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A New Oxidation of 3-Bromocamphor to Camphorquinone

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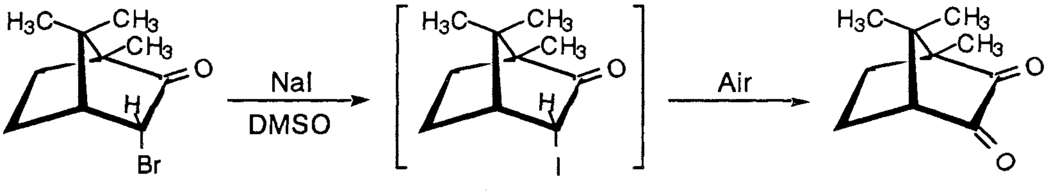
3-Bromocamphor was oxidized in DMSO by bubbling air in the presence of sodium iodide to give camphorquinone quantitatively. The oxidation was found to proceed under mild conditions by a radical mechanism.

It is well known that camphorquinone (1,7,7-trimethylbicyclo[2.2.1]heptan-2,3-dione) is used not only as an initiator for visible-light sensitive polymerization in a dental area but also as an important chiral intermediate for the synthesis of natural products.1) The only method for industrial production of camphorquinone is a direct oxidation of camphor with selenium dioxide (SeO_2).2) Selenium dioxide is a good reagent for the oxidation of reactive methylene groups to carbonyl groups.3) However, since selenium dioxide and the selenium-containing reaction intermediates cause toxic side-effects for dental treatments, it is urgent to develop an alternative method for the camphorquinone synthesis. When a common oxidizing agent such as potassium permanganate ($KMnO_4$), chromium trioxide (CrO_3), potassium dichromate ($K_2Cr_2O_7$), or nitric acid was used, no camphorquinone was obtained, that is, the ring cleavage or non-specific oxidation of camphor readily occurred giving the dicarboxylic compound, 1,2,2-trimethylcyclopentane-1,3-dicarboxylic acid (camphoric acid) or other oxidation products.4) In this paper, we wish to report a simple and convenient air-oxidation of 3-bromocamphor to camphorquinone.



1 3-Bromocamphor

2

3 Camphorquinone

Table 1. Oxidation of 3-bromocamphor[a)]

Entry	Solvent	Additives[b)]	Atmosphere	Time/h	Yield/% of Camphorquinone[c)]
1	DMSO	none	N_2	6	1
2	DMSO	NaI	N_2	24	11
3[d)]	DMSO	NaI	air	5	42
4	DMSO	NaI	air	1	40
5	DMSO	NaI	air	3	93
6	DMSO	NaI	air	6	97
7	DMF	NaI	air	6	79
8	HMPA	NaI	air	6	94
9	Toluene	NaI	air	6	1
10	Xylene	NaI	air	6	1

a) 3-Bromocamphor: 2.5 mmol, reaction temperature: 150 °C.
b) NaI: 10 mmol. c) Determined by gas chromatography.
d) Reaction temperature: 130 °C.

A typical procedure for the preparation of camphorquinone is as follows: Endo-(+)-3-bromocamphor (0.58 g, 2.5 mmol) was dissolved in 3 ml of dimethyl sulfoxide in the presence of sodium iodide (1.5 g, 10 mmol) and then the mixture was kept at 150 °C for 6 h while air (100 - 150 ml/min) was bubbled into the mixture. After cooling, water (100 ml) and a small amount of sodium thiosulfate were added to the mixture. The mixture was extracted with ethyl acetate. The organic layer was washed with water several times and dried over anhydrous sodium sulfate. Camphorquinone (0.42 g, 97%) was obtained after removal of ethyl acetate and subsequent column chromatography on silica gel etuted with hexane-ethyl acetate; mp 198 - 199 °C, $[\alpha]_D^{20}$ = +102.5° (c 2, toluene), (lit.[2b)] mp 200 - 202 °C, $[\alpha]_D^{20}$ = +100° (c 2, toluene)). The product was identified by comparison of its NMR and IR spectra with those of an authentic (+)-camphorquinone. (-)-Camphorquinone was also obtained from (-)-3-bromocamphor by the same procedure as above; mp 198 - 199 °C, $[\alpha]_D^{20}$ = -102.5° (c 2, toluene), (lit.[2b)], mp 200 - 203 °C, $[\alpha]_D^{20}$ = -101° (c 2, toluene)).

Table 1 summarizes the results of oxidation of 3-bromocamphor. When the reaction was carried out in DMSO at 150 °C under nitrogen atmosphere, no oxidation product was obtained and the starting 3-bromocamphor was recovered (entry 1). Silver (I) perchlorate and sodium bicarbonate did not stimulate for the oxidation. However, addition of sodium iodide at the same temperature gave a small amount of camphorquinone after 24 h (entry 2). When air was bubbled into the reaction mixture, the oxidation proceeded significantly faster to

Table 2. Effect of radical initiators and an inhibitor on the oxidation of 3-bromocamphor[a]

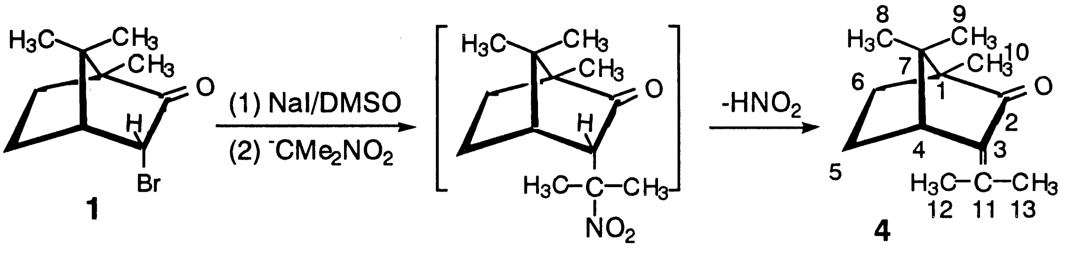
Entry	Additives[b]	Temp/°C	Time/h	Yield[c]/%		
				3	**2**	**1**
11	NaI	100	1	52	1	46
12	NaI and AIBN	100	1	57	1	41
13	NaI and BPO	100	1	52	1	43
14	NaI and HQ	150	6	0	66	28
15	NaI	150	1	74	7	19
16	NaI and L	150	1	83	4	13
17	NaI and D	150	1	35	8	57

a) 3-Bromocamphor: 2.5 mmol, Air was bubbled into the reaction mixture.
b) AIBN: α, α'-azobisisobutylonitrile (0.25 mmol),
BPO: benzoyl peroxide (0.25 mmol), HQ: hydroquinone (2.5 mmol),
L: irradiated with lights at 254 and 366 nm, D: in the dark.
c) Determined by gas chromatography.

afford camphorquinone in 97% yield (entry 6). Although aprotic polar solvents such as DMSO, DMF, and HMPA were found to be effective, toluene and xylene gave no oxidation products.

In general, oxidation of alkyl halides to the corresponding carbonyl compounds in DMSO is called the Kornblum oxidation and the reaction proceeds by an S_N2 reaction mechanism followed by concerted elimination of a proton and dimethyl sulfide.5) However, formation of dimethyl sulfide and hydrogen halide was not observed in our reaction and oxygen played an important role in the oxidation. Therefore, it is clear that the mechanism of the present oxidation is different from that of the Kornblum oxidation.

In order to gain an insight into the mechanism, the effects of radical initiators, an inhibitor, and irradiation with lights on the oxidation were investigated. Addition of such radical initiators as α, α' -azobisisobutylonitrile (AIBN) and benzoyl peroxide (BPO) gave no effect on the rate of oxidation (entries 11 - 13) as shown in Table 2, but hydroquinone (HQ), a radical inhibitor, inhibited the reaction (entry 14). Furthermore, when the reaction was carried out by irradiation with lights of 254 and 366 nm, the yield of camphorquinone increased (entry 16) compared with the reaction in the dark (entry 17). These results suggest that the oxidation of 3-bromocamphor should involve a radical process.6) Therefore we investigated whether **1** acts as an electrophile of radical chain substitution reaction ($S_{RN}1$). When 2-nitro-2-propyl anion was added to a mixture of **1** and NaI in DMSO at 150 °C under nitrogen atmosphere, olefinic product **4**[7] was obtained in 45% yield by the $S_{RN}1$ processes.[8] Thus, it is obvious that **1** has a tendency to undergo a radical reaction by choosing the appropriate reaction conditions. Further studies on the reaction mechanism involving a single electron transfer process are in progress.



In conclusion, the oxidation of 3-bromocamphor in DMSO in the presence of NaI by blowing air proceeded smoothly to afford camphorquinone in excellent yield. This reaction offers a good alternative method for the synthesis of camphorquinone.

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7) IR (neat): 1651, 1625 cm^{-1}(C=C-C=O). EI-MS (m/z, %): 192 (M^+, 100). ^1H NMR ($CDCl_3$) : δ 0.78 (3H, s, 8-CH_3), 0.91 (3H, s, 9-CH_3), 0.93 (3H, s, 10-CH_3), 1.26 - 1.43 (2H, m, CH), 1.57 - 1.72 (1H, m, CH), 1.81 (3H, s, 13-CH_3), 1.90 - 2.00 (1H, m, CH), 2.18 (3H, s, 12-CH_3), 2.65 - 2.67 (1H, d, J = 5 Hz, CH). ^{13}C NMR ($CDCl_3$): δ 9.48 (10-C), 18.65 (8-C), 20.28 (9-C), 20.29 (12-C), 22.85 (13-C), 26.30 (5-C), 30.40 (6-C), 45.83 (7-C), 49.42 (4-C), 58.68 (1-C), 136.94 (11-C), 141.59 (3-C), 208.39 (2-C).
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