Selective Aromatic Chlorination and Bromination with *N*-Halogeno Amines in Acidic Solution

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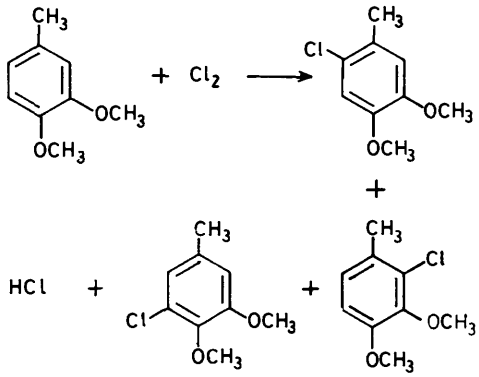
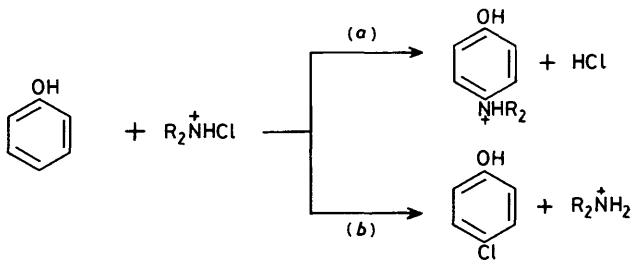
1,2-Dimethoxybenzene and 3,4-dimethoxytoluene are efficiently chlorinated by *N*-chlorodialkylamines in sulphuric acid. The reaction has a very marked selectivity for monochlorination of the *para*-position. The chlorination and bromination of monoalkylbenzenes (toluene, ethyl-, and isopropylbenzenes) under the same conditions is much less selective, but the *para*/*ortho* ratio can be reversed going from unsubstituted alkyl groups in the *N*-halogeno amines to alkyl groups substituted at the β-position by electron-withdrawing groups [morpholine, piperazine, bis(cyanoethyl)amine]. *m*-Xylene is chlorinated with high selectivity at the 4-position. The nature of the chlorinating species is discussed.

N-Halogenoamines in acidic solution are very versatile reagents for the homolytic aromatic[1] and alkenic[2] amination and the halogenation of alkanes,[3] and benzylic positions.[3] In all these reactions the large synthetic interest is mainly related to the exceptional regio- and chemo-selectivities determined by the high sensitivity to the polar effects of the alkylaminium radical ($R_2\dot{N}H$) reactions.[1-4]

Recently, Lindsay Smith *et al.*[5] reported that the nuclear chlorination of anisole and phenol with *N*-chloro amines in acidic media is characterized by a high selectivity at the *para*-position. These authors remark: 'More recently, the research of Minisci and co-workers into redox-initiated aromatic amination using *N*-chloroamines, has shown that chlorination can occur as a side reaction in these systems with the more electron-rich substrates. In none of the investigations above was the isomeric composition of the chloroaromatics reported.' That is certainly true as it concerns the publication in scientific reviews. However, we had observed the particularly interesting selectivity of this nuclear aromatic halogenation and developed it in patents[6] owing to the potential practical applications. For practical reasons the investigation was particularly directed towards the halogenation of 1,2-dimethoxybenzene derivatives and commercial alkylbenzenes (toluene, ethylbenzene, cumene, *m*-xylene). The results reported in the patents,[6] where the scientific discussion is necessarily limited, are now discussed in this paper.



Scheme 1.



Scheme 2.

Results and Discussion

Chlorination of 1,2-Dimethoxybenzene Derivatives.—2-Chloro-4,5-dimethoxytoluene is a useful intermediate for the production of the 2-chloro-4,5-dimethoxybenzaldehyde and 2-chloro-4,5-dimethoxybenzoic acid, both of which are used in the synthesis of pharmaceuticals and insecticides. The chlorination of 3,4-dimethoxytoluene is the simplest way of obtaining 2-chloro-4,5-dimethoxytoluene. The conventional chlorination with molecular chlorine (Scheme 1) is characterized by two main disadvantages concerning the regio- and chemo-selectivity: considerable amounts of the other two isomers with chlorine in the 3- and 6-position are formed and the amount of dichlorinated derivatives becomes increasingly significant as the conversions increase.

During the attempted homolytic amination of activated aromatic compounds, we encountered difficulties using relatively small concentrations of Fe^{II} salt to initiate the free-radical chain reaction; nuclear chlorination successfully competed with the aromatic amination[1] (Scheme 2). It was observed, however, that a single isomer generally predominated in the nuclear chlorination, so we used the same procedure, but in the absence of the Fe^{II} salt, to chlorinate the 3,4-dimethoxytoluene.[6] As the chlorinating agent we particularly favoured *N*-chlorodicyclohexylamine for the following practical reasons: (*a*) dicyclohexylamine is a cheap, commercial product, easily obtained by reductive ammonolysis of cyclohexanone; (*b*) it is easy to recover and recycle at the end of the reaction, making it an almost catalytic process (Scheme 3)

Using a 1:0.9 ratio of 3,4-dimethoxytoluene to *N*-chlorodicyclohexylamine in 98% H_2SO_4 at −10 to 0 °C, the chlorination occurred with quantitative conversion of the *N*-

Table 1. Chlorination of 3,4-dimethoxytoluene and veratrole

Aromatic substrate	*N*-Chloro amine[a]	Conversion (%)[b]	Yield (%)[c]
3,4-Dimethoxytoluene	Dicyclohexyl	90	92
3,4-Dimethoxytoluene	Di-isobutyl	87	91
3,4-Dimethoxytoluene	Di-isopropyl	88	93
3,4-Dimethoxytoluene	Piperidine	84	90
Veratrole	Dicyclohexyl	89	94
Veratrole	Di-isobutyl	87	92

[a] Molar ratio of aromatic substrate: *N*-chloro amine = 1:0.9. [b] Conversion of the aromatic substrate. [c] Yields of isolated, pure 1-chloro-2-methyl-4,5-dimethoxybenzene and 1-chloro-3,4-dimethoxybenzene, based on aromatic substrate; the g.l.c. yields are in all cases higher than 96% and show less than 1% of other monochlorinated isomers.

$$R_2NH + NaClO \longrightarrow R_2NCl + NaOH$$

$$R_2NCl + ArH \longrightarrow R_2NH + ArCl$$

$$ArH + NaClO \longrightarrow ArCl + NaOH$$

Scheme 3.

chloroamine (10% of 3,4-dimethoxytoluene, used in excess, remains unchanged) and the yield of isolated, pure, distilled 2-chloro-4,5-dimethoxytoluene,[6] based on the converted dimethoxybenzene, was 92%. G.l.c. of the crude reaction product revealed less than 1% of the other monochlorinated isomers. Other *N*-chloro amines (di-isopropyl, di-isobutyl, piperidine) give similar results and 1,2-dimethoxybenzene is selectively chlorinated in the 4-position (Table 1). These results completely agree with the more recent data reported for phenol and anisole by Lindsay Smith.[5]

Chlorination and Bromination of Alkylbenzenes.—Chlorination and bromination of both nuclear and benzylic positions of alkylbenzenes have important industrial applications and we have shown[4] how the use of protonated *N*-halogeno amines gives rise to the most selective benzylic halogenation so far known.

The electrophilic chlorination of toluene by Cl_2 is an important industrial process, in which the isomer distribution in the *ortho*/*para* positions is almost statistical (only small amounts of the *meta* isomer are formed) so that the *ortho* isomer is considerably predominant. Since the *p*-chlorotoluene is commercially more valuable than the *ortho* isomer, several attempts were made to increase the amount of the *para* isomer.[7] The use of dialkyl-*N*-chloro amines without polar substituents in the alkyl group, as in di-isopropyl-, di-isobutyl-, and dicyclohexyl-amine, and piperidine in acidic media in the presence or absence of Fe^{III} salts, leads mainly to nuclear substitution and only to a small amount (1—3%) of benzylic chlorination, but a substantial change of the isomer ratio compared with the use of Cl_2 is not observed. This is in clear contrast with the behaviour of more activated aromatic compounds (hydroxy and methoxy derivatives and acetanilides).

When an electron-withdrawing group is present in the β-position, as in the case of morpholine, piperazine, 3,3′-iminodipropiononitrile, the regioselectivity is reversed and the *p*-chlorotoluene becomes the prevailing isomer.

The *para*/*ortho* isomer ratio is similar with ethylbenzene and somewhat higher with isopropylbenzene, whereas *m*-xylene gives substantial amounts of a single monochloro derivative (>97%) (chloro-2,4-dimethylbenzene) and small amounts (<3%) of other monochloro and dichloro derivatives. Bromination of toluene with *N*-bromomorpholine gives the same selectivity as the chlorination with *N*-chloromorpholine. The results are reported in Table 2.

All the results described clearly suggest that the regioselectivity in the halogenation of the *ortho*/*para* positions of alkoxy- and alkyl-benzenes by protonated *N*-chloro amines is not governed by steric effects, and that polar effects must play a major role. In particular, the more hindered *N*-chlorodialkylamines (di-isopropyl, di-isobutyl, dicyclohexyl) give, with toluene, more of the *ortho* isomer than do the less hindered *N*-chloromorpholine and *N*-chloropiperazine. The selectivity in the *para* position increases either by increasing the electron availability of the aromatic ring or the electron deficiency of the protonated *N*-chloro amine.

The interpretation of the results is complicated by the fact that molecular chlorine could play a role according to the chain of the Scheme 4.

$$R_2\overset{+}{N}HCl + HCl \longrightarrow R_2\overset{+}{N}H_2 + Cl_2$$

$$ArH + Cl_2 \longrightarrow ArCl + HCl$$

Scheme 4.

An analogous mechanism involving Cl_2 takes place in benzylic or aliphatic halogenation, when the substrate is deactivated by electron-withdrawing substituents.[8] If it is assumed that *N*-halogeno amines are softer halogenating agents than are molecular chlorine or Cl^+, greater *para* substitution can be expected, since the frontier-electron population is larger at the *para* position (*i.e.* the HOMO–LUMO interaction is stronger). Thus a simple explanation of the observed selectivities could be related to the nature of the halogenating agent. When the reaction of the *N*-halogeno amine with the aromatic substrate is fast the extent of the chlorine process depicted in Scheme 4 is minimized, the *N*-halogeno amine is the main halogenating agent, and the selectivity in the *para* position is high. The reaction rate can then be increased by increasing either the reactivity of the aromatic ring or that of the *N*-halogeno amine. The reaction rate is increased, all the other conditions being equal, by increasing the electron availability of the aromatic ring, as in dimethoxybenzenes and *m*-xylene, or the electron deficiency of the halogeno amine: the halogenating agent would be mainly the *N*-halogeno amine in these cases, which accounts for the high selectivity in the *para* position. With the less activated monoalkylbenzenes the reaction is slower and the action of molecular chlorine according to the Scheme 4 could be responsible of the low *para* selectivity with unsubstituted alkyl groups in the *N*-chloro amine.

The importance of the polar characteristics of the aromatic substrate and of the *N*-chloro amine in determining the high *para* selectivity suggests an alternative interpretation: a charge-transfer complex (Scheme 5) could result from the initial interaction between the *N*-chlorodialkylammonium ion and the more reactive aromatic substrates.

$$ArH + R_2\overset{+}{N}HCl \rightleftharpoons \left[\begin{array}{c} Ar\text{–}\overset{+}{H}\cdot\ R_2\ddot{N}H\ Cl\cdot \\ \text{or } R_2\overset{+}{N}H\ Cl^- \end{array}\right] \longrightarrow ArCl + R_2\overset{+}{N}H_2$$

charge-transfer complex

Scheme 5.

The high selectivity should be related to the collapse of the charge-transfer complex. In this case the extent of the charge-transfer complex formation, and therefore the selectivity, should increase with the electron availability of the aromatic ring and the electron deficiency of the *N*-chloroammonium salt (low ionization potential of the aromatic substrate and high electron

Table 2. Halogenation of alkylbenzenes

Aromatic substrate	*N*-Chloro amine[a]	Conversion (%)	Isomer distribution (%)		
			o	*p*	*m*
Toluene	Dicyclohexyl	60	61	39	<1
Toluene	Di-isobutyl	58	60	40	<1
Toluene	Piperidine	62	58	42	<1
Toluene	Morpholine	62	35	65	<1
Toluene	Piperazine	68	39	61	<1
Toluene	2,6-Dimethylmorpholine	35	40	60	<1
Toluene	Bis-(2-cyanoethyl)amine	54	44	56	<1
Toluene	*N*-Bromomorpholine[b]	68	35	65	<1
Ethylbenzene	Morpholine	60	37	63	<1
Cumene	Morpholine	35	27	73	<1
meta-Xylene	Morpholine	77	2,4-Dimethylchlorobenzene >97		

[a] Molar ratio of aromatic substrate: *N*-halogeno amine = 1:1.1. [b] Bromotoluenes are formed.

affinity of the *N*-chloroammonium ion), independently of a Cl_2 mechanism. This would also explain the high chemoselectivity in which only traces of dichlorinated derivatives are formed from high conversions of the aromatic substrates. The introduction of chlorine reduces the electron availability (increases the ionization potential) of the aromatic ring and the extent of a charge-transfer complex formation.

Experimental

All the materials were commercial reagent grade.

N-*Halogeno Amines.*—Slightly different procedures were used depending on whether the aromatic substrate was an alkoxy- or alkyl-benzene derivative.

(*a*) A solution of the *N*-chloro amine in alkylbenzenes was prepared according to the following typical procedure: di-isobutylamine (41.7 g) was added dropwise to a stirred and cooled mixture of toluene (23 g) and 13% NaOCl solution (500 ml) at 20 °C. The mixture was stirred for 1 h at room temperature after which time the organic layer was separated, washed with 10% NaCl solution, dried (Na_2SO_4), and directly utilized in the chlorination reaction.

The solutions of the other *N*-chloro amines in alkyl aromatic compounds were similarly prepared, and the preparative procedure for the *N*-bromomorpholine solution in toluene using NaOBr is similar. The yields of *N*-halogeno amines were in the range of 90—95%.

(*b*) For the chlorination of dimethoxybenzenes, the *N*-chloro amines were isolated according to the following typical procedures: (*i*) dicyclohexylamine (104 g, 0.57 mol) was added dropwise to a stirred, cooled solution of NaOCl (13%; 1 350 ml, 2.4 mol) at 20 °C. The mixture was stirred for 90 min at room temperature, the organic layer was separated, washed with saturated aqueous Na_2SO_4 and used directly in the subsequent chlorination: yield 96%. (*ii*) $(C_6H_{11})_2NH{\cdot}H_2SO_4$ (160 g, 0.57 mol) was added to a stirred, cooled solution of NaOCl (13%; 405 ml), 0.68 mol) at 20 °C. The mixture was stirred for 90 min at room temperature and worked up as in (*i*): yield 94%.

Chlorination of 3,4-*Dimethoxytoluene.*—3,4-Dimethoxybenzene (112.8 g, 0.72 mol) and *N*-chlorodicyclohexylamine (136.8 g, 0.64 mol) were added dropwise to a stirred, cooled (−10 to 0 °C) solution of H_2SO_4 (98%; 281 g). The mixture was stirred and cooled for 90 min between −10 and 0 °C, then poured onto ice and extracted with ether. Dicyclohexylamine (96%) was recovered by making the aqueous solution alkaline. The ethereal extract was washed with saturated aqueous $NaHCO_3$, then with saturated aqueous NaCl and dried (Na_2SO_4). After the solvent had been evaporated, the residue was distilled through an Oldershaw column (20 plates and 1″) which gave unchanged 3,4-dimethoxytoluene (11.3 g) and 2-chloro-4,5-dimethoxytoluene (114.3 g), b.p. 54—55 °C/9.5 mmHg. The purity of the distilled product was higher than 99% according to g.l.c. analysis. The conversion of 3,4-dimethoxytoluene was 90%. The conversion of *N*-chlorodicyclohexylamine was 100%. The yield of isolated product was 92%. The g.l.c. of the crude product before the distillation revealed the presence of the unchanged 3,4-dimethoxytoluene, 2-chloro-4,5-dimethoxytoluene, and traces (<3%) of other three unidentified by-products. 2-Chloro-4,5-dimethoxytoluene was identified by comparison of spectra (i.r., n.m.r., m.s.) with those of authentical sample. The n.m.r. spectrum showed four singlets at δ 2.2 (3 H, CCH_3), 3.7 (6 H, 2 OCH_3), 6.54 (1 H, 3-H), and 6.7 (1 H, 6-H).

The same procedure was utilized with other *N*-chloro amines and veratrole; the 1,2-dimethoxy-4-chlorobenzene was identified by comparison of spectra with those of an authentic sample. The results are reported in Table 1.

Halogenation of Alkylbenzenes: General Procedure.—A solution of *N*-chloromorpholine (31.4 g, 0.26 mol) and toluene (22.11 g, 0.24 mol) was added dropwise over 12 min to a stirred, cooled solution of H_2SO_4 (98%; 120 g) at 20 °C. The mixture was stirred at room temperature (20—25 °C) for an additional 1 h and then poured onto ice. The organic layer was separated and the aqueous solution was extracted with ether. G.l.c. analysis of the organic extracts revealed a toluene conversion of 62% and an *ortho*-:*para*-chlorotoluene ratio of 35:65. Fractional distillation of the crude product gave *o*-chlorobenzene (6.1 g) and *p*-chlorobenzene (11.3 g), practically pure to the g.l.c. analysis. The same procedure was used for all the results reported in Table 2. The reaction products were identified by comparison of spectra with those of authentic samples.

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