Tunable Condensations between Ninhydrin and Sulfonium Salts Catalyzed by SeO_2 and Cs_2CO_3 Leading to Highly Functionalized Vinyl Alcohols or Vinyl Sulfides

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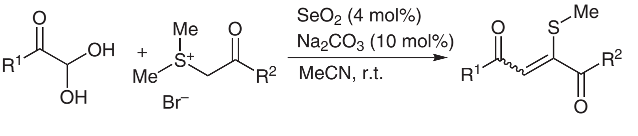
Received 22 October 2008

Abstract: Condensation reactions between ninhydrin and sulfonium salts catalyzed by SeO_2 and Cs_2CO_3 afforded highly functionalized vinyl alcohols and vinyl sulfides. In the reaction of ninhydrin with dipropyl phenacylsulfonium bromide catalyzed by SeO_2 at room temperature in MeCN, highly functionalized vinyl alcohols were formed in good yields and high selectivities. When dimethyl phenacylsulfonium iodide was used in place of dipropyl phenacylsulfonium bromide, vinyl sulfides were produced in moderate to good yields.

Key words: catalysis, condensation, ninhydrin, selenium, sulfur ylide

Selenium dioxide is known primarily for hydroxylation of activated carbon-bearing positions, particularly at allylic (or propargylic) sites.[1] Such allylic oxidation can also be performed using a catalytic amount of selenium dioxide in combination with other co-oxidatants.[2] Synthetic applications of selenium dioxide for the introduction of the carbonyl functionality at activated positions,[3] for the dehydrogenation of highly activated saturated sites,[4] and for the oxidative bond cleavage have been investigated extensively.[5] It has also been reported that nitrile can be prepared from the corresponding aldehyde via conversion to the aldoxime, followed by catalytic selenium dioxide mediated elimination.[6]

We recently reported that α-oxoaldehydes react with sulfonium salts in the presence of a catalytic amount of selenium dioxide and Na_2CO_3, yielding vinyl sulfides via the C–C bond formation followed by SeO_2-catalyzed elimination process (Scheme 1).[7] We presumed that selenium dioxide plays a dual role: it acts both as a Lewis acid and a base. This idea prompted us to extend this reaction to 1,2,3-tricarbonyl compounds. Herein, we report a new selenium dioxide catalyzed reaction of vicinal tricarbonyl coumpounds[8] **1** with sulfonium salts **2** to synthesize vinyl alcohols and vinyl sulfides, respectively (Table 1).



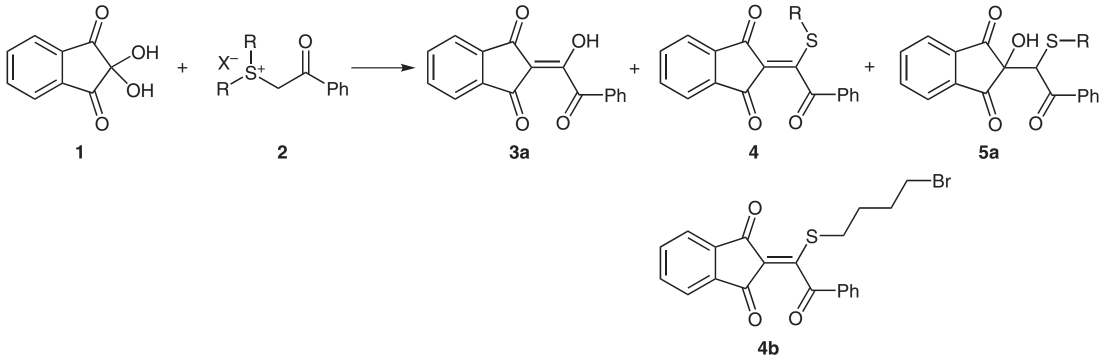
Scheme 1

Since ninhydrin has long been known to be a stable reactant of proven value in synthesis and analysis, it was selected for this study. In our initial experiments we found that reaction of ninhydrin (**1**) with dimethyl phenacyl sulfonium bromide (**2a**) catalyzed by SeO_2 (5 mol%), Cs_2CO_3 (10 mol%) in MeCN at room temperature for 7 hours afforded a mixture of vinyl alcohol **3a** and vinyl sulfide **4a** in 77% yield (**3a**/**4a** = 77:23, Table 1, entry 1). Other bases were also examined in the reaction; K_2CO_3 and Na_2CO_3 led to lower yields of the products, and Li_2CO_3 did not catalyze the reaction (entries 2–4). The effect of the molar ratio of SeO_2 to Cs_2CO_3 on the yield and the selectivity was also investigated. The highest selectivity (**3a**/**4a** = 83:17) was achieved when using 10 mol% of SeO_2 and 20 mol% of Cs_2CO_3 (entry 6). The use of a higher or lower amount of SeO_2 gave lower selectivities (entries 5, 7, 8). It was notable that when **2a** was replaced by tetramethylene phenacyl sulfonium bromide (**2b**), the reaction afforded the corresponding vinyl sulfide **4b** as a major product (**3b**/**4b** = 25:75, entry 9). In the case of dipropyl phenacyl sulfonium bromide (**2c**), vinyl alcohol **3a** became the predominant product (**3a**/**4a** ≤ 99:1, entries 10, 11). These observations suggested that the steric hindrance had a profound influence on the selectivity. When the counteranion was an iodide **2d**, the major product was vinyl sulfide **4a** (**3a**/**4a** ≤ 99:1, entries 12, 13). This indicated that iodide was a better nucleophile than bromide to substitute the thioether of the sulfonium salts. In contrast, without SeO_2, the reaction between ninhydrin (**1**) and sulfonium salt **2a** catalyzed by Cs_2CO_3 or Na_2CO_3 yielded trace amount of **3a** and **4a** (**3a** + **4a** <5%) and the major product was **5a** (35%, entry 14).

Based on these experiments, the following mechanism is proposed. For SeO_2-catalyzed synthesis of vinyl alcohols (Scheme 2), the reaction was stepwise. Initial attack of sulfur ylide **I**, generated from sulfonium salt **2** and Cs_2CO_3, on ninhydrin (**1**) led to a betaine **II**. Since betaine **II** could not eliminate sulfide immediately,[7] it then accepted a proton to form an intermediate **III** and to regenerate the hydroxide anion. Addition of SeO_2 to intermediate **III** led to an intermediate **IV**. When R was the more hindered propyl group and the anion was the less nucleophilic bromide, intermediate **IV** underwent an in-

SYNLETT 2009, No. 5, pp 0823–0827
Advanced online publication: 24.02.2009
DOI: 10.1055/s-0028-1087944; Art ID: W16808ST

Table 1 The Reaction of Ninhydrin (**1**) with Sulfonium Salts **2** Catalyzed by SeO_2 and Cs_2CO_3

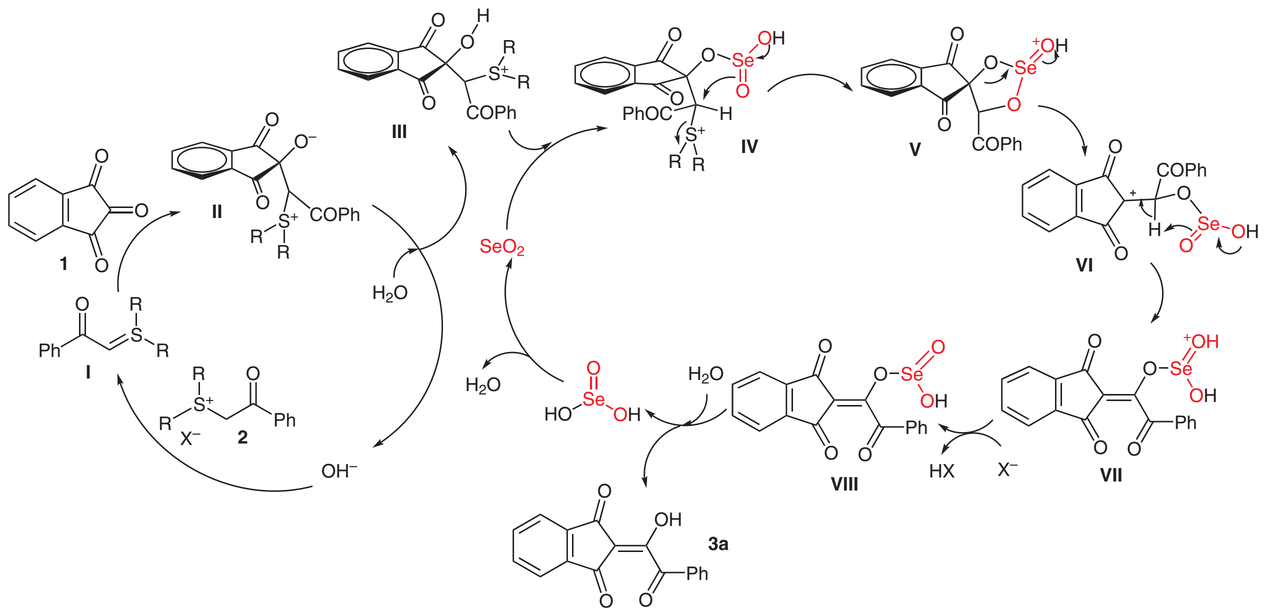


Entry	Sulfonium salts **2**	R	X	Base (mol%)	SeO_2 (mol%)	Time (h)	Product	Yield (%)[a]	3/4
1	**2a**	Me	Br	Cs_2CO_3 (10)	5	7	**3a**, **4a**	77	77:23
2	**2a**	Me	Br	K_2CO_3 (10)	5	7	**3a**, **4a**	53	76:24
3	**2a**	Me	Br	Na_2CO_3 (10)	5	24	**3a**, **4a**	27	74:26
4	**2a**	Me	Br	Li_2CO_3 (10)	5	24	–	<5	–
5	**2a**	Me	Br	Cs_2CO_3 (10)	10	3	**3a**, **4a**	88	64:36
6	**2a**	Me	Br	Cs_2CO_3 (10)	20	2.5	**3a**, **4a**	78	83:17
7	**2a**	Me	Br	Cs_2CO_3 (10)	30	13	**3a**, **4a**	70	75:25
8	**2a**	Me	Br	Cs_2CO_3 (20)	5	3	**3a**, **4a**	84	79:21
9	**2b**	$-(CH_2)_4-$	Br	Cs_2CO_3 (10)	5	7	**3a**, **4b**[d]	27	25:75
10	**2c**	Pr	Br	Cs_2CO_3 (10)	5	7	**3a**	70	>99:1
11[b]	**2c**	Pr	Br	Cs_2CO_3 (10)	20	7	**3a**	83	>99:1
12	**2d**	Me	I	Cs_2CO_3 (10)	5	2	**4a**	73	<1:99
13[b]	**2d**	Me	I	Cs_2CO_3 (10)	10	4	**4a**	77	<1:99
14[c]	**2a**	Me	Br	Cs_2CO_3 (10)	0	24	**3a**, **4a** (**5a**)	<5 (35)	–

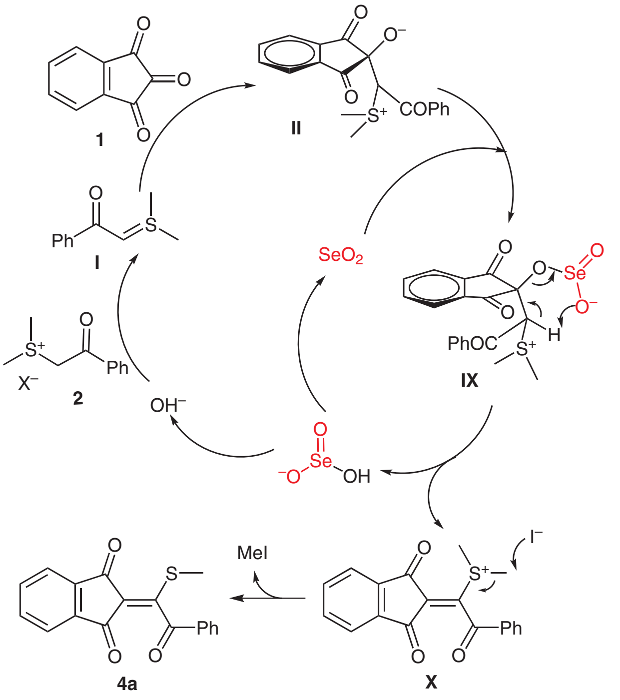
[a] Yields and ratios determined by HPLC.
[b] Isolated yields.
[c] The yield in parenthesis is for **5a**.
[d] Structure of **4b** shown above.

tramolecular displacement of dialkyl sulfide by selenate to give an intermediate **V**. It then underwent ring opening followed by the deprotonation to yield a selenate intermediate **VIII** which further hydrolyzed to give product **3a** and selenious acid.[9] On the other hand, when R was the less hindered methyl group and the anion was the more nucleophilic iodide, betaine **II** reacted with selenium dioxide to form an intermediate **IX** (Scheme 3). This was followed by an intramolecular deprotonation via a six-membered cyclic transition state to lose $HSeO_3^-$ to yield a sulfonium salt **X**. Attack of the iodide on the methyl group then led to sulfide **4a**. The released hydrogenselenite anion could then regenerate hydroxide anion and selenium dioxide.[9] In contrast, without SeO_2, intermediate **III** underwent an S_N2 nucleophilic substitution by halide to form **5** (Scheme 4).

To further prove the mechanism as well as to expand the scopes of the catalytic reaction, we treated ninhydrin (**1**) and a variety of aryl and heteroaryl derived dipropyl sulfonium bromides **2** with a catalytic amount of SeO_2 and Cs_2CO_3. As shown in Table 2, the dipropyl sulfonium salts bearing electron-withdrawing or electron-donating substituents were all compatible to the reaction conditions and led to the corresponding vinyl alcohol **3** in 60–92% yields in high selectivities (Table 2, entries 1–7). Additionally, it should be mentioned that sulfonium salts bearing electron-withdrawing groups such as **2c** and **2d**, were more reactive and selective than those bearing electron-donating groups such as **2g**–**2j**. In the case of **2k** and **2l**, the reactions did not yield any product (entries 8, 9). These facts were in agreement with the proposed mecha-



Scheme 2 Plausible mechanism of SeO_2-catalyzed condensations between ninhydrin (**1**) and sulfonium salts **2** leading to vinyl alcohols **3**

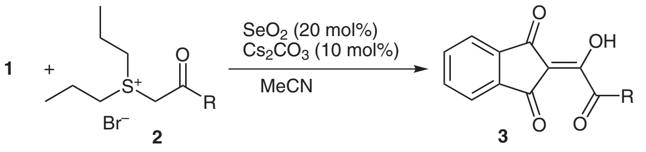


Scheme 3 Plausible mechanism of SeO_2-catalyzed condensations between ninhydrin (**1**) and sulfonium salts **2** leading to vinyl sulfides **4**

nism. This was caused by the relative weak acidity of the sulfonium salts.

When iodide was the counter anion of the sulfonium salts, vinyl sulfide **4** was obtained as the major product in 48–77% yield (**3a**/**4a** ≤ 1:99; Table 3, entries 1–6). Aliphatic substituted sulfonium iodides **2r** and **2t** did not react with ninhydrin (**1**) to give the desired products (entries 7, 9), which was probably due to the slightly weaker acidity of the aliphatic sulfonium salts. In the case of **2s**, a similar

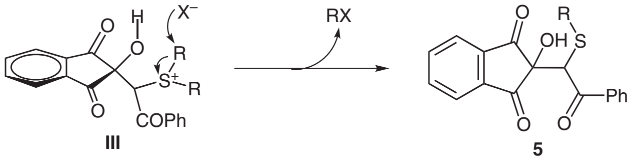
Table 2 SeO_2-Catalyzed Reaction of Ninhydrin (**1**) with Sulfonium Salts **2** to Yield Vinyl Alcohols[10]



Entry	2	R	3	Time (h)	Yield (%)[a]	3/4
1	**2c**	Ph	**3a**	7	83	>99:1
2	**2e**	4-FC_6H_4	**3c**	5	90	>99:1
3	**2f**	4-ClC_6H_4	**3d**	5	92	>99:1
4[b]	**2g**	4-$MeOC_6H_4$	**3e**	24	71	82:18
5[b]	**2h**	4-$AcOC_6H_4$	**3f**	24	73	90:10
6[b]	**2i**	4-MeC_6H_4	**3g**	24	70	95:5
7[b]	**2j**	2-furyl	**3h**	24	60	75:25
8	**2k**	Me	**3i**	24	0	
9	**2l**	EtO	**3j**	24	0	

[a] Isolated yields; ratios determined by HPLC.

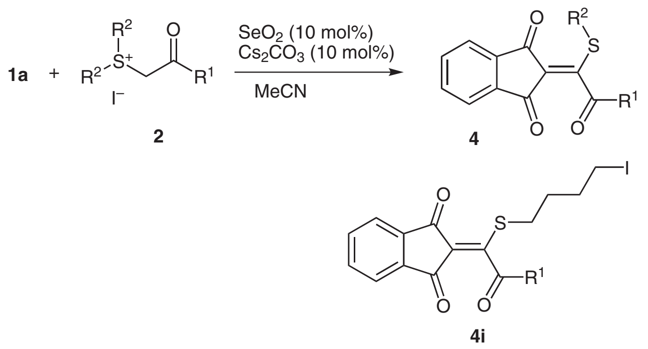
[b] Ratios determined by ^1H NMR spectroscopy of the crude product.



Scheme 4 The mechanism of the formation of compound **5**

pattern of condensation and dealkylation was followed. Dealkylation resulted in the fission of the ring, leading to the corresponding vinyl sulfide **4i** with a long chain (entry 8).

Table 3 SeO_2-Catalyzed Reaction of Ninhydrin (**1**) with Sulfonium Salts **2** to Yield Vinyl Sulfides[11]



Entry	2	R^1	R^2	4	Time (h)	Yield (%)[a]
1	**2d**	Ph	Me	**4a**	4	77
2	**2m**	4-ClC_6H_4	Me	**4c**	4	66
3	**2n**	4-$AcOC_6H_4$	Me	**4d**	18	60
4	**2o**	4-$MeOC_6H_4$	Me	**4e**	12	55
5	**2p**	2-$MeOC_6H_4$	Me	**4f**	24	72
6	**2q**	2-thiophene	Me	**4g**	12	48
7	**2r**	Me	Me	**4h**	20	0
8	**2s**	Ph	$-(CH_2)_4-$	**4i**[b]	20	50
9	**2t**	EtO	Me	**4j**	24	0

[a] Isolated yields.

[b] Structure shown above.

In conclusion, we have developed simple procedures for the synthesis of vinyl alcohols and vinyl sulfides from the reaction of ninhydrin and sulfonium salts catalyzed by Cs_2CO_3 and SeO_2. The reactions are highly chemoselective if the anion or the size of alkyl groups of the sulfonium is properly chosen. From ninhydrin both vinyl alcohols and vinyl sulfides products could be obtained in fair to good yields.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Acknowledgment

We thank NSFC (20572078) for financial support.

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(10) **Typical Procedure for Preparing Compound 3**
A mixture of ninhydrin (**1**, 178 mg, 1.0 mmol), dipropyl phenacylsulfonium bromide (**2c**, 317 mg, 1.0 mmol), SeO_2 (22 mg, 0.2 mmol), and Cs_2CO_3 (33 mg, 0.1 mmol) in MeCN (10 mL) was stirred for 7 h at r.t. After complete consumption of the starting materials (TLC), MeCN was removed in vacuum to give yellow solid. The residue was treated with aq H_2SO_4 (10%, 1 mL) followed by brine (10 mL), and extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were dried over anhyd Na_2SO_4. The extracts were then concentrated under reduced pressure, and the residue was purified by column chromatography (eluent: PE–EtOAc) on SiO_2 to give a 83% yield of **3a**.
^1H NMR (500 MHz, $CDCl_3$): $\delta = 8.07$ (d, $J = 7.4$ Hz, 1 H), 7.98 (d, $J = 7.5$ Hz, 2 H), 7.91–7.84 (m, 3 H), 7.65 (t, $J = 7.4$ Hz, 1 H), 7.52 (t, $J = 7.8$ Hz, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 189.24$, 186.09, 185.49, 142.78, 139.22, 138.95, 136.21, 136.20, 134.67, 132.37, 131.09, 129.48, 129.06, 124.03, 123.95 ppm. IR (KBr): $\nu = 1737$, 1699, 1670, 1622, 1589, 1451, 1354, 1330, 1246, 1121, 1060, 810, 741, 688 cm^{-1}. ESI-MS: m/z (%) = 277.2 (100) $[M^+ - H]$. Anal. Calcd for $C_{17}H_{10}O_4$: C, 73.38; H, 3.62. Found: C, 73.33; H, 3.61.

(11) **Typical Procedure for Preparing Compound 4**
A mixture of ninhydrin (**1**, 178 mg, 1.0 mmol), dimethyl phenacylsulfonium iodide (**2d**, 308 mg, 1.0 mmol), SeO_2 (11 mg, 0.1 mmol), and Cs_2CO_3 (33 mg, 0.1 mmol) in MeCN (10 mL) was stirred for 4 h at r.t. After complete consumption of starting materials (TLC), MeCN was removed in vacuum to give yellow solid. The residue was treated with brine (10

mL) and extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were dried over anhyd Na_2SO_4. The extracts were then concentrated under reduced pressure, and the residue was purified by column chromatography (eluent: PE–EtOAc) on SiO_2 to give a 77% yield of **4a**.
^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.02 (d, *J* = 7.7 Hz, 2 H), 7.92 (d, *J* = 7.3 Hz, 1 H), 7.76–7.68 (m, 3 H), 7.64 (t, *J* = 7.2 Hz, 1 H), 7.51 (d, *J* = 7.6 Hz, 2 H), 2.28 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 190.68, 189.56, 185.92, 165.82, 141.61, 139.97, 134.95, 134.91, 134.73, 129.27, 128.71, 124.25, 123.36, 122.80, 14.46 ppm. IR (KBr): ν = 1672, 1595, 1551, 1451, 1351, 1246, 1153, 1076, 1043, 836, 737, 690 cm^{-1}. ESI-MS: *m/z* (%) = 309.4 (100) [M^+ + H]. Anal. Calcd for $C_{18}H_{12}O_3S$: C, 70.11; H, 3.92. Found: C, 70.15; H, 3.98.