



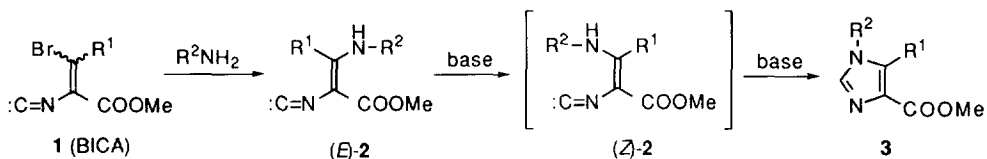
A Novel Synthesis of Methyl 5-Substituted Thiazole-4-carboxylates Using 3-Bromo-2-isocyanoacrylates (BICA)

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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 studies¹ on biologically interesting amino acids and heterocyclic compounds using multifunctional 3-substituted 3-bromo-2-isocyanoacrylates(BICA)(**1**), we recently reported² 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**.



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-carboxylates³ (**5**) which are useful intermediates⁴ 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

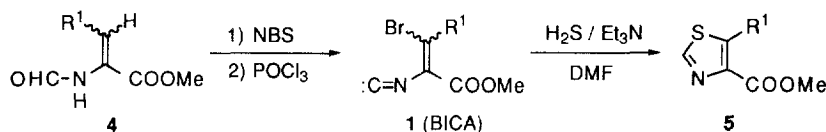


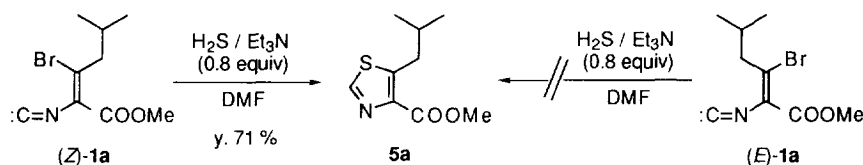
Table 1 Yields and physical properties of thiazoles (5)

Entry	R ¹	Yield (%) ^a	mp (°C)	¹ H-NMR (CDCl ₃)		Product
				C ² -H	COOCH ₃	
1	CH ₂ CH(CH ₃) ₂	89	syrup	8.63	3.95	5a
2	CH(CH ₂ CH ₃) ₂	71	syrup	8.64	3.90	5b
3	C ₆ H 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 H₂S in the presence of triethylamine (Et₃N) 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

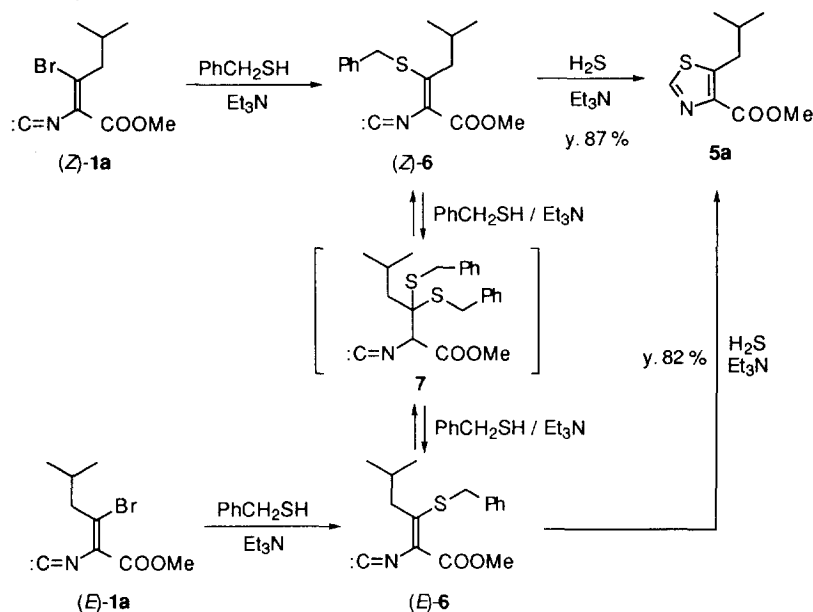


been reported in most cases of addition-elimination reactions of vinyl halides,⁸ and were much different from those of the reaction of BICA with primary amines,² which exhibited selective formation of *E*-enamine **2** without any relation to the geometry of **1**.

Next, **1a** was treated with a different amount of benzyl hydrosulfide in the presence of Et₃N 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-isocyano-hexenoate (**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

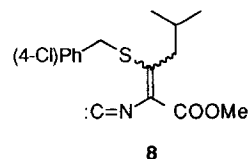
hydrosulfide, (2.0 equiv) was examined in DMF at room temperature for 1 h to afford a mixture of methyl 3-(4-chlorobenzyl)thio-5-methyl-2-isocyanoheptenoate (**8**)¹¹ and **6** as expected. Further, a reaction of a mixture of (*Z*)- and (*E*)-**6** with 1.2 equiv of H₂S in the presence of Et₃N was carried out in DMF at room temperature for 0.5 h. In consequence, the addition of H₂S 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 PhCH₂SH

Entry	Substrate	Equiv of PhCH ₂ SH	Yield (%) ^a	Ratio ^b of (<i>Z</i>) / (<i>E</i>)- 6
1	(<i>Z</i>)- 1a	0.8	67	20 : 1
2	(<i>Z</i>)- 1a	1.2	88	1 : 1
3	(<i>E</i>)- 1a	0.8	64	1 : 19
4	(<i>E</i>)- 1a	1.2	92	1 : 1

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



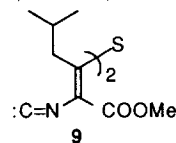
The assignment of the *Z* and *E* configuration of the olefins (**1**, **6**, **8**) was based on comparison of correlation of ¹H NMR spectral data.^{2,10,12}

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 essential for the formation of **5** by an intramolecular α -addition of the β -thiol group to the isonitrile group.

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- A 0.5 M solution in DMF was used. Sodium hydrosulfide (NaSH) can be used instead of H_2S / Et_3N .
- Compound **9** was isolated in 47 % yield. **9**: mp. 112-114 °C (dec); ^1H NMR (δ in CDCl_3) 0.99 (d, 6H, $J = 6.6$ Hz, $\text{CH}(\text{CH}_3)_2$), 2.03 (m, 1H, CHMe_2), 2.49 (d, 2H, $J = 7.1$ Hz, CH_2CHMe_2), 3.88 (s, 3H, COOCH_3).
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- (Z)-**6**: prisms. mp. 64-65 °C (AcOEt-Hexane); ^1H NMR (δ in CDCl_3) 1.01 (d, 6H, $J = 6.7$ Hz, $\text{CH}(\text{CH}_3)_2$), 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; ^1H NMR (δ in CDCl_3) 1.10 (d, 6H, $J = 6.7$ Hz, $\text{CH}(\text{CH}_3)_2$), 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).
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- (Z)-**8**: needles. mp. 87-88 °C (AcOEt-Hexane); ^1H NMR (δ in CDCl_3) 1.00 (d, 6H, $J = 6.7$ Hz, $\text{CH}(\text{CH}_3)_2$), 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); ^1H NMR (δ in CDCl_3) 1.10 (d, 6H, $J = 6.7$ Hz, $\text{CH}(\text{CH}_3)_2$), 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).
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