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FREE RADICAL CHLORINATION AND ONE-ELECTRON OXIDATION OF ARYLCYCLOPROPANES. DESIGNER PROBES FOR CYTOCHROME P-450 HYDROXYLATION MECHANISMS

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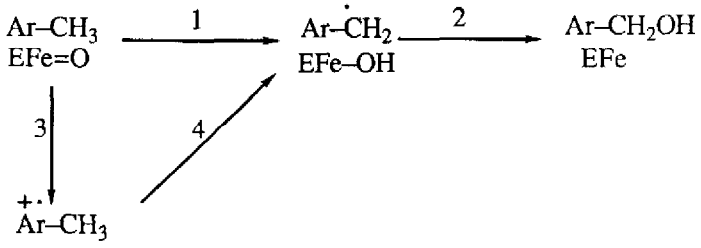
Abstract: Arylcyclopropyl radicals can be formed under mild conditions (phase-transfer-catalyzed chlorination) and give rise to cyclopropyl products; in contrast one-electron oxidation of arylcyclopropanes by $Mn(OAc)_3$ leads to fragmentation of the cyclopropane ring and the formation of acyclic products.

The commonly accepted mechanism for cytochrome P-450-catalyzed aliphatic hydroxylation involves rate limiting H-abstraction followed by hydroxyl recombination (steps 1 and 2, Scheme I).[1] Recent experiments with aminocyclopropanes,[2,3] dihydropyridines[4] and polycyclic aromatic[5] or strained[6] hydrocarbons reveal that in addition to abstracting hydrogen atoms, cytochrome P-450 can also abstract *electrons* from some substrates. One-electron abstraction is the rate-limiting step in the classical ECE mechanism for benzylic functionalization of methylarenes such as p-methoxytoluene.[7] These considerations suggest cytochrome P-450 (EFe=O in Scheme I) might be able to effect benzylic hydroxylation by a one-electron pathway (e.g. step 3, Scheme I), at least for substrates with sufficiently low oxidation potentials.

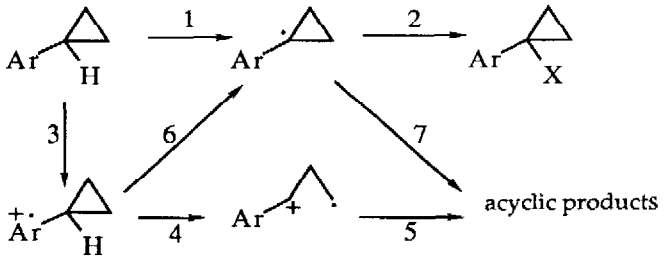
Scheme I



We felt that a good way to explore this possibility would be to use arylcyclopropanes as probe substrates, on the assumption that electron abstraction from the π-system would lead *not* to deprotonation at the benzylic carbon (cf. step 6, Scheme II), but rather to fragmentation of the cyclopropane ring (cf. step 4, Scheme II). On the other hand the classical H-abstraction / HO-recombination mechanism should still be able to lead to "normal" oxidation products, i.e. arylcyclopropanols (steps 1 and 2, Scheme II). We have now tested these speculations by

submitting phenylcyclopropane, **1**, and its p-methoxy derivative, **2**,[8] to free-radical chlorination as a test for steps 1, 2, and 7 of Scheme II, and to one-electron oxidation with manganic acetate as a test for steps 3, 4, and 6 in Scheme II.

Scheme II



For free-radical chlorination the hypochlorite-based phase transfer catalysis method of Fonouni was used.[10,11] In this system **1** was ca. 20-fold less reactive than toluene, and gave a mixture of 4 products. To aid in identification of chlorination products, **3**, **5**, **7**, and **8** were synthesized.[12] The chlorination products were identified as **3-6** by GC/MS and 500 MHz ^{1}H NMR after separation by preparative GC on carbowax; **7** and **8** were not formed. In contrast chlorination of **2** gave only **9** in a rapid reaction.

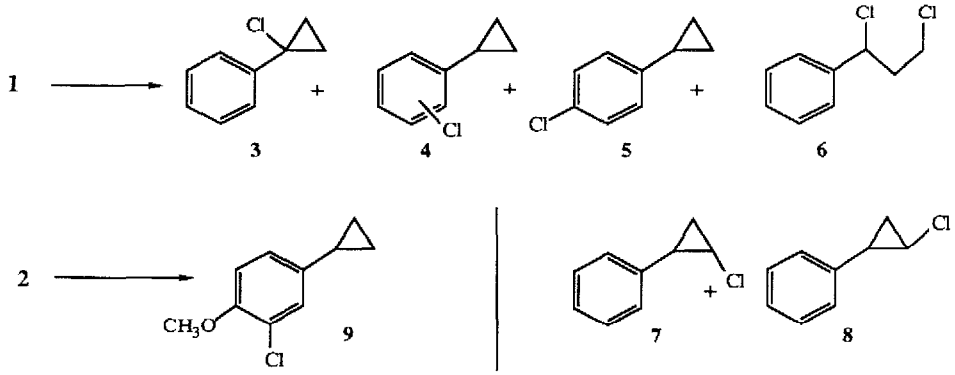


Table: Distribution of products from chlorination of **1** under phase transfer catalyzed conditions with change in pH.

initial pH	products (% of total)		
	3	**4+5**	**6**
8.04	<1	76	23
8.19	4	47	49
8.40	9	27	64
8.60	26	19	52
8.82	39	19	42
9.02	41	15	44

The Fonouni system is pH-dependent and at pH 7-8, where Cl_2 formation is more likely (the pKa of HOCl is 7.4), **3** was a very minor product (< 1%), whereas at pH 8.8-10.8, **3** accounted for 41% of all products. Since cyclopropyl groups greatly activate aromatic rings toward electrophilic substitution, especially halogenation,[13] it is likely that **4**, **5**, and **9** are formed in this fashion from the Cl_2 inevitably present in low-pH hypochlorite solutions. Consistent with this, we observed (Table) that raising the pH from 8.0 to 9.0 decreased the yield of **4** and **5** from 76% to 15%.

The formation of **6** is more complex. Electrophiles (e.g. Cl_2) also attack cyclopropane rings, and this almost certainly accounts for the formation of **6** at low pH. As the reaction pH was raised the yield of **6** steadily rose to 64% at pH 8.6 and then decreased to 44% at pH 9.0. Since Cl_2 addition to **1** is not likely at high pH, another mechanism, possibly a radical chain reaction, must be involved. It seems highly unlikely that **6**, a *dichloride adduct* (as opposed to a chloroalcohol or allylic chloride), could arise *via* rearrangement of a cyclopropyl radical (step 7 in Scheme II). Other evidence indicating the stability of cyclopropyl radicals[14] to skeletal rearrangement may be found in the photolysis of diacylperoxides,[15] decomposition of cyclopropylcarbonyl hypobromites (Hunsdieker reaction)[16] and the NCS chlorination of cyclopropane carboxylic acid.[17] Thus formation of **3** indicates that *aryl*cyclopropyl radicals can be formed under mild conditions (i.e. phase-transfer-catalyzed chlorination) and retain their cyclic identity to a large degree when reacting to give stable products.

Manganic acetate in acetic acid[7] at 70°C oxidizes p-methoxytoluene (E_O = 1.82 V)[18] smoothly to p-methoxybenzyl alcohol (19%, 25hr.), but it does not oxidize toluene (E_O = 2.61 V).[18] We find that it also fails to oxidize **1**, even after 24 hr, whereas it cleanly oxidizes **2** (72% conversion in 24 hr) to 1-(p-methoxyphenyl)propane-1,3-diol diacetate, **10** (96% of total product).

The above results nicely corroborate our expectations about H-abstraction vs. electron abstraction from arylcyclopropanes as formulated in Scheme II (and in particular, that steps 6 and 7 are insignificant), thus lending credence to our proposal that arylcyclopropanes might be good probes for electron-abstraction mechanisms in P-450-catalyzed benzylic hydroxylations, at least for electron-rich substrates. Studies of the oxidation of **1** and **2** by cytochrome P-450 are just beginning in our laboratory. Meanwhile we note that cytochrome P-450 is reported[19] to oxidize **1** to *benzoic acid*, a remarkable feat that deserves further investigation!

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8) p-Methoxyphenylcyclopropane, **2**, was synthesized from p-methoxystyrene, CH_2I_2 and Et_2Zn using the modified Simmons-Smith reaction described by Furukawa *et al* [9]. NMR : δ = 0.61(dd, 2H), 0.87 (m, 2H), 1.85 (m, 1H), 3.75 (s, 3H), 6.79 (d, 2H), 7.00 (d, 2H).

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12) For **3**, α–chlorostyrene was heated with $PhHgCBr_3$ to form 1,1-dibromo-2-chloro-2-phenyl-cyclopropane which was then reduced with excess tributyltin hydride. NMR ($CDCl_3$): δ = 1.25 (m, 2H), 1.49 (m, 2H), 7.27 (m, 1H), 7.34 (d 2H), 7.46 (d,2H). For **5**, p-chlorostyrene was treated with CH_2I_2 and Et_2Zn using the method described by Furukawa et al.[9] NMR ($CDCl_3$) gave δ = 0.65 (m, 2H), 0.96 (m,2H), 1.87 (m,1H), 6.99 (d,2H), 7.21 (d,2H).For **7** and **8**, 1,1-dichloro-2-phenylcyclopropane [13] was reduced with excess tributyltin hydride to a mixture of **7**, **8**, and a trace of **1**. NMR of 7 ($CDCl_3$) gave δ =1.40 (m,1H), 1.45 (m, 1H) 2.31 (m,1H), 3.12 (m,1H), 6.98 (m,2H), 7.14 (m, 1H) ,7.20, (m,2H). NMR of **8** ($CDCl_3$) gave δ = 1.24 (m, 1H), 1.44 (m,1H), 2.44 (m,1H) 3.39 (m,1H) 7.18 (m, 3H), 7.38 (m, 2H). All C_9H_9Cl isomers gave similar EI mass spectra, except for a possibly diagnostic peak at m/e 125 unique to the spectra of the aryl halides **4** and **5**. Extensive NMR decoupling studies supported the assigned structures.

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