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Stereoselective Synthesis of (*Z*)-Enethiols and Their Derivatives: Vinylic S_N2 Reaction of (*E*)-Alkenyl(phenyl)-λ^3-iodanes with Thioamides

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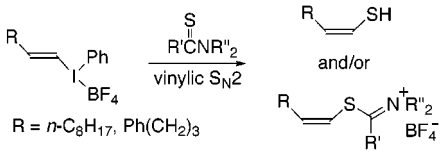
ABSTRACT



Exposure of (*E*)-β-alkylvinyl(phenyl)-λ^3-iodanes to thioamides in dichloromethane at room temperature was found to result in a bimolecular nucleophilic substitution (S_N2) at the vinylic carbon atom to give inverted (*Z*)-enethiols and/or (*Z*)-*S*-vinylthioimidonium salts. Vinylic S_N2 reactions with thioureas are also discussed.

Hypervalent alkenyl(phenyl)-λ^3-iodanes are highly reactive species in the reaction with nucleophiles because of the very high leaving ability of λ^3-phenyliodanyl groups.[1] We were interested to see that (*E*)-β-alkylvinyl(phenyl)-λ^3-iodanes **1** underwent a bimolecular nucleophilic substitution (S_N2) at the vinylic carbon atoms,[2] given that vinylic S_N2 reactions have been considered to be high-energy, low-probability processes and, as such, have been neglected for a long time. Nucleophiles that may participate in vinylic S_N2 reaction with **1** include halides, dialkyl sulfides and selenides, phosphoroselenoates, dithiocarbamates, and carboxylic acids.[1,3] Formamides with rather low nucleophilicity also act as a nucleophile toward (*E*)-β-alkylvinyliodanes **1** and afford (*Z*)-vinyl formates stereoselectively via vinylic S_N2 reaction.[4] This reaction requires heating at 50 °C. We report herein vinylic S_N2 reaction of (*E*)-β-alkylvinyl(phenyl)-λ^3-iodanes **1** with thioamides, which proceeds under mild conditions and yields (*Z*)-enethiols and/or (*Z*)-*S*-vinylthioimidonium salts with exclusive inversion of configuration, depending on the structure of thioamides and/or on the workup procedure.

Thioamides are more nucleophilic than the corresponding amides,[5] and thus nucleophilic substitutions of (*E*)-λ^3-vinyliodanes **1** with thioamides proceed even at room temperature. However, in contrast to the reaction with formamides that affords inverted (*Z*)-vinyl formates stereoselectively, no formation of the corresponding (*Z*)-vinyl thioformates was observed in the reaction with thioforma-

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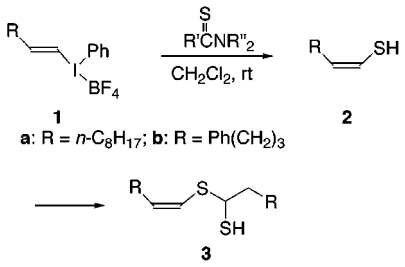
mides, but instead, (*Z*)-enethiols **2** were obtained selectively (Scheme 1). Exposure of (*E*)-1-decenyl(phenyl)-λ^3-iodane **1a**

Scheme 1



to *N*,*N*-dimethylthioformamide (3 equiv) in dichloromethane at room temperature for 20 h results in nucleophilic vinylic substitutions. After quenching the reaction mixture with water, extraction with dichloromethane, and evaporation under aspirator vacuum afforded a mixture of (*Z*)-enethiol **2a** (70%) and iodobenzene (44%). Yields of the products were determined by ^{1}H NMR, because (*Z*)-enethiol **2a** is labile and tends to readily dimerize to (*Z*)-1-decenyl 1-mercaptodecyl sulfide (**3a**) upon further purification by silica gel chromatography or upon attempted removal of the byproduct iodobenzene under high vacuum.[6] Reactions with thioacetamide and thiobenzamide also afforded (*Z*)-enethiol **2a** stereoselectively (Table 1). Similarly, (*E*)-5-phenyl-1-

Table 1. Synthesis of (*Z*)-Enethiols **2** by Reaction of Vinyl-λ^3-iodanes **1** with Thioamides[a]

entry	1	thioamide (equiv)	*t* (h)	2	yield (%)[b]
1	**1a**	Me_2NCHS (3.0)	20	**2a**	70
2	**1a**	$MeCSNH_2$ (1.1)	23	**2a**	82
3	**1a**	$PhCSNH_2$ (1.1)	52	**2a**	47[c]
4	**1b**	Me_2NCHS (3.0)	30	**2b**	82

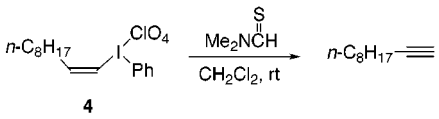
[a] Reactions were carried out in dichloromethane at room temperature under nitrogen. [b] Yields were determined by ^{1}H NMR. [c] (*Z*)-1-Decenyl 1-mercaptodecyl sulfide (**3a**) was obtained in 32% yield.

pentenyl-λ^3-iodane **1b** gave (*Z*)-enethiol **2b** in 82% yield upon reaction with *N*,*N*-dimethylthioformamide.

Small vicinal coupling constants between the vinylic protons of **2a** (J = 9.6 Hz) and **2b** (J = 8.9 Hz) in ^{1}H NMR clearly indicate a *cis* structure.[7,8] No evidence for formation of either the (*E*) isomer of **2** or the corresponding thioaldehyde tautomer was found. In general, thioaldehydes are highly unstable in solution and readily tautomerize into the corresponding enethiols provided that they have α-enethiolizable hydrogen atoms.[5,9] For instance, a stereoisomeric mixture of (*E*)- and (*Z*)-1-mercaptopropenes was the only product obtained from ethyl 1-propenyl sulfide in the reaction with lithium in liquid ammonia.[10] Facile enethiolization of thioaldehydes is probably due to the weak π-bond of thiocarbonyl groups.[11] Methods for synthesizing acyclic enethiols of the type RCH═CHSH are very limited and often inefficient in terms of stereoselectivity and yields of the products.[7b,c] The reaction described above provides a novel method for the synthesis of aliphatic (*Z*)-enethiols **2** in a highly stereoselective manner under mild conditions.

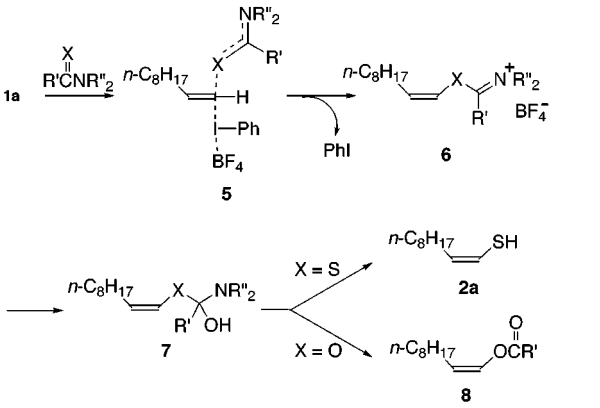
Attempts at nucleophilic substitution of (*Z*)-1-decenyl-(phenyl)-λ^3-iodane **4** with *N*,*N*-dimethylthioformamide resulted exclusively in the reductive elimination of iodobenzene yielding 1-decyne (93%), as observed in the reaction of **4** with *N*,*N*-dimethylformamide (Scheme 2).[4]

Scheme 2



The exclusive inversion of configuration observed strongly suggests a vinylic S_N2 mechanism for the reaction of (*E*)-λ^3-vinyliodanes **1** with thioamides, which is shown in Scheme 3. Nucleophilic attack by sulfur atoms of thioamides

Scheme 3

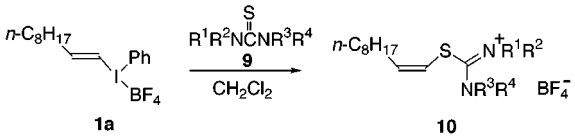


on **1a** from the side opposite the hyperleaving group PhI-(BF_4) would produce the inverted (*Z*)-*S*-vinylthioimidonium salt **6** (X = S) stereoselectively via an S_N2 transition state **5**.[1,12] Subsequent hydrolysis of (*Z*)-*S*-vinylthioimidonium salt **6** affords the retained (*Z*)-enethiol **2a** via decomposition of the intermediate **7**, derived from **6** by the addition of water. In fact, it was possible to detect formation of the intermediate (*Z*)-*S*-vinylthioimidonium salt **6** when the reaction mixture was purified without treatment with water. For instance, (*Z*)-*S*-vinylthioimidonium salt **6a** (R′ = Me, R″ = H, X = S) was obtained in the reaction of **1a** with thioacetamide in 87% yield when the reaction mixture was purified by decantation with ether and hexane. Reaction of **1a** with thiobenzamide also afforded the inverted (*Z*)-*S*-vinylthioimidonium salt **6b** (R′ = Ph, R″ = H, X = S) in 77% yield after decantation. These (*Z*)-*S*-vinylthioimidonium salts **6a** and **6b** are labile and highly susceptible to hydrolysis with water, yielding (*Z*)-enethiol **2a** and/or the dimer **3a**.

As shown in Scheme 3, decomposition modes of tetrahedral intermediates **7** will determine the structure of products. In the vinylic S_N2 reaction of **1a** with amides yielding the (*Z*)-vinyl ester **8**, intervention of the intermediates **7** (X = O) has also been proposed, in which liberation of amino groups (or ammonio groups) preferentially takes place. In marked contrast, tetrahedral sulfur analogues **7** (X = S) collapse to (*Z*)-enethiol **2a** exclusively with the vinylthio group being released. These results probably reflect differences in leaving ability of the vinylthio groups and the vinyloxy groups.

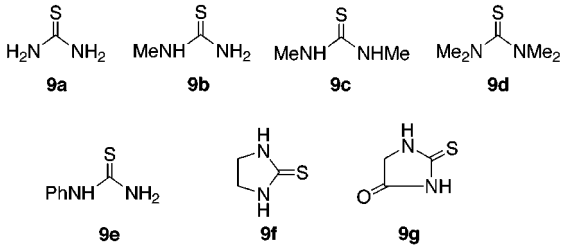
Thioureas also act as good nucleophiles in vinylic S_N2 reactions of (*E*)-λ^3-vinyliodanes **1**. Thus, nucleophilic substitution of (*E*)-1-decenyl(phenyl)-λ^3-iodane **1a** with thiourea (**9a**) (1.1 equiv) in dichloromethane took place at room temperature and gave, after decantation with hexane at −78 °C, (*Z*)-*S*-vinylisothiouronium salt **10a** in 77% yield (Table 2, entry 1). Other acyclic **9b**−**e** and cyclic **9f** thioureas also undergo vinylic S_N2 reaction with **1a** to give (*Z*)-*S*-vinylisothiouronium salts **10b**−**f** in good to excellent yields**.** Here again, exclusive inversion of configuration was observed in the reaction, and no formation of the (*E*) isomer of **10** was detected. To our knowledge, synthesis of (*Z*)-*S*-vinylisothiouronium salts has not been reported previously.[13]

Table 2. Synthesis of Vninylisothiouronium Salts **10** by Reaction of λ^3-Iodane **1a** with Thioureas **9**[a]

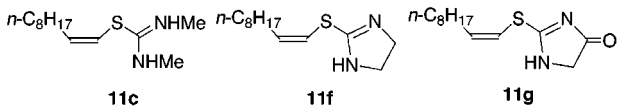


entry	**9** (equiv)	*T* (°C)/*t* (h)	**10**	yield (%)[b]
1	**9a** (1.2)	25/17	**10a**	77
2	**9b** (1.2)	25/8	**10b**	63
3	**9c** (1.0)	25/16	**10c**	76
4	**9d** (1.1)	25/24	**10d**	91
5	**9e** (1.0)	25/10	**10e**	68
6	**9f** (1.0)	25/21	**10f**	92
7	**9g** (1.2)	50/62	**10g**	0[c]

[a] Reactions were carried out in dichloromethane under nitrogen. [b] Isolated yields. [c] (*Z*)-*S*-Vinylisothiourea **11g** was obtained in 51% yield.

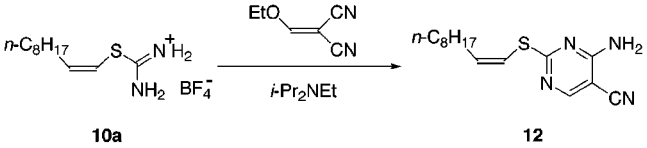


In contrast to (*Z*)-*S*-vinylthioimidonium salts **6**, (*Z*)-*S*-vinylisothiouronium salts **10** proved to be stable toward hydrolysis with water; in fact, the reaction of **1** with thioureas **9a**−**f** did not show, after aqueous workup, any sign of formation of the hydrolysis product (*Z*)-enethiol **2a**. In addition, exposure of isothiouronium salts **10c** and **10f** to aqueous sodium carbonate solution at room temperature did not give (*Z*)-enethiol **2a** at all, but instead, (*Z*)-*S*-vinylisothioureas **11c** and **11f** were obtained in high yields.



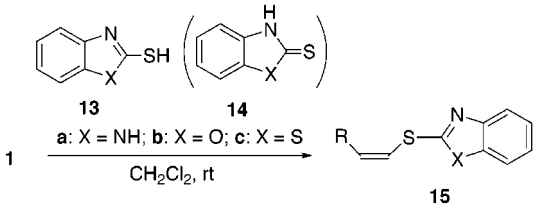
Isothiouronium salts are useful building blocks for the synthesis of heterocycles such as triazines, pyrimidines, and thiazoles.[14] As an example, we have prepared substituted pyrimidine **12** in 56% yield from isothiouronium salt **10a** by the reaction with (ethoxymethylidene)malononitrile in the presence of diisopropylethylamine in DMF at room temperature (Scheme 4).

Scheme 4



All of the 2-mercapto heterocycles **13a**−**c**, tautomers of thioamides **14a**−**c**, also react with (*E*)-λ^3-vinyliodanes **1** via a vinylic S_N2 pathway; thus, 2-mercaptobenzimidazole (**13a**), 2-mercaptobenzoxazole (**13b**), and 2-mercaptobenzothiazole (**13c**), on treatment with (*E*)-1-decenyl(phenyl)-λ^3-iodane **1a** in dichloromethane at room temperature, afforded (*Z*)-vinyl sulfides **15a**−**c** in high yields (Table 3). These reactions proceed with complete inversion of configuration. As

Table 3. Synthesis of (*Z*)-Vinylsulfides **15** by Reaction of Iodanes **1** with Thiols **13**[a]



entry	**1**	13 (equiv)	*t* (h)	**15**	yield (%)[b]
1	**1a**	**13a** (1.2)	9	**15a**	80
2	**1a**	**13b** (1.2)	44	**15b**	89
3	**1a**	**13c** (1.2)	11	**15c**	91
4	**1b**	**13c** (1.2)	22	**15d**	83

[a] Reactions were carried out in dichloromethane at room temperature under nitrogen. [b] Isolated yields.

observed in the reaction of (*Z*)-vinyl-λ^3-iodane **4** with *N*,*N*-dimethylthioformamide (Scheme 2), reductive elimination yielding 1-decyne takes place exclusively in the reaction of **4** with 2-mercaptobenzothiazole (**13c**).

In conclusion, we have shown that thioamides and their derivatives act as good nucleophiles in vinylic S_N2 reactions with (*E*)-β-alkylvinyl(phenyl)-λ^3-iodanes, and these reactions proceed under mild conditions.

Supporting Information Available: Experimental details and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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