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CYCLOCONDENSATION OF N-PROP-2-YNYL- AND N-PENTADIYNYL-*o*-PHENYLENEDIAMINES WITH PHENYL ISOTHIOCYANATE

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Cyclocondensation of N-prop-2-ynyl-o-phenylenediamine with phenyl isothiocyanate leads to the formation of 1-(3-arylprop-2-ynyl)-2,3-dihydro-1H-benzimidazole-2-thiones. In the reactions of diacetylene derivatives – N-penta-2,4-diynyl-o-phenylenediamine - with phenyl isothiocyanate the formation of two heterocyclic nuclei occurs simultaneously to form [1,3]thiazolidino[3,2-a]benzimidazoles.

Keywords: 1-(3-arylprop-2-ynyl)-2,3-dihydro-1H-benzimidazol-2-thiones, N-penta-2,4-diynyl-*o*-phenylenediamine, phenyl isothiocyanate, N-prop-2-ynyl-*o*-phenylenediamines, [1,3]thiazolidino[3,2]benzimidazoles, cyclocondensation.

Derivatives of [1,3]thiazolo[3,2-*a*]benzimidazole are of interest as a result of their wide range of biological activity. The known methods for the synthesis of [1,3]thiazolo[3,2-*a*]benzimidazole heterocyclic system are based on the use of derivatives of benzimidazole and further conversions directed at creation of the 1,3-thiazole ring [1-6]. In the literature there are also examples of cyclization of acetylenic derivatives, namely 2-(prop-1-ynylthio)benzimidazoles, to obtain [1,3]thiazolo[3,2-*a*]benzimidazoles [5, 6].

We have observed previously that the reaction of N-penta-2,5-diynylamines with phenyl isothiocyanate led to the formation of 5-(prop-2-ynylidene)-2-phenyliminothiazolidines as a result of cyclization of the intermediately formed thiourea [7].

In the present paper results are presented of the reaction of N-prop-2-ynyl- and N-penta-2,4-diynyl-substituted *o*-phenylenediamines with phenyl isothiocyanate, the objective of which was to examine the possibility of forming two heterocyclic rings simultaneously for the synthesis of thiazolo[3,2-*a*]benzimidazole system. The synthesis of the initial acetylenic and diacetylenic derivatives of *o*-phenylenediamine was carried out according to previously developed method [8].

The reactions of 1-prop-2-ynyl-*o*-phenylenediamines **1a,b** with phenyl isothiocyanate in boiling acetonitrile led to the formation of 1-(3-arylprop-2-ynyl)benzimidazole-2-thiones **2a,b**, isolated in yields of about 50%.

The ^{1}H NMR spectra of compounds **2a,b** contain signals of an NH proton at ~ 12 ppm. In the ^{13}C NMR spectra two signals at 80-90 ppm are present characteristic of carbon atoms of an acetylenic bond. So we have observed the formation of a benzimidazole ring, but subsequent nucleophilic attack of the mercapto group on the triple bond, which might lead to the formation of a 1,3-thiazolidine ring, did not occur.

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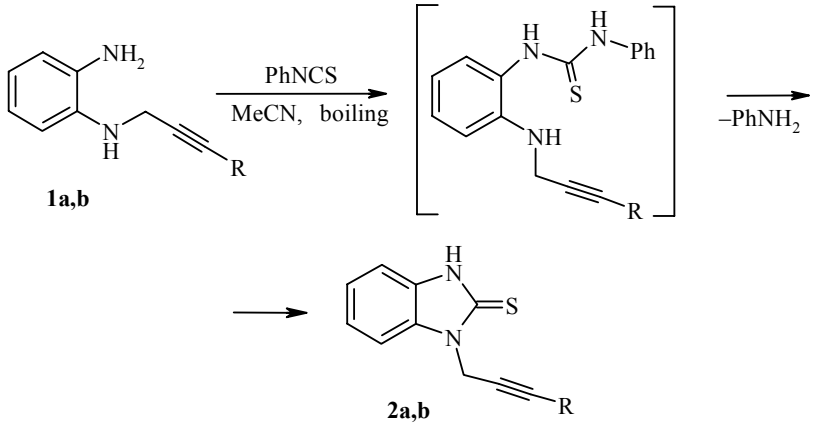
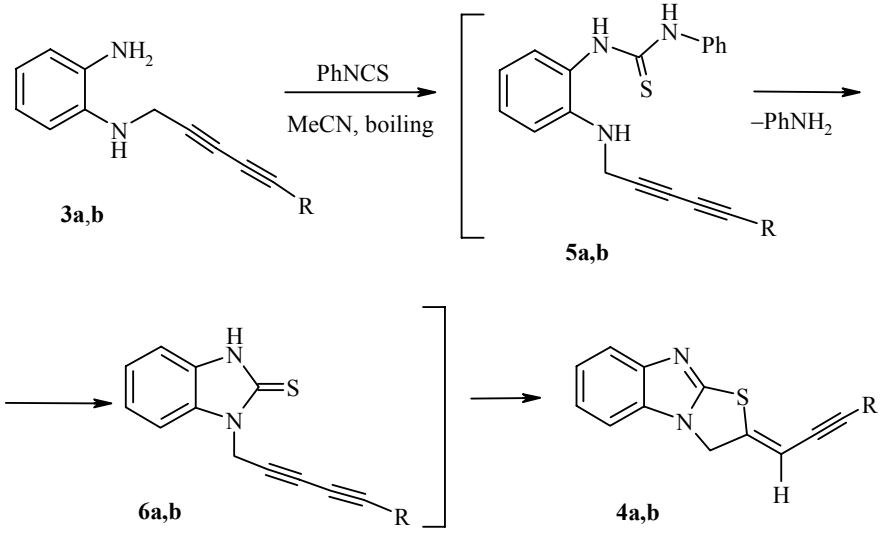


a R = Ph, 45% , **b** R = 4-BrC_6H_4, 46%

In contrast to the monoacetylenic derivatives of *o*-phenylenediamine the reactions of N-penta-2,4-diynyl-*o*-phenylenediamines **3a,b** with phenyl isothiocyanate in analogous conditions led to the formation of [1,3]thiazolidino[3,2-*a*]benzimidazoles **4a,b** in 43 and 47% yields respectively.

The intermediate compounds in the first stage of the reaction are the corresponding thioureas **5**, which was shown with the example of N-5-phenylpenta-2,4-diynyl-*o*-phenylenediamine **3b**. Its reaction with phenyl isothiocyanate at room temperature gives the thiourea **5b**, isolated in 75% yield.



a R = *n*-Bu, 43%, **b** R[1] = Ph, 47%

In the cases of the derivatives of *o*-phenylenediamine **3a,b** carrying out the reaction in boiling acetonitrile lead to cascading cyclization and fixation of the benzimidazole-2-thiones **6a,b** formed was not successful.

The ^{1}H NMR spectra of compounds **4a,b** are characterized by doublets of the protons of the methylene group at about 5 ppm and triplet of the vinyl proton in the region of 6 ppm with $^4J \sim 2$ Hz. The configuration of the *exo*-double bond was shown on the basis of the existence of NOE between the protons of the methylene group and the proton at the *exo*-double bond.

The difference in the behavior of the mono- and diacetylenic derivatives of *o*-phenylenediamine in the cyclocondensation reactions with phenyl isothiocyanate is explained by the greater reactivity of the conjugated systems of the triple bonds with respect to nucleophilic attack of the mercapto group which occur *trans*-stereospecifically. The reaction of N-penta-2,4-diynyl-*o*-phenylenediamines with phenyl isothiocyanate is the first example of the synthesis of [1,3]thiazolidino[3,2-*a*]benzimidazoles in which two heterocyclic nuclei are formed simultaneously.

EXPERIMENTAL

Elemental analyses were obtained with a Hewlett-Packard 185B. IR spectra of KBr disks (4000-400 cm^{-1}) were recorded with a Specord IR-75 instrument. ^1H and ^{13}C NMR spectra were recorded on a Bruker DRX 300 (300 and 75 MHz respectively). Chemical shifts were measured relative to the residual signals of the solvent ($^1H/^{13}C$: 7.28/77.16; 2.50/39.52 ppm respectively). Mass spectra were measured on a CPX-1321 (EI) instrument with direct injection, ionization energy 70 eV (temperature of the ionization chamber 200°C). Chem. pure solvents (Vekton) were redistilled before use. TLC analysis was carried out on Kieselgel 60 F254 (Merck) aluminum plates. The acetylene and diacetylene derivatives of *o*-phenylenediamine **1a,b** and **3a,b** starting materials were made by method [8], 1-bromo-2,4-diynes and 3-arylpropargyl bromides were prepared from the corresponding alcohols by method [9].

N-Phenyl-N'-[2-(5-phenylpenta-2,4-diynyl)aminophenyl]thiourea (5b). A solution of PhNCS (570 mg, 5 mmol) in MeCN (10 ml) was added to amine **3b** (1.23 g, 5 mmol) in acetonitrile (10 ml). The reaction mixture was stirred at room temperature until the initial amine had completely disappeared (TLC monitoring, ~3 h). At the end of the reaction the solvent was evaporated, the residue was filtered off, washed with a small amount of acetonitrile to give the thiourea **5b** (1.43 g, 75%) as light-yellow crystals; mp 178-180°C. ^1H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 4.20 (2H, d, *J* = 5.7, CH_2); 5.63 (1H, t, *J* = 5.7, NH); 6.7 (1H, t, *J* = 7.5, Ar-H); 6.81 (1H, d, *J* = 8, Ar-H); 7.08-7.6 (12H, m, Ar-H); 9.01 (1H, s, NH); 9.67 (1H, s, NH). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 32.9, 66.1, 73.7, 76.3, 83.0, 111.8, 116.9, 120.4, 123.5, 124.3, 125.2, 127.4, 128.3, 128.7, 128.8, 129.8, 132.4, 139.6, 142.9, 180.6. Found, %: C 75.40; H 5.14; N 11.08. $C_{24}H_{19}N_3S$. Calculated, %: C 75.56; H 5.02; N 11.01.

Reaction of N-Prop-2ynyl- (1a,b) and N-Pent-2,4-diynyl-*o*-phenylenediamines 3a,b with Phenyl Isothiocyanate (**General Method**). Compounds **1** or **3** (5 mmol) in acetonitrile (10 ml) were placed in a flask fitted with a reflux condenser and PhNCS (0.57 g, 5 mmol) in MeCN (10 ml) was added with stirring. The mixture was heated to boiling while stirring for 1 h until the starting amine had completely disappeared (TLC monitoring). At the end of the reaction the solvent was evaporated, the residue was filtered off, washed with a small amount of acetonitrile and recrystallized from an ethanol–hexane mixture.

1-(3-Phenylprop-2-ynyl)-1,3-dihydro-2H-benzimidazole-2-thione (2a) was obtained as white needles (590 mg, 45%); mp 166-167°C. IR spectrum, ν, cm^{-1}: 3137, 3058, 2983, 2930, 1621, 1598, 1505, 1461, 1388, 1339, 1230, 1201, 1136, 988, 756, 735, 690. ^1H NMR spectrum (DMSO-d_6–CCl_4, 1:4), δ, ppm (*J*, Hz): 5.33 (2H, s, CH_2); 7.10-7.32 (6H, m, Ar-H); 7.34-7.44 (3H, m, Ar-H); 12.82 (1H, s, NH). ^{13}C NMR spectrum (DMSO-d_6–CCl_4, 1:4), δ, ppm: 33.6, 82.8, 84.0, 109.3, 110.0, 122.0, 122.1, 122.7, 128.1, 128.3, 131.3, 131.5, 132.0, 168.5. Mass spectrum, *m/z* (I_{rel}, %): 266 $[M+2]^+$(6), 264 $[M]^+$ (100), 263 (60), 262 (12), 231 (22), 115 (86), 90 (12). Found, %: C 72.64; H 4.62; N 10.54. $C_{16}H_{12}N_2S$. Calculated, %: C 72.70; H 4.58; N 10.60.

1-[3-(4-Bromophenyl)prop-2-ynyl]1,3-dihydro-2H-benzimidazole-2-thione (2b) was obtained as colorless needles (780 mg, 46%); mp 212-213°C. IR spectrum, ν, cm^{-1}: 3139, 3061, 2983, 2920, 1621, 1505, 1460, 1427, 1339, 1229, 1193, 1136, 1072, 987, 822, 736. ^1H NMR spectrum (DMSO-d_6–CCl_4, 1:4), δ, ppm (*J*, Hz): 5.32 (2H, s, CH_2); 7.1-7.26 (3H, m, Ar-H); 7.31 (2H, d, *J* = 8.4, Ar-H); 7.34-7.40 (1H, m, Ar-H); 7.43 (2H, d, *J* =8.4, Ar-H); 12.82 (1H, s, NH). ^{13}C NMR spectrum (DMSO-d_6–CCl_4, 1:4), δ, ppm: 33.5, 82.9, 84.2, 109.2,

110.0, 121.1, 122.0, 122.4, 122.7, 126.5, 131.3, 131.9, 133.2, 168.5. Mass spectrum, *m/z* (I_{rel}, %): 346 $[M + 4]^+$ (6), ^{81}Br; 345 $[M+3]^+$ (24), ^{81}Br; 344 $[M+2]^+$ (100), ^{81}Br; 343 $[M+1]^+$ (53), ^{79}Br; 342 $[M]^*$ (98), ^{81}Br; 341 $[M-H]^+$ (98), ^{79}Br; 341 $[M]^+$(32), ^{79}Br; 263 (23); 262 (11); 195 (61); 193 (64); 131 (14); 122 (11); 114 (30); 113 (18); 103 (18); 88 (10). Found, %: C 55.97, H 3.34, N 7.95. $C_{16}H_{11}BrN_2S$. Calculated, %: C 55.99; H 3.23; N 8.16.

(*Z*)-2-Hept-2-ynylidene[1,3]thiazolidino[3,2-*a*]benzimidazole (4a) was obtained as light-yellow crystals (570 mg, 43%); mp 154-155°C. IR spectrum, ν, cm^{-1}: 3047, 3022, 2954, 2931, 2869, 2860, 2208, 1612, 1583, 1481, 1446, 1388, 1375, 1282, 790, 759, 746. ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 0.95 (3H, t, *J* = 7.1, CH_3); 1.42-1.63 (4H, m, $2CH_2$); 2.44 (2H, t, *J* = 5.1, CH_2); 5.03 (2H, t, *J* = 2.2, CH_2); 5.87 (1H, t, *J* =2.2, CH); 7.18-7.23 (3H, m, Ar-H); 7.63-7.65 (1H, m Ar-H). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 14.0, 19.8, 22.4, 49.0, 76.8, 101.0, 104.6, 109.1, 119.6, 122.6, 122.7, 133.8, 145.6, 148.5, 155.8. Mass spectrum, *m/z* (I_{rel}, %): 270 $[M+2]^+$ (5), 268 $[M]^+$ (100), 239 (14), 229 (53), 211 (14), 206 (10), 167 (14). Found, %: C 71.63, H 6.03, N 10.18. Calculated for $C_{16}H_{16}N_2S$, %: C71.61, H 6.01, N 10.44.

(*Z*)-2-(3-Phenylprop-2-ynylidene)[1,3]thiazolidino[3,2-*a*]benzimidazole (4b) was obtained as colorless crystals (670 mg, 47%); mp 219-220.5°C. IR spectrum, ν, cm^{-1}: 3049, 3008, 2920, 2850, 2191, 1608, 1583, 1479, 1436, 1388, 1377, 1334, 1309, 1282, 1249, 1203, 1147, 1068, 690, 657. ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 5.11 (2H, d, *J* = 2.2, CH_2); 6.08 (3H, t, *J* = 2.2, CH); 7.18-7.25 (3H, m, Ar-H); 7.33-7.40 (3H, m, Ar-H); 7.48-7.55 (2H, m, Ar-H); 7.65-7.72 (1H, m, Ar-H). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm : 49.3, 85.12, 99.3, 104.0, 109.1, 119.7, 122.7, 122.8, 122.9, 128.9, 131.9, 133.9, 138.3, 147.3, 155.5. Mass spectrum, *m/z* (I_{rel}, %): 290 $[M+2]^+$ (4), 288 $[M]^+$ (100), 287 $[M-1]^+$ (58), 256 (23), 255 (16), 230 (18), 139 (12), 114 (9), 102 (8). Found, %: C 74.76; H 4.2; N 9.63. $C_{18}H_{12}N_2S$. Calculated, %: C 74.97; H 4.19; N 9.71.

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