Pergamon

Tetrahedron Letters, Vol. 36, No. 2, pp. 257-260, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(94)02186-4

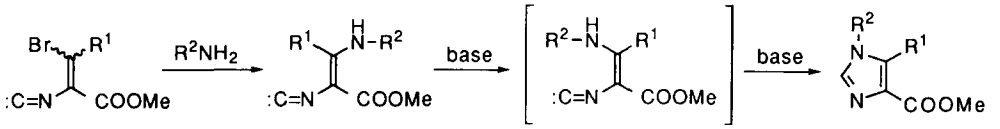
A Novel Synthesis of Methyl 5-Substituted Thiazole-4-carboxylates Using 3-Bromo-2-isocyanoacrylates (BICA)

Masaki Yamada, Toshio Fukui, and Ken-ichi Nunami*

Research Laboratory of Applied Biochemistry, Tanabe Seiyaku Co., Ltd.,
16-89, Kashima-3-chome, Yodogawa-ku, Osaka, 532 Japan

Abstract: A novel synthetic method for methyl 5-substituted thiazole-4-carboxylates (**5**) by the reaction of methyl 3-substituted 3-bromo-2-isocyanoacrylates(BICA)(**1**) with hydrogen sulfide in the presence of triethylamine in *N,N*-dimethylformamide was explored, and the reaction mechanism was elucidated.

During our synthetic studies[1] on biologically interesting amino acids and heterocyclic compounds using multifunctional 3-substituted 3-bromo-2-isocyanoacrylates(BICA)(**1**), we recently reported[2] a novel synthesis of a variety of methyl 1,5-disubstituted imidazole 4-carboxylates (**3**) by the reaction of BICA(**1**) with primary amines in the presence of a base. The mechanistic study suggested a Michael reaction of an amine with BICA followed by β-elimination of hydrogen bromide exclusively afforded (*E*)-methyl *N*,3-disubstituted 3-amino-2-isocyanoacrylates (**2**), which successively underwent geometric isomerization to *Z*-isomers with a base and subsequent cyclization gave imidazoles **3**.

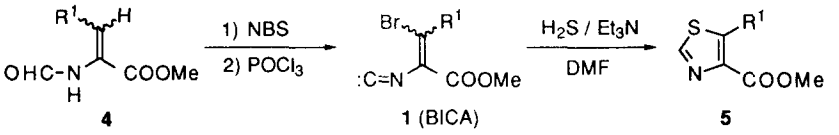


1 (BICA) (*E*)-**2** (*Z*)-**2** **3**

In this paper we wish to designate an extension of the reactivity of BICA to the efficient synthesis of various types of methyl 5-substituted thiazole-4-carboxylates[3] (**5**) which are useful intermediates[4] for pharmaceuticals and agriculturals, and to propose the reaction mechanism.

Namely, the reaction of (*E*)- and/or (*Z*)-BICA(**1**), which were prepared by the bromination and subsequent dehydration of corresponding methyl 3-substituted 2-formylaminoacrylates (**4**) by the procedure reported by us,[5] with 1.2 equiv of hydrogen sulfide (H_2S)[6] at room temperature for 0.5 h in *N,N*-dimethylformamide (DMF) exclusively afforded desired methyl 5-substituted thiazole-4-carboxylates (**5**) in good yields as shown in Scheme 1 and Table 1.

Scheme 1



4 **1 (BICA)** **5**

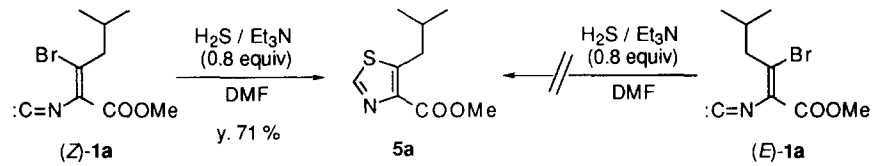
Table 1 Yields and physical properties of thiazoles (5)

Entry	R^1	Yield (%)[a]	mp (°C)	^{1}H-NMR ($CDCl_3$)		Product
				C^2-H	$COOCH_3$	
1	$CH_2CH(CH_3)_2$	89	syrup	8.63	3.95	**5a**
2	$CH(CH_2CH_3)_2$	71	syrup	8.64	3.90	**5b**
3	C_6H_{13}	73	syrup	8.61	3.95	**5c**
4	Ph	83	98-100	8.75	3.84	**5d**
5	Ph(4-Cl)	82	88-90	8.79	3.87	**5e**

[a] Isolated yield of **5** from **1**.

In order to elucidate the reaction mechanism of the formation of **5**, (*Z*)- and (*E*)-**1a** were treated first with 0.8 equiv of H_2S in the presence of triethylamine (Et_3N) in DMF respectively (Scheme 2). Consequently, the reaction using (*Z*)-**1a** resulted in the formation of desired thiazole **5a** in 71% yield. In contrast, (*E*)-**1a** gave a complex mixture,[7] while **5a** was not detected. These results suggested that the substitution reaction of the β-bromo group by the thiol proceeded with retention of the configuration as has

Scheme 2



(*Z*)-**1a** **5a** (*E*)-**1a**

been reported in most cases of addition-elimination reactions of vinyl halides,[8] and were much different from those of the reaction of BICA with primary amines,[2] which exhibited selective formation of *E*-enamine **2** without any relation to the geometry of **1**.

Next, **1a** was treated with a different amount of benzyl hydrosulfide in the presence of Et_3N in DMF, and the results are summarized in Table 2. When (*Z*)- or (*E*)-**1a** was treated with 0.8 equiv of benzyl hydrosulfide, (*Z*)- or (*E*)-methyl 3-benzylthio-5-methyl-2-isocyanohexenoate (**6**)[9] was respectively obtained with retention of the geometric configuration of BICA (**1a**) (entry 1,3). In contrast, the reaction of (*Z*)- or (*E*)-**1a** with 1.2 equiv of benzyl hydrosulfide gave almost 1:1 mixture of the geometric isomers (*Z*)- and (*E*)-**6** in each case (entry 2,4). It seemed that an addition-elimination of the second thiol to **6** caused the isomerization of the double bond affording a mixture of (*Z*)- and (*E*)-**6** via benzyl dithian (**7**).[10] To confirm an addition of the second thiol to **6**, a reaction of isolated (*Z*)-**6** with 4-chlorobenzyl

hydrosulfide, (2.0 equiv) was examined in DMF at room temperature for 1 h to afford a mixture of methyl 3-(4-chlorobenzyl)thio-5-methyl-2-isocyanohexenoate (**8**)[11] and **6** as expected. Further, a reaction of a mixture of (*Z*)- and (*E*)-**6** with 1.2 equiv of H_2S in the presence of Et_3N was carried out in DMF at room temperature for 0.5 h. In consequence, the addition of H_2S to **6** and subsequent cyclization proceeded to afford thiazole **5a**. These results were completely different from that of the reaction of BICA with primary amines, which showed the second amine did not act as a nucleophile for a Michael reaction, but as a base to accelerate the isomerization of *E*-enamine (**2**) to *Z*-enamine.[2]

Scheme 3

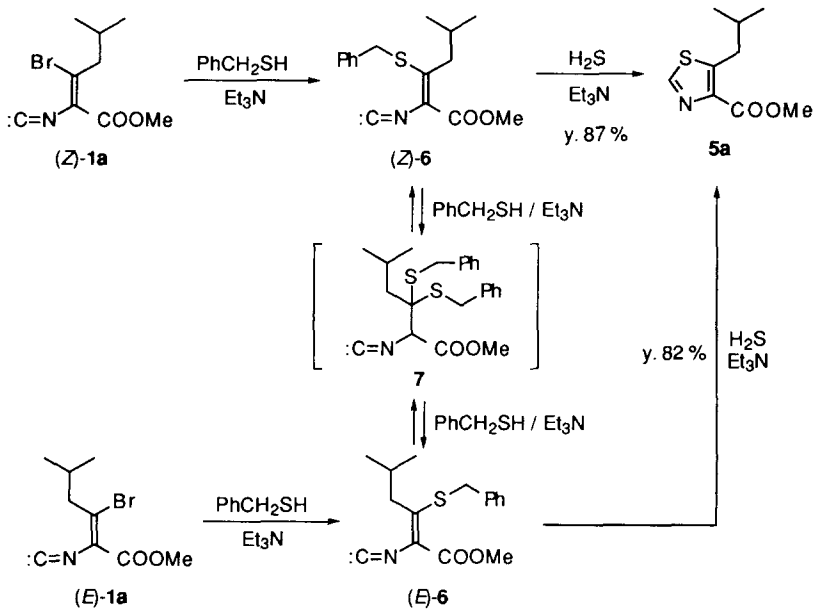
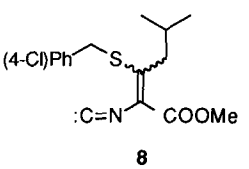


Table 2 Reaction of BICA (1a) with $PhCH_2SH$

Entry	Substrate	Equiv of $PhCH_2SH$	Yield (%)[a]	Ratio[b] of (*Z*) / (*E*)-**6**
1	(*Z*)-**1a**	0.8	67	20 : 1
2	(*Z*)-**1a**	1.2	88	1 : 1
3	(*E*)-**1a**	0.8	64	1 : 19
4	(*E*)-**1a**	1.2	92	1 : 1



8

[a] Isolated yield of **6** from **1**. [b] Ratios were determined by ^1H NMR.

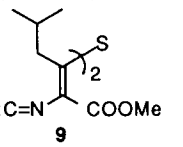
The assignment of the *Z* and *E* configuration of the olefins (**1**,**6**,**8**) was based on comparison of correlation of ^1H NMR spectral data.[2,10,12]

In conclusion, we have exploited a novel and efficient preparation of methyl 5-substituted thiazole-4-carboxylates (**5**) using a useful synthetic intermediate BICA(**1**). The mechanistic study suggested a substitution reaction of the first thiol with BICA proceeded with retention of the configuration. An addition-elimination of the second thiol to β-thioacrylates caused the isomerization of the double bond, which was essencial for the formation of **5** by an intramolecular α-addition of the β-thiol group to the isonitrile group.

Acknowledgement: We wish to thank Drs. Kazuo Matsumoto, Keisuke Kawashima, Mamoru Suzuki, and Masami Takahashi of our research laboratory for their useful comments and encouragement throughout this study.

References and Notes:

1. (a) Hiramatsu, K.; Nunami, K.; Hayashi, K.; Matsumoto, K. *Synthesis* **1990**, 781. (b) Nunami, K.; Hiramatsu, K.; Hayashi, K.; Matsumoto, K. *Tetrahedron* **1988**, *44*, 5467.
2. Nunami, K.; Yamada, M.; Fukui, T.; Matsumoto, K. *J. Org. Chem.*, in press.
3. (a) Tamura, Y.; Miyamoto, T.; Shimooka, K.; Masui, T. *Chem. Pharm. Bull.* **1971**, *19*, 119. (b) Hartman, G. D.; Weinstok, L. M. *Synthesis* **1976**, 681. (c) Suzuki, M.; Moriya, T.; Matsumoto, K.; Miyoshi, M. *Synthesis* **1982**, 874.
4. (a) Murakami, Y.; Shimura, K.; Saito, Y. Jap. Patent JP 01 305 072; *Chem. Abstr.* **1990**, *112*, 216919k. (b) Walter, G.; Rene, I.; Emilio, K. Eur. Patent EP 532 581; *Chem. Abstr.* **1990**, *113*, 40671c.
5. (a) Suzuki, M.; Nunami, K.; Moriya, T.; Matsumoto, K.; Yoneda, N. *J. Org. Chem.* **1978**, *43*, 4933. (b) Suzuki, M.; Nunami, K.; Matsumoto, K.; Yoneda, N.; Kasuga, O.; Yoshida, H.; Yamaguchi, T. *Chem. Pharm. Bull.* **1980**, *28*, 2374. (c) Nunami, K.; Suzuki, M.; Yoneda, N. *Chem. Pharm. Bull.* **1982**, *30*, 4015.
6. A 0.5 M solution in DMF was used. Sodium hydrosulfide (NaSH) can be used instead of H_2S / Et_3N.
7. Compound **9** was isolated in 47 % yield. **9**: mp. 112-114 °C (dec); ^{1}H NMR (δ in $CDCl_3$) 0.99 (d, 6H, J = 6.6 Hz, $CH(CH_3)_2$), 2.03 (m, 1H, $CHMe_2$), 2.49 (d, 2H, J = 7.1 Hz, CH_2CHMe_2), 3.88 (s, 3H, $COOCH_3$).



9

8. (a) Truce, W. E.; Gobarty, M. L. *J. Org. Chem.* **1970**, *35*, 2113. (b) Rappoport, Z. *Acc. Chem. Res.* **1981**, *14*, 7. (c) Ancos, B.; Maestro, C. M.; Martin, F. F. *Synthesis* **1988**, 136.
9. (*Z*)-**6**: prisms. mp. 64-65 °C (AcOEt-Hexane); ^{1}H NMR (δ in $CDCl_3$) 1.01 (d, 6H, J = 6.7 Hz, $CH(CH_3)_2$), 1.96 (m, 1H, $CHMe_2$), 2.98 (d, 2H, J = 7.2 Hz, CH_2CHMe_2), 3.80 (s, 3H, $COOCH_3$), 4.16 (s, 2H, CH_2Ph), 7.36 (br-s, 5H, ArH).
(*E*)-**6**: syrup; ^{1}H NMR (δ in $CDCl_3$) 1.10 (d, 6H, J = 6.7 Hz, $CH(CH_3)_2$), 2.10 (m, 1H, $CHMe_2$), 2.71 (d, 2H, J = 7.2 Hz, CH_2CHMe_2), 3.83 (s, 3H, $COOCH_3$), 4.09 (s, 2H, CH_2Ph), 7.36 (br-s, 5H, ArH).
10. Kolar, A. J.; Olsen, R. K. *J. Org. Chem.* **1980**, *45*, 3246.
11. (*Z*)-**8**: needles. mp. 87-88 °C (AcOEt-Hexane); ^{1}H NMR (δ in $CDCl_3$) 1.00 (d, 6H, J = 6.7 Hz, $CH(CH_3)_2$), 1.95 (m, 1H, $CHMe_2$), 2.95 (d, 2H, J = 7.2 Hz, CH_2CHMe_2), 3.80 (s, 3H, $COOCH_3$), 4.13 (s, 2H, CH_2Ph), 7.28-7.36 (m, 5H, ArH).
(*E*)-**8**: needles. mp. 51-54 °C (AcOEt-Hexane); ^{1}H NMR (δ in $CDCl_3$) 1.10 (d, 6H, J = 6.7 Hz, $CH(CH_3)_2$), 2.08 (m, 1H, $CHMe_2$), 2.69 (d, 2H, J = 7.2 Hz, CH_2CHMe_2), 3.84 (s, 3H, $COOCH_3$), 4.05 (s, 2H, CH_2Ph), 7.24-7.34 (m, 5H, ArH).
12. (a) Srinivasan, A,; Richards, K. D.; Olsen, R. K. *Tetrahedron Lett.* **1976**, 891. (b) Rich, D. H.; Tam, J.; Mathiaparanan, P.; Grant, J. *Synthesis* **1975**, 402. (c) Brown, A. G.; Smake, T. C. *J. Chem. Soc., Chem. Commun.* **1969**, 1489.

(*Received in Japan* 12 *September* 1994)