*, 1996, 4, Y. Sugita, S. Yin, and I. Yokoe, *Heterocycles*, 2000, **53**, 2191, S. K. Kotovskaya, Z. M. Baskakova, S. A. Romanova, V. N. Charushin, and O. N. Chupakhin, *Russ. J. Chem.*, 2001, **37**, 564.

2. S. Hayashibe, H. Itahana, M. Okada, A. Kohara, K. Maeno, K. Yahiro, I. Shimada, K. Tanabe, K. Negoro, T. Kamikubo, and S. Sakamoto, Patent, WO0059913 (2000) (*Chem. Abst.*, 2000, **133**, 768).
3. H. E. Faith, U.S. Patent, US 2, 405, 820 (1946) (*Chem. Abst.*, 1946, **40**, 7233).
4. In **3**, irradiation of the singlet H-3 significantly affected the large doublet H-5. In **2,** significant enhancement of the small doublet H-5 was observed on irradiation of the singlet H-3.
5. The ^{1}H-NMR spectrum of *S*-alkylated intermediates (**6**) in DMSO-d_6; [**cryst-6a**] δ 3.66, 3.74, 3.79(total 3H, each s, OCH_3 on **6d, trans-6a/6c, cis-6a/6c**, 2:5:3 ratio), 5.03(0.5H, s, H-2 on **trans-6a/6c**), 5.79(0.3H, d, *J* = 5.4 Hz, H-2 on **cis-6a/6c**), 6.45-6.57(0.8H, br, H-3 on **cis-** and **trans-6a/6c**), 7.45, 7.54, 7.55, 7.56, 7.59(total 1H, each d, *J* = 8.8 Hz, H-5 on **cis/trans-6a**, H-8 on **cis/trans-6c** and H-7 on **6d**), 7.70-7.90(1H, m, H-6 on **cis/trans-6a**, H-7 on **cis/trans-6c** and H-6 on **6d**), 7.95, 7.97, 8.05, 8.12, 8.17(1H, each d, *J* = 1.5 Hz, H-8 on **cis/trans-6a** and H-5 on **cis/trans-6c** and H-4 on **6d**), 8.43(0.2H, s, H_{vinyl} on **6d**), 12.75(br) ppm; [**cryst-6c·HCl**] δ 3.70, 3.74, 3.79(total 3H, each s, OCH_3 on **6d, trans-6a/6c, cis-6a/6c**, 2:2:1 ratio), 5.04(0.4H, d×2, each *J* = 1.2 Hz, H-2 on **trans-6a/6c**), 5.81(0.2H, d, *J* = 5.4 Hz, H-2 on **cis-6a/6c**), 6.43-6.62(0.6H, m, H-3 on **cis-** and **trans-6a/6c**), 7.58, 7.62, 7.67, 7.68, 7.73(total 1H, each d, *J* = 8.8 Hz, H-5 on **cis/trans-6a**, H-8 on **cis/trans-6c** and H-7 on **6d**), 7.80-8.00(1H, m, H-6 on **cis/trans-6a**, H-7 on **cis/trans-6c** and H-6 on **6d**), 8.07, 8.13, 8.16, 8.21, 8.25(total 1H, each d, *J* = 1.5 Hz, H-8 on **cis/trans-6a** and H-5 on **cis/trans-6c** and H-4 on **6d**), 8.55(0.4H, s, H_{vinyl} on **6d**) ppm.