THE EFFICIENT SYNTHESIS OF 1,2-DIOXETANES FROM INDENE AND 1,2-DIHYDRONAPHTHALENE

Charles W. Jefford* and Marcelo Ferrufino Deheza
Department of Organic Chemistry, University of Geneva
1211 Geneva 4, Switzerland

Abstract- Indene (1), 1-methylindene (7), 2-methylindene (10), 1,2- and 1,4-
dihydronaphthalenes (3 and 18) were converted into their trans-1,2-bromo-
hydroperoxides. The latter on treatment with a mixture of AgO/AgOSO2CF3 in
CH2Cl2 at room temperature gave the corresponding 1,2-dioxetanes in yields of
90, 88, 80, 80, and 50% respectively. The cis-disposed bromo-hydroperoxide
obtained from 7 was unreactive on treatment with the silver mixture. Similar
treatment of the trans-bromo-hydroperoxide obtained from 3,3-dimethylindene
(14) was equally without effect, no dioxetane being formed.

INTRODUCTION

Although 1,2-dioxetanes are familiar chemical entities, they tend to be difficult to prepare on account of
their intrinsic thermal instability. Monocyclic 1,2-dioxetanes are the best known mainly through their use
in various chemiluminescent assays. Less common are cis-fused bicyclic analogues which have only
been obtained in special cases. Examples are provided by certain dihydropyrans and N-methyl- or N-
acylindoles which on photo-oxygenation furnish the corresponding dioxetanes often in low yield as
transient adducts. Despite many attempts at synthesis, the 1,2-dioxetanes of indene (1) and 1,2-
dihydronaphthalene (3) have remained elusive. In practice only three synthetic methods are available,
photosensitized oxygenation which is limited to olefins unable to undergo hydroperoxidation,
oxygenation by electron transfer, and dehydrohalogenation of vicinal hydroperoxy halides. Contrary to
earlier reports, the photo-oxygenation of 1 in different solvents gave no dioxetane (2), only hydroperoxide
derivatives (Scheme 1). Similar behavior was observed for 3; the dioxetane (4) not being obtained.
Application of the traditional method, namely the action of base on trans-2-bromo-1-hydroperoxyindane
(5), derived from 1 by bromohydroperoxidation, gave the desired 1,2-dioxetane (2), but in only 2%
yield. We now report a new procedure that enables 1,2-dioxetanes to be readily prepared in high yield
from indene (1), 1-methylindene (7), 2-methylindene (10), and 1,2- and 1,4-dihydronaphthalenes (3 and 18).

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RESULTS AND DISCUSSION

First, we re-examined the reaction of 5 with various silver salts, namely the acetate, trifluoroacetate, trifluorosulfonate, benzoate, tetrafluoroborate, and with silver oxide as in the original procedure. In no case did 5 show any sign of reaction. In marked contrast, the simple expedient of treating 5 in dichloromethane solution successively with silver oxide and silver trifluorosulfonate at room temperature delivered the desired dioxetane (2) in 90% yield (Scheme 1). Chromatographic purification was straightforward, incurring no decomposition. In fact, 2 remained intact on keeping for several weeks at 0 °C. However, at room temperature cleavage to the bis-aldehyde (6) was complete within a day.

\[ \text{Scheme 1} \]

\[ \text{Scheme 2} \]

a) \text{H}_2\text{O}_2, \text{MeCONHBr} \quad \text{b) Ag}_2\text{O, AgOSO}_2\text{CF}_3, \text{CH}_2\text{Cl}_2, \text{rt} \]
The Ag$_2$O/AgOSO$_2$CF$_3$ mixture (hereinafter termed the Ag-mixture) was equally effective in bringing about the cyclization of other trans-bromo-hydroperoxides. Bromo-hydroperoxidation of 1-methylindene (7) furnished the trans- and cis-2-bromo-1-hydroperoxides (8 and 13). Submission of the trans isomer (8) to the Ag-mixture gave dioxetane (9) in 88% yield (Scheme 2). Similar treatment of trans-2-bromo-1-hydroperoxy-2-methylindene (11), obtained from 2-methylindene (10), afforded a high yield (80%) of the corresponding dioxetane (12). Formation of the four-membered ring clearly entails nucleophilic attack by the distal oxygen atom of the hydroperoxide group on the rear lobe of the C-Br bond with displacement of bromide ion. When the S$_{n}$2-type geometry is unattainable as exemplified by the cis-isomer (13), dehydrobromination to ent-9 did not occur. For similar reasons, the trans-bromo-hydroperoxide (15) derived from 3,3-dimethylindene (14) is also unreactive when treated with the Ag-mixture. Dioxetane (16) was not formed. Evidently, the 1,3-steric interaction between the methyl and hydroperoxy groups prevents the latter from lining up correctly with the back side of the bromomethyl carbon atom.

Scheme 3

Just like 5, the homologous trans-bromo-hydroperoxide (17), obtained from 1,2-dihydronaphthalene (3), on conventional treatment with base was reported to give just a trace, less than 2%, of the 1,2-dioxetane (4).\textsuperscript{10} Here again, recourse to the Ag-mixture dramatically remedied the situation. Dehydrobromination of 17 proceeded smoothly giving the dioxetane (4) in 80% yield (Scheme 3). The Ag-mixture was less effective in converting the trans-2-bromo-3-hydroperoxide (19) to the isomeric dioxetane (20), a yield of only 50% being observed. Nonetheless, this yield is vastly superior to that of 2% previously reported for an impure sample of 20.\textsuperscript{10}

The efficacy of the Ag-mixture may be due to the combination of basic and acidic properties. The base, Ag$_2$O, abstracts a proton from the hydroperoxy group while the silver salt as a Lewis acid complexes with the bromine atom thereby creating a ‘soft’ carbocation. The concerted action of the two reagents creates the new O-C bond by trans elimination of hydrogen bromide.
CONCLUSION
The present results demonstrate that the action of Ag$_2$O/Ag$_2$SO$_2$CF$_3$ in CHCl$_3$ at room temperature brings about the cyclization of monocyclic trans-disposed 1,2-bromo-hydroperoxides to cis-fused bicyclic 1,2-dioxetanes in high yield provided that the hydroperoxy group can adopt the necessary orientation with respect to the center undergoing displacement. The results also suggest that the Ag-mixture would improve the reactivity of acyclic bromo-hydroperoxides which never give more than 30% of dioxetane when treated separately either with base or silver salts.$^9$,$^{11}$

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EXPERIMENTAL PART
1. General. All solvents were either puriss grade (Fluka or Aldrich) or distilled prior to use. Column chromatography: Merck silica gel 60 (230-400 mesh). Mps were determined on a Reichert hot stage microscope and are uncorrected. IR: Perkin-Elmer-681 spectrophotometer. $^1$H- and $^{13}$C-NMR: Bruker-AMX-400, Bruker-WH-360, Varian-XL-200 spectrometers; chemical shifts (δ) in ppm relative to internal TMS (= 0 ppm), coupling constants (J) in Hz; commercial CDCl$_3$ was used without further purification. Elemental analyses were carried out by Dr. H.J. Eder, Microchemistry Service, Institute of Pharmaceutical Chemistry, University of Geneva.

2. Starting materials. Indene (1) and 1,2-dihydronaphthalene (3) were purchased from Fluka, 9471 Buchs, Switzerland. 1-Methylindene (7), 2-methylindene (10), and 3,3-dimethylindene (14) and 1,4-dihydronaphthalene (18) were prepared according to standard procedures.$^{12-15}$

3. 1,2-Bromo-hydroperoxides. For reasons of safety, only 30% aq. H$_2$O$_2$ was used. All the experiments described below were conducted with great care behind safety screens. The corresponding known bromohydrins which were obtained as minor products were not characterized. All compounds with the exception of 6 and 20 were obtained as racemic mixtures. For the sake of clarity, structures in the Schemes are depicted as single enantiomers.

3.1. (1RS,2RS)-2-Bromo-1-hydroperoxyindane (5). To a solution of 1 (1.0 g, 8.62 mmol) in Et$_2$O (50 mL), cooled to 0 °C, was added 30% aq. H$_2$O$_2$ (8 mL, 70 mmol) with stirring. After stirring for 30 min, MeCONHBr (1.19 g, 8.62 mmol) was added. The resulting mixture was vigorously stirred for 2 h at 0 °C. Next the ethereal solution was washed successively with aq. NaHCO$_3$ (5%, 4 x 50 mL), H$_2$O (3 x 50 mL), dried (MgSO$_4$), and evaporated. The resulting residue was purified by column chromatography (silica gel, CH$_2$Cl$_2$, eluent) giving the bromohydrin$^*$ (559 mg, 30%) and 5 as a white solid (680 mg, 35%). mp: 85-87 °C (recrystallized from CH$_2$Cl$_2$). IR (CCl$_4$): 3610, 3550, 1610, 1450, 1380, 1360,
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1220, 1160, 1120, 1025, 960 cm$^{-1}$. $^1$H-NMR (360 MHz): $\delta$ 3.27 (dd, $J = 17.5, 3.0$ Hz, 1H), 3.82 (dd, $J = 17.5, 6.6$ Hz, 1H), 4.86 (ddd, $J = 6.6, 3.1, 2.1$ Hz, 1H), 5.67 (d, $J = 2.1$ Hz, 1H), 7.25-7.50 (m, 4H), 8.10 (s, 1H). $^{13}$C-NMR (90.6 MHz): $\delta$ 41.7, 48.8, 95.9, 125.1, 126.3, 127.4, 130.3, 135.8, 142.4. Anal. Calcd for $C_{47}H_{37}O_2Br$: C 47.18, H 3.96, Br 34.88. Found: C 47.09, H 4.01, Br 34.92.

3.2. (1RS,2RS)-2-Bromo-1-hydroperoxy-1-methylindane (8) and (1SR,2RS)-2-Bromo-1-hydroperoxy-1-methylindane (13). The procedure in section 3.1. was repeated with 7. A mixture of 8 and 13 were obtained in a ratio of 4:1 (53%). By column chromatography (silica gel, CH$_2$Cl$_2$, eluent) 8 was obtained pure as a colorless oil. IR (CCl$_4$): 3560, 3410, 1590, 1490, 1460, 1380, 1335, 1230, 1085, 960 cm$^{-1}$. $^1$H-NMR (360 MHz): $\delta$ 1.62 (s, 3H), 3.42 (d, $J = 8.5$ Hz, 2H), 4.42 (t, $J = 8.5$ Hz, 1H), 7.2-7.4 (m, 4H), 7.82 (s, 1H). $^{13}$C-NMR (90.6 MHz): $\delta$ 21.7, 40.7, 52.8, 93.9, 123.3, 124.7, 127.5, 128.4, 140.2, 141.1. Anal. Calcd for $C_{19}H_{15}O_2Br$: C 49.40, H 4.56. Found: C 49.38, H 4.61.

3.3. (1RS,2RS)-2-Bromo-1-hydroperoxy-1-methylindane (11). Repetition of the procedure in section 3.1. with 10 gave 11 in 64% yield as a white solid. mp: 55-56 °C (recrystallized from CH$_2$Cl$_2$). IR (CCl$_4$): 3510, 1610, 1480, 1460, 1445, 1425, 1380, 1330, 1310, 1230, 1150, 1055, 985 cm$^{-1}$. $^1$H-NMR (360 MHz): $\delta$ 1.62 (s, 3H), 3.14 (dd, $J = 16.5, 7.0$ Hz, 1H), 3.62 (dd, $J = 16.5, 7.0$ Hz, 1H), 5.02 (t, $J = 7.0$ Hz, 1H), 7.25-7.4 (m, 4H), 7.95 (s, 1H). $^{13}$C-NMR (90.6 MHz): $\delta$ 21.7, 40.7, 52.8, 93.9, 123.3, 124.7, 127.5, 128.4, 140.2, 141.1. Anal. Calcd for $C_{19}H_{15}O_2Br$: C 49.40, H 4.56. Found: C 49.38, H 4.61.

3.3. (1RS,2RS)-2-Bromo-1-hydroperoxy-3,3-dimethylindane (15). Repetition of the procedure in section 3.1. with 14 gave 15 in 74% yield as a colorless solid. mp: 57-59 °C (recrystallized from CH$_2$Cl$_2$). IR (CCl$_4$): 3557, 1475, 1465, 1405, 1385, 1368, 1335, 1315, 1200, 910 cm$^{-1}$. $^1$H-NMR (360 MHz): $\delta$ 1.27 (s, 3H), 1.42 (s, 3H), 4.45 (d, $J = 7.5$ Hz, 1H), 5.60 (d, $J = 7.5$ Hz, 1H), 7.2-7.45 (m, 4H), 8.32 (s, 1H). $^{13}$C-NMR (90.6 MHz): $\delta$ 26.1, 41.6, 50.3, 69.9, 96.2, 124.8, 126.7, 127.2, 129.9, 137.3, 143.0. Anal. Calcd for $C_{21}H_{17}O_2Br$: C 51.38, H 5.09, Br 31.07. Found: C 51.30, H 5.00, Br 31.20.

3.4. (1RS,2RS)-2-Bromo-1-hydroperoxy-1,2,3,4-tetrahydronaphthalene (17). Submission of 3 to the procedure in section 3.1. gave the bromohydridin$^{15}$ (47%) and 17 (40%) as colorless crystals. mp: 75-76 °C (recrystallized from CH$_2$Cl$_2$). IR (CDCl$_3$): 3525, 1480, 1445, 1425, 1320, 1260, 1160, 1030, 978, 940, 900 cm$^{-1}$. $^1$H-NMR (360 MHz): $\delta$ 2.30 (m, 1H), 2.48 (ddddd, $J = 14.5, 10.0, 5.7, 3.0$ Hz, 1H), 2.86 (dt, $J = 17.0, 4.5$ Hz, 1H), 3.08 (dd, $J = 17.0, 10.0, 5.7$ Hz, 1H), 4.97 (m, 1H), 5.15 (d, $J = 3.1$ Hz, 1H), 7.1-7.45 (m, 4H), 8.35 (s, 1H). $^{13}$C-NMR (90.6 MHz): $\delta$ 25.7, 26.6, 48.0, 85.3, 126.4, 128.8, 130.1, 131.1, 137.1, 137.2. Anal. Calcd for $C_{16}H_{11}O_2Br$: C 49.41, H 4.56, Br 32.87. Found: C 49.67, H 4.55, Br 32.40.
3.5 (2R,3RS)-2-Bromo-3-hydroperoxy-1,2,3,4-tetrahydronaphthalene (19). Submission of 18 to the procedure in section 3.1 gave the bromohydrin (48%) and 19 (45%) as colorless crystals. mp: 37-38 °C (recrystallized from CH₂Cl₂). IR (CDCl₃): δ 3525, 1490, 1410, 1360, 1320, 1250, 1165, 1035, 910 cm⁻¹. ¹H-NMR (360 MHz): δ 3.03 (dd, J = 17.8, 5.5 Hz, 1H), 3.23 (dd, J = 17.8, 4.8 Hz, 1H), 3.44 (dd, J = 17.8, 5.5 Hz, 1H), 3.62 (dd, J = 17.8, 4.8 Hz, 1H), 4.54 (dd, J = 11.0, 5.5 Hz, 1H), 4.70 (m, 1H), 7.05-7.25 (m, 4H), 8.15 (s, 1H). ¹³C-NMR (90.6 MHz): δ 30.7, 35.9, 46.5, 82.7, 126.4, 126.7, 128.5, 128.9, 132.1, 132.6. Anal. Calcd for C₁₆H₁₂O₂Br: C 49.41, H 4.56, Br 32.87. Found: C 49.37, H 4.59, Br 32.41.

4. 1,2-Dioxetanes. Owing to their thermal instability, recrystallization was not attempted; purification was effected by chromatography at low temperature.

4.1. (1RS,2SR)-1,2-Epidioxyindane (2). To a solution of 5 (160 mg, 0.69 mmol) in CH₂Cl₂ (5 mL) was added Ag₂O (231 mg, 1.0 mmol) followed by Ag₂O₃SO₂CF₃ (257 mg, 1.0 mmol). The mixture was stirred at 16 °C and the progress of the reaction followed by TLC. On completion after 90 min, the yellow solution was filtered over Celite and purified directly by flash chromatography (silica gel, CH₂Cl₂) at -20 °C. Dioxetane 2 was obtained as a colorless solid (92 mg, 90%). mp: 43 °C. ¹H-NMR (360 MHz): δ 3.24 (dd, J = 18.0, 4.7 Hz, 1H), 3.46 (d, J = 18.0 Hz, 1H), 6.34 (m, 2H), 7.35-7.60 (m, 4H). ¹³C-NMR (90.6 MHz): δ 40.1, 86.6, 89.5, 125.9, 126.2, 127.8, 130.7, 139.6, 144.2. The dialdehyde (6) was also obtained (8 mg, 8%).

4.2. (1RS,2SR)-1-Methyl-1,2-epidioxyindane (9). Submission of 8 to the procedure in section 4.1 afforded 9 by chromatography at 0 °C as a yellow oil (88%). ¹H-NMR (360 MHz): δ 1.87 (s, 3H), 3.20 (dd, J = 18.0, 4.6 Hz, 1H), 3.35 (d, J = 18.0 Hz, 1H), 5.97 (d, J = 4.6 Hz, 1H), 7.40 (m, 4H). ¹³C-NMR (90.6 MHz): δ 20.8, 36.9, 91.4, 95.7, 123.3, 126.2, 127.8, 130.3, 142.6, 142.9.

4.3. (1RS,2SR)-2-Methyl-1,2-epidioxyindane (12). Submission of 11 to the procedure in section 4.1 afforded 12 by chromatography at 0 °C as a colorless solid (80%). mp: 3-6 °C. ¹H-NMR (360 MHz): δ 1.90 (s, 3H), 3.05 (d, J = 18.0 Hz, 1H), 3.47 (d, J = 18.0 Hz, 1H), 5.95 (s, 1H), 7.35-7.45 (m, 4H). ¹³C-NMR (90.6 MHz): δ 22.6, 454, 92.8, 94.3, 125.9, 127.6, 130.4, 143.4, 145.6.

4.4. No reaction was detected on treating 13 and 15 according to the procedure in section 4.1.

4.5. (1RS,2SR)-1,2-Epidioxy-1,2,3,4-tetrahydronaphthalene (4). Submission of 17 to the procedure in section 4.1. afforded 4 by chromatography at 0 °C as a yellow oil (80%). ¹H-NMR (360 MHz): δ 1.54 (m, 1H), 2.30 (m, 1H), 2.90 (m, 1H), 3.72 (m, 1H), 5.82 (m, 1H), 6.44 (d, J = 7.2 Hz, 1H), 7.2-7.40 (m, 4H). ¹³C-NMR (90.6 MHz): δ 24.9, 28.0, 80.4, 81.4, 126.5, 128.7, 129.8, 130.3, 131.8, 141.4.

4.6. (2RS,3SR)-2,3-Epidioxy-1,2,3,4-tetrahydronaphthalene (20). Submission of 19 to the procedure in section 4.1. afforded 20 by chromatography at 0 °C as a yellow oil (50%). ¹H-NMR (360 MHz): δ 2.86 (d, J = 16.5 Hz, 2H), 3.04 (dd, J = 16.5, 1.0 Hz, 2H), 5.93 (m, 2H), 7.10-7.30 (m, 4H). ¹³C-NMR (90.6 MHz): δ 33.75, 80.3, 127.3, 129.3, 133.3.
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