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Hydroxy-Group-Facilitated Vinylic Iodination of *ortho*-Vinylnaphthols Using Molecular Iodine

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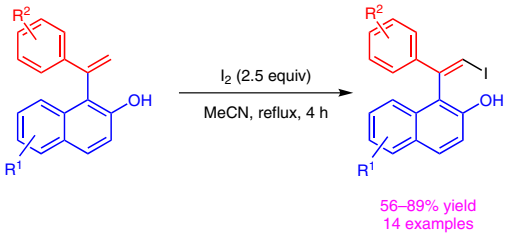

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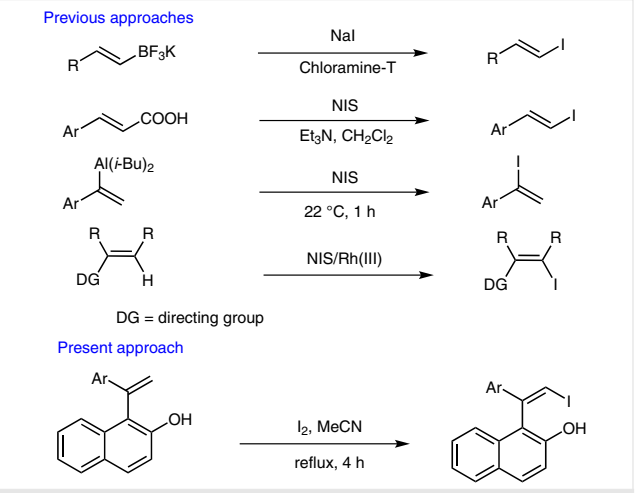
Abstract An efficient and simple one-pot method for the iodination of *ortho*-vinylnaphthols using molecular iodine is disclosed. The reaction is believed to proceed through formation of quinone methide intermediate. The method tolerates different functional groups and provides corresponding *ortho*-iodovinylnaphthols in good to excellent yields.

Key words vinylnaphthol, iodovinylnaphthols, molecular iodine, iodination

The vinyl iodides are the multipurpose building blocks to synthesize organic molecules via transition-metal-catalyzed cross-coupling reaction.[1] The vinyl iodide moiety is also a key fragment for several natural products and drug molecules.[2] The classical method to synthesize vinyl iodides is hydrazone iodination where iodine reacts with hydrazone in the presence of a non-nucleophilic base such as trimethylamine. Since then, several methods were developed for the synthesis of vinyl iodides.[3] In recent years synthesis of vinyl iodides have been achieved through halogen exchange by CuI in the presence of amine ligands,[4] iodination of organotrifluoroborates,[5] decarboxylative iodination of carboxylic acids by *N*-iodosuccinimide (NIS) in the presence of trimethylamine,[6] hydroalumination–iodination of alkynes,[7] hydrozirconation–iodination of alkynes, ruthenium-catalyzed silylative coupling followed by NIS-mediated iododesilylation,[8] and rhodium-catalyzed iodination of vinylic C–H bonds.[9] Commercial availability of vinyl halides is much less than aryl halides and there has been much interest in efficient methods for their preparation. The development of facile synthetic methods for vinyl halides is still required. Herein, we report our finding on hydroxy-group facilitated vinylic iodination of *ortho*-vinylnaphthols using molecular iodine (Scheme 1). To the best of our knowledge this is the first report on vinylic iodination of *ortho*-vinylnaphthols.

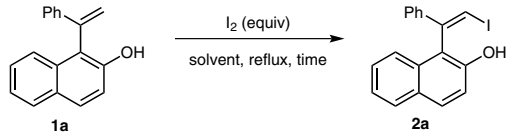


Scheme 1 Existing routes and our approach for vinylic iodination

In our previous study on iodine-mediated synthesis of naphthofurans,[10] formation of 1-(2-iodo-1-phenylvinyl)-naphthalen-2-ol (**2a**) was observed instead of expected 1-phenylnaphthofuran when the reaction was performed with iodine in the absence of base. Structure of **2a** was elucidated by spectral data. In the ^{1}H NMR spectrum of **2a**, a characteristic singlet appeared at δ = 7.63 ppm for vinylic proton and at δ = 5.20 ppm for hydroxyl proton along with other proton peaks. In the ^{13}C NMR spectrum, the characteristic peak for vinylic carbon attached to iodo appeared at δ = 86.1 ppm along with all other carbons. Finally, a peak at *m/z* = 373.0087 in the HRMS spectrum corresponding to molecular ion $C_{18}H_{14}IO$ $[M + H]^+$ confirmed the structure of **2a**.

To improve the yield of iodinated product and understand the underlying mechanism we performed several experiments. Initially, when **1a** was treated with 1.5 equivalents of I_2 without K_2CO_3 under reflux conditions in acetonitrile for 2 hours, **2a** was isolated in 52% yield (Table 1, entry 1). Increasing reaction duration and concentration of iodine increased the yield of **2a** (Table 1, entries 1–4). However, increasing loading of of iodine more than 2.5 equivalents did not increase the yield of **2a** (Table 1, entry 5). To improve the yield of this reaction, we examined the solvent effect. In THF, DMSO, and toluene, **2a** was obtained in 86%, 71%, and 62% yield, respectively, whereas in acetone **2a** was not formed (Table 1, entries 6–9). It is also worth mentioning that prolonged reaction time (12 h) failed to improve the yield of **2a** (Table 1, entry 10). Decrease in yield on increasing time is due to the fact that at higher temperature product **2a** is unstable. Formation of **2a** was not observed when **1a** was treated HI alone. Similarly use of other iodine sources such as NIS, KI, and IBD did not result in formation of **2a**. In case of NIS instead of **2a** the cyclized product 1-phenylnaphtho[2,1-*b*]furan was formed in 10% yield.

Table 1 Optimization of Reaction Conditions[a]



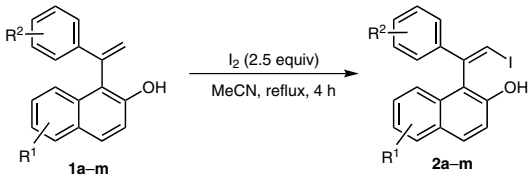
1a **2a**

Entry	Iodine source (equiv)	Solvent	Time (h)	Yield (%)[b]
1	I_2 (1.5)	MeCN	2	52
2	I_2 (1.5)	MeCN	4	63
3	I_2 (2.0)	MeCN	4	73
4	I_2 (2.5)	MeCN	4	89
5	I_2 (4.0)	MeCN	4	83
6	I_2 (2.5)	THF	4	86
7	I_2 (2.5)	DMSO	4	71[c]
8	I_2 (2.5)	toluene	4	62
9	I_2 (2.5)	acetone	4	n.r.[d]
10	I_2 (2.5)	MeCN	12	74
11	HI (2.0)	MeCN	8	n.r.
12	NIS (2.0)	MeCN	1	–[e]
13	KI (2.0)	MeCN	8	n.r.[d]
14	IBD (2.0)	MeCN	1	n.r.[d]

[a] Reagents and conditions: **1a** (1.0 mmol), I_2 (1.5–4.0 equiv), solvent (3 mL) at reflux conditions.
[b] Isolated yield.
[c] 80 °C.
[d] No reaction
[e] Cyclized product, 1-phenylnaphtho[2,1-*b*]furan was formed in 10%.

Having the optimized conditions in hand, we next investigated the general application of this process. *ortho*-Vinylnaphthols having various substituent groups reacted well with molecular iodine under the optimized conditions to generate the corresponding iodovinylnaphthols. The results are summarized in Table 2. The reaction is of general nature and tolerated different functional groups such as methoxy, methyl, bromo, and fluoro on both the aryl and naphthyl ring and gave good to excellent yields (56–89%) of iodovinylnaphthols. However, reaction of 4-methoxy-2-(1-phenylvinyl)phenol and 3-buten-1-ol with iodine under optimized reaction conditions did not result in the formation of expected iodovinyl derivatives, which mean that the substrate scope for this reaction is limited to *ortho*-vinylnaphthols.

Table 2 Synthesis of Iodovinylnaphthols[a,12]



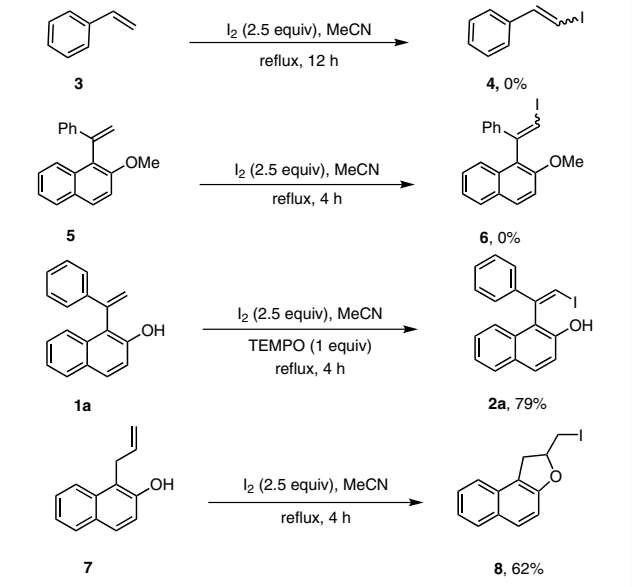
1a–m **2a–m**

Entry	R^1	R^2	Product **2**	Yield (%)[b]
1	H	H	**2a**	89
2	H	4-Me	**2b**	77
3	H	4-MeO	**2c**	84
4	H	4-F	**2d**	65
5	7-MeO	H	**2e**	61
6	7-MeO	4-Me	**2f**	63
7	7-MeO	4-F	**2g**	68
8	6-Br	H	**2h**	69
9	6-Br	4-Me	**2i**	72
10	6-Br	4-MeO	**2j**	76
11	6-Ph	H	**2k**	61
12	6-Ph	4-Me	**2l**	66
13	4-$MeOC_6H_4$	H	**2m**	67
14	3,4-$(MeO)_2C_6H_3$	H	**2n**	56

[a] Reaction conditions: **3** (1.0 mmol), I_2 (2.5 equiv), MeCN (3 mL) reflux for 4 h.
[b] Isolated yield.

To understand the underlying mechanism some control experiments were performed (Scheme 2). Reaction of styrene and 2-methoxy-1-(1-phenylvinyl)naphthalene failed to give the corresponding iodinated product under the optimized conditions. On the other hand, reaction of **1a** with iodine in the presence of radical scavenger TEMPO (1.0 equiv) gave **2a** in 79% yield. Also, reaction of **1a** with iodine (1.0 equiv) in the presence of HI (1.0 equiv) was much slower, and only 50% conversion was observed after 8 hours indicating that HI is not catalyzing this transformation. *ortho*-Allylnaphthol (**7**) on reaction with iodine under these conditions gave 2-(iodomethyl)-1,2-dihydronaphtho[2,1-*b*]furan (**8**) in 62% yield. Formation of **8** is reported in the litera-

ture to occur through 5-*exo*-trig type iodocyclization.[11] These control experiments suggested that the reaction is assisted by the hydroxyl group, involves formation of iodonium ion and proceeds through nonradical mechanism pathway.



Scheme 2 Control experiments

The stereochemistry about the double bond was determined by the 2D NOSEY experiment. In the 2D NOSEY spectrum of **2f** (Figure 1), strong correlations indicating through-space coupling among the vinylic proton and protons at the C_2 and C_6 carbons of the tolyl ring established that both groups (vinylic proton and tolyl ring) were situated in the same orientation and hence double bond in **2f** has *Z*-geometry.

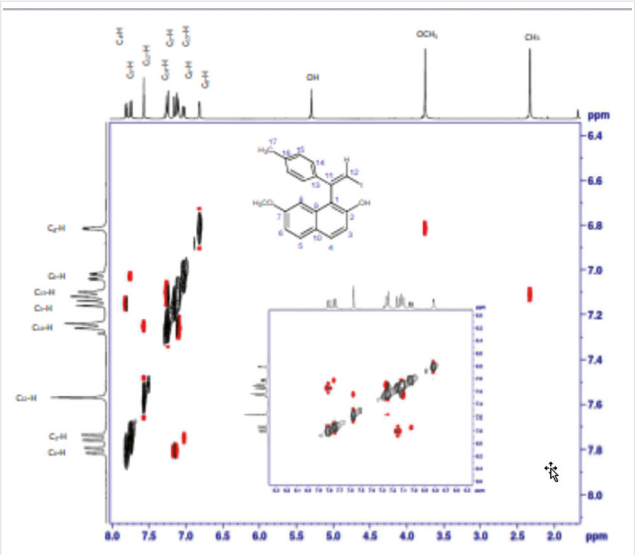
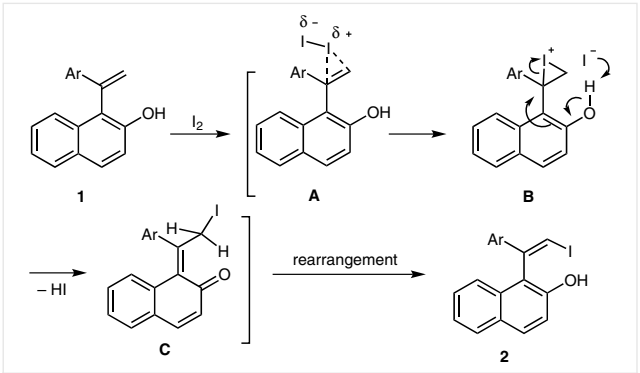


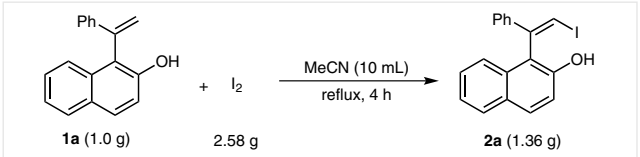
Figure 1 2D NOSEY spectrum of **2f**

Based on control experiments and literature reports[13] the plausible reaction mechanism for vinylic iodination of *ortho*-vinylnaphthols is proposed in Scheme 3. It is believed that initially interaction of the vinylic bond and molecular iodine leads to intermediate **A**, which further converts into iodonium intermediate **B**. Elimination of HI generates *ortho*-quinone methide intermediate **C**. Intramolecular rearrangement of **C** gives vinyl iodide derivative **2**.



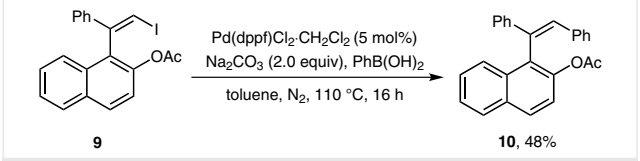
Scheme 3 Plausible mechanism of vinylic iodination of *ortho*-vinylnaphthols

Further to demonstrate the efficiency and scalability of the developed methodology, a gram-scale reaction for the synthesis of **2a** was performed. As shown in Scheme 4, **2a** could be readily synthesized in 1.36 grams (90%) from 1.0 gram of **1a** in a gram-scale synthesis.



Scheme 4 Gram-scale synthesis of **2a**

Finally, the synthetic utility of iodovinylnaphthol was demonstrated via acylation followed by Suzuki coupling reaction. When acylated iodovinylnaphthol, 1-(2-iodo-1-phenylvinyl)naphthalen-2-yl acetate (**9**), was reacted with phenylboronic acid in the presence of 5 mol% $Pd(dppf)Cl_2$, the desired coupled product 1-(1,2-diphenylvinyl)naphthalen-2-yl acetate (**10**) was obtained in 48% yield (Scheme 5).



Scheme 5 Synthetic utility of *ortho*-vinylnaphthol

In summary we have demonstrated a straightforward, atom-economical, high-yielding procedure for the synthesis of iodovinylnaphthols. Use of molecular iodine, metal-free conditions, good functional-group tolerance, no pre-activation requirement of the vinylic group, and high yield are the salient features of the present methodology. The synthetic utility, efficiency, and scalability of the method are clear. We hope that this methodology will find widespread use in organic synthesis.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1560559.

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(12) **Synthesis of 2a**
In an oven-dried 25 mL round-bottom flask compound **1a** (246 mg, 1.0 mmol), I_2 (634 mg, 2.5 mmol), and MeCN (3 mL) was added. The reaction mixture was refluxed for 4 h. After cooling the reaction mixture, the reaction was quenched with $Na_2S_2O_3$ solution and extracted with EtOAc (2 × 5 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and then concentrated on rotatory evaporator under vacuum. The crude product was purified by column chromatography over silica gel (100–200 mesh) using hexane–EtOAc as eluent to give **2a** as an off-white viscous liquid.
Spectral Data for Selected Compounds
1-(2-Iodo-1-phenylvinyl)naphthalen-2-ol (2a)
Yield 89%; off-white viscous liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.86 (d, *J* = 9.0 Hz, 1 H), 7.81 (dd, *J* = 8.19, 2.30 Hz, 1 H), 7.63 (s, 1 H), 7.49 (dd, *J* = 8.19, 2.30 Hz, 1 H), 7.40–7.21 (m, 8 H), 5.20 (s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 149.4, 146.9, 138.7, 131.5, 130.4, 129.1, 129.0, 128.9, 128.3, 127.1, 126.5, 124.1, 123.7, 121.1, 117.7, 86.0. IR: 756, 1188, 1250, 3055, 3496 cm^{-1}. ESI-HRMS: *m/z* calcd for $C_{18}H_{14}IO^+$ [M + H]$^+$: 373.0084; found: 373.0087.
1-(2-Iodo-1-*p*-tolylvinyl)-7-methoxynaphthalen-2-ol (2f)
Yield 63%; viscous liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.80 (d, *J* = 8.8 Hz, 1 H), 7.74 (d, *J* = 8.9 Hz, 1 H), 7.57 (s, 1 H), 7.25 (d, *J* = 8.2 Hz, 2 H), 7.14 (d, *J* = 8.8 Hz, 1 H), 7.11 (d, *J* = 8.1 Hz, 2 H), 7.03 (dd, *J* = 8.9, 2.5 Hz, 1 H), 6.81 (d, *J* = 2.4 Hz, 1 H), 5.32 (s, 1 H), 3.75 (s, 3 H), 2.33 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.6, 150.0, 147.0, 138.9, 136.1, 132.9, 130.0, 129.8, 129.7, 126.4, 124.5, 120.6, 115.8, 115.0, 103.2, 84.7, 55.2, 21.2. IR: 795, 825, 1242, 1621, 3063, 3441 cm^{-1}. ESI-HRMS: *m/z* calcd for $C_{20}H_{18}IO_2^+$ [M + H]$^+$: 417.0346; found: 417.0351.
6-(3,4-Dimethoxyphenyl)-1-(2-iodo-1-phenylvinyl)naphthalen-2-ol (2n)
Yield 56%; pale yellow liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.97 (s, 1 H), 7.91 (d, *J* = 8.2 Hz, 1 H), 7.71–7.48 (m, 3 H), 7.40–7.12 (m, 8 H), 6.96 (d, *J* = 7.3 Hz, 1 H), 5.29 (s, 1 H), 3.95 (s, 3 H), 3.92 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 149.4, 149.2, 148.5, 146.9, 138.7, 136.4, 134.0, 130.5, 130.5, 129.4, 129.0, 128.9, 126.7, 126.5, 125.7, 124.6, 121.1, 119.5, 118.1, 111.6, 110.5, 86.0, 56.0. IR: 818, 1134, 1512, 1597, 3055, 3526 cm^{-1}. ESI-HRMS: *m/z* calcd for $C_{26}H_{22}IO_3^+$ [M + H]$^+$: 509.0608; found: 509.0611.
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