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OXIDATIONS BY METHYL(TRIFLUOROMETHYL)DIOXIRANE. 4.[1] OXYFUNCTIONALIZATION OF AROMATIC HYDROCARBONS

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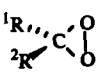
Abstract: By using the title dioxirane (**1a**), naphthalene (**2**), phenanthrene (**3**), and anthracene (**4**) have been converted into *anti*-naphthalene-1,2;3,4-dioxide (**2'**), phenanthrene-9,10-oxide (**3'**), and anthraquinone (**4'**), respectively, in high yield and under mild conditions. However, the transformation of pyrene (**5**) - an higher homologue of the polycyclic aromatic hydrocarbon series - into the corresponding arene oxide was found to procced much less effectively.

IT is well established that polycyclic aromatic hydrocarbons (PAH) require metabolic activation, i.e. oxidation, by mixed function oxygenases to express their mutagenic potential.[2,3] Several careful studies have shown that relatively unstable arene oxides are the primary metabolites of PAH activation.[2] Thus, extensive synthetic methods have been developed for the preparation of these important intermediates;[3-16] in many cases, multistep syntheses are required.[4] In the *direct* conversion of PAH into arene oxides,[12-16] methods adopting classic oxidation reagents (e.g., peroxy acids, hypochlorite)[13,14] have often led to only limited success, since many of the oxides are quite sensitive to acid, water, or nucleophiles.[2-4]

Recently, a new class of powerful oxidants has been introduced, [18,19] which shows great versatility in dealing with problems arising in the synthesis of sensitive epoxides.[17-22] This is the family of dioxiranes **1**, the smallest ring peroxide species containing carbon.[18,19]



1

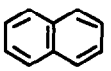
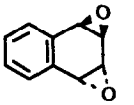
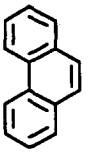
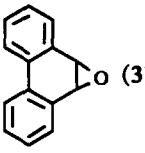
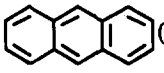
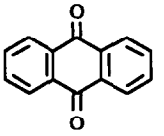
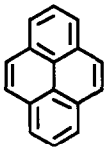
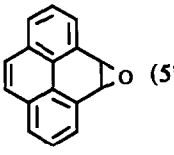
(**1a**: $^1R = CF_3$, $^2R = CH_3$; **1b**: $^1R = {}^2R = CH_3$)

Since their introduction as versatile epoxidation reagents,[20] both *in situ* and isolated[23-26] dioxiranes have now grown to constitute a new entry into selective oxidation of organic compounds.[18,19] The oxidation of PAH by *in situ* dimethyldioxirane (**1b**) has been reported by Murray et al.; [17] yields in arene oxides from 8 to 60% were reported, during 1.5 to 8 h reaction time.[15] Naphthalene could be converted by **1b** into its 1,2;3,4-dioxide, albeit in 5% yield only.[17,18b] Later, Agarwal et al.[16] showed that, starting with isolated **1b** and arene oxides, arene dioxides can be obtained in a single step, although yields can be low in some instance. For example, pyrene-4,5;9,10-dioxide was obtained from the 4,5-oxide in 7% yield only.[16] In 1988, we have reported on the isolation and characterization of methyl(trifluoromethyl)dioxirane (**1a**).[26] Since we noticed that this dioxirane presents a reactivity by far in excess to that of **1b** (while maintaining high selectivity),[1,26] it was desirable to explore its potential in the oxidation of representative arenes.

First, we could verify that, at variance with that recorded for **1b**,[17,18b] dioxirane **1a** is reactive toward benzene, although this is a rather slow reaction requiring hours rather than minutes. Similar to certain enzymic processes, deep seated oxidation products are formed,[27] among which *cis,cis*- and *trans,trans*-muconic dialdehyde[28,29] could be identified (Table I). The aldehydes might have arisen from a benzene oxide/oxepin mixture initially formed, by way of further oxidation and ring opening.[28]

Then, data concerning the reactivity of **1a** toward some PAH substrates of choice were collected. Typical results results are presented in Table I.

Table I. Reactions of Isolated Methyl(trifluoromethyl)dioxirane (1a) with Representative Arenes in CH_2Cl_2/TFP.

Substrate	Solvent	R, (1a/S)[a]	T (°C)	Reactn time	Conversion (%)[b]	Product	Yield (%)[c]
Benzene	TFP/F113[d]	0.20.	0.	6. h	12.[e]	O=CHCH=CH-CH=CHCH=O[f]	35.[g]
 (2)	CH_2Cl_2/TFP[h]	2.2	- 20.	30. min	92.	 (2')	90.[g]
	,,	2.1	- 22.	40. min	97.		98.[g,i]
 (3)	CH_2Cl_2/TFP[h]	1.1	- 20.	8. min	>96.	 (3')	96.[g]
 (4)	CH_2Cl_2/TFP[h]	4.5	0.	30. min	>98.	 (4')	80.[g]
 (5)	CH_2Cl_2/TFP[j]	1.1	- 20.	5. min	12.	 (5')	10.[k]
	,,	2.2	- 20.	5. min	30.		8.[i,k]

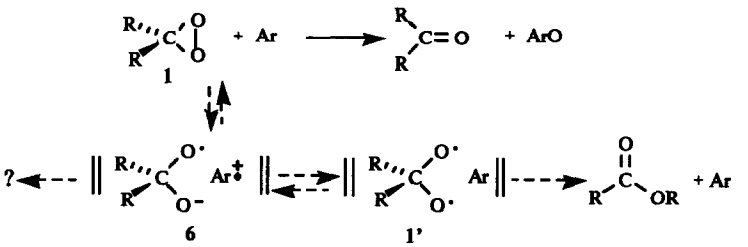
[a] Ratio of dioxirane to substrate initial concentrations. [b] As determined by glc monitoring (SE 30 or OV 101, 30 m × 0.25 μm i.d. capillary column.) of substrate consumed. [c] Based on stoicheiometric substrate consumed. [d] Composition of solvent mixture: benzene/TFP/F113 (1:3:1). [e] Based on a 1:1 stoicheiometry of benzene to dioxirane. [f] As a 1:1.5 mixture of *Z,Z-* and *E,E-* muconic dialdehyde, by ^{1}H nmr analysis (cf., ref. 28). [g] Isolated yield. [h] Mixed solvent, ratio 3:1. [i] Reaction run in the presence of suspended Na_2HPO_4, as a solid buffer (see text). [j] Mixed solvent, ratio 8:1. [k] As estimated by ^{1}H nmr analysis, based on integration of the singlet resonance at δ 4.85 (- 20 °C) [lit. δ 4.83 (ref. 33)] due to the oxiranyl protons.

Inspection of data in Table I suggests that the title dioxirane can serve in the oxyfunctionalization of the lower homologues of the PAH series. The following procedure is representative. A cold (- 20 °C) aliquot (5 mL, 2.75 mmol) of a dried dioxirane **1a** solution[26] [0.55 M in 1,1,1-trifluoro-2-propanone (TFP)] was rapidly added to a stirred solution of naphthalene (2) (0.17 g, 1.33 mmol) in CF_2ClCCl_2F (Freon 113) kept at -20 °C; the mixture also contained dry Na_2HPO_4 in suspension (to act as a solid buffer), and CF_2ClCCl_3 (Freon 112) as an internal standard. Gc or gc/ms monitoring revealed that the substrate had been consumed during 40 min, while hplc monitoring[30] allowed us to estimate that the yield in naphthalene 1,2;3,4-dioxide (2')[12a] is practically quantitative (Table I). For product isolation, the suspended Na_2HPO_4 salt was filtered off and the volatile solvent mixture removed under slight vacuum (400 mm Hg), leaving 0.21 g (1.31 mmol, yield ≥ 98 %) of the dioxide 2'[31] (mp 98.5-100 °C; lit.[12a] 99-100 °C).[32] Concerning the *anti* configuration of 2', most telling is the $J_{2,3}$ value[12a] of 1.88 Hz determined upon analysis of the AA'BB' system of oxiranyl protons.[12a,31]

Apparently, employing the title dioxirane in the synthesis of the dioxide 2' and of phenanthrene-9,10-oxide (3') offers certain advantages over existing direct oxidation methods.[12-17] The oxidation of anthracene (4) to anthraquinone (4') also works satisfactorly, although excess dioxirane is necessary to achieve complete conversion of the substrate (Table I). In this reaction, ^{1}H nmr monitoring indicates that 9-hydroxy-anthracene and 9,10-dihydroxy-anthracene are formed as intermediate oxidation products. By way of contrast, in the reaction of pyrene (5) with **1a**, in moderate excess over stoicheiometric, only partial substrate conversion occurs, and the yield of pyrene-4,5-oxide (5')[14b,33] is decidedly low. The ^{1}H nmr spectra of the reaction solution at -20 °C revealed that besides 5' other oxidation products are formed; one of these was tentatively identified as pyrene-4,5;9,10-dioxide,[11,16] based on the singlet resonance at δ 4.64 relative to the oxiranyl protons.[34,35]

It is not immediately clear why dioxirane **1a**, which is extremely efficient in the oxyfunctionalization of naphthalene and of phenanthrene, should become progressively less effective on going to anthracene, to pyrene. With respect to this, one clue comes from the observation that, in the reaction of the dioxirane with pyrene at -20 °C, glc[36] and ^{1}H nmr analyses reveal formation of methyl trifluoroacetate CF_3COOCH_3. This ester was also found to arise in the "decomposition" of **1a** in the absence of substrate, although this occurs much more slowly (e.g., 6% dioxirane loss during 48 h, at -20 °C).[26] The rearrangement of dioxiranes into esters is thought to occur via bis(oxy) methylene biradicals (1').[18a,19] If this is the case, recalling that the redox potential for the Ar / $Ar^{+\bullet}$ couple drops from 2.08 to 1.60 V on passing from naphthalene to pyrene, one might be tempted to accomodate our findings as outlined in Scheme I.

Scheme I



In short, whenever the arene (Ar in Scheme I) possesses an accessible oxidation potential, leakage from straightforward O-transfer may occur, leading to radical couple 6. The latter might serve to generate bis(oxy) radical 1', which in turn would quickly collapse into the ester.

In line with this hypothesis is the observation that, when pyrene (5) is made to react with **1a**, the reaction solution is not ESR silent. For instance, a solution of 0.05 M 5 and 0.06 M **1a** in TFP at -30 °C turns green upon mixing, yielding a poorly resolved ESR spectrum. This has features essentially identical with the ESR spectrum of $[pyrene]^{+\bullet}$ (obtained upon reaction of pyrene with CF_3SO_3H), and it is in good agreement with the resonance pattern simulated using literature hyperfine splitting constants for this species (i.e., a_H = 5.38, 1.18, and 2.12 *G*).[37] Under the conditions described, the ESR absorption is observed to decay with time, fading away during 30-45 min. As to the radical pair 6 in Scheme I, it is likely that the dioxirane radical ion $1^{-\bullet}$ would quickly evolve to yield its bis(oxy) methylene form $^-$O-CMe(CF_3)-O$^\bullet$; the latter should posses significant nucleophilic character. Then, the configuration mixing model[38] would predict that the interaction of this radical ion with an extensively delocalized $Ar^{+\bullet}$ system , rather than bond formation, results in a single-electron back shift, yielding the bis(oxy) radical 1' (Scheme I).

We have pointed out elsewhere that the process sketched in Scheme I has several interesting facets to pursue,[18a,19] rising a number of mechanistic incognita. For one, the various patterns available to bis(oxy) methylene radical ions need to be ascertained. Be the mechanistic details as it may, results herein suggest that the efficiency of dioxiranes in generating arene oxides from PAH becomes somewhat impaired when dealing with the higher homologues of the series. This observation should be useful in assessing the role of dioxiranes as generators of mutagenic species in polluted urban atmospheres.[17]

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(30) Analytical hplc analyses were run on a Perkin-Elmer model 3B instrument and LC-85B absorption detector, equipped with a 250 mm × 4.6 mm i.d. Erbasil C-18 column, H_2O/MeCN 20:80 to 50:50 solvent programming, 1 mL/min.
(31) Further purification was achieved by subambient (5 °C) flash chromatography [Merck silica gel 60 silanised, 70-230 mesh, n-hexane/Et_2O (50:50)] obtaining 0.20 g (yield > 94% of *anti*-naphthalene-1,2;3,4-dioxide (**2'**): mp 101-102 °C [lit.[11a] 99-100 °C]; ^1H nmr [11a] (acetone-d_6, 200 MHz) δ 3.74 (^1H,^4H) and 3.97 (^2H,^3H) (AA'BB', 4 H, $J_{1,2}$ = 4.11, $J_{1,3}$ = 0.79, $J_{1,4}$ = 0, $J_{2,3}$ = 1.88, $J_{2,4}$ = 0.79, and $J_{3,4}$ = 4.11 Hz), 7.43 (m, 4 H, ArH); $\{^1H\}^{13}C$ nmr ($CDCl_3$, 50 MHz) δ 51.94, 54.74, 129.42, 131.50; ms (70 eV) *m/z* (rel abund) 160 (23, M^+), 133 (11), 132 (95), 131 (96), 116 (34), 115 (18), 105 (10), 104 (72), 103 (100), 102 (23), 89 (18), 78 (79), 77 (70), 76 (20), 75 (16), 74 (18), 65 (11), 63 (41), 62 (22), 61 (10), 52 (17), 51 (66), 50 (38).
(32) By following the same procedure, the Freon solvent can be substituted with CH_2Cl_2, and the solid Na_2HPO_4 buffer omitted, which leds to somewhat lower (80-85%) substrate conversion, and to slightly inferior yields (88-90%) of the dioxide **2'**.
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(35) This signal disappeared on warming to 20 °C, in line with the high susceptibility to rearrangement recorded for this arene oxide (cf., ref 34).
(36) Supelcowax wide-bore capillary column (60 m × 0.75 mm i.d., 1 mm film thickness).
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