Aromatic chlorination of ω -phenylalkylamines and ω -phenylalkylamides in carbon tetrachloride and α , α , α -trifluorotoluene

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Received 6th April 2006, Accepted 25th May 2006 First published as an Advance Article on the web 8th June 2006 DOI: 10.1039/b605010g

The aromatic halogenation of simple alkylbenzenes with chlorine proceeds smoothly in acetic acid but is much less efficient in less polar solvents. By contrast chlorination of ω -phenylalkylamines, such as 3-phenylpropylamine, occurs readily in either acetic acid, carbon tetrachloride or α, α, α -trifluorotoluene, and in the latter solvents gives high proportions of ortho-chlorinated products. These effects are attributable to the involvement of N-chloroamines as reaction intermediates, with intramolecular delivery of the chlorine electrophile. ω-Phenylalkylamides, such as 3-phenylpropionamide, also easily undergo aromatic chlorination in carbon tetrachloride and α, α, α -trifluorotoluene. These reactions generally show a first-order dependence on the substrate concentration, but not on the amount of chlorine. With carbon tetrachloride, very similar reaction rates are observed with chlorine concentrations ranging from 0.1–1.5 M. In α, α, α -trifluorotoluene, the rates reach a plateau at a chlorine concentration of approximately 0.2 M. These features indicate that the reactions proceed via the formation of intermediates which evidence suggests may be the corresponding O-chloroimidates. Irrespective of the mechanistic details, the reactions are remarkably rapid, being faster than analogous reactions in acetic acid and three to four orders of magnitude more rapid than reactions of simple alkylbenzenes in carbon tetrachloride. Therefore, chlorination of the amines and amides may be accomplished without the need for highly polar solvents, added catalysts or large excesses of chlorine, which are often employed for electrophilic aromatic substitutions. Although the use of carbon tetrachloride is becoming increasingly impractical due to environmental concerns, the trifluorotoluene is a suitable alternative.

Introduction

Electrophilic aromatic substitution is one of the most widely used and extensively studied classes of organic reactions.¹ Some of the factors that affect the reactivity towards substitution include substituents on the aromatic substrate, the nature of the electrophile and the polarity of the solvent. Chlorination of monoalkylbenzenes with chlorine typically requires a polar solvent, such as acetic acid, or a Lewis acid catalyst such as iron or aluminium trichloride. Amines have been found to catalyse chlorination of activated aromatic species in non-polar solvents and this has been attributed to in situ formation of Nchloroamines.² N-Chloroamines have also been used directly as reagents for aromatic chlorination, usually in acidic media.³ N-Chlorosuccinimide is reported to effect aromatic chlorination in carbon tetrachloride in the presence of silica.⁴ Amides react with molecular chlorine to give N-haloamides5 and, in the case of acetanilides, such species are known to rearrange under acidic conditions to give aromatic chlorides.6 Each of the above processes

radical and ionic processes.8

Results and discussion

involves intermolecular delivery of the chlorine to the aromatic moiety, except in the case of the acetanilides where one of the

proposed mechanisms for aromatic substitution involves migra-

tion of chlorine within the conjugated π -system. Intramolecular

delivery of a nitro group through coordination to a functionalised

alkyl substituent has been exploited to enhance reaction rates and

control the regioselectivity in electrophilic aromatic nitrations⁷

but, to the best of our knowledge, no such chaperon effect has

been reported for aromatic chlorinations. In this context, we now

report the efficient chlorination of ω-arylalkylamines and amides

in either carbon tetrachloride or α, α, α -trifluorotoluene, without

added catalyst. The latter solvent is attracting increasing attention

as an environmentally benign option that is resistant to both free

For the purpose of comparison, we first examined the chlorination

otherwise identical conditions, to allow for direct analysis using ¹H

NMR spectroscopy. As expected,9 the reactions are second order,

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Table 1 Rate constants and product ratios for chlorination of compounds $1a{-}5a$ in CD_3CO_2D at 25 $^\circ C$



depending directly on the concentrations of both the substrates **1a–5a** and chlorine. The second order reaction rate constants and the ratios of the products **1b–5b** : **1c–5c** are summarised in Table 1.

The data for the reactions of toluene (1a) and ethylbenzene (2a) are in good agreement with literature values.¹⁰ Isobutylbenzene (3a) is less reactive than either of these and affords a smaller proportion of the *ortho*-substituted product 3b, presumably due to the greater bulk of the alkyl substituent. The ratios of formation of the chlorides 4b,c and 5b,c are very similar to that of the ethylbenzene derivatives 2b and 2c, but the reaction rates for the acid 4a and the ester 5a are around an order of magnitude slower than those of the alkylbenzenes 1a–3a. This decrease is too large to be attributed to remote inductive deactivation by the carboxyl groups of the acid 4a and the ester 5a and is more consistent with a general field effect.

Using either carbon tetrachloride or α, α, α -trifluorotoluene instead of acetic acid, but under otherwise identical conditions, the reactivity of the alkylbenzenes **1a–5a** is reduced by at least two to three orders of magnitude. For example, in carbon tetrachloride there is no evidence of chlorination of compounds **1a–5a** by ¹H NMR spectroscopy after four days, indicating that the second order rate constants for these processes are $<3 \times 10^{-7}$ M⁻¹ s⁻¹. The reduced rates are consistent with the lower polarity of these solvents.

Such marked solvent effects on the reaction rates are not seen with either the amines **6a–8a** or the amides **9a–16a**. Reactions of the amines **6a–8a** in either acetic acid, carbon tetrachloride or α, α, α -trifluorotoluene cleanly give the chlorides **6b,c–8b,c**, that were characterised as their acetate salts by comparison with literature data.¹¹

Relative to the reactions of compounds **1a–5a**, the amines **6a–8a** give higher proportions of the *ortho*-chlorinated products **6b–8b**, particularly in the cases of the ethylamine **6a** and the propylamine **7a** and their reactions in carbon tetrachloride and α,α,α -trifluorotoluene (Table 2). The second order rate constant

Table 2 Product ratios for chlorination of the amines $6a{-}8a$ in various solvents at 25 $^{\circ}\mathrm{C}$

$(CH_2)_2NH_2$ R^1 R^2 6	(CH ₂ R ² 7) ₃ NH ₂ (($\begin{array}{c} CH_2)_4 NH_2 \\ R^1 \\ R^2 \\ R^2 \\ B \\ R \\ R$	= R ² = H = CI, R ² = H = H, R ² = CI
Product ratio 6b–8b : 6c–8c				
Starting material		$\overline{CD_3CO_2D}$	CCl_4	CF ₃ Ph
$\begin{array}{l} Ph(CH_2)_2NH_2 \ (\textbf{6a}) \\ Ph(CH_2)_3NH_2 \ (\textbf{7a}) \\ Ph(CH_2)_4NH_2 \ (\textbf{8a}) \end{array}$		 40	>95:5 ^{<i>a</i>} 77 : 23 62 : 38	81 : 19 67 : 33 60 : 40

^a One product within limits of detection using ¹H NMR spectroscopy.

for reaction of 3-phenylpropylamine (7a) in acetic acid at 25 °C was determined to be 7.6 \times $10^{\scriptscriptstyle -5}~M^{\scriptscriptstyle -1}$ s^-1, similar to those values obtained for compounds 1a-5a in this solvent. In contrast, whereas compounds 1a-5a are much less reactive in either carbon tetrachloride or α, α, α -trifluorotoluene, the reactivity of the amines 6a-8a in these solvents is qualitatively similar to that in acetic acid. The reactions of the amines 6a-8a in carbon tetrachloride and α, α, α -trifluorotoluene are heterogeneous, with a colourless precipitate forming in each case, so it was impractical to determine rate constants for these processes. Nevertheless, in either acetic acid, carbon tetrachloride or α, α, α -trifluorotoluene with approximately 1 M chlorine, the reactions proceed to 90% completion in 10 h. This compares with less than 5% reaction after four days for the reactions of compounds 1a-5a in carbon tetrachloride, and is particularly remarkable considering that the reactions of the amines 6a-8a in either carbon tetrachloride or α, α, α -trifluorotoluene are heterogeneous and presumably require exchange between the solid and solution phases for complete reaction to occur.

When each of the amines **6a–8a** was added to a solution of chlorine in carbon tetrachloride, a precipitate formed almost instantaneously. The ¹H NMR spectra of the filtered solutions are quite different to those of the parent amines **6a–8a**. For 2-phenylethylamine (**6a**) the triplet methylene resonances move from δ 2.7 and 2.9 ppm, to δ 3.1 and 3.9 ppm, while for the propylamine **7a** and the butylamine **8a**, one of the triplet methylene resonances shifts downfield by around 0.9 ppm. This is consistent with the formation of *N*-chloroamines.³ The hydrogen chloride by-product likely results in the formation of the corresponding *N*-chloroamine hydrochlorides, which would account for the observed precipitates.

A simple explanation for the high reactivity of the amines 6a-8a in carbon tetrachloride and a,a,a-trifluorotoluene is therefore that the reactions are proceeding *via* the corresponding *N*-chloroamines, with intramolecular delivery of the chlorine. This would account for the formation of the greater proportion of the *ortho*-chlorinated product **6b** from the more constrained ethylamine **6a**, an effect that is also observed to some extent with the propylamine **7a**.

Reactions of the amides **9a–16a** give clean mixtures of the chlorides **9b,c–16b,c**. These compounds were either fully characterised or identified by comparison with literature data. In acetic acid,

the chlorination of 3-phenylpropionamide (10a) affords a 61 : 39 ratio of the products 10b and 10c. The reaction was established to be a second order process, for which the rate constant was determined to be 4.1 \times 10⁻⁵ $M^{\rm -1}$ s^{-1}, similar to those values obtained for compounds 1a-5a and 7a in this solvent. The ratios of the products of the reactions of the amides 9a-16a in carbon tetrachloride and α, α, α -trifluorotoluene, and the pseudo-first order rate constants for the reactions of the primary and secondary amides 9a-15a are summarised in Table 3. In these solvents the reactions of the primary and secondary amides 9a-15a generally show a first-order dependence on the substrate concentration, but not on the amount of chlorine. With carbon tetrachloride, very similar reaction rates are observed with chlorine concentrations ranging from 0.1–1.5 M. In α, α, α -trifluorotoluene, the rates reach a plateau at a chlorine concentration of approximately 0.2 M. The onset of the pseudo-first order reactions of the acetamides 12a-14a is delayed, by approximately one hour for the phenylethylamide

12a and ten minutes in the other two cases. These induction periods correspond to approximately 10% of the time taken for reaction of 90% of the substrates. The reaction of the tertiary amide **16a** in carbon tetrachloride is even more peculiar, showing no evidence of reaction detectable by ¹H NMR spectroscopy for the first 6–7 hours, but then effectively going to completion within the next 3 hours.

These features indicate that the reactions of the amides **9a– 15a** in carbon tetrachloride and α,α,α -trifluorotoluene proceed *via* the formation of intermediates, which react to give the chlorides **9b,c–15b,c** in rate-determining first order processes, the rates of which are not proportional to the concentration of chlorine. The ¹H NMR spectra recorded at early stages of reaction indicate formation of another species that, in the cases of the acetamide **9a**, the propionamide **10a**, the acetamide **12a** and the *N*methylpropionamide **15a** were identified as the corresponding *N*chloroamides by comparison with authentic samples. Alone, such





^{*a*} Yields of the crude mixtures of the chlorides **9b,c–16b,c** were essentially quantitative. ^{*b*} Reactions displayed first order kinetics after an induction period of approximately 1 h for **12a** and 10 min for **13a** and **14a**. ^{*c*} Reaction of the tertiary amide **16a** displayed neither first nor second order kinetics, going to completion within 3 h after an induction period of 6–7 h.

15b,c, however, as the chloride derived from the propionamide 10a was found to be inert when left to stand in carbon tetrachloride in the absence of chlorine, for extended periods at 25 °C. It was also considered that the reactive intermediates could be the protonated N-chloroamides, formed through reaction with hydrogen chloride that would be present as a by-product of the N-chloroamide formation. This possibility was also discounted, however, as the N-chloropropionamide does not react when left to stand in carbon tetrachloride containing added hydrogen chloride, but in the absence of chlorine, for extended periods at 25 °C. Adding hydrogen chloride part-way through the reaction of the propionamide 10a with chlorine also has no effect on the rate of aromatic chlorination. On this basis we tentatively suggest that the reactive intermediates are O-chloroimidates 19 present as minor components in equilibrium with amides 17 and N-chloroamides 18, with the equilibration requiring both chlorine and hydrogen chloride (Scheme 1), possibly as the hydrogen chloride perchloride complex.¹² The equilibration must then be rapid relative to the rate of the subsequent aromatic substitution.

materials do not account for the formation of the chlorides 9b,c-



Scheme 1 Putative formation of O-chloroimidate reaction intermediates.

The tertiary amide **16a** is unable to react to give either an *N*-chloroamide or an *O*-chloroimidate, with hydrogen chloride as a by-product. It follows that, in this case, the reaction probably involves analogous charged species [*e.g.*, $RC(OCI)=N^+Me_2$]. Presumably the reason for the peculiar delay observed in the onset of this reaction is that the acid required for catalytic formation of the reactive intermediates only becomes available through the initial stages of the electrophilic aromatic substitution. The reaction then becomes autocatalytic.

Irrespective of the mechanistic details of the reactions of the amides 9a–15a in carbon tetrachloride and α, α, α -trifluorotoluene, they are remarkably rapid. To draw a meaningful comparison between these pseudo-first order chlorinations and others that are second order, it is necessary to specify a chlorine concentration. Accordingly, with 0.13 M chlorine, the reaction of the propionamide **10a** in carbon tetrachloride ($k' = 1.7 \times 10^{-4} \text{ s}^{-1}$) is approximately thirty times faster than its reaction in acetic acid $(k' = 5.3 \times 10^{-6} \text{ s}^{-1} = 0.13 \times (k) 4.1 \times 10^{-5} \text{ M}^{-1} \text{ s}^{-1}).$ Furthermore, using 0.1 M chlorine, the reactions of the amides 9a-15a are typically three to four orders of magnitude faster than those of compounds 1a-5a in carbon tetrachloride. For example, with 0.1 M chlorine the second and pseudo-first order rate constants for the reactions of compounds 1a-5a are all $<3 \times$ 10^{-7} M⁻¹ s⁻¹ and $< 3 \times 10^{-8}$ s⁻¹, respectively, whereas the first order rate constants for the reactions of the phenylpropionamide 10a at

similar chlorine concentrations are $1.7 \times 10^{-4} \text{ s}^{-1}$ (0.13 M chlorine) in carbon tetrachloride and $4.4 \times 10^{-4} \text{ s}^{-1}$ (0.05 M chlorine) in α,α,α -trifluorotoluene.

It seems likely that the reactions of the amides **9a–16a** involve mostly intramolecular delivery of the chlorine electrophile, however, the corresponding intermolecular reactions are also accelerated. This is demonstrated by the increase in the pseudo-first order rate constant for the reaction of toluene (**1a**) in carbon tetrachloride with 1 M chlorine, from $<3 \times 10^{-7}$ s⁻¹ to 1.5×10^{-6} s⁻¹, through the addition of 0.015 M 3-phenylpropionamide (**10a**). This preliminary experiment shows that simple amides might also find application as chlorination catalysts in nonpolar solvents. In any event, the reactions of the amines **6a–8a** and the amides **9a–16a** in carbon tetrachloride and α,α,α -trifluorotoluene proceed efficiently, without the need for either highly polar solvents, added catalysts or large excesses of chlorine, that are often employed for electrophilic aromatic chlorinations.

Experimental

General experimental

NMR spectra were recorded on either a Varian Gemini 300 spectrometer or a Varian Inova 500 spectrometer. Electron impact mass spectra (MS) were recorded on a VG Autospec double focussing trisector mass spectrometer operating at 70 eV. The Research School of Chemistry Analytical Services Unit at the Australian National University carried out the elemental analyses. Melting points (mp) were determined on a Kofler hot-stage melting point apparatus under a Reichert microscope and are uncorrected. Chromatography was performed on a Chromatotron model 7924T using plates prepared with Merck-Silica gel 60 PF₂₅₄ containing gypsum. HPLC was performed using a reverse-phase YMC-Pack ODS-AQ 250 \times 20 mm column, eluting with a mixture of acetonitrile–water at a flow rate of 10 mL min⁻¹.

Chlorine was provided by BOC Gases. Toluene (1a) and ethylbenzene (2a) were purchased from Ajax. Acetic acid, carbon tetrachloride, (2-methylpropyl)benzene (3a), 3-phenylpropionic acid (4a), 3-phenylpropylamine (7a) and 4-phenylbutylamine (8a) were obtained from Sigma-Aldrich. 2-Chlorotoluene (1b) was bought from EGA-Chemie. 4-Chlorotoluene (1c) and 2-phenylethylamine (6a) were purchased from BDH. α,α,α -Trifluorotoluene was obtained from Fluka and acetic acid- d_4 from Cambridge Isotope Laboratories Inc., MA. Carbon tetrachloride was purified according to the procedure described by Armarego and Perrin.¹³ To ensure that acetic acid and acetic acid- d_4 were free of water, they were each treated with 1% (v/v) of the corresponding anhydride.

Stock solutions of chlorine in acetic acid, acetic acid- d_4 , carbon tetrachloride and a,a,a-trifluorotoluene were prepared by passing chlorine through the solvents at room temperature until the solutions were bright yellow. Chlorine concentrations were determined by measuring the absorbance at 380 nm. Calibration graphs of absorbance *versus* chlorine concentration were prepared by iodometric titration of iodine, produced by adding potassium iodide to the solutions.¹⁴

The amides **9a–11a**, **15a** and **16a** were prepared by treatment of the corresponding carboxylic acids with thionyl chloride and then either ammonia, methylamine or dimethylamine. The acetamides **12a–14a** were prepared from the corresponding amines **6a–8a** by

acetylation with acetic anhydride. The physical and spectroscopic data for these compounds are consistent with literature values.¹⁵

Methyl 3-phenylpropionate (5a). 3-Phenylpropionic acid (**4a**) (1.5 g, 10 mmol) was stirred with thionyl chloride (1.2 g, 10 mmol) for 0.5 h, then the resultant mixture was added dropwise to dry methanol (50 mL) cooled to 0 °C. The solution was stirred at room temperature for 0.5 h, and then it was concentrated under reduced pressure. Chromatography of the residue on silica, eluting with dichloromethane, gave the ester **5a** as a colourless oil (1.54 g, 95%). ¹H NMR (CDCl₃) δ 7.35 (m, 5H), 3.68 (s, 3H), 2.96 (t, *J* 8.0 Hz, 2H), 2.64 (t, *J* 8.0 Hz, 2H). The physical and spectroscopic data for this compound are consistent with literature values.¹⁶

General procedure for preparation of the chlorides 1b,c-5b,c. Solutions of compounds 1a-5a (2-10 mmol) in acetic acid (100 mL) containing chlorine (1 M) were left to stand in the dark at 25 °C for 4-48 h, until all of the starting materials 1a-5a had been consumed as determined by TLC analysis. Excess chlorine was then removed by passing nitrogen through the solutions until the yellow colour faded, then the mixtures were concentrated under reduced pressure. HPLC of the residues, followed by recrystallisation in the cases of the chlorides 4b,c, afforded the products 1b,c-5b,c either as discrete compounds or as mixtures of the regioisomers.

2-Chlorotoluene (1b) and 4-chlorotoluene (1c). Reaction of toluene (1a) with chlorine in acetic acid according to the general procedure gave a 92% yield of a 56 : 44 mixture of the chlorides 1b and 1c, which was characterised by comparison of its ¹H NMR spectrum with those of commercial samples of the individual components. ¹H NMR (CD₃CO₂D) δ 7.19 (m, 4H), 2.34 (s, 0.56 × 3H), 2.29 (s, 0.44 × 3H).

2-Chloroethylbenzene (2b) and 4-chloroethylbenzene (2c). Reaction of ethylbenzene (2a) with chlorine in acetic acid according to the general procedure gave a 90% yield of a 52 : 48 mixture of the chlorides 2b and 2c as a colourless oil, which was characterised by comparison of its ¹H NMR spectrum with literature data.^{17 1}H NMR (CCl₄) δ 7.15 (m, 4H), 2.74 (q, *J* 7.5 Hz, 0.52 × 2H), 2.60 (q, *J* 7.5 Hz, 0.48 × 2H), 1.24 (t, *J* 7.5 Hz, 0.52 × 3H), 1.22 (t, *J* 7.5 Hz, 0.48 × 3H); ¹H NMR (CD₃CO₂D) δ 7.21 (m, 4H), 2.73 (q, *J* 7.5 Hz, 0.52 × 2H), 2.59 (q, *J* 7.5 Hz, 0.48 × 2H), 1.20 (m, 3H).

2-Chloro-(2-methylpropyl)benzene (3b) and 4-chloro-(2-methylpropyl)benzene (3c). Reaction of (2-methylpropyl)benzene (**3a**) with chlorine in acetic acid according to the general procedure gave an 85% yield of a 38 : 62 mixture of the chlorides **3b** and **3c** as a colourless oil. ¹H NMR (CD₃CO₂D) δ 7.24 (m, 4H), 2.60 (d, *J* 7.0 Hz, 0.38 × 2H), 2.44 (d, *J* 7.0 Hz, 0.62 × 2H), 1.96 (m, 0.38 × 1H), 1.82 (m, 0.62 × 1H), 0.90 (m, 6H); ¹³C NMR (CDCl₃) δ 143.2, 140.0, 139.2, 131.3, 130.4, 129.4, 128.1, 127.1, 126.3, 44.7, 42.6, 30.2, 28.7, 22.4, 22.2; MS *m*/*z* (%) 170 (M⁺⁺, 10), 168 (M⁺⁺, 25), 127 (35), 125 (100); (Found: C, 71.08; H, 7.71%. C₁₀H₁₃Cl requires C, 71.21; H, 7.77%).

3-(2-Chlorophenyl)propionic acid (4b) and 3-(4-chlorophenyl)propionic acid (4c). Reaction of 3-phenylpropionic acid (4a) with chlorine in acetic acid according to the general procedure gave a 1 : 1 mixture of the chlorides 4b and 4c, which were separated by HPLC. For 3-(2-chlorophenyl)propionic acid (4b): colourless crystals; 37%; mp 94–96 °C (lit.¹⁸ mp 96 °C); ¹H NMR (CD₃CO₂D) δ 7.28 (m, 4H), 3.06 (t, *J* 8.0 Hz, 2H), 2.70 (t, *J* 8.0 Hz, 2H); ¹H NMR (CDCl₃) δ 7.28 (m, 4H), 3.08 (t, *J* 7.5 Hz, 2H), 2.72 (t, *J* 7.5 Hz, 2H); HPLC acetonitrile–water (60 : 40), *R*_T 5.6 min. The spectroscopic data for this compound are consistent with literature values.¹⁹ For 3-(4-chlorophenyl)propionic acid (4c): colourless crystals; 42%; mp 119–121 °C (lit.²⁰ mp 120–122 °C); ¹H NMR (CD₃CO₂D) δ 7.27 (d, *J* 8.5 Hz, 2H), 7.20 (d, *J* 8.5 Hz, 2H), 2.92 (t, *J* 8.0 Hz, 2H), 2.68 (t, *J* 8.0 Hz, 2H); ¹H NMR (CDCl₃) δ 7.27 (d, *J* 8.5 Hz, 2H), 7.14 (d, *J* 8.5 Hz, 2H), 2.93 (t, *J* 7.5 Hz, 2H), 2.67 (t, *J* 7.5 Hz, 2H); HPLC acetonitrile–water (60 : 40), *R*_T 6.4 min. The spectroscopic data for this compound are consistent with literature values.²⁰

Methyl 3-(2-chlorophenyl)propionate (5b) and methyl 3-(4chlorophenyl)propionate (5c). Reaction of methyl 3phenylpropionate (5a) with chlorine in acetic acid according to the general procedure gave a 51 : 49 mixture of the chlorides 5b and 5c, which were separated by HPLC. For methyl 3-(2chlorophenyl)propionate (5b): colourless oil; 41%; ¹H NMR (CD₃CO₂D) δ 7.24 (m, 4H), 3.66 (s, 3H), 3.04 (t, J 8.0 Hz, 2H), 2.66 (t, J 8.0 Hz, 2H); ¹H NMR (CDCl₃) δ 7.22 (m, 4H), 3.68 (s, 3H), 3.08 (t, J 8.0 Hz, 2H), 2.65 (t, J 8.0 Hz, 2H); HPLC acetonitrile-water (60 : 40), $R_{\rm T}$ 10.2 min. The spectroscopic data for this compound are consistent with literature values²¹ and those of an authentic sample prepared by treatment of the acid 4b with thionyl chloride and methanol. For methyl 3-(4-chlorophenyl)propionate (5c): colourless oil; 41%; ¹H NMR (CCl₄) & 7.25 (d, J 8.5 Hz, 2H), 7.17 (d, J 8.5 Hz, 2H), 3.65 (s, 3H), 2.90 (t, J 8.0 Hz, 2H), 2.64 (t, J 8.0 Hz, 2H); ¹H NMR (CD₃CO₂D) & 7.26 (d, J 8.5 Hz, 2H), 7.17 (d, J 8.5 Hz, 2H), 3.65 (s, 3H), 2.90 (t, J 7.5 Hz, 2H), 2.63 (t, J 7.5 Hz, 2H); HPLC acetonitrile-water (60 : 40), R_T 11.7 min. The spectroscopic data for this compound are consistent with literature values²² and those of an authentic sample prepared by treatment of the acid 4c with thionyl chloride and methanol.

Determination of the rates of reaction of compounds 1a-5a with chlorine

Solutions of compounds **1a–5a** (*ca.* 1 mg) in acetic acid- d_4 (0.5 mL) containing chlorine (0.1–1.0 M), in NMR tubes sealed with Rototite[®] valves, were maintained in the dark at 25 °C for 4–48 h. ¹H NMR spectra of the mixtures were recorded at regular intervals and integrated to determine the ratios of the residual starting materials **1a–5a** and the products **1b,c–5b,c**. Second order rate constants, *k*, for the reactions were then derived from these data according to eqn (1),²³ where [A] is the concentration of compound **1a–5a**. The rate constants are summarised in Table 1. The ratios of the products **1b,c–5b,c** formed in these reactions are indistinguishable from those of the reactions carried out in unlabelled acetic acid.

$$-d[A]/dt = k[A][Cl_2]$$
(1)

Using carbon tetrachloride as the solvent but under otherwise identical conditions, there was no evidence of chlorination of compounds **1a–5a** after 4 days, even at the highest chlorine concentration (1.0 M).

General procedure for preparation of the chlorides 6b,c-8b,c

Reactions of compounds **6a–8a** with chlorine as described above for the synthesis of the chlorides **1b,c–5b,c**, except that the reactions were carried out in either acetic acid, carbon tetrachloride or α,α,α -trifluorotoluene, and the heterogeneous mixtures involved when using the latter two solvents were stirred, affording the chlorides **6b,c–8b,c**, which were treated with acetic acid and characterised as their colourless acetate salts by comparison with literature data.¹¹ The ratios of formation of the regioisomers **6b,c– 8b,c** in the various solvents are summarised in Table 2.

2-(2-Chlorophenyl)ethylamine (6b). ¹H NMR (CD₃CO₂D) δ 7.29 (m, 4H), 3.32 (t, *J* 8.0 Hz, 2H), 3.15 (t, *J* 8.0 Hz, 2H); HPLC acetonitrile–water–acetic acid (49 : 49 : 2), *R*_T 5.8 min.

2-(4-Chlorophenyl)ethylamine (6c). ¹H NMR (CD₃CO₂D) δ 7.32 (m, 4H), 3.30 (t, *J* 8.0 Hz, 2H), 3.01 (t, *J* 8.0 Hz, 2H); HPLC acetonitrile–water–acetic acid (49 : 49 : 2), *R*_T 6.2 min.

3-(2-Chlorophenyl)propylamine (7b). ¹H NMR (CD₃CO₂D) δ 7.28 (m, 4H), 3.14 (t, *J* 7.5 Hz, 2H), 2.84 (t, *J* 7.5 Hz, 2H), 2.07 (m, 2H); HPLC acetonitrile–water–acetic acid (49 : 49 : 2), $R_{\rm T}$ 6.1 min.

3-(4-Chlorophenyl)propylamine (7c). ¹H NMR (CD₃CO₂D) δ 7.30 (m, 4H), 3.09 (t, *J* 7.5 Hz, 2H), 2.70 (t, *J* 7.5 Hz, 2H), 2.09 (m, 2H); HPLC acetonitrile–water–acetic acid (49 : 49 : 2), $R_{\rm T}$ 6.4 min.

4-(2-Chlorophenyl)butylamine (8b). ¹H NMR (CD₃CO₂D) δ 7.26 (m, 4H), 3.12 (m, 2H), 2.77 (t, *J* 8.0 Hz, 2H), 1.80 (m, 4H); HPLC acetonitrile–water–acetic acid (49 : 49 : 2), $R_{\rm T}$ 5.9 min.

4-(4-Chlorophenyl)butylamine (8c). ¹H NMR (CD₃CO₂D) δ 7.25 (m, 4H), 3.10 (m, 2H), 2.63 (t, *J* 8.0 Hz, 2H), 1.85 (m, 4H); HPLC acetonitrile–water–acetic acid (49 : 49 : 2), $R_{\rm T}$ 6.2 min.

General procedure for preparation of the chlorides 9b,c-16b,c

Reactions of compounds **9a–16a** with chlorine as described above for the synthesis of the chlorides **1b,c–5b,c**, except that the reactions were carried out in either acetic acid, carbon tetrachloride or α,α,α -trifluorotoluene, afforded the chlorides **9b,c–16b,c**. The ratios of formation of the regioisomers **9b,c–16b,c** in the various solvents are summarised in Table 3. The pairs of regioisomers **9b–16b** and **9c–16c** were separated using HPLC.

2-(2-Chlorophenyl)acetamide (9b). Colourless crystals; mp 171–172 °C (lit.²⁴ mp 168–172 °C); ¹H NMR (CCl₄) δ 7.35 (m, 4H), 3.66 (s, 2H); ¹H NMR (CD₃CO₂D) δ 7.34 (m, 4H), 3.78 (s, 2H); HPLC acetonitrile–water (50 : 50), $R_{\rm T}$ 8.0 min. The spectroscopic data for this compound are consistent with literature values.²⁴

2-(4-Chlorophenyl)acetamide (9c). Colourless crystals; mp 180–182 °C (lit.²⁴ mp 180–182 °C); ¹H NMR (CCl₄) δ 7.35 (d, *J* 8.0 Hz, 2H), 7.25 (d, *J* 8.0 Hz, 2H), 3.39 (s, 2H); ¹H NMR (CD₃CO₂D) δ 7.30 (m, 4H), 3.61 (s, 2H); HPLC acetonitrile–water (50 : 50), *R*_T 8.4 min. The spectroscopic data for this compound are consistent with literature values.²⁴

3-(2-Chlorophenyl)propionamide (10b). Colourless crystals; mp 115–116 °C (lit.²⁵ 119 °C); ¹H NMR (CCl₄) δ 7.19 (m, 4H), 5.70 (bs, 1H), 5.51 (bs, 1H), 3.02 (t, *J* 7.5 Hz, 2H), 2.43 (t, *J* 7.5 Hz, 2H); ¹H NMR (CD₃CO₂D) δ 7.20 (m, 4H), 3.06 (t, *J* 7.0 Hz, 2H), 2.61 (t, *J* 7.0 Hz, 2H); HPLC acetonitrile–water (60 : 40), *R*_T 7.2 min. The spectroscopic data for this compound are consistent with literature values. $^{\rm 26}$

3-(4-Chlorophenyl)propionamide (10c). Colourless crystals; mp 127–128 °C (lit.²⁷ 129–130 °C); ¹H NMR (CCl₄) δ 7.19 (d, *J* 8.5 Hz, 2H), 7.09 (d, *J* 8.5 Hz, 2H), 5.50 (bs, 1H), 5.00 (bs, 1H), 2.87 (t, *J* 7.5 Hz, 2H), 2.37 (t, *J* 7.5 Hz, 2H); ¹H NMR (CD₃CO₂D) δ 7.26 (d, *J* 8.5 Hz, 2H), 7.20 (d, *J* 8.5 Hz, 2H), 2.92 (t, *J* 8.0 Hz, 2H), 2.58 (t, *J* 8.0 Hz, 2H); HPLC acetonitrile–water (60 : 40), *R*_T 7.9 min.

4-(2-Chlorophenyl)butyramide (11b). Colourless crystals; mp 96–97 °C; ¹H NMR (CCl₄) δ 7.17 (m, 4H), 2.75 (t, *J* 7.5 Hz, 2H), 2.11 (t, *J* 7.5 Hz, 2H), 1.89 (m, 2H); ¹H NMR (CDCl₃) δ 7.24 (m, 4H), 5.65 (bs, 2H), 2.79 (t, *J* 7.5 Hz, 2H), 2.28 (t, *J* 7.5 Hz, 2H), 1.98 (apparent quintet, *J* 7.5 Hz, 2H); ¹³C NMR (CDCl₃) δ 175.2, 138.9, 133.9, 130.5, 129.5, 127.5, 126.8, 35.0, 32.7, 25.3; MS *m*/*z* (%) 199 (M⁺⁺, 5), 197 (M⁺⁺, 16), 162 (23), 125 (26), 89 (18), 59 (100); HPLC acetonitrile–water (60 : 40), *R*_T 7.9 min; (Found: C, 60.55; H, 5.98; N, 6.98%. C₁₀H₁₂CINO requires C, 60.76; H, 6.12; N, 7.09%).

4-(4-Chlorophenyl)butyramide (11c). Colourless crystals; mp 95–98 °C (lit.²⁸ mp 112–113 °C); ¹H NMR (CCl₄) δ 7.18 (d, J 8.0 Hz, 2H), 7.07 (d, J 8.0 Hz, 2H), 5.59 (bs, 1H), 5.05 (bs, 1H), 2.61 (t, J 7.5 Hz, 2H), 2.09 (t, J 7.5 Hz, 2H), 1.89 (m, 2H); ¹H NMR (CDCl₃) δ 7.24 (d, J 8.0 Hz, 2H), 7.10 (d, J 8.0 Hz, 2H), 5.50 (bs, 2H), 2.64 (t, J 7.5 Hz, 2H), 2.22 (t, J 7.5 Hz, 2H), 1.95 (apparent quintet J 7.5 Hz, 2H); ¹³C NMR (CDCl₃) δ 176.9, 139.5, 131.7, 129.8. 128.5, 34.7, 34.3, 26.6; MS *m*/*z* (%) 199 (M⁺⁺, 8), 197 (M⁺⁺, 27), 125 (27), 59 (100); HPLC acetonitrile–water (60 : 40), *R*_T 9.1 min; (Found: C, 60.63; H, 6.20; N, 7.04%. C₁₀H₁₂ClNO requires C, 60.76; H, 6.12; N, 7.09%).

N-(2-(2-Chlorophenyl)ethyl)acetamide (12b). Colourless oil; ¹H NMR (CCl₄) δ 7.22 (m, 4H), 5.38 (b, 1H), 3.42 (apparent q, J 7.0 Hz, 2H), 3.92 (t, J 7.0 Hz, 2H), 1.64 (s, 3H); ¹H NMR (CDCl₃) δ 7.28 (m, 4H), 5.53 (b, 1H), 3.53 (apparent q, J 7.0 Hz, 2H), 2.96 (t, J 7.0 Hz, 2H), 1.95 (s, 3H); HPLC acetonitrile–water (60 : 40), $R_{\rm T}$ 9.5 min. The spectroscopic data for this compound are consistent with literature values.²⁹

N-(2-(4-Chlorophenyl)ethyl)acetamide (12c). Colourless crystals; mp 94–95 °C (lit.²⁹ mp 96 °C); ¹H NMR (CCl₄) δ 7.23 (d, J 8.0 Hz, 2H), 7.09 (d, J 8.0 Hz, 2H), 5.20 (b, 1H), 3.37 (apparent q, J 7.0 Hz, 2H), 2.75 (t, J 7.0 Hz, 2H), 1.83 (s, 3H); ¹H NMR (CDCl₃) δ 7.26 (d, J 8.5 Hz, 2H), 7.12 (d, J 8.5 Hz, 2H), 5.45 (b, 1H), 3.48 (apparent q, J 7.0 Hz, 2H), 2.79 (t, J 7.0 Hz, 2H), 1.94 (s, 3H); HPLC acetonitrile–water (60 : 40), $R_{\rm T}$ 10.2 min. The spectroscopic data for this compound are consistent with literature values.²⁹

N-(3-(2-Chlorophenyl)propyl)acetamide (13b). Colourless oil; ¹H NMR (CCl₄) δ 7.17 (m 4H), 3.39 (apparent q, *J* 7.0 Hz, 2H), 2.74 (t, *J* 7.5 Hz, 2H), 1.85 (s, 3H), 1.79 (m, 2H); ¹H NMR (CDCl₃) δ 7.23 (m, 4H), 5.58 (b, 1H), 3.29 (apparent q, *J* 7.0 Hz, 2H), 2.76 (t, *J* 7.5 Hz, 2H), 1.96 (s, 3H), 1.83 (m, 2H); ¹³C NMR (CDCl₃) δ 170.1, 138.9, 133.7, 130.4, 129.5, 127.5, 126.9, 39.1, 30.9, 29.5, 23.3; MS *m*/*z* (%) 213 (M⁺⁺, 18), 211 (M⁺⁺, 59), 176 (19), 152 (29), 125 (34), 117 (53), 103 (25), 89 (17), 73 (100); HPLC acetonitrilewater (60 : 40), *R*_T 9.0 min; (Found: C, 62.40; H, 6.99; N, 6.43%. C₁₁H₁₄CINO requires C, 62.41; H, 6.67; N, 6.62%). *N*-(3-(4-Chlorophenyl)propyl)acetamide (13c). Colourless oil; ¹H NMR (CCl₄) δ 7.18 (d, *J* 8.0 Hz, 2H), 7.06 (d, *J* 8.0 Hz, 2H), 5.55 (b, 1H), 3.15 (apparent q, *J* 7.5 Hz, 2H), 2.58 (t, *J* 7.5 Hz, 2H), 1.83 (s, 3H), 1.75 (m, 2H); ¹H NMR (CDCl₃) δ 7.23 (d, *J* 8.5 Hz, 2H), 7.09 (d, *J* 8.5 Hz, 2H), 5.60 (b, 1H), 3.26 (apparent q, *J* 7.0 Hz, 2H), 2.61 (t, *J* 8.0 Hz, 2H), 1.95 (s, 3H), 1.78 (m, 2H); ¹³C NMR (CDCl₃) δ 170.2, 139.8, 131.7, 129.7, 128.5, 39.2, 32.5, 31.3, 23.3; MS *m/z* (%) 213 (M⁺⁺, 11), 211 (M⁺⁺, 39), 176 (13), 152 (27), 125 (24), 117 (48), 73 (100); HPLC acetonitrile–water (60 : 40), *R*_T 9.8 min; (Found: C, 62.20; H, 6.69; N, 6.83%. C₁₁H₁₄ClNO requires C, 62.41; H, 6.67; N, 6.62%).

N-(4-(2-Chlorophenyl)butyl)acetamide (14b). Colourless oil; ¹H NMR (CCl₄) δ 7.11 (m 4H), 5.50 (b, 1H) 3.19 (apparent q, *J* 7.0 Hz, 2H), 2.73 (t, *J* 7.5 Hz, 2H), 1.84 (s, 3H), 1.63 (m, 2H), 1.54 (m, 2H); ¹H NMR (CDCl₃) δ 7.23 (m, 4H), 5.50 (b, 1H), 3.27 (apparent q, *J* 6.5 Hz, 2H), 2.75 (t, *J* 7.0 Hz, 2H), 1.97 (s, 3H), 1.83 (m, 4H); ¹³C NMR (CDCl₃) δ 170.3, 140.4, 131.5, 129.7, 128.4, 39.5, 34.7, 29.0, 28.5, 23.1; MS *m*/*z* (%) 227 (M⁺⁺, 45), 225 (M⁺⁺, 91), 148 (24), 131 (36), 125 (80), 100 (100), 87 (98), 72 (92); HPLC acetonitrile–water (55 : 45), *R*_T 7.3 min; (Found: C, 63.36; H, 7.07; N, 6.04%. C₁₂H₁₆CINO requires C, 63.86; H, 7.14; N, 6.21%).

N-(4-(4-Chlorophenyl)butyl)acetamide (14c). Colourless needles; mp 89–90 °C; ¹H NMR (CCl₄) δ 7.18 (d, *J* 8.5 Hz, 2H), 7.04 (d, *J* 8.5 Hz, 2H), 5.15 (b, 1H), 3.17 (apparent q, *J* 7.0 Hz, 2H), 2.60 (t, *J* 7.5 Hz, 2H), 1.84 (s, 3H), 1.61 (m, 2H), 1.46 (m, 2H); ¹H NMR (CDCl₃) δ 7.25 (d, *J* 8.5 Hz, 2H), 7.15 (d, *J* 8.5 Hz, 2H), 5.95 (b, 1H), 3.23 (apparent q, *J* 6.5 Hz, 2H), 2.58 (t, *J* 7.0 Hz, 2H), 1.96 (s, 3H), 1.55 (m, 4H); ¹³C NMR (CDCl₃) δ 170.3, 140.4, 131.5, 129.7, 128.4, 39.5, 34.7, 29.0, 28.5, 23.1; MS *m*/*z* (%) 227 (M⁺⁺, 27), 225 (M⁺⁺, 86), 138 (28), 100 (78), 87 (100), 72 (85); HPLC acetonitrile–water (55 : 45), *R*_T 8.1 min; (Found: C, 63.44; H, 7.20; N, 6.75%. C₁₂H₁₆ClNO requires C, 63.86; H, 7.14; N, 6.21%).

N-Methyl-3-(2-chlorophenyl)propionamide (15b). Colourless oil; ¹H NMR (CCl₄) δ 7.18 (m, 4H), 6.05 (b, 1H), 2.98 (t, *J* 7.5 Hz, 2H), 2.67 (d, *J* 5.0 Hz, 3H), 2.37 (t, *J* 7.5 Hz, 2H); ¹³C NMR (CDCl₃) δ 172.5, 138.3, 133.7, 130.7, 129.5, 127.8, 127.0, 36.3, 29.2, 26.3; MS *m/z* (%) 197 (M⁺⁺, 2), 162 (100), 125 (28), 103 (26); HPLC acetonitrile–water (60 : 40), *R*_T 10.5 min; (Found: C, 60.55; H, 6.09; N, 7.18%. C₁₀H₁₂ClNO requires C, 60.76; H, 6.12; N, 7.09%).

N-Methyl-3-(4-chlorophenyl)propionamide (15c). Colourless needles; mp 126–127 °C; ¹H NMR (CCl₄) δ 7.18 (d, *J* 8.5 Hz, 2H), 7.07 (d, *J* 8.5 Hz, 2H), 5.00 (b, 1H), 2.87 (t, *J* 7.5 Hz, 2H), 2.70 (d, *J* 5.0 Hz, 3H), 2.28 (t, *J* 7.5 Hz, 2H); ¹³C NMR (CDCl₃) δ 172.3, 139.4, 131.9, 129.7, 128.6, 38.2, 31.0, 26.3; MS *m/z* (%) 199 (M⁺⁺, 28), 197 (M⁺⁺, 100), 138 (57), 103 (39); HPLC acetonitrile-water (60 : 40), *R*_T 11.6 min; (Found: C, 60.34; H, 5.94; N, 7.02%. C₁₀H₁₂CINO requires C, 60.76; H, 6.12; N, 7.09%).

N,*N*-Dimethyl-3-(2-chlorophenyl)propionamide (16b). Colourless oil; ¹H NMR (CCl₄) δ 7.19 (m, 4H), 2.99 (t, *J* 7.5 Hz, 2H), 2.91 (s, 3H), 2.86 (s, 3H), 2.50 (t, *J* 7.5 Hz, 2H); ¹H NMR (CDCl₃) δ 7.25 (m, 4H), 3.08 (t, *J* 7.5 Hz, 2H), 2.95 (s, 6H), 2.62 (t, *J* 7.5 Hz, 2H); ¹³C NMR (CDCl₃) δ 171.9, 138.9, 133.9, 130.9, 129.4, 127.7, 126.9, 37.2, 35.4, 33.3, 29.5; MS m/z (%) 211 (M⁺⁺, 4), 176 (100), 139, (21) 125 (28), 102 (24), 72 (27); HPLC acetonitrile–water (60 : 40), R_T 12.0 min; (Found: C, 62.70; H, 6.51; N, 6.53%. C₁₁H₁₄ClNO requires C, 62.41; H, 6.67; N, 6.62%).

N,*N*-Dimethyl-3-(4-chlorophenyl)propionamide (16c). Colourless oil; ¹H NMR (CCl₄) δ 7.17 (d, *J* 8.5 Hz, 2H), 7.10 (d, *J* 8.0 Hz, 2H), 3.30 (s, 3H), 2.86 (m, 5H), 2.46 (t, *J* 7.5 Hz, 2H); ¹H NMR (CDCl₃) δ 7.25 (d, *J* 8.5 Hz, 2H), 7.15 (d, *J* 8.5 Hz, 2H), 2.94 (t, *J* 7.5 Hz, 2H), 2.92 (s, 6H), 2.59 (t, *J* 7.5 Hz, 2H); ¹³C NMR (CDCl₃) δ 171.9, 139.9, 131.8, 129.8, 128.5. 37.1, 35.5, 35.0, 30.6; MS *m*/*z* (%) 213 (M⁺⁺, 35), 211 (M⁺⁺, 100), 138 (44), 125 (84), 103 (44), 86 (42), 72 (73); HPLC acetonitrile–water (60 : 40), *R*_T 13.5 min; (Found: C, 62.71; H, 6.61; N, 6.62%. C₁₁H₁₄CINO requires C, 62.41; H, 6.67; N, 6.62%).

Determination of the rates of reaction of compounds 9a–16a with chlorine

The rate of reaction of the amide **10a** in acetic acid was determined as described above for the rates of reaction of compounds **1a–5a**. The reactions of the amides **9a–15a** in carbon tetrachloride, and of **9a–11a** in α,α,α -trifluorotoluene, were examined in a similar fashion, except that the results were not consistent with second order reactions, so instead pseudo-first order rate constants, k', for the reactions were derived from the data according to eqn (2).²³ The reaction of the tertiary amide **16a** did not follow either first or second order kinetics. The rate constants for the reactions of **9a–15a** and the ratios of formation of the products **9b,c–16b,c** are summarised in Table 3.

$$-d[A]/dt = k'[A]$$
(2)

Preparation of the N-chloride of 3-phenylpropionamide 10a

The amide **10a** was treated with an equimolar quantity of *tert*-butyl hypochlorite in chloroform and the solution was stirred at room temperature in the dark for 24 h. The solvent was then removed under reduced pressure and the residue was chromatographed on silica, eluting with dichloromethane, to give *N*-chloro-3-phenylpropionamide; colourless liquid; ¹H NMR (CCl₄) δ 7.08 (m, 5H), 6.30 (b, 1H), 2.95 (t, *J* 7.5 Hz, 2H), 2.53 (t, *J* 7.5 Hz, 2H); ¹³C NMR (CDCl₃) δ 172.2, 139.9, 128.6, 128.2, 126.4, 36.7, 31.7; MS *m*/*z* (%) 186 (M⁺⁺, 10), 184 (M⁺⁺, 18), 148 (85), 117 (56), 105 (88), 91 (100); (Found: C, 58.64; H, 5.52; N, 7.87%. C₉H₁₀CINO requires C, 58.87; H, 5.49; N, 7.63%).

Acknowledgements

Support of this work by the Australian Research Council and the Plastics and Chemicals Industries Association Inc. (Australia), and the award of an Australian Postgraduate Award (Industry) to P. G. D. in collaboration with Australian Vinyls Corp. Ltd., are gratefully acknowledged.

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