PERKIN 2

Rate-determining nitrogen inversion in the isomerisation of isoimides to imides and azides to tetrazoles: direct observation of intermediates stabilized by trifluoroethyl groups

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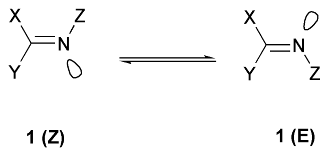
Reaction of *N*-alkyl- and *N*-trifluoroalkylbenzimidoyl chlorides **2** in the presence of either acetate or azide ion leads initially to the formation of the corresponding isoimides **4(Z)** and imidoyl azides **8(Z)** (both of which could be observed spectroscopically). These are formed *via* nucleophilic trapping of the nitrilium cations **3** in aqueous organic solutions. Subsequently these imidoyl acetates and azides rearrange to the more stable imides **5** or tetrazoles **9**. These rearrangements are characterised by a low dependence on solvent polarity and insensitivity to added salts, indicating that the rate-determining step is the isomerisation of the initially formed *Z*-isomer of the imine to the *E*-isomer (imine nitrogen inversion) rather than the subsequent N⟶O acyl group transfer or cyclisation. The Hammett ρ value (-0.4), obtained for the rearrangement of the imidoyl azides to the tetrazoles, compares well to other systems where the rate-determining step (nitrogen inversion) was similar. Nitrogen inversion in these imine systems is therefore significantly slower (*ca.* 10-fold relative to an ethyl group) in the presence of the trifluoroethyl group on nitrogen.

Introduction

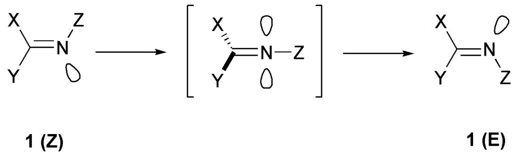
Imines **1** exist in two stereoisomeric forms (Scheme 1), in direct analogy to alkenes, with the *cis* (*Z*) and *trans* (*E*) forms. Unlike most alkyl- or aryl-substituted alkenes, the ground state interconversion of imines may be observed spectroscopically in some cases at room temperature in the absence of added catalysts. However, the rates of interconversion vary a great deal, depending on the substituents.[1] The influence of substituents on the imino nitrogen is markedly greater than that of substituents at carbon; this is especially pronounced for heteroatom substituents[2] whose presence can lead to a very significant reduction in the isomerisation rates. Typically, for aryl-substituted compounds, the reaction constant at carbon is less than -0.5 and at nitrogen greater than 1.0, that is, electron-withdrawing substituents in direct conjugation with the imino nitrogen have an accelerating effect, whereas substituents on the aryl groups on the imino carbon have the opposite effect.[1] Bulky substituents attached to nitrogen may also have a strong accelerating effect in these reactions.[3]



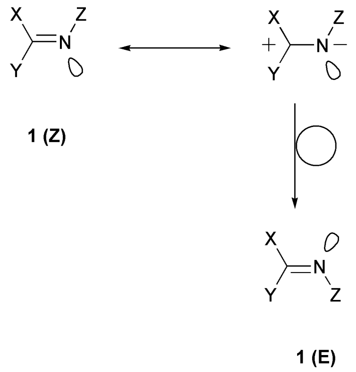
Scheme 1

The detailed mechanism of interconversion has been the subject of considerable debate. The reaction is relatively insensitive to solvent polarity,[4] which strongly favours the lateral shift mechanism, involving a nitrogen lone pair inversion, as shown in Scheme 2. The alternative torsional mechanism which involves C=N bond rotation, as shown in Scheme 3, may be important as a contributor or even the dominant pathway in some cases.[5]

Previous investigations demonstrated that *Z* to *E* interconversion could be the rate-determining step in a number of reactions such as intramolecular acyl transfer.[6,7] Although the intermediates could not be observed in most cases, these reactions show behaviour which is typical of other C=N bond isomerisation reactions, including the observation of acid catalysis.[2b,8]



Scheme 2



Scheme 3

The use of heteroatoms, such as nitrogen or oxygen, attached directly to the imine nitrogen in order to slow nitrogen inversion has been successful in many cases. However this strategy does have the disadvantage that the N–heteroatom bond may be weak and subsequent cleavage of this bond may occur readily, leading to the loss of the useful stereochemical information incorporated in the original reaction.

We now report that the introduction of the *N*-trifluoroethyl group permits the observation of the intermediates formed on trapping of simple *N*-alkylnitrilium ions by both azide and acetate ions and that their subsequent reactions can also be followed; the key factor in allowing the observation of the

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individual steps in the formation of tetrazoles and imides in these systems is the significant slowing of nitrogen inversion by the trifluoroethyl group, which is quantified by this study.

Results and discussion

Formation of nitrilium ions 3 from imidoyl halides 2

The *N*-trifluoroethyl- and *N*-isopropylimidoyl chlorides **2a** to **2e** were shown to undergo hydrolysis to the amide **7** in aqueous dioxane (1,4-dioxane) *via* rate-determining loss of chloride ion to form the nitrilium cation **3**.[9] The observation of strong common ion[10] and solvent effects confirms the presence of the nitrilium cation as the initial intermediate in these reactions.

(a) Common ion effect. The rates of hydrolysis of the imidoyl chlorides **2** were found to be sensitive to their initial concentration; even when **2** was reacted at 5×10^{-4} M, the chloride ion released in the course of the reaction was sufficient to slow the reaction appreciably. At lower concentrations (5×10^{-5} M), the rate was, however, independent of the concentration of substrate. The presence of the common ion effect confirms that the reaction proceeds through an intermediate with the loss of chloride ion to give the nitrilium cation **3** in the rate-determining step.

(b) Solvent effect. Studies of the hydrolysis of these imidoyl chlorides provides additional evidence for the presence of the nitrilium cation **3** in the course of these reactions. Rate constants were obtained in various water–dioxane solvent mixtures at 25 °C. Plotting log k_{obs} against the corresponding Y values of Fainberg and Winstein[11] gave the following m values: 1.22 (for **2a**); 1.61 (**2c**); and 1.11 (**2e**).

The m value measures the susceptibility of the substrate to the ionising power of the solvent mixture. The high m values reflect the fact that the positive charge formed is not highly delocalised, but is concentrated mainly on the $-C{\equiv}N^{+}-$ group itself.

Trapping of 3 by acetate anion to form isomides 4(Z)

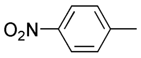
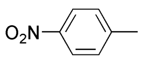
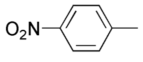
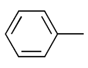
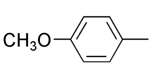
Having established the presence of nitrilium ions as intermediates we have found that, in the presence of acetate as a nucleophile, the nitrilium cations **3** undergo selective trapping.[12] We now report that, in the presence of carefully selected concentrations of sodium acetate, the nitrilium ions **3a**–**3e** are trapped by acetate ion to give intermediates **4(Z)**, which we have now found can be detected when the nitrogen carries a trifluoroethyl group. The solvent used in these trapping reactions contained a high percentage of water in order to ensure that the ionisation of **2** to **3** is rapid. Although these isoimide intermediates **4(Z)** have not been isolated, they are stable enough such that their appearance and further reactions can be monitored using conventional UV and FTIR spectroscopy and HPLC analysis (see Scheme 4).

Contrary to a recent report,[13] structures [such as **4(Z)**] analogous to the acetate-trapped products of these nitrilium cations have been previously reported and documented extensively.[12]

Rates of rearrangement of 4(Z) to 4(E). The isoimides **4(Z)** then undergo a slower subsequent reaction (identified as the conversion to the imides **5**). The rate constants for this reaction could be measured either from HPLC relative peak areas for **4**, **5** and **7** or from the change in optical density using UV spectroscopy and are reported in Table 1. The final products formed from **4** were confirmed by isolation, and also from UV and HPLC analysis of authentic samples, as the imides **5**.

Confirmation that the reaction being studied was rearrangement of **4(Z)** to **4(E)** rather than, say, formation of the nitrilium ion **3** or the isoimide **4(Z)**, was obtained by studying the effect of (a) changing the concentration of acetate ion and (b) water content (Table 2). In both cases the reaction being studied [conversion of **4(Z)** to **4(E)**] was essentially independent of acetate ion and on changing the solvent content from 80 : 20 dioxane–water to 60 : 40 dioxane–water a modest 2-fold rate decrease was observed.

Table 1 First-order rate constants at 25 °C for rearrangement of isoimides **4(Z)** and azides **8(Z)** formed upon reaction of imidoyl chlorides **2** with acetate or azide nucleophiles, in 6 : 4 water–dioxane

			Rate constant k/s^{-1}	
R^1	R^2	R^3	Imides **4(Z)**[a]	Azides **8(Z)**[b]
 **a**	$-CF_3$	–H	2.77×10^{-4}	5.86×10^{-3}
 **b**	$-CH_3$	–H	2.62×10^{-3}	—
 **c**	$-CH_3$	$-CH_3$	4.55×10^{-3}	2.91×10^{-2}
 **d**	$-CF_3$	–H	—	6.22×10^{-3}
 **e**	$-CF_3$	–H	—	8.24×10^{-3}

[a] Ionic strength 1.0 M ($NaClO_4$). [b] Ionic strength 0.1 M (NaN_3). The substrate concentrations were 10^{-4} M; the acetate-trapped products were all measured at 300 nm while the azides were measured at different wavelengths as follows: (**c**) 270, (**d**) 260 and (**e**) 300 nm. Rate constants were based on the mean of three values.

Table 2 Rate constants for the rearrangement of the isoimide **4(Z)a** to the imide **5a** at 25 °C in 80 : 20 dioxane–water

[NaOAc]/M	10^4k/s^{-1}
0.8	4.28
0.5	4.25
0.1	4.17
0.04	4.32

The trapping of the nitrilium cations **3** with acetate anion was also monitored using FTIR spectroscopy (see Fig. 1).

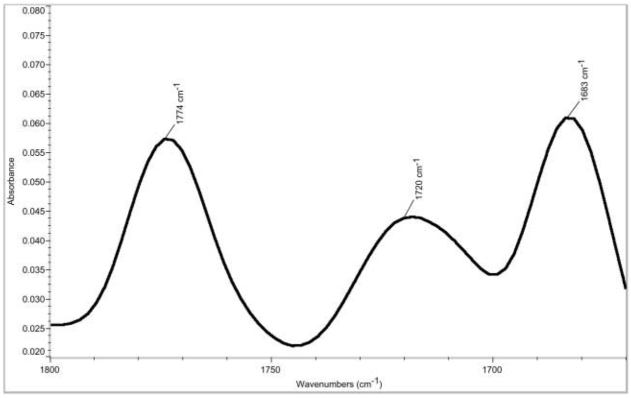
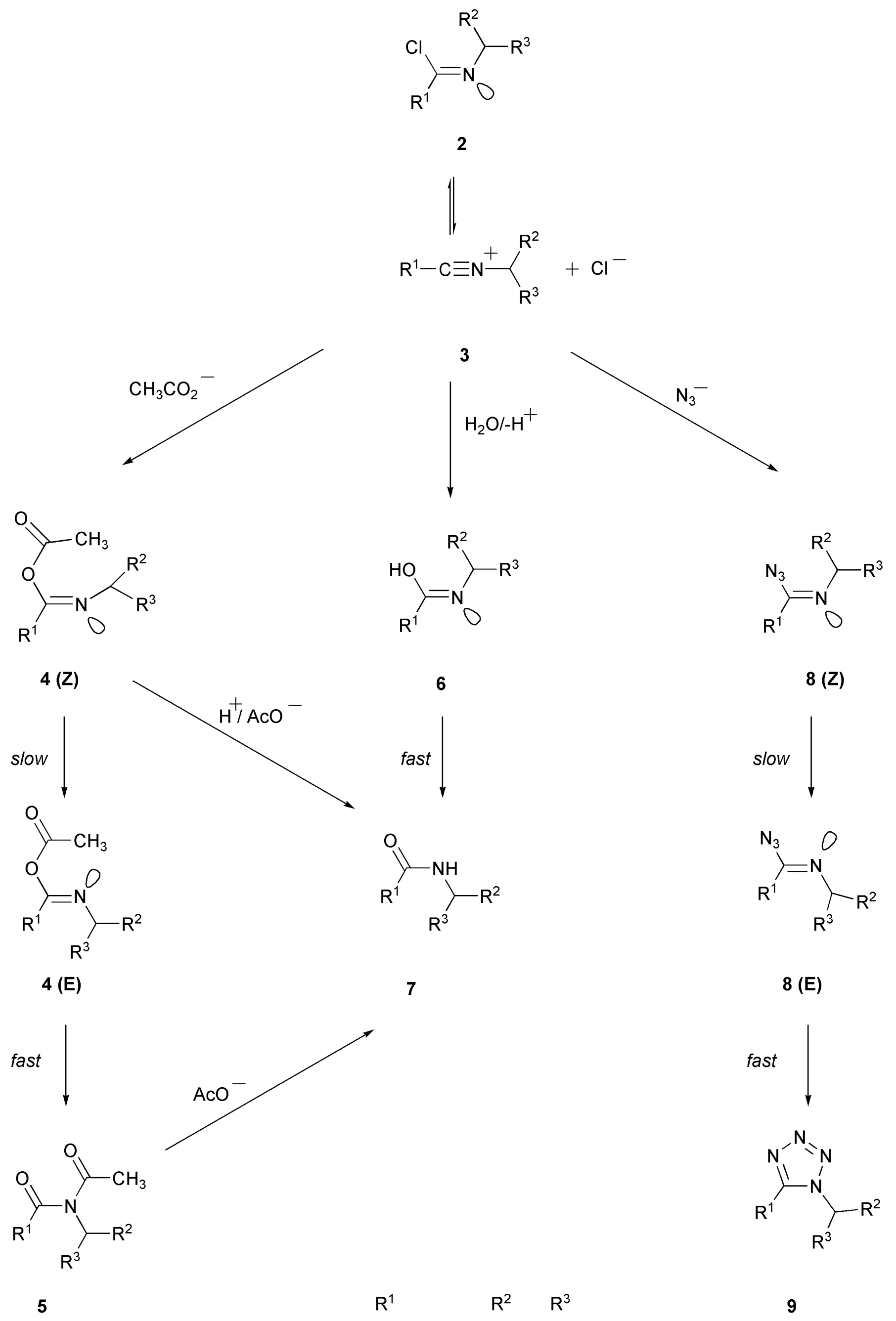


Fig. 1 IR spectrum of the *Z*-isomer **4a**, formed by trapping the nitrilium cation **3a** using acetate ion.

Formation of the *Z*-isomer **4a** was observed at 1774 cm^{-1}, which is in the same region as that observed for vinylic acetates[14] and *O*-acylisoureas.[15] Absorbances at 1720 and 1683 cm^{-1}, assigned to the imide product **5a**, were also observed. The IR spectrum of the *Z*-isomer **4a** and its rearrangement



	R^1	R^2	R^3
a	$4\text{-}NO_2C_6H_4$	CF_3	H
b	$4\text{-}NO_2C_6H_4$	CH_3	H
c	$4\text{-}NO_2C_6H_4$	CH_3	CH_3
d	Ph	CF_3	H
e	$4\text{-}MeOC_6H_4$	CF_3	H

Scheme 4

to **5a** as a function of time are shown in Figs. 1 and 2, respectively.

Having established the structures of these intermediate acetates **4(Z)**, the less stable intermediates carrying an *N*-alkyl group were also successfully examined (see Table 1). Overall the presence of an *N*-trifluoroethyl group reduces the rate of isomerisation *ca.* 10-fold (relative to an *N*-ethyl group).

Effect of acid on trapping and isomerisation. In the presence of acid the rate of reaction of the isoimide **4(Z)** increases (see Table 3). Subsequent HPLC product analysis showed that under these conditions the amide **7** (retention time 6.91 min) was formed in addition to the imide **5** (retention time 9.79 min), from the intermediate isoimide **4** (retention time 14.16 min) (see Fig. 2).

Table 3 Observed rate constants for the reaction of the isoimide **4(Z)** formed from **2a** (1×10^{-4} M) at 25 °C, 60 : 40 water–dioxane and in the presence of acetic acid–acetate buffer (ionic strength 1.0 M) measured at 300 nm

[NaOAc]/M	[AcOH]/M	$10^4k_{obs}/s^{-1}$
0.66	0.33	7.60
0.50	0.50	14.8
0.33	0.66	26.5

As the overall rate of reaction of **4** increases with increasing acid, the amide **7** becomes correspondingly the major product, formed from the isoimide by acid-catalysed ester hydrolysis (giving as final products up to 90% amide, 10% imide). In theory, acid-catalysed rearrangement of the isoimide (**4**) to

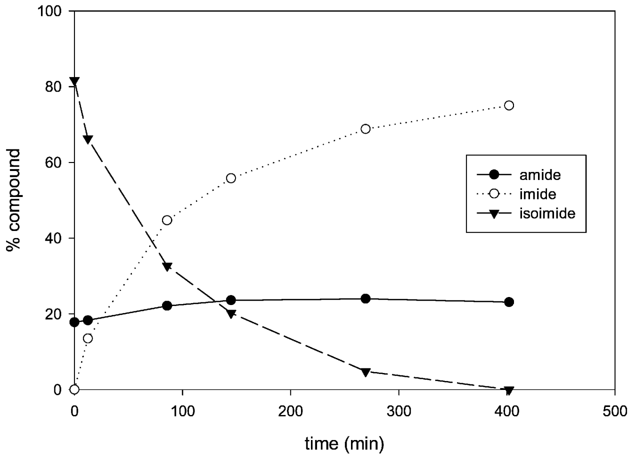


Fig. 2 Graph showing the relationship between the imide **5a**, isoimide **4a** and amide **7a** with time in 0.04 M sodium acetate, at an ionic strength of 1.0 M ($NaClO_4$).

imide **5** is possible since acid catalysis of imine isomerisation is known. However, the product analysis shows that the formation of **7** rather than **5** is enhanced by acid, which rules this out.

Below pH 4 the trapping of the nitrilium ion **3** cannot be carried out successfully with $HOAc–AcO^-$ since the concentration of the acetate ion (which is the active trap) becomes much reduced relative to acetic acid concentration. Similarly, at very low acetate concentrations (<0.02 M) larger percentages of amide **7** were formed; this is presumably because under these conditions there is not enough acetate present to trap the nitrilium ion formed, relative to the reaction of **3** with water (giving the amide **7**). At much higher concentrations of acetate (1.0 M), even at pH 7, the amide **7** was also produced on reaction with **3**, probably by attack of the acetate ion on the isoimide **4**, which was formed initially. We have found that the best region for maximising the degree of formation of the isoimide **4** and minimising the subsequent competitive side reactions is 0.04–0.1 M sodium acetate.

Stability of the imides 5. It was also observed that the imide products **5** were not stable in the reaction medium. Further reaction of the imide with acetate ion occurs giving the amide **7** as product when it is left standing for long periods of time. For example, only 15% of the imide **5a** remains when a pure sample is left standing in 1 M sodium acetate for 5 h. Fig. 3 shows a plot of a time course of this reaction for **5a**, using HPLC to analyse the products.

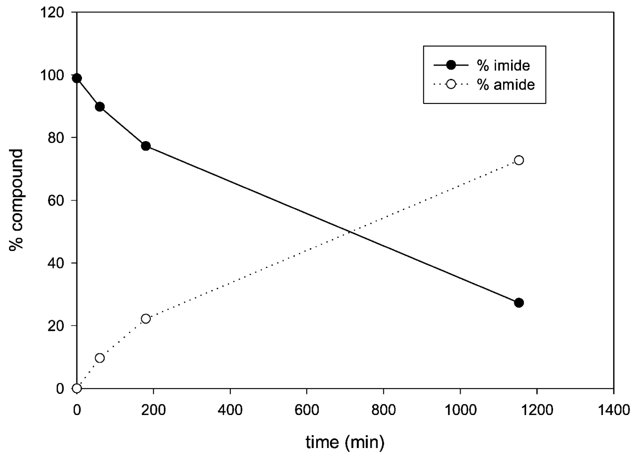


Fig. 3 Plot of the reaction of **5a** in the presence of 0.08 M sodium acetate at 25 °C.

Trapping by azide to form imidoyl azides 8(Z)

Using azide ion as nucleophile, the nitrilium ions **3** were selectively trapped to give the imidoyl azides **8(Z)** as intermediates. The appearance of these intermediates was identified by IR spectroscopy with absorbances at 2136 and 2038 cm^{-1} when a 2,2,2-trifluoroethyl group was present on nitrogen (**8a**). The intensities of these absorbances were shown to decrease with time (Fig. 4) as the azide **8a** was converted to the corresponding tetrazole **9a**. D_2O was used for the IR measurements since H_2O interfered with the spectral range being studied.

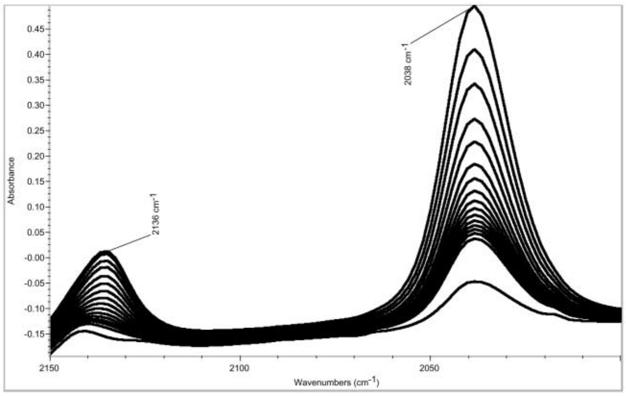


Fig. 4 IR spectrum of the *Z*-isomer **8a** formed when the nitrilium ion **3a** is trapped using azide ion. The initial 16 scans are shown and also the final scan.

A rate constant of $5.6 \times 10^{-3}\ s^{-1}$ was calculated from the UV spectroscopy measurements (measured in 6 : 4 H_2O–dioxane). Both reactions (formation and subsequent rearrangement of **8a**) were measured at 25 °C. A plot of absorbance *versus* time is shown in Fig. 5.

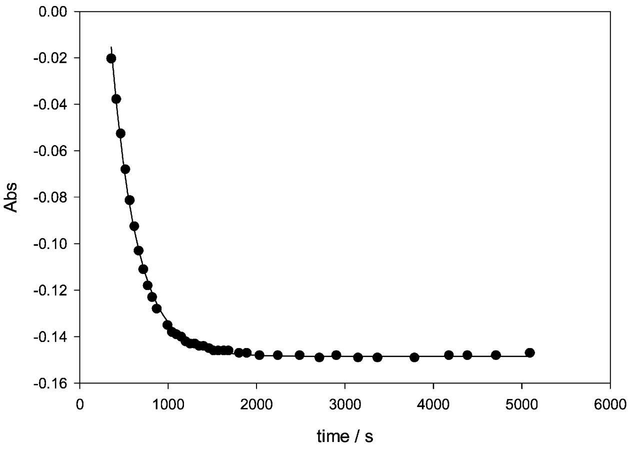


Fig. 5 Plot of absorbance *versus* time for the isomerisation of *Z*-imidoyl azide **8a** to the tetrazole **9a**.

A three-point Hammett plot for the conversion of **8(Z)** to **9** (obtained using substituents *p*-NO_2, H, *p*-MeO) in 80 : 20 dioxane–water gave a ρ value of −0.4 for variation of an aryl substituent located at R^1. This value indicates that the conversion of **8(Z)** to **9** is only slightly susceptible to electronic effects, and the negative sign suggests that the reaction is aided by electron donation, which agrees with previous literature reports on other reactions where nitrogen inversion (by the lateral shift mechanism) is thought to be rate-determining.[7b] The effect of the water content of the solvent on the rate of isomerisation of **8(Z)** is shown in Fig. 6; as the water content increases the rate of isomerisation decreases slightly. Since the ground state of **8(Z)** is relatively more polar than the transition state, an increase in the solvent polarity should stabilise the former thus increasing the barrier to inversion.

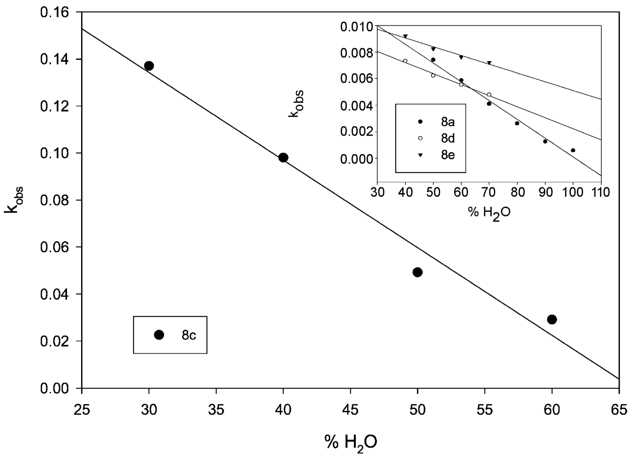


Fig. 6 First-order rate constants for the isomerisation of imidoyl azides **8a**, **8d**, **8e** and **8c** in dioxane–water mixtures.

Comparison of reactions of 4(Z) and 8(Z)

The observed rate constants for rearrangement of the preformed *Z*-isomers **4** and **8** were measured over a wide range of salt and solvent compositions. Rate constants obtained for these reactions measured in a single solvent, 6 : 4 water–dioxane, are listed together in Table 1 for easy comparison. The rate constants for the isomerisation of the azides **8(Z)** to the tetrazoles **9** are approximately an order of magnitude faster than the corresponding rate constant for rearrangement of the acetates **4(Z)** to **5**.

The overall observed behaviour may be summarised using Scheme 4. Both formation and trapping of the nitrilium cation **3** by the incoming nucleophile are rapid when a highly aqueous solvent is used; this leads to the formation of the *Z*-isomer **4** or **8**,[16] which then isomerises *via* rate-determining nitrogen inversion to the *E*-form [**4(E)** or **8(E)**], which then undergoes either rapid O⟶N acyl group migration or cyclisation.

Conclusion

The rate of nitrogen inversion in the imines **4** and **8** is reduced by *ca.* 10-fold, relative to an *N*-ethyl or -isopropyl group, by the introduction of an *N*-trifluoroethyl group. This permits the observation of the intermediate *Z*-imidoyl azides and acetates by HPLC and FTIR spectroscopy for the first time. Consequently direct measurement of the rates of nitrogen inversion can be performed. We conclude that these steps are rate-determining† in the conversion of **4(Z)** to **5** and of **8(Z)** to **9**, rather than the subsequent O⟶N acyl group migration or tetrazole formation, respectively. The trifluoroethyl group, which slows nitrogen inversion significantly, is therefore a useful substituent in controlling the rates of reactions that are limited by this process.

Experimental

General

Melting points were determined using either a Gallenkamp melting point block or a Büchi 530 melting point apparatus and are uncorrected. ^1H NMR spectra were recorded at 60 MHz on a JEOL JNM-PMX60 spectrometer and at 270 MHz on a JEOL JMN-GX270 FT spectrometer. ^{13}C NMR spectra were recorded at 67.80 MHz on the high field instrument and were all completely decoupled, unless otherwise stated. In all ^{13}C spectra a 135 DEPT was carried out. IR spectra were recorded on a Perkin Elmer 1710 FT spectrometer or on a Mattson Instruments Galaxy Series FTIR 3000 spectrometer. A VG Analytical 7070 mass spectrometer, with attached INCOS 2400 data system, in the EI mode, was used for recording mass spectra. Ultraviolet and visible spectra were recorded on a Philips PU8700 series UV spectrophotometer. Thin layer chromatography (TLC) was performed on Merck precoated silica gel 60F254 slides. Merck silica 60 (Art 7748) was used for preparative layer chromatography (PLC), and Merck silica 9385, particle size 0.04–0.063 mm, for flash column chromatography. Solvents were dried according to standard literature procedures. Microanalyses were carried out by the Microanalytical Laboratory, University College Dublin.

Kinetic method

Reactions were initiated by injecting 10–20 µL of the substrate solution (*ca.* 0.01 M) in dry, peroxide-free dioxane into a UV quartz cuvette containing 2 cm^3 of the reaction medium. All reactions were monitored spectrophotometrically covering several half lives, at the appropriate wavelength. Pseudo-first-order rate constants were obtained as the slope from plots of $\ln(A_t - A)$ *versus* the time expressed in seconds, where A_t is the absorbance of the solution at any time t, and A is the absorbance at "infinite" time, optimised using an iterative linear least squares program. Solvent mixtures were made up by mixing the appropriate volumes. Solvents were HPLC grade, and were dried when required using standard techniques. HPLC was performed using a C18-u-bondupack column, and a standard UV detector, 60 : 40 acetonitrile–water was used as solvent at a flow rate of 0.6 $cm^3\ min^{-1}$.

IR analytical method

The trapping reactions of the nitrilium ion **3a** were monitored using a Nicolet Impact 410 FTIR Spectrometer. A solvent mixture of 6 : 4 D_2O–CH_3CN was employed, as its absorption in the infrared spectrum did not interfere with the spectral range being studied. A solution of *N*-(2,2,2-trifluoroethyl)-*p*-nitrobenzimidoyl chloride **2a**, in dry CH_3CN was added dropwise to a stirred solution of sodium azide–sodium acetate in D_2O–CH_3CN. After the addition was complete the solution (0.1 M concentration) was injected *via* a syringe into the IR cell consisting of CaF_2 cell windows with Teflon spacers.

Substrates

The imidoyl chlorides **2** were synthesised by treatment of the corresponding amides **7** with thionyl chloride or phosphorus pentachloride as already described.[9] The synthesis and physical properties of a number of the imidoyl chlorides **2a**–**2d** have also been reported.[9]

***N*-(2,2,2-Trifluoroethyl)-*p*-methoxybenzamide (7e).** A solution of freshly distilled triethylamine (4.86 g, 0.048 mol) and 2,2,2-trifluoroethylamine (4.77 g, 0.048 mol) in dry diethyl ether (100 cm^3) was added dropwise, over 30 min, to a vigorously stirred solution of *p*-anisoyl chloride (8.22 g, 0.048 mol) in dry diethyl ether. The reaction mixture was refluxed for 3 h and upon cooling; the solids were dissolved in water. The ethereal layer was washed with 1 M hydrochloric acid and brine. After drying ($MgSO_4$) and concentration of the ethereal layer, the residual solid was recrystallised from ethanol. A white solid was obtained, yield, 8.92 g (80%), mp 129–130 °C (Found: C, 51.27; H, 4.33; N, 5.99; F, 24.90. $C_{10}H_{10}F_3NO_2$ requires C, 51.51; H, 4.32; N, 6.00; F, 24.44%); ν_{max} (KBr)/cm^{-1} 1646 (C=O), 1156 (CF_3, st); λ_{max} (dioxane)/nm 250 (ε = 13400); δ_H (270 MHz,

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† As noted by a referee, in order to establish that the rate-determining step is nitrogen inversion, the free energy barrier (ΔG) should be evaluated from the rate constants and compared with ΔG values previously reported for planar inversion in comparable imidates or amidines, see review by Jennings and Wilson.[17] However accurate ΔG values of nitrogen inversion for *O*-acyl imidates do not exist and we also had specific difficulty in making measurements at variable temperatures, which would be required in order to estimate activation barriers.

CD_3COCD_3) 3.98 (3H, s, O$C\mathit{H_3}$), 4.42 (2H, q, J = 8.97 Hz, $C\mathit{H_2}$), 7.34 (2H, d, J = 6.5 Hz, *H3*, *H5*), 8.22 (2H, d, J = 6.5 Hz, *H2*, *H6*); δ_C (68 MHz, $CDCl_3$) 40.94 (q, J_{FC} = 34.4 Hz, $\mathit{C}H_2$), 55.44 (1C, q, $\mathit{C}H_3$), 124.57 (1C, q, J_{FC} = 278.3 Hz, CF_3), 113.56 (2C, d, *C*H, *C3*, *C5*), 129.42 (2C, d, *C*H, *C2*, *C6*), 125.66 (1C, s, *C1*), 162.67 (1C, s, *C4*), 167.54 (1C, s, *C*=O); *m*/*z* 233 (M$^+$, 10%), 135 (100), 107 (15), 77 (48).

***N*-(2,2,2-Trifluoroethyl)-*p*-methoxybenzimidoyl chloride (2e).** Phosphorus pentachloride (0.13 g, 0.006 mol) was added to a solution of the amide **7e** (0.125 g, 0.006 mol) in dry benzene (25 cm^3). After refluxing for 12 h, the benzene and phosphorus oxychloride were removed by distillation to yield a yellow oil which was purified by passing through a layer of Merck silica 7734, particle size 0.063–0.2 mm, using dry CH_2Cl_2 as eluant. Yield, 0.098 g (65%). Found: C, 47.48; H, 3.58; N, 5.48; F, 22.76; Cl, 13.98. $C_{10}H_9F_3ClNO$ requires C, 47.73; H, 3.60; N, 5.57; F, 22.69, Cl, 14.12%); ν_{max} (KBr)/cm^{-1} 1662 (C=N), 1155 (CF_3, st), 689 (CF_3, st); λ_{max} (dioxane)/nm 274 (ε = 177000); δ_H (270 MHz, $CDCl_3$) 3.85 (3H, s, $C\mathit{H_3}$), 4.14 (2H, q, J = 9.34 Hz, $C\mathit{H_2}$), 6.90 (2H, d, J = 9.16 Hz, *H3*, *H5*), 7.99 (2H, d, J = 9.16 Hz, *H2*, *H6*).

5-*p*-Nitrophenyl-1-(2,2,2-trifluoroethyl)tetrazole (9a). A solution of *N*-(2,2,2-trifluoroethyl)-*p*-nitrobenzimidoyl chloride **2a** (0.43 g, 0.0016 mol) in Analar acetone (20 cm^3) was added dropwise to a vigorously stirred solution of sodium azide (2.08 g, 0.032 mol) in 1 : 1 acetone–water (50 cm^3). The mixture was left stirring at room temperature overnight. The acetone was then removed by distillation. The resulting white precipitate was filtered and washed with water. The pure product was obtained by passing through a layer of Merck silica 7734, particle size 0.063–0.2 mm, using dry CH_2Cl_2 as eluant. Yield, 0.295 g (68%), mp 118–120 °C (Found: C, 39.47; H, 2.17; N, 25.14; F, 20.72. $C_9H_6F_3N_5O_2$ requires C, 39.57; H, 2.21; N, 25.64; F, 20.86%); λ_{max} (dioxane)/nm 272 (ε = 12200); ν_{max} (KBr)/cm^{-1} 1537 (conj. cyclic sys.), 1445 (N=N), 1171 (CF, st); δ_H (270 MHz, $CDCl_3$) 5.08 (2H, q, J = 7.69 Hz, $C\mathit{H_2}$), 7.91 (2H, d, J = 8.98 Hz, *H3*, *H5*), 8.48 (2H, d, J = 8.98 Hz, *H2*, *H6*); δ_C (68 MHz, $CDCl_3$–CD_3COCD_3) 48.79 (q, $^2J_{FC}$ = 36.6 Hz, $\mathit{C}H_2$), 122.25 (q, $^1J_{FC}$ = 279.4 Hz, $\mathit{C}F_3$), 124.66, 130.61 (4C, d, *C*H, aromatic), 129.31 (1C, s, *C1*), 149.92 (1C, s, *C4*), 154.34 (1C, s, *C*=N); *m*/*z* 273 (M+, 60%), 76 (40), 83 (100).

5-*p*-Nitrophenyl-1-isopropyltetrazole (9c). Compound **9c** was similarly prepared in 56% yield, mp 122–124 °C. (Found: C, 51.14; H, 4.68; N, 30.24. $C_{10}H_{11}N_5O_2$ requires C, 51.52; H, 4.72; N, 30.03%); λ_{max} (dioxane)/nm 272 (ε = 12,200); δ_H (270 MHz, $CDCl_3$) 2.02 (6H, d, J = 6.59 Hz, ($C\mathit{H_3}$)$_2$), 5.27 (1H, sept, J = 6.59 Hz, C*H*), 7.93 (2H, d, J = 8.97 Hz, *H3*, *H5*), 8.45 (2H, d, J = 8.97 Hz, *H2*, *H6*); *m*/*z* 233 (M$^+$, 25%), 191 (15), 76 (20), 43 (100).

5-Phenyl-1-(2,2,2-trifluoroethyl)tetrazole (9d). Yield 64% (Found: C, 47.33; H, 3.08; N, 24.21; F, 25.38. $C_9H_7F_3N_4$ requires C, 47.39; H, 3.06; N, 24.55; F, 24.98%); λ_{max} (dioxane)/nm 243 (ε = 6,900); δ_H (270 MHz, $CDCl_3$) 5.02 (2H, q, J = 7.75 Hz, $C\mathit{H_2}$), 7.6 (5H, m, aromatic); *m*/*z* 228 (M$^+$, 1%), 186 (100), 77 (62).

5-*p*-Methoxyphenyl-1-(2,2,2-trifluoroethyl)tetrazole (9e). Yield, 50%, mp 104–106 °C (Found: C, 46.52; H, 3.51; N, 21.70; F, 22.07. $C_9H_6F_3N_5O_2$ requires C, 46.80; H, 3.53; N, 20.49; F, 20.87%); λ_{max} (dioxane)/nm 253 (ε = 13,200); δ_H (270 MHz, $CDCl_3$) 3.52 (3H, s, O$C\mathit{H_3}$), 4.43 (2H, q, J = 7.69 Hz, $C\mathit{H_2}$), 6.42 (2H, d, J = 7 Hz, *H3*, *H5*), 6.81 (2H, d, J = 7 Hz, *H2*, *H6*); *m*/*z* 258 (M$^+$, 10%), 215, (100), 108 (20), 90 (40).

***N*-Acetyl-*N*-(2,2,2-trifluoroethyl)-*p*-nitrobenzamide (5a).** A solution of *N*-(2,2,2-trifluoroethyl)-*p*-nitrobenzimidoyl chloride (0.45 g, 0.0017 mol) in Analar acetone (1 cm^3) was added to a stirred solution of sodium acetate (2.78 g, 0.035 mol) and acetic acid (0.5 cm^3) in 1 : 1 acetone–water (12 cm^3). After stirring at room temperature overnight, the acetone was removed and the aqueous residue was extracted with chloroform. After drying ($MgSO_4$), the organic layer was removed and the crude product was purified by column chromatography. Yield, 0.35 g, 72% (Found: C, 45.80; H, 3.29; N, 9.62; F, 19.67. $C_{11}H_9F_3N_2O_4$ requires C, 45.53; H, 3.12; N, 9.65; F, 19.64%); ν_{max} (KBr)/cm^{-1} 1720 (C=O), 1681 (C=O), 1535 (NO_2, as stretch), 1150 (CF, st); λ_{max} (dioxane)/nm 260 (ε = 11,700); δ_H (270 MHz, $CDCl_3$) 2.21 (3H, s, $C\mathit{H_3}$), 4.56 (2H, q, J = 8.61 Hz, $C\mathit{H_2}$), 7.81 (2H, d, *H2*, *H6*), 8.36 (2H, d, *H3*, *H5*); δ_C (68 MHz, $CDCl_3$) 25.66 (1C, q, $\mathit{C}H_3$), 45.39 (q, $^2J_{FC}$ = 35.4 Hz, $\mathit{C}H_2$), 123.69 (q, $^1J_{FC}$ = 280.5 Hz, $\mathit{C}F_3$), 124.34, 129.25 (4C, d, *C*H, aromatic), 140.27 (1C, s, *C1*), 150.01 (1C, s, *C4*), 171.35, 171.29 (2C, s, *C*=O); *m*/*z* 290 (M$^+$, 5%), 150 (60), 104 (20), 76 (15), 43 (100).

***N*-Acetyl-*N*-ethyl-*p*-nitrobenzamide (5b).** Compound **5b** was similarly formed in 67% yield (Found: C, 56.18; H, 5.22; N, 11.73. $C_{11}H_{12}N_2O_4$ requires C, 55.95; H, 5.08; N, 11.86%); ν_{max} (KBr)/cm^{-1} 1710 (C=O), 1679 (C=O); ν_{max} (dioxane)/nm 237 (ε = 7900); δ_H (270 MHz, $CDCl_3$) 1.28 (3H, t, J = 7.35 Hz, $C\mathit{H_3}$), 2.15 (3H, s, $C\mathit{H_3}$), 3.49 (2H, q, J = 7.35 Hz, $C\mathit{H_2}$), 7.90 (2H, d, J = 8.98 Hz, *H3*, *H5*), 8.25 (2H, d, J = 8.98 Hz, *H2*, *H6*); *m*/*z* 236 (M$^+$, 20%), 150 (55), 76 (52), 43 (100).

***N*-Acetyl-*N*-isopropyl-*p*-nitrobenzamide (5c).** Compound **5c** was formed in 65% yield (Found: C, 56.23; H, 6.64; N, 11.45. $C_{12}H_{14}N_2O_4$ requires C, 56.91; H, 6.76; N, 11.06%); ν_{max} (KBr)/cm^{-1} 1704 (C=O), 1685 (C=O), 1527 (NO_2, as stretch); λ_{max} (dioxane)/nm 236 (ε = 7800); δ_H (270 MHz, $CDCl_3$) 1.44 (6H, d, J = 6.78 Hz, ($C\mathit{H_3}$)$_2$), 2.11 (3H, s, $C\mathit{H_3}$), 4.47 (1H, sept, J = 6.78 Hz, C*H*), 7.81 (2H, d, J = 8.97 Hz, *H3*, *H5*), 8.31 (2H, d, J = 8.97 Hz, *H2*, *H6*); δ_C (68 MHz, $CDCl_3$–CD_3COCD_3) 20.53 (2C, q, $\mathit{C}H_3$), 26.59 (1C, q, $\mathit{C}H_3$), 50.90 (1C, d, *C*H), 124.11, 129.15 (4C, d, *C*H, aromatic), 142.30 (1C, s, *C1*), 149.76 (1C, s, *C4*), 172.83, 172.95 (2C, s, *C*=O); *m*/*z* 250 (M$^+$, 25%), 193 (10), 150 (45), 76 (20), 43 (100).†

References

1 H. O. Kalinowski and H. Kessler, *Top. Stereochem.*, 1973, **7**, 295.

2 (*a*) D. Y. Curtin, E. J. Grubbs and C. G. Mc Carty, *J. Am. Chem. Soc.*, 1966, **88**, 2775; (*b*) K. J. Dignam and A. F. Hegarty, *J. Chem. Soc., Perkin Trans. 2*, 1979, 1437.

3 Z. Rappoport and R. Ta-Shma, *Tetrahedron Lett.*, 1972, **52**, 5281; H. Kessler, *Angew. Chem., Int. Ed. Engl.*, 1970, **9**, 219; R. Knorr, T. P. Hoang, J. Mehlstaubl, M. Hintermeyer-Hilpert, H.-D. Ludemann, E. Lang, G. Sextl, W. Rattay and P. Bohrer, *Chem. Ber.*, 1993, **126**, 217.

4 H. Kessler, *Tetrahedron Lett.*, 1968, **15**, 2041; H. Kessler and D. Leibfritz, *Tetrahedron Lett.*, 1969, **6**, 427; H. Kessler and D. Leibfritz, *Tetrahedron*, 1970, **26**, 1805; D. Leibfritz and H. Kessler, *J. Chem. Soc., Chem. Commun.*, 1970, 655; H. Kessler, P. F. Bley and D. Leibfritz, *Tetrahedron*, 1971, **27**, 1687.

5 M. Raban, *J. Chem. Soc., Chem. Commun.*, 1970, 1415; M. Raban and E. Carlson, *J. Am. Chem. Soc.*, 1971, **93**, 685; G. E. Hall, W. J. Middleton and J. D. Roberts, *J. Am. Chem. Soc.*, 1971, **93**, 4778; T. J. Lang, G. J. Wolber and R. D. Bach, *J. Am. Chem. Soc.*, 1981, **103**, 3275.

6 D. G. McCarthy and A. F. Hegarty, *J. Chem. Soc., Perkin Trans. 2*, 1977, 1080; D. G. McCarthy and A. F. Hegarty, *J. Chem. Soc., Perkin Trans. 2*, 1977, 1085.

7 (*a*) A. F. Hegarty, K. Brady and M. Mullane, *J. Chem. Soc., Chem. Commun.*, 1978, 871; (*b*) A. F. Hegarty, K. Brady and M. Mullane, *J. Chem. Soc., Perkin Trans. 2*, 1980, 535.

8 W. B. Jennings, S. Al-Showiman, M. S. Tolley and D. R. Boyd, *J. Chem. Soc., Perkin Trans. 2*, 1975, 1535.

9 A. F. Hegarty, S. J. Eustace, N. M. Tynan, N. N. Pham-Tran and M. T. Nguyen, *J. Chem. Soc., Perkin Trans. 2*, 2001, 1239.

10 I. Ugi, F. Beck and U. Fetzer, *Chem. Ber.*, 1962, **95**, 126; A. F. Hegarty, J. D. Cronin and F. L. Scott, *J. Chem. Soc., Perkin Trans. 2*, 1975, 429.

11 A. H. Fainberg and S. Winstein, *J. Am. Chem. Soc.*, 1956, **78**, 2770.

12 A. F. Hegarty, *Acc. Chem. Res.*, 1980, **13**, 448.

13 R. W. Darbeau, E. H. White, N. Nunez, B. Coit and M. Daigle, *J. Org. Chem.*, 2000, **65**, 1115.

14 D. H. Williams and I. Fleming, *Spectroscopic Methods in Organic Chemistry*, McGraw-Hill, London, 1995, 5th edn., p. 46.

15 M. T. Mc Cormack, PhD Thesis, National University of Ireland, 1976.

16 J. E. Johnson and S. C. Cornell, *J. Org. Chem.*, 1980, **45**, 4144.

17 W. B. Jennings and V. E. Wilson, *Acyclic Organonitrogen Stereodynamics*, eds. J. B. Lambert and Y. Takeuchi, VCH, New York, 1992, pp. 219–224.