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A NEW METHOD FOR THE SYNTHESIS OF 5-BROMO(ARYL)METHYLENE-SUBSTITUTED HYDANTOINS*

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It has been shown that bromination of 5-aryl-5-benzylidene-3,5-dihydro-4H-2-methylthioimidazol-4-one in methylene chloride at room temperature leads to the addition of bromine at the double bond, but the the reaction of 5-aryl-3,5-dihydro-4H-2-methylthio-5-(2-pyridylmethylene)imidazol-4-one gave complex compound of the starting materials. After boiling both of the compounds obtained in ethanol the corresponding 5-[bromo(aryl)methylene]imidazolidine-2,4-diones were obtained.

Keywords: 5-aryl-3,5-dihydro-4H-2-methylthioimidazol-4-ones, hydantoins, imidazoline-2,4-diones, bromination, addition-elimination.

In recent years hydantoins (4-oxoimidazolidin-2-ones) and 2-thiohydantoins (4-oxoimidazolidine-2-thiones) have been actively investigated in connection with the wide spectrum of their biological activity. Apart from this hydantoins and thiohydantoins are precursors in the synthesis of a wide range of organic compounds, for example, amino acids [1-5].

We have shown previously that 3-methyl-5-benzylidenethiohydantoin reacts with bromine in acetic acid, adding Br_2 at the C=C double bond, with further substitution of one of the bromine atoms by an ethoxy group on reaction with ethanol [6, 7].

In this work the possibility of obtaining 5-bromo(aryl)methylene-substituted hydantoins by the bromination of 2-aryl- and hetarylmethylene-substituted 2-thiohydantoins has been demonstrated. The 5-aryl-3,5-dihydro-4H-2-methylthioimidazol-4-ones were obtained by a previously described method [8]. Bromination of S-alkylated derivatives of 2-thiohydantoin were carried out by slow addition of a solution of 1.1 equiv of bromine in CH_2Cl_2 to a solution of compound **1** or **2** in the same solvent. From the bromination of 2-methylthio-5-(phenylmethylene)-3-phenyl-3,5-dihydro-4H-imidazol-4-one we isolated the product of the addition of bromine to the double bond of the 2-thiohydantoin **3**, which degraded on standing. In the case of the S-alkylated derivative of 2-thiohydantoin containing a pyridomethylene substituent at position 5, a complex of 2-methylthio-5-(2-pyridylmethylene)-3.5-dihydro-4H-imidazol-4-one with bromine **4** was formed. In the ^{1}H NMR spectrum signals of aromatic systems of this compound are shifted to the weak-field region. Boiling both compounds **3** and **4** in ethanol gave compounds **5** and **6**, containing a bromoarylmethylene unit.

* Dedicated to Academician B. A. Trofimov on his 70th jubilee.

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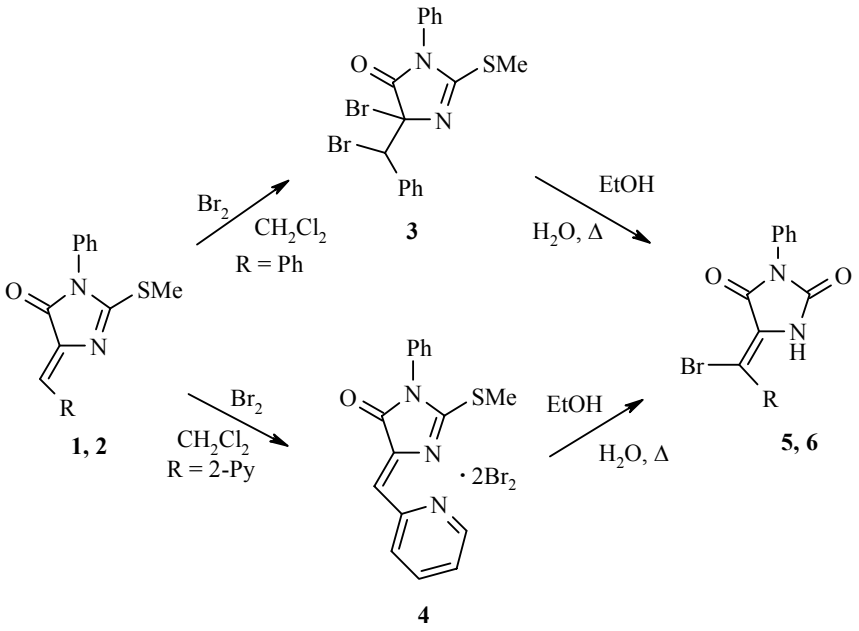
Compounds **5** and **6** are hydantoins, i.e., hydrolysis of the methylthio group occurs in the course of the reaction. A similar substitution of an SMe group by an oxygen atom has been described previously in the literature [9], but it usually takes place under more vigorous conditions.



1, 5 R = Ph, **2, 6** R = 2-Py

So we have developed a suitable method for the preparation of 5-[bromo(aryl)methylene]imidazoline-2,4-diones starting from the available 5-arylmethylene-3,5-dihydro-4H-2-methylthioimidazol-4-ones. The reaction occurs by addition-elimination, accompanied by hydrolysis of the methylthio groups. Note that this hydrolysis does not require the use of an acid catalyst as described in the literature examples [9], which gives this reaction promise for the transformation of substrates which are sensitive to the presence of acids.

EXPERIMENTAL

^{1}H NMR spectra were recorded on a Bruker AVANCE instrument (400 MHz) with HMDS as internal standard. Elemental analyses of the compounds synthesized were carried out on a Carlos-Erba CHN analyzer.

5-Bromo-5-[(bromo)benzyl]-2-methylthio-3-phenyl-3,5-dihydro-4H-imidazol-4-one (3). A solution of bromine (0.06 g, 0.37 mmol) in CH_2Cl_2 (10 ml) was added with stirring at room temperature to a solution of 2-methylthio-5-phenylmethylene-3-phenyl-3,5-dihydro-4H-imidazol-4-one (**1**) in methylene chloride (10 ml), stirring was continued for 2 h, monitored by TLC. Compound **3** (0.12 g, 83%) was obtained as a yellow oil which crystallized on standing in the air after evaporation of the solvent in vacuum. Mp 172°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 7.45 (10H, m, C_6H_5), 5.94 (1H, s, CHBr), 2.89 (3H, s, SCH_3). Found, %: C 45.01; H 3.23; N 6.07. $C_{17}H_{14}Br_2N_2OS$. Calculated, %: C 44.90; H 3.08; N 6.16.

Complex of 2-Methylthio-5-(2-pyridyl)methylene-3-phenyl-3,5-dihydro-4H-imidazol-4-one (2) and Bromine (4). The reaction was carried out as for the preparation of compound **3**. Complex compound **4** was obtained as a yellow powder from compound **2** (0.2 g, 0.68 mmol) and bromine (0.13 g, 0.75 mmol); mp 144°C (decomp.) ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 9.03 (1H, dd, $J_{6,4}$ = 1, $J_{6,5}$ = 5, H-6 Py); 8.84 (1H, dd,

$J_{3,5}$ = 1, $J_{3,4}$ = 8, H-3, Py); 8.23 (1H, ddd, $J_{4,6}$ = 1, $J_{4,3}$ = 8, $J_{4,5}$ = 8, H-4 Py); 7.68 (1H, ddd, $J_{5,3}$ = 1, $J_{5,6}$ = 5, $J_{5,4}$ = 8, H-5 Py); 7.14 (5H, m, C_6H_5); 6.95 (1H, s, CH=); 2.56 (3H, s, SCH_3). Found, % C 31.33; H 2.41; N 7.06. $C_{16}H_{13}Br_4N_3OS$. Calculated, %: C 31.22; H 2.11; N 6.82.

5-[Bromo(phenyl)methylene]-3-phenylimidazolidine-2,4-dione (5). Ethanol (5 ml) was added to compound **3** (0.1 g, 0.22 mmol). The mixture was boiled for 1-2 min, a light-yellow precipitate which formed on cooling was filtered and dried in air. Yield 0.06 g (80%) of compound **5**. Mp 211-213°C. ^{1}HNMR spectrum ($CDCl_3$), δ, ppm: 10.21 (1H, s, NH); 6.98 (10H, m, C_6H_5). Found, %: C 56.10; H 3.21; N 8.24. $C_{16}H_{11}BrN_2O_2$. Calculated, %: C 55.98; H 3.21; N 8.16.

5-[bromo(2-pyridyl)methylene]-3-phenylimidazolidine-2,4-dione (6) was made analogously to compound **5** from compound **4** (0.1 g, 0.16 mmol) with a yield of 0.05 g (89%); mp 192-195°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 11.78 (1H, s, NH); 8.66 (1H, dd, $J_{6,5}$ = 4.9, $J_{6,3}$ = 1, H-6 Py); 8.25 (1H, dd, $J_{3,4}$ = 8, $J_{3,5}$ = 1, H-3 Py); 7.93 (1H, ddd, $J_{4,6}$ = 1, $J_{4,5}$ = 7.7, $J_{4,3}$ = 8, H-4 Py); 7.42 (6H, m, C_6H_6+Py). Found, %: C 52.20; H 3.09; N 11.99. $C_{15}H_{10}BrN_3O_2$. Calculated, %: C 52.33; H 2.91; N 12.21.

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