JOC*Note*

Synthesis of 2,4-Disubstituted Thiazoles from (*Z*)-(2-Acetoxyvinyl)phenyl-λ^3-iodanes: Nucleophilic Substitution of α-λ^3-Iodanyl Ketones with Thioureas and Thioamides

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Abstract: In the presence of triethylamine, (*Z*)-(2-acetoxy-1-alkenyl)phenyl-λ^3-iodanes react with thioureas or thioamides in MeOH to give 2,4-disubstituted thiazoles directly in good yields. The reaction probably involves generation of highly reactive α-λ^3-iodanyl ketones through ester exchange of the *β*-acetoxy group with liberation of methyl acetate, followed by nucleophilic substitutions with thioureas or thioamides.

Hantzsch reaction of α-halocarbonyl compounds with thioureas or thioamides provides a useful method for the synthesis of thiazoles.[1,2] Recently, Moriarty and Prakash reported an efficient modification that utilizes α-tosyloxy ketones in place of α-halocarbonyl compounds.[3] The method involves a reaction of ketones with [hydroxy(tosyloxy)iodo]benzene in refluxing acetonitrile, which produces α-tosyloxy ketones through the intermediate formation of α-λ^3-iodanyl ketones.[4] α-Tosyloxy ketones subsequently undergo cyclization by the reaction with thioureas to give 2-aminothiazoles. It occurred to us that α-λ^3-iodanyl ketones would directly undergo cyclization by the reaction with thioureas or thioamides, without converting to the corresponding α-tosyloxy ketones, because of the very high leaving group ability of phenyl-λ^3-iodanyl groups, which show a leaving group ability about 10^6 times greater than the superleaving group triflate.[5] We report herein a reaction of α-λ^3-iodanyl ketones, generated in situ from (*Z*)-(*β*-acetoxyvinyl)-(phenyl)-λ^3-iodanes **1**, with thioureas or thioamides. The reaction affords substituted thiazoles **2** under mild conditions.[6]

SCHEME 1

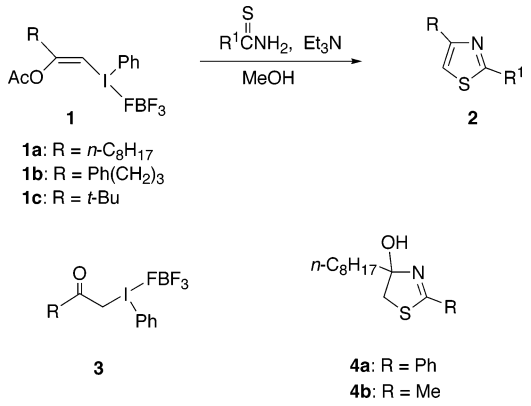

TABLE 1. Synthesis of Thiazoles 2 from (*Z*)-(*β*-Acetoxyvinyl)(phenyl)-λ^3-iodanes 1[a]

entry	λ^3-iodane **1**	R^1CSNH_2 (R^1)	conditions *T* (°C), time (h)	product **2**	yield (%)[b]
1	**1a**	NH_2	25, 5	**2a**	91
2	**1b**	NH_2	25, 5	**2b**	83
3	**1a**	NHPh	25, 5	**2c**	91
4	**1b**	NHPh	25, 5	**2d**	79
5	**1c**	NHPh	25, 5	**2e**	86
6	**1a**	Ph	25, 3 then 65, 17	**2f**	95
7	**1a**	Me	25, 3 then 65, 20	**2g**	43

[a] Reactions were carried out using 1.2 equiv of an amide and 1.2 equiv of Et_3N in methanol under nitrogen. [b] Isolated yields.

Recently, we found a new strategy for generation of α-λ^3-iodanyl ketones:[7] reaction of (*Z*)-(2-acetoxy-1-alkenyl)-(phenyl)-λ^3-iodane **1** with MeOH in the presence of triethylamine at room temperature results in ester exchange and generates α-(phenyl-λ^3-iodanyl) ketone **3** with liberation of methyl acetate. The α-λ^3-iodanyl ketone **3** is a highly reactive species toward nucleophilic substitutions, because of a hyperleaving group ability of the phenyl-λ^3-iodanyl group,[5] and reacts directly with thioureas or thioamides to give the substituted thiazoles **2**. Thus, exposure of (*Z*)-(2-acetoxy-1-decenyl)(phenyl)(tetrafluoroborato)-λ^3-iodane (**1a**) to thiourea (1.2 equiv) and triethylamine (1.2 equiv) in methanol at room temperature gave, after purification by preparative TLC, 2-aminothiazole **2a** in 91% yield (Scheme 1). Reaction of vinyl-λ^3-iodanes **1b** and **1c** with thiourea and/or *N*-phenylthiourea under our conditions also afforded the 4-substituted 2-aminothiazoles **2** in good yields (Table 1). Synthesis of thiazole derivatives by reaction with thioamides requires heating of the reaction mixture (Table 1, entries 6 and 7). When the reaction of vinyl-λ^3-iodane **1a** with thiobenzamide and thioacetamide was carried out at room temperature, no dehydration to thiazoles **2** was observed and instead the cyclized alcohols **4a** and **4b** were obtained in 87 and 82% yields, respectively.

Cyclic thiourea tautomers, 2-mercaptoimidazoline, and 2-mercapto-3,4,5,6-tetrahydropyrimidine, by the reaction

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(2) Metzger, J. V. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon Press: New York, 1984; Vol. 6, pp 235−332.
(3) (a) Moriarty, R. M.; Vaid, B. K.; Duncan, M. P.; Levy, S. G.; Prakash, O.; Goyal, S. *Synthesis* **1992**, 845. (b) Prakash, O.; Rani, N.; Goyal, S. *J. Chem. Soc., Perkin Trans. 1* **1992**, 707. (c) Prakash, O.; Saini, N.; Sharma, P. K. *Synlett* **1994**, 221.
(4) Koser, G. F.; Relenyi, A. G.; Kalos, A. N.; Rebrovic, L.; Wettach, R. H. *J. Org. Chem.* **1982**, *47*, 2487.
(5) (a) Okuyama, T.; Takino, T.; Sueda, T.; Ochiai, M. *J. Am. Chem. Soc.* **1995**, *117*, 3360. (b) Ochiai, M. In *Topics in Current Chemistry, Hypervalent Iodine Chemistry*; Wirth, T., Ed.; Springer-Verlag: Berlin, 2003; pp 5−68.
(6) For synthesis of thiazoles from 1-alkynyl(phenyl)-λ^3-iodanes, see: Wipf, P.; Venkatraman, S. *J. Org. Chem.* **1996**, *61*, 8004.
(7) (a) Ochiai, M.; Nishitani, J.; Nishi, Y. *J. Org. Chem.* **2002**, *67*, 4407. (b) Ochiai, M.; Kitagawa, Y.; Yamamoto, S. *J. Am. Chem. Soc.* **1997**, *119*, 11598. (c) Ochiai, M.; Kitagawa, Y. *Tetrahedron Lett.* **1998**, *39*, 5569. (d) Ochiai, M.; Kitagawa, Y. *J. Org. Chem.* **1999**, *64*, 3181.

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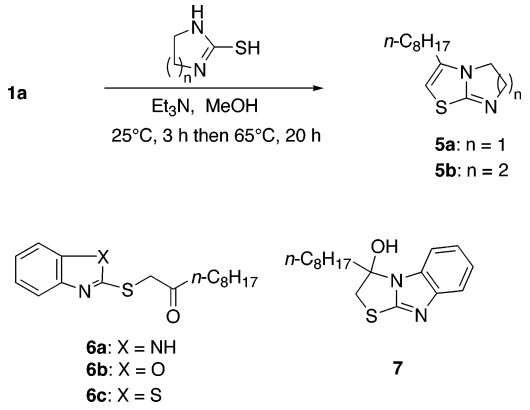
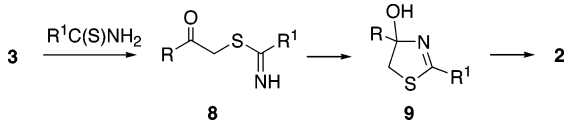
SCHEME 2



SCHEME 3



with vinyl-λ^3-iodane **1a**, produced bridgehead heterocycles **5a** (45%) and **5b** (64%) (Scheme 2). On the other hand, in the reaction with 2-mercaptobenzimidazole, the simple substitution product α-thio ketone **6a** was obtained in 69% yield. Similarly, 2-mercaptobenzoxazole and 2-mercaptobenzothiazole afforded α-thio ketones **6b** and **6c** in quantitative yields. In $CDCl_3$ solution at 25 °C, the α-thio ketone **6a** exists in equilibrium with the cyclized alcohol **7** in a ratio of 65:35, which was determined by ^{1}H NMR.[8]

Direct synthesis of 2,4-disubstituted thiazoles **2** from vinyl-λ^3-iodanes **1** probably involves the following reaction sequences (Scheme 3): (1) in situ generation of α-λ^3-iodanyl ketones **3** via ester exchange, followed by the nucleophilic substitutions with thioureas or thioamides yielding α-thio ketones **8** and (2) intramolecular cyclization and subsequent dehydration of the resulting alcohol **9**. The presence of the 2-amino group in **9** will increase the rate of dehydration by the donation of the lone pairs of electrons.

Experimental Section

General Information. For general experimental details, see ref 6b. (*Z*)-(2-Acetoxy-1-decenyl)- **1a**, (*Z*)-(2-acetoxy-5-phenyl-1-pentenyl)- **1b**, and (*Z*)-(2-acetoxy-3,3-dimethyl-1-butenyl)-(phenyl)-λ^3-iodanes **1c** were prepared from the corresponding 1-alkynyl(phenyl)-λ^3-iodanes[9] via Michael addition of acetic acid in the presence of sodium acetate according to the literature procedure.[7b]

General Procedure for Synthesis of 2,4-Disubstituted Thiazole 2. A Typical Example (Table 1, Entry 1): 2-Amino-4-octylthiazole (2a). To a stirred solution of (*Z*)-(2-acetoxy-1-decenyl)-λ^3-iodane **1a** (25 mg, 0.05 mmol) and thiourea (5 mg, 0.06 mmol) in dry methanol (1.5 mL) was added triethylamine (6.2 mg, 0.06 mmol) under nitrogen at room temperature, and the mixture was stirred for 5 h. After removal of the solvent under reduced pressure, the residue was dissolved in diethyl ether (30 mL) and water (10 mL). The organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated. Purification by preparative TLC (hexanes−ethyl acetate 9:5) gave thiazole **2a** (9.9 mg, 91%) as colorless plates (from dichloromethane−hexane): mp 55−56 °C; IR (KBr) 3428, 2923, 1609, 1511 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.08 (s, 1H), 4.87 (br s, 2H), 2.52 (t, J = 7.5 Hz, 2H), 1.63 (quint, J = 7.5 Hz, 2H), 1.38−1.20 (m, 10H), 0.87 (t, J = 6.6 Hz, 3H); MS *m*/*z* (relative intensity) 212 (M^+, 12), 127 (34), 114 (100); HRMS *m*/*z* calcd for $C_{11}H_{20}N_2S$ (M^+) 212.1347, found. 212.1340. Anal. Calcd for $C_{11}H_{20}N_2S$: C, 62.22; H, 9.49; N, 13.19. Found: C, 62.00; H, 9.50; N, 13.19.

General Procedure for Synthesis of α-Thio Ketones 6. A Typical Example: 1-(2-Benzimidazolylthio)-2-decanone (6a). To a stirred solution of (*Z*)-(2-acetoxy-1-decenyl)-λ^3-iodane **1a** (33 mg, 0.07 mmol) and 2-mercaptobenzimidazole (12 mg, 0.08 mmol) in dry methanol (3 mL) was added triethylamine (8 mg, 0.08 mmol) under nitrogen at room temperature, and the mixture was stirred for 3 h and then refluxed for 20 h. After removal of the solvent under reduced pressure, the residue was dissolved in diethyl ether and water. The organic layer was washed with water and brine, dried, and concentrated. Purification by preparative TLC (hexanes−ethyl acetate 1:2) gave **6a** (14 mg, 69%) as a yellow solid. ^{1}H NMR (in $CDCl_3$ at 25 °C) showed that the ketone **6a** exists in equilibrium with the cyclized alcohol **7** in a ratio of 65:35.[8] **Compound 6a:** IR ($CHCl_3$) 3450, 3020, 2928, 1714, 1440 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55−7.44 (m, 2H for **6a**), 7.44−7.37 (m, 2H for **7**), 7.22−7.16 (m, 2H for **6a**), 7.14−7.09 (m, 2H for **7**), 4.07 (s, 2H for **6a**), 3.93 (d, J = 11.7 Hz, 1H for **7**), 3.73 (d, J = 11.7 Hz, 1H for **7**), 2.62 (t, J = 7.4 Hz, 2H for **6a**), 2.41−2.25 (m, 2H for **7**), 1.66−1.49 (m, 2H for **6a** and **7**), 1.38−1.18 (m, 10H for **6a** and **7**), 0.87 (t, J = 7.4 Hz, 3H for **6a** and **7**); MS *m*/*z* (relative intensity) 304 (M^+, 28), 164 (100), 150 (34), 131(16); HRMS *m*/*z* calcd for $C_{17}H_{24}N_2OS$ (M^+) 304.1632, found 304.1609.

Supporting Information Available: Characterization of compounds **2b**−**g**, **4a**, **4b**, **5a**, **5b**, **6b**, and **6c** and ^{1}H NMR spectra of compounds: **2b**, **2d**−**g**, **4b**, **5a**, **5b**, and **6a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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