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

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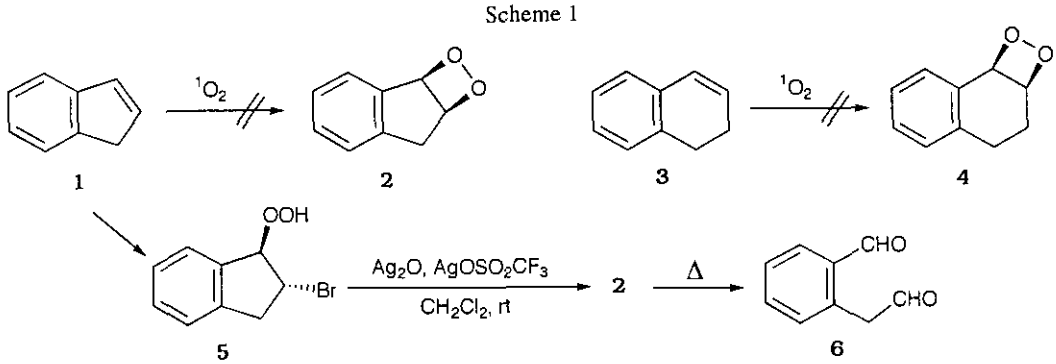
Abstract- Indene (**1**), 1-methylindene (**7**), 2-methylindene (**10**), 1,2- and 1,4-dihydronaphthalenes (**3** and **18**) were converted into their *trans*-1,2-bromo-hydroperoxides. The latter on treatment with a mixture of $Ag_2O/AgOSO_2CF_3$ in CH_2Cl_2 at room temperature gave the corresponding 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.[1] Monocyclic 1,2-dioxetanes are the best known mainly through their use in various chemiluminescent assays.[2] Less common are *cis*-fused bicyclic analogues which have only been obtained in special cases. Examples are provided by certain dihydropyrans[3] and *N*-methyl- or *N*-acylindoles[4] 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,[5] oxygenation by electron transfer,[6] and dehydrohalogenation of vicinal hydroperoxy halides.[7] Contrary to earlier reports, the photo-oxygenation of **1** in different solvents gave no dioxetane (**2**), only hydroperoxide derivatives (Scheme 1).[8] Similar behavior was observed for **3**; the dioxetane (**4**) not being obtained.[8] 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.[9] 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**).

This paper is dedicated to the journal *Heterocycles* on the occasion of its 50th anniversary.

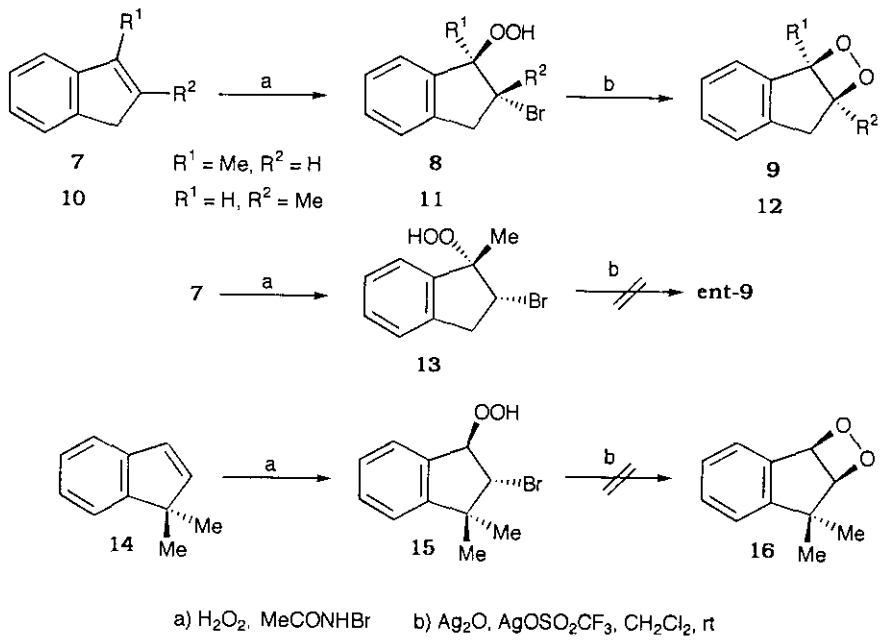
Scheme 1



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.

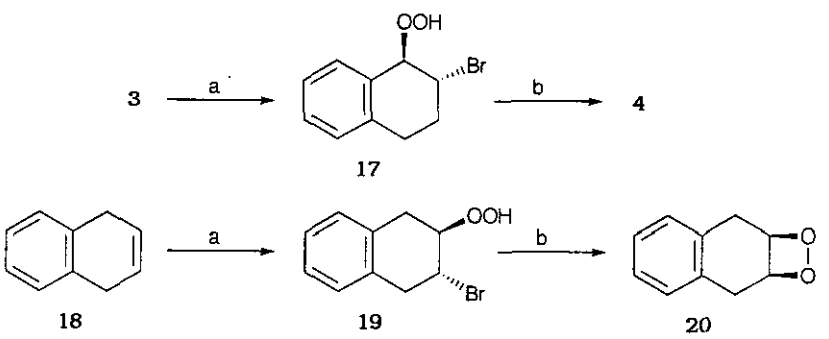
Scheme 2



a) H_2O_2, MeCONHBr b) Ag_2O, $AgOSO_2CF_3$, CH_2Cl_2, rt

The $Ag_2O/AgOSO_2CF_3$ 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_N2-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



a) H_2O_2, MeCONHBr b) Ag_2O, $AgOSO_2CF_3$, CH_2Cl_2, rt

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**).[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**.[10]

The efficacy of the Ag-mixture may be due to the combination of basic and acidic properties. The base, Ag_2O, 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 $Ag_2O/AgOSO_2CF_3$ in $CHCl_2$ 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]

ACKNOWLEDGMENTS

We are indebted to the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases for providing a stipend to M.F.D. We thank Dr. Toshihide Hatsui, Kyushu University, Fukuoka, Japan, for helpful discussions. Thanks are also due to Messieurs A. Pinto and J.P. Saulnier for the NMR measurements.

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_2O_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. (1*RS*,2*RS*)-2-Bromo-1-hydroperoxyindane (**5**). To a solution of **1** (1.0 g, 8.62 mmol) in Et_2O (50 mL), cooled to 0 °C, was added 30% aq. H_2O_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_2O (3 x 50 mL), dried ($MgSO_4$), and evaporated. The resulting residue was purified by column chromatography (silica gel, CH_2Cl_2, eluent) giving the bromohydrin[16] (559 mg, 30%) and **5** as a white solid (680 mg, 35%). mp: 85-87 °C (recrystallized from CH_2Cl_2). IR (CCl_4): 3610, 3550, 1610, 1450, 1380, 1360,

1220, 1160, 1120, 1025, 960 cm^{-1}. ^{1}H-NMR (360 MHz): δ 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): δ 41.7, 48.8, 95.9, 125.1, 126.3, 127.4, 130.3, 135.8, 142.4. Anal. Calcd for $C_9H_9O_2Br$: C 47.18, H 3.96, Br 34.88. Found: C 47.09, H 4.01, Br 34.92.

3.2. (1*RS*,2*RS*)-2-Bromo-1-hydroperoxy-1-methylindane (**8**) and (1*SR*,2*RS*)-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_2Cl_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): δ 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), 7.7 (s, 1H). ^{13}C-NMR (90.6 MHz): δ 20.3, 41.6, 55.3, 89.6, 124.2, 124.3, 127.5, 129.7, 140.3, 141.8. Anal. Calcd for $C_{10}H_{11}O_2Br$: C 49.40, H 4.56. Found: C 49.18, H 4.48.

The *cis*-isomer (**13**) was not obtained completely pure. The following spectral properties for **13** were deduced from the impure product. ^{1}H-NMR (360 MHz): δ 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): δ 21.7, 40.7, 52.8, 93.9, 123.3, 124.7, 127.5, 128.4, 140.2, 141.1. Anal. for impure mixture. Calcd for $C_{10}H_{11}O_2Br$: C 49.40, H 4.56. Found: C 49.38, H 4.61.

3.3. (1*RS*,2*RS*)-2-Bromo-1-hydroperoxy-2-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_2Cl_2). IR (CCl_4): 3510, 1610, 1480, 1460, 1445, 1425, 1380, 1330, 1310, 1230, 1150, 1055, 985 cm^{-1}. ^{1}H-NMR (360 MHz): δ 2.12 (s, 3H), 3.46 (d, J = 17.5 Hz, 1H), 3.52 (t, J = 17.5 Hz, 1H), 5.56 (s, 1H), 7.3-7.5 (m, 4H), 7.82 (s, 1H). ^{13}C-NMR (90.6 MHz): δ 26.8, 41.6, 50.3, 69.9, 96.2, 124.8, 126.7, 127.2, 129.9, 137.3, 143.0. Anal. Calcd for $C_{10}H_{11}O_2Br$: C 49.40, H 4.56, Br 32.87. Found: C 49.39, H 4.61, Br 32.92.

3.3. (1*RS*,2*RS*)-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_2Cl_2). IR (CCl_4): 3557, 1475, 1465, 1405, 1385, 1368, 1335, 1315, 1200, 910 cm^{-1}. ^{1}H-NMR (360 MHz): δ 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): δ 26.1, 27.7, 45.1, 61.6, 93.2, 122.6, 124.1, 127.5, 129.7, 135.8, 148.9. Anal. Calcd for $C_{11}H_{13}O_2Br$: C 51.38, H 5.09, Br 31.07. Found: C 51.30, H 5.00, Br 31.20.

3.4. (1*RS*,2*RS*)-2-Bromo-1-hydroperoxy-1,2,3,4-tetrahydronaphthalene (**17**). Submission of **3** to the procedure in section 3.1. gave the bromohydrin[15] (47%) and **17** (40%) as colorless crystals. mp: 75-76 °C (recrystallized from CH_2Cl_2). IR ($CDCl_3$): 3525, 1480, 1445, 1425, 1320, 1260, 1160, 1030, 978, 940, 900 cm^{-1}. ^{1}H-NMR (360 MHz): δ 2.30 (m, 1H), 2.48 (dddd, J = 14.5, 10.0, 5.7, 3.0 Hz, 1H), 2.86 (dt, J = 17.0, 4.5 Hz, 1H), 3.08 (ddd, 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): δ 25.7, 26.6, 48.0, 85.3, 126.4, 128.8, 130.1, 131.1, 137.1, 137.2. Anal. Calcd for $C_{10}H_{11}O_2Br$: C 49.41, H 4.56, Br 32.87. Found: C 49.67, H 4.55, Br 32.40.

3.5 (2*RS*,3*RS*)-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 CH_2Cl_2). IR ($CDCl_3$): 3525, 1490, 1410, 1360, 1320, 1250, 1165, 1035, 910 cm^{-1}. ^{1}H-NMR (360 MHz): δ 3.03 (dd, *J* = 17.8, 5.5 Hz, 1H), 3.23 (dd, *J* = 17.8, 6.4 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). ^{13}C-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 $C_{10}H_{11}O_2Br$: 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. (1*RS*,2*SR*)-1,2-Epidioxyindane (**2**). To a solution of **5** (160 mg, 0.69 mmol) in CH_2Cl_2 (5 mL) was added Ag_2O (231 mg, 1.0 mmol) followed by $AgOSO_2CF_3$ (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, CH_2Cl_2) at -20 °C. Dioxetane **2** was obtained as a colorless solid (92 mg, 90%). mp: 43 °C. ^{1}H-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). ^{13}C-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%).[17]

4.2. (1*RS*,2*SR*)-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%). ^{1}H-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). ^{13}C-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. (1*RS*,2*SR*)-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. ^{1}H-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). ^{13}C-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. (1*RS*,2*SR*)-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%). ^{1}H-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). ^{13}C-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. (2*RS*,3*SR*)-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%). ^{1}H-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). ^{13}C-NMR (90.6 MHz): δ 33.75, 80.3, 127.3, 129.3, 133.3.

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Received, 8th September, 1998