AROMATIC CHLORINATION OF TOLUENE AND OF ANISOLE USING CLAY-SUPPORTED IRON(III) CHLORIDE AND m-CHLOROPERBENZOIC ACID. A BIOMIMETIC APPROACH

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In the presence of meta-chloroperbenzoic acid, clay-supported ferric chloride is an efficient aromatic chlorinating agent for toluene and anisole. Influence of various experimental factors such as the nature of the solvent, the peracid or the metallic cation were investigated. These reactions represent a laboratory equivalent to biological halogenations through oxidation of halide ions by peroxidases in the presence of hydrogen peroxide.

1. Introduction

We report here chlorination of anisole and toluene, as test aromatic substrates, with a heterogeneous system of reagents and catalyst. For this purpose, we borrow a leaf from the album of Nature: our procedure is inspired by enzymatic chlorinations among various organisms.

Work by Kovacic et al. [1] has pioneered use of metallic chlorides to effect aromatic nuclear chlorinations. However, these reactions suffer from an abundance of side- and coupling products. It was clear that chloride ions lacked the required electrophilicity: prior oxidation into positive chlorine is a pre-requisite. For this purpose, a number of oxidizing agents can be thought of: Chip and Grossert [2] have resorted to the combination of titanium tetrachloride and trifluoroperacetic acid; Kochi et al. [3] have resorted to the lithium chloride-benzoyl peroxide pair; whereas Eberson and Wistrand [4] have used the lithium chloride-sodium persulfate association. In the presence of 18-crown-6, potassium chloride and meta-chloroperbenzoic acid [5] or nitrobenzenesulfonyl peroxides [6] can also effect halogenation of aromatic rings.

Based on the analogy with aromatic nitrations, which we have performed successfully with metallic *nitrates* impregnated on the acidic K10 montmorillonite [7], we set to explore the kindred aromatic chlorinations, when the reagent consists of a clay-supported metallic *chloride*. In this rational manner, we conceived the basis system for our reagent, viz. ferric chloride supported on the K10 montmorillonite ("clayfec") in the presence of meta-chloroperbenzoic acid (MCPBA).

2. Experimental

Technical 50–60% meta-chloroperbenzoic acid was purchased from Janssen. Peracetic [8], permaleic [9], monoperphtalic [9] acids and peracidic Duolite C433 resin [10] were prepared according to previously published procedures.

2.1. PREPARATION OF CLAY-SUPPORTED FERRIC CHLORIDE ("CLAYFEC")

In a 1-litre pear-shaped evaporating flask, anhydrous ferric chloride (5.4 g, 100 mmol of Cl^-) is dissolved in methanol (100 ml). K10 clay (14.6 g) is then dispersed in the solution with vigorous stirring. The solvent is evaporated under reduced pressure (rotary evaporator, water aspirator) on a water bath at 50 °C. After 15 mn, the dry solid crust adhering to the flask is flaked off and crushed with a spatula; drying is resumed under the same conditions for another 15 mn. Weighing the resulting yellow powder is necessary to determine its exact chloride content as 1 or 2 g of solvent are still present.

2.2. AROMATIC CHLORINATION: TYPICAL PROCEDURE

Iodometric titration of technical 50–60% meta-chloroperbenzoic acid indicated an effective 44% active oxygen availability. 4.9 g of this material (12.5 mmol of MCPBA) are dissolved in 50 ml of dichloromethane. The solution is dried over magnesium sulfate and perfused uniformally during a total time of 25 mn in a suspension of "clayfec" (2.5 g, 12.5 mmol of Cl^-), aromatic substrate (5 ml, toluene: 47 mmol, anisole: 46 mmol), and dichloromethane (20 ml) while stirring at room temperature. Stirring is maintained for an additional 15 mn. The reaction mixture is then filtered off and the solid is rinsed with two portions of dichloromethane (10 ml each). Filtrate composition is determined by G.C. using an internal standard. Yield calculations are based on the available chloride anions.

3. The solid reagent

3.1. EXPLORATORY EXPERIMENTS

As an exothermic process takes place when MCPBA is added to a suspension of "clayfec", slowly dropping a peracid solution was thought to afford a better

Table 1
Influence of the rate of admission of MCPBA on the chlorination of toluene and of anisole by "clayfec".

MCPBA addition time (mn)	yields (%) and regioselectivities (ortho, para)	
	toluene	anisole
a few sec	37(66,34)	73(28,72)
10	49(67,33)	86(27,73)
25	62(64,36)	97(26,74)
50	64(64,36)	7(40,60)
100	53(64,36)	0
250	53(64,36)	0

control of the reaction. Thus, exploratory experiments were carried out perfusing a solution of MCPBA in dichloromethane. These showed a critical parameter to consist of the rate of addition of MCPBA to the reaction flask (table 1). The optimum time-delivery turned out to be addition of 50 ml of the dichloromethane solution of MCPBA (0.25 M) during a total time of 25 mn.

3.2. INFLUENCE OF THE SOLID SUPPORT AND OF THE MODE OF ATTACHMENT

We have investigated a variety of solid supports (table 2); and a few solvents from which evaporation leads to impregnation of ferric chloride onto the support, presumably via coordination of the metal to the surface silanol and alanol groups present on these solids (table 3). The conclusion is that the best results are obtained with the K10 montmorillonite clay. Furthermore, impregnating the solid from an alcoholic solution of ferric chloride is an essential part of the process. Weighing the solid reagent after preparation reveals the presence of residual solvent, thus confirming the importance of solvation.

Table 2
Influence of the solid support on the chlorination of toluene and of anisole by supported ferric chloride in the presence of MCPBA.

solid support	yields (%) and regioselectivities (ortho, para)	
	toluene	anisole
none	5(86,14)	0
neutral Al_2O_3	36(63,37)	3(45,55)
SiO_2	37(60,40)	87(20,80)
xonotlite	15(59,41)	62(6,94)
HAB A40 zeolite	1	5(20,80)
NaY zeolite	8(60,40)	55(18,82)
K10 clay	62(64,36)	97(26,74)

Table 3
Influence of the impregnation of "clayfec" on the chlorination of toluene and of anisole in the presence of MCPBA.

impregnation solvent	yields (%) and regioselectivities (ortho, para)	
	toluene	anisole
none [a]	56(66,34)	0
acetone	4(100,0)	0
water	6(63,37)	92(11,89)
ethanol	41(62,38)	97(18,82)
methanol	62(64,36)	97(26,74)
methanol [b]	1	8(70,30)

[a] A mixture of anhydrous ferric chloride (0.68 g; 12.5 mmol of Cl^-) and of K10 clay (1.82 g) was used for these experiments.

[b] After preparation as stated in the experimental part, "clayfec" was dried at 110 ° C under vacuum for 2.5 hours.

Table 4
Chlorination of toluene and of anisole in the presence of MCPBA using "clayfec" stored during a variable period ([a] in a stoppered vial or [b] in an open flask).

Conservation time	yields (%) and regioselectivities (ortho, para)	
	toluene	anisole
none [a]	47(63,37)	95(18,82)
1 day [a]	48(63,37)	95(19,81)
1 week [a]	47(62,38)	92(18,82)
1 month [a]	42(62,38)	91(17,83)
1 month [b]	17(65,35)	71(16,84)

3.3. CONSERVATION OF THE SUPPORTED FERRIC CHLORIDE

The resulting "clayfec" reagent remains fully active for over a month if stored in a stoppered vial (table 4). The activity drops markedly when "clayfec" is left in humid air for a period of days or of weeks.

3.4. INFLUENCE OF THE METAL

We have tested a number of metallic chlorides. Among them, NH_4Cl, NaCl, KCl, $CrCl_3.6H_2O$, $MnCl_2$, $FeCl_2.4H_2O$, $CoCl_2.6H_2O$, $CdCl_2$, and $HgCl_2$ gave no reaction at all. Results obtained with other salts are gathered in table 5. While essentially no reaction is observed with alkali metal chlorides, most transition metal halides give only slightly better results; and the highest yields are obtained with ferric chloride, either using the anhydrous or the hexahydrated salt. Ferrous chloride, on the other hand, was totally unreactive. This can be attributed to the oxidation of iron (II) ions by MCPBA. Such a reaction is well-known to occur in

Table 5

Chlorination of toluene and of anisole by clay-supported metallic chlorides in the presence of MCPBA (* there liquid chlorides were simply mixed with K10).

metallic chloride	yields (%) and regioselectivities (ortho, para)	
	toluene	anisole
LiCl	0	40(5, 95)
$CaCl_2$	11(64,36)	56(15,85)
$TiCl_4^*$	58(66,34)	67(32,68)
$FeCl_3$	62(64,36)	97(26,74)
$FeCl_3.6H_2O$	52(64,36)	82(20,80)
$NiCl_2$	3(75,25)	5(0,100)
$CuCl_2$	6(76,24)	41(15,85)
$ZnCl_2$	6(76,24)	14(33,67)
$AlCl_3$	0	8(45,55)
$SiCl_4^*$	45(63,37)	59(21,79)
$SnCl_4^*$	11(75,25)	2
$SbCl_5^*$	13(70,30)	2
$BiCl_3$	16(63,37)	27(34,66)

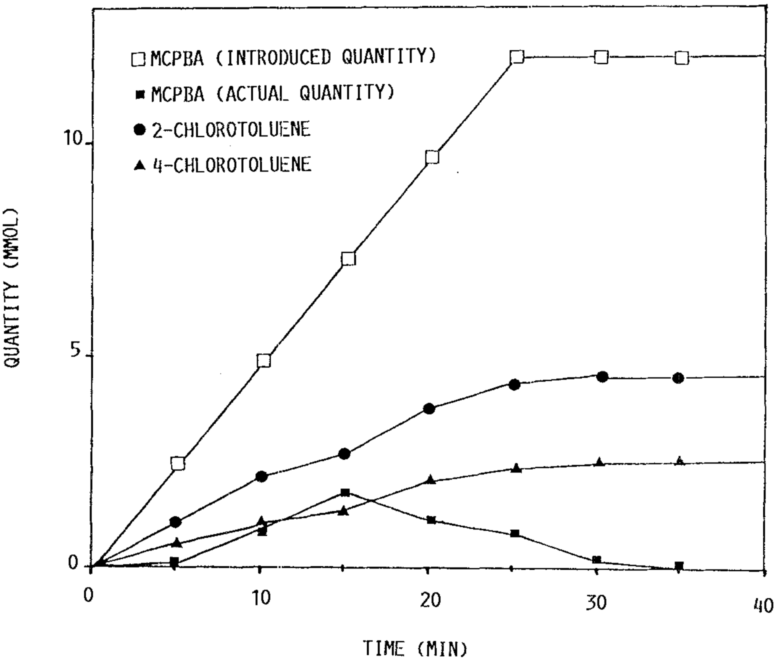


Fig. 1. Time course of the chlorination of toluene and of anisole by "clayfec" (11 mmol of Cl^-) in the presence of MCPBA (12.5 mmol) added at a constant rate of 30 $mmol.h^{-1}$. Samples were removed from the reaction mixture every 5 mn. Iodometric titrations of MCPBA were carried out in the presence of potassium fluoride to complex ferric ions, chloroaromatics were analyzed by G.C. using an internal standard.

mixtures of hydrogen peroxide and ferrous salts (Fenton's reagent) [11]. The poor results obtained with other high valency transition metal chlorides than ferric chloride could be related to the rate of decomposition of the peracid. Yet, studying the decomposition of perbenzoic acid in benzene, Lederer et al. [12] have found that the catalytic activity of transition metal 2,4-pentanedionates decreases in the order Mn(III) > Co(II) = Co(III) > Cr(III) ⋙ Fe(III).

3.5. TIME COURSE OF THE REACTION

Monitoring the concentrations of MCPBA and of the reaction products with time (fig. 1) shows that MCPBA has disappeared totally after 40 mn, without an induction period, even if chlorination is not complete. The o : p product distribution is time-invariant for toluene chlorination, while it decreases from 0.82 after 5 min to 0.34 after 25 min in the chlorination of anisole.

4. The medium

4.1. INFLUENCE OF THE SOLVENT

Comparison of various common solvents (table 6) shows that the best overall results are obtained in dichloromethane and in chloroform. Use of more polar solvents, likely to dissolve away $FeCl_3$ and thus to hasten decomposition of MCPBA from catalysis by the metallic salt, completely prevents the chlorination of toluene and significantly affects that of the more activated anisole (note however the outstanding *para* preference in acetone). Another possible cause is catalysis of MCPBA decomposition by radicals generated from these oxygenated solvent molecules as previously noted in the case of perbenzoic acid [13].

Table 6.
Influence of the solvent on the chlorination of toluene and of anisole by "clayfec" in the presence of MCPBA.

solvent	yields (%) and regioselectivities (ortho, para)	
	toluene	anisole
dichloromethane	62(64,36)	97(26,74)
chloroform	45(66,34)	91(17,83)
carbon tetrachloride *	1	20(22,78)
n-hexane *	17(76,24)	76(29,71)
acetone	0	55 (4,96)
ethanol	0	79(23,77)
diethyl ether	0	72(28,72)

* dissolution of MCPBA in these media was not complete. The resulting suspension has been added to the other reagents in a few seconds.

Table 7
Influence of the peracid on the chlorination of toluene and of anisole by "clayfec".

oxidizing agent	yields (%) and regioselectivities (ortho, para)	
	toluene	anisole
$H_2O_2 + CH_3COCl$	34(71,29)	29(65,35)
$H_2O_2 + (CF_3CO)_2O$	14(74,26)	2
PBA	33(63,37)	84(19,81)
MCPBA	62(64,36)	97(26,74)

4.2. INFLUENCE OF THE PERACID

We have made a comparative study of several peracids, viz. peracetic, permaleic, monoperphtalic, perbenzoic (PBA), MCPBA, and combinations of acetyl chloride, acetic acid and anhydride, or trifluoroacetic anhydride with hydrogen peroxide (30%). A peracidic polymeric resin (Duolite C433) was also tried. Runs which have led to chlorinated derivatives are described in table 7. Only perbenzoic acid is near-equivalent to MCPBA and can replace it in a satisfactory way for the chlorination of anisole. In the toluene case, it leads however to strongly diminished yields.

4.3. INFLUENCE OF THE TEMPERATURE

Four reaction temperatures were investigated (table 8), and the happy finding is that the optimum results are obtained at room temperature. As was foreseen, the *para* selectivity was greatest at the lowest temperature.

5. Discussion

The regioselectivities observed when using clay-supported ferric chloride in conjunction with MCPBA sharply differ from those obtained without added oxidiser, using either a metallic chloride alone or impregnated on alumina. They

Table 8
Influence of the temperature on the chlorination of toluene and of anisole by "clayfec" in the presence of MCPBA.

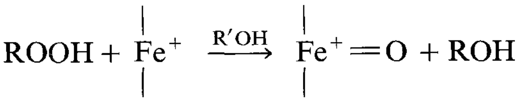
temperature	yields (%) and regioselectivities (ortho, para)	
	toluene	anisole
−10 °C	24(58,42)	62(16,84)
0 °C	34(60,40)	80(21,79)
room temp. (±20 °C)	62(64,36)	97(26,74)
reflux (±40 °C)	51(62,38)	81(28,72)

Table 9
Isomer distribution for the chlorination of toluene under various experimental conditions.

chlorinating agent and conditions	regioselectivities (ortho, meta, para)	reference
$FeCl_3$/K10 + MCPBA (room temp., CH_2Cl_2)	(64, 0, 36)	This work
$FeCl_3$ (40 ° C)	(16, 0, 84)	[14]
Cl_2 (room temp., $FeCl_3$ cat.)	(63, 2, 35)	[15]
Cl_2 (25 ° C, AcOH)	(60, 0, 40)	[16]
HOCl (25 ° C, H_2O, $HClO_4$ cat.)	(75, 2, 23)	[17]

are intermediate between those obtained with molecular chlorine and hypochlorous acid under various experimental conditions (tables 9 and 10). The oxidation of chloride ions into more electrophilic species is therefore obvious even if their final oxidation state cannot be precised from the data in our hands.

Despite this, the analogy with a number of natural processes is rather evident. They make use of an inorganic chloride, such as sodium chloride, activated by oxidation (typically with hydrogen peroxide generated in situ), in the presence of the metallic center of a metalloenzyme, which generally consists of a porphyrin occupied by a ferric ion [22]. The mechanism of these reactions involves oxidation of peroxidases by peroxides into an intermediate compound which further reacts with halide ions [23]. Recent studies on model iron (III) porphyrins have shown that a two-electron-oxidized "oxene" species is initially formed under the action of a peracid or a peroxide [24,25]. Its formation results from the heterolytic cleavage of the oxygen-oxygen bond and is strongly catalyzed by alcohols (eq. (1)).



$$ROOH + \overset{|}{\underset{|}{Fe^+}} \xrightarrow{R'OH} \overset{|}{\underset{|}{Fe^+}}{=}O + ROH \qquad (1)$$

R = acyl, alkyl; R′ = H, alkyl.

The intervention of such an iron (IV) intermediate in our reactions would rationalize the good results obtained with ferric chloride as compared with other metallic chlorides and the strong influence of the alcoholic impregnation solvent.

Table 10
Isomer distribution for the chlorination of anisole under various experimental conditions.

chlorinating agent and conditions	regioselectivities (ortho, para)	reference
$FeCl_3$/K10 + MCPBA (room temp., CH_2Cl_2)	(26,74)	This work
$CuCl_2/Al_2O_3$ (100 ° C, C_6H_5Cl)	(3,97)	[18]
Cl_2 (room temp., CCl_4)	(21,79)	[19]
Cl_2 (room temp., AcOH)	(21,79)	[20]
HOCl (room temp., H_2O)	(40,60)	[21]

6. Conclusions

We have much improved upon the useful ratio of metallic chloride to aryl chloride product. When metallic chlorides are used without added oxidizer, the reaction equation is:

$$\mathrm{ArH} + 2\mathrm{FeCl_3} \rightarrow \mathrm{ArCl} + \mathrm{HCl} + 2\mathrm{FeCl_2}, \tag{2}$$

i.e. one chlorine out of six is effective. By contrast, we use all of the chlorine atoms in $FeCl_3$; it suffices to use 1/3 equivalent of ferric chloride per ArH substrate: for a gain in reagent mass of a factor six. The reactions reported here with supported metallic chlorides have other advantages: ease of set-up and of work-up; ease of product isolation from ferric chloride; much cleaner reactions, in terms of the elimination of side products and of coupling products; quantitative yield (anisole chlorination) and good regioselectivities approaching specificity (anisole chlorination, again).

Finally, the procedure reported here can be labeled as *biomimetic*, as is represents a laboratory equivalent to biological halogenations through oxidation of halide ions by peroxides in the presence of hydrogen peroxide.

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