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Development of a Selective Friedel–Crafts Alkylation Surrogate: Safe Operating Conditions through Mechanistic Understanding

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Supporting Information

ABSTRACT: This article describes a selective one-pot, Friedel–Crafts acylation/ketone reduction protocol, effectively a surrogate for the Friedel–Crafts alkylation reaction with a primary alkyl halide. A potentially dangerous failure mode was identified, resulting in the uncontrolled evolution of hydrogen. A series of mechanistic experiments, including analysis by ^{27}Al NMR, was undertaken, and the reaction mechanism elucidated. Finally, the use of React IR to ensure real-time reaction safety was demonstrated.

INTRODUCTION

The Friedel–Crafts alkylation reaction allows the functionalization of aromatic systems with carbon electrophiles to form new carbon–carbon bonds.[1] The reaction has broad scope and has been exploited in numerous industrial applications such as the production of high octane gasoline,[2] synthetic rubber,[3] and bulk chemicals such as ethylbenzene and styrene.[4] Nonetheless, there are significant synthetic limitations. The product is more reactive than the starting material, and so polyalkylation is a frequently encountered problem.[1] Furthermore, a mixture of *ortho*- and *para*-substituted products is observed with unbiased substrates.[1b] Finally, the reaction proceeds *via* a cationic intermediate which imposes restrictions on the electrophile: primary cations rearrange rapidly by Wagner–Meerwein hydride shift to afford more stable secondary cations, and thus, it is not possible to introduce primary alkyl groups other than benzyl, allyl, methyl, and ethyl.[1] For example, attempted alkylation of benzene with *n*-propyl bromide afforded predominantly the isopropyl product.[5]

In contrast, Friedel–Crafts acylation is a highly selective process favoring monosubstituted products with almost exclusive *para* selectivity, controlled by the electronic bias of the aromatic ring and steric bulk of the metal-coordinated electrophile.[6] Consequently, *n*-alkyl chains are generally introduced to aromatic systems by a two-step process starting with Friedel–Crafts acylation. The resultant ketone moiety can be exhaustively reduced by a plethora of methods including Clemmensen reduction,[7] Wolff–Kishner reduction,[8] hydrogenation,[9] or a combination of silane and either protic[10] or Lewis acid.[11] At the inception of this project, a single report of a one-pot Friedel–Crafts acylation/reduction protocol to generate an *n*-alkyl-substituted benzene existed,[12] although a second appeared during the course of our studies.[13]

As part of our histamine antagonist programme we sought a short, high-yielding manufacturing route to alkyl chloride **1**. Key attributes were scalability of processes, stability of intermediates and products to extended processing times, and purification and isolation by crystallization and filtration. As such, intermediates and products were isolated as their crystalline hydrochloride salts as the free bases are oils. The most direct route would be through a selective Friedel–Crafts alkylation of phenyl ether **2**, but the likelihood of multiple alkylation products, intramolecular cyclization, and dimerization led us to discount this approach. A Friedel–Crafts acylation/ketone reduction protocol seemed an attractive alternative (Scheme 1).

The route started with a straightforward alkylation of hexamethyleneimine with 3-phenoxypropyl bromide **3**. The product **2** is isolated in excellent yield as its HCl salt. The reaction is much faster under phase transfer conditions than using a heterogeneous base in organic solvent, and gives very little quaternary ammonium salt byproduct. With this material in hand, we set about examining a series of Lewis acids and solvents for the Friedel–Crafts acylation, using both relevant literature precedent[14] and a PCA-guided approach.[15] The tertiary amine present in the substrate complicates matters by coordinating an equivalent of Lewis acid, even when its HCl salt is used. The use of catalytic methods is therefore precluded, and at least two equivalents of Lewis acid are required. The results of our preliminary screen are shown (Table 1).

By far the best results were achieved using $AlCl_3$ in apolar aprotic solvents, although reasonable conversion was observed using iron and indium chlorides. DCM is the best solvent since it fully solubilises the reaction mixture and we were unable to detect the *ortho* isomer by HPLC or NMR. Keto-chloride **4** is an oil and thus difficult to isolate and purify on large scale. We circumvented this issue by formation and crystallization of the hydrochloride salt (Scheme 2). However, both the salt and free base were unstable to extended processing times during aqueous workup, and on storage under inert conditions at 6 °C. The major degradants are keto-alcohol **5** and dihydrofuran **6**, formed presumably *via* cyclic oxonium species **7**. This also accounts for the observation that keto-chloride **4** is a potent alkylating agent and is genotoxic as indicated by positive AMES test, whereas **1** is AMES negative.[16]

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Scheme 1. Planned route to alkyl chloride 1

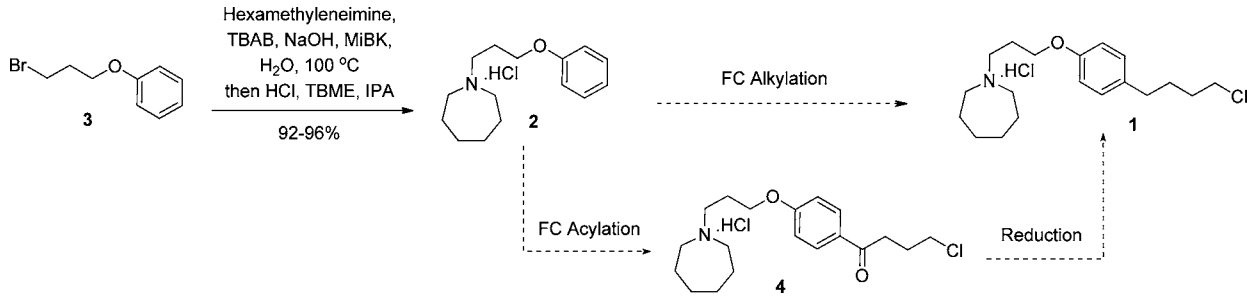
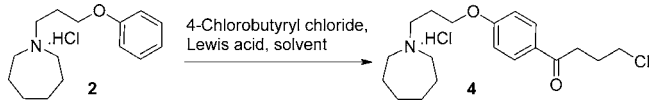


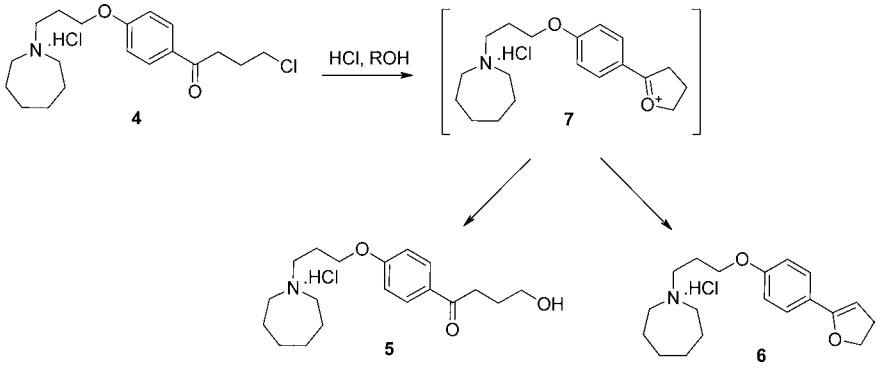
Table 1. Lewis acid screen for a Friedel–Crafts acylation reaction[a]



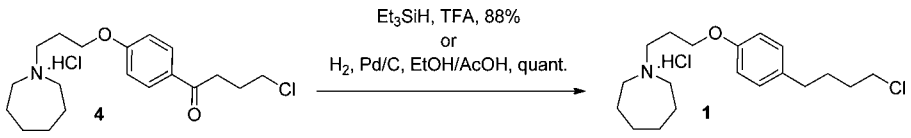
solvent	Lewis acid	% conversion to product[b]	solvent	Lewis acid	% conversion to product
DCM	$AlCl_3$	>99	DCM	$FeCl_3$	80
THF	$AlCl_3$	0	toluene	$FeCl_3$	38
toluene	$AlCl_3$	83	DCM	$ZnCl_2$	7
acetone	$AlCl_3$	0	toluene[a]	Zn	0
acetophenone	$AlCl_3$	0	DCM	$Zn(OTf)_2$	13
chloroform	$AlCl_3$	70	$MeNO_2$	$Zn(OTf)_2$	0
p-xylene	$AlCl_3$	76	none	$Bis(OTf)_2$	7
TBME	$AlCl_3$	0	DCM	$Bis(OTf)_2$	0
heptane	$AlCl_3$	71	DCM	$Sc(OTf)_2$	11
EtOAc	$AlCl_3$	0	DCM	$BF_3{\cdot}OEt_2$	0
trifluorotoluene	$AlCl_3$	10	DCM	$InCl_3$	67
cyclopentyl methyl ether	$AlCl_3$	0	DCM	$BF_3{\cdot}OEt_2$	19[c]
chlorobenzene	$AlCl_3$	40			
$MeNO_2$	$AlCl_3$	29			

[a]Conditions: 4-chlorobutyryl chloride (0.11 mL, 1.1 equiv, 0.94 mmol) was added to a mixture of Lewis acid (1.88 mmol, 2.2 equiv) and substrate (0.20 g, 0.86 mmol) in solvent (2 mL) at 0 °C and allowed to warm slowly to ambient temperature. a) Reaction carried out at 110 °C. [b]Conversion measured by HPLC analysis of the reaction mixture. [c]Using mixed anhydride rather than acid chloride.

Scheme 2. Stability of 4



Scheme 3. Reduction of 4



Nonetheless, we were able to isolate material of sufficient purity to investigate the subsequent reduction. This process was found to occur readily, either by hydrogenation over a palladium catalyst or by triethylsilane reduction in neat trifluoroacetic acid.[9,10] Unfortunately, reduction using triethylsilane and stoichiometric TFA in organic solvents was not successful. Interestingly, the intermediate alcohol is slow to reduce under hydrogenation conditions, but not observed

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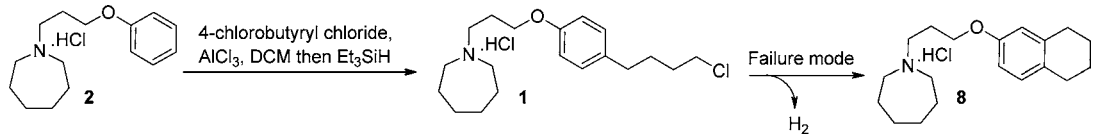
Scheme 4. Telescoped FC acylation/reduction



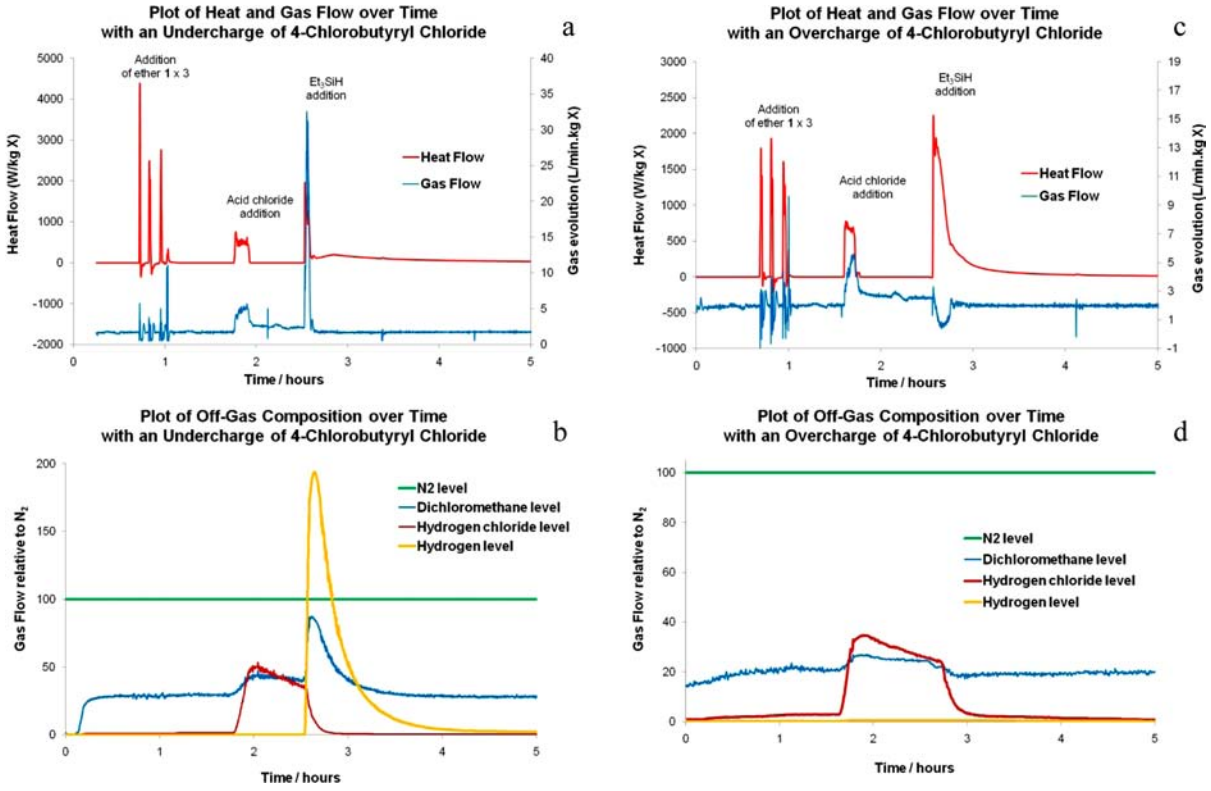


Figure 1. Heat flow, gas flow, and gas composition of telescoped reactions.

under the silane conditions. The hydrogenation reaction gave the product in good yield and purity, but some material was lost to hydrolysis and protodechlorination (Scheme 3). We were unable to limit protodechlorination by using a range of additives that have been reported to suppress Pd insertion into the C−Cl bond.[17] While this two-step protocol is suitable for laboratory-scale synthesis, several factors led us to question its suitability as a manufacturing process: (1) Any processing delays during workup of the Friedel−Crafts acylation would result in increased hydrolysis, lower yield, and a reduction in purity as the keto-alcohol is difficult to purge by crystallisation. (2) The rate of hydrolysis and dechlorination is increased in the absence of hydrogen in the reduction. Again, processing delays would lead to a reduction in yield and purity. (3) The use of trifluoroacetic acid as a solvent on multikilogram scale is precluded due to its toxicity, volatility, corrosivity, and difficulty in handling subsequent waste streams. (4) Chloroketone **4**, unlike alkyl chloride **1**, is genotoxic and unstable with respect to hydrolysis, and thus difficulties would be encountered handling and storing it on scale.

We therefore sought alternatives to this procedure. We speculated that judicious choice of Lewis acid would allow us to carry out a Friedel−Crafts acylation followed by silane-mediated ketone reduction in one pot. Indeed, precedent for such a process exists.[12,13] We were therefore delighted to find that simply adding triethylsilane to the finished Friedel−Crafts acylation reaction mixture quickly afforded the reduced product **1**. We next began the process of optimizing individual reaction parameters resulting in the following ideal conditions: **2** is treated with 2.2 equiv of $AlCl_3$ to ensure consistently complete conversion, followed by 1.1 equiv of 4-chlorobutyryl chloride at 0 °C. Once reaction is complete, 4 equiv of triethylsilane is added, and the reduction is complete in less than 1 h. When the amount of acid chloride is reduced to 1 equiv, the reaction follows a different course: tetrahydronaphthalene **8** is the major product, formed by intramolecular Friedel−Crafts alkylation of the now more active product (Scheme 4). The silane addition is exothermic and accompanied by significant and rapid evolution of gas, initially thought to be HCl by simple pH paper test. Concerned by the scalability of this process, we carried out a series of control experiments, varying individual parameters and measured reaction calorimetry, gas flow, and off-gas composition.

To understand the cause of the cyclization event, we treated chloride **1** with various acidic species in DCM at 0 °C. In the presence of HCl, there is no reaction. In the presence of $AlCl_3$, **1** cyclizes rapidly to afford tetrahydronaphthalene **8**. Treatment with a combination of HCl and $AlCl_3$ (1:1 ratio) returns **1** uncyclized. Next, we treated keto-chloride **4** with the same combinations of acids and added triethylsilane to each. In the presence of HCl, no reaction occurs. In the presence of $AlCl_3$, slow reduction is observed, followed by cyclization to **8**. When

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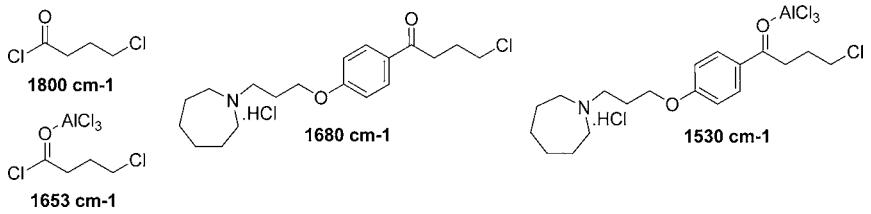

Figure 2. IR stretching frequencies for proposed reaction intermediates.

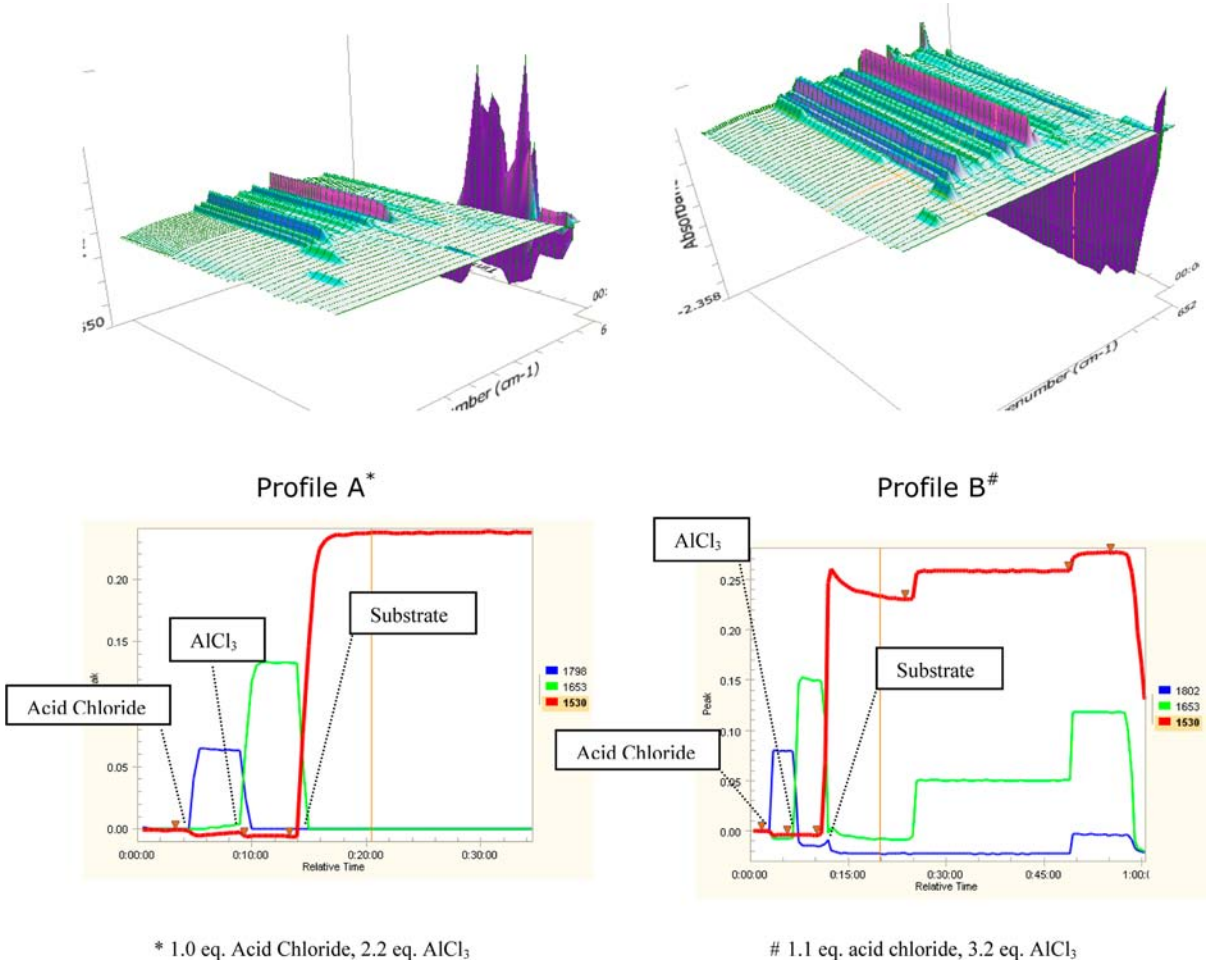

Figure 3. IR profiles of the two possible failure modes.

$AlCl_3$ and HCl are combined, the reduction is rapid, but no cyclization occurs. This suggests that $HAlCl_4$ is the species responsible for mediating the reduction, while free $AlCl_3$ is responsible for the subsequent cyclization. The role of excess acid chloride is therefore to coordinate any free $AlCl_3$. To further test this hypothesis we added tetra-*n*butylammonium chloride to a Friedel–Crafts acylation carried out with 1.0 equiv of acid chloride. Addition of triethylsilane then led to smooth reduction of the ketone moiety without further cyclisation. We next monitored the heat output, gas flow, and off-gas composition of reactions carried out with an undercharge and an excess of 4-chlorobutyryl chloride (Figure 1).

As can be seen from both heat plots, the addition of **2** to a suspension of $AlCl_3$ in DCM is exothermic. Subsequent additions of 4-chlorobutyryl chloride and triethylsilane are also exothermic, but heat output is addition rate-controlled and so not considered an issue for scale-up. In the case where 4-chlorobutyryl chloride is undercharged (Figure 1a), each exotherm is accompanied by a gas evolution. Correlating this with the off-gas composition (Figure 1b), it can be seen that HCl is evolved on addition of acid chloride. However, when triethylsilane is added, the evolved gas is hydrogen. This evolution can be reproduced by simply combining triethylsilane and $AlCl_3$ in DCM. In fact, only sub-stoichiometric $AlCl_3$ is required to consume the silane.[18] When an excess of acid chloride is added (Figure 1c), HCl is still evolved. However, now when triethylsilane is added, the gas flow stops, (if anything, gas seems to be absorbed by the reaction), and no hydrogen is detected in the off-gases (Figure 1d).

To safely run this process on multikilogram scale, we need to be able to control both the reaction outcome and any evolution of gas. The potential generation of a mixture of HCl and H_2 gases with entrained DCM vapour presents a significant engineering challenge from an environmental emissions perspective as the individual components must be treated very differently: HCl is trapped using a caustic scrubber, DCM

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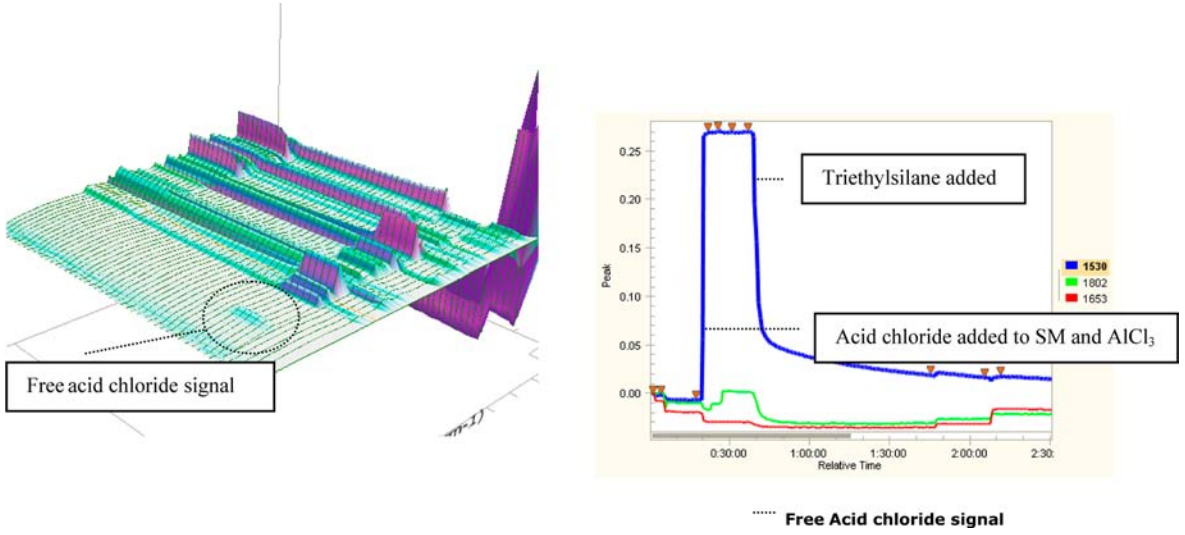
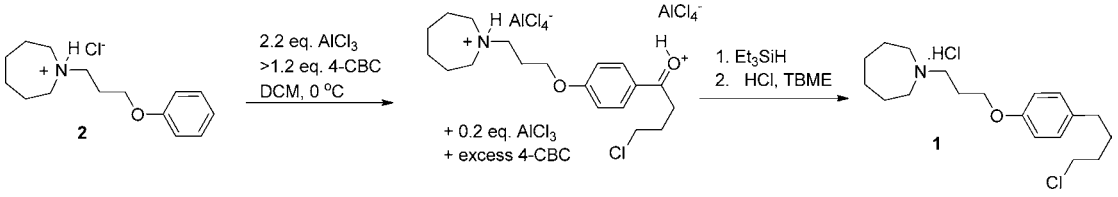


Figure 4. IR profile of successful reaction.

Scheme 5. Mechanistic proposal



is collected using a low-temperature secondary condenser and collection vessel, whereas H_2 must be vented to the atmosphere as quickly as possible to prevent the build-up of an explosive atmosphere. Rather than attempt this complex and potentially hazardous task, we felt the best solution was to ensure the correct ratio of $AlCl_3$ to 4-chlorobutyryl chloride, thus ensuring that the reaction was not going to produce hydrogen before addition of the silane by a noninvasive real-time analytical technique. The IR stretching frequencies of different carbonyl compounds are diagnostic of structure.[19] We therefore investigated ReactIR as an analytical tool to probe various reaction components. We began our studies by determining diagnostic IR stretching frequencies for each of our presumed reaction components. We were pleased to find distinct and separable carbonyl signals for both free and aluminium-bound acid chloride and chloroketone species (Figure 2).[20]

Coordination to $AlCl_3$ lowers the stretching frequency of the carbonyls in both cases by around 150 cm^{-1}. Monitoring the changes in these signals over time allowed us to follow the reaction quite clearly and potentially adjust the charge of acid chloride to ensure an excess is present before silane is added. Experiments were carried out by adding 4-chlorobutyryl chloride, $AlCl_3$, and ether **2** successively to DCM so that a background signal could be measured and the signals for bound and unbound acid chloride detected. This change in addition order does not affect the outcome of the reaction. We next monitored the reaction carried out in two possible failure modes: with an undercharge of acid chloride (1.0 equiv, Figure 3A) and with an overcharge of $AlCl_3$ (3.2 equiv, Figure 3B). On addition of acid chloride, the peak at 1800 cm^{-1} is observed, but disappears on addition of $AlCl_3$ to give the signal for aluminium-bound acid chloride at 1653 cm^{-1}. When ether **2** is added, signals for acid chloride disappear, being replaced by the aluminium-bound chloroketone signal at 1530 cm^{-1}, thus indicating a rapid acylation reaction. In neither case is unbound acid chloride detected. Both reactions would fail on addition of silane; hydrogen would be evolved rapidly, and the product would cyclize to afford tetrahydronaphthalene **8**.

We next demonstrated that reaction B could be recovered by charging more acid chloride. A further 0.4 equiv was added, resulting in reappearance of the signal for aluminium-bound acid chloride (1653 cm^{-1}). On addition of a further 0.8 equiv, the signal for free acid chloride (1800 cm^{-1}) reappears. Addition of triethylsilane then gave clean reduction of all the carbonyl groups to afford **1** with no H_2 evolution and no destructive cyclisation.

Finally, we monitored a reaction carried out under optimized processing conditions using an excess of 4-chlorobutyryl chloride. Gratifyingly, the signal for free acid chloride (1800 cm^{-1}) is observed prior to silane addition which then gives clean conversion to product **1** (Figure 4).

We propose the following mechanism for the reaction: the first equivalent of aluminium is sequestered by the protonated nitrogen as an $[AlCl_4]^-$ counterion. The second equivalent then mediates the Friedel–Crafts acylation generating a further equivalent of HCl, forming additional $[AlCl_4]^-$. The excess of $AlCl_3$ (0.2 equiv) can then cause cyclisation and hydrogen evolution unless coordinated with excess acid chloride (Scheme 5).

To test this hypothesis, we applied ^{27}Al NMR to investigate the nature of the aluminium species present at the failure modes before and after acylation.[21] We first acquired reference spectra of $AlCl_3$ alone and with addition of tetrabutylammonium chloride (TBAC) in DCM-d_2. All species present in both spectra fall in the expected chemical shift region for tetrahedral halide complexes.[22] A single broad resonance at 92.9 ppm (line

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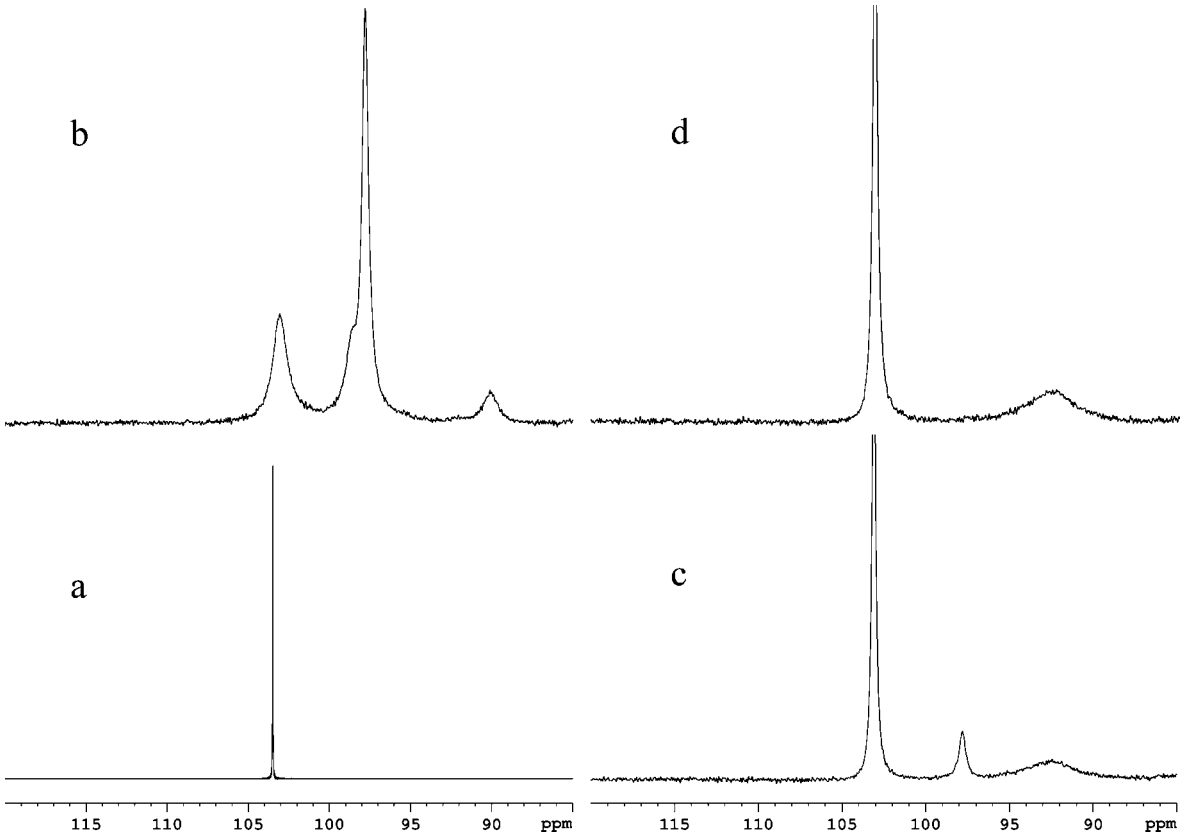

Figure 5. ^{27}Al NMR of (a) $[AlCl_4]^-$ complex and reaction mixtures (b) prior to acid chloride addition, (c) with undercharged acid chloride, (d) with excess acid chloride.

width 183 Hz) is observed with $AlCl_3$ which may correspond to the Al_2Cl_6 dimer, and with the addition of TBAC a single narrow resonance at 103.5 ppm (line width 3 Hz) is observed which corresponds to the $[AlCl_4]^-$ complex (see Figure 5a). A solution to represent the reaction prior to acylation was next prepared with $AlCl_3$ and ether **2** in a 1:2.2 molar ratio in DCM-d_2 and a spectrum acquired (see Figure 5b).

The resulting data show a main resonance at 97.8 ppm (line width 60 Hz) and a series of lesser, broad resonances at 103.1, 98.5, and 90.1 ppm. It is most likely that the resonance at 103.1 ppm is from the $[AlCl_4]^-$ complex with a broader line width of 127 Hz as a consequence of being in equilibrium with other aluminium species in solution. The individual identities of these other species are not known, but they also lie within the expected region for tetrahedral halide complexes and may represent different arrangements of $AlCl_3$ coordinated to ether **2**. Finally we acquired spectra of reactions performed with an undercharge (0.7 eq.) and an excess (1.5 eq.) of acid chloride, with samples being taken following the acid chloride addition but before silane addition (Figures 5c and d, respectively). In both spectra the predominant resonance is at 103.1 ppm, corresponding to the $[AlCl_4]^-$ complex, and they also share a broad resonance at 92.5 ppm which, from the IR data, may possibly represent $AlCl_3$ coordinated to the carbonyl produced by the acylation. There is an additional resonance observed in the undercharged reaction (Figure 5c) at 98.0 ppm which was also present in the solution prior to acylation and thus is potentially from a coordination of $AlCl_3$ with part of the product module originating from ether **2**.

These spectra confirm the presence of $[AlCl_4]^-$ in the reaction mixture along with other aluminium species and support our mechanistic interpretation that an excess of acid chloride is required to completely sequester $AlCl_3$ and prevent the exothermic cyclisation and hydrogen evolution events.

In summary, we have developed a Friedel–Crafts acylation/reduction protocol, effectively a Friedel–Crafts alkylation reaction, to make a key intermediate in the synthesis of a potential histamine antagonist drug. Concerns over the robustness of the reaction led us to a series of experiments to determine the reaction mechanism. Furthermore, we have demonstrated ReactIR as a real-time, nonintrusive, analytical technique to provide a basis of safety for large-scale reactions.

■ EXPERIMENTAL SECTION

General Methods. All reactions were carried out in water-, methanol-, and acetone-washed glassware under a nitrogen atmosphere. Solvents and reagents were used without any purification or drying. ^{1}H and ^{13}C NMR spectra were acquired on a Bruker spectrometer at frequencies of 400 and 100 MHz, respectively. High-resolution mass spectra were recorded on a linear ion trap combined with a Fourier transform ion cyclotron resonance mass spectrometer using an electrospray ionisation source operated in positive ion mode. IR spectra were recorded as solids. HPLC chromatograms were recorded on a C18(2) column at 40 °C; eluent gradient: 100% 0.05% v/v TFA in water to 95% 0.05% v/v TFA in MeCN over 8 min. Heat output data was measured in a Mettler Toledo MidTemp RC1$_e$ vessel. Gas flow and composition was recorded using a Hiden Analytical HPR20 gas analyzer. Melting points were recorded using an automated melting point apparatus.

1-(3-Phenoxypropyl)azepane Hydrochloride ***2****. Method A.* 3-Phenoxypropyl bromide (752 g, 3.5 mol) is added to stirred

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suspension of potassium carbonate (1.06 kg, 7.7 mol) in TBME (3.75 L), followed by hexamethylene imine (692 g. 7.0 mol) and then the mixture heated to reflux for 18 h. Once complete the reaction mixture is cooled to 40 °C, diluted with TBME (3.75 L) before succinic anhydride (384 g, 3.25 mol) is added portionwise and stirred for 30 min. The resulting mixture is washed with water (2 × 7.5 L) and the organic layer dried by azeotropic distillation to 4.5 L total volume under atmospheric pressure. The resulting solution is cooled to 40 °C and diluted with TBME (7.5 L), and the HCl salt of the product is precipitated by addition of HCl in 2-propanol (772 mL of 5−6 M solution) over 40 min. The resulting slurry is cooled to 20 °C over 1 h, aged for 2 h, and filtered. The wet cake is washed with TBME (2 × 1.5 L) and dried *in vacuo* to give 1-(3-phenoxypropyl)azepane hydrochloride as a white solid (848 g, 3.14 mol, 90%); δ_H (400 MHz, $CDCl_3$) 12.40−12.15 (1H, brs), 7.32−7.28 (2H, m), 6.98 (1H, t, J = 7.4 Hz), 6.87 (2H, d, J = 8.6 Hz), 4.08 (2H, t, J = 5.5 Hz), 3.63−3.55 (2H, m), 3.24 (2H, brt, J = 7.5 Hz), 3.03−2.94 (2H, m), 2.50−2..32 (2H, m), 2.26−2.15 (2H, m), 1.93−1.83 (4H, m), 1.75−1.65 (3H, m); δ_C (100 MHz, $CDCl_3$) 158.2, 129.6, 121.3, 114.4, 64.8, 55.3, 54.6, 27.0, 24.5, 23.4; ν_{max} cm^{-1} (solid) 1472, 1493, 1587, 1600, 2512, 2935; HRMS: m/z calcd for $C_{15}H_{24}NO$ 234.1852: found 234.1853; mp 138−140 °C.

Method B. 3-Phenoxypropyl bromide (100 g, 0.47 mol) is added to a stirred mixture of hexamethylene imine (61.7 mL, 0.54 mol) and tetrabutylammonium bromide (15.0 g, 46.5 mmol) in MiBK (300 mL) and sodium hydroxide solution (74.4 mL of 10 M solution made up with water to 300 mL total volume). The reaction mixture is then stirred at reflux for 45 min. Once complete, the reaction is cooled to 40 °C before acetyl chloride (8.26 mL, 0.12 mol) is added and the reaction stirred for 1 h. The layers are separated, and the aqueous layer is washed with MiBK (400 mL); the combined organic layers are washed with water (600 mL) and then dried by azeotropic distillation to 400 mL total volume at atmospheric pressure. TBME (1.5 L) is added followed by HCl in 2-propanol (102 mL of 5−6 M solution), the resulting slurry is stirred for 30 min, then cooled to room temperature, and then aged for 1 h. The slurry is filtered, washed with TBME (2 × 200 mL), and dried *in vacuo* to give 1-(3-phenoxypropyl)azepane hydrochloride as a white solid (118.5 g, 0.44 mol, 94% theory); analytical data as above.

1-(3-(4-(4-Chlorobutyl)phenoxy)propyl)azepane Hydrochloride ***1***. 1-(3-Phenoxypropyl)azepane hydrochloride **2** (750 g, 2.78 mol) is added portionwise to a stirred suspension of aluminium chloride (818 g, 6.12 mol) in dichloromethane (7.5 L) at 0 °C. 4-Chlorobutyryl chloride (374 mL, 3.34 mol) is then added over 20 min, maintaining the internal temperature below 5 °C. The reaction mixture is then stirred for at least 5 min until complete conversion as judged by HPLC analysis. Triethylsilane (1.78 L, 11.1 mol) is added over 1 h, maintaining the internal temperature below 5 °C; then the reaction mixture is stirred for 30 min. Once reaction is complete, the reaction mixture is added portionwise to an aqueous HCl solution (7.5 L of 2 M solution), maintaining the internal temperature below 10 °C; the biphasic mixture is then stirred for 10 min. Once settled the lower organic layer is separated, and the aqueous layer is washed with DCM (2.5 L); the combined organic phases are dried by azeotropic distillation at ambient pressure to 4.5 L total volume. TBME (13.5 L) is added over 45 min at 40 °C and the resulting slurry stirred for at least 1 h. The slurry is then cooled to 20 °C over 1 h, aged for a further 1 h, filtered, washed with TBME (2 × 2.3 L) and dried *in vacuo* to afford 1-(3-(4-(4-chlorobutyl)phenoxy)propyl)azepane hydrochloride as a white solid (962 g, 2.70 mol, 96% theory); δ_H (400 MHz, $CDCl_3$) 12.30−12.10 (1H, brs), 7.08 (2H, d, J = 8.7 Hz), 6.78 (2H, d, J = 8.7 Hz), 4.04 (2H, t, J = 5.6 Hz), 3.61−3.51 (4H, m), 3.25−3.20 (2H, m), 3.02−2.94 (2H, m), 2.58 (2H, t, J = 7.1 Hz), 2.47−2.39 (2H, m), 2.25−2.15 (2H, m), 1.92−1.60 (10H, m); δ_C (100 MHz, $CDCl_3$) 156.5, 134.7, 129.4, 114.3, 64.9, 55.3, 54.6, 44.9, 34.1, 32.0, 28.7, 26.9, 24.4, 23.4; ν_{max} cm^{-1} (solid) 1509, 1584, 1610, 2514, 2594, 2864, 2602, 2940; HMRS m/z calcd for $C_{19}H_{31}ClNO$ 324.2094: found 324.2082; mp 120−122 °C.

1-(4-(3-(Azepan-1-yl)propoxy)phenyl)-4-chlorobutan-1-one Hydrochloride ***4***. 1-(3-Phenoxypropyl)azepane hydrochloride **2** (300 g, 1.11 mol) is added portionwise to a stirred suspension of aluminium(III) chloride (327 g, 2.45 mol) in DCM (3.4 L) at 0 °C. Chlorobutyryl chloride (170 mL, 1.33 mol) is then added over 20 min, maintaining the internal temperature below 5 °C. The reaction mixture is then stirred for 5 min. Once complete, ethanol (600 mL) is added over 10 min, maintaining the internal temperature below 10 °C. Aqueous HCl solution (3 L of a 5 M solution) is then added over 30 min, maintaining the internal temperature below 20 °C and the mixture stirred for 10 min. Once settled the lower organic layer is separated and the aqueous layer is extracted with DCM (1.8 L) and the combined organic phases dried by azeotropic distillation at ambient pressure to 1.2 L total volume. IPA (1.2 L) is added and the reaction mixture is again distilled under atmospheric conditions to 1.2 L total volume. TBME (4.8 L) is added over 45 min at 40 °C and the resulting slurry stirred for at least 1 h. The slurry is then cooled to 10 °C over 1 h, aged for a further hour, filtered, washed with TBME (2 × 1 L) and dried *in vacuo* to afford 1-(4-(3-(azepan-1-yl)propoxy)-phenyl)-4-chlorobutan-1-one hydrochloride **4** as a white solid (369 g, 0.99 mol, 94% theory); δ_H (400 MHz, $CDCl_3$) 12.25−12.10 (1H, brs), 7.95 (2H, d, J = 8.6 Hz), 6.92 (2H, d, J = 8.6 Hz), 4.7 (2H, t, J = 5.4 Hz), 3.67 (2H, t, J = 6.4 Hz), 3.63−3.55 (2H, m), 3.29−3.23 (2H, m), 3.12 (2H, t, J = 7.1 Hz), 3.04−2.97 (2H, m), 2.54−2.44 (2H, m), 2.26−2.14 (4H, m), 1.93−1.81 (4H, m), 1.72−1.81 (2H, m); δ_C (100 MHz, $CDCl_3$) 197.4, 162.0, 130.3, 130.2, 114.1, 65.1, 55.0, 54.6, 44.6, 34.9, 26.8, 26.8, 24.2, 23.3; ν_{max} cm^{-1} (solid) 1509, 1596, 1673s, 2499, 2592, 2935; HMRS m/z calcd for $C_{19}H_{29}ClNO_2$ 338.1881: found 338.1878; mp 110−114 °C.

1-(3-((5,6,7,8-Tetrahydronaphthalen-2-yl)oxy)propyl)-azepane Hydrochloride ***8***. 1-(3-(4-(4-Chlorobutyl)phenoxy)-propyl)azepane hydrochloride **1** (1.43 g, 3.97 mmol) was taken up in DCM (15 mL) under N_2. $AlCl_3$ (1.52 g, 11.4 mmol) was added in three portions over 2 h and the resultant solution aged at ambient temperature for 18 h, at which point all the input material was consumed as indicated by HPLC. The mixture was cooled to 0 °C and quenched by slowly adding 2 M HCl (30 mL) dropwise to afford a cloudy emulsion. The mixture was poured into a separating funnel and IMS (5 mL) and DCM (15 mL) were added resulting in a clear organic phase. The organic fraction was decanted and the aqueous re-extracted with DCM (20 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and evaporated down to 15 mL. TBME (50 mL) was added and the mixture evaporated down to 20 mL, resulting in precipitation of an off-white solid. The slurry was filtered and washed with TBME, then dried over a weekend at 30 °C under vacuum to afford 1-(3-((5,6,7,8-tetrahydronaphthalen-2-yl)oxy)propyl)azepane hydrochloride **8** (960 mg, 2.96

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mmol, 75%) as a white solid; δ_H (400 MHz, $CDCl_3$) 12.20−12.06 (1H, brs), 6.96 (1H, d, J = 8.2 Hz), 6.61 (1H, d, J = 8.2 Hz), 6.5 (1H, s), 4.02 (2H, t, J = 5.6 z), 3.60−3.53 (2H, m), 3.25−3.19 (2H, m), 3.01−2.94 (2H, m), 2.75−2.67 (4H, m), 2.45−2.38 (2H, m), 2.22−2.14 (2H, m), 1.94−1.82 (4H, m), 1.80−1.72 (4H, m), 1.70−1.60 (2H, m); δ_C (100 MHz, $CDCl_3$) 156.0, 138.4, 130.0, 130.0, 114.3, 112.1, 64.8, 55.3, 54.5, 29.6, 28.5, 26.9, 24.5, 23.3, 23.3, 23.0; ν_{max} cm^{-1} (solid) 1500, 1583, 1605, 2510, 2591, 2927; HMRS m/z calcd for $C_{19}H_{30}NO$ 288.2322: found 288.2320; mp 152−156 °C.

Chlorotriethylsilane. δ_H (400 MHz, CD_2Cl_2) 1.02 (9H, t, J = 7.8 Hz), 0.82 (6H, q, J = 7.8 Hz).

1,1,1,2,2,2-Hexaethyldisiloxane. δ_H (400 MHz, CD_2Cl_2) 0.94 (18H, t, J = 7.9 Hz), 0.54 (9H, q, J = 7.9 Hz).

■ ASSOCIATED CONTENT

Supporting Information

NMR spectra for key compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(21) The isotope Al^{27} is 100% naturally abundant, has a nuclear spin of $^5/_2$ and a relative sensitivity of approximately 0.2 compared to ^1H as unity. Nuclei with spin > $^1/_2$ and are known as *quadrupolar*. Such nuclei have nonspherical charge distribution which couples with the electric field gradient at the nucleus to give a resultant quadrupolar coupling. The magnitude of the electric field gradient represents the symmetry of the electron distribution around the nucleus; hence, in the example discussed in this article, aluminium complexes with less symmetry experience a greater quadrupolar coupling effect than those with greater symmetry. The quadrupolar effect provides an efficient pathway for spin−lattice relaxation, leading to potentially much shorter T_1 values and so greater line widths. These can be many hundreds of Hz in the case of highly asymmetric species. The spectra shown here were acquired on a Bruker AV-II 500 MHz spectrometer at a frequency of 130 MHz using a single-pulse experiment and 64 transients acquired with 16k data points each and a recycle delay of between 1 and 10 s as appropriate for the T_1 of the species in each sample. All spectra were referenced externally to $[Al(H_2O)_6]^{3+}$ at 0.00 ppm, a solution of which was formed by dissolving $AlCl_3$ in water.

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