

# NEW RING TRANSFORMATION REACTION OF IMIDAZOTHIAZOLE WITH ACETYLENIC ACID ESTERS

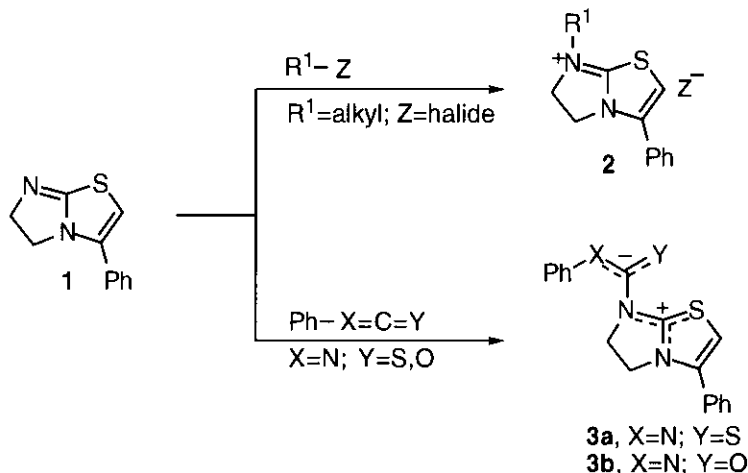
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**Abstract** - 3-Phenyl-5,6-dihydroimidazo[2,1-*b*]thiazole (**1**) as a nucleophile reacted with acetylenic acid esters such as ethyl propiolate and dimethyl acetylenedicarboxylate to give the new ring transformation compounds (2-oxo-imidazoline-1-yl)acrylic acid ethyl esters (**6a-b**) and [2-oxo-imidazoline-1-yl]but-2-enedioic acid diethyl esters (**7a-b**), respectively. Similarly, treatment of reactive imidazo[2,1-*b*]thiazolium betaines (**3a-b**) with acetylenic acid derivatives led to the corresponding ring transformation compounds. This reaction proceeded by the participation of water, and the resulting compounds were obtained in a mixture of *cis* and *trans* isomers.

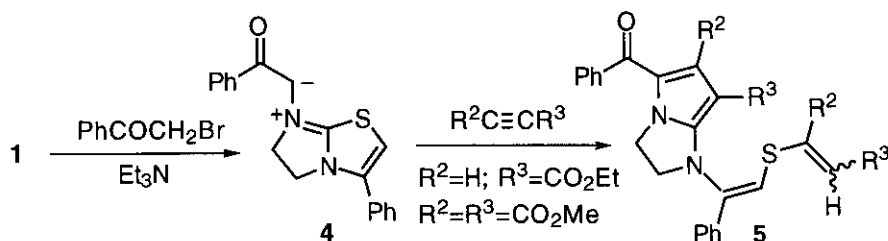
3-Phenyl-5,6-dihydroimidazo[2,1-*b*]thiazole (**1**)<sup>1-4</sup> has been synthesized by condensing cyclic thiourea<sup>5</sup> with phenacyl bromide. Thiazolo compound (**1**) can be used as a strong nucleophile and the alkylation of **1** occurs exclusively at the 7-position.<sup>6</sup> Thus, reaction of **1** with alkyl halides or electrophiles gave the quarternary ammonium salts (**2**) or the corresponding betaines<sup>7-8</sup> (**3a-b**), respectively (Scheme 1).

Scheme 1



In our previous work, we reported<sup>9</sup> the 1,3-dipolar cycloaddition of 3-phenyl-7-(2-phenyl-2-oxoethyl)-5,6-dihydroimidazo[2,1-*b*]thiazolium betaine (4) with acetylenic dipolarophiles to give the geometric *cis/trans* isomers (5) as shown in Scheme 2. We found also recently that bicyclic imidazo- and pyrimidinothiazoles are extremely basic.<sup>10</sup>

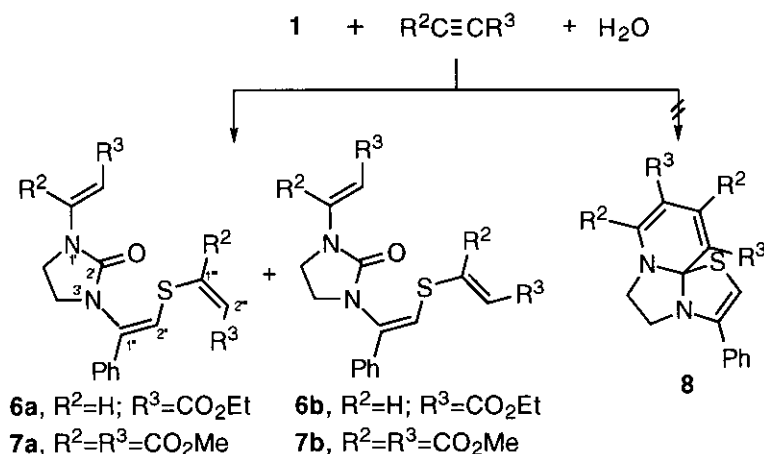
Scheme 2



We report here on the new ring transformation reaction of 1 with acetylenic acid esters such as ethyl propiolate and dimethyl acetylenedicarboxylate.

Treatment of thiazolo compound (1) with ethyl propiolate and dimethyl acetylenedicarboxylate in the presence of water gave the new ring transformation compounds (2*E*)-3-[3-[2-(1*Z* and 1*E*)-(2-ethoxycarbonylvinyl)sulfanyl)-(1*Z*)-1-phenylvinyl]-2-oxo-imidazolin-1-yl]acrylic acid ethyl esters (6*a-b*) and (2*E*)-2-[3-[2-(1*Z* and 1*E*)-(1,2-bisethoxycarbonylvinyl)sulfanyl)-(1*Z*)-1-phenylvinyl]-2-oxo-imidazolin-1-yl]but-2-enedioic acid diethyl esters (7*a-b*), respectively (Scheme 3).

Scheme 3



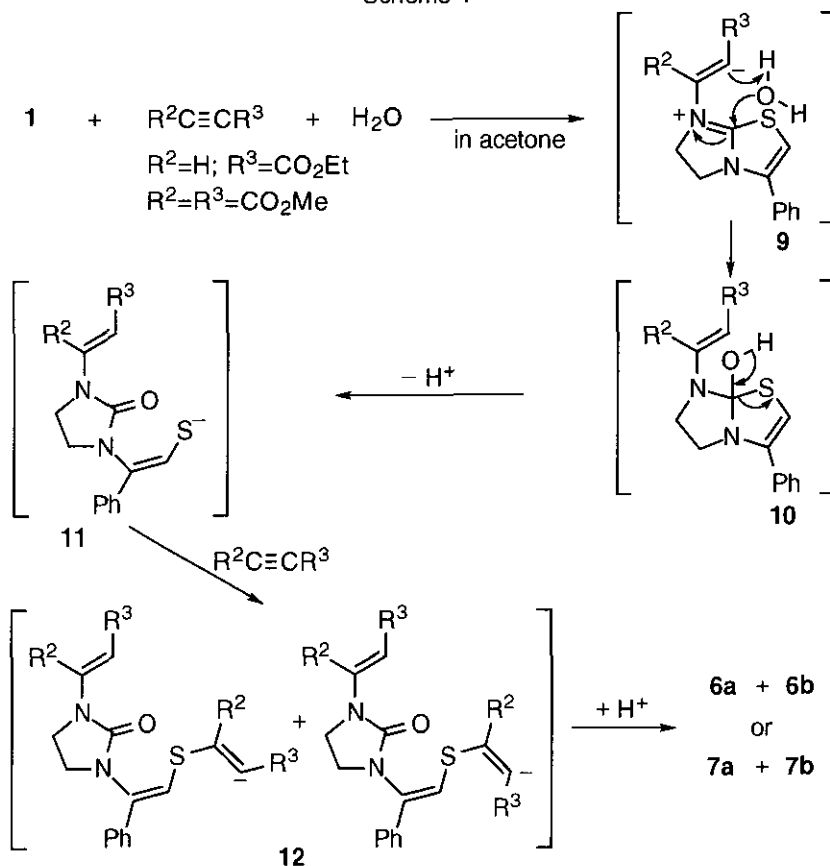
The reaction readily proceeded in acetone at room temperature and the resulting products were isolated by column chromatography as a mixture of *cis/trans* geometric isomers. However, 3-phenyl-4,5-dihydro-1-thia-3*a*,5*a*-diazacyclopenta[*c*]indene-7,9-dicarboxylic acid diethyl ester (8) which we also expected to form *via* 2:1 cycloaddition reaction<sup>11</sup> was not

isolated.

These ring transformation compounds (**6a-b**) and (**7a-b**) also can be prepared by treatment of reactive betaines (**3a-b**) with ethyl propiolate and dimethyl acetylenedicarboxylate, respectively, under reflux in acetone. In this case phenyl isothiocyanate or phenyl isocyanate group of betaine was easily displaced by the strong electrophiles such as acetylenic acid esters.

The COSY spectrum of mixture (**6a-b**) showed that the  $C_3H$  signals of *trans* and *cis* isomers at  $\delta$  8.02 and 7.99 (d, 1H,  $J=14.1$  Hz and  $J=14.1$  Hz, respectively) were coupled with the  $C_2H$  signals of those at  $\delta$  4.95 and 4.92 (d, 1H,  $J=14.1$  Hz and  $J=14.1$  Hz, respectively). The presence of  $C_1'''H$  signals at  $\delta$  7.59 and 7.21 (d, 1H,  $J=15.3$  Hz and  $J=9.9$  Hz, *trans* and *cis* isomers, respectively) was also indicated by the coupling with the  $C_2'''H$  signals at  $\delta$  5.86 and 5.84 (d, 1H,  $J=15.3$  Hz and  $J=9.9$  Hz, *trans* and *cis* isomers, respectively). The  $^{13}C$  NMR spectrum exhibited carbon signals which comprise ester groups in the  $\delta$  167.2-164.8 region and carbonyl groups at  $\delta$  153.0 and 152.9. The  $C_3H$ ,  $C_2H$ ,  $C_2''H$ ,  $C_2'''H$  and  $C_1'''H$  signals were correlated with the carbon signals at  $\delta$  139.7 ( $C_3$ ), 139.5 ( $C_3$ ), 97.4 ( $C_2$ ), 97.1 ( $C_2$ ), 118.9 ( $C_2''$ ), 117.3 ( $C_2'''$ ), 115.0 ( $C_2'''$ ), 146.1 ( $C_1'''$ ) and 143.6 ( $C_1'''$ ), respectively, by HETCOR spectrum of mixture. The MS of mixture exhibited a molecular ion peak at  $m/z$  416.

Scheme 4



Structure elucidation of compounds (**7a-b**) was established in the same manner described above. In the  $^1\text{H}$  NMR spectrum of **7a-b**, the  $\text{C}_3\text{H}$  ( $\delta$  5.14 and 5.11),  $\text{C}_2''\text{H}$  ( $\delta$  6.44 and 6.63) and  $\text{C}_2'''\text{H}$  ( $\delta$  6.00 and 6.60) signals of *cis* and *trans* isomers were found as the singlet. The presence of ester groups (in the  $\delta$  166.0-163.5 region) and carbonyl groups ( $\delta$  152.0 and 151.9) of mixture were observed by  $^{13}\text{C}$  NMR spectrum. And the  $\text{C}_3\text{H}$ ,  $\text{C}_2''\text{H}$  and  $\text{C}_2'''\text{H}$  signals showed correlations with the carbon signals at  $\delta$  97.1 ( $\text{C}_3$ ), 96.7 ( $\text{C}_3$ ), 122.4 ( $\text{C}_2''$ ), 116.7 ( $\text{C}_2''$ ), 119.4 ( $\text{C}_2'''$ ) and 114.7 ( $\text{C}_2'''$ ), respectively. The MS of **7a-b** was characterized by molecular ion peak at  $m/z$  504.

A plausible reaction mechanism for the ring transformation is shown in Scheme 4. First, the nucleophilic addition of thiazolo compound (**1**) to acetylenic acid ester gave the reactive betaine (**9**). Then, bridgehead carbon attack by the participation of water occurred to give the intermediate (**10**). At that time the stereochemistry of **10** is to be fixed to *trans* configuration by six membered ring formation with water as a source of protons at **9**. Subsequent thiazole ring opening by deprotonation gave thiol anion compound (**11**). Nucleophilic attack of thiol anion to another acetylenic acid ester followed by the protonation of **12** led to the geometric isomers (**6a-b**) or (**7a-b**).

## EXPERIMENTAL

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. IR were recorded on a Analect FX-6160 FT-IR spectrometer as potassium bromide pellets.  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectra were obtained on a 300 MHz Gemini Varian nmr spectrometer using tetramethylenesilane as the reference. Multiplicity was simplified as follows: s=singlet, d=doublet, t=triplet, q=quartet, and m=multiplet. MS were determined on a Hewlett-Packard model 5988A GC-MS spectrometer. Microanalyses were performed with Perkin-Elmer 240 C elemental analyzer. Column chromatography was carried out using silicagel (230-400 mesh).

### General Procedure for the Preparation of Ring Transformation Compounds (**6a-b**) and (**7a-b**).

Method A (Using Thiazolo Compound (**1**)): To a solution of **1** (1.0g, 4.95 mmol) in 30 mL of acetone containing a small amount of water, the appropriate acetylenic acid esters (9.9 mmol) in 5mL of acetone was added dropwise. The reaction mixture immediately turned purple and was stirred for 30 min at rt. The resulting solution was concentrated and the residue was chromatographed on silica gel(*n*-hexane/ethyl acetate=3/1). The combined solutions containing product were distilled off and the resulting solid was filtered to afford the ring transformation compounds.

**(2E)-3-[3-[2-(1Z and 1E)-(2-Ethoxycarbonylvinylylsulfanyl)-(1Z)-1-phenylvinyl]-2-oxo-imidazolidin-1-yl]acrylic acid ethyl esters (6a and 6b):** This compound (a 1:1 mixture of 6a and 6b) was obtained using ethyl propiolate in a yield of 0.48 g (23.3%) as a sticky brown solid<sup>12</sup>, mp 51.0-53.0 °C; IR (KBr):  $\nu$  2957, 1720 (C=O), 1691, 1601, 1401, 1322, 1257, 1142  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.02 and 7.99 (d, 1H,  $J=14.1$  Hz and  $J=14.1$  Hz,  $\text{C}_3\text{H}$  of *trans* and *cis* isomers, respectively), 7.59 and 7.21 (d, 1H,  $J=15.3$  Hz and  $J=9.9$  Hz,  $\text{C}_1'''\text{H}$  of *trans* and *cis* isomers, respectively), 7.38-7.19 (m, 5H, ArH), 6.72 and 6.58 (s, 1H,  $\text{C}_2''\text{H}$  of *cis* and *trans* isomers, respectively), 5.86 and 5.84 (d, 1H,  $J=15.3$  Hz and  $J=9.9$  Hz,  $\text{C}_2'''\text{H}$  of *trans* and *cis* isomers, respectively), 4.95 and 4.92 (d, 1H,  $J=14.1$  Hz and  $J=14.1$  Hz,  $\text{C}_2\text{H}$  of *trans* and *cis* isomers, respectively), 4.19-4.05 (m, 4H,  $2\times\text{COOCH}_2\text{CH}_3$ ), 3.63 (s, 4H,  $2\times\text{NCH}_2$ ), 1.18 (t, 6H,  $J=7.1$  Hz,  $2\times\text{COOCH}_2\text{CH}_3$ );  $^{13}\text{C}$  NMR (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  167.2 (COO), 166.4 (COO), 166.2 (COO), 164.8 (COO), 153.0 (CO), 152.9 (CO), 146.1 ( $\text{C}_1'''$ ), 143.6 ( $\text{C}_1''$ ), 139.7 ( $\text{C}_3$ ), 139.5 ( $\text{C}_3$ ), 134.9, 134.3, 129.7, 129.5, 129.3, 129.2, 128.9, 126.5, 126.3, 125.9, 118.9 ( $\text{C}_2''$ ), 117.3 ( $\text{C}_2'''$ ), 115.0 ( $\text{C}_2'''$ ), 97.4 ( $\text{C}_2$ ), 97.1 ( $\text{C}_2$ ), 60.8, 60.2, 42.5, 42.2, 40.7, 14.8, 14.7; MS:  $m/z$  285 (100), 416 ( $\text{M}^+$ ).

**(2E)-2-[3-[2-(1Z and 1E)-(1,2-Bisethoxycarbonylvinylylsulfanyl)-(1Z)-1-phenylvinyl]-2-oxo-imidazolidin-1-yl]but-2-enedioic acid diethyl esters (7a and 7b):** This compound (a 3:1 mixture of 7a and 7b) was obtained using dimethyl acetylenedicarboxylate in a yield of 1.12 g (44.9%) as a pale yellow solid, mp 60.0-62.0 °C; IR (KBr):  $\nu$  2952, 1736 (C=O), 1703, 1607, 1413, 1342, 1247, 1166  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.37-7.27 (m, 5H, ArH), 6.63 and 6.44 (s, 1H,  $\text{C}_2''\text{H}$  of *trans* and *cis* isomers, respectively), 6.60 and 6.00 (s, 1H,  $\text{C}_2'''\text{H}$  of *trans* and *cis* isomers, respectively), 5.14 and 5.11 (s, 1H,  $\text{C}_3\text{H}$  of *cis* and *trans* isomers, respectively), 3.90, 3.87, 3.69, and 3.68 (s, 12H,  $4\times\text{COOCH}_3$  of *cis* isomer), 3.87, 3.83, 3.78, and 3.68 (s, 1H,  $4\times\text{COOCH}_3$  of *trans* isomer), 3.91-3.62 (m, 4H,  $2\times\text{NCH}_2$ );  $^{13}\text{C}$  NMR (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  166.0 (COO), 165.9 (COO), 165.3 (COO), 165.0 (COO), 163.9 (COO), 163.5 (COO), 152.0 (CO), 151.9 (CO), 146.9, 144.7, 140.2, 137.2, 134.4, 133.8, 129.8, 129.2, 129.1, 129.0, 126.5, 125.9, 122.4 ( $\text{C}_2''$ ), 119.4 ( $\text{C}_2'''$ ), 116.7 ( $\text{C}_2''$ ), 114.7 ( $\text{C}_2'''$ ), 97.1 ( $\text{C}_3$ ), 96.7 ( $\text{C}_3$ ), 53.4, 53.2, 53.0, 52.9, 52.0, 51.5, 42.3, 42.0, 41.7, 41.6; MS:  $m/z$  274 (100), 504 ( $\text{M}^+$ ). Anal. Calcd for  $\text{C}_{23}\text{H}_{24}\text{N}_2\text{O}_9\text{S}$ : C, 54.75; H, 4.80; N, 5.56. Found: C, 54.60; H, 4.76; N, 5.47.

**Method B (Using Betaines 3a-b):** To a solution of the appropriate betaines (3a-b) (1.0g) dissolved by heating in 300 mL of acetone containing a small amount of water was gradually added the appropriate electrophiles (2 eq.) in 5mL of acetone. The resulting mixture was refluxed for 1 h and cooled to rt. Then, the solvent was evaporated *in vacuo* and the residue was chromatographed on silica gel (*n*-hexane/ethyl acetate=3/2). The combined solutions containing product were distilled off and the resulting solid was filtered to afford the ring transformation compounds.

**6a-b** (a 4:1 mixture of 6a and 6b) and **7a-b** (a 2:1 mixture of 7a and 7b) were obtained using 3-phenyl-5,6-dihydro-7-[*N*-phenyl(thiocarbamoyl)]imidazo[2,1-*b*]thiazolium betaine (3a) in 49.7 and 53.3% yields, respectively.

**6a-b** (a 1:1 mixture of **6a** and **6b**) and **7a-b** (a 2:1 mixture of **7a** and **7b**) were obtained using 3-phenyl-5,6-dihydro-7-[*N*-phenyl(carbamoyl)]imidazo[2,1-*b*]thiazolium betaine (**3b**) in 42.3 and 52.9% yields, respectively.

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12. When ring transformation compounds (a 1:1 mixture of **6a** and **6b**) were obtained, these compounds were a little sticky brown solid. Thus, it was difficult to obtain the accurate data of microanalysis.

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