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MECHANISM OF FORMATION OF 3-METHYL DERIVATIVES OF IMIDAZO[2,1-*b*]THIAZOLES AND THEIR BENZO ANALOGS IN THE REACTIONS OF 2-MERCAPTOIMIDAZOLE AND 2-MERCAPTOBENZIMIDAZOLE WITH 1,3-DICHLOROACETONE UNDER PHASE-TRANSFER CATALYSIS CONDITIONS

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The mechanism of the unexpected formation of 3-methyl derivatives of imidazo[2,1-b]thiazoles in the system 2-mercaptoimidazole–1,3-dichloroacetone–solid K_2CO_3–solid KI–18-crown-6–toluene has been studied. The structure of 3-methyl[1,3]thiazolo[3,2-a]benzimidazole has been confirmed using X-ray structural analysis.

Keywords: 3-methyl derivatives of imidazo[2,1-*b*]thiazoles, phase-transfer catalysis, X-ray structural analysis.

Imidazo[2,1-*b*]thiazoles have a broad spectrum of biological activity [1]. The main method for synthesizing 3-methyl-substituted imidazo[2,1-*b*]thiazoles and 3-methyl[1,3]thiazolo[3,2-*a*]benzimidazoles is based on the reaction of 2-mercaptoimidazoles with chloroacetone in ethanol [2] or alkaline ethanol [3]. 3-Methylbenzo[4,5]imidazo[2,1-*b*]thiazoles have also been obtained through the reaction of 2-mercaptobenzimidazoles with acetone in the presence of I_2 [4] or H_2SO_4–AcOH [5]. In addition, 3-methyl[1,3]thiazolo-[3,2-*a*]benzimidazole is prepared *via* cyclization of 2-propargylthiobenzimidazole in the system $Hg(OAc)_2$–H_2SO_4–acetic acid [6] or from 2-(2-bromo-2-propenylthio)benzimidazole under phase-transfer catalytic conditions in the system KOH–benzyltriethylammonium chloride–DMSO [7]. There is also evidence in the literature for the deiodination of 3-iodomethyl-2,3-dihydro[1,3]thiazolo[3,2-*a*]benzimidazole to 3-methyl[1,3]-thiazolo[3,2-*a*]benzimidazole in alkaline medium [8].

In the reactions of the thiols **1-4** with 1,3-dichloroacetone in the system solid K_2CO_3–solid KI–18-crown-6–toluene the single reaction products in place of the expected chloromethyl derivatives are the methyl heterocycles **5-8** which are low melting, crystalline materials (see Experimental).

We have carried out several experiments to determine the mechanism of formation of compounds **5-8**. In the first we have shown that refluxing 1,3-dichloroacetone with excess solid KI and solid K_2CO_3 forms 1,3-diiodoacetone. The reaction of transfer of halogens from one molecule of 1,3-dihaloacetone to another

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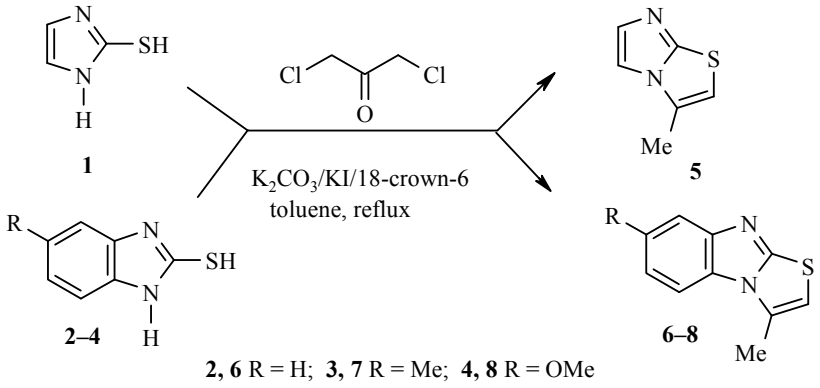
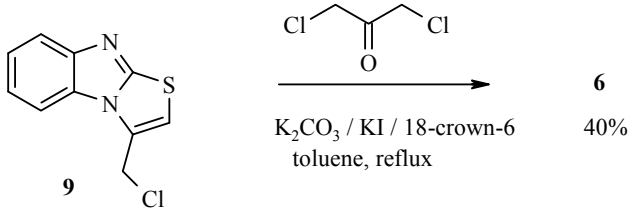
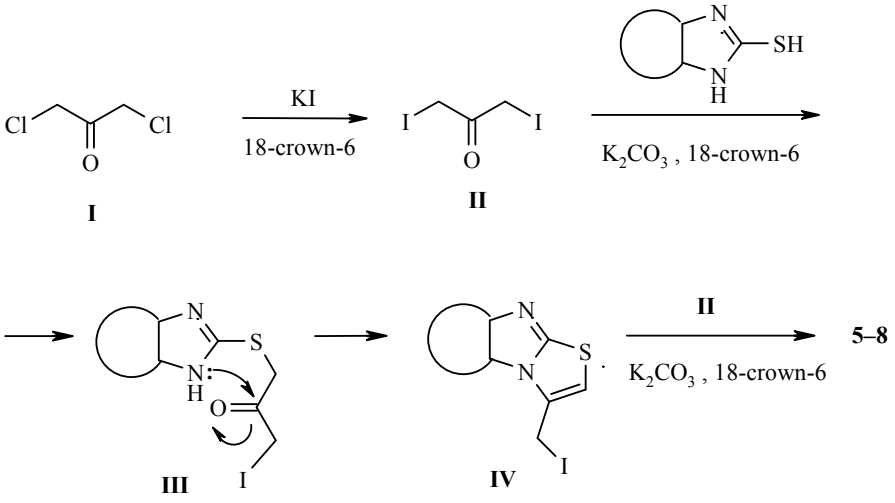
(i.e. formation of polyhalo acetones, a so called "halogen dance") virtually does not occur. Instead we propose that the first stage of the reaction occurs by the usual mechanism to give the iodomethyl intermediate **IV** *via* the S-alkyl derivative **III** [9].



However, as we had no enough proof of the mechanism of formation of the methyl derivatives **5-8**, we have synthesized the 3-chloromethyl[1,3]thiazolo[3,2-*a*]benzimidazole (**9**) by a known method [10]. With the aim of identifying the dechlorination products we have carried out the reaction of compound **9** in the system 1,3-dichloroacetone (1 equivalent)–solid K_2CO_3 (4 equivalents)–solid KI (4 equivalents)–18-crown-6 (10 mol %)–toluene at 110ºC.



In fact, after refluxing the reaction mixture for 24 h, chromatomass-spectrometric data for the reaction mixture showed the presence of 3-methyl[1,3]thiazolo[3,2-*a*]benzimidazole (**6**) (40%) hence we propose that deiodination of the iodomethyl derivative **IV** occurs at the final stage of the reaction.



With the aim of unambiguously determining the structure of compound **6** an X-ray analysis of its crystals was undertaken. The molecule of the compound is planar within accuracy limits. The bond lengths of S–C(2) and S–C(5) are 1.746(3) and 1.732(3) Å. The bond lengths of the double bonds C(2)=C(3) and C(5)=N(6) are 1.336(4) and 1.307(3) Å. Overall, the geometric parameters of the molecule are close to the parameters for the other three thiazolobenzimidazoles for which a structure has been established [11, 12]. In the crystal structure the molecule is packed at distances no less than the sum of the van der Waal radii of the contacting atoms.

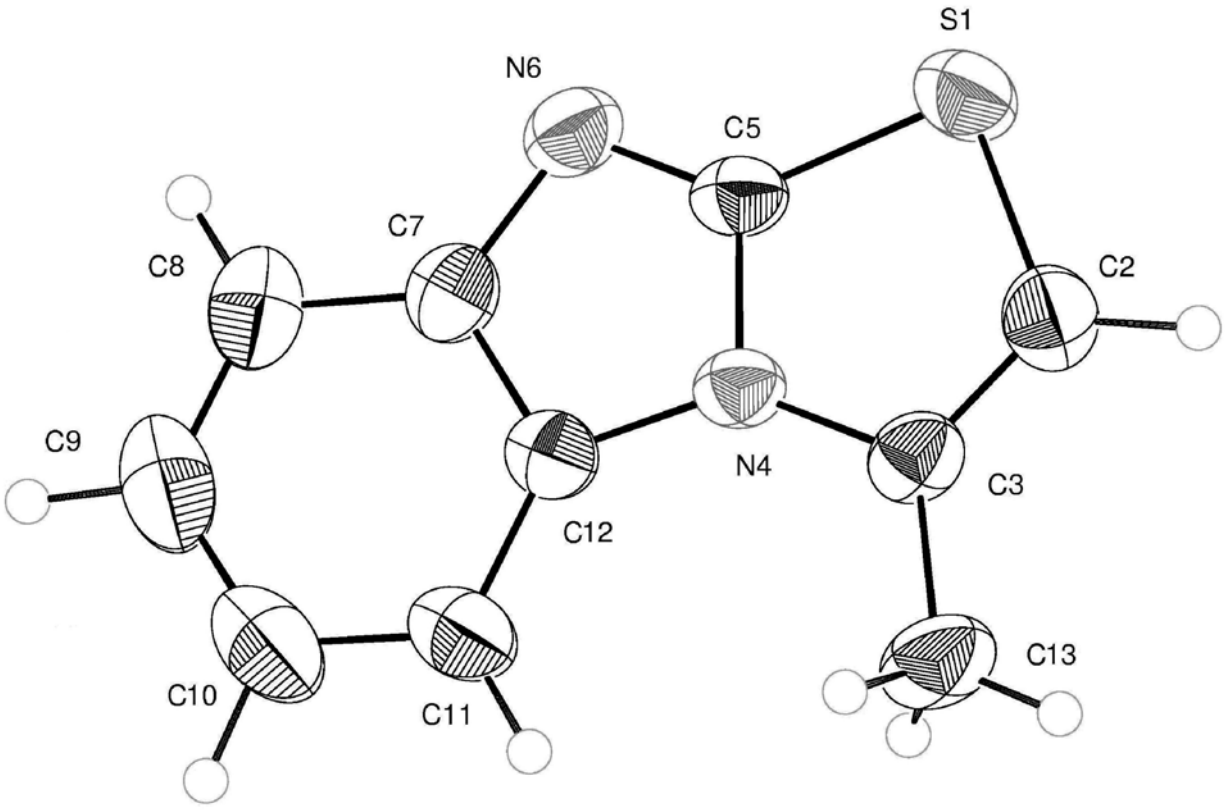


Fig. 1. Molecule of 3-methyl[1,3]thiazolo[3,2-*a*]benzimidazole (**6**) with atomic numbering and thermal vibration ellipsoids.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Varian 200 Mercury spectrometer (200 MHz) using $CDCl_3$ with HMDS (δ 0.05 ppm) as internal standard and mass spectra on an HP GC-MS 6890 chromato-mass spectrometer with ionization energy 70 eV.

2-Mercaptoimidazole (**1**), 2-mercaptobenzimidazoles **2-4**, 1,3-dichloroacetone (96%), and 18-crown-6 (all from Alfa Aesar) were used without additional purification.

Synthesis of 3-Methylimidazo[2,1-*b*]thiazole (5) [13]. 1,3-Dichloroacetone (0.63 g, 5 mmol) was added to a suspension of 2-mercaptoimidazole **1** (0.5 g, 5 mmol), finely divided solid K_2CO_3 (2.76 g, 20 mmol) and solid KI (3.34 g, 20 mmol), and 18-crown-6 (0.13 g, 0.5 mmol) in toluene (30 ml). The reaction mixture was refluxed for 12 h, filtered, and the solvent was evaporated under reduced pressure. The product was

separated by column chromatography on silica gel using a mixture of hexane and ethyl acetate (1:1) as eluent. Yield of product **5** 0.08 g (12%). ^{1}H NMR spectrum, δ, ppm: 2.39 (3H, s, CH_3); 6.42 (1H, s, H-2); 7.08 and 7.34 (2H, two s, imidazole protons). Mass spectrum, *m/z* (I_{rel}, %): 138 $[M]^+$ (100), 93 (17), 71 (12).

3-Methyl[1,3]thiazolo[3,2-*a*]benzimidazole (6) was prepared similarly to compound **5**. Reaction time 12 h, yield 19%. ^{1}H NMR spectrum, δ, ppm: 3.34 (3H, s, CH_3); 6.86 (1H, s, H-2); 7.21-7.38, 7.66-7.70, and 7.95-7.99 (4H, all m, Ar). Mass spectrum, *m/z* (I_{rel}, %): 188 $[M]^+$ (100), 143 (23), 102 (16), 75(7). Found, %: C 63.26; H 4.17; N 14.61. $C_{10}H_8N_2S$. Calculated, %: C 63.80; H 4.28; N 14.88.

TABLE 1. Crystallographic Parameters for Compound **6** and Parameters for the Refinement of the Crystallographic Structure

Parameter	
Empirical formula	$C_{10}H_8N_2S$
Molecular weight	188.252
Crystal form	Prism
Crystal size, mm	0.12 × 0.17 × 0.28
Crystal system	Monoclinic
Unit cell parameters:	
a, Å	7.0531(2)
b, Å	12.9645(4)
c, Å	9.9273(4)
β, deg	100.753(1)
Unit cell volume, *V*, Å^3	891.81(5)
Space group	$P2_1/n$
Number of molecules in the cell, *Z*	4
F(000)	392
Compound density, ρ_{calc}, g/cm^3	1.402
Maximum angle, $2\theta_{max}$, deg.	55.0
Miller index intervals	$-9 \le h \le 9$ $-16 \le k \le 15$ $-12 \le l \le 12$
Absorption coefficient, μ, mm^{-1}	0.31
Number of reflections	
overall	3806
independent	2124 (R_{int} = 0.026)
with $I > 3\sigma(I)$	1631
R-Factor	0.046
R-Index for all reflections (R_1, wR_2)	0.063, 0.238
Number of refinement parameters	118
GOOF	0.970
$\Delta\rho_{max}$	0.44

3,7-Dimethyl[1,3]thiazolo[3,2-*a*]benzimidazole Monohydrate (7) was prepared similarly to compound **5**. Reaction time 25 h, yield 1%. ^{1}H NMR spectrum, δ, ppm: 2.50 and 2.71 (6H, two s, CH_3); 6.30 (1H, s, H-2); 7.03-7.19 and 7.63-7.67 (2H, two m, H-5,6); 7.57 (1H, s, H-8). Mass spectrum, *m/z* (I_{rel}, %): 202 $[M]^+$ (100), 157 (7), 89 (8). Found, %: C 60.19; H 5.46; N 11.96. $C_{11}H_{12}N_2OS$. Calculated, %: C 59.97; H 5.49; N 12.72.

7-Methoxy-3-methyl- [1,3]thiazolo[3,2-a]benzimidazole Monohydrate (8) was prepared similarly to compound **5**. Reaction time 11 h, yield 8%. ^{1}H NMR spectrum, δ, ppm: 2.69 and 3.88 (6H, two s, CH_3); 6.31 (1H, s, H-2); 6.84-6.89 and 7.62-7.67 (2H, two m, H-5,6); 7.25 (1H, s, H-8). Mass spectrum, *m/z* (I_{rel}, %): 218 $[M]^+$ (100), 203 (39), 175 (71), 109 (7). Found, %: C 55.30; H 5.21; N 12.11. $C_{11}H_{12}N_2O_2S$. Calculated, %: C 55.91; H 5.12; N 11.86.

X-ray Structural Analysis of Compound 6. The diffraction picture for compound **6** was obtained on a Bruker-Nonius KappaCCD automatic X-ray diffractometer. Solution of the crystal structure was carried out by the direct method and refined in full-matrix least-squares analysis for all of the non-hydrogen atoms using the *maXus* [14] program package. The positions of the hydrogen atoms were localized using electron density Fourier difference synthesis and refined in the isotropic approximation involving the "riding" model. Crystallographic parameters for compound **6** and the structural refinement parameters are given in Table 1.

Data for the geometric structure of compound **6** has been placed in the Cambridge Structural Database (reference CCDC 721277).

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