PERKIN 2

The Darbeau–White–Gibble reaction: an *N*-nitrosoamide-mediated Ritter-type reaction. Part I. A study of electronic, steric, and orbital effects in the nucleophile [1a]

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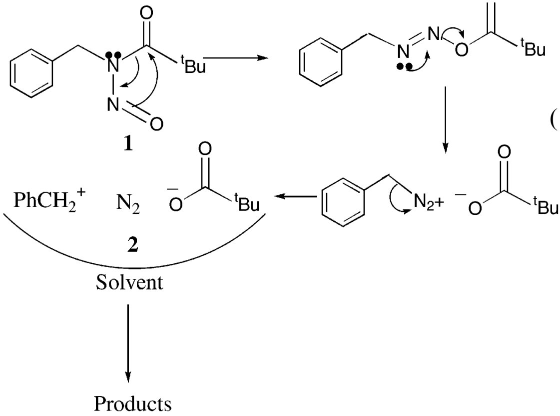
Benzyl cations were generated *via* thermal decomposition of *N*-benzyl-*N*-nitrosopivalamide in molten 4-R-substituted benzonitriles (R = NH_2, Me_2N, MeO, Me, H, F, and CF_3). In each case, the benzyl cation was intercepted competitively by pivalate ion to yield benzyl pivalate and by the benzonitriles to yield the corresponding *N*-4-R-benzonitrilium ion. The latter onium ions reacted with pivalate ion to form benzimidic anhydrides which rearranged to yield *N*-4-R-benzoyl-*N*-pivaloylbenzylamines (*i.e.* unsymmetrical diacylamines). The yield of diacylamines (maximum ~10.6% for R = H) is smaller than from the corresponding reactions in acetonitrile and varied systematically with the nature and location of the R group on the aromatic nucleus. Both electron-releasing and electron-withdrawing groups at the *para* position effected a diminution of the yield of diacylamine; indeed for R = NH_2, no diacylamine was formed. *ortho* Substitution of the aromatic nucleus resulted in significantly diminished yields of diacylamine, as did nucleophilic attack on the nitrilium ion by pivalate rather than acetate. Thus, both electronic and steric effects in nucleophilic attack on the nitrilium carbon were observed. The ratios of counterion-derived product to solvent-derived product for both the first-formed benzyl cation and the less reactive benzonitrilium ion are similar. This observation is interpreted in terms of the intermediacy of nitrogenous entity-separated ion-pairs in these deaminations.

Introduction

N-Benzyl-*N*-nitrosopivalamide (**1**, NBNNP) undergoes unimolecular[2] thermolysis to produce very short-lived nitrogenous entity-separated ion-pairs (NESIPs; **2**) containing the benzyl cation and pivalate ion initially separated by a nitrogen molecule [eqn. (1)].[1b,3] The carbenium ion of the NESIP is exceedingly reactive due, in part, to the low activation energy required for the loss of the nitrogen molecule from the alkanediazonium precursor, thus allowing the cation to be formed with minimal solvent participation.[1,3] Additionally, the temporary screening of the cation from its counterion by the sheer physical presence of the nitrogenous molecule results in the maximal positive charge at the electron-deficient center.[1b,3] When the cation, *e.g.* phenylcarbenium ion, is stable and devoid of β-hydrogens, S_N1-type reaction with the counterion and the solvent is its only fate. Cation–solvent reactions must occur before diffusion of the nitrogenous molecule from between the ions in the solvent cage as the latter process leads to internal collapse of the ion-pair to give the corresponding ester. Thus, the N_2 molecule is implicated in the partitioning of the carbocation between its nascent counterion and the medium; the longer the N_2 molecule remains in the pocket between the ions, the greater opportunity that is afforded the carbenium ion to interact with the medium.



(1)

Essentially then, the counterion and the solvent compete for the carbenium ion and the high speed of the carbenium–counterion reaction to yield an ester, limited by the rate of diffusion of N_2 into the medium, results in the carbenium ion having only a limited time to react with the medium before undergoing ion-pair collapse with the counterion.[3a,c,f] The yield of solvent-derived products (SDPs) increases with the reactivity of the cation, with the mole fraction and nucleophilicity of the active solvent, and in an inverse manner with the nucleophilicity of the counterion.[3a] The yield of SDP also generally rises, but to a lesser extent, with decreasing temperature[3a,g] and when the nitrogenous molecule is N_2O rather than N_2.[3a]

The reactions of the carbenium ion with nucleophiles may be irreversible if the products, *e.g.* carboxylate esters or alkylated aromatics, are stable under the reaction conditions.[3a] However, ionization of products from both solvent–carbenium ion (*e.g.* onium ions from phenylcarbenium ion–acetone reactions)[4a] and ion-pair collapse (*e.g.* labile benzyl esters, such as those formed when the counterion is triflate[1b,3b]) have been observed.

In a previous study, the utility of the deamination of *N*-nitrosoamides in nitriles as an alternative method of preparation of unsymmetrical diacylamines (DAAs) in modest yields was reported.[1b] In that study, **1** was allowed to decompose in

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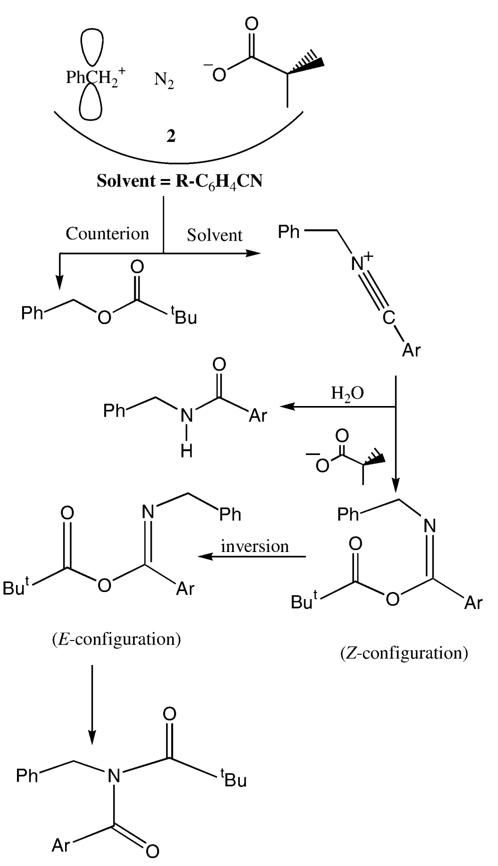
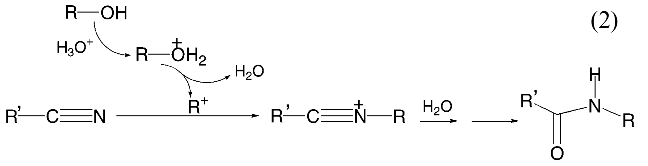
acetonitrile to form the corresponding ester as well as the *N*-benzylacetonitrilium ion. The onium ion was scavenged by pivalate to form the labile (*Z*)-ethanimidic anhydride, which isomerized by inversion through nitrogen into the (*E*)-diastereomer; rearrangement of the latter yielded *N*-acetyl-*N*-pivaloylbenzylamine (Scheme 1) in 23% yield.[1b]



Scheme 1 Reaction pathways for nitrogen-separated ion-pairs in benzonitriles.

This (Darbeau–White–Gibble) reaction may be considered as a variation of the Ritter reaction [eqn. (2)]. This version,



$$R'\text{—}C{\equiv}N \xrightarrow{R^+} R'\text{—}C{\equiv}\overset{+}{N}\text{—}R \xrightarrow{H_2O} R'C(=O)NHR \qquad (2)$$

however, differs from the traditional Ritter reaction in three ways; (1) the source of the carbocation is deamination rather than alcohol protolysis; (2) the principal scavenger of the nitrilium ion is the nascent counterion of the deaminative carbenium ion rather than water, and (3) the major product is a DAA rather than an amide. Since traditional methods of unsymmetrical DAA preparations are low yielding, require forcing conditions, and are otherwise flawed,[1b] the nitrosoamide-mediated Ritter-type reaction may represent a synthetically viable alternative route to this class of compounds.

In an effort to systematically examine this cascade of reactions, and to further delineate the mechanism of this reaction as well as the limitations of the methodology, the decomposition of **1** in substituted benzonitriles was investigated. The benzonitriles were chosen because appropriate substitution of the aromatic nucleus allowed methodical investigation of any electronic and/or steric effects operational in the reaction. Additionally, because the aromatic nucleus has a +R effect on groups involving a benzylic atom multiply bonded to one more electronegative than it (*e.g.*, carbonyl, iminyl, sulfonyl, *etc.*), we anticipated that the nucleophilicity of benzonitrile would be larger than that of acetonitrile and might thus result in larger yields of SDP.

N-Nitrosoamide **1** was again used as the source of the benzyl cation in this study because of its convenient rate of decomposition ($t_{1/2}$ ~30 min in PhCN at 25 °C) arising from steric acceleration of the rearrangement step [eqn. (1)] by the *tert*-butyl group.[2] Further, a more direct comparison of the present results in benzonitrile *versus* those obtained previously in acetonitrile[1b] could be made.

Results and discussion

Decomposition of *N*-benzyl-*N*-nitrosopivalamide (1) in 4-R-substituted benzonitriles

Compound **1** was allowed to decompose in the molten 4-R-benzonitriles; for R = NH_2 and Me_2N the decomposition temperature was 90 °C and for R = MeO, Me, H, F, CF_3, the reactions were run at 60 °C. Our preference would have been to carry out all of these decompositions at 25 °C because the companion study in acetonitrile was performed at that temperature.[1b]† Additionally, we had previously observed that nitrosoamide decomposition in equimolar benzene–toluene mixtures at elevated temperatures resulted in diminished yields of SDP.[3a,g]† Heating to 60 °C was necessary in the cases of R = MeO, Me, H, F, and CF_3 because it was the lowest common temperature at which those 4-R-benzonitriles were liquid ‡ § (at 760 Torr). Similarly 90 °C was the lowest temperature at which the *p*-amino- and *p*-dimethylaminobenzonitriles were molten. A previous study[4b] has shown that only (molten) solvents and the counterion in the solvent cage can effectively compete for the caged deaminatively generated carbenium ion, and as such the benzonitriles would all have to be in the liquid phase (*i.e.* solvent) to enter efficiently into bimolecular reaction with the carbenium ion. The product distribution was stable to prolonged exposure to 60 °C,§ but prolonged heating at 90 °C resulted in DAA decomposition. However, no appreciable decomposition occurs after heating of the product mixture at 90 °C for ~1 h, so data reported here were taken in this safe window after decomposition.

The product distribution as a function of the 4-R substituent (Table 1) was determined by ^1H NMR spectroscopy, looking specifically at the methylenic protons of the benzyl signals of the products. The mixed DAAs were identified based partially upon the established chemistry of the nitrile group in the presence of the deaminatively generated benzyl cations.[1b] Also their chemical shifts (δ 4.77–4.83) were in the same region as that of the (benzylic methylene) signal of *N*-acetyl-*N*-pivaloylbenzylamine (δ 4.82, prepared in a previous study[1b]). The benzyl-4-R-benzamides (δ 4.64–4.65) were identified in a similar fashion ($\delta_{\text{benzyl benzamide}} = 4.65$). The other products, benzyl pivalate (δ 5.10) and benzyl alcohol (δ 4.56) were identified from their chemical shifts and by spiking with authentic material.

The data (Table 1) show that as the 4-R-group is varied from CF_3, to MeO, to NH_2, the yield of mixed diacylamines rises from ~8 to ~11.0% and then falls again to 0%. There are three

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† The yields of DAA from decomposition of *N*-nitrosoamide, **1**, in acetonitrile at 25[1b] and 90 °C are indistinguishable at ~23%.[3g]

‡ The melting points of the 4-R-benzonitriles used in the present study are: R = NH_2 (mp = 83–85 °C); Me_2N (mp = 73–75 °C); MeO (mp = 57–59 °C); R = Me (mp = 26–28 °C); R = H (mp = −12 to −14 °C); R = CF_3 (mp = 39–41 °C); R = F (mp = 35–37 °C). Source: Aldrich Handbook of Fine Chemicals and Laboratory Equipment 2000–2001.

§ The product mixture (including benzyl pivalate) is stable under the current conditions as illustrated by the fact that a sample solution after total decomposition of **1** in benzonitrile at 60 °C was kept at 60 °C for 2 more days; no significant change in the product distribution was observed (*vide supra*).

Table 1 Product distribution [a] from the decomposition of *N*-benzyl-*N*-nitrosoamides [b] in 4-R-C_6H_4CN and *o*-toluonitrile at 60 °C

	Relative yield(%)					
		Solvent-derived products				
R	Ester	DAA	Benzylbenzamides	Benzyl alcohol	%SDP	% Benzamide of SDP
NBNNP Decomposition						
p-NH_2	100.0 [c]	0.0	0.0	0.0	0.0	0.0
p-Me_2N	90.1 [c]	8.7	1.2	0.0	10.1	12.9
p-MeO	86.1 [c]	11.0	2.8	0.1	13.8	20.3
p-Me	86.4 [c]	10.7	2.9	0.0	13.6	21.3
o-Me	85.9 [c]	0.1	14.0	0.0	14.1	99.3
H	84.5 [c]	10.6	4.9	0.0	15.1	32.5
p-F	88.9 [c]	9.8	1.3	0.0	11.1	11.7
p-CF_3	89.7 [c]	8.1	2.2	0.0	10.3	21.4
NBNNA Decomposition						
H	85.0 [d]	13.0	1.9	0.1	14.9	12.8

[a] Average of at least triplicate runs. Max std deviations: ester ~0.3; DAA ~0.2; amide ~0.3; alcohol ~0.2. [b] Concentration ~0.045 M. [c] Ester = benzyl pivalate. [d] Ester = benzyl acetate.

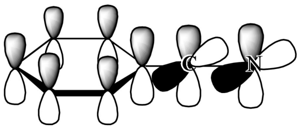

Fig. 1 A simple view of the orientation of the p-orbitals in the benzonitriles.

interesting aspects of this result: (1) the yields of DAAs are significantly smaller in the benzonitriles [even with powerful electron-withdrawing and electron-releasing groups (EWGs and ERGs, respectively) at the *para* position of the aromatic nucleus] than in the acetonitrile case where 23% mixed DAA was observed;[1b]† (2) the yield of mixed diacylamines is maximal for R = MeO (and approximates those for R = Me and H); and (3) in general, relative to R = H, both ERGs and EWGs effect a relative decrease in % DAA (Table 1). Thus, for the very strongly electron-releasing NH_2 group, no DAA is formed at all.

With respect to the first observation, the nitrilic N of the benzonitriles would be expected to be more nucleophilic than that of acetonitrile because of π-donation to it by the aromatic nucleus (although some hyperconjugation would be expected with acetonitrile). To the extent that this is true, the benzonitriles would intercept more of the phenylcarbenium ions than would acetonitrile. However, the phenyl group evidently effects a deactivation of the *N*-benzylbenzonitrilium ion with respect to nucleophilic attack. This deactivation, which is believed to possess both an electronic and a steric component (*vide infra*), ostensibly leads to lower yields of SDP including the mixed DAAs.

The electronic deactivation by the phenyl group probably arises from π-electron donation towards the positive nitrilium N (where the electron demand is higher than in the uncharged nitrile). This +R resonance effect minimizes the electrophilicity of the nitrilium carbon and makes it less prone to nucleophilic attack. Consequently a smaller yield of nitrilium ion-derived product (*i.e.* SDP) is formed, as observed.

With regard to the phenyl ring's steric deactivation of the nitrilium ion, the following argument is made. A simple view of the orientation of the p-orbitals in the benzonitriles (Fig. 1) reveals that in order for stabilizing conjugation to exist between the phenyl ring and the nitrile group, one of the p-orbitals on the nitrilium carbon (and by extension, a p-orbital on the nitrilium N) must be coplanar with the p-orbitals on the aromatic nucleus. Since the p-orbital on the nitrilium C that is coplanar with those on the aromatic nucleus is involved in bonding, it is essentially unavailable (or at least less available) than is the one orthogonal to it. Consequently, nucleophilic attack on the nitrilium carbon is obliged to occur perpendicular to the aromatic π-cloud and coplanar with the skeleton of the aromatic nucleus (Fig. 2). Indeed, molecular models indicate that the *ortho* protons are almost in the direct path of the incoming nucleophile (Fig. 2) thus mitigating against nucleophilic attack on the nitrilium ion and diminishing the yields of SDP.

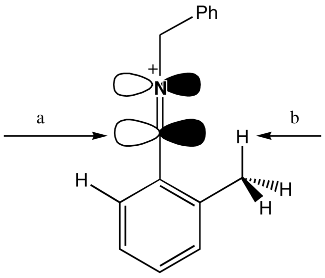

Fig. 2 Pathways for nucleophilic attack on the benzonitrilium ion.

A free energy correlation analysis of the data

The Yukawa–Tsuno equation is $\log(k_R/k_H) = \rho[\sigma_R + r(\sigma_R^+ - \sigma_R)]$ where *k*, *ρ* and *σ* have their usual meanings and *r* is a measure of the through-conjugation occurring in the system. When $r = 1$, as in the reference solvolysis of 2-aryl-2-chloropropanes, the relationship simplifies to the Hammett-type relationship: $\log(k_R/k_H) = \rho\sigma_R^+$. In the present case, since a cationic site is also generated in resonance with the aromatic nucleus, an *r* value of unity is assumed. Further if the Curtin–Hammett relationship applies, then the yields of the DAAs are assumed to be related to their rates of formations, hence the term '$\log[(\%DAA)_R/(\%DAA)_H]$' replaces '$\log(k_R/k_H)$'. A plot (Fig. 3) of our data using $\log[(\%DAA)_R/(\%DAA)_H]$ *vs.* the appropriate σ_p term[5a] (Table 2) for the series Me_2N to CF_3 yields a smooth binomial curve ($R^2 = 0.954$). In this plot, σ_p^+ values are used for R = Me_2N, MeO, and Me where through-conjugation would be expected to feature between the R-group and the nitrilium unit. However, σ_p values are employed for R = F and CF_3 since their effect on the reaction center is likely to be limited to induction in which case the more traditional Hammett equation: $\log(k_R/k_H) = \rho\sigma_p$, applies. For R = H, $\sigma_p = \sigma_p^+ = 0$, by definition.

Presumably, the resonance interaction between the aromatic nucleus and the α-nitrile group would be mediated by the electronic nature of the 4-R group. Thus, strong ERGs would enhance the electron density and hence the nucleophilicity of the nitrilic N. Consequently, the nucleophilicity of the nitriles

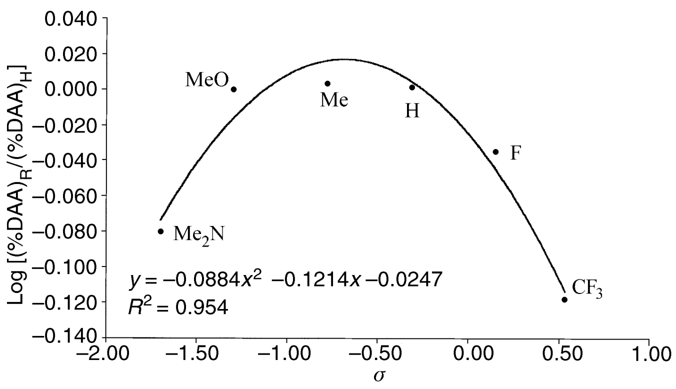

Fig. 3 Yukawa–Tsuno-type plot for the decomposition of *N*-benzyl-*N*-nitrosopivalamide in 4-R-benzonitriles. σ_p^+ and σ_p used for σ as appropriate.

Table 2 Free energy data from the decomposition of *N*-benzyl-*N*-nitrosoamide in 4-R-benzonitriles at 60 and 90 °C

R	%DAA	$(\%DAA)_R/(\%DAA)_H$	$\log[(\%DAA)_R/(\%DAA)_H]$	σ
NH_2	0.0	0.0		-1.3 [a]
Me_2N	8.8	0.80	-0.080	-1.7 [a]
MeO	11.0	1.01	0.003	-0.78 [a]
Me	10.7	1.00	0.002	-0.31 [a]
H	10.6	1.00	0.000	0.000
F	9.8	0.92	-0.035	0.15 [b]
CF_3	8.1	0.76	-0.120	0.53 [b]

[a] σ_p^+ used. [b] σ_p used.

would rise in the order CF_3 to Me_2N¶ with the former being least adept at capturing the benzyl cation and the latter being the most proficient at it. In short, both the rates of formation (and the yields) of the benzonitrilium ion would be greatest when R = Me_2N¶ and least when R = CF_3.

Diametrically opposed to the ERGs' electronic enhancement of the rates of formation and (hence) yields of the nitrilium ions, however, is their electronic deactivation of the nitrilium ions to nucleophilic attack. This would be so since the greater the flow of electron density to the nitrilium carbon, the more resistant it would be to nucleophilic attack and thus the smaller would be the yield of mixed diacylamine.

A similar argument can be constructed for the opposing effects of EWGs on the yields of DAAs. Hence, EWGs would diminish the nucleophilicity of the nitrile and reduce its ability to capture the benzyl cation. This effect would ostensibly lead to diminution of the %DAA. However, EWGs would subsequently increase the electrophilicity of the nitrilium ion and lead to an enhancement of the yield of DAA.

From the non-linearity of the Yukawa–Tsuno-type plot (Fig. 3), it would appear then that both of these opposing factors are significant, and are governed by similar activation energies. Thus, the non-linearity supports the reasonable assertion that the rate-determining step for DAA formation occurs after the comparatively fast ion–molecule (*i.e.* benzyl cation–benzonitrile) interactions and ion-pair (*i.e.* benzonitrilium ion–pivalate ion) combination so that both of these steps will affect the yields of DAA.

Since the maximal yield of DAA arises roughly for R = H (Table 1) it would suggest that both EWGs and ERGs reduce the yield of DAA. The former do so by reducing the ability of the starting nitrile to capture the cation and the latter by compromising nucleophilic attack on the nitrilium ion. Since both reactions evidently have similar activation energies, maximization of %DAA would require a group that does not abate either event, *i.e.* one that is neither electron-withdrawing nor releasing: H (as observed).

However, although the above argument is generally true, *i.e.* diminished yields of DAA are observed for EWGs and the ERGs Me_2N and NH_2 relative to H; no relative diminution is observed for the ERGs MeO and Me. The source of this inconsistency is unclear and is currently under further study.

Decomposition of *N*-benzyl-*N*-nitrosopivalamide in *o*-toluonitrile

To probe the veracity of the steric argument (*vide supra*), **1** was allowed to decompose in *o*-toluonitrile at 60 °C. The data (Table 1) show that the yield of mixed diacylamine was only 0.1%. This significant diminution in the DAA yield supports the belief that the nucleophile is obliged to attack in the plane of the aromatic nucleus and is therefore prone to steric hindrance by groups, *e.g.*, methyl, at the *ortho*-position. It is interesting that even though only one of the two electronically viable approaches to the nitrilium C is completely impeded, almost no attack from the other side occurs as evidenced by the low yield of DAA. Since only one of two faces is electronically deactivated (*vide supra*) then, from a purely statistical viewpoint, a 50% decrease in yield would have been expected. The virtual absence of DAA under these circumstances suggests that the methyl group may exert more than just steric hindrance of the approach of the nucleophile during its attack on the nitrilium ion. An electronic and/or enhanced (or "supersteric") effect may be involved.[4c] This issue is under further investigation.[4c]

Decomposition of *N*-benzyl-*N*-nitrosoacetamide in benzonitrile

As a further test of the steric argument, and to illustrate the sensitivity of the reaction to steric effects in the nucleophile, *N*-benzyl-*N*-nitrosoacetamide (NBNNA) was decomposed in benzonitrile at 60 °C. The nitrosoacetamide was chosen because the nucleophilic counterion it generates is acetate, which, although roughly as nucleophilic as pivalate [$n_{\text{acetate}} \approx n_{\text{pivalate}} = 4.3_{(\text{in MeOH})}$[5b]], is significantly smaller than the pivalate group (formed when **1** is decomposed). The data (Table 1) show that the yield of unsymmetrical DAA is 13% (*vs.* 10.6% when the counterion is pivalate). This 23% increase in the yield of mixed diacylamine is ostensibly due to diminished steric interactions between the acetate ion and the nitrilium carbon. Evidently, the carboxylate oxygens in their approach to the available lobe of the p-orbital of the nitrilium C must come sufficiently close to the *ortho* hydrogen for significant steric interaction between it and the alkyl groups (Me and ^{t}Bu).

The virtual absence of benzyl alcohol

Table 1 shows that the yield of the alcohol is essentially zero for all decompositions suggesting that the formation of alcohol is unaffected by the identity or position of the aromatic sub-

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¶ Although the σ_p^+ for Me_2N is larger than that for NH_2 the question of steric inhibition of resonance arises.[6] Thus, the Me_2N group may be less adept than NH_2 at pushing electron density to the nitrile/nitrilium system *via* the aromatic nucleus because interactions between the methyl groups and the *o*-protons ostensibly twist the lone pair of electrons on N out of plane with the aromatic ring.[6]

stituent or by the nature of the carboxylate. This observation suggests that the pathway leading to the formation of benzyl alcohol is essentially independent of that leading to SDPs and ester. Since the latter are produced from a common intermediate—the benzyl cation—it would appear that alcohol formation in this case does not involve capture of water by the benzyl cation since this reaction would be expected to be sensitive to the electrophilicity of the cation.

In previous studies, the formation of benzyl alcohol was attributed to hydrolyses of the labile *N*-nitrosoamides rather than water-interception of transient intermediates along the reaction pathway (*e.g.* benzyl cations, *etc.*).[1b,4a] The low mole fraction of water in the medium minimizes the likelihood of significant benzyl cation–water reaction.[1b,3a,4a]

The yield of benzyl pivalate

To the extent that the nucleophilicities of the benzonitriles rise through the series R = CF_3 to R = Me_2N,¶ the number of first-formed phenylcarbenium ions that are intercepted by the nitrile should also rise in that order. Since formation of ester and benzonitrilium ion are competitive events, if the benzonitrilium ions were formed irreversibly, then the yield of ester would be expected to fall markedly in the series R = CF_3 to R = Me_2N.¶ The fact that this is not observed (Table 1) suggests that the formation of the nitrilium ion is a reversible process.

The first-generation phenylcarbenium ion formed by deamination of **1** must be reversibly intercepting the nitrile to form the nitrilium ion. The latter is scavenged by the counterion and by water but also dissociates to re-form a benzyl cation–solvent ion-pair. The carbenium ion in this latter ion–solvent pair would be more complexed than is the first-generation species because of greater exposure to both solvent and counterion as the nitrogen departure progresses. Consequently, this generation of benzyl cation would be expected to be less reactive than the first-formed species.[4a]

The yields of *N*-benzylbenzamides

The *N*-benzylbenzamides are believed to arise from scavenging of the *N*-benzylnitrilium ions by adventitious moisture present in the hygroscopic nitriles (Scheme 1).‖ The benzamides, which are also considered to be SDPs because they are derived from the nitrilium intermediates, vary significantly in yield with both the identity and position of the substituent on the aromatic nucleus (Table 1). Interestingly, when a methyl group is present at the *o*-position, the relative yield of the benzylbenzamide (with respect to SDPs) is >99%. This result is consistent with the presence of much larger steric hindrance to nucleophilic attack at the nitrilium C in the *o*-toluonitrilium species. Consequently, small nucleophiles like water are more adept at intercepting the ion than their bulkier competitor—pivalate.

Interestingly, however, if only the SDPs are considered, then, with the exception of the case when the substituent is *o*-Me, the relative yield of the benzamides from the substituted benzonitriles is roughly the same [*e.g.* 21.3% (R = *p*-Me), 21.4% (R = CF_3), 20.3% (R = *p*-MeO); Table 1]. This observation suggests that roughly 20% of the *N*-benzylnitrilium ions (without *o*-substitution) are intercepted by moisture leading to amide formation‖** (Scheme 1). Evidently, (1) the nitrilium ions possess no significantly greater liberty to "choose" their nucleophiles than the phenylcarbenium ions that spawned them because the latter yield ~87% product from reaction with the counterion while the former yield ~80% product from the same species (Table 1). (2) This result suggests that the highly reactive benzyl cations are more selective than their derivative benzonitrilium ions despite the fact that the latter would be more stable by at least the energy of the C–N σ-bond and significant ion–dipole stabilization by the now proximal solvent molecules.

Table 3 Product distributions [a] from ion-pair collapse and solvent interaction for benzyl cations and benzonitrilium ions from the decomposition of *N*-benzyl-*N*-nitrosoamides in 4-R-C_6H_4CN at 60 °C

Cation	Relative yield(%) Ion-pair collapse	Solvent-derived product
Benzyl	87 [b]	13 [b]
Nitrilium	~80 [c]	~20 [c]

[a] Averaged data from Table 1; *o*-toluonitrile data were excluded.[b] Std dev. ~1.1.[c] Std.dev. ~1.2.

It may be that the nascent counterion of the carbenium ion has a positional advantage over the medium for scavenging the carbenium ion. However, once the carbenium ion reacts with solvent, the resulting nitrilium ion evidently remains in the original cage and still has an opportunity to interact with adventitious moisture.

It would appear though that the counterion is still favored over water by this second-generation electrophile probably because (1) it is still close to the newly formed nitrilium ion and is coulombically drawn to the latter after the rapid departure of N_2 from between the initial ion-pair and (2) by the time the nitrilium ion forms, N_2 diffusion would have progressed appreciably to begin exposing the new nitrilium ion to the counterion for ion-pair collapse to the imidic anhydride.

Stereoelectronic effects in partitioning of deaminatively generated nitrilium ions

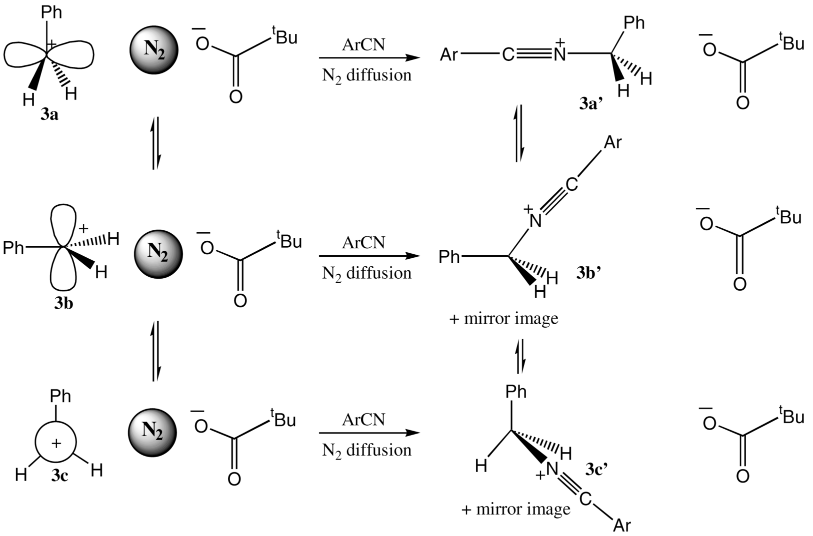
Two issues, however, remain to be addressed: (1) why is there such a similarity between the relative yields (Table 3) from ion-pair collapse *vs.* reaction with solvent for both the highly reactive benzyl cation (for which the solvent is ArCN + trace H_2O) and the less reactive benzonitrilium ion (for which the solvent is functionally trace H_2O)? Additionally, (2) why are the yields of DAA significantly smaller in the benzonitrile series than with acetonitrile, even though electronic effects appear to favor the former?

It cannot be reasonably argued that a similarity exists between the reactivities of the deaminatively generated benzyl cation and its product from ion–molecule reaction—the benzonitrilium ion (*vide supra*). If the reactivities are so disparate why does DAA not form essentially exclusively from the more selective nitrilium ion, in the solvent cage with the counterion? How do trace water molecules have the chance to interact with the nitrilium ion prior to ion-collapse?

Consider Scheme 2 in which the orientations of the benzyl cations formed from dediazoniation of the benzenediazonium ion are shown. The cations are drawn to show their spectrum of positions relative to the pivalate ion. Of the positions of the rapidly rotating benzyl cations, the only one that can lead directly to the ester is **3a** in which a lobe of the p-orbital is oriented directly at pivalate. Structures **3b** and **3c** after rotation to **3a** (about the *z*- and *y*-axes, respectively) may also lead to the ester. However, all of these species can lead to nitrilium ion (even **3a** as long as the N_2 molecule shields it from pivalate) and on nitrilium ion formation, from **3a**, two hurdles to DAA formation arise. (1) The reaction site for DAA formation is now significantly removed from the necessary nucleophile pivalate:

‖ *N*-Benzylacetamide is formed in similar fashion from nucleophilic attack by water on the acetonitrilium ion when NBNNP is decomposed in acetonitrile–water mixtures.[1b]

** There is the possibility of an S_N reaction between the pivalate and the benzyl carbon of species **3a′** to form an ester. This route to ester formation evidently does not significantly enhance the yield of ester probably because the reaction is S_N1 and the tight ion-pair formed is in equilibrium with **3a′**. The existence of the steady-state population of **3a′** and the ion-pair then will not appreciably affect the product distribution, as is observed.



Scheme 2 Orientations of benzyl cations and their nitrilium ions relative to pivalate ions in the solvent cage.

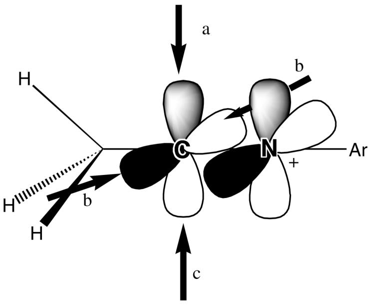


Fig. 4 Pathways of approach of pivalate to the nitrilium C. Pathways "a" and "c" are very facile; pathways "b" are at a dihedral angle of ~60 ° from the H atoms roughly in their approach.

not only is it several bonds away, it is now on the opposite face of the organic cation†† (2) The nitrilium ion is at least 124% heavier that the antecedent benzyl cation‡‡ and thus translates and rotates much more slowly.

The stereoelectronic requirement for DAA formation would involve translation/rotation of the ions relative to each other such that the pivalate ion effectively travels to the other face of the nitrilium ion to attack the electron-deficient, sp-hybridized carbon. This process must extend beyond the lifetime of the NESIP (*i.e.* N_2 diffusion is likely to be complete before nitrilium ion–pivalate ion collapse) because NESIPs do not even survive long enough to allow complete scrambling of stereochemistry from chiral nitrosoamides through cation rotation,[3c] or scrambling of carboxylate oxygens.[3c] Thus even after N_2 diffusion, the nitrilium ion–pivalate reaction to DAA is delayed by steric difficulties.

The nitrilium ion, therefore, having only two "predators" (pivalate and H_2O) is afforded significant opportunity to react with water even though the latter is only modestly nucleophilic and present in trace amounts. Thus the yield of amide (SDP with respect to the nitrilium ion) is larger than what would have been predicted based upon the electrophilicity of the onium ion, the low nucleophilicity and mole fraction of water in the medium. It is important to appreciate that although there are five options for benzyl cation interactions with solvent [left lobe (of the p-orbital) of **3a**, top and bottom lobes of **3b** and front and back lobes of **3c**] there is only one option for ion-collapse (right lobe of **3a**). Further, the only species capable of forming ester can be diverted into SDP.

The low mobility of the benzonitrilium ion and the inherent difficulty in orienting groups for reaction to DAA would also explain the relatively low yield of DAA in the benzonitrile series. Even for benzonitrile, *i.e.* when 4-R = H, however, the onium ion is 73% more massive than that in the acetonitrile case. As a result, the acetonitrilium ions are ostensibly more agile than are the benzonitrilium ions and are thus capable of meeting the stereoelectronic requirement for DAA formation much faster than the benzonitrile cases. This greater mobility would lead to the observed larger yields of DAA from ion-pair collapse.

Since resonance interactions are absent between the CH_3 and CN groups in acetonitrile (except for some hyperconjugation), the pivalate ion would ostensibly be free to attack either one of four lobes of the p-orbitals on the nitrilium C (*vs.* only two in the benzonitrilium ion; Figs. 1, 4). Further, because the methyl hydrogens in the acetonitrilium ion do not impose the same steric restrictions on the bonding approach of pivalate ion, ion-collapse is more favored in tight acetonitrilium–pivalate ion-pairs than in the corresponding benzonitrilium ion case. Consequently, the yield of DAA is larger from deaminations in acetonitrile than in benzonitrile, as observed.

Summary

The formation of mixed diacylamines from deamination of nitrosoamides in nitriles (the Darbeau–White–Gibble reaction) appears to be a general phenomenon extendable beyond the simple aliphatic cases.[1b] The yield of diacylamines is sensitive to electronic and steric effects as well as to orbital considerations in the nitrile. In general, electron-releasing groups enhance the nucleophilicity of the nitrile N, facilitating capture of the benzyl cation; however, they exert a yield decreasing effect by diminishing the electrophilicity of the sp-hybridized C of the nitrilium adduct. Conversely, EWGs diminish the yield of the nitrilium intermediate by reducing the nucleophilicity of the N, but subsequently make the nitrilium ion more electrophilic. The interplay of these opposing effects results in curvature of the Yukawa–Tsuno plot (Fig. 3). The plot has a maximum at approximately R = H since this group does not abate the kinetics of either the nitrile–benzyl cation, or the nitrilium–carboxylate reactions. The *ortho*-methyl group dramatically diminishes the yield of DAA in a fashion that cannot be reasonably accounted for only by steric hindrance to the approach of the nucleophile.

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†† The mass of the benzyl cation is 91 whereas the mass of the *N*-benzylbenzonitrilium ion is 204; a 124% enhancement in mass even with 4-R = H.

‡‡ The relative yield of amide varies from ~12% (R = F) to ~33% (R = H) (Table 1); the mean, mode and median values are all ~20%.

Interestingly, the yields of products from solvent interception relative to those from ion-collapse are similar from both the highly reactive first-formed benzyl cation and the significantly less reactive benzonitrilium ion. This observation suggests that the deaminatively generated carbenium ions on reaction with solvent molecules form onium ions that reside inside the original solvent cage. Because the reaction site on the nitrilium ion is now distal and is on the other face relative to the counterion, there is a significant pause in effecting reaction between the carboxylate ion and the nitrilium C. During this delay the nitrilium ions are appreciably scavenged by even trace species of low nucleophilicity such as water. The duration of the interlude prior to ion-pair collapse is mediated by the mass of the nitrilium ion and of the counterion: the larger these species, the longer is the delay and the larger is the yield of solvent-derived product. These observations are consistent with the model of nitrogenous entity-separated ion-pairs in deamination.

Experimental

Materials and methods

All commercial reagents were reagent grade and were used without further purification. Chemical shifts in the ^{1}H NMR spectra are reported in ppm downfield from internal tetramethylsilane. Spectra were recorded on JEOL Eclipse$^+$ 300 MHz FT-NMR, Perkin Elmer 1600 Series FT-IR, and Beckman Model 25 UV–Vis Spectrometers.

Stability of *N*-benzyl-*N*-nitrosopivalamide; handling and storage

N-Benzyl-*N*-nitrosopivalamide is thermolabile and was stored under N_2 in capped tubes immersed in liquid nitrogen. It is labile in the presence of acids, bases, and moisture; being photolabile it was handled in the dark. **Caution!** Nitrosoamides should be handled with extreme care because of their possible mutagenicity[7a] and carcinogenicity (local and systemic).[7b] Efficient fume hoods and appropriate personal protection (chemical-resistant gloves, safety glasses, lab coat, *etc.*) are recommended when handling these compounds.

***N*-Benzylpivalamide.** *N*-Benzylpivalamide was prepared by the method of Heyns and von Bebenburg;[8a] mp (ether–hexane) 81–82 °C (lit.[8b] mp 81–82 °C); IR (KBr) ν_{max}/cm−^{1} 3309 (NH), 1689 (C=O), 1375 (^{t}Bu); ^{1}H NMR ($CDCl_3$) δ 1.27 (9H, s, ^{t}Bu), 4.44 (2H, d, $J = 7$ Hz, CH_2), 5.90 (1H, br s, NH), 7.26–7.32 (5H, m, Ph); UV λ_{max} (Et_2O)/nm 284 (ε/dm^3 mol^{-1} cm^{-1} 209).

***N*-Benzyl-*N*-nitrosopivalamide (1).** Compound **1** was prepared by the method described in ref. 1*b*. IR (Neat) ν_{max}/cm^{-1} 1720 (C=O), 1605 (N=O), 1375 (^{t}Bu); ^{1}H NMR (CD_3CN) δ 1.45 (9H, s, ^{t}Bu), 4.97 (2H, s, CH_2), 7.05–7.40 (5H, m, Ph); UV λ_{max} (CH_2Cl_2)/nm 275, 400, and 394sh (ε/dm^3 mol^{-1} cm^{-1} 500, 63, 66).

Decomposition of nitrosoamide (1)

In a typical run, ~75 µl of **1** were added to 750 mg of the appropriate nitrile in an Opticlear™ vial. The sample was then placed in an oven at 60 °C for 1 h (~12 half-lives). The sample was taken out of the oven and 200 µl were removed and added to 400 µl of $CDCl_3$ in an NMR tube and NMR spectra were recorded. The products observed were benzyl pivalate (δ 5.10), *N*-aryl-*N*-pivaloylbenzylamine (~δ 4.82), benzyl-4-R-benzamides (δ 4.65), and benzyl alcohol (δ 4.56). The methyl signals of the pivaloyl groups of the compounds in this study are indistinguishable from each other.

Proof of thermal stability of product mixture

At 60 °C. The product mixture from a decomposition of **1** in benzonitrile (R = H) at 60 °C was analyzed and the distribution was found to be ester 84.6, DAA 10.4, benzamide 5.0, benzyl alcohol 0.0%. The mixture was heated at 60 °C for 48 h and then reanalyzed: ester 84.3, DAA 10.1, benzamide 5.0, benzyl alcohol 0.6%. This result indicates that the product distribution is statistically unchanged on prolonged heating and that the product mixture is stable at 60 °C. Trace benzyl alcohol present after heating ostensibly arises from hydrolysis of the ester and diacylamine.

At 90 °C. The product mixture from a 40 min (~12 half-lives) decomposition of **1** in 4-dimethylaminobenzonitrile was analyzed by ^{1}H NMR spectroscopy and its composition was found to be ester 90.1, DAA 8.7, benzyl alcohol 1.2%. The sample was heated at 90 °C and its composition was determined at 20 min intervals. No significant change was observed until $t = 100$ min: ester 89.0, DAA = 8.4, benzyl alcohol = 1.5%. The extra benzyl alcohol ostensibly arises from hydrolysis (*vide supra*).

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