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One-Pot Synthesis of Novel Monoterpenoid Ethers.[1]

By R. Chidgey and H. M. R. Hoffmann[2]

Chemistry Department, University College, London WC1H OAJ, England and
Institut für Organische Chemie, Technische Universität, D-3000 Hannover, Germany

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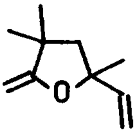
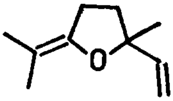
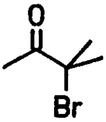
In general, the electrophilic intermediate(s) generated from α,α'-dihaloketones and zinc-copper couple behave as latent allyl cations which combine with conformationally mobile dienes to yield two types of cyclic ketones, namely 4-cycloheptenones and vinylcyclopentanones.[1] We now show that the simple change in reducing agent from zinc to sodium iodide in the presence of copper leads to completely different products, namely 2-alkylidene-5-vinyltetrahydrofurans. Under these conditions the five- and seven-membered ketones obtained via reaction with zinc-copper couple[1] are formed in a very minor amount only. A typical experiment is as follows.

Finely divided copper bronze (1.5 g) and sodium iodide (6.0 g, 40 mmol) were weighed into a 120 ml reaction flask which was flushed with nitrogen. After addition of acetonitrile (40 ml) the sodium iodide was dissolved by using a vibromixer. 2-Methylbutadiene (2.77 g, 40 mmol) and 1,3-dibromo-3-methyl-2-butanone (2.44 g, 10 mmol) were dissolved in acetonitrile (5 ml) and the resulting solution was transferred to a pressure equilibrating funnel, which was connected to the flask under nitrogen. The solution was added dropwise with vigorous stirring, the reaction temperature not being allowed to exceed 30°. After complete addition (ca. 90 min) stirring was continued for at least 9 h, the approximate time required for complete debromination. The reaction mixture was worked up by liquid-liquid extraction with isopentane at -30°, the low temperature extractor being used.[3] After 3 h the extraction was complete, and the isopentane was evaporated (0°, 200 mm) to leave a greenish-yellow oily product (0.33 g) which was analyzed by preparative GLC, NMR and comparison with authentic compounds (see Table I). As expected it was difficult to separate the new monoterpenoid ethers, which readily underwent valence isomerization and decomposed on heating and attempted distillation. Eventually, compounds 1a, 2 and 3 were separated on the basis of their boiling points (20 ft silicon oil preparative column), the monobromoketone being eluted first, followed by the major ether 1a and minor ether 2. 3,3,5-Trimethyl-2-methylene-5-vinyltetrahydrofuran (1a) is a previously unknown monoterpenoid ether which was identified spectroscopically and chemically. NMR (neat, TMS, 60 MHz) δ 1.17 (s, 3H), 1.20 (s, 3H), 1.32 (s, 3H); 2.1, 1.9, 1.83, 1.63 (AB quartet, J_{AB} = 12 Hz, 2H, 4.08, 3.65 (AB quartet, J_{AB} = 2 Hz, 2H), 4.8-5.43, 5.7-6.23 (ABC pattern, 3H). IR (CCl_4, cm^{-1}) 1670 (s) (enol ether $>C=C<$) MS (20 eV, rel. intensities) m/e 152 (91) (M^+), 137 (46), 123 (18), 119 (18), 110 (30),

Table I. Products from the Iodide Ion Promoted Dehalogenation of 1,3-Dibromo-3-methyl-2-butanone in the Presence of 2-Methylbutadiene.[a]

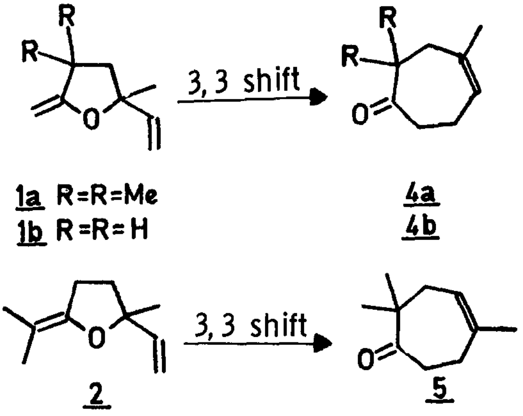
Reducing Agent	Solvent	Products			Oxyallyl Dimer[b]
		 1a	 2	 3	
Li I	MeCN	19	7	7	67
Na I	MeCN	35	8	26	31
$(nBu)_4N$ I	MeCN	11	5	68	16
Na I	DME	25	8	58	9

[a] Normalized to 100%; the carbocyclic adducts 4a, 5, and 2,2,3-trimethyl-3-vinylcyclopentanone were formed in 2% yield, irrespective of the iodide soucre.

[b] Presumably acylic dimer (s).

96 (55), 95 (91), 81 (53), 70 (46), 68 (55), 67 (100), 55 (51), 43 (55), 41 (82). Anal. Calcd for $C_{10}H_{16}O$: C 78,9, H, 10.6. Found: C 77.6, H, 10.5.

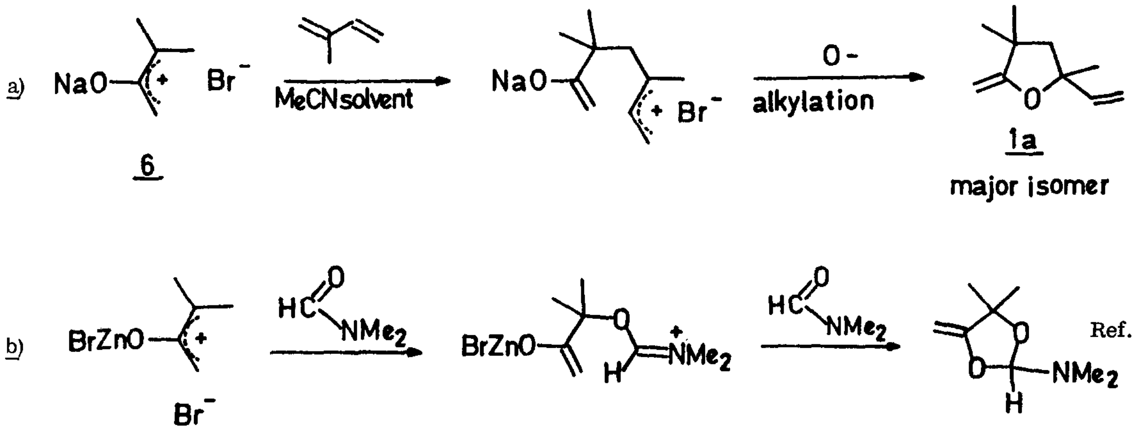
The minor vinyl ether 2, which was identified mass-spectroscopically and by its thermal rearrangement into karahanaenone (5),[4,6] had already been postulated by Demole[5] as an intermediate of the dehydrobromination of the product from linalol and N-bromosuccinimide. The structure of vinyl ether 1a was further corroborated by a detailed study of its Claisen rearrangement into the carbocyclic ketone 4a (Scheme 1), the activation parameters (E_a = 34.3 kcal/mol;$\Delta H^{\ddagger}$ = 33.4 kcal/mol,$\Delta S^{\ddagger}$ = -2.3 e.u. at 169°C) being in good agreement with those determined by Rhoads et al. for the rearrangement of the related allyl vinyl ether 1b which lacks the gem-dimethyl groups (E_a = 33.6 kcal/mol,$\Delta G^{\ddagger}$ = 32.7 kcal/mol, $\Delta S^{\ddagger}$ = -5.6 e.u. at 170°).[7]



Scheme 1. Formation of 2,2,4-trimethylcyclohept-4-enone (4a) and karahanaenone (5) via Claisen rearrangement.

It should be noted that under the experimental conditions of the NaI/Cu procedure the two seven-membered ketones 4a and 5 and 2,2,3-trimethyl-3-vinylcyclopentanone[4] constitute only about 2% of the overall product, whereas the cyclic enol ethers 1a and 2 and monobromoketone 3 account for about 70%.

A probable intermediate of the NaI/Cu reaction is the oxyallyl species 6, which in the first, intermolecular reaction stage acts as an electrophile, and in the ring closure step as a nucleophile via its enolate oxygen. It will be seen that the initial combination with carbon atom C-1 of 2-methylbutadiene occurs preferentially at the more alkylated tertiary terminus to yield eventually 1a rather than 2 [Scheme 2, path a)] as the major isomer.



Ref. 3.

Scheme 2. Cyclic enol ethers via demasking of the metal oxyallyl oxygen.

When applied to conjugated dienes such as cyclopentadiene and furan,[8] the Na I/Cu procedure gives bridged 4-cycloheptenones rather than cyclic enol ethers, as in the present instance. Clearly, conformational mobility of the diene component is important in determining the nature of the products. Furthermore, related reactions leading to cyclic ethers are known even with zinc oxyallyls, provided a suitable ligand is present, especially dimethylformamide[3] [Scheme 2, path b)] and to some extent, 1,2-dimethoxyethane/acetonitrile,[1] which is capable of demasking the oxyallyl oxygen. Finally, 1,1-dimethyl-2-oxyallyl is a useful isoprenoid building block which offers shortcuts in the synthesis of mono- and higher terpenes.

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References and Notes

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