A Convenient Synthesis of 1-Aryl-2-propanone Precursors of α-Methyldopa

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A simple two-step approach to 1-(3,4-dimethoxyphenyl)- and 1-[3,4-(methylenedioxy)phenyl]-2-propanone (**4a** and **4b**), useful intermediates for α-methyldopa, is described. It is based on the epoxidation of the widely available methyleugenol (1-allyl-3,4-dimethoxybenzene, **1a**) and safrole [1-allyl-3,4-(methylenedioxy)benzene, **1b**] with hydrogen peroxide catalyzed by tungsten peroxo complex **2a** under two-phase conditions, followed by isomerization of the intermediate epoxides **3a** and **3b** by lithium iodide.

1-Aryl-2-propanones **4a–c** are useful precursors of α-methyldopa,[2] one of the most important antihypertensive agents.[3] Among the many synthetic routes to **4a–c**,[2,4–7] an interesting one entails the oxidation of the corresponding 1-aryl-1-propenes (ArCH=CHMe) with organic peracids (peracetic or performic acid), followed by heating with mineral acid.[7] This procedure, however, utilizes internal olefins that must be made by alkali-isomerization of the terminal ones, which instead are available in large amounts as main components of several essential oils.[8] Moreover, it makes use of rather expensive and/or potentially dangerous oxidants. Finally, it involves the recovery or disposal of sizeable amounts of organic acids at the end of the reaction.

As part of our studies on new oxidative processes with hydrogen peroxide,[9–16] we found quaternary ammonium (phosphonium) tetrakis(oxodiperoxotungsto)phosphates and -arsenates (**2**), especially **2a**, to be effective catalysts for the two-phase epoxidation of simple, monosubstituted alkenes,[11,12,14] which are known to react poorly with aqueous hydrogen peroxide under homogeneous conditions in the presence of metal catalysts based on group VA,B and VIA,B elements, unless water is continuously removed.[17]

On this basis, an approach to ketones **4a–c** from the corresponding allylbenzenes **1a–c** via isomerization of the intermediate epoxides **3a–c**, using aqueous hydrogen peroxide as the primary oxidant, looked quite attractive to us.

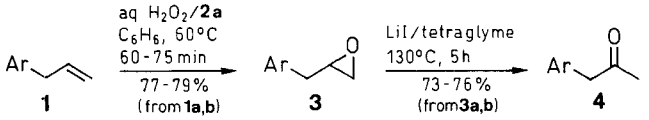
Terminal epoxides, however, are known to give mainly aldehydes rather than ketones on isomerization with the usual acid catalysts.[18] Their selective conversion into methyl ketones[19,20] has been achieved only by using certain transition-metal salts or complexes as catalysts, such as samarium diiodide,[21] samarium iodide oxide, samarium diiodide *tert*-butoxide, dicobalt octacarbonyl,[22] and manganese diiodide. On the other hand, these catalysts require rather delicate working conditions, are very expensive, and not sufficiently stable for practical purposes, or, as we found, cause concurrent isomerization of the olefin, if any is present with its epoxide in the reaction medium,[23] or are markedly depressed or inhibited by the presence of the alkene.[24] This would be troublesome in our procedure, where an excess of olefin is needed in the epoxidation step to obtain the best results.[14]

We thus looked for alternative catalysts to achieve our planned approach to **4a–c** satisfactorily. Except for **3c**,[20] no data were available on the isomerization of the 1-aryl-2,3-epoxypropanes of our interest.

The ability of the above mentioned transition-metal derivatives to act as selective catalysts for isomerization of terminal epoxides to ketones has been accounted for[20] in terms of the presence of both a Lewis acid and a soft nucleophilic center[25] in their molecule. This would bring about ring opening of the Lewis acid activated epoxide by attack of the nucleophilic center at the primary carbon in an S_N2-like process (leading to ketone) rather than through formation of the more stable carbocation (leading to aldehyde), as in the acid-catalyzed isomerization.

We envisaged that lithium iodide, an appropriate combination of a hard cation and a soft anion, might be the right catalyst for our purpose. In fact, it brought about clean rearrangement to ketone of methyleugenol oxide [3,4-dimethoxy-1-(2,3-epoxypropyl)benzene, **3a**] and safrole oxide [3,4-(methylenedioxy)-1-(2,3-epoxypropyl)-benzene, **3b**] (molar ratio epoxide: catalyst = 50:1) in 73 and 76% yields, respectively, and no aldehyde was detected. Moreover, on addition of the olefin, no isomerization of the latter took place. However, with eugenol oxide [4-hydroxy-3-methoxy-1-(2,3-epoxypropyl)benzene, **3c**], the use of the lithium iodide catalyst resulted only in the formation of heavy materials, together with some unchanged epoxide. Furthermore, unlike **3a** and **3b**, intermediate epoxide **3c** could not be obtained from the corresponding olefin 4-hydroxy-3-methoxy-1-allylbenzene (**1c**) by the hydrogen peroxide/**2** oxidizing system, due to the presence of the free, oxidation-sensitive, phenolic hydroxy group. Therefore, the preparation of 1-(4-hydroxy-3-methoxyphenyl)-2-propanone (**4c**) according to the proposed route turned out to be totally unfeasible.[26] Nevertheless, we could develop a two-step, efficient catalytic synthesis of the desired 1-(3,4-dimethoxyphenyl)- and 1-[3,4-(methylenedioxy)phenyl]-2-propanone (**4a** and **4b**) from the corresponding olefins methyleugenol (**1a**) and safrole (**1b**) without isolating the intermediate epoxides. The very active catalyst complex **2a** in combination with hydrogen peroxide was used in the epoxidation step.

Briefly, the synthesis consists in reacting 40% w/v aqueous hydrogen peroxide with a benzene solution of **1a,b** (in ca. 30% molar excess over the oxidant) at 60 °C under vigorous stirring in the presence of catalyst **2a**, followed by phase separation, removal of **2a** and the solvent from the organic layer, and treatment of the oily residue, dissolved in tetraglyme, with catalytic amounts of lithium iodide under nitrogen at 130 °C. Conventional workup gives methyl ketones **4a** and **4b** in an overall yield of 58% based on hydrogen peroxide, with a 69 and 72% selectivity on the olefin, respectively. Isomerization of



2 = $Q_3\{XO_4[W(O)(O_2)_2]_4\}$
Q = "onium group"; X = P, As
a: Q = $(C_8H_{17})_3NMe$; X = P

1,3,4	Ar
a	3,4-$(MeO)_2C_6H_3$
b	3,4-(methylenedioxy)C_6H_3
c	3-MeO,4-HOC_6H_3

intermediate epoxides **3a** and **3b** to ketones **4a** and **4b** is complete in 5 hours, whereas epoxidation of olefins **1a** and **1b** requires 75 and 60 minutes, respectively.

A few points of the synthesis are noteworthy. After the first step, it is essential to remove the catalyst complex **2a** from the reaction mixture, otherwise the epoxide will fail to rearrange to methyl ketone, probably because methyltrioctylammonium iodide is formed, which we have found to be inactive as a catalyst. As mentioned above, isomerization of **3a,b** to ketone is best carried out in polyether solvents, but can be accomplished even without solvent in shorter times (3 h instead of 5 h) with only a modest decrease (< 5%) in the yield. Instead, it is mostly inhibited operating under an oxygen atmosphere, an intractable residue being obtained mainly, together with the unchanged epoxide.

The use of lithium salts as catalysts for the epoxide-carbonyl rearrangement has previously been reported,[27-29] but little attention has so far been paid to lithium iodide in this respect. In our hands, lithium bromide was found to be a poor isomerization catalyst (e.g., 32% of **4a** obtained from **3a** after 5 hours, with 22% of unchanged epoxide, the remainder being heavy materials), while in the presence of lithium tetrafluoroborate (a salt of a hard anion) epoxides **3a,b**, as expected,[29] rearranged in about 30 minutes to the corresponding aldehydes in 60 and 57% yields (GC analysis), respectively.

The remarkable, specific ability of lithium iodide to catalyze ketone formation from terminal epoxides that we have observed with compounds **3a,b** appears to have a broader scope. Thus, in preliminary experiments (2,3-epoxypropyl)benzene, 1,2-epoxyoctane as well as 1,2-epoxydodecane were selectively isomerized in the same way to the corresponding ketones in 76, 61, and 66% isolated yields, respectively.[30] In general, this simple and comparatively inexpensive procedure may turn out to be advantageous in organic synthesis.

Most reagents were of commercial quality from freshly opened containers and were purchased from either Fluka or Aldrich. Reagent quality solvents were used without further purification. Catalyst complex methyltrioctylammonium tetrakis(oxodiperoxotungsto)phosphate (**2a**) was prepared according to the reported procedure.[14] Eugenol oxide (**3c**) was prepared by the standard method from the corresponding olefin **1c** and *m*-chloroperbenzoic acid. Methyleugenol oxide (**3a**) and safrole oxide (**3b**) were obtained in the course of our synthetic procedure (see below and Ref. 32). All products prepared are known. Their identity was confirmed by microanalyses, spectral data, and comparison with authentic samples. Column chromatography was carried out using Merck silica gel 60 (70–230 mesh). TLC analyses were performed on precoated silica gel 60F-254 plates, and spots were detected by observation under a 254-nm source, by spraying with a $KMnO_4$ solution, or by exposure to iodine fumes, according to the product. GC analyses were performed on a HRGC 5300 Carlo Erba flame ionization instrument, using a 25 m × 0.32 mm i.d. OV-1 (0.1–0.15 μm film) (Carlo Erba Strumentazione) or a 30 m × 0.32 mm i.d. SPB-1 (1.0 μm film) (Supelco) bonded-phase, fused silica capillary column, with column temperature programming. Boiling points are uncorrected.

1-(3,4-Dimethoxyphenyl)-2-propanone (4a):
A 100-mL three-necked, round-bottomed flask equipped with mechanical stirrer, thermometer, and a reflux condenser was charged with methyltrioctylammmonium tetrakis(oxodiperoxotungsto)phosphate[31] (**2a**; 0.700 g, 0.31 mmol), methyleugenol (**1a**; 14.55 g, 98% pure, 80 mmol), benzene (35 mL), and 40% w/v H_2O_2 (5.10 mL, 60 mmol). The vigorously stirred mixture was brought to 60°C and kept at this temperature for 75 min (~ 98% conversion of H_2O_2, iodometric titration). (***Caution:*** thermal control was required for about 60 min due to the exothermicity of the reaction.) The two-phase mixture was cooled to r.t. and the organic phase was separated[32] and diluted with Et_2O (30 mL). In order to remove catalyst **2a**, the organic solution was first stirred with a solution of Na_2CO_3 (0.75 g) and Na_2SO_3 (0.75 g) in water (10 mL) for a few minutes, then separated, dried (Na_2SO_4), and passed through a short column (2.5 cm diameter) of silica gel (50 g). Et_2O (~ 300 mL, previously dried over Na_2SO_4) was then passed through the column to ensure complete elution of the products. After removal of the solvent, the catalyst-free residual oil was put into a Schlenk tube, which was equipped with a magnetic bar stirrer. Tetraglyme (8 mL) was placed into the tube, air was flushed out with dry N_2, and anhydrous LiI (0.130 g, 0.97 mmol) was added. N_2 was passed through the tube for a few minutes again, then the gas flow was stopped, and the resultant dark-red mixture was stirred at 130°C (bath temperature) for 5 h under N_2. After cooling, the mixture was eluted on a column (4.5-cm diameter) of silica gel (250–260 g) using Et_2O/hexane (1:1) as eluent, collecting the fractions with R_f = 0.72 and R_f = 0.27 corresponding to the excess alkene and to the desired product. On evaporation of the former fraction under reduced pressure, unreacted **1a** (5.33 g) was recovered, while evaporation of the latter afforded **4a** as a yellow oil; yield: 6.80 g (58%, on H_2O_2 charged); purity: 98% (GC); bp 93°C/0.15 Torr [Lit.[33] 146–147°C/6 Torr].

^1H NMR ($CDCl_3$/TMS, 300 MHz): δ = 2.09 (s, 3H, CH_3), 3.58 (s, 2H, CH_2CO), 3.81 (s, 6H, 2 OCH_3), 6.66 (X of ABX, 1 H_{arom}, J_{BX} = 1.9 Hz, J_{AX} = 0 Hz), 6.74 (center of AB of ABX, 2 H_{arom}, J_{AB} = 8.1 Hz, J_{BX} = 1.9 Hz, J_{AX} = 0 Hz).

1-[3,4-(Methylenedioxy)phenyl]-2-propanone (4b):
In the above-described apparatus, a vigorously stirred mixture of catalyst **2a**[31] (0.700 g, 0.31 mmol), safrole (**1b**; 13.24 g, 98% pure, 80 mmol), benzene (35 mL), and 40% w/v H_2O_2 (5.10 mL, 60 mmol) was heated to 60°C and kept at this temperature for 60 min (~ 98% conversion of H_2O_2). (***Caution:*** thermal control was required for about 45 min due to the exothermicity of the reaction.) The mixture was cooled to r.t., the organic phase was separated[32] and diluted with Et_2O (30 mL). Following the same procedure used for **4a**, catalyst **2a** was removed, the solvent evaporated, the oily residue dissolved in tetraglyme (18 mL) and treated with anhydrous LiI (0.130 g, 0.97 mmol) at 130°C for 5 h. After cooling, the mixture was chromatographed on silica gel in the same way as described for **4a** using Et_2O/hexane (1:3) as the eluant, collecting the fractions with R_f = 0.80 and R_f = 0.20 corresponding to the excess alkene and to the desired product. On evaporation of the former fraction under reduced pressure, unreacted **1b** (5.17 g) was recovered, while evaporation of the latter afforded **4b** as a yellow oil; yield: 6.25 g

(58%, on H_2O_2 charged); purity: 98% (GC); bp 80°C/0.20 Torr [Lit.[34] 168°C/17 Torr].

^1H NMR ($CDCl_3$/TMS, 300 MHz): δ = 2.13 (s, 3H, CH_3), 3.58 (s, 2H, CH_2CO), 5.92 (s, 2H, OCH_2O), 6.66 (X of ABX, 1 H_{arom}, J_{BX} = 1.6 Hz, J_{AX} = 0 Hz), 6.69 (center of AB of ABX, 2 H_{arom}, J_{AB} = 7.9 Hz, J_{BX} = 1.6 Hz, J_{AX} = 0 Hz).

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Satisfactory epoxidation of 1-octene with 70% H_2O_2 in dioxane has been recently reported[35] using trioctylammonium tungstate combined with the phenylphosphonic acid ligand as catalyst. However, a very large molar excess (10:1) of olefin over the oxidant is required.
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(21) SmIO, which is formed *in situ* on deoxygenation of the epoxide by SmI_2, is the true catalyst.[20]
(22) Preliminary dismutation to cobaltate, the actual isomerizing agent,[19,20] is required.
(23) As an example, in the isomerization of **3b** (10 mmol) by $Co_2(CO)_8$ (0.5 mmol) in MeOH (3 mL) at 60°C under Ar in the presence of safrole **1b** (5 mmol), after 3 h about 50% of **1b** isomerized to isosafrole (GC), while the expected **4b** was formed. The presence of both epoxide and olefin appears to be necessary for isomerization of the latter to occur.
(24) In the isomerization of **3a** and **3b** (4 mmol) by anhydrous MnI_2 (0.097 mmol) in diglyme (2 mL) at 130°C under N_2 in the presence of the related olefin **1a** and **1b** (2 mmol), after 10.5 h the conversion of the epoxide was ca. 45 and 4% (GC), respectively, while in the absence of the olefin approached 100% in both cases.
(25) A basic center is also present in the lanthanide catalysts.[20]
(26) Also the use of the protected, easily epoxidable[14] *O*-acetyleugenol as the starting material met with no success. Only negligible catalytic activity was shown by LiI for the *O*-acetyleugenol oxide isomerization (molar ratio epoxide: LiI = 20:1), due to the observed fast catalyst deactivation. Correspondingly, **3c** and 1-[4-hydroxy(or 4-acetoxy)-3-methoxyphenyl]-1-propene iodohydrin were found in the reaction mixture, together with the unchanged epoxide (major product) and some of the expected ketone (GC/MS analysis). Acetate and lithium ions were found (ion chromatography) in the aqueous solution resulting from treatment of the reaction mixture with water, while iodide ions were not detected.
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(30) In the absence of the solvent (tetraglyme), a 10–12% decrease in the yield of the ketone was observed. In the case of (2,3-epoxypropyl)benzene, a sudden effervescence with evolution of white fumes occurred as soon as the LiI catalyst was put into contact with the epoxide.
(31) Due to its syrupy nature, **2a** was preferably used as a CH_2Cl_2 solution of known concentration, then removing the solvent.
(32) To isolate the epoxide, the solvent was removed and the oily residue was eluted on silica gel as described for the related ketone (see experimental section). R_f, % yield (on H_2O_2), bp: 0.33, 79, 83°C/0.05 Torr [Lit.[36] 165–170°C/15 Torr] (**3a**); 0.40, 77, 111–112°C/2 Torr [Lit.[37] 116–118°C/4 Torr] (**3b**).
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