7.1 Hz); 3.96 (q, 1 H, CH, J = 7.1 Hz); 8.43 (s, 1 H, SCH); 9.73 (s, 1 H, CH=O). ^{13}C NMR ($CDCl_3$), δ: 198.2 (CH=O); 146.7 (C-5); 139.2 (C-3); 135.4 (C-4); 46.1 (CH); 14.4 (CH_3).

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Alkynylisothiazoles

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A new synthesis of mono- and dialkynylisothiazoles by cross-coupling of bromine- and iodine-containing isothiazoles with terminal acetylene moieties in the $PdCl_2(PPh_3)_2$—CuI—NEt_3 catalytic system has been developed.

Key words: haloisothiazoles, cross-coupling, palladium, acetylenes.

In recent years, Pd-catalyzed cross-coupling of halogenated derivatives of aromatic and heteroaromatic compounds with terminal acetylene moieties has been studied extensively.[1,2] Based on these reactions, conjugated arylacetylenes[3,4] as well as acetylene derivatives of thiophene,[5—8] pyridine,[5,6,9—12] pyrazole,[5] pyrimidine,[5] thiazole,[7] indole,[13] pyridazine,[14] and isoxazole[15] have been obtained. Many of these compounds have the properties of organic semiconductors[16,17] or liquid crystals,[18,19] or find use in the synthesis of biologically active compounds.[8,9,20] Some alkynylthiophenes are found in plants.[21]

To our knowledge, the reaction of terminal acetylenes with haloisothiazoles has not been reported. Probably, 2-(α-methylbenzyl)-4-(phenylethynyl)isothiazol-3-one obtained by the reaction of the corresponding bromoisothiazolone with phenylethynyltributylstannane[24] is the only known acetylene derivative of isothiazole, a heterocycle incorporated in many biologically active compounds.[22,23]

The purpose of this work was to study the cross-coupling of terminal acetylenes with bromine- and iodine-containing isothiazoles, to estimate the relative reactivity of halogen atoms at positions 3—5 of the isothiazole ring in this reaction, and to synthesize alkynylisothiazoles with one or two acetylene groups on this basis.

The previously synthesized[25] tribromoisothiazole, 3,4-dibromo-5-iodoisothiazole, 3-bromo-4,5-diiodoisothiazole, and 3-bromo-4-iodoisothiazole were used as the starting haloisothiazoles. Acetylene, phenylacetylene, oct-1-yne, propargyl alcohol, and methyl propargyl ether served as the acetylenic components of the reaction. Copper phenylacetylenide obtained preliminarily[26] was used in the reaction, or condensation was carried out in the catalytic system $PdCl_2(PPh_3)_2$—CuI—NEt_3. This

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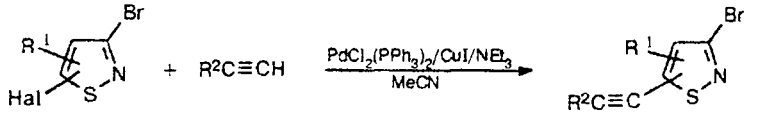
Table 1. Reaction conditions and yields of the products (**1**—**10**) in reactions of bromo- and iodoisothiazoles with terminal acetylenes



R^1	Hal	R^2	Pd-cat., (mol.%)	T /°C	τ /h	Products (yield (%))[a]
4-Br	5-Br	Ph[b]	0	117	10	—
4-Br	5-Br	Ph	4	18	10	**1** (56), **5** (34)
4-Br	5-Br	n-C_6H_{13}	4	18	10	**2** (20)[c]
4-Br	5-Br	CH_2OH	4	18	10	**3** (56)
4-Br	5-Br	CH_2OMe	4	18	10	**4** (41)
4-Br	5-I	Ph	2	18	10	**1** (59), **5** (35)
4-I	5-I	Ph	2	18	10	**6** (45), **5** (42), **8** (45)
4-I	5-I	CH_2OMe	2	18	10	**7**(58), **8** (35)
5-H	4-I	Ph	4	50	8	**9** (49), **5** (29)
5-PhC≡C	4-I	CH_2OMe	4	50	8	**10** (42)

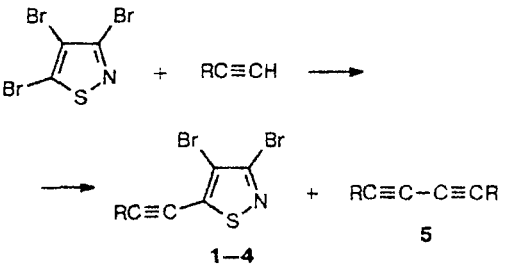
[a] The yield of diacetylene **5** was calculated with respect to phenylacetylene. The yields of other compounds were calculated with respect to the starting amount of the haloisothiazole. [b] The preliminarily obtained copper phenylacetylenide[26] was used in the reaction. [c] Yield with respect to the reacted haloisothiazole.

catalytic system has been used previously in the coupling of acetylenes with aryl and hetaryl halides.[1—3] The choice of MeCN as the solvent was due to the convenience of isolation of the reaction products.[7,11] The data obtained are listed in Table 1.

One can see from Table 1 that tribromoisothiazole does not react with copper phenylacetylenide on boiling in pyridine for several hours (Stephens—Castro reaction conditions[26,27]). However, it was found that tribromoisothiazole readily reacts with terminal acetylenes at 20 °C in the presence of the catalytic system $PdCl_2(PPh_3)_2$—CuI—NEt_3 to give cross-coupling products (**1**—**4**). The yields of the latter are affected by the quantity of $PdCl_2(PPh_3)_2$. 5-Alkynyl-3,4-dibromoisothiazoles **1**—**4** are obtained in 20—56% preparative yields when 4 mol.% of $PdCl_2(PPh_3)_2$ is used, while when 2 mol.% is used, the yields decrease abruptly. Changing the amount of CuI within 30—70% does not affect considerably the yields of alkenylisothiazoles.

The reaction of tribromoisothiazole with phenylacetylene gave, along with compound **1**, 1,4-diphenylbuta-1,3-diyne (**5**). The formation of compound **5** probably results from homo-coupling of two phenylacetylene molecules in the coordination environment of the Pd-catalyst.[6] The formation of compound **5** as a result of the Glaser reaction (oxidative coupling of two acetylene molecules on treatment with copper salts and oxygen) appears unlikely, since the reactions were carried out in dry MeCN in a nitrogen atmosphere. TLC with UV visualization did not detect products (similar to compound **5**) of homo-coupling of other alkylacetylenes. We did not make any additional attempts to identify and isolate 1,4-dialkylbutadiynes.

Unsubstituted acetylene does not form products of cross-coupling with tribromoisothiazole in the $PdCl_2(PPh_3)_2$—CuI—NEt_3 system even at 80 °C. According to TLC data, the reaction mixture contains a product of partial reduction of tribromoisothiazole, 3,4-dibromoisothiazole. The latter was identified by comparison with a specimen obtained by an independent method.[25]



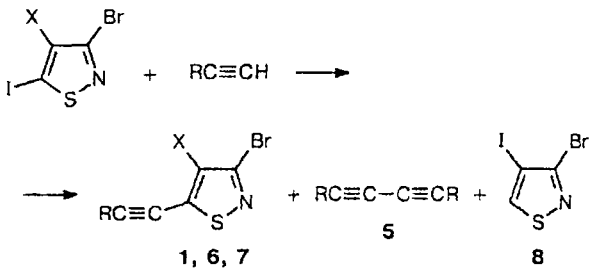
R = Ph (**1**, **5**), n-C_6H_{13} (**2**), CH_2OH (**3**), CH_2OCH_3 (**4**)

Reagents and conditions: $PdCl_2(PPh_3)_2$/CuI/NEt_3, MeCN, 20 °C.

The bromine atoms at positions 3 and 4 of the isothiazole ring have lower reactivity than the bromine atom at position 5: attempts to introduce the second phenylacetylene group in compound **1** failed even when the reaction was carried out at 80 °C in the presence of 5% of the Pd-catalyst. Similarly, 3,4-dibromoisothiazole does not undergo cross-coupling with phenylacetylene under the conditions specified.

It could be assumed that haloisothiazoles containing more reactive iodine atoms would be more reactive in cross-coupling. In fact, reactions of 3,4-dibromo-5-iodoisothiazole with terminal acetylenes in the $PdCl_2(PPh_3)_2$—CuI—NEt_3 system occur when as little

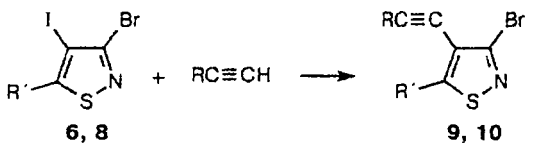
as 2 mol.% of the Pd-catalyst is used. These reactions give the corresponding 5-alkynyl-3,4-dibromo- and 5-alkynyl-3-bromo-4-iodoisothiazoles (**1**, **6**, **7**) in 45—58% yields. Reactions of 3,4-dibromo-5-iodoisothiazole and 3-bromo-4,5-diiodoisothiazole with acetylenes give 3,4-dibromoisothiazole and 3-bromo-4-iodoisothiazole (**8**), respectively, as side products. 3,4-Dibromoisothiazole was found in the reaction mixture by TLC; compound **8** was isolated in 35—45% yield. The formation of deiodination products has been reported earlier in the cross-coupling of aryl iodides with terminal acetylenes in the presence of a Pd-catalyst.[3]



1: X = Br, R = Ph
6: X = I, R = Ph
7: X = I, R = CH_2OCH_3

Reagents and conditions: $PdCl_2(PPh_3)_2$/CuI/NEt_3, MeCN, 20 °C.

We showed that 3-bromo-4-iodoisothiazoles can exchange an iodine atom for an acetylene group in reactions with terminal acetylenes under metal-complex catalysis conditions. For example, 3-bromo-4-iodoisothiazole (**8**) reacts with phenylacetylene in the catalytic system $PdCl_2(PPh_3)_2$ (4 mol.%)—CuI (50 mol.%)—NEt_3 (2.5 mol. equiv.) at 50 °C to give 3-bromo-4-(phenylethynyl)isothiazole (**9**) in 49% yield. The reaction of 3-bromo-4-iodo-5-(phenylethynyl)isothiazole (**6**) with methoxymethylacetylene under similar conditions gave 3-bromo-4-(3-methoxypropyn-1-yl)-5-(phenylethynyl)isothiazole (**10**), the first representative of isothiazoles with two acetylene groups, in 42% yield.

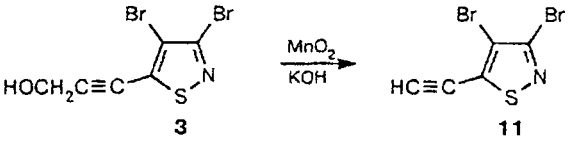


6: R′ = C≡CPh
8: R′ = H

9: R = Ph, R′ = H
10: R = CH_2OCH_3, R′ = PhC≡C

Reagents and conditions: $PdCl_2(PPh_3)_2$/CuI/NEt_3, MeCN, 50 °C.

Unlike in the case of phenylacetylene, treatment of 3,5-dibromo-5-ethynylisothiazole (**11**) (obtained by deoxymethylation of compound **3** with MnO_2 and KOH by a known procedure[11]) does not form a product of cross-coupling with 3-bromo-4-iodoisothiazole (**8**) at 50 °C in the presence of 4% of the Pd-catalyst.



The alkynylisothiazoles synthesized (**1**, **3**, **4**, **6**, **7**, **9**—**11**) are stable crystalline compounds. Compound **2** was obtained as an oil containing (^{13}C NMR data) ~80% of unreacted tribromoisothiazole, which we were unable to separate. The structure of 5-alkynyl-3,4-dibromoisothiazoles was assigned to compounds **1**—**4** because the products of coupling of tribromoisothiazole and 3,4-dibromo-5-iodoisothiazole with phenylacetylene had identical ^{13}C NMR spectra. The structure of compounds **6** and **7** as 5-alkynyl-3-bromo-4-iodoisothiazoles follows from their ^{13}C NMR spectra, in which the signals of C(4) are considerably shifted upfield (90.0 and 90.3 ppm), as is characteristic of C atoms located at position 4 of the isothiazole ring and bonded to iodine (the chemical shifts of the C(4) and C(5) atoms in 3-bromo-4,5-diiodoisothiazole are 101.0 and 117.2 ppm, respectively).[25] The structure of product **9** agrees with the absence of strong-field signals of heterocycle carbons (δ < 122) in the ^{13}C NMR spectrum, which indicates the absence of an iodine atom in molecule **9**. The chemical composition of compounds **1**, **3**, **4**, **6**, **7**, **9**—**11** was confirmed by elemental analysis.

The possible mechanism of the reaction of bromo- and iodoisothiazoles with terminal acetylenes in the $PdCl_2(PPh_3)_2$—CuI—NEt_3 catalytic system is probably similar to that suggested previously for cross-coupling involving aryl- and hetaryl halides.[1,2,6] The discovered preferential involvement of halogen atoms at position 5 of the isothiazole ring in this reaction correlates with the data on the higher reactivity of the atoms specified in reactions with nucleophilic reagents.[22,23]

Experimental

^1H and ^{13}C NMR spectra were recorded on a Bruker AM-300 spectrometer at frequencies of 300.13 (^1H) and 75.5 (^{13}C) MHz. The chemical shifts of ^1H and ^{13}C NMR signals were measured relative to $CDCl_3$ (δ 7.27 and 76.9). TLC was carried out on Silpearl UV-250 silica gel. The starting isothiazoles were synthesized according to the procedure in Ref. 25. MeCN was purified by repeated distillation with P_2O_5. Methoxymethylacetylene was obtained according to a known procedure.[28] Activated MnO_2 was obtained according to a reported method.[29]

Synthesis of alkynylisothiazoles (general procedure). Acetylene (0.60 mmol) was added to a suspension of a haloisothiazole (0.30 mmol), $PdCl_2(PPh_3)_2$ (0.004 g, 0.005 mmol for 5-iodo derivatives or 0.008 g, 0.011 mmol for all other compounds), and CuI (0.03 g, 0.16 mmol) in dry MeCN (2 mL). The

mixture was purged with nitrogen, and NEt_3 (0.11 mL, 0.08 g, 0.79 mmol) was added with stirring. The reaction mixture was stirred in a nitrogen atmosphere. After the reaction ceased, the solvent was evaporated, and the residue was dissolved in the system $CHCl_3$ (5 mL)—25% aqueous NH_3 (5 mL). The organic layer was separated, and the aqueous layer was extracted with $CHCl_3$ (2×2 mL). The combined organic phase was dried with $MgSO_4$. The solvent was removed, and the products were isolated by TLC on silica gel. The temperatures, reaction times, and product yields are presented in Table 1.

Compounds **1**—**11** were obtained.

3,4-Dibromo-5-(phenylethynyl)isothiazole (1), R_f = 0.54 (petroleum ether), m.p. 87—91 °C (hexane). Found (%): C, 38.82; H, 1.66; Br, 45.69; S, 9.17. $C_{11}H_5Br_2NS$. Calculated (%): C, 38.51; H, 1.46; Br, 46.62; S, 9.33. ^{1}H NMR: 7.39—7.46 (m, 3 H, *m*-H, *p*-H); 7.57—7.62 (m, 2 H, *o*-H). ^{13}C NMR: 145.5 (C-5); 140.2 (C-3); 116.1 (C-4); 120.8 (C_{ipso}); 105.9, 76.6 (2 —C≡); 131.7, 129.9, 128.5 (Ph).

3,4-Dibromo-5-(1-octynyl)isothiazole (2), R_f = 0.75 (petroleum ether), oil. ^{13}C NMR: 144.8 (C-5); 140.1 (C-3); 115.5 (C-4); 109.2, 68.8 (2 —C≡); 31.2, 28.4, 27.9, 22.5, 20.1, 14.0 (*n*-C_6H_{13}).

3,4-Dibromo-5-(3-hydroxypropyn-1-yl)isothiazole (3), R_f = 0.18 ($CHCl_3$), m.p. 74—75 °C (hexane). Found (%): C, 24.34; H, 1.21; Br, 53.31; S, 10.49. $C_6H_3Br_2NOS$. Calculated (%): C, 24.26; H, 1.01; Br, 53.84; S, 10.78. ^{1}H NMR: 2.58 (br.s, 1 H, OH); 4.62 (s, 2 H, CH_2). ^{13}C NMR: 144.8 (C-5); 140.5 (C-3); 116.6 (C-4); 104.4, 73.0 (2 —C≡); 51.4 (CH_2).

3,4-Dibromo-5-(3-methoxypropyn-1-yl)isothiazole (4), R_f = 0.23 (CCl_4), m.p. 41—43 °C (hexane). Found (%): C, 27.21; H, 1.70; Br, 51.22; S, 10.24. $C_7H_5Br_2NOS$. Calculated (%): C, 27.03; H, 1.61; Br, 51.41; S, 10.30. ^{1}H NMR: 3.48 (s, 3 H, CH_3); 4.43 (s, 2 H, CH_2). ^{13}C NMR: 145.0 (C-5); 140.5 (C-3); 116.8 (C-4); 102.5, 73.9 (2 —C≡); 60.3 (CH_3O); 58.2 (CH_2).

1,4-Diphenylbuta-1,3-diyne (5), R_f = 0.75 (petroleum ether), m.p. 85—86 °C (hexane) (Ref. 30: m.p. 86—87 °C). ^{1}H NMR: 7.35—7.42 (m, 3 H, *m*-H, *p*-H); 7.54—7.60 (m, 2 H, *o*-H).

3-Bromo-4-iodo-5-(phenylethynyl)isothiazole (6), R_f = 0.54 (petroleum ether), m.p. 106—109 °C (hexane). Found (%): C, 34.02; H, 1.45; Br, 21.37; I, 32.06; S, 8.14. $C_{11}H_5BrINS$. Calculated (%): C, 33.86; H, 1.28; Br, 20.50; I, 32.56; S, 8.21. ^{13}C NMR: 150.7 (C-5); 144.5 (C-3); 90.0 (C-4); 121.0 (C_{ipso}); 105.5, 78.8 (2 —C≡); 131.8, 130.0, 128.5 (Ph).

3-Bromo-4-iodo-5-(3-methoxypropyn-1-yl)isothiazole (7), R_f = 0.23 (CCl_4), m.p. 61—63 °C (hexane). Found (%): C, 24.16; H, 1.64; Br, 22.10; I, 35.09; S, 8.85. $C_7H_5BrINOS$. Calculated (%): C, 23.48; H, 1.40; Br, 22.33; I, 35.47; S, 8.94. ^{13}C NMR: 150.1 (C-5); 144.8 (C-3); 90.3 (C-4); 101.9, 75.8 (2 —C≡); 60.2 (CH_3); 58.1 (CH_2).

3-Bromo-4-(phenylethynyl)isothiazole (9), R_f = 0.37 (CCl_4), m.p. 69—71 °C (hexane). Found (%): C, 50.16; H, 2.42. $C_{11}H_6BrNS$. Calculated (%): C, 50.02; H, 2.27. ^{1}H NMR: 7.36—7.43 (m, 3 H, *m*-H, *p*-H); 7.56—7.62 (m, 2 H, *o*-H); 8.68 (s, 1 H, SCH). ^{13}C NMR: 150.6 (C-5); 140.9 (C-3); 122.2 (C-4); 123.2 (C_{ipso}); 94.5, 80.0 (2 —C≡); 131.8, 129.2, 128.6 (Ph).

3-Bromo-4-(3-methoxypropyn-1-yl)-5-(phenylethynyl)isothiazole (10), R_f = 0.22 (CCl_4), m.p. 70—72 °C (hexane). Found (%): C, 54.38; H, 3.17; Br, 23.98; S, 9.55. $C_{15}H_{10}BrNOS$. Calculated (%): C, 54.24; H, 3.01; Br, 24.07; S, 9.64. ^{1}H NMR: 3.52 (s, 3 H, CH_3); 4.45 (s, 2 H, CH_2); 7.39—7.47 (m, 3 H, *m*-H, *p*-H); 7.54—7.61 (m, 2 H, *o*-H).

3,4-Dibromo-5-ethynylisothiazole (11). 3,4-Dibromo-5-(3′-hydroxypropyn-1′-yl)isothiazole (**3**) (0.1 g, 0.33 mmol) was added to a suspension of KOH (0.1 g, 1.78 mmol) and MnO_2[29] (0.29 g, 3.33 mmol) in dry benzene (3 mL). The suspension was stirred for 1 h and then filtered. The precipitate was washed with benzene (3×3 mL), and the filtrate was concentrated to give 0.06 g (66%) of compound **11**, m.p. 81—84 °C (hexane), R_f = 0.27 (petroleum ether). Found (%): C, 22.58; H, 0.49; Br, 59.81; S, 11.83. C_5HBr_2NS. Calculated (%): C, 22.49; H, 0.37; Br, 59.90; S, 11.99. ^{13}C NMR: 144.4 (C-5); 140.5 (C-3); 117.5 (C-4); 94.0 (CH); 71.0 (—C≡).

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Ambident isothiocyanatomethanide anion for regioselective synthesis of thiazoles

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Under the action of methyl isothiocyanate, the ambident isothiocyanatomethanide anion, which was generated by deprotonation of methyl isothiocyanate with lithium diisopropylamide, was readily and selectively transformed to 5-methylaminothiazole-2-thiolate.

Key words: methyl isothiocyanate, lithium diisopropylamide, deprotonation, isothiocyanatomethanide anion, heterocyclization, alkylation, thiazoles.

Recently,[1] we reported the reaction of isothiocyanatomethanide anion (**2**), which was generated by *in situ* deprotonation of methyl isothiocyanate (**1**) with lithium diisopropylamide (LDA), with trimethylchlorosilane. This reaction is a new simple route for the synthesis of mono-, bis-, and tris(trimethylsilyl)methyl isothiocyanates. We have also found[2] that the reaction of methyl isothiocyanate with the superbasic potassium diisopropylamide—lithium *tert*-butoxide system opens an unexpectedly simple route to difficultly accessible derivatives of imidazole.

In this work, we report briefly the results of our continuing studies of deprotonation of nonactivated isothiocyanates with superbases. We found that changes in the nature of the counter-ion in diisopropylamide and in isothiocyanatomethanide anion **2**, the reaction temperature, and the rate and order in which the reagents are introduced into the reaction allow one to change fundamentally the pathway of this reaction. Thus, when the K^+ counter-ion was replaced by the Li^+ cation and the reaction was carried out at low temperature (−100 to −50 °C) in a THF—hexane mixture, ambident anion **3** underwent rapid quantitative cyclization to 5-methylaminothiazole-2-thiolate (**4**). Derivatives of thiazole, for example, 5-dimethylamino-2-methylthiothiazole (**6**), were readily and selectively synthesized by lithiation of compound **4** and alkylation of the resulting dianion **5** with alkyl halide or dialkyl sulfate. Compound **6** was obtained in one preparative stage in high yield. The possible pathway of the reaction is shown in Scheme 1.

The structure of thiazole **6** was confirmed by IR and ^1H NMR spectra. The composition corresponds to the molecular formula $C_6H_{10}N_2S_2$.

Experimental

The IR spectra were recorded on a Specord IR-75 spectrophotometer in thin films. The ^1H NMR spectra were recorded on a Varian EM-390 spectrometer (90 MHz; ~20% solution in

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