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HIGH SITE-SELECTIVITY IN THE CHLORINATION OF ELECTRON-RICH AROMATIC COMPOUNDS BY N-CHLORAMMONIUM SALTS

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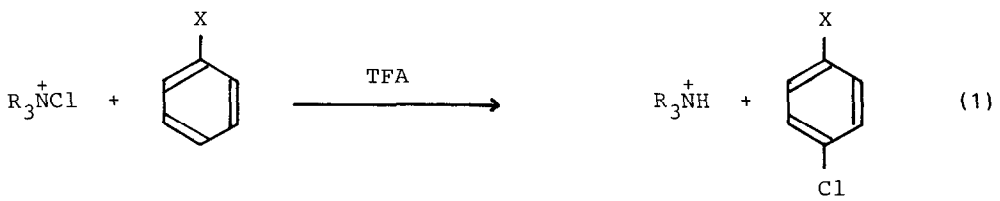
N-Chlorammonium salts are efficient and very site-selective monochlorinating agents for electron-rich aromatic compounds.

The requirement for halogenated aromatic compounds on a large scale has led to the study of a wide range of halogenating agents; these include, halogens, interhalogens, compounds with halogen bonded to oxygen, sulphur and nitrogen and metal halides.[1] One aim of this research has been to develop methods for the site-selective monohalogenation of aromatic compounds.[2,3] In this respect, we report here the efficient 4-chlorination of aromatic compounds, containing an electron donating (+M) substituent, by N-chlorammonium salts [Reaction (1)]. To our knowledge these are the most site-selective monochlorinating agents known.



(1)

Table 1 records the product distributions obtained from the chlorination of a selection of aromatic compounds. In a typical reaction the aromatic substrate is added to an equivalent quantity of N-chloropiperidine (NCP) dissolved in trifluoroacetic acid (TFA) at room temperature. The extent of the reaction was followed by ^1H n.m.r. spectroscopy which showed the quantitative conversion of the N-chlorammonium ion to protonated amine and chloroaromatics. All the reactions of the substrates in Table 1 are complete in a few minutes except those of 2- and 4-chloroanisole which require > 24 h. Benzene and toluene are only chlorinated very slowly and the latter does not show the marked site-selectivity of the compounds in Table 1.

TABLE 1 Product distributions from the chlorination of a selection of aromatic compounds[a]

Substrate	Chlorinating agent	Product	Product distribution (%)[b]
Anisole	NCP or NCTA	2-chloroanisole	1
		4-chloroanisole	99
Phenol	NCP or NCTA	2-chlorophenol	3
		4-chlorophenol	97
Aniline	NCTA	2-chloroaniline	4
		4-chloroaniline	94
		2,4-dichloroaniline	2
1,2-Dimethoxybenzene	NCP	4-chloro-1,2-dimethoxybenzene	93.5
		dichloro-1,2-dimethoxybenzene	6.5
2-Chloroanisole	NCTA	2,4-dichloroanisole	100
2-Methylphenol	NCP or NCTA	4-chloro-2-methylphenol	98.5
		6-chloro-2-methylphenol	1.5
3-Methylphenol	NCP	4-chloro-3-methylphenol	93
		4,6-dichloro-3-methylphenol	3
1,4-Dimethoxybenzene	NCP or NCTA	2-chloro-1,4-dimethoxybenzene	98
		dichloro-1,4-dimethoxybenzene	2
4-Chloroanisole	NCTA	2,4-dichloroanisole	100

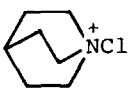
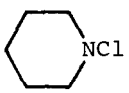
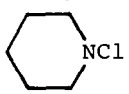
[a] An equivalent quantity of aromatic substrate and N-chloropiperidine (NCP) or N-chlorotriethylammonium chloride (NCTA) in trifluoroacetic acid at room temperature.

[b] Product analyses by g.l.c. following work-up of reaction.

The generality of the chlorination was confirmed with anisole and five N-chloramine derivatives namely, N-chlorotriethylammonium chloride[4] and perchlorate,[4] N-chlorotrimethylammonium acetate,[5] N-chloro-1-azoniabicyclo-[2.2.2]octane acetate[5] and N-chloropiperidine[6] (Table 2). The high site-selectivity of N-chlorammonium ion chlorinations is very evident when the product distributions from these reactions are compared with the values from other chlorinating agents (Table 2). Some of the reactions (anisole, phenol and

2-methylphenol) were also carried out in aqueous sulphuric acid in place of TFA and the site-selectivity of the chlorination was shown to increase with the acidity of the solvent. The product distributions from reactions in 50% (v/v) sulphuric acid closely resemble those from TFA solutions.

TABLE 2 Product distributions from the chlorination of anisole by a selection of reagents

Chlorinating agent	Solvent	Chloroanisole isomer distribution (%) 2	4
$Et_3\overset{+}{N}Cl\ Cl^-$	TFA	1	99
$Et_3\overset{+}{N}Cl\ ClO_4^-$	TFA	1	99
$Me_3\overset{+}{N}Cl\ OAc^-$	TFA	3	97
 OAc^-	TFA	trace	100
	TFA	1	99
	(50% v/v) H_2SO_4	1	99
Cl_2	TFA	32	68
Cl_2/CF_3CO_2Ag	TFA/TFA anhydride	42	58
HOCl	H_2O	40	60[a]
^tBuOCl	$AcOH/H_2SO_4$	35.5	64.5[b]

[a] Ref. 7; [b] Ref. 8.

The above data eliminate molecular chlorine in TFA or chlorinetrifluoroacetate, which could be formed by nucleophilic displacement on the chlorine of the N-chlorammonium ion [Reaction (2)], as the active chlorinating species.

$$X^- + Cl-\overset{|}{\underset{|}{N^+}}- \xrightarrow{H^+} XCl + H-\overset{|}{\underset{|}{N^+}}- \qquad (2)$$

$X^- = Cl^-$ or $CF_3CO_2^-$

In preliminary mechanistic investigations we have used competition experiments to obtain the relative reactivities of phenol, 2-methylphenol, anisole, 2-chloroanisole and 1,2-dimethoxybenzene towards 4-chlorination. Hammett treatments of the data and least mean squares analyses give ρ values of -6.69 ± 0.06 and -7.43 ± 0.06 for the NCP and NCTA reactions respectively. These large and negative values are within the range of values reported for

other electrophilic aromatic substitutions in general[9] and for chlorinations in particular.[1,10] This suggests, in agreement with conclusions from earlier kinetic studies,[11] that the mechanism is electrophilic aromatic substitution by an N-chlorammonium ion. The site-selectivity for 4-chlorination could be attributed to the bulk of the electrophile in an analogous manner to the selectivity of chlorination by sulphuryl chloride with diphenylsulphide and aluminium trichloride[2b] or of aromatic substitutions with thallium(III) reagents.[12] However, an alternative mechanism involving an electron-transfer chain reaction[13] and the formation of aromatic radical cations cannot be excluded. The strong directive effects of the substituent in the latter mechanism can be rationalised in terms of the preferred electron distribution in the aromatic radical cation. Similar arguments involving radical anions have been used to explain the orientation effects observed in the Birch reduction of aromatic compounds.[14] Work is in progress to distinguish between these two possibilities.

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