with the coupling constants of equatorial C(6)-H of **5** (t, J=8 Hz) at δ 4.76 and axial C(6)-H of **6** (dd, J=12, 4 Hz) at δ 4.50. This assignment was further verified by comparing the ^{1}H NMR spectrum after acetylation of **3** and **4** mixture (Ac_2O, DMAP, pyridine).

8. The relative stereochemistry of **10-13** was verified by comparing the ^{1}H NMR spectra of the compounds prepared from solvolysis of cyclohexene oxide in methanol followed by acetylation.
9. Kishi, Y.; Aratani, M.; Tanino, H.; Fukuyama, T.; Goto, T.; Inoue, S.; Sugiura, S.; Kakoi, H. *J. Chem. Soc., Chem. Commun.* **1972**, 64.

Synthesis of Thiazole Derivatives *via* Lewis Acid Promoted Reactions of Diazopyruvate with Thioamides

Hong-Seok Kim*, Il-Chun Kwon, and Ju-Young Lee

Department of Industrial Chemistry, Kyungpook National University, Taegu 702-701, Korea

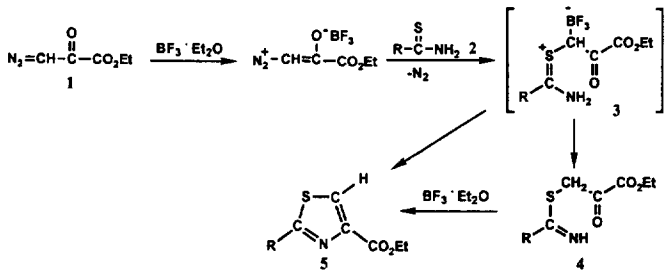
Received September 26, 1994

The thiazole derivatives are found as sub-unit of many biologically important and structurally complex natural products such as theonezolide,[1] leinamycin,[2] and bleomycin.[3] It has been well documented that bithiazole derivatives cleave duplex DNA either in the presence of oxygen and ferrous ion[4] or irradiation.[5] Consequently the development of new, efficient, and general methods for the synthesis of thiazoles continues to be an attractive objective. Several different synthetic approaches to thiazoles have been developed.[6]

Thiocarbonyl ylildes have been the subject of much interest in recent years due to their potential roles as intermediates in a variety of reactions, including the five-membered ring sulfur heterocycles.[7] The carbene approach to sulfur ylide formation by thermal, photochemical, and transition metal catalyzed reaction has been extensively explored.[8] However, the Lewis acid catalyzed ylide formation of α-diazocarbonyl compounds has received little attention.

In continuation of our work on the use of α-diazocarbonyl compounds for the synthesis of heterocycles such as β-furoic acid,[9] γ-pyrone,[10] and oxazole,[11] we have attempted to develop a new route to thiazoles based on cyclization of thiocarbonyl ylide, which generated from the Lewis acid-promoted reaction of α-diazocarbonyl compounds with thioamide.

Initial studies on the Lewis acid-promoted reactions of α-diazocarbonyl compounds with thioamides were carried out with ethyl diazopyruvate. Reaction of diazopyruvate **1** with thiobenzamide **2a** (R=Ph) in the presence of Lewis acid (*e.g.*, BF_3·Et_2O, $AlCl_3$, $FeCl_3$) at room temperature, after aqueous work-up, resulted in S-alkylisothiobenzamide **4a** in good to excellent yields.[12] Use of 2 equiv of Lewis acids to the 1 : 1 mixture of **1** and thiobenzamide **2a** afforded the following



Scheme 1.

Table 1. Lewis Acid Promoted Reactions of Diazopyruvate 1 with Thioamides

Thioamide (2) R	Reagent	Reaction[a] conditions	Product	Yield (%)[b]	mp (℃)
2a C_6H_5	BF_3·Et_2O	A	**4a**	97	109-110
2a C_6H_5	$AlCl_3$	A	**4a**	54	109-110
2a C_6H_5	$FeCl_3$	A	**4a**	30	109-110
2a C_6H_5	BF_3·Et_2O	B	**5a**	82	48-49
2a C_6H_5	$AlCl_3$	B	**5a**	79	48-49
2a C_6H_5	$FeCl_3$	B	**5a**	20	48-49
2b 4-O_2N-C_6H_4	BF_3·Et_2O	A	**4b**	60[c]	150-152
2b 4-O_2N-C_6H_4	BF_3·Et_2O	B	**5b**	72	152-154
2c 4-CH_3O-C_6H_4	BF_3·Et_2O	B	**5c**	89	97-98
2d 2-CH_3O-C_6H_4	BF_3·Et_2O	B	**5d**	87	86-87
2e 4-CH_3-C_6H_4	BF_3·Et_2O	B	**5e**	97	44.5-45
2f 4-CH_3O_2C-C_6H_4	BF_3·Et_2O	B	**5f**	51	121.5-122
2g 4-Cl-C_6H_4	BF_3·Et_2O	B	**5g**	68	100-100.5
2h 2-C_5H_4N	BF_3·Et_2O	B	**5h**	41	70.5-71
2i CH_3	BF_3·Et_2O	B	**5i**	57	57-57.5
2j $C_6H_5CH_2$	BF_3·Et_2O	B	**5j**	49	77-78
2k $C_6H_5CH_2CH_2$	BF_3·Et_2O	B	**5k**	75	51

[a]Method A: Ethyl diazopyruvate (1 mmol) in ether (5 mL) was added to the mixture of thioamide (1 mmol)-Lewis acid (2 mmol) in ether (5 mL) for 2 h under Ar at 0 ℃ and then the reaction mixture was stirred for 3-7 h at room temperature. Method B: Ethyl diazopyruvate (1 mmol) in DME (5 mL) was added to the mixture of thioamide (1 mmol)-Lewis acid (2 mmol) in DME (5 mL) for 2 h under Ar at 0 ℃ and then the reaction mixture was refluxed for 3-7 h. [b]Isolated yield. [c]Also thiazole **5b** was obtained in 17% yield.

yields of isothiobenzamide **4a**, BF_3·Et_2O (97%), $AlCl_3$ (54%), $FeCl_3$ (30%).

Treatment of 4-nitrothiobenzamide **2b** with **1** in 2 equiv of boron trifluoride at room temperature gave rise to a mixture of the corresponding isothiobenzamide **4b** and thiazole **5b** in the yields of 60 and 17%, respectively. This result suggests that diazopyruvate **1** under the Lewis acid condition generate initially thiocarbonyl ylide **3** which yield **5** by the loss of water as shown in Scheme 1.

We have found that boron trifluoride promoted reactions of diazopyruvate with thioamides at room temperature produce the corresponding S-alkylisothioamide derivatives **4** in preparatively useful yield.

Treatment of the isothiobenzamide **4a** with 1 equiv of bo-

ron trifluoride in refluxing benzene gave thiazole **5a** in 91% yield.[12]

The direct synthesis of thiazole was also achieved by treatment of thioamides with diazopyruvate **1** in the presence of the Lewis acid at high temperature. Common solvents (*e.g.*, THF, DME, Et_2O, $ClCH_2CH_2Cl$) can be used with the best result in DME.

The representative results of the reactions between diazopyruvate **1** and various aryl and alkylthioamides are summarized in Table. The reaction proceeds with aliphatic and aromatic thioamides with different functional groups. However, the relative yields of the products were found to be influenced by the nature of the R groups attached to thioamide. Aromatic thioamides gave higher yields than aliphatic counterparts. Substitution on *para* position of thiobenzamide by an electron-widhdrawing group retarded the yields of **5**.

Typical procedure is as follows. To a solution of thiobenzamide (1 mmol) and BF_3-etherate (2 mmol) in 5 mL of dry DME was added ethyl diazopyruvate (1 mmol) in DME (5 mL) by a syringe pump over 2 h at 0 ℃. The mixture was stirred for 1 h at room temperature to complete ylide formation, and then refluxed for 5 h. The product was extracted 3 times with ethyl acetate, washed with sat. $NaHCO_3$, brine, dried over Na_2SO_4, and concentrated. The residue was chromatographed on silica gel eluted with 20% ethyl acetate in hexane to give 0.82 mmol of ethyl 2-phenyl-1,3-thiazole-4-carboxylate (82% yield).[12]

Thus the present procedure provides a convenient synthetic approach to the functionalized thiazole derivatives, and further mechanistic study is currently in progress.

Acknowledgment. This work was supported in part by CBM and the Basic Research Institute Program, Ministry of Education, Korea (BSRI-94-3402).

References

1. Kobayashi, J.; Kondo, K.; Isibashi, M.; Walchli, M. R.; Nakamura, T. *J. Am. Chem. Soc.* **1993**, *115*, 6661.
2. Kanada, Y.; Fukuyama, T. *J. Am. Chem. Soc.* **1993**, *115*, 8451.
3. (a) Umezawa, H. *Pure Appl. Chem.* **1971**, *28*, 665. (b) Umezawa, H. In *Bleomycin: Current Status and New Developments*; Carter, S. K.; Crooke, S. T.; Umezawa, H., Eds.; Academic Press: New York, 1978.
4. (a) Sugiura, Y.; Takita, T.; Umezawa, H. *Metal Ions in Biological Systems*; Siegel, H., Ed.; Marcel Dekker: New York, 1985. (b) Hecht, S. M. *Acc. Chem. Res.* **1986**, *19*, 383. (c) Stubbe, J.; Kozarich, J. W. *Chem. Rev.* **1987**, *87*, 1107. (d) Boger, D. L.; Menezes, R. F.; Dang, Q.; Yang, W. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 261.
5. Quada, J. C.; Levy, M. J.; Hecht, S. M. *J. Am. Chem. Soc.* **1993**, *115*, 12171.
6. (a) Albizati, K. F.; Martin, V. A.; Agharahimi, M. R.; Stolze, D. A. *Bioorganic Marine Chemistry Vol. 6*; Scheuer, P. J., Ed.; Springer Verlag: Berlin, 1992; p 43. (b) Nakamura, Y.; Shin, C.; Umemura, K.; Yoshimura, J. *Chem. Lett.* **1992**, 1005. (c) Pettit, G. R.; Nelson, P. S.; Holzapfel, C. W. *J. Org. Chem.* **1985**, *50*, 2654. (d) Schmidt, U.; Gleich, P.; Griesser, H.; Utz, R. *Synthesis*, **1986**, 992. (e) Hamada, Y.; Shibata, M.; Sugiura, T.; Kato, S.; Shioiri, T. *J. Org. Chem.* **1987**, *52*, 1252. (f) North, M.; Pattenden, G. *Tetrahedron* **1990**, *46*, 8267. (g) Bredenkamp, M. W.; Holzapfel, C. W.; van Zyl, W. J. *Synth. Commun.* **1990**, *20*, 2235. (h) Johnson, R. A.; Moder, K. P.; Ward, T. L. *J. Org. Chem.* **1992**, *57*, 2869.
7. (a) Fang, F. G.; Danishefsky, S. J. *Tetrahedron Lett.* **1989**, *30*, 2747. (b) Fang, F. G.; Maier, M. E.; Danishefsky, S. J. *J. Org. Chem.* **1990**, *55*, 831. (c) Potts, K. T.; Murphy, P. *J. Chem. Soc. Chem. Commun.* **1984**, 1348.
8. (a) Padwa, A.; Krumpe, K. E. *Tetrahedron* **1992**, *48*, 5385. (b) Padwa, A.; Hornbuckle, S. F. *Chem. Rev.* **1991**, *91*, 263. (c) Adams, J.; Spero, D. M. *Tetrahedron* **1991**, *47*, 1765. (d) Kim, G.; Kang, S.; Keum, G. *Tetrahedron Lett.* **1994**, *35*, 3747.
9. Wenkert, E.; Ananthanarayan, T. P.; Ferreira, V. F.; Hoffmann, M. G.; Kim, H.-S. *J. Org. Chem.* **1990**, *55*, 4975.
10. Kim, H.-S.; Yoon, Y. H. *Bull. Korean Chem. Soc.* **1993**, *14*, 159.
11. Kim, H.-S., Kim, S. H.; Lee, H. K. *Bull. Korean Chem. Soc.* **1993**, *14*, 524.
12. The compounds obtained were fully characterized (^1H and ^{13}C, MS, mp, IR) and showed satisfactory micro analytical data. Selected analytical data: **4a**: mp 109-110 ℃ (CH_2Cl_2-hexane); IR (KBr) 3241, 3137, 3068, 2991, 2813, 1752 (α-keto ester), 1590, 1245, 1186, 1030, 949, 691 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.88 (m, 2H, *o* of Ph), 7.39 (m, 3H, *m, p* of Ph), 4.50 (bs, 1H, NH), 4.31 (q, J=7.3 Hz, 2H, O-CH_2CH_3), 3.99 (d, J=12 Hz, 1H, S-CH_aH_b-C=O), 3.53 (d, J=12 Hz, 1H, S-CH_aH_b-C=O), 1.31 (t, J=7.3 Hz, 3H, CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.6 (*C*=O), 170.9 (ester *C*=O), 132.4 (*q* of Ph), 132.1 (*p* of Ph), 128.7 (*o* of Ph), 128.5 (*m* of Ph), 105.6 (*C*=NH), 62.9 (O-CH_2), 40.7 (S-CH_2-CO), 14.0 (CH_3); MS 234 (3), 178 (M-$CO_2CH_2CH_3$, 100), 158 (M-$COCO_2CH_2CH_3$, 13), 104 (Ph-C=NH^+, 100); Anal. Calcd for $C_{12}H_{13}NO_3S$: C, 57.35; H, 5.21; N, 5.57. Found: C, 56.56; H, 5.19; N, 5.47. **5a**: mp 48-49 ℃ (CH_2Cl_2-hexane); IR (KBr) 3130, 2979, 1729 (C=O), 1466, 1339, 1212, 1096, 1023, 772 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.15 (s, 1H, thiazole-H), 7.99-8.02 (m, 2H, *o* of Ph), 7.43-7.47 (m, 3H, *m, p* of Ph), 4.45 (q, J=7.1 Hz, 2H, O-CH_2CH_3), 1.43 (t, J=7.1 Hz, 3H, CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.8 (C=O), 161.4 (C-2), 148.1 (C-4), 132.8 (*q* of Ph), 130.6 (*p* of Ph), 128.9 (*o* of Ph), 126.9 (*m* of Ph and C-5), 61.4 (O-CH_2), 14.3 (CH_3); MS 233 (M^+, 18), 188 (M-OCH_2CH_3, 27), 160 (M-$CO_2CH_2CH_3$, 13); Anal. Calcd for $C_{12}H_{11}NO_2S$: C, 61.79; H, 4.76; N, 6.01. Found: C, 61.68; H, 4.72; N, 5.76.