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Reactions between 1,1-Dicyano-2-phenylallyl Anion and Some Substituted Trifluoromethanesulfonates. Part 2. Kinetics and Mechanism†

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The reaction between 1,1-dicyano-2-phenylallyl anion (potassium salt) (**1**) and N^1,N^2,N^2-trimethyl-N^1-(2,2-dimethylpropionyl)amidinium triflate (**2a**) in acetonitrile was monitored by HPLC. The reaction between the salts was instantaneous, yielding a tetrahedral intermediate (**3a**) which decomposed within one minute at room temperature, apparently by a first order process, to give *N*-(4,4-dicyano-3-phenyl-1,3-butadienyl)-*N*,2,2-trimethylpropanamide (**5**) and dimethylamine (**6a**). Then, in a higher order process, **5** and **6a** react to give 2-(3-dimethylamino-1-phenyl-2-propenylidene)-1,3-propanedinitrile (**4a**) and *N*,2,2-trimethylpropanamide (**7**). When the mixture of the two salts (**1** and **2a**) was quenched (H_3O^+) immediately after mixing, **4a** and **7** were the only products. Owing to difficulties in purification and handling of salts **1** and **2**, the analytical results of the kinetic runs were considerably scattered. Therefore, the kinetic studies were concentrated on simulation of the latter step, thus the reaction of presynthezised **5** with diethylamine (**6b**) was used to establish the reaction order. Both conventional and pseudo-first-order kinetics lead to the conclusion that the reaction is of overall third order, first order in amide **5** and second order in diethylamine; the latter molecule adds nucleophilically to the amide to form the Michael adduct, the tetrahedral intermediate **3b**, and subsequently acts as a base in the β-elimination of the adduct.

Recently[1] we reported on the reaction between 1,1-dicyano-2-phenylallyl anion (**1**) with N^1,N^2,N^2-trimethyl-2,2-dimethylpropionylamidinium trifluoromethanesulfonate (**2a**) which resulted in the formation of 2-(3-dimethylamino-1-phenyl-2-propenylidene)-1,3-propanedinitrile (**4a**) and *N*-(4,4-dicyano-3-phenyl-1,3-butadienyl)-*N*,2,2-trimethylpropanamide (**5**) in good yields (Scheme 1).

It was suggested that a tetrahedral mechanism was involved with **3** as intermediate‡ and that competetive expulsion of the amido and the dimethylamino group took place. Since we observed that the product ratio **4**/**5** was time-dependent, we began kinetic studies to obtain some more information about the mechanism.

Facing great problems in establishing the reaction orders, we soon realized that secondary reactions might take place. Thus, it was discovered that amide **5** reacted with dimethylamine to give amine **4a**, and, in fact, this principle was used to prepare amine **4c** in good yields from **5** and pyrrolidine. This process is suggested to consist of a Michael addition to give the tetrahedral intermediate **3a** (observed by HPLC) which then decomposes to give the highly conjugated amine **4a** (Scheme 2).

Equimolar amounts of **1** and **2a** in acetonitrile were mixed, samples were withdrawn, quenched with aqueous hydrochloric acid and analyzed by HPLC. As stated earlier[1] no hydrolysis products of the starting materials **1** or **2a** were observed, indicating that the primary reaction to form the tetrahedral intermediate **3** has an extremely low activation energy. The only products observed, after acidic quenching necessary to perform the HPLC analyses, were the amine **4a** and the amide **5**, both having the *trans* configuration. Conformationally this is explicable as shown in Scheme 3 where rotamer **3B** definitely represents the higher energy state. Thus formation of *cis*-products is therefore highly unlikely.

A schematic plot of amine **4** concentration vs. time given in Fig. 1, indicates that the decomposition of the tetrahedral intermediate **3** in the presence of acid (used for quenching for analytical purposes) is somewhat complex.

† Part 1: Ref. 1. A preliminary report was given at 6th European Symposium on Organic Reactivity, Louvain-la-Neuve, Belgium, July 24–29, 1997.
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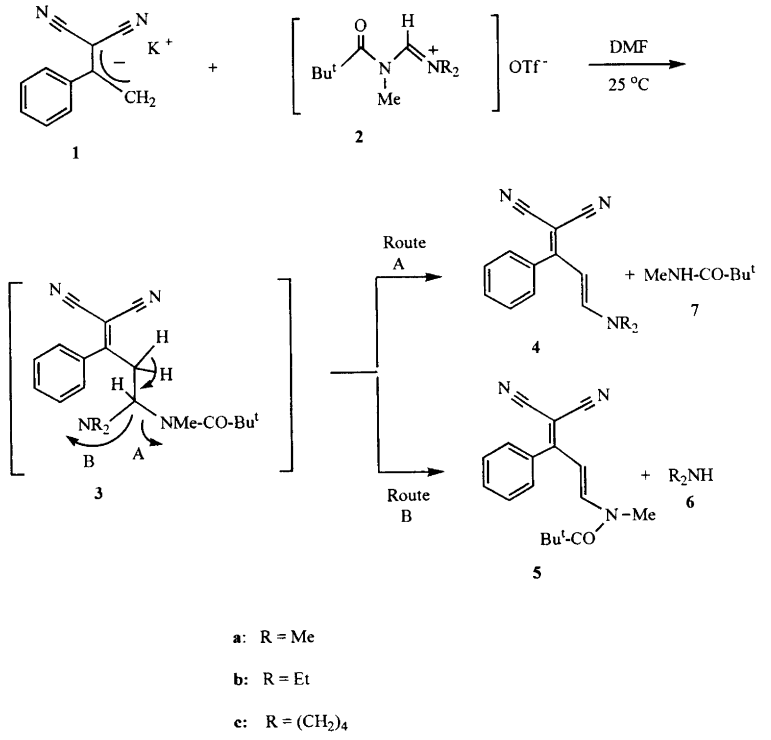
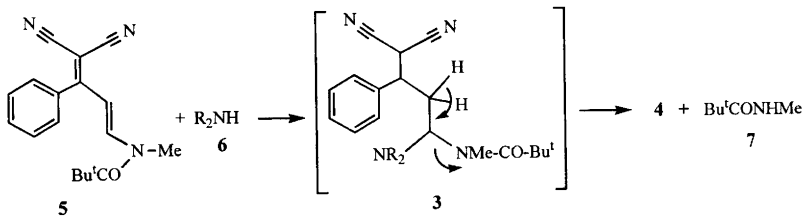
‡ A small, but short-lived peak was observed using normal-phase HPLC (CH_2Cl_2 elution).



Scheme 1.



Scheme 2.

In the very early stages of the reaction, the amine **4** concentration is very high, decreasing to a minimum after about one minute and then gradually increasing so that at the end only amine **4** is present. We interpret this as a fast first order decomposition of intermediate **3** to give amide **5** which in the next step reacts with dimethylamine (the elimination product of the fast decomposition) in a higher-order reaction (Scheme 4). Thus we are faced with a reaction under kinetic/thermodynamic control where the amide **5** is the kinetic and the amine **4** the thermodynamic product (Fig. 2).

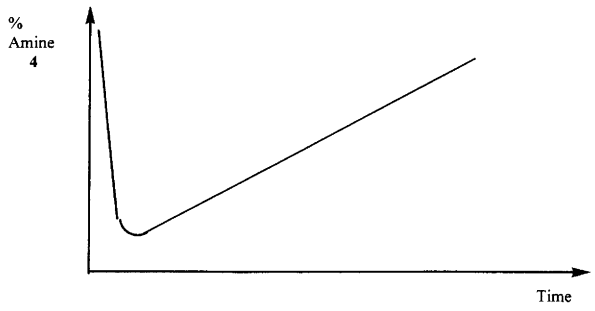
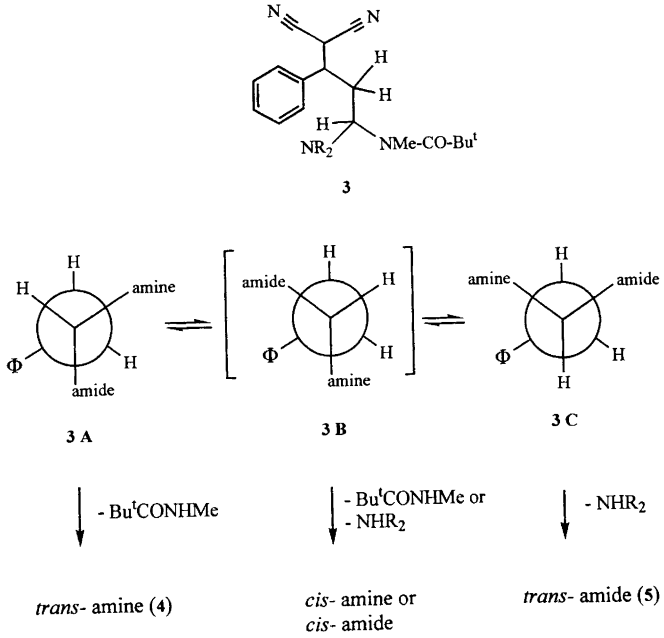


Fig. 1. Concentration of amine **4** as a result of the acidic quenching of analytical samples.

The observed high concentration of amine **4** in the early stages of the reaction must be the result of acidic decomposition of the intermediate **3**, a surprising result as one would expect that the amino nitrogen atom should be the more basic site in the intermediate **3**, thereby rendering this group the favored leaving group leading to amide **5**.

The point of protonation of amides has been a matter of controversy. However, NMR studies of solvent effects on rotation barriers in *N,N*-dimethylbenzamides indicate that increased polarity of the solvent gives higher barriers with the protic solvent water at the top.[2] This is attributed to hydrogen bonding involving the carbonyl oxygen atom increasing the contribution of resonance form **Y** (Fig. 3).

A similar conclusion was reached by observing the rotation barriers of *N,N*-dialkylamides in dibromomethane and tetrachloromethane, the higher barrier being observed in the weakly hydrogen bond-donor solvent

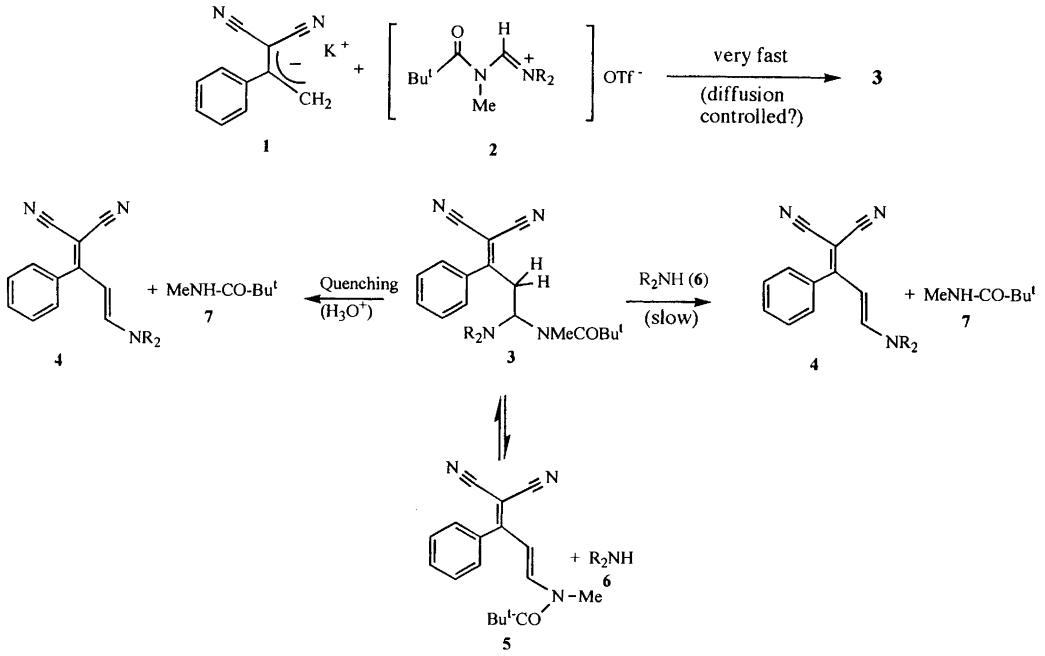


Scheme 3.

dibromomethane.[3] *Ab initio* quantum chemical calculations of the two possible protonated formamides gave a preference for the *O*-protonated species by about 60 kJ mol^{-1}.[4]

When the two alternative sites for protonation of **3** are considered the similarities between the tautomers are obvious for geometrical reasons [Fig. 4(a)]. Thus the transition state (b) for the elimination step can be described by two six-membered resonance structures, both of high symmetry. Since the amido group is considered to be the better leaving group, the observation that the amine **4** is the elimination product is reasonable for kinetic reasons.

Owing to the very fast decomposition of the tetrahedral intermediate **3a** it was difficult to get enough points to estimate firmly the reaction order, but there were strong indications of the expected first-order reaction leading to amide **5**. After about one minute, its concentration was at its maximum and a slow increase of the amine **4a**, the thermodynamic product, was observed (Fig. 1).



Scheme 4.

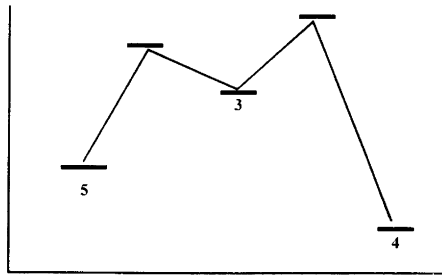
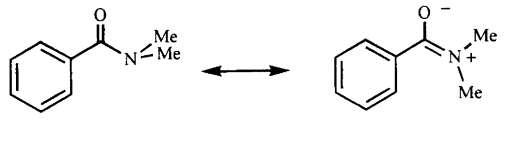


Fig. 2. Decomposition of tetrahedral intermediate **3** under kinetic/thermodynamic control.



X Y

Fig. 3. Resonance structures of *N,N*-dimethylbenzamide.

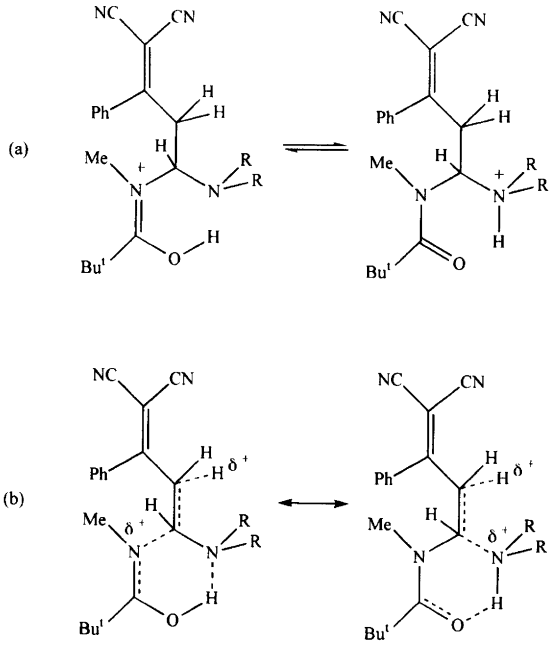


Fig. 4. Tautomers (a) of protonated tetrahedral intermediate **3** and (b) transition state resonance structures of protonated **3** in the elimination process.

The reacting salts **1** and **2** were very difficult to purify and handle, thus we decided to simulate this last step of the reaction between the allyl anion **1** and the amidinium ions **2** simply by studying the reaction between synthezised amide **5** and some dialkylamines, in particular diethylamine (Scheme 2). A possible reaction scheme is given in eqn. (1).

$$\mathbf{5} + \mathbf{6} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathbf{3} \xrightarrow{k_2} \mathbf{4} + \mathbf{7} \qquad (1)$$

Using a more practical notation (where A, B, C, D and E represent species **5**, **6**, **3**, **4** and **7**, respectively) this reaction scheme could be described by the differential rate equation (2)[5] obtained by steady-state approximation involving the tetrahedral intermediate **3**,

$$dx/dt = \{k_1 k_2/(k_{-1} + k_2)\}[A_0 - x][B_0 - x]$$
$$= k_{obs}[A_0 - x][B_0 - x] \qquad (2)$$

x being the fraction of starting material **5** reacted at time t. Using equimolar runs ($A_0 = B_0$), eqn. (2) is reduced to (2b):

$$dx/dt = k_{obs}[A_0 - x]^2 \qquad (2b)$$

and the integrated rate equation (3) becomes:

$$[x]/[A_0][A_0 - x] = k_{obs}t \qquad (3)$$

The second-order plot (Fig. 5) shows serious negative deviation from linearity from as early as 10% reaction. The most probable reason for this deviation is that amine **6** in addition to being a nucleophile in the primary Michael addition step forming the intermediate **3**, also acts as a base in the β-elimination step leading to the products **4** and **7**, adding an extra reaction scheme (4) for the decomposition of the tetrahedral intermediate **3**.

$$\mathbf{3} + \mathbf{6} \xrightarrow{k_3} \mathbf{4} + \mathbf{6}(H^+) + \mathbf{7}^- \qquad (4)$$

The position of equilibrium (5) will determine in what way one should accommodate the reaction scheme (4) in the total kinetic expression.

$$\underset{\mathbf{6}(H^+)}{Et_2NH_2^+} + \underset{\mathbf{7}^-}{Bu^tCON^-Me} \underset{}{\overset{K_{eq}}{\rightleftharpoons}} \underset{\mathbf{6}}{Et_2NH} + \underset{\mathbf{7}}{Bu^tCONHMe} \qquad (5)$$

Acid–base parameters are not available for **7**, but using acetamide ($pK_{HA} = 15.1$ in H_2O[6]) as a model compound and combining it with the pK_{BH^+} value for diethylamine (11.04 in H_2O[7]), a preference for the left hand side of equilibrium (5) would be $1.1 \times 10^4 : 1$ in aqueous solution. Even in acetonitrile solution one should expect that the equilibrium (5) is very much displaced towards the ionic forms, thus third-order kinetics should be the better expression (6):[8]

$$dx/dt = k_{obs}[A]_t[B]_t, \qquad (6)$$

where $[A]_t = [A_0 - x]$ and $[B]_t = [B_0 - 2x]$ with the integ-

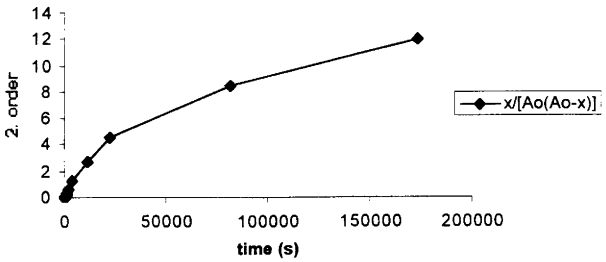


Fig. 5. Second order plot for the reaction of **5** with **6** according to eqn. (3).

rated form (7):

$$2x/(2[A]_0-[B]_0)([B]_0-2x)[B]_0+\{1/(2[A]_0-[B]_0)^2\}$$
$$\ln[A]_0([B]_0-2x)/([A]_0-x)[B]_0=k_{obs}t \quad (7)$$

Table 1 gives the experimental results using eqn. (7).

All third-order plots showed an upwards curvature trend, indicating that the actual reaction goes faster than could be accounted for by the kinetic expressions (6) and (7). Total compliance to third order conditions would require that virtually all the secondary amine **6** stays protonated througout the reaction, an assumption violating the principle of the acid/base equilibrium (5). Although the deprotonation of the diethylammonium ion must be considered to be very fast, the available concentration of the free amine must be low, but constant.

That the equimolar reaction (Table 1) does not go to completion within the observation time is probably a result of the low momentary concentration of free diethylamine at the end causing the Michael addition step to be extremely slow.

Instead of trying to include the equilibrium reaction (5) in the total kinetic expression, another approach was followed, i.e. the so-called isolation or pseudo-*n*th-order method,[9] using a large excess of one of the reaction components in eqn. (8).

$$d[D]/dt=k[A]^x[B]^y \quad (8)$$

Using a large excess of diethylamine **6b** (20–60 mol equiv.) the reactions followed straight pseudo-first-order plots, i.e. $x=1$ (Table 1). Rate equation (8) is then reduced to eqn. (9):

$$d[D]/dt=k_{obs}[A] \quad (9)$$

where

$$k_{obs}=k[B]^y \quad (10)$$

Table 1. Kinetic results for the reaction between amide **5** and diethylamine **6b** in acetonitrile.

Molar ratio **5**/**6b**	Linearity limit[a]	r^2 [b]	k_{obs} ($\times 10^3$)[c]	Conversion into product **4**
Third-order results, according to eqn. (7), at 15±0.5 °C				
1:1	21%	0.9932	3.0	76% (after 48 h)
1:2	24%	0.9988	2.8	100% (after 4 h)
1:3	30%	0.9924	7.2	100% (after 20 min)
Pseudo-first-order results, according to eqn. (9), at −30 ±0.5 °C				
1:20	98%	0.9934	0.19	100% (after 4.5 h)
1:50	96%	0.9958	1.04	100% (after 45 min)
1:60	96%	0.9892	1.72	100% (after 26 min)

[a]Limit of linearity with acceptable regression constant ($r^2 \geqslant 0.99$). [b]Regression constant. [c]$l^2\,mol^{-2}\,s^{-1}$ for third order reactions and s^{-1} for pseudo-first-order reactions.

Thus, one could use (10) to obtain both the overall rate constant k and the reaction order of **6** (y) simply by determination of k_{obs} as a function of the excess concentration of **6** [eqn. (11)].

$$\log k_{obs}=\log k+y\log[B] \quad (11)$$

Using the observed values for k_{obs} for different concentrations of **6** from Table 1, one obtains $\log k_{obs}=-2.314+1.96\log[B]$ ($r^2=0.9959$), leading to the conclusion that the reaction between amide **5** and diethylamine **6b** is of overall third order, first order in amide **5**, and second order in diethylamine **6b**, $d[D]/dt=k[A][B]^2$ with $k=4.85\times10^{-3}\,l^2\,mol^{-2}\,s^{-1}$ at −30 °C.

In conclusion, we feel that the results obtained for the model reaction can be used to give an accurate description of the kinetics for the reaction between the salts **1** and **2**, i.e. a very fast, perhaps diffusion-controlled, reaction to give intermediate **3** which decomposes by a fast first-order process to give amide **5** and alkylamine **6**, which then in the final step reacts by a third-order process similar to the model reaction to give final products, amine **4** and amide **7**. This final step must be slow and governed by the unfavorable position of equilibrium (5) keeping the available concentration of amine **6** low, but constant on the reaction timescale.

Experimental

General. Melting points are uncorrected. Infrared spectra were recorded on a Nicolet Magna 550 FTIR spectrometer using an attenuated total reflectance (ATR) ZnSe plate for solid samples. High resolution NMR spectra (^1H and ^{13}C) were recorded on Bruker Spectrospin Avance DPX 200 and DPX 300 spectrometers, ultraviolet spectra on a Shimadzu UV-260 spectrophotometer and mass spectra were obtained using a Fison Instrument VG ProSpec Q. HPLC analyses were carried out on a Perkin Elmer Series 2 liquid chromatograph using a C18 Supelco column, 25 cm, 4.6 mm, particle size 5 mm, pore size 5 Å. The UV detector was a Perkin Elmer LC 75 connected to a Hewlett–Packard HP-3396A Integrator.

All solvents used were dried according to literature recommendations.[10]

2-(3-Dimethylamino-1-phenyl-2-propenylidene)-1,3-propanedinitrile (**4a**) [m.p. 142–143 °C (acetone–pentane)] was prepared according to a literature procedure.[1]

2-(3-Diethylamino-1-phenyl-2-propenylidene)-1,3-propanedinitrile (**4b**) was prepared from 2-(1-phenylethylidene)-1,3-propanedinitrile and *N,N*-diethylformamide dimethylacetal in 52% yields.[11] M.p. 139.0–139.5 °C (2-propanol), lit. 139–141 °C.[12] X-ray single crystal data.[13] IR: ν_{max} 2201 (m), 1602 (s), 1502(m) cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.6–7.5 (3 H, m), 7.3–7.2 (2 H, m), 6.67 (1 H, d, *J* 12.5 Hz), 5.92 (1 H, d, *J* 12.5 Hz), 3.42 (2 H, q, *J* 7.1 Hz), 3.22 (2, q, *J* 7.1 Hz), 1.29 (3 H, t, *J* 7.1 Hz), 1.16 (3 H, t, *J* 7.1 Hz). ^{13}C NMR ($CDCl_3$): δ

171.8, 154.2, 134.8, 129.9, 128.7, 128.5, 116.8, 116.4, 97.6, 63.6, 51.2, 43.2, 14.4, 11.7. MS [EI, 70 eV: *m/z* (% rel int.)]: 251 (100, [M^+]), 236 (54, [$M-Me]^+$, 222 (4), 179 (26), 56 (48). UV [MeOH (log ε)]: λ 391 (4.71), 272 (3.84), 205 (4.15) nm.

2-(1-Phenyl-3-pyrrolidin-1-yl-2-propenylidene)-1,3-propanedinitrile (**4c**). To *N*-(4,4-dicyano-3-phenyl-1,3-butadienyl)-*N*,2,2-trimethylpropanamide (**5a**)[1] (0.5 g, 1.70 mmol) in acetonitrile (5 ml) was added pyrrolidine (0.133 g, 1.90 mmol). The reaction was stirred for 15 min after which acetonitrile was removed, the crude product dissolved in dichloromethane and filtered through a short SiO_2 column. Yellow crystals, 73%, m.p. 154–155 °C (chloroform–pentane), lit. 152.5–154.0 °C.[11] X-ray single crystal and spectroscopic data.[13]

N,N-*Diethylformamide dimethylacetal* was prepared according to literature procedures[14] from *N,N*-diethylformamide (10.10 g, 0.1 mol), dimethyl sulfate (12.60 g, 0.1 mol), sodium (2.30 g, 0.1 mol) and methanol (30 ml). The product (clear liquid) was obtained in 21% yield. B.p. 48 °C/23 mmHg. ^{1}H NMR ($CDCl_3$): δ 4.49 (1 H, s), 3.25 (6 H, s), 2.64 (4 H, q, *J* 7.2 Hz), 0.97 (6 H, t, *J* 7.2 Hz). ^{13}C NMR ($CDCl_3$): δ 112.3, 53.6, 40.5, 13.7.

N-*Methyl-2,2-dimethylpropionitrilium trifluoromethanesulfonate and* N^1,N^2,N^2-*trimethyl*-N^1-*2,2-dimethylpropionylamidinium trifluoromethanesulfonate* were prepared according to a literature procedure.[1]

N^1-*Methyl*-,N^2,N^2-*diethyl*-N^1-*2,2-dimethylpropionylamidinium trifluoromethanesulfonate* was prepared according to a literature procedure[15] and obtained in 93% yield (clear oil). IR: ν_{max} 1728 (m) and 1660 (s). ^{1}H NMR ($CDCl_3$): δ 8.42 (1 H, s), 3.8–3.6 (4 H, m), 3.48 (3 H, s), 1.4–1.3 (6 H, m), 1.30 (9 H, s). ^{13}C NMR ($CDCl_3$): δ 178.8, 158.8, 120.4 (q, *J* 340 Hz, CF_3), 52.6, 46.4, 41.4, 36.7, 27.8, 13.3, 12.4.

N^1-*Methyl*-,N^2,N^2-*tetramethylene*-N^1-*2,2-dimethylpropionylamidinium trifluoromethanesulfonate* was prepared in accordance with a literature procedure[15] and obtained in 94% yield (white crystals). IR: ν_{max} 1720 (m), 1673 (s) and 1550 (s) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 8.54 (1 H, s), 4.1–4.0 (2 H, m), 3.9–3.8 (2 H, m), 3.58 (3 H, s), 2.1–1.9 (4 H, m), 1.33 (9 H, s). ^{13}C NMR ($CDCl_3$): δ 178.5, 155.1, 120.4 (q, *J* 320 Hz, CF_3), 57.2, 51.8, 41.2, 35.7, 27.9, 25.4, 23.1.

Kinetics. Stock solutions of amide **5** and diethylamine (**6b**) in acetonitrile were prepared and stored at ambient temperature. From these solutions reaction solutions were made with concentrations 0.194 M (**5**)+0.194 M (**6b**) (1:1), 0.194 M (**5**)+0.388 M (**6b**) (1:2), 0.194 M (**5**)+0.582 M (**6b**) 1:3, 0.00948 M (**5**)+0.190 M (**6b**) (1:20), 0.00948 M (**5**)+0.475 M (**6b**) (1:50) and 0.00948 M (**5**)+0.570 M (**6b**) (1:60). Reaction temperatures, see Table 1. Samples (10 µl) were withdrawn (syringe), quenched with HCl–80% MeOH and analyzed by reversed-phase HPLC using 80% methanol as the eluting solvent at a rate of 1 ml min^{-1}. Retention times: Amine **4** 3.9 min, amide **5** 5.2 min, baseline separation). Rate constants were calculated using eqn. (7). Results in Table 1, averages from 2–4 experiments.

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