Palladium-catalyzed reaction of bromine- and iodine-containing isothiazoles with olefins

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3-Bromo-4-alkenylisothiazoles were synthesized by the reaction of 3-bromo-4-iodoisothiazole with olefins in the presence of palladium acetate.

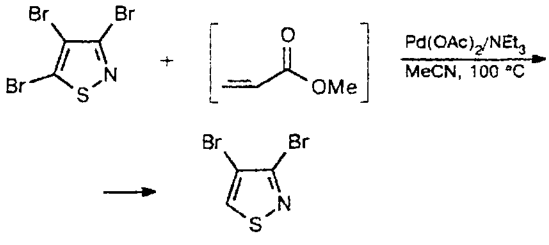
Key words: haloisothiazoles, coupling reaction, palladium, olefins.

Although the coupling of olefins with organic halides in the presence of palladium (Heck reaction) is widely used to form new C—C bonds in aromatic and heteroaromatic compounds,[1–3] there are no reported examples of the synthesis of conjugated alkenylisothiazoles, compounds with pronounced biological activity,[4] by this reaction. For example, 5-bromo-3-methylisothiazole does not form coupling products with styrene, acrylonitrile, and ethyl acrylate, but dimerizes under reaction conditions.[5] Recently, the synthesis of alkenylisothiazoles by a more complex method, namely, by a reaction of 4-bromoisothiazol-3-one with tributylvinyltin, was reported.[6]

To determine the possibility of obtaining alkenylhaloisothiazoles, we studied the reaction of bromine- and iodine-containing polyhaloisothiazoles with terminal olefins in the Pd(OAc)$_2$—NEt$_3$ system. This system has been used previously in reactions of aryl and hetaryl iodides with olefins.[1,7] NEt$_3$ serves as a base required for hydrogen halide elimination from a palladium complex formed in the reaction.[1–3]

The reaction was carried out starting from tribromoisothiazole, 3-bromo-4-iodothiazole, and 3,4-dibromo-5-iodothiazole synthesized previously.[8] Styrene, methyl acrylate, acrylonitrile, and allyl alcohol were used as the olefin components. The reaction was performed in MeCN, the solvent widely used in the Heck reaction.[1]

It was found that tribromoisothiazole and 3,4-dibromo-5-iodothiazole do not form products of coupling with methyl acrylate in the Pd(OAc)$_2$—NEt$_3$ catalytic system at 20 °C. An increase in reaction temperature to 100 °C results in disappearance of the starting isothiazole and formation of a dehalogenation product, 3,4-dibromoisothiazole (**1**). Compound **1** was not isolated from the reaction mixture but was identified using TLC by comparison with a sample obtained by an independent method.[8] Methyl acrylate is not involved in the reaction, as was confirmed by the synthesis of compound **1** from tribromoisothiazole and Pd(OAc)$_2$—NEt$_3$ in the absence of an olefin. The reduction of aryl halides to aromatic hydrocarbons under conditions of Pd-catalyzed coupling has been reported previously.[9]



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We were able to synthesize coupling products in the case of 3-bromo-4-iodothiazole. Its reactions with methyl acrylate, styrene, and acrylonitrile at 100 °C give the corresponding 4-alkenyl-3-bromoisothiazoles (**2**—**4**) in 29—60% yields. The data obtained are presented in Table 1. An eightfold excess of acrylonitrile is required to obtain compound **4** in preparative yield. In addition, the reaction gives a side product, 3,3′-dibromo-4,4′-biizothiazole (**5**), which is also formed under the same conditions in the absence of an olefin.

The reaction of 3-bromo-4-iodoisothiazole with allyl alcohol results in a complex mixture of products. We were able to isolate compound **5** and 3-bromo-4-(1-oxoprop-2-yl)isothiazole (**6**) from this mixture. The formation of bisisothiazole **5** is suppressed by using an

Table 1. Reaction conditions and yields of reactions of 3-bromo-4-iodothiazole with olefins

R	Olefin (mol. equiv.)	Pd(OAc)$_2$ (mol.%)	Time /h	Reaction products (yield (%))
CO$_2$Me	1.2	5	10	**2** (29), **5** (9)
Ph	2	5	10	**3** (60), **5** (9)
CN	2	5	20	**4** (13), **5** (13)
CN	8	5	20	**4** (33), **5** (13)
CH$_2$OH	2	3	5	**6** (6), **5** (13)
CH$_2$OH	8	3	1	**6** (13)

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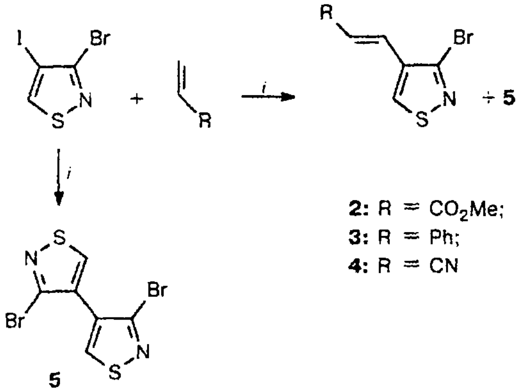
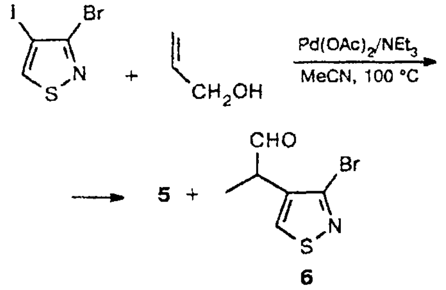


2: R = CO_2Me;
3: R = Ph;
4: R = CN

i. $Pd(OAc)_2/NEt_3$, MeCN, 100 °C

eightfold excess of allyl alcohol. A possible mechanism of the formation of compound **6** involves coupling of the haloisothiazole with allyl alcohol through the C(2) atom followed by rearrangement of the primary reaction product by the scheme suggested previously.[10]



The mechanism of the reaction of 3-bromo-4-iodoisothiazole with olefins is probably similar to that suggested earlier for Pd-catalyzed coupling involving aryl halides.[1—3,9] The reduction of $Pd(OAc)_2$ to Pd(0) is confirmed by the formation of palladium black in this reaction.

The compounds **2—5** synthesized are stable crystals, while compound **6** is an oil. Their structure was confirmed by ^1H and ^{13}C NMR spectra. The vicinal arrangement of olefin protons in compounds **2—4** was confirmed by the equal intensity, and hence similar relaxation times, of ^{13}C NMR signals of the carbon atoms bound to these protons. The *E*-configuration of substituents in products **2** and **4** was confirmed by the magnitude of the coupling constant between the olefin protons (15—16 Hz) in ^1H NMR spectra.[11] By analogy, compound **3**, in which the chemical shifts of these protons coincide, was also assigned the structure of a *E*-adduct. Although the Heck reaction gives not only *E*- but also *Z*-isomers, the formation of the latter in the reaction of 3-bromo-4-iodoisothiazole with olefins was not detected. The empirical formulas of compounds **2—5** were confirmed by elemental analyses.

Thus, we demonstrated the possibility of direct introduction of an unsaturated group at position 4 of the isothiazole ring by the reaction of 3-bromo-4-iodoisothiazole with olefins in the $Pd(OAc)_2$—NEt_3 catalytic system.

Experimental

^1H and ^{13}C NMR spectra were recorded in $CDCl_3$, acetone-d_6, and DMSO-d_6 on a Bruker AM-300 spectrometer at frequencies of 300.13 MHz (^1H) and 75.5 MHz (^{13}C). The chemical shifts of ^1H and ^{13}C signals were measured relative to DMSO-d_6 (δ 2.50 and 39.5), acetone-d_6 (δ 2.07 and 30.00), and $CDCl_3$ (δ 7.27 and 76.9). TLC was performed on Silpearl UV-250 silica gel. The reactions were monitored by TLC on Silufol UV-254 by detecting the disappearance of the spot corresponding to the starting haloisothiazole. The olefins and NEt_3 were purified by distillation. MeCN was dried by distillation over P_2O_5. The haloisothiazoles were obtained by the method reported previously.[8]

Reaction of 3-bromo-4-iodoisothiazole with olefins (general procedure). An alkene (see Table 1) and NEt_3 (0.24 mL, 0.174 g, 1.72 mmol) were added to a solution of 3-bromo-4-iodoisothiazole (0.2 g, 0.69 mmol), $Pd(OAc)_2$ (0.005 g, 0.022 mmol for allyl alcohol; 0.008 g, 0.035 mmol for the other olefins) in dry acetonitrile (2 mL) preliminarily purged with nitrogen. The mixture was heated in a sealed vessel at 100 °C for a period of time indicated in Table 1. The solvent was evaporated *in vacuo*, and the products were isolated by TLC on silica gel.

Compounds **2—6** were obtained.

***trans*-3-Bromo-4-(2-methoxycarbonylethenyl)isothiazole (2)**, R_f = 0.52 (benzene), m.p. 101—104 °C (hexane). ^1H NMR (acetone-d_6), δ: 3.77 (s, 3 H, CH_3); 6.66 (d, 1 H, CH, *J* = 16.0 Hz); 7.60 (d, 1 H, CH, *J* = 16.0 Hz); 9.49 (s, 1 H, SCH). ^{13}C NMR (acetone-d_6), δ: 166.9 (C=O); 150.7 (C-5); 139.7 (C-3); 134.1 (C-4); 134.3, 123.1 (—C=C—); 52.2 (CH_3O). Found (%): C, 33.95; H, 2.35; Br, 31.91; S, 12.0. $C_7H_6BrNO_2S$. Calculated (%): C, 33.88; H, 2.42; Br, 32.23; S, 12.91.

***trans*-3-Bromo-4-(2-phenylethenyl)isothiazole (3)**. R_f = 0.4 (CCl_4), m.p. 95—96 °C (hexane). ^1H NMR ($CDCl_3$), δ: 7.09 (s, 2 H, HC=CH); 7.32—7.48 (m, 3 H, *m*-H, *p*-H); 7.49—7.61 (m, 2 H, *o*-H); 8.63 (s, 1 H, SCH). ^{13}C NMR ($CDCl_3$), δ: 142.6 (C-5); 138.8 (C-3); 136.2 (C-4); 136.1 (C_{ipso}); 133.1, 118.3 (—C=C—); 128.7, 128.4, 126.6 (Ph). Found (%): C, 49.89; H, 3.24; Br, 29.80; S, 11.96. $C_{11}H_8BrNS$. Calculated (%): C, 49.64; H, 3.01; Br, 30.05; S, 12.03.

***trans*-3-Bromo-4-(2-cyanoethenyl)isothiazole (4)**. R_f = 0.4 (CCl_4), m.p. 152—155 °C (CCl_4). ^1H NMR ($CDCl_3$), δ: 5.98 (d, 1 H, CH, *J* =15.0 Hz); 7.42 (d, 1 H, CH, *J* = 15.0 Hz); 8.83 (s, 1 H, SCH). ^{13}C NMR ($CDCl_3$), δ: 148.9 (C-5); 139.6 (C-3); 133.7 (C-4); 140.6, 101.3 (—C=C—); 117.8 (CN). Found (%): C, 33.61; H, 1.55; Br, 36.74; S, 14.51. $C_6H_3BrN_2S$. Calculated (%): C, 33.50; H, 1.40; Br, 37.18; S, 14.89.

3,3′-Dibromo-4,4′-biisothiazole (5). R_f = 0.64 (benzene), m.p. 226—227 °C ($CHCl_3$). ^1H NMR (DMSO-d_6), δ: 9.25 (s, 1 H, CH). ^{13}C NMR (DMSO-d_6), δ: 152.9 (C-5); 138.6 (C-3); 130.0 (C-4). Found (%): C, 22.23; H, 0.63; Br, 49.53; S, 20.27. $C_6H_2Br_2N_2S_2$. Calculated (%): C, 22.10; H, 0.61; Br, 49.05; S, 19.64.

3-Bromo-4-(1-oxopropyl-2)isothiazole (6). R_f = 0.50 (benzene), oil. ^1H NMR ($CDCl_3$), δ: 1.50 (d, 3 H, CH_3, *J* =

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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