Hypervalent Iodine

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Thiazole Synthesis by Cyclocondensation of 1-Alkynyl(phenyl)-λ^3-iodanes with Thioureas and Thioamides**

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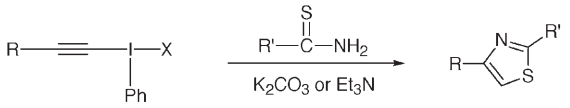
In 1996, Wipf and Venkatraman reported an efficient method for the synthesis of thiazoles, which involved the cyclocondensation of hypervalent 1-alkynyl(phenyl)-λ^3-iodanes with thioureas or thioamides.[1] For instance, the reaction of phenylethynyl(phenyl)(mesylato)-λ^3-iodane (**1a**) (X = OMs, Ms = methanesulfonyl) with thiourea in methanol in the presence of triethylamine at 0 °C directly afforded 2-amino-4-phenylthiazole (**2**; R = Ph, R′ = NH_2) in a good yield (Scheme 1). 1-Hexynyl-λ^3-iodane **1b** (X = OMs) also produced the thiazole **2** (R = *n*Bu, R′ = NH_2 or Ph) by reaction with thiourea or thiobenzamide. This direct method for the synthesis of thiazoles based on the cyclocondensation of 1-alkynyl-λ^3-iodanes was applied to the synthesis of 2-mercaptothiazoles and selenazoles.[2]



1a: R = Ph
1b: R = *n*Bu
1c: R = *t*Bu
1d: R = *n*-C_8H_{17}
X = OMs or BF_4

Scheme 1. Synthesis of thiazoles.

The one-step thiazole synthesis developed by Wipf and Venkatraman is a very useful reaction, as many biologically active natural products contain thiazole moieties.[3] They proposed a reaction mechanism that involves a unique [3,3]-sigmatropic rearrangement of an initially formed 1-alkynyl(iminothio)-λ^3-iodane **3** through ligand exchange on the hypervalent iodine. Reductive elimination of the resulting vinyliodonium ylide **4** generates an α-thioamido alkylidene carbene **5**, which undergoes an intramolecular cyclization to yield 2,4-disubstituted thiazole **2** (Scheme 2, pathway A).[4] The more common Michael addition pathway with the initial formation of an isomeric vinyliodonium ylide **6** was discarded, and it was proposed that this Michael addition pathway would provide thiazoles **8** with an inverse C4,C5-substitution pattern through successive reductive elimination of iodobenzene and intramolecular 1,5 N–H insertion of the alkylidene carbene **7** (pathway B).[1]

It occurred to us that a third mechanism (pathway C) that involved the Michael addition of thio nucleophiles followed by a 1,2-rearrangement of the iminothio group in the alkylidene carbene **7**, instead of the intramolecular 1,5 N–H insertion, thus yielding the alkynyl sulfide **9**, seems to be a more attractive alternative. Further intramolecular cyclization of **9** probably provides **2** selectively. In fact, the 1,2-rearrangement of sulfenyl groups in alkylidene carbenes is known to be a facile and very rapid process because of the excellent migratory aptitude of sulfenyl groups.[5] Furthermore, it has been shown that soft sulfur nucleophiles, such as thiolates,[6] thiosulfonates,[7] phosphorodithioates,[8] thiocyanates,[9] and sulfinates,[10] preferentially undergo Michael additions towards 1-alkynyl(phenyl)-λ^3-iodanes. We report herein some evidence that **9** is a reactive intermediate in the cyclocondensation of hypervalent 1-alkynyl(phenyl)-λ^3-iodanes with thioureas or thioamides and that the thiazole synthesis probably proceeds through pathway C.

The cyclocondensations of 1-alkynyl(phenyl)-λ^3-iodanes with thioureas or thioamides that yield **2** were carried out in the presence of a base, such as potassium carbonate or triethylamine.[1] The reaction course, however, dramatically changed without a base being present. Thus, when the reaction of phenylethynyl-λ^3-iodane **1a** (X = OMs) with thiourea (1 equiv) was carried out in dichloromethane at −78→10 °C under nitrogen in the absence of triethylamine, no formation of **2** (R = Ph, R′ = NH_2) was observed; instead, a hitherto unknown *S*-(phenylethynyl)isothiouronium mesylate **9**-MsOH (R = Ph, R′ = NH_2) was isolated in 82% yield after repeated decantation with hexane.[11] The IR spectrum of this salt showed the characteristic peak of the triple bond at 2180 cm^{-1}, as well as the strong absorption of the iminium group at 1683 and 1662 cm^{-1}, whereas the ^{13}C NMR spectra revealed two peaks of acetylenic carbon atoms at $\delta = 65.8$ and 106.6 ppm.

Single crystals of **9**-MsOH for X-ray structural analysis were grown from a mixture of methanol/dichloromethane/hexane.[12] Figure 1a illustrates a planar *S*-(1-alkynyl)isothiouronium structure with the sum of the C(9)-centered bond angles Σ°C(9) = 359.97°. Interestingly, the phenyl and the isothiouronium groups lie almost on the same plane, with a dihedral angle of 8.19(3)°.

It should be noted that exposure of *S*-(phenylethynyl)-isothiouronium mesylate (**9**-MsOH) to an aqueous saturated solution of $NaHCO_3$ at room temperature produced a moderate yield (51%) of 2-amino-4-phenylthiazole (**2**) through an intramolecular 5-endo digonal cyclization. The same type of intramolecular cyclization in substituted *S*-alkynylisothiouronium salts has been reported.[11,13] These results suggest that methanesulfonic acid generated from λ^3-iodane **1a** (X = OMs) during the reaction with thiourea (Scheme 2) probably inhibits the intramolecular cyclization of **9** (R = Ph, R′ = NH_2) under our conditions by formation of

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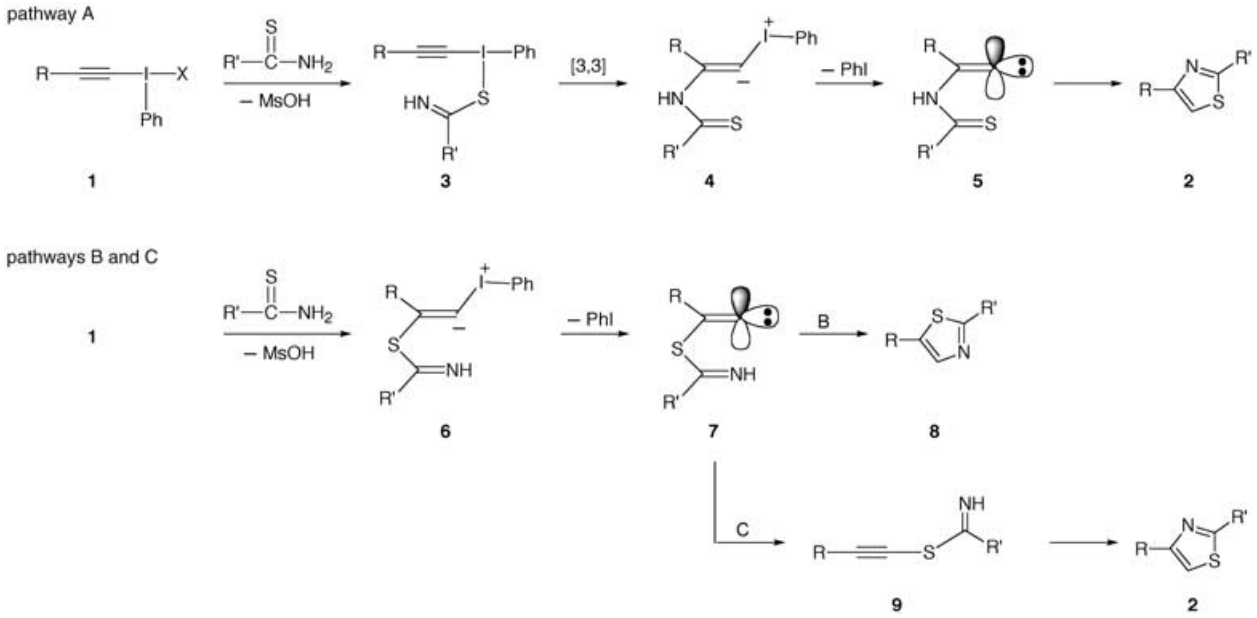


Scheme 2. Possible reaction mechanisms.

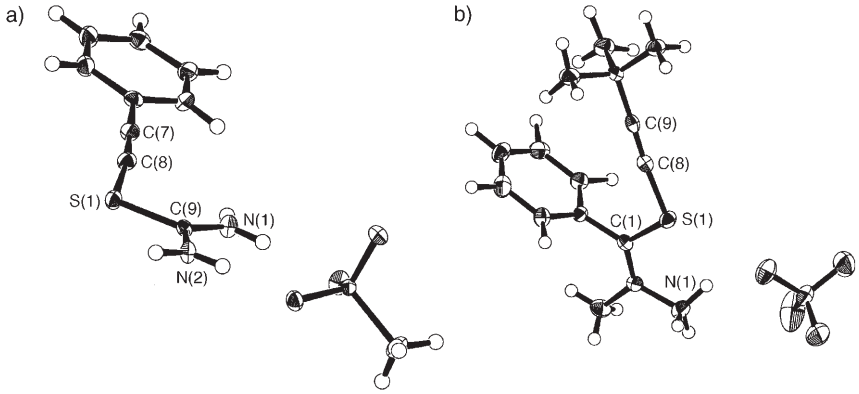


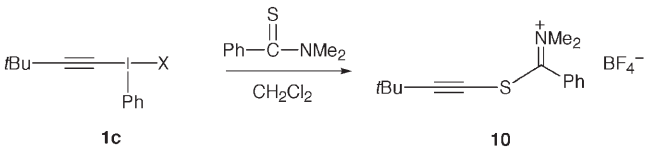
Figure 1. ORTEP drawing of a) isothiouronium salt **9**-MsOH (R = Ph, R′ = NH_2) and b) thiobenzimidonium salt **10**. Selected interatomic distances [Å] and angles [°]: **9**-MsOH: C(7)-C(8) 1.193(1), S(1)-C(8) 1.6888(8), S(1)-C(9) 1.7695(7), C(8)-S(1)-C(9) 102.19(4); **10**: C(8)-C(9) 1.187(2), S(1)-C(8) 1.691(2), S(1)-C(1) 1.752(1), C(8)-S(1)-C(1) 101.69(7).

the **9**-MsOH. Treatment with a base regenerates the free sulfide **9** which undergoes spontaneous cyclization at room temperature. The isolation and cyclization of **9**-MsOH clearly indicate that this alkynyl sulfide **9** is probably a reactive intermediate in the one-step 2-aminothiazole synthesis in the presence of a base, which is compatible with the alkylidene carbene pathway C.

Comparable results were obtained from the reaction with thioamides. Reaction of 1-decynyl(tetrafluoroborato)-λ^3-iodane (**1d**)[14] (X = BF_4) with thiobenzamide in dichloromethane at −78 °C→room temperature afforded a 69:31 mixture of *S*-(1-decynyl)thiobenzimidonium tetrafluoroborate (**9**-HBF_4; R = *n*-C_8H_{17}, R′ = Ph) and 4-octyl-2-phenylthiazolium tetrafluoroborate (**2**-HBF_4; R = *n*-C_8H_{17}, R′ = Ph) quantitatively (as shown by ^{1}H NMR spectroscopic analysis of a crude reaction mixture). The thioimidonium salt **9**-HBF_4 is highly labile and tends to undergo intramolecular cyclization; thus, even the attempted purification of the crude product by decantation with hexane/diethyl ether at room temperature resulted in partial cyclization, and the ratio of **9**-HBF_4/**2**-HBF_4 was reversed to 31:69 (91 % yield). Treatment with a base (Na_2CO_3/H_2O) accelerates the cyclization and gave 4-octyl-2-phenylthiazole (**2**)[15] in 93 % yield. Reaction of 1-hexynyl-λ^3-iodane **1b** (X = BF_4) with thiobenzamide also afforded a 94:6 mixture of labile *S*-(1-hexynyl)thiobenzimidonium tetrafluoroborate **9**-HBF_4 and 4-butyl-2-phenylthiazolium tetrafluoroborate **2**-HBF_4 (for each R = *n*Bu, R′ = Ph), which on treatment with a solution of 5 % aqueous Na_2CO_3 produced 4-butyl-2-phenylthiazole (**2**)[1] in a high yield (87 %).

Isolation and full characterization of the labile *S*-(1-alkynyl)thiobenzimidonium salts were achieved by reaction of the more-sterically demanding 3,3-dimethyl-1-butynyl-λ^3-iodane **1c** (X = BF_4) with thiobenzamide, followed by acidification of the reaction mixture with $HBF_4 \cdot Me_2O$ (1 equiv). This procedure makes the quantitative isolation of *S*-(3,3-dimethyl-1-butynyl)thiobenzimidonium tetrafluoroborate (**9**-HBF_4) as pale-yellow needles possible. Treatment with a base (Na_2CO_3/H_2O) afforded 4-*tert*-butyl-2-phenylthiazole (**2**)[16] in 96 % yield.

N,*N*-Dimethylthiobenzamide seems to be an attractive nucleophile in the reaction, because the resulting *N*,*N*-dimethylthiobenzimidonium salts cannot undergo the intramolecular 5-endo digonal cyclization. In fact, *S*-(3,3-dimethyl-1-butynyl)thiobenzimidonium salt **10** was isolated as stable colorless plates by the reaction of *N*,*N*-dimethylthiobenzamide with 3,3-dimethyl-1-butynyl-λ^3-iodane **1c** (X = BF_4) in 98 % yield (Scheme 3). The structure of the



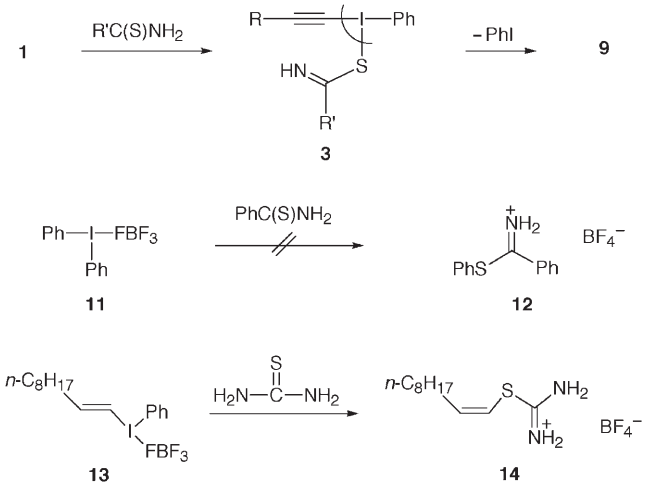
1c **10**

Scheme 3. Synthesis of (*S*)-(3,3-dimethyl-1-butynyl)thiobenzimidonium salt **10**.

salt **10** was firmly established by solid-state structure analysis (Figure 1b).[12]

All of these results indicate that the one-step thiazole synthesis using 1-alkynyl(phenyl)-λ^3-iodanes **1** developed by Wipf and Venkatraman involves the intermediate formation of the alkynyl sulfides **9** (and/or their salts), probably produced through the Michael addition of thioureas or thioamides and 1,2-shift in the alkylidene carbenes **7**. This Michael addition has been well established as the most common reaction pathway for 1-alkynyl-λ^3-iodanes with soft nucleophiles.[17,18]

An alternative mechanism that leads to the formation of **9** involves a tandem ligand exchange and ligand-coupling process at the iodine(III) center (Scheme 4). This tandem



1 **3** **9** **11** **12** **13** **14**

Scheme 4. A mechanism that involves tandem ligand exchange and ligand-coupling reactions.

process does not, however, seem to take place, as the attempted reaction of diphenyl-λ^3-iodane **11** with thiobenzamide did not show any evidence of the formation of the ligand-coupling product **12** and **11** was recovered (95%). Further evidence against the ligand-coupling mechanism was reported recently:[19] that is, the reaction of (*E*)-1-decenyl-(phenyl)-λ^3-iodane **13** with thiourea resulted in unusual vinylic S_N2 displacement that yields the inverted (*Z*)-(*S*)-vinylisothiouronium salt **14** stereoselectively in a good yield (Scheme 4). In this reaction, no formation of the ligand-coupling product, the (*E*)-(*S*)-vinylisothiouronium salt, was detected.

In conclusion, the isolation and the intramolecular cyclization of (*S*)-(1-alkynyl)isothiouronium and (*S*)-(1-alkynyl)thiobenzimidonium salts indicate that these species are probably involved in the cyclocondensation of hypervalent 1-alkynyl(phenyl)-λ^3-iodanes with thioureas or thioamides yielding thiazoles.

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[12] Crystal data for **9**-MsOH (R = Ph, R′ = NH_2): $C_{10}H_{12}N_2O_3S_2$, colorless block, dimensions $0.50\times0.50\times0.30$ mm^3, orthorhombic, $P2_12_12_1$ (No. 19), $a = 6.271(1)$, $b = 12.077(2)$, $c = 16.638(3)$ Å, $V = 1260.0(4)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.436$ g cm^{-3}. Data collected on a Rigaku RAXIS-RAPID imaging plate diffractometer with $Mo_{K\alpha}$ radiation ($\lambda = 0.71075$ Å) at $T = 93$ K, $2\theta_{max} = 54.9°$, 12160 reflections measured, of which 12112 unique ($R_{int} = 0.017$), $\mu = 4.20$ cm^{-1}. $R = 0.026$, $R_w = 0.025$. For **10**: $C_{15}H_{20}BF_4NS$, colorless block, dimensions $0.30\times0.30\times0.20$ mm^3, monoclinic, $P2_1/c$ (No. 14), $a = 11.756(5)$, $b = 23.188(8)$, $c = 12.865(5)$ Å, $\beta = 105.24(3)°$, $V = 3383(2)$ Å^3, $Z = 8$, $\rho_{calcd} = 1.308$ g cm^{-3}. $Mo_{K\alpha}$ radiation ($\lambda = 0.71075$ Å) at $T = 93$ K, $2\theta_{max} = 54.8°$, 31313 reflections measured, of which 30889 unique ($R_{int} = 0.076$), $\mu = 2.24$ cm^{-1}. $R = 0.122$, $R_w = 0.145$. CCDC-269174 (**9**-MsOH) and -269175 (**10**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
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