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Reactivity of 7-Dithiocarboxy-imidazo[2,1-b]thiazolium-betaine with Aliphatic Alkylating Agents

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Abstract□We have reported earlier on the reactivity of 7-dithiocarboxy-3-phenyl-5,6-dihydro imidazo[2,1-b]thiazolium-betaine with several *para*-substituted phenacyl bromides. In this work reactions of 7-dithiocarboxy-3-phenyl(or methyl)-5,6-dihydro imidazo[2,1-b]thiazolium-betaine with a series of aliphatic alkylating agents of α-halo ketone, γ-halo keto ester and α-halo ester were examined for the similar purpose. In case of α-halo ketone or γ-halo keto ester such as α-chloro acetone or ethyl 4-chloro acetoacetate new biheterocyclic compound was obtained via ring transformation reaction. However, reaction of the betaine with methyl(or ethyl) bromoacetate used as a α-halo ester, gave, instead, S-alkylated quarternary ammonium salt.

Keywords□7-Dithiocarboxy-3-substituted-5,6-dihydro imidazo[2,1-b]thiazolium-betaine, Alkylating agent, α-Halo ketone, γ-Halo keto ester, α-Halo ester, Reactivity, Ring transformation reaction, S-Alkylated quarternary ammonium salt, C-H Acidity of methylene protons.

Some 3-substituted-5,6-dihydro imidazo[2,1-b] thiazoles(2) and their salts were well known for their pharmacological properties such as antidepressant[1], antiinflammatory[2], anthelmintic[3], hypoglycemic and growth promotant activities.[4]

For the synthesis and reaction of thiazolo compounds[5,6] various studies have been carried out and it was already found that the corresponding imidazo[2,1-b]thiazolium-betaine[7] was prepared by reacting 3-substituted-5,6-dihydro imidazo[2,1-b]thiazole(2) with isocyanate, isothiocyanate or carbon disulfide. And ring transformation reaction by treatment of 7-phenyl(thiocarbamoyl)-3-substituted-5,6-dihydro imidazo[2,1-b]thiazolium-betaine with alkylating agents was known.[8,9] On reaction of 7-dithiocarboxy-3-phenyl-5,6-dihydro imidazo [2,1-b]thiazolium-betaine with *para*-substituted phenacyl bromides[10], we found that ring transformation compound was obtained on the occasion of reaction using electron withdrawing substituent, while when the substitutent was electron donating group quarternary ammonium salt was formed.

With relation to the above we carried out the reaction of 7-dithiocarboxy-3-substituted-5,6-dihydro imidazo[2,1-b]thiazolium-betaine(3) with a series of aliphatic alkylating agents to examine the reactivity for the ring transformation reaction.

EXPERIMENTAL METHODS

Materials and instrumentation

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. ^{1}H-NMR spectra were obtained on AM-200-SY Brucker nmr spectrometer. Chemical shift values from TMS were reported on the δ scale. Infrared spectra were recorded on a Analect FX-6160 FT-IR infrared spectrometer using either potassium bromide pallet or sodium chloride cell. Elemental analyses were carried out by Perkin-Elmer Model 240c elementary analyzer. Kieselgel 60(70-230 mesh ASTM, MERCK) was used for column chromatography.

General procedure for the preparation of ring transformation compounds.

2-[2-(7-Acetyl-5-thioxo-2,3-dihydro-1H-imidazo[1,2-c] thiazol-1-yl)-2-phenylvinylthio] acet-

(5a).

In a 1000 m*l* round bottomed flask equipped with a reflux condenser 1.0g (3.59 mmol) of 7-dithiocarboxy-3-phenyl-5,7-dihydro imidazo[2,1-b] thiazolium-betaine was dissolved with heating in 600 m*l* of acetone. To this solution was added an equimolar amount of chloroacetone (0.33g, 3.59 mmol) and refluxed for 3 hrs. When reaction is completed, a reaction mixture is cooled. Then, the white solid (6) (HBr salt, M.p. >250 °C) precipitated is filtered off, and the filtrate was concentrated, chromatographed on silica-gel (eluting solvents; *n*-hexane/ethyl acetate = 1.5:1). The combined fractions containing product were distilled and resulting residual product was dried in vacuo. Yield 0.26g (18.6%); M.P. 137-138 °C; IR(KBr) 1728(m), 1647 (s), 1559(s) cm^{-1}; ^{1}H-NMR($CDCl_3$) δ 2.0(s, 3H, CH_3), 2.3(s, 3H, CH_3), 3.6(s, 2H, SCH_2), 4.2-4.3 (m, 4H, NCH_2CH_2N), 6.4(s, 1H, =CH), 7.3(s, 5H, ArH); Anal. Calcd. for $C_{18}H_{18}N_2O_2S_3$: C, 55.36; H, 4.65; N, 7.16. Found: C, 55.2; H, 4.62; N, 7.02.

Ethyl 4-[2-(7-ethoxycarbonylacetyl-5-thioxo-2,3,-dihydro-1H-imidazo[1,2-c]thiazol-1-yl)-2-phenylvinylthio]acetoacetate (5b).

0.50g (3.59 mmol) of ethyl 4-chloroacetoacetate as a alkylating agent was used. Yield 0.29g(15.1%); IR(NaCl) 1737(m), 1561(m)cm^{-1}; ^{1}H-NMR($CDCl_3$) δ1.2-1.3(m, 6H, CH_3), 3.3(s, 2H, SCH_2), 3.6(d, 2H, ring-$COCH_2CO$, 15.7Hz), 3.7(s, 2H, $COCH_2CO$), 4.0-4.3(m, 8H, NCH_2CH_2N, OCH_2), 6.4(s, 1H, =CH), 7.3(s, 5H, ArH).

General procedure for the preparation of quarternary ammonium salts:
7-[Methoxycarbonylmethylenethio)thiocarbonyl]-3-phenyl-5,6-dihydro imidazo[2,1-b]thiazolium bromide (7a).

In 300 m*l* of acetone 0.50g (1.80 mmol) of 7-dithiocarboxy-3-phenyl-5,6-dihydro imidazo[2,1-b] thiazolium-betaine was dissolved with heating. An equimolar amount of methyl bromoacetate (0.28g, 1.80 mmol) was added to this solution. During the reaction is developing, solid is precipitated. A reaction mixture was further refluxed for two hours, and cooled. The resulting solid was collected by filtration and dried. Yield 0.59g (76.0%); M.P. 195-197 °C; IR(KBr) 1735(s), 1514(s), 1307(s)cm^{-1}; ^{1}H-NMR(DMSO-d_6) δ3.7(s, 3H, OCH_3), 4.4(s, 2H, SCH_2), 4.9-5.1(m, 4H, NCH_2CH_2N), 7.6-7.7(m, 5H, ArH), 7.8(s, 1H, =CH); Anal. Calcd. for $C_{15}H_{15}BrN_2O_2S_3$: C, 41.77; H, 3.51; N, 6.49. Found; C, 41.9; H, 3.49; N, 6.47.

7-[(Methoxycarbonylmethylenethio]thiocarbonyl]-3-methyl-5,6-dihydro imidazo[2,1-b]thiazolium bromide (7b).

0.50g (2.31 mmol) of 7-dithiocarboxy-3-methyl-5,6-dihydro imidazo[2,1-b]thiazolium-betaine and 0.35g (2.31 mmol) of methyl bromoacetate were used. Yield 0.62g (72.5%); M.P. 172-173 °C; IR(KBr) 1740(s), 1587(m), 1506(m)cm^{-1}; ^{1}H-NMR(DMSO-d_6) δ 2.4(d, 3H, CH_3, 1Hz), 3.7(s, 3H, OCH_3), 4.4(s, 2H, SCH_2), 4.8-5.1(m, 4H, NCH_2CH_2N), 7.4(d, 1H, =CH, 1.1Hz); Anal. Calcd. for $C_{10}H_{13}BrN_2O_2S_3$: C, 32.52; H, 3.55; N, 7.59. Found: C, 32.70; H, 3.57; N, 7.52.

7-[(Ethoxycarbonylmethylenethio)thiocarbonyl]-3-phenyl-5,6-dihydro imidazo[2,1-b]thiazolium bromide (8a).

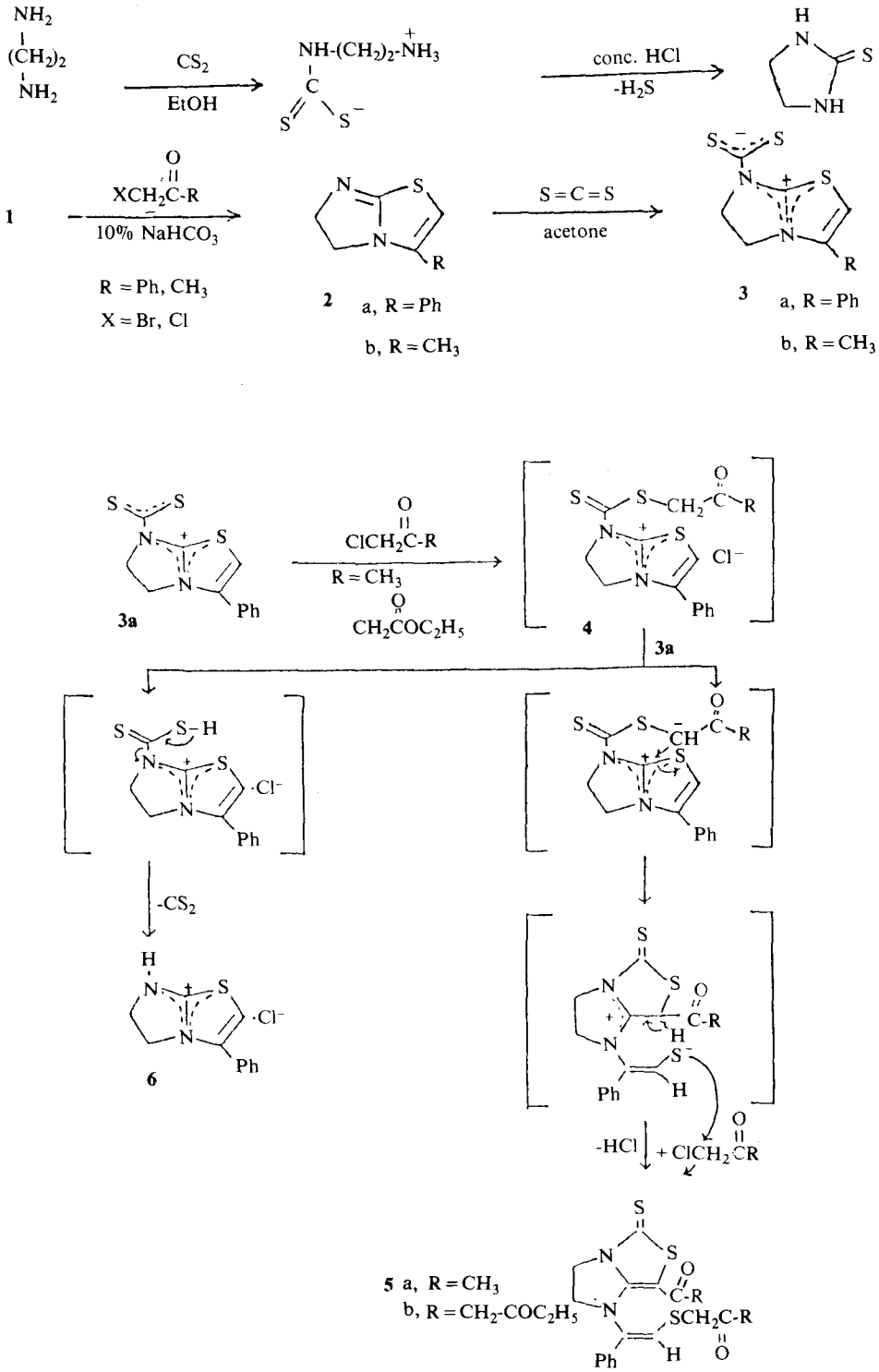
0.50g (1.80 mmol) of 7-dithiocarboxy-3-phenyl-5,6-dihydro imidazo[2,1-b]thiazolium-betaine and 0.30g(1.80 mmol) of ethyl bromoacetate were used. Yield 0.52g (65.0%); M.P. 165.5-167 °C; IR(KBr) 1735(s), 1511(s), 1294(s)cm^{-1}; ^{1}H-NMR(DMSO-d_6) δ1.3-1.4(t, 3H, CH_3, 7.1Hz), 4.2-4.3(q, 2H, OCH_2, 7.1Hz), 4.5(s, 2H, SCH_2), 5.0-5.2(m, 4H, NCH_2CH_2N), 7.7-7.8(m, 5H, ArH), 7.9(s, 1H, =CH).

7-[(Ethoxycarbonylmethylenethio)thio carbonyl]-3-methyl-5,6-dihydro imidazo[2,1-b]thiazolium bromide (8b).

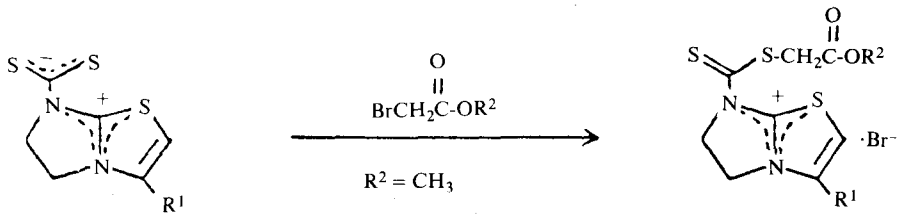
0.50g (2.31 mmol) of 7-dithiocarboxy-3-methyl-5,6-dihydro imidazo[2,1-b]thiazolium-betaine and 0.39g (2.31 mmol) of ethyl bromoacetate were used. Yield 0.61g (68.9%); M.P. 167-158 °C; IR(KBr) 1745(s), 1505(m), 1393(s)cm^{-1}; ^{1}H-NMR(DMSO-d_6) δ1.2-1.3(t, 3H, CH_3, 7.1Hz), 2.4(d, 3H, CH_3, 1.2Hz), 4.1-4.2(q, 2H, OCH_2, 7.1Hz), 4.4(s, 2H, SCH_2), 4.8-5.1(m, 4H, NCH_2CH_2N), 7.4(d, 1H, =CH, 1.2Hz).

RESULTS AND DISCUSSION

3-Substituted-5,6-dihydro imidazo[2,1-b]thiazole 2 was synthesized in 70-80% yields according to the method introduced by Wilson and Woodger.[5] 7-Dithiocarboxy-3-substituted-5,6-dihydro imidazo [2,1-b]thiazolium-betaine[7](3) was prepared by treating 2 with carbon disulfide as an electrophile in acetone. At this time the betaine, 3 was obtained in 80-90% yields as yellow solids.


NH2
(CH2)2
NH2
CS2
EtOH
NH-(CH2)2-NH3
conc. HCl
-H2S
1
XCH2C-R
10% NaHCO3
R = Ph, CH3
X = Br, Cl
2 a, R = Ph
b, R = CH3
S=C=S
acetone
3 a, R = Ph
b, R = CH3
3a
ClCH2C-R
R = CH3
CH2COC2H5
4
-CS2
6
-HCl
+ ClCH2CR
5 a, R = CH3
b, R = CH2-COC2H5
SCH2C-R

Scheme 1



3 a, R^1 = Ph

b, R^1 = CH_3

7 a, R^1 = Ph, R^2 = CH_3
b, R^1 = CH_3, R^2 = CH_3

8 a, R^1 = Ph, R^2 = C_2H_5
b, R^1 = CH_3, R^2 = C_2H_5

We have reported[10] formation of new heterocycles on reaction of 3 with *para*-substituted phenacyl bromides. In this work various aliphatic alkylating agents were used for our experiment. When the betaine, 3a dissolved in acetone was reacted with α-halo ketone or γ-halo keto ester (e.g., α-chloro acetone or ethyl 4-chloro acetoacetate), new biheterocyclic compound was obtained through a mechanism as shown in scheme 1. Following the reaction, 2-[2-(7-acetyl-5-thioxo-2,3-dihydro-1H-imidazo[1,2-c]thiazol-1-yl)-2-phenylvinylthio]acetone (5a) or ethyl 4-[2-(7-ethoxycarbonylacetyl-5-thioxo-2,3-dihydro-1H-imidazo[1,2-c]thiazol-1-yl)-2-phenylvinylthio]acetoacetate (5b) formed via ring transformation reaction was isolated from a reaction mixture by column chromatography (eluting solvent; *n*-hexane/ethyl acetate = 1.5:1) and identified by various spectroscopic methods and elemental analyses.

^{1}H-NMR spectrum of 5b synthesized by reacting 3a with ethyl 4-chloroacetoacetate showed that two protons of methylene linked with carbonyl group near to thiazole ring appear to the AB quartet on account of prochirality of large ring system. Similar examples[11] also are found in several compounds having large ring system. Though 5b was purely isolated by column chromatography, it was not solidified.

On the other hand, in case that the betaine 3 was reacted with α-halo ester (e.g., methyl bromoacetate or ethyl bromoacetate), quarternary ammonium salt 7-[(methoxycarbonylmethylenethio)thiocarbonyl]-3-phenyl (or methyl)-5,6-dihydro imidazo[2,1-b]thiazolium bromide(7) or 7-[(ethoxycarbonylmethylenethio)thiocarbonyl]-3-phenyl(or methyl)-5,6-dihydro imidazo[2,1-b]thiazolium bromide(8) was obtained. The products are intermediates of ring transformation reaction and formed because the reaction did not proceed further. It appears that because C-H acidity of methylene protons of intermediate formed by reaction with α-halo ester is not sufficient to give the corresponding products to 5, a thiazole ring opening doesn't take place.

In conclusion, the selectivity of ring transformation reaction was discovered with α-halo ketone and γ-halo keto ester. However, when the reaction was performed with a variety of α-halo esters in the hope of having the same results, quarternary ammonium salts were obtained instead, due to the lower acidity of α-halo ester than α-halo ketone and γ-halo keto ester for C-H acidity of methylene protons.

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