A Convenient Synthesis of 2-Alkyl-2-methyltetrahydrofurans from 4-Methylalk-4-en 1-ols Catalyzed by Iodine

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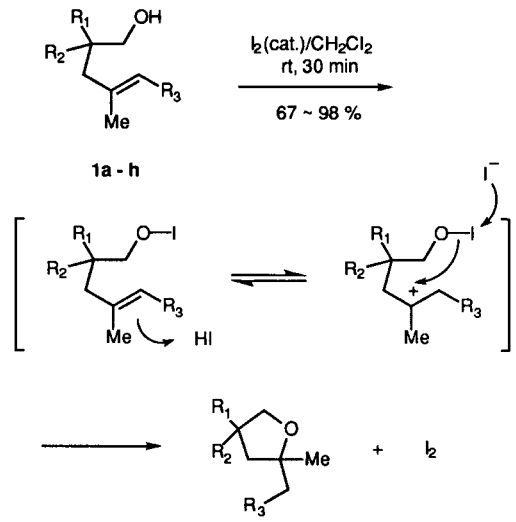
Abstract: Cyclization of 4-methylalk-4-en-1-ols in the presence of a catalytic amount of iodine in dichloromethane gave exclusively 2-alkyl-2-methyltetrahydrofurans under mild conditions in high yields.

Key words: iodine catalyst, non-iodine containing cyclic etherification, 4-methylalk-4-en-1-ols, 2-alkyl-2-methyltetrafurans

The iodine mediated electrophilic cyclization of unsaturated alcohols to substituted tetrahydrofurans is a useful procedure for the stereocontrolled synthesis of these compounds and polyether antibiotics.[1] Furthermore, the stereocontrolled haloetherifications of 4-methylalk-4-en-1-ols **1** in aqueous sodium hydrogen carbonate/acetonitrile/iodine or the protected 4-methylpent-4-en-1-ols in iodine/acetonitrile/0 °C resulted in formation of the 2-iodomethyl-2-methyltetrahydrofurans were well documented.[1,2] However, we recently reported unanticipated results from the reaction of 2-(*β*-methylallyl)phenols and 2-isobutenylphenols with iodine in nonpolar aprotic solvents affording the corresponding 2,2-dimethyl-2,3-dihydrobenzofurans without iodine containing products.[3a] Similarly, the iodine-catalyzed *γ*-lactonization of *γ*-methyl-*γ,δ*-pentenoic acids resulted in the corresponding *γ,γ*-dimethyl-*γ*-butyrolactones with trace amounts of iodolactonization products.[3b] In continuing our study, we wish to report that extention of our systems to 4-methyl-4-alken-1-ols **1** offered very effective synthetic method of 2-alkyl-2-methyltetrahydrofurans **2** under mild reaction conditions and easy workups.

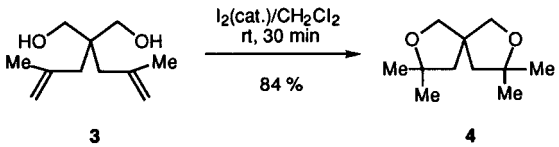
In order to optimize the conditions for iodine-catalyzed cyclization, we examined solvent effect on 4-methyl-2,2-diphenyl-pent-4-enol (**1f**) as a model substrate with iodine (0.2 equiv.) in various solvents at room temperature for 30 minutes. 4-Methyl-2,2-diphenylpent-4-enol (**1f**) with iodine (0.2 equiv.) was completely cyclized to 2,2-dimethyl-4,4-diphenyltetrahydrofuran (**2f**) without any formation of iodinated products in nonpolar aprotic solvents such as hexane, benzene, diethyl ether, and dichloromethane. But the reaction in polar aprotic or protic solvents such as tetrahydrofuran, *N,N*-dimethylformamide, or methanol gave a mixture of **2f** and the iodinated products.

Although the reaction was conducted in an anhydrous nonpolar aprotic solvent to avoid the external proton source which may generate hydrogen iodide from iodine,[3–4] it was assumed that the reaction of 4-methylalk-4-en-1-ol **1** with iodine should generate hydrogen iodide. The key feature of the mechanism may involve the addition of hydrogen iodide, which is initially formed by the interaction of iodine with free hydroxy group, to the double bond generating tertiary carbocation. The steric hindrance of 4-methyl group may be effective to prohibit addition of iodine to the double bond.



Scheme 1

Various 4-hydroxymethyl-2,2-dimethyltetrahydrofurans **2a–e** were obtained in good yields through the iodine-catalyzed reaction of the corresponding 4-methylpent-4-en-1-ols **1a–e**. Similarly, 4-methyl-2,2-diphenylhex-4-en-1-ol (**1g**) and 4-methyl-2,2-diphenylhept-4-en-1-ol (**1h**) gave almost quantitatively the corresponding 2-ethyl-2-methyl-4,4-diphenyltetrahydrofuran (**2g**) and 2-methyl-4,4-diphenyl-2-propyltetrahydrofuran (**2h**), respectively (Scheme 1). The reaction of 2,2-bis(2-methallyl)propane-1,3-diol (**3**) with iodine under the same conditions gave 3,3,8,8-tetramethyl-2,7-dioxaspiro[4,4]nonane (**4**) in 84 % yield (Scheme 2).



3 **4**

1–2	R_1	R_2	R_3	1–2	R_1	R_2	R_3
a	H	CH_2OH	H	**e**	Benzyl	CH_2OH	H
b	CH_3	CH_2OH	H	**f**	Ph	Ph	H
c	CH_2OH_3	CH_2OH	H	**g**	Ph	Ph	CH_3
d	n-Butyl	CH_2OH	H	**h**	Ph	Ph	CH_2CH_3

Scheme 2

Table. Synthesis of 2-Alkyl-2-methyltetrahydrofurans from 4-Methylalk-4-en-1-ols Catalyzed by Iodine[a]

Product	Yield[b] (%)	bp (°C/Torr) or mp (°C)	Molecular formula[c]	IR[d] (neat) ν_{C-O} (cm^{-1})	^1H NMR[e] ($CDCl_3$/TMS) δ, J (Hz)
2a	67	72/0.01	$C_7H_{14}O_2$	1049	1.22 (s, 3H), 1.30 (s, 3H), 1.46 (dd, 1H, *J* = 12.4), 1.90 (dd, 1H, *J* = 12.4), 2.62 (m, 1H, *J* = 7.2), 2.77 (br, OH), 3.58 (dd, 2H, *J* = 7.2), 3.66 (dd, 1H, *J* = 9.0), 3.97 (dd, 1H, *J* = 9.0)
2b	71	72/0.03	$C_8H_{16}O_2$	1041	1.12 (s, 3H), 1.28 (s, 6H), 1.50 (d, 1H), *J* = 12.8), 1.71 (d, 1H, *J* = 12.8), 2.90 (br, OH), 3.46 (q, 2H, *J* = 9.0), 3.49 (d, 1H, *J* = 9.0), 3.78 (d, 1H, *J* = 9.0)
2c	72	80/0.01	$C_9H_{18}O_2$	1047	0.88 (t, 3H), 1.24 (s, 3H), 1.28 (s, 3H), 1.36–1.58 (m, 2H), 1.57 (s, 2H), 2.31 (br, OH), 3.51 (d, 2H), 3.53 (d, 1H, *J* = 9.2), 3.77 (d, 1H, *J* = 9.2)
2d	95	94~95/0.01	$C_{11}H_{22}O_2$	1054	0.91 (t, 3H), 1.25 (s, 3H), 1.28 (s, 3H), 1.36–1.63 (m, 6H), 1.58 (d, 2H), 2.57 (br, OH), 3.48 (s, 2H), 3.50 (d, 1H, *J* = 9.2), 3.75 (d, 1H, *J* = 9.2)
2e	97	135/0.01	$C_{14}H_{20}O_2$	1045	1.23 (s, 3H), 1.26 (s, 3H), 1.51 (d, 1H, *J*= 13), 1.74 (d, 1H, *J* = 13), 2.29 (br, OH), 2.80 (q, 2H, *J* = 13.4), 3.43 (q, 2H, *J* = 11), 3.72 (q, 2H, *J* = 9.2), 7.17–7.33 (m, 5H)
2f	83	51	$C_{18}H_{20}O$	1050	1.24 (s, 6H), 2.66 (s, 2H), 4.49 (s, 2H), 7.17–7.36 (m, 10H)
2g	98	125~126/0.001	$C_{19}H_{22}O$	1061	0.89 (t, 3H, *J* = 7.4), 1.09 (s, 3H), 1.52 (m, 2H), 2.59 (q, 2H, *J* = 12.8), 4.32 (d, 1H, *J* = 9.4), 4.56 (d, 1H, *J* = 9.4), 7.14–7.37 (m, 10H)
2h	98	152/0.001	$C_{20}H_{24}O$	1060	0.85 (t, 3H, *J* = 7.0), 1.06 (s, 3H), 1.28–1.47 (m, 2H), 2.57 (q, 2H, *J* = 12.4), 4.29 (d, 1H, *J* = 9.4), 4.55 (d, 1H, *J* = 9.4), 4.55 (d, 1H, *J* = 9.4), 7.12–7.34 (m, 10H)
4	84	35–36/0.001	$C_{11}H_{20}O_2$	1040	1.23 (s, 6H), 1.15 (s, 6H), 1.73 (s, 4H), 3.54 (d, 2H, *J* = 8.4), 3.73 (d, 2H, *J* = 8.4)

[a] Substrate and iodine (0.2 eq.) in CH_2Cl_2 were allowed to react for 30 min.
[b] Isolated yield after column chromatography using Merck silica gel (70–230 mesh).
[c] Satisfactory microanalyses obtained: C ± 0.32, H ± 0.29.
[d] Obtained by Shimadzu IR-435 spectrometer.
[e] Recorded on a Bruker AM-300 spectrometer with TMS as internal standard.

The attempted reaction of pent-4-en-1-ol, 5-methylhex-4-en-1-ol, and hex-4-en-1-ol (a mixture of *E* and *Z* isomers) gave a mixture of iodinated and noniodinated cyclized products, respectively.

2-Methyl-2-(β-methalyl)propane-1,3-diol (1b); Typical Procedure:
Compound **1b**[5] was obtained by reduction of diethyl methyl (β-methallyl)malonate[4a] with $LiAlH_4$ in Et_2O.

4-Methyl-2,2-diphenylpent-4-en-1-o1 (1f); Typica1 Procedure:
Compound **1f**[7] was obtained by reduction of 4-methyl-2,2-diphenylpent-4-enoic acid[6] with $LiAlH_4$ in Et_2O.

4-Butyl-4-hydroxymethyl-2,2-dimethyltetrahydrofuran (2d); Typical Procedure:
Iodine (0.05 g, 0.2 mmol) was added to a stirred solution of **1d** (0.20 g, 5 mmol) in anhyd CH_2Cl_2. After stirring for 30 min, the organic layer was quenched with a 5 % aq $Na_2S_2O_3$ to remove iodine. After usual extractive workup, the crude product was purified on silica gel column chromatography using EtOAc/ hexane (1:10) as an eluent to give **2d** (0.19 g, 95 %).

The other tetrahydrofurans **2a–2h** and **4** were obtained in the same manner.

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