PERKIN 2

Kinetic stability of novel nitrile ylides

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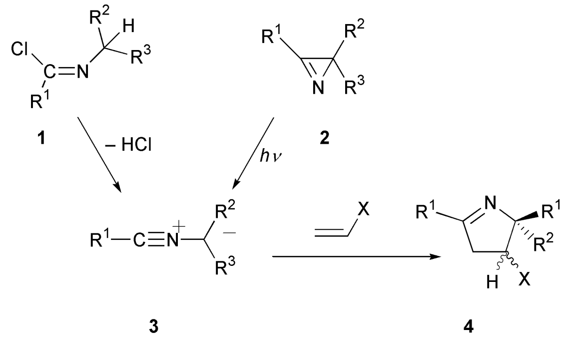
A series of relatively stable novel trifluoromethyl substituted nitrile ylides have been generated by base promoted elimination of hydrogen chloride from the corresponding imidoyl chlorides in acetonitrile and aqueous dioxane solution at 25 °C. The formation and decay of these sometimes highly coloured species was monitored spectrophotometrically. The rates of formation were first order in base, and the subsequent reaction with solvent was acid catalysed at high pH's in aqueous systems. Studies in aqueous dioxane indicated that the more stable ylides were also the slowest to form. In acetonitrile as solvent, the ylides underwent addition of solvent at rates which were independent of the base concentration and relatively insensitive to the nature of the substituents. In a number of cases, cycloaddition products were also isolated confirming the 1,3-dipolar nature of these compounds. Protonation of the ylides has also been studied both experimentally in aqueous solution and theoretically. While formation of nitrilium ions by protonation of the ylide carbon atoms is unlikely in aqueous solution since the corresponding amides are not observed as products, these ions have been calculated to be the most favoured protonated forms of ylides either in the gas phase or in a continuum of solvent, irrespective of its polarity. *Ab initio* calculations were carried out using molecular orbital methods (HF, MP2 and CCSD(T)) with basis sets ranging from 6-31G(d) to 6-311++G(3df,2p) and density functional theory (B3LYP) in conjunction with the polarizable continuum model (PCM) for treating non-specific solvent effects. This discrepancy between experiment and theory suggests a probable involvement of specific solvent interaction in inducing a higher thermodynamic stability of either nitrile carbon or NO_2^- oxygen protonated forms *via* hydrogen-bonded complexes.

Introduction

The chemistry of nitrile ylides (**3**), as pioneered by Huisgen,[1–4] has been the subject of interest for over 40 years.[5,6] They are designated by a C–N–C framework connected by two σ bonds containing six electrons in π and η orbitals, which may adopt a bent or linear structure depending on the substituents.[6–9] Nitrile ylides undergo reactions which are typical of 1,3-dipoles, that is, they display electrophilic and nucleophilic activity at positions 1 and 3 or may react in the 1,3 positions in concerted cycloadditions.[1c] Examples of such reactions include dimerisations,[5,10–13] or cycloadditions.[5,14–19]

They may be generated by a number of methods, including thermolysis,[20–24] and photolysis.[5,25–27] Base promoted elimination of HCl from the corresponding imidoyl chloride (**1**) in organic solvents, or photolysis of 2*H*-azirines (**2**) are probably the most convenient routes for the generation of a wide variety of ylides (**3**). These in turn may be trapped by electron deficient alkenes, such as acrylonitrile or methyl acrylate yielding two possible diastereomeric 4-substituted 1-pyrrolines (**4**) as illustrated in Scheme 1. Other methods of generation have also been used, which in some instances have led to the isolation of cycloadducts which have been characterised by conventional techniques.[28–30]

We now wish to report that when appropriately substituted (particularly by strongly electron withdrawing CF_3 and *p*-nitrophenyl groups) that these nitrile ylides are surprisingly stable in aqueous solution and their formation and further reactions can be monitored spectrophotometrically at high pH.



	R1	R2	R3
a	Ph	CF_3	H
b	Ph	CF_3	CF_3
c	$4\text{-}NO_2C_6H_4$	CF_3	H
d	$4\text{-}NO_2C_6H_4$	CH_3	H
e	$4\text{-}NO_2C_6H_4$	CH_3	CH_3
f	$4\text{-}NO_2C_6H_4$	CF_3	CF_3
j	H	H	H
k	CH_3	CF_3	CF_3
l	$NO_2C_6H_4$	H	H

Scheme 1

We also present a theoretical study of the preferred protonation sites of nitrile ylides, which seeks to understand their kinetic behaviour in aqueous solution.

Results and discussion

Nitrilium ion formation

The hydrolysis of imidoyl chlorides (**1**) in water–dioxane mixtures gave the expected behaviour in good ionising solvents,

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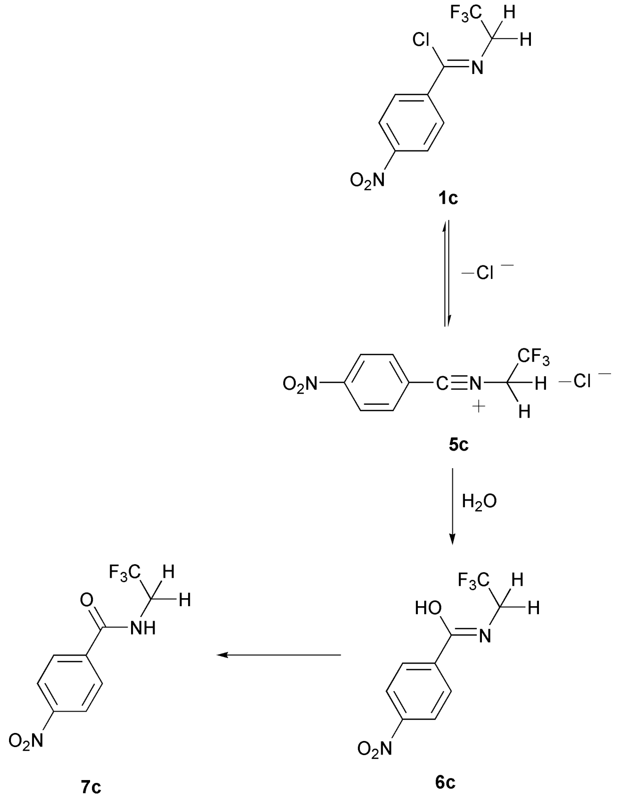
Table 1 Summary of rate constants for the based catalysed formation of ylides **3** from imidoyl halides **1** and subsequent reaction with solvent[a]

		Formation (k/M^{-1} s^{-1})		Further reaction (10^3k/s^{-1})	
Nitrile ylide (**3**)	λ_{max}/nm	Solvent H_2O–dioxane[b]	CH_3CN[c]	Solvent H_2O–dioxane[d]	CH_3CN[e]
3b	340	14.4 (±2.1)	—	8.4 (±0.7)	—
3c	480	1.03 (±0.09)	7.05 (±0.33)	0.32 (±0.04)	7.0 (±1.2)
3d	520	—	0.80 (±0.25)		[f]
3f	460	9.4 (±1.3) × 10^{-3}	—	Slow	Slow

[a] Substrate concentrations in the range 0.1 to 1.0 mM. [b] 60 : 40, sodium hydroxide used as base. [c] Potassium *tert*-butoxide used as base. [d] 60 : 40, base independent rates. [e] Mean values. [f] Linear dependence on base observed.

that is, hydrolysis occurs *via* rate determining formation of the nitrilium cation (**5**) in neutral solution yielding the corresponding amides (**7**) as products following rapid reaction of the nitrilium cations with water (Scheme 2). These reactions are characterised by a strong solvent dependence and large common ion rate depressions were observed throughout. Reaction rates were also retarded for those compounds with electron withdrawing substituents, consistent with the accepted mechanism of reaction *via* rate determining nitrilium cation (**5**) formation under these reaction conditions.[31,32]



Scheme 2

Nitrile ylide formation

The behaviour of imidoyl chlorides **1** with R^2 and/or R^3 = CF_3 in *basic* aqueous solution is quite different. Reaction *via* the nitrilium cation can be retarded by using lower water concentrations, and in the presence of base, a base catalysed reaction becomes the dominant pathway, examples of which are shown in Fig. 1; we assign this to nitrile ylide **3** formation. The nitrile ylides formed (which are long lived at high pH) are typified by long wavelength absorbances giving brightly coloured solutions when a nitro group is present in R^1 (see Fig. 2). The wavelengths of the absorbance maxima (Table 1) provide a useful chromophore for monitoring the rates of formation and subsequent decay of these species. In all cases, the observed rates of nitrile ylide formation increased with base concentration, in aqueous dioxane, giving the second order rate constants which are listed in Table 1. The pH "window" over which these reactions could be studied was quite narrow since the further reaction of the nitrile ylides (see below) was acid catalysed in aqueous solution in the pH range where the rate of formation, which was base catalysed, could be followed.

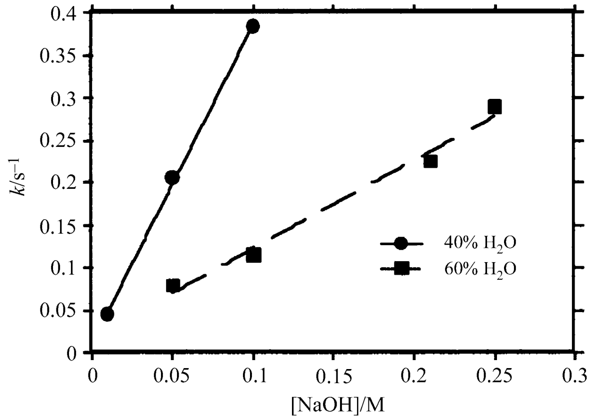


Fig. 1 Observed rate constants for the sodium hydroxide promoted formation of nitrile ylide (**3c**) in 60 : 40 and in 40 : 60 water–dioxane; all substrate concentrations were 0.25 mM.

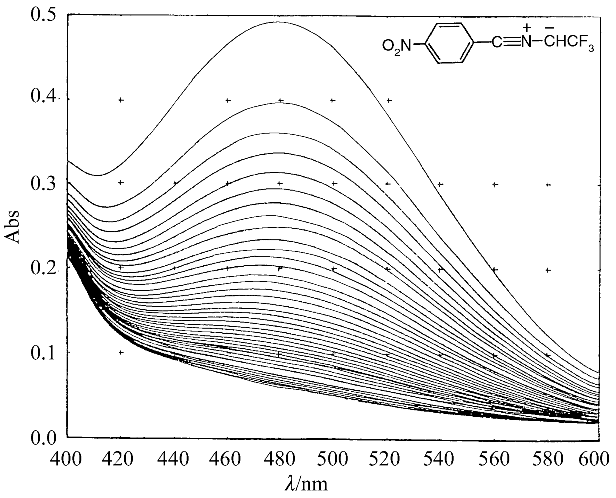


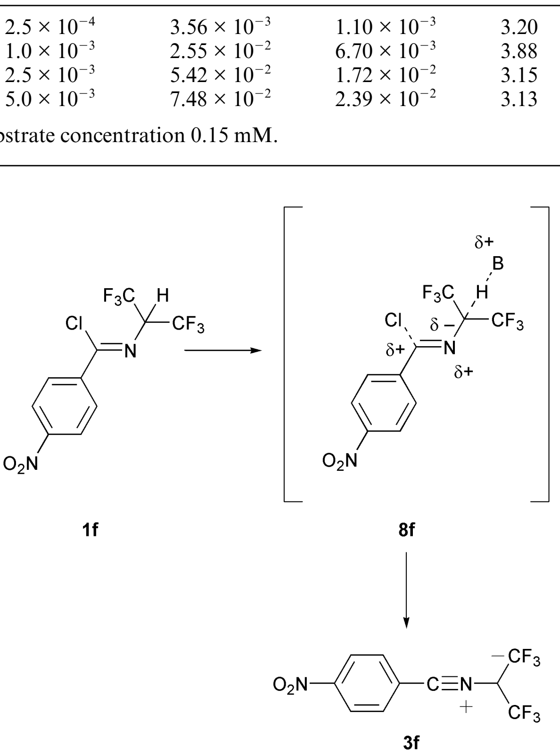
Fig. 2 Repetitive scan of the UV-Visible spectrum showing the decay in the absorbance associated with nitrile ylide **3c** formed from the chloride **1c** in 60 : 40 water–dioxane containing 0.25 M sodium hydroxide.

For comparison we have found that the rates of ylide formation could also be studied in acetonitrile solution under anhydrous conditions. Potassium *tert*-butoxide solubilised by the presence of 18-C-6 was found to be the base of choice. Broadly similar behaviour to that in aqueous systems was observed, that is, the rates of formation increase with increasing concentration of the base, *tert*-butoxide ion (Table 1). These

Table 2 Observed first order rate constants for the reaction of imidoyl chloride (**1b**), and its deuterated analogue in basic medium, 60 : 40 water–dioxane at 25 °C[a]

[NaOH]/M	k_H/s^{-1}	k_D/s^{-1}	k_H/k$_D$
2.5×10^{-4}	3.56×10^{-3}	1.10×10^{-3}	3.20
1.0×10^{-3}	2.55×10^{-2}	6.70×10^{-3}	3.88
2.5×10^{-3}	5.42×10^{-2}	1.72×10^{-2}	3.15
5.0×10^{-3}	7.48×10^{-2}	2.39×10^{-2}	3.13

[a] Substrate concentration 0.15 mM.



Scheme 3

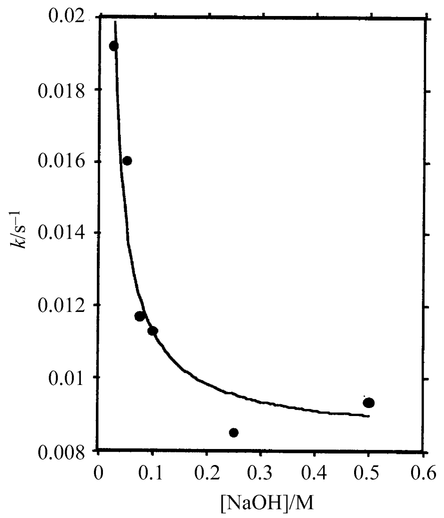


Fig. 3 Observed rate constants for the subsequent reaction of nitrile ylide **3b** *versus* sodium hydroxide concentrations, in 60 : 40 water–dioxane; all substrate concentrations were 1.25 μM.

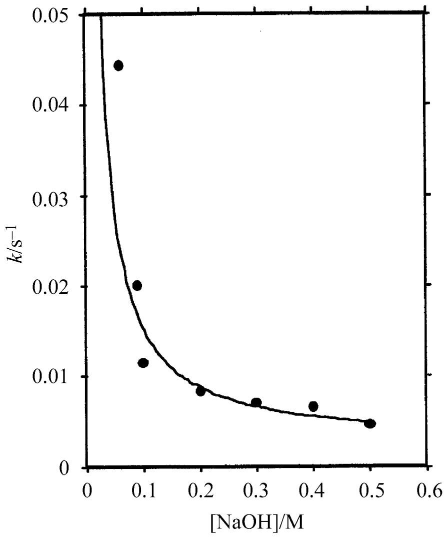


Fig. 4 Observed rate constants for the reaction of nitrile ylide **3c** *versus* sodium hydroxide concentrations, in 60 : 40 water–dioxane.

base catalysed reactions are sensitive to a change in substituent R^1, in that electron withdrawing groups decrease the rate of formation of **3**, especially for those compounds possessing a *p*-nitrophenyl group as R^1. Again, a trend is observed on changing substituents R^2 and R^3. Electron withdrawing substituents (increasing the number of CF_3 groups), lead to an increase in rate. This favours the E2 mechanism for these 1,3-eliminations, as shown in Scheme 3. This is supported by the observation of a substantial primary isotope effect for the base catalysed reaction when the C–H being removed was replaced by C-^{2}H for one of the imidoyl chlorides (**1b**) (Table 2).

Ylide stability

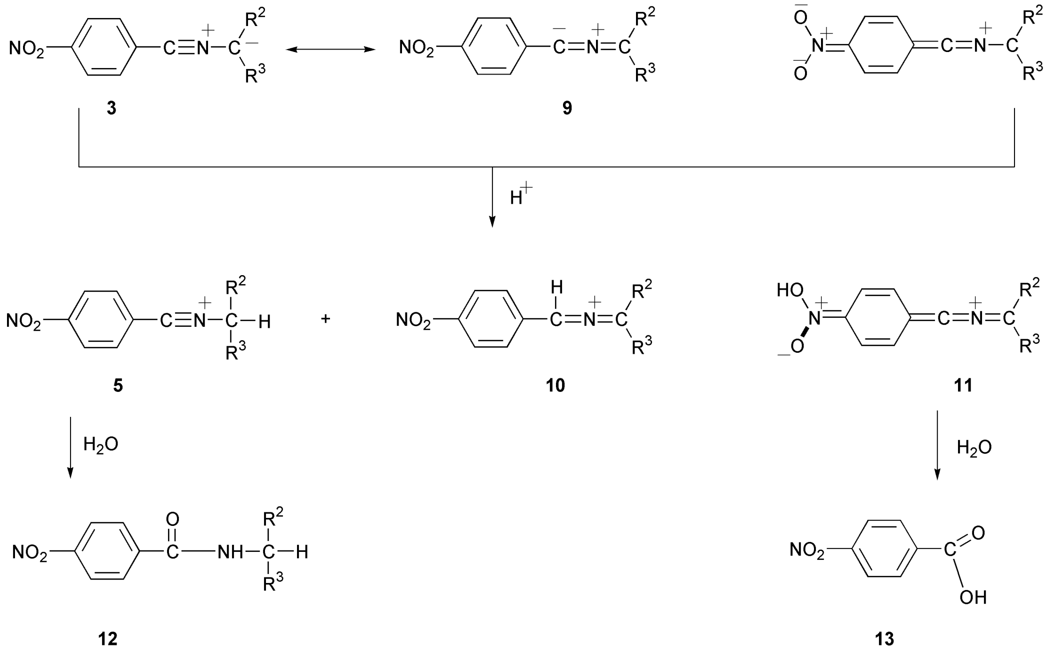
The ylides **3** carrying strongly electron withdrawing substituents were generally found to be quite stable in the presence of high base concentrations. The initial absorbance in the presence of high base concentrations was also independent of base concentration. The subsequent decay in absorbance, associated with further reaction of the nitrile ylide, was almost independent of base at very high base concentrations but became acid catalysed at lower base concentration, as seen in Figs. 3 and 4. The observation of both pH independent reactions and acid catalysis in aqueous systems indicates that the reaction with water occurs by direct attack by water on the ylide and *via* initial protonation of the ylide. The ylide **3f** appears to be quite stable (in dilute aqueous solution in the presence of base it remained unchanged for a week at 25 °C), but could not be isolated to date, presumably due to dimerisation.

Protonation of the ylide (**3**) can occur on two carbon (and in the case of the *p*-nitrophenyl substituted compounds, two oxygen) sites (see Scheme 4). Protonation of the ylide carbon would yield, as the initial product, the nitrilium cation (**5**). This however is not occurring since the nitrilium ion would be expected to yield the amide **12** (on rapid reaction with water), which was not detected as the product of reaction as shown by careful HPLC analysis under these conditions. An alternative mechanism is therefore suggested, where protonation of **3** gives the aza-allenium ion (**11**) which then undergoes nucleophilic attack by water to yield the acid (**13**) which was observed using HPLC as the product of reaction. The possibility that the carboxylic acid (**13**) was formed upon hydrolysis of the amide (**12**) was ruled out, as in separate experiments the amides were found to be stable to hydrolysis under the conditions used. Results of a theoretical study of protonation sites will be presented in a following section.

In acetonitrile, the ylides underwent reaction with the solvent at rates which were independent of the base concentration and the rates of decay of the ylides show little variation under these conditions. Compound **3d** showed different behaviour, showing an increased rate of reaction on increasing base concentrations, probably due to competing trapping by the base in this case (in the absence of trifluoromethyl groups).

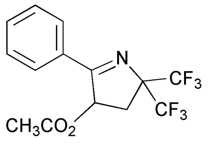
Trapping of nitrile ylides

In order to confirm the identity of the nitrile ylides formed under these conditions, trapping reactions were also carried out in a number of cases using a variety of dipolarophiles, including acrylonitrile and methyl acrylate. These confirmed that the coloured species were in fact the 1,3-dipoles. For



Scheme 4

example preparative scale isolation of cycloadducts was successful in the case of ylide **3b**, which formed isomeric products (**14** and **15**) in the presence of methyl acrylate, and in the presence of *p*-nitrobenzaldehyde efficient recovery of oxazoline **16** was effected.



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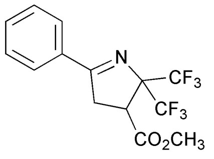

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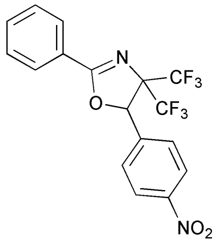

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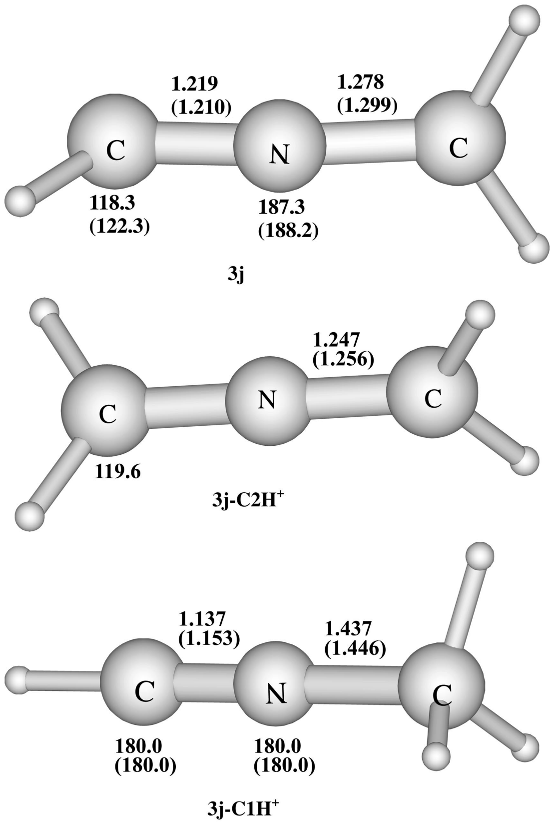

3j

3j-C2H$^+$

3j-C1H$^+$

Fig. 5 Selected geometrical parameters of the unsubstituted nitrile ylide **3j** and its two protonated forms **3j-C1H$^+$** and **3j-C2H$^+$** obtained from B3LYP/6-311++G(d,p) and MP2/6-311++G(d,p) (values in parentheses) calculations. Bond lengths are given in Å and bond angles in degrees.

Ab initio calculations on the protonation of nitrile ylides

In order to probe further the protonation process, we have also carried out *ab initio* calculations[33] on a number of model species. For the sake of consistency, the nitrile ylides considered are labelled by number **3**, followed by a letter, **f**, **j**, **k** and **l**. The protonated sites include the nitrile carbon, ylide carbon and oxygen of the substituent. Geometrical parameters of the unsubstituted parent nitrile ylide **3j** using the molecular orbital MP2/6-311 ++ G(d,p) and density functional theory B3LYP/6-311 ++ G(d,p) methods are summarised in Fig. 5. It is confirmed that the neutral nitrile ylide does not have a linear and planar framework but a strongly bent shape at the nitrile carbon and a quasi-perpendicular conformation of the two terminal groups. Protonation of either ylide or nitrile carbon leads to linear structures. Calculated proton affinities of the unsubstitued parent molecule listed in Table 3 show that, even though the absolute values change with respect to the method and basis set used, the ylide carbon is found to be consistently the most basic site, in agreement with earlier results using lower-level calculations.[34,35] The higher the level of theory used, the larger the energy difference in favour of the protonated ylide carbon. Our best estimate at CCSD(T)/6-311++G(3df,2p) + ZPE suggests a difference of 21 kJ mol^{-1} in favour of the nitrilium ion **3j-C1H$^+$** over the aza-allenium ion **3j-C2H$^+$** (Fig. 5). The proton affinity of the parent nitrile ylide is calculated to be 966 ± 10 kJ mol^{-1}, thus suggesting that the ylide carbon is a relatively highly basic centre.

Fig. 6 displays the geometries of the three neutral substituted species **3k**, **3l** and **3f**. The compound **3f** having two CF_3 groups

Table 3 Calculated proton affinities (kJ mol^{-1}) of the unsubstituted nitrile ylide **3j**

Level[a]	PA (nitrile carbon)[b] **3j-C2H$^+$**	PA (ylide carbon)[b] **3j-C1H$^+$**
B3LYP/6-31G(d)	958	959
B3LYP/6-311++G(d,p)	938	944
MP2/-311++G(d,p)	956	981
CCSD(T)/6-311++G(3df,2p)	945	966

[a] Based on optimised geometries at the level indicated. MP2-geometries were used for CCSD(T) calculations.[b] Including zero-point energy computed at the B3LYP/6-31G(d) level.

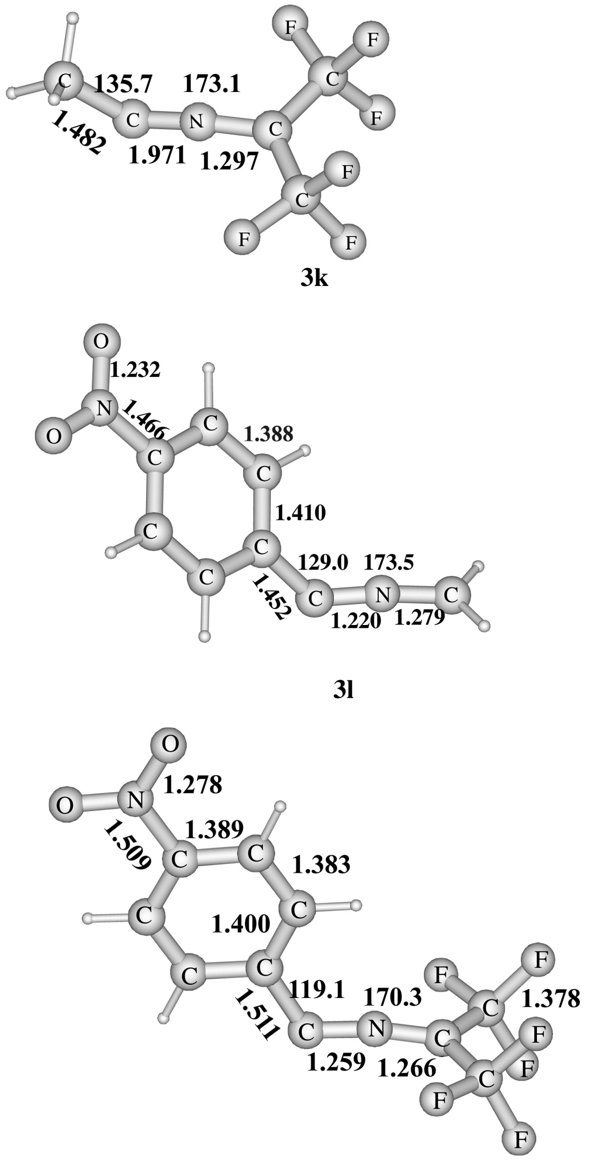

Fig. 6 Selected geometrical B3LYP/.6-31G(d) parameters of three neutral substituted nitrile ylides **3k, 3l** and **3f**. Bond lengths are given in Å and bond angles in degrees.

on the ylide carbon and a *p*-nitrophenyl group on the nitrile carbon is actually one of the compounds studied in our experiments described above. To simplify the presentation of data, geometries of the protonated species are not shown here. The calculated proton affinities of substituted nitrile-ylides are summarised in Table 4. Again, it is found that the ylide carbon protonation is favoured over the others. Incorporation of two electron-withdrawing CF$_3$ groups at the ylide carbon in **3k** tends to reduce significantly the proton affinities (PAs) at both carbons by up to 70 kJ mol^{-1} (comparison of PAs of **3j** and **3k**). In contrast, substitution of a *p*-NO$_2$-phenyl group at the nitrile carbon in **3l** results in a large increase of the PAs (up to 50 kJ mol^{-1}). Combination of both effects in the substituted 1,3-dipole **3f** still gives a significant reduction of the PAs relative to unsubsituted **3l** (up to 36 kJ mol^{-1}). Apparently, the effects induced by two CF$_3$ groups and a *p*-nitrophenyl group are not additive. On the other hand, protonation at the oxygen atom of the NO$_2$ group yields the least stable ion in both systems **3l** and **3f**. Thus it can be concluded that in the gaseous phase, the ylide carbon remains consistently the most basic site of the nitrile ylides.

In an attempt to evaluate the effect of the solvent on the relative stabilities of the protonated isomers, we have also used the polarisable continuum model (PCM)[36] to treat the stabilisation of a molecular system by a solvent continuum which is characterised by a relative permittivity. Calculated results are summarised in Table 5. Because the geometries of the ions were not reoptimised within the solvent continuum, this evaluation provides rather a crude estimate of the stabilisation energy induced by the solvation of the continuum. In addition, the PCM represents mainly the Coulombic effect which is usually not a major fraction of the solvation energy. Nevertheless, the results obtained consistently point out a higher stabilisation of the nitrilium cations (ylide carbon protonated species), irrespective of the continuum polarity as measured by its relative permittivity (ε). It turns out that the higher this polarity, the larger the stabilisation energy. These calculated results therefore contrast with the observations stated above in which the nitrilium cations are not the primary products formed upon protonation of nitrile ylides in water–dioxane solution. Such a discrepancy might arise from the fact that in aqueous solution, water oligomers usually provide strong specific interaction with the solute through hydrogen-bonds. The presence of an NOOH$^+$ group, which is isoelectronic with a carboxylic acid functional group, in the oxygen protonated forms might result in stronger H-bonded complexes with water clusters. The importance of specific solvent interaction is well documented.[37–39] Nevertheless, a detailed investigation of this problem is beyond the scope of this paper.

In summary, we have reported in the present paper the generation and reactivity of a series of relatively stable and novel nitrile ylides. The stability is due to the presence of trifluoromethyl (CF$_3$) groups. The rates of formation of ylides were first-order in base and the subsequent reaction with solvent was acid catalysed at high pHs in aqueous solution. Nitrile ylides also underwent typical 1,3-diploar cycloadditions with trapping dipolarophiles. Regarding the protonation of ylides, while protonation of the ylide carbon atoms yielding nitrilium ions were shown experimentally to be unlikely in aqueous solution, *ab inito* quantum chemical computations indicated that this process is consistently favoured either in the gaseous phase or in a solvent continuum, irrespective of its polarity. The varience is likely due to the presence of specific solvent interaction in an aqueous medium through hydrogen-bonded complexes.

Experimental

General

Melting points were determined using either a Gallenkamp melting point block or a Büchi 530 melting point apparatus and

Table 4 Calculated proton affinities (kJ mol^{-1}) at different sites of three substituted nitrile ylides considered

	Species[a]	B3LYP/6-31G(d,p)	B3LYP/6-311+G(d,p)	MP2/6-311+G(d,p)
3k	Ylide carbon	910	873	895
	Nitrile carbon	912	867	859
3l	Ylide carbon	1014	990	—
	Nitrile carbon	986	960	—
	Oxygen (NO_2)	904	892	—
3f	Ylide carbon	900	908	—
	Nitrile carbon	914	875	—
	Oxygen (NO_2)	869	827	—

[a] B3LYP/6-31G(d)-optimised geometries. Proton affinities are computed at the indicated level with ZPE corrections.

Table 5 Solvation free energies (ΔG_{solv}) of the protonated forms in different media characterised by relative permittivity ε using the PCM method

		ΔG_{solv}/kJ mol^{-1} [b]			
Species[a]	Protonated forms	Acetone ($\varepsilon = 21$)	Nitromethane ($\varepsilon = 38$)	DMSO ($\varepsilon = 47$)	Water ($\varepsilon = 78$)
3j	Ylide carbon	−207	−209	−211	−244
	Nitrile carbon	−192	−193	−194	−222
3k	Ylide carbon	−193	−191	−193	−239
	Nitrile carbon	−183	−181	−183	−217
3l	Ylide carbon	−196	−194	−198	−232
	Nitrile carbon	−195	−192	−195	−231
	Oxygen	−160	−157	−159	−191
3f	Ylide carbon	−193	−188	−190	−241
	Nitrile carbon	−183	−178	−180	−215
	Oxygen	−162	−156	−158	−202

[a] Based on B3LYP/6-31G(d)-optimised geometries in the gas phase.[b] From PCM calculations at the HF/6-31G(d) level.

are uncorrected. ^1H NMR spectra were recorded at 50 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; ε values are given in units of dm^3 mol^{-1} cm^{-1}. Thin layer chromatography (TLC) was performed on Merck precoated kieselgel 60F$_{254}$ 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. HPLC chromatography was performed using a C18 u-bondupack column and a standard UV detector. 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 quartz cell cuvette containing 2 ml of the reaction medium. All reactions were monitored spectrophotometrically covering several half lives, using a Philips PU 8700 series spectrophotometer at the appropriate wavelength. Pseudo first order rate constants were obtained as the slope from plots of ln ($A_t - A_\infty$) *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 t_∞ optimised using an interactive linear least squares programme. Solvent mixtures were made up by mixing the appropriate volumes at 25 °C. Solvents were HPLC grade, and were dried when required using standard techniques.

Substrates

Imidoyl chlorides. In all cases substrates were synthesised from the corresponding amide and either thionyl chloride or phosphorus pentachloride, as appropriate.

From thionyl chloride. The corresponding amide was heated in an excess of thionyl chloride for 1 to 2 h. The excess thionyl chloride was distilled at reduced pressure to yield the required product. In some cases, excess heating resulted in isolation of the nitrile following a reverse Ritter reaction.

*N-Ethyl-p-nitrobenzimidoyl chloride (**1d**).* Yield: 97%; ν_{max} (KBr)/cm^{-1} 1670 (C=N), 1528 (NO_2, as stretch), 1349 (NO_2, s stretch); λ_{max} (dioxane)/nm 273 ($\varepsilon = 13500$); δ_H (270 MHz, $CDCl_3$; TMS) 1.36 (3H, t, $J = 7.33$ Hz, CH_3), 3.79 (2H, q, $J = 7.33$ Hz, CH_2), 8.17 (2H, d, $J = 9.16$ Hz, H3 & H5), 8.26 (2H, d $J = 9.16$ Hz, H2 & H6).

*N-Isopropyl-p-nitrobenzimidoyl chloride (**1e**).* Yield: 93%; ν_{max} (KBr)/cm^{-1} 1658 (C=N), 1514 (NO_2, as stretch), 1348 (NO_2, s stretch); λ_{max} (dioxane)/nm 273 ($\varepsilon = 12700$); δ_H (270 MHz, $CDCl_3$; TMS) 1.36 (3H, t, $J = 7.33$ Hz, CH_3), 3.79 (2H, q, $J = 7.33$ Hz, CH_2), 8.17 (2H, d, $J = 9.16$ Hz, H3 & H5), 8.26 (2H, d, $J = 9.16$ Hz, H2 & H6).

From phosphorus pentachloride. The amide was heated at reflux with a slight excess of phosphorus pentachloride in dry benzene. The reaction times were variable, but complete conversion was usually achieved after 24 h reflux. After the required length of time the benzene and phosphorus oxychloride were removed by distillation at reduced pressure. Purification was achieved by flash column chromatography using dry dichloromethane as an eluant.

*N-(2,2,2-Trifluoroethyl)benzimidoyl chloride (**1a**).* Bp 60–61 °C, 2 mmHg (Found: C, 49.58; H, 3.32; N, 6.39; F, 26.11; Cl, 16.21. $C_9H_7ClF_3N$ requires C, 48.78; H, 3.18; N, 6.39; F, 26.11; Cl, 16.21); ν_{max} (KBr)/cm^{-1} 1668 (C=N); λ_{max} (dioxane)/nm 246 ($\varepsilon = 14300$), 207 ($\varepsilon = 6100$); δ_H (270 MHz, $CDC1_3$; TMS) 4.15 (2H, q, $J = 9.3$ Hz, CH_2), 7.370–7.52 (3H, m, H3, H4 & H5), 8.06–8.01 (2H, m, H2 & H6); δ_C (68 MHz, $CDCl_3$) 55.11 (q, $J_{FC} = 33.3$Hz, CH_2), 128.52, 129.14, 130.52 (q, $J_{FC} = 276.2$ Hz,

CF_3), 132.27, 134.82 (C1), 148.27 (C=N); *m*/*z* 221 (M^+, 1%), 186 (100), 77 (62).

*N-[2,2,2-Trifluoro-1-(trifluoromethyl)ethyl]benzimidoyl chloride (**1b**).* Formed using the general procedure outlined above but using a 12 h reflux. The product was an oil, formed in 98% yield (Found: C, 40.75; H, 2.12; N, 4.88; F, 40.28; Cl, 11.97. $C_{10}H_6F_6ClN$ requires C, 41.47; H, 2.09; N, 4.48; F, 39.36; Cl, 12.24%); ν_{max} (KBr)/cm^{-1} 1654 (C=N); λ_{max} (dioxane)/nm 253 (ε = 40404); δ_H (270 MHz, $CDCl_3$; TMS) 5.12 (1H, septet, *J* = 6.2 Hz, CH), 7.54 (3H, m, H3, H4 & H5), 8.12 (2H, d, *J* = 8.6 Hz, H2 & H6); δ_C (68 MHz, $CDCl_3$) 67.34 (septet, J_{FC} = 31.2Hz, CH), 125.99 (q, J_{FC} = 284.8 Hz, CF_3), 128.76, 130.00, 133.45, 134.23 (C1), 154.94 (C-C1).

*N-(2,2,2-Trifluoroethyl)-p-nitrobenzimidoyl chloride (**1c**).* Bp 169–171 °C, 1.5 mmHg (Found: C, 40.38; H, 2.41; N, 10.36; F, 21.01; Cl, 13.62. $C_9H_6ClF_3N_2O_2$ requires C, 40.55; H, 2.27; N, 10.51; F, 21.38; Cl, 13.30%); ν_{max} (KBr)/cm^{-1} 1663 (C=N), 1526 (NO_2, as stretch), 1352 (NO_2, s stretch); λ_{max} (dioxane)/nm 266 (ε = 13600), 212 (ε = 8000); δ_H (270 MHz, $CDCl_3$; TMS) 4.22 (2H, q, *J* = 9.1 Hz, CH_2), 8.23 (2H, d, *J* = 9.1 Hz, H2 & H6), 8.30 (2H, d, *J* = 9.1 Hz, H3 & H5); δ_C (68 MHz, $CDCl_3$; $CDCl_3$) 55.38 (q, J_{FC} = 33.3 Hz, CH_2), 123.95 (1C, q, J_{FC} = 278.3 Hz, CF_3), 124.01 (C3 & C5), 128.47 (C2 & C6), 130.70 (C1), 139.94 (C=N), 149.55 (C4); *m*/*z* 266 (M^+, 3%), 231 (100), 185 (70), 102 (35), 76 (45).

*N-[2,2,2-Trifluoro-1-(trifluoromethyl)ethyl]-p-nitrobenzimidoyl chloride (**1f**).* The product was an oil; yield 97% (Found: C, 36.48; H, 1.59; N, 7.91; F, 34.6; C1, 11.06. $C_{10}H_5F_6C1N_2O_2$ requires C, 35.9; H, 1.49; N, 8.37; F, 34.08; Cl, 10.60%); ν_{max} (KBr)/cm^{-1} 1657 (C=N), 1529 (NO_2, as stretch), 1348 (NO_2, s stretch); λ_{max} (dioxane)/nm 269 (ε = 18500); δ_H (270 MHz, $CDC1_3$; TMS) 5.15 (1H, septet, *J* = 6.23 Hz, CH), 8.29 (2H, d, *J* = 8.4 Hz, H3 & H5), 8.35 (2H, d, *J* = 8.45 Hz, H2 & H6); δ_C (68 MHz, $CDCl_3$) 66.51 (septet, J_{FC} = 31.2 Hz, CH), 121.32 (q, J_{FC} = 282.6 Hz, CF_3), 128.44, 130.92, 139.21, (C1), 150.67 (C4), 153.26 (C=N).

Amides. Most of the amides were synthesised by treating the acid chloride with one equivalent of amine in dry ether, in the presence of one molar equivalent of dry triethylamine. Aqueous work up, using dichloromethane to solubilise the amide in some cases, yielded solids which were recrystallised from either ethanol or industrial methylated spirit (IMS). The bis(trifluoromethyl) substituted amides were prepared from the corresponding benzamide and hexafluoroacetone, as described at the end of this section.

N-(2,2,2-Trifluoroethyl)benzamide. Formed in 88% yield; mp 117–118 °C (lit.,[40] 115–116 °C) (Found: C, 53.29; H, 3.96; N, 6.84; F, 27.87. $C_9H_8F_3NO$ requires C, 53.21; H, 3.97; N, 6.89; F, 28.05%); ν_{max} (KBr)/cm^{-1} 3264 (NH), 1673 (C=O); λ_{max} (dioxane)/nm 227 (ε = 9800); δ_H (270 MHz, $CDC1_3$; TMS) 4.03 (2H, dq, *J* = 4.4, 9.1 Hz, CH_2), 7.37 (2H, dd, *J* = 7.7, 7.3 Hz, H3 & H5), 7.49 (1H, dd, *J* = 7.5, 7.3 Hz, H4), 7.81 (2H, d, *J* = 7.1 Hz, H2 & H6), 8.09 (1H, br t, NH); δ_C (68 MHz, $CDCl_3$) 40.83 (q, J_{FC} = 34.4 Hz, CH_2), 117.98, 122.10, 124.15 (q, J_{FC} 279.3 Hz, CF_3), 128.41, 131.95, 133.07 (C1), 168.55 (C=O); *m*/*z* 203 (M^+, 40%), 105 (100), 77 (43).

N-(2,2,2-Trifluoroethyl)-p-nitrobenzamide. Formed in 78% yield; mp 128–130 °C (Found: C, 43.59; H, 3.12; N, 11.18; F, 22.62. $C_9H_7F_3N_2O_3$ requires C, 43.56; H, 2.84; N, 11.29; F, 22.97%); ν_{max} (KBr)/cm^{-1} 3314 (NH), 1653 (C=O), 1525 (NO_2, as stretch), 1353 (NO_2, s stretch); λ_{max} (dioxane)/nm 262 (ε = 12200); δ_H (270 MHz, $CDC1_3$; TMS) 4.11 (2H, dq, *J* = 4.2, 9.1 Hz, CH_2), 8.04 (2H, d, *J* = 9.0 Hz, H2 & H6), 8.27 (2H, d, *J* = 8.8 Hz, H3 & H5), 8.46 (1H, br t, NH); δ_C (68 MHz, $CDCl_3$) 41.25 (q, J_{FC} = 35.0 Hz, CH_2), 124.28 (q, J_{FC} = 278.3 Hz, CF_3), 128.85 (C3 & C5), 139.07 (C1), 149.954 (C4), 166.86 (C=O); *m*/*z* 248 (M^+, 36%), 150 (100), 76 (20).

N-Ethyl-p-nitrobenzamide. Formed in 72% yield; mp 145–146 °C (Found: C, 55.28; H, 5.28; N, 14.26. $C_9H_{10}N_2O_3$ requires C, 55.69; H, 5.15; N, 14.43%); ν_{max} (KBr)/cm^{-1} 3273 (NH), 1638 (C=O), 1520 (NO_2, as stretch), 1345 (NO_2, s stretch); λ_{max} (dioxane)/nm 265 (ε = 11300); δ_H (270 MHz, $CDCl_3$; TMS) 1.28 (3H, t, *J* = 7.31 Hz, CH_3), 3.52 (2H, dq, *J* = 7.31, 5.68 Hz, CH_2), 6.44 (1H, br s, NH), 7.94 (2H, d, *J* = 8.98 Hz, H3 & H5), 8.27 (2H, d, *J* = 8.98 Hz, H2 & H6); δ_C (68 MHz, $CDCl_3$–CD_3COCD_3) 14.73 (CH_3), 35.31 (CH_2), 123.71, 128.81, 140.98 (C1), 149.68 (C4), 165.48 (C=O); *m*/*z* 194 (M^+, 38%), 150 (100), 104 (50), 76 (52).

N-Isopropyl-p-nitrobenzamide. Formed in 68% yield; mp 151–153 °C (Found: C, 57.54; H, 5.90; N, 13.49. $C_{10}H_{12}N_2O_3$ requires C, 57.69; H, 5.80; N, 13.46%); ν_{max} (KBr)/cm^{-1} 3302 (NH), 1637 (C=O), 1519 (NO_2, as stretch), 1348 (NO_2, s stretch); λ_{max} (dioxane)/nm 266 (ε = 11000); δ_H (270 MHz, $CDC1_3$; TMS) 1.28 (6H, d, *J* = 6.59 Hz, CH_3), 4.28 (1H, septet, *J* = 6.59 Hz, CH), 6.49 (1H, br s, NH), 7.94 (2H, d, *J* = 8.98 Hz, H3 & H5), 8.24 (2H, d, *J* = 8.98 Hz, H2 & H6); δ_C (68 MHz, $CDCl_3$–CD_3COCD_3) 22.54 (CH_3), 42.41 (CH), 123.61, 128.16, 140.56 (C1), 149.26 (C4), 164.79 (C=O); *m*/*z* 208 (M^+, 15%), 193 (15), 150 (40).

N-[2,2,2-Trifluoro-1-(trifluoromethyl)ethyl]benzamide. A solution of benzamide (2.4g, 0.02 mol) and a catalytic amount of dried toluene-*p*-sulfonic acid (0.2g, 1 mmol) in dry dichloromethane (100 ml) was sealed in a pressure reactor. The vessel was flushed with dry nitrogen for one hour then the hexafluoroacetone gas was added to a pressure of approximately 10 psi. The sealed reaction was stirred for 24 hours at room temperature by which time the pressure had dropped. The vessel was flushed through with nitrogen into water bubblers for 30 minutes before filtration, and the resulting yellow solution was washed with water, dried ($MgSO_4$) and the organic solvent was removed.

Pyridine (3.32 g, 3.4 ml, 1.0 mmol) and trifluoroacetic anhydride (4.40 g, 2.8 ml, 0.02 mol) were added simultaneously dropwise, over 30 min, to an ice-cold well stirred solution of the resulting solid (0.02 mol) in dry diethyl ether (30 ml). After another hour at 0 °C the mixture was filtered to remove a white precipitated solid.

Solid sodium borohydride (0.378 g, 0.01 mol) was added slowly to this solution, and the reaction mixture was stirred at room temperature for 48 h. After addition of ice, hydrochloric acid was added to bring the pH to approximately 4. The ethereal layer was separated, washed with brine, dried ($MgSO_4$) and the solvent removed. A flash column using chloroform as eluant resulted in the isolation of a white solid which was recrystallised from IMS. Yield, 3.95g (73%); mp 147–149 °C (lit.,[41] 149 °C) (Found: C, 44.23; H, 2.60; N, 5.13; F, 42.01. Calcd for $C_{10}H_7F_6NO$ C, 44.28; H, 2.58; N, 5.17; F, 42.07%); ν_{max} (KBr)/cm^{-1} 3280 (NH), 1663 (C=O); λ_{max} (dioxane)/nm 239 (ε = 3700); δ_H (270 MHz, $CDCl_3$; TMS) 5.62 (1H, d septet, *J* = 6.97, 3.29 Hz, CH), 6.57 (1H, br d, NH), 7.55 (3H, m, H3, H4 & H5), 7.83 (2H, d, *J* = 8.6 Hz, H2 & H6); δ_C (68 MHz, $CDCl_3$) 52.67 (qq, J_{FC} = 33.3 Hz, CH), 122.01 (q, J_{FC} = 282.6 Hz, CF_3), 127.67, 128.49, 132.53, 132.25 (C1), 168.55 (C=O); *m*/*z* 271 (M^+, 20%), 105 (100), 77 (60).

N-[2,2,2-Trifluoro-1-(trifluoromethyl)ethyl]-p-nitrobenzamide. The synthesis was carried out according to the above procedure, using *p*-nitrobenzamide in place of benzamide, yield 3.90 g (62%); mp 167–168 °C (Found: C, 38.07; H, 1.87; N, 8.41; F, 35.31. $C_{10}H_6N_2O_3F_6$ requires C, 38.01; H, 1.91; N, 8.87; F, 36.07%); ν_{max} (KBr)/cm^{-1} 3264 (NH), 1673 (C=O), 1541 (NO_2, as stretch), 1340 (NO_2, s stretch); λ_{max} (dioxane)/nm 258 (ε = 11800); δ_H (270 MHz, $CDCl_3$; TMS) 6.22 (1H, qq, *J* = 7.69 Hz, CH), 8.14 (2H, d, J = 8.98 Hz, H3 & H5), 8.35 (2H, d, *J* = 8.98 Hz, H2 & H6), 10.16 (1H, br d, *J* = 7.69 Hz, NH); δ_C (68 MHz, $CDCl_3$) 55.96 (qq, J_{FC} = 32.3 Hz, CH), 126.10 (q, J_{FC} = 278.3 Hz, CF_3), 132.21 (C1), 132.49 (C3 & C5), 136.19 (C2 & C6), 136.57 (C4), 171.76 (C=O); *m*/*z* 316 (M^+, 12%), 150 (100), 104 (32), 76 (35).

Trapped products. Triethylamine (0.21 g, 0.002 mol) was added to a solution of *N*-[2,2,2-trifluoro-1-(trifluoromethyl)-ethyl]benzimidoyl chloride (**1b**) (0.50 g, 0.0017 mol) and the dipolarophile (methyl acrylate, 6 mmol or *p*-nitrobenzaldehyde, 2 mmol) in dry benzene. The solution was heated under reflux for three days, followed by solvent removal and the product was subsequently purified by column chromatography.

*2-Phenyl-3- and -4-acetoxy-5,5-bis(trifluoromethyl)4,5-dihydro-1H-pyrrole (**14, 15**).* Formed as ~1 : 1 mixture; yield 0.35g (52%). **15**: δ_H (270 MHz, $CDCl_3$; TMS) 2.69 (1H, dd, $J_{bc} = 6.96$ Hz, $J_{ab} = 14.7$ Hz, CH), 2.85 (1H, dd, $J_{ac} = 10.08$ Hz, $J_{ab} = 14.7$ Hz, CH), 3.82 (3H, s, CH_3), 4.48 (1H, dd, $J_{bc} = 6.96$ Hz, $J_{ac} = 10.07$ Hz, CH), 7.50 (3H, m, H3, H4 & H5), 7.92 (2H, m, H2 & H6). **14**: J_{cb} (*anti*) 9.6 Hz, J_{ca} (*syn*) 14.5 Hz; J_{ab} (*gem*) 17.3 Hz.

*2-Phenyl-4,4-bis(trifluoromethyl)-5-p-nitrophenyl-4,5-dihydrooxazole (**16**).* Yield 0.35 g (52%); mp 118–119 °C (Found: C, 50.17; H, 2.50; N, 6.70; F, 27.82. $C_{17}H_{10}F_6N_2O_3$ requires C, 50.52; H, 2.47; N, 6.93; F, 28.20%); ν_{max} (KBr)/cm^{-1} 1645 (C=N), 1528 (NO_2, as stretch), 1351 (NO_2, s stretch); δ_H (270 MHz, $CDCl_3$; TMS) 6.12 (1H, s, CH), 7.61 (5H, m, aromatic), 8.13 (2H, d, $J = 8.8$ Hz, H3 & H5), 8.29 (2H, d, $J = 8.8$ Hz, H2 & H6); δ_C (68 MHz, $CDCl_3$–CD_3COCD_3) 82.25 (CH), 121.53 (q, $J_{FC} = 275.1$ Hz, CF_3), 123.74, 124.74 (C1′), 128.18, 128.93, 129.45, 133.83, 139.19 (C1), 148.51 (C4′), 170.09 (C=N); *m/z* 404 (M^+, 5%), 253 (100), 103 (45), 77 (50).

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