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About the Direction of Selective Alkylation and Cyanoethylation of Benzimidazoles, Benzothiazoles and Benzopyrimidines

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Abstract: Selective alkylation and cyanoethylation of 2H(methyl) benzimidazoles (**1, 2**), benzimidazolin-2-one (**3**) and -2-thione (**4**), benzothiazolin-2-thione (**5**) and 2-methyl-benzopyrimidin-4-one (**6**, 2-methylquinazolin-4-one) have been studied. It was found that in the case of alkylation of 2H(methyl)benzimidazoles and benzimidazolin-2-thione by aliphatic halogen carboxylic acid esters and / or amides reaction leads to the formation of selectively N3- and S-alkyl derivatives. Interaction of benzothiazolin-2-thione and 2-methyl-benzopyrimidin-4-one with acrylonitrile takes place mono-cyanoethylation, but in the case of benzimidazolin-2-one takes place di-cyanoethylation reaction. It was revealed that formation of mono- and / or di-substituted products **7-13** dependence on the structure of starting compounds and the reaction conditions (reaction temperature and time, ratio of reagents). It should be noted that the obtained compounds are important synthons for further investigations. The structure of synthesized compounds (**7-13**) was confirmed by IR- and ^{1}H NMR-spectroscopy.

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INTRODUCTION

Benzimidazoles [Radha et al., 2011; Li et al., 1992; Tunçbilek et al., 1997; Mariappan et al., 2015; Padalkar et al., 2012], benzothiazolines [Ali and Siddiqui, 2013; Sun et al., 2013; Wang et al. 2011; Saeed et al., 2010; Caputo et al., 2012] and benzopyrimidines [Shakhidoyatov and Elmuradov, 2014; Rohokale and Kshirsagar, 2016; Kiruthiga et al., 2009; Appani et al., 2016; Chang et al., 2016; Lu et al., 2015; El-Hashash et al., 2015; Bowman et al., 2007] are very interesting objects with plural reactivity and different biological activity in the field of agriculture [Zakirova et al., 2016] and medicine. There are in the molecule of them an ambifunctional fragments with secondary N1, N3 and S atoms. It gives possibility to carry out the electrophilic and nucleophilic substitution and / or addition, for example alkylation, acetylation, arylsulfonation, cyanoalkylation and etc. In this case usually are take part or N1, N3 atoms either more polarized C=S bonds. It gives possibility to synthesis of many novel N- or S-isomeric derivatives.

Together with it among of the imidazole, thiazoline and pyrimidine skeleton heterocycles, which are condensed with benzene ring there are effective drugs for veterinary (albendazole) and medicine (dibazole) [Mashkovskii, 2004], and preparations with antifungal and herbicidal [*Fungicides*, Ed. Melnikov, 1980], antimicrobial [Tunçbilek et al., 1997; Padalkar et al., 2012; Saeed et al., 2010; Appani et al., 2016], antibacterial [Radha et al., 2011; Mariappan et al., 2015; Ali and Siddiqui, 2013; Rohokale and Kshirsagar, 2016], cytotoxic [Ali and Siddiqui, 2013; Saeed et al., 2010; Caputo et al., 2012; Wang et al. 2011], radiosensitive [Li et al., 1992], antituberculosis [Lu et al., 2015], and antibiotic [Chang et al., 2016] properties and etc.

MATERIALS AND METHODS

^{1}H NMR spectra was recorded in CD_3COCD_3, CD_3OD and CD_3OD+$CDCl_3$, on Unity 400$^+$ and Varian 400-MR spectrometer operating accordingly at 400 MHz. Hexamethyldisiloxcane (HMDSO) was used as internal standard, chemical shift δ of ^{1}H was recorded in ppm.

Mps were measured on a Boetius and MEL-TEMP apparatus manufactured by Barnstead International (USA) and were uncorrected. IR spectra were recorded on IR Fury System 2000 (Perkin-Elmer) as KBr pellets.

The reactionary process was monitored by TLC on Whatman UV-254 precoated aluminum plates using C_6H_6/CH_3COCH_3 (1:1, 10:1), C_6H_6/CH_3OH (2:1, 10:1), $CHCl_3$/CH_3OH (8:1 and 10:1) solvent systems and developed plates were visualized under UV lamp and/or iodine tank where necessary. Solvents were purified by standard procedures. Organic solutions were dried over

anhydrous Na_2SO_4 and concentrated with a RVO-64 ROT VAC Evaporator at reduced pressure.

Synthesis of (N,N-dibutylaminoacetyl)-benzimidazole (7).

In 10 ml DMF was dissolved 1.16 g (0.01 mol) benzimidazole (**1**), 2.055 ml (0.01 mol) N,N-dibutylchloroacetamide and 1.38 g (0.01 mol) K_2CO_3. The reaction mixture was heated on a water bath at 80-90^{0}C for 24 hours. After completion of the reaction (monitoring by TLC) and cooling to the reaction mixture was added 50 ml of water and the precipitated crystals were filtered, washed with water and dried. After recrystallization from acetone the reaction product **7** has been obtained in good yield.

Yield: 1.79 g (63 %), mp 110-112^{0}C, R_f=0.8 (C_6H_6/CH_3COCH_3 (1:1)). H^1 NMR (CD_3COCD_3): 7.96 (1H, s, H-2), 7.57 (1H, dd, *J*=2.0, *J*=6.4, H-4), 7.33 (1H, dd, *J*=1.8, *J*=6.3, H-7), 7.14 (1H, td, *J*=1.6, *J*=7.2, H-5), 7.11 (1H, td, *J*=1.6, *J*=7.2, H-6), 5.21 (2H, s, O=C-$\underline{CH_2}$), 3.42 (2H, t, *J*=6.8, N-$\underline{CH_2}$), 3.28 (2H, t, *J*=7.5, N-$\underline{CH_2}$), 1.60-1.67 (2H, m, N-$(CH_2)_2\underline{CH_2}$-CH_3), 1.32-1.48 (4H, m, C_2H_5-$\underline{CH_2}$-CH_2-N-CH_2-$\underline{CH_2}$-C_2H_5), 1.15-1.24 (2H, m, N-$(CH_2)_2\underline{CH_2}$-CH_3), 0.922 (3H, t, *J*=7.3, CH_3), 0.81 (3H, t, *J*=7.3, CH_3). IR (KBr) cm^{-1}: 2956, 2931 (ν_{CH2}), 1637 ($\nu_{C=O}$), 1475 ($\nu_{C=N}$).

(N,N-Dibutylaminoacetyl)-2-methylbenzimidazole (8).

The mixture of 1.32 g (0.01 mol) 2-methylbenzimidazole (**2**), 2.055 ml (0.01 mol) N,N-dibutylchloroacetamide and 1.38 g (0.01 mol) of K_2CO_3 was refluxed in 10 ml of DMF at 80-90^{0}C for 24 h. To the mixture 60 ml of chloroform was added and washed with water, solvent was distilled off the precipitated crystals were filtered, washed with water and dried. The obtained compound was recrystallized from water.

Yield: 2.4 g (80 %), mp 99-100^{0}C, R_f=0.8 ($CHCl_3/CH_3OH$ (8:1)). H^1 NMR (CD_3COCD_3): 7.45 (1H, dd, *J*=2.3, *J*=5.8, H-4), 7.21 (1H, dd, *J*=2.3, *J*=5.9, H-7), 7.04 (2H, td, *J*=2.4, *J*=5.8, H-5,6), 5.1 (2H, s, O=C-$\underline{CH_2}$), 3.44 (2H, t, *J*=6.8, N-$\underline{CH_2}$), 3.28 (2H, t, *J*=7.6, N-$\underline{CH_2}$), 2.37 (3H, s, 2-CH_3), 1.64-1.71 (2H, m, N-$(CH_2)_2\underline{CH_2}$-CH_3), 1.32-1.48 (4H, m, C_2H_5- $\underline{CH_2}$-CH_2-N-CH_2-$\underline{CH_2}$-C_2H_5), 1.15-1.25 (2H, m, N-$(CH_2)_2\underline{CH_2}$-CH_3), 0.93 (3H, t, *J*=7.3, CH_3), 0.81 (3H, t, *J*=7.3, CH_3). IR (KBr) cm^{-1}: 2957, 2929 (ν_{CH2}), 1638 ($\nu_{C=O}$), 1464 ($\nu_{C=N}$).

(N^1,N^3-Dicyanoethyl)-benzimidazolin-2-one (9).

The mixture of 0.67 g (5 mmol) benzimidazolin-2-one (**3**), 1.66 ml (1.325 g, d=0.797 g/ml, 25 mmol) acrylonitrile and 0.032 g (0.8 mmol) of NaOH in 40 ml ethanol was refluxed at 80-85^{0}C in water bath for 8 h. The obtained precipitates was filtered off, and treated with 4 % NaOH, washed with water and dried. The synthesized compound (**9**) was recrystallized from ethanol.

Yield: 0.29 g (43 %), mp 166-168^{0}C, R_f=0.5 (C_6H_6/CH_3COCH_3 (10:1)). H^1 NMR (CD_3OD+$CDCl_3$): 7.29 (2H, td, *J*=3.1, *J*=5.8, H-4,7), 7.18 (2H, dt, *J*=3.2, *J*=5.8, H-5,6), 4.24 (4H, t, *J*=6.6, N-$\underline{CH_2}$), 2.95 (4H, t, *J*=6.6, N-$\underline{CH_2}$).

2-Ethoxycarbonyl-methylthio-benzimidazole (10).

The mixture of 0.75 g (5 mmol) benzimidazolin-2-thone (**4**), 0.53 ml (0.61 g, d=1.15 g/ml, 5 mmol) of chloroacetic acid ethyl ester and 1.5 ml of triethylamine (1.01 g, d=0.72 g/ml, 5 mmol) in 50 ml acetone was refluxed in water bath for 16 h. After cooling the formed precipitates was filtered off, washed with water and dried. The obtained compound (**10**) was recrystallized from benzene.

Yield: 1.0 g (84.7 %), mp 96^{0}C, R_f=0.5 ($CHCl_3/CH_3OH$ (10:1)). H^1 NMR (CD_3OD): 7.44 (2H, dd, *J*=3.2, *J*=6.0, H-4,7), 7.16 (2H, tt, *J*=3.2, *J*=6.0, H-5,6), 4.13 (2H, q, *J*=2.0, *J*=7.1, $CO_2\underline{CH_2}$), 4.08 (2H, s, S-$\underline{CH_2}$), 1.16 (3H, t, *J*=7.1, CH_3).

2-Methoxycarbonyl-ethylthio-benzimidazole (11).

The mixture of 0.75 g (5 mmol) benzimidazolin-2-thione (**4**), 0.56 ml (0.83 g, d=1.48 g/ml, 5 mmol) of bromopropionic acid methyl ester and 1.0 g (7 mmol) of K_2CO_3 in 30 ml acetone was refluxed in water bath for 24 h. After cooling the formed precipitates was filtered off, washed with water and dried. The obtained compound (**11**) was recrystallized from acetone.

Yield: 0.29 g (40 %), mp 82-84^{0}C, R_f=0.8 (C_6H_6/CH_3OH (10:1)). H^1 NMR (CD_3OD): 7.42 (1H, dd, *J*=3.2, *J*=6.0, H-4), 7.27 (1H, dd, *J*=3.2, *J*=6.0, H-7), 7.18 (2H, tt, *J*=3.3, *J*=7.2, H-5,6), 4.58 (2H, t, *J*=7.0, S-$\underline{CH_2}$), 3.61 (3H, s, OCH_3), 2.87 (2H, t, *J*=7.0, $\underline{CH_2}CO_2CH_3$).

2-Cyanoethylthiobenzothiazole (12).

The mixture of 16.7 g (0.1 mol) benzothiazolin-2-thione (**5**), 12.3 ml (9.8 g, d=0.797 g/ml, 0.185 mol) of acrylonitrile, 1.0 g (0.025 mol) of K_2CO_3 in 100 ml ethanol was refluxed in water bath for 8 h and left for the night. The formed precipitate was treated with 2 % NaOH and was filtered off, washed with water and dried. The synthesized compound (**12**) was recrystallized from ethanol.

Yield: 12.86 g (77 %), mp 175-176^{0}C, R_f=0.8 (C_6H_6/CH_3OH (2:1)). H^1 NMR (CD_3OD+$CDCl_3$): 7.6 (2H, dd, *J*=0.7, *J*=7.9, H-4,7), 7.5 (1H, td, *J*=1.2, *J*=7.4, H-5), 7.37 (1H, td, *J*=1.1, *J*=7.8, H-6), 4.78 (2H, t, *J*=6.8, S-$\underline{CH_2}$), 3.08 (2H, t, *J*=6.8, $\underline{CH_2}$-CN).

2-Methyl-3-cyanoethyl-quinazolin-4-one (13).

The mixture of 0.5 g (3 mmol) 2-methyl-quinazolin-4-one (**6**), 0.4 ml (0.32 g, d=0.797 g/ml, 6 mmol) of acrylonitrile, 10 mg (0.25 mmol) NaOH in 30 ml ethanol was refluxed in water bath for 5-6 h and left for the night. The formed precipitate was treated with 2 % NaOH and was filtered off, washed with water and dried. The obtained product (**13**) was recrystallized from ethanol.

Yield: 0.2 g (40 %), mp 152-154^{0}C, R_f=0.4 (C_6H_6/CH_3OH (10:1)). H^1 NMR (CD_3OD): 8.19 (1H, dd, *J*=1.0, *J*=8.0, H-5), 7.8 (1H, td, *J*=1.5, *J*=7.2, H-7), 7.6 (1H, d, *J*=8.2, H-8), 7.5 (1H, td, *J*=1.1, *J*=8.1, H-6), 4.43 (2H, t, *J*=6.8, N-$\underline{CH_2}$), 3.02 (2H, t, *J*=6.8, $\underline{CH_2}$-CN), 2.74 (3H, s, CH_3).

RESULTS AND DISCUSSION

Bicyclic benzimidazoles (**1-4**), benzothiazole (**5**) and quinazolin-4-one (**6**) are objects of research (Fig.1):

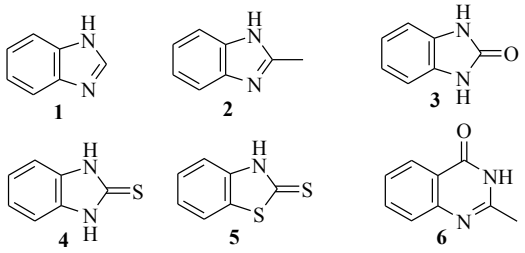


Fig.1

These compounds which containing the ambifunctional fragments (**a-f**) are very reactive. Fragments **a-f** in the reaction conditions can be simultaneously in other mesomeric forms **a'-f'** (Fig.2):

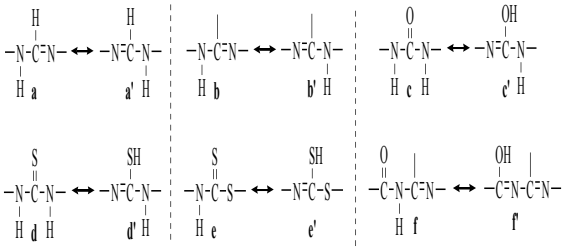
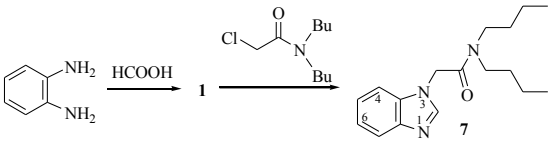


Fig.2

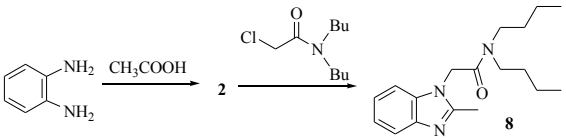
Therefore, we were interested to study alkylation and cyanoethylation, which may lead to the formation of new N-mono-, N, N-di- and S-mono substituted derivatives. The formation of a particular isomer is dependent on the structure of the initial reagents, reaction conditions (temperature, reaction time) and the ratio of reactants.

We synthesized benzimidazole (**1**) by cyclization of o-phenylenediamine and formic acid. This compound **1** can react into alkylation with N,N-dibutylchloroacetamide in the presence of K_2CO_3. Wherein is formed corresponding N^3-monoalkyl derivative (**7**) (scheme 1):



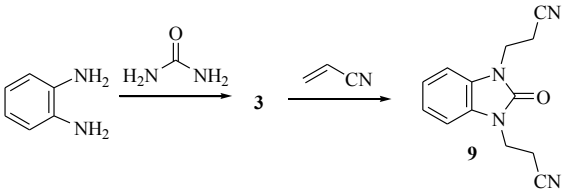
Scheme 1

We studied alkylation of 2-methylbenzimidazole (**2**) and obtained the same result; i.e is also formed the N^3-monoalkyl derivative (**8**). It should be emphasized that starting compound **2** produced by interaction o-phenylene diamine and acetic acid in good yield (scheme 2):



Scheme 2

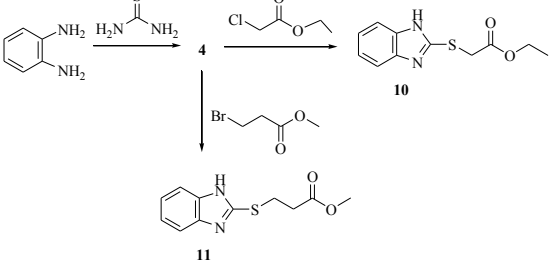
Cyclization of o-phenylene diamine and urea leads to the formation of benzimidazolin-2-one (**3**), which in molecule consists two secondary endocyclic N^1,N^3-atoms in positions 1 and 3. It was studied electrophilic addition of acrylonitrile to the compound **3** in the presence of NaOH. It was revealed that reaction by the excess of acrylonitrile gives only N^1,N^3-dicyanoethyl-benzimidazolin-2-one (**9**) in 43% yield (scheme 3):



Scheme 3

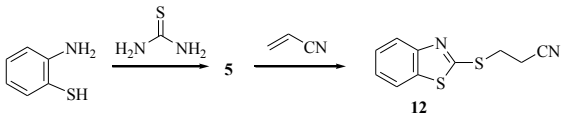
Wherein not revealed the formation of O^2-alkyl product.

Continuing our investigations we studied alkylation of benzimidazolin-2-thone (**4**) with ethyl esters of chloroacetic- and bromopropionic acids; wherein in both case are formed selectively S-alkyl derivatives (**10, 11**). Starting compound **4** have been got by cyclization of o-phenylene diamine and thiourea (scheme 4):



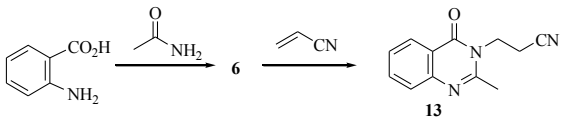
Scheme 4

Interaction of o-aminothiophenol and thiourea leads to the formation of benzothiazolin-2-thone (**5**), which under action of acrylonitrile turn into S^2-cyanoethyl benzothazoline (**12**) in 77% yield; i.e. wherein in this reaction takes part the more polarized S atom (scheme 5):



Scheme 5

In order to expand the studied reactions we studied cyanoethylation of 2-methyl-quinazolin-4-one (**6**) with acrylonitrile; wherein it was found that the corresponding N^3-cyanoethyl-2-methyl-quinazolin-4-one (**13**) is formed in 40% yield. Starting compound **6** easily formed by cyclization of anthranilic acid with acetic acid amide (scheme 6):



Scheme 6

The synthesized compounds **7-13** are new. The structure of them has been confirmed by physical research methods, such as ^{1}H NMR- and IR-spectroscopy.

CONCLUSION

It was revealed that selective alkylation and cyanoethylation of 2H(methyl)benzimidazoles, benzimidazolin-2-one and -2-thione, benzothiazolin-2-thione and 2-methyl-benzopyrimidin-4-one goes selectively on the N- and / or S-atoms. It was found that alkylation of 2H(methyl)benzimidazoles and benzimidazolin-2-thione by aliphatic halogen carboxylic acid esters and / or amides leads to the formation of only N^3- and S-alkyl derivatives. It was shown that reaction of benzothiazolin-2-thione and 2-methyl-benzopyrimidin-4-one with acrylonitrile goes by mono-cyanoethylation, but in the case of benzimidazolin-2-one takes place di-cyanoethylation. It was revealed that formation of mono- and / or di-substituted products dependence on the structure of starting compounds and the reaction conditions. It should be noted that the obtained compounds are important synthons for further investigations. Research in this area continues.

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