Conclusions

Since the rates of nitrogen inversion in hydroxylamines and their conjugate bases are the same, we conclude that the effect of increased lone-pair repulsion of $-O^-$ is equal to the σ-inductive effect of its reduced electronegativity. These two effects happen to cancel nearly exactly, so that there is no net effect. This cancellation represents a challenge to MO calculations. It is no surprise that these two effects had not previously been separated, since both do contribute and neither can be ignored.

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Improved Methods for the N-Nitration of Amides

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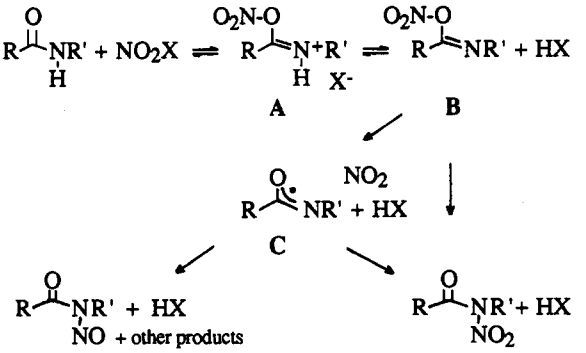
The reactivity of several nitrating mixtures with amides has been compared. Ammonium nitrate/trifluoroacetic anhydride, morpholinium nitrate/trifluoroacetic anhydride, and morpholinium nitrate/heptafluorobutyric anhydride are the reagents of choice since, in CH_2Cl_2 at 0 °C, they give *N*-alkyl-*N*-nitrocarboxamides and *N*-nitrolactams in excellent yields. Mechanistic details of these nitrations have been elucidated. Trifluoroacetyl nitrate, which arises from the reaction $R_2NH_2^+NO_3^- + 2(CF_3CO)_2O \rightarrow CF_3COONO_2 + CF_3CONR_2 + 2CF_3COOH$, appears to cause the direct N-nitration of carboxamides.

Introduction

During the past recent years, our group has been taking advantage of the enhanced reactivity of *N*-alkyl-*N*-nitrosoamides and *N*-alkyl-*N*-nitroamides (henceforward called nitrosoamides and nitroamides) with different nucleophiles, to convert RCONHR′ into RCONHR″, RCOSR″, $RCON_3$, etc. under mild conditions.[1] The amide activation by means of the NO_2 group seemed preferable since nitroamides react much more rapidly with nucleophiles than nitrosoamides and, in general, turn out to be more stable thermally.[2] However, nitroamides show an important shortcoming: their preparation usually requires acidic media and long reaction times and proceeds in variable yields. In fact, under classical nitration conditions (HNO_3/Ac_2O),[3] many simple aliphatic amides and lactams are nitrated only in 40–80% yields. When the substrates contain hindered amide groups, their nitration cannot be carried out successfully; in addition, attempts to nitrate these substrates under either more vigorous or different reaction conditions have been reported to give variable amounts of nitrosoamides[4] besides poor yields of nitroamides. In other words, N-nitration of most amides is an unsolved problem that deserves further attention.

Scheme I



The appearance of three interesting communications[5-7] related to the subject has prompted us to summarize results which we have obtained during the past recent years. Suri and Chapman[5] have reported that 2-pyrrolidinone can be N-nitrated in 30% yield[8] in nitromethane with a mixture of NH_4NO_3 and TFAA, a procedure developed by Crivello to nitrate aromatic compounds at rt.[9] Carvalho et al. have shown that imidoyl nitrates, prepared from imidoyl chlorides and silver nitrate, rearrange to nitroamides by an intramolecular mechanism involving likely the homolytic cleavage of the O–NO_2 bond,[6] and more recently that a mixture of $Bu_4N^+NO_3^-$ and TFAA in

(1) (a) Garcia, J.; Vilarrasa, J. *Tetrahedron Lett.* **1982**, *23*, 1127. (b) Garcia, J.; González, J.; Segura, R.; Urpí, F.; Vilarrasa, J. *J. Org. Chem.* **1984**, *49*, 3322. (c) Garcia, J.; González, J.; Segura, R.; Vilarrasa, J. *Tetrahedron* **1984**, *16*, 3121. (d) Torra, N.; Urpí, F.; Vilarrasa, J. *Tetrahedron* **1989**, *45*, 863. (e) Berenguer, R.; Garcia, J.; Vilarrasa, J. *Synthesis* **1989**, 305. (f) For a related work, see: Romea, P., Urpí, F.; Vilarrasa, J. *J. Org. Chem.* **1989**, *54*, 3209.

(2) White, E. H.; Grisley, D. W. *J. Am. Chem. Soc.* **1961**, *83*, 1191.

(3) Campbell, R.; Peterson, C. J. *J. Org. Chem.* **1963**, *28*, 2294 and references cited therein.

(4) (a) In some cases, this may be attributed to the decomposition of the nitrating agent in the reaction medium to give lower nitrogen oxides (see refs 2 and 1b), which may mainly occur when the nitration is too slow. In other cases, the cause may be the presence of impurities in the reagent; for example, it has been proved that some commercial samples of NO_2BF_4 contain significant percentages of $NOBF_4$: Elsenbaumer, R. L. *J. Org. Chem.* **1988**, *53*, 437. (b) Nitration of ureas by different reagents also leads to nitrosoureas as major products (and to the cleavage of the CO–N bond). See: White, E. H.; Ryan, T. J.; Hahn, B. S., Erickson, R. H. *J. Org. Chem.* **1984**, *49*, 4860 and refs 14–16 therein. (c) Imidoyl nitrates may give nitrosoamides as well. See: Carvalho, E.; Norberto, F.; Rosa, E.; Iley, J.; Patel, P. *J. Chem. Res., Synop.* **1985**, 132. According to these authors, the most appropriate conditions to avoid nitrosoamides as byproducts are the use of dilute solutions, low temperatures, and exclusion of light.

(5) Suri, S. C.; Chapman, R. D. *Synthesis* **1988**, 743. (The nitration of 2-pyrrolidinone with HNO_3/Ac_2O had been earlier reported: Coburn, M. D.; Ungnade, H. E. *J. Heterocycl. Chem.* **1965**, *2*, 308.)

(6) Carvalho, E.; Iley, J.; Rosa, E. *J. Chem. Soc., Chem. Commun.* **1988**, 1249.

(7) (a) Carvalho, E.; Iley, J.; Norberto, F.; Rosa, E. *J. Chem. Res., Synop.* **1989**, 260. (b) We have obtained a similar yield of *N*-nitro-2-pyrrolidinone under their conditions, but also substantial amounts of *N*-(trifluoroacetyl)-2-pyrrolidinone as byproduct.

(8) We have confirmed this result of Suri and Chapman (ref 5); the final mixture also contains starting amide and *N*-trifluoroacetyl-2-pyrrolidinone. If the reagents are mixed at room temperature, 18% of *N*-nitro-2-pyrrolidinone and 12% of *N*-nitroso-2-pyrrolidinone are obtained.

(9) Crivello, J. V. *J. Org. Chem.* **1981**, *46*, 3056. For the nitration of enol acetates with this reagent mixture, see Dampawan, P.; Zajac, W. W. *Synthesis* **1983**, 545. For a very recent, comprehensive review on nitration reagents, see: Olah, G. A.; Malhotra, R.; Narang, S. C. *Nitration, Methods and Mechanisms*; VCH: New York, 1989.

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CH_2Cl_2,[7a] a reagent reported by Masci for aromatic nitration,[10] gives 40–96% N-nitration yields (46% in the case of 2-pyrrolidinone[7b]).

Results and Discussion

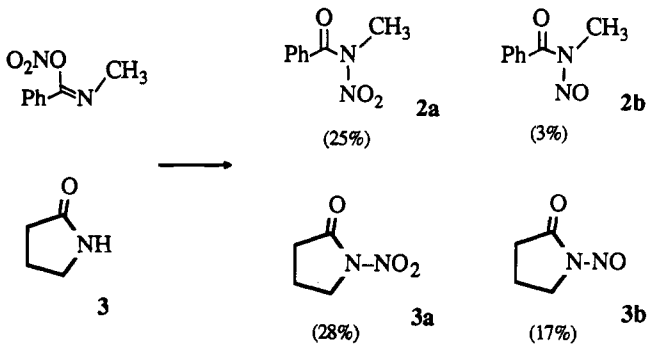
Comparison of Nitrating Agents. Nitronium salts such as nitronium tetrafluoroborate ($NO_2^+BF_4^-$), which might may be considered among the most electrophilic nitrating agents among the available reagents, are unable to nitrate amides such as *N*-methylnonanamide (**1**), *N*-methylbenzamide (**2**), and 2-pyrrolidinone (**3**) in significant yields. In CH_3CN solution at several temperatures (from −40 °C to rt), and in the presence of different amounts of pyridine or 2,6-lutidine, we have obtained *mixtures of the starting amides, nitrosoamides, and nitroamides (in minor amounts)*.

Using a more hindered base like 2,6-di-*tert*-butyl-4-methylpyridine gave a 80% yield of *N*-methyl-*N*-nitrobenzamide (**2a**, with only 15% of the corresponding nitroso derivative **2b**), and a 60% yield of *N*-nitro-2-pyrrolidinone (**3a**, with 20% of the nitrosolactam **3b**), under the optimum conditions reported as supplementary material. These results, although interesting, were disappointing for us since these substrates were rather favorable.

Apparently, a base is needed in the reaction flask to neutralize, at least, the tetrafluoroboric acid produced because of the NO_2/H exchange that involves any nitration. Despite this observation, as the relatively strong coordination of nonhindered pyridines with nitronium ion[11] could be responsible for the poor nitration percentages, we studied the reaction of amides and nitronium ion in the absence of base. However, without pyridine, no nitration of amides **1–3** was observed at all.[12]

We explain the facts as follows:[13] the nitronium ion interacts principally with the hard nucleophilic center—the carbonyl oxygen—to give a certain percentage of intermediate A (see Scheme I).[14] In the absence of base the set of possible equilibria are stopped here; after workup, the hydrolysis product of A—the amide—predominates. However, in the presence of base, A is converted into B, an unstable intermediate that may be quickly transformed to a mixture of products, including the nitrosoamide, nitroamide, and amide, through intermediate C, in agreement with the results of Carvalho et al.[4c,6] Thus, in the absence of pyridine, almost no deprotonation from A to B occurs; on the other hand, with excess of pyridine, the nitronium ion is so strongly "trapped" that A is not obtained. The relative success of 2,6-di-*tert*-butyl-4-methylpyridine may be attributed to the fact that it has poor coordinating ability with the nitronium ion[11e] but can still function as a base.

Scheme II



Other possible nitrating mixtures have been investigated in this work: **ammonium nitrate** and **triflic anhydride**, **morpholinium nitrate** and **acetic anhydride**, and **ammonium nitrate** and **trifluoroacetic anhydride**. *The first two were found to be ineffective.* By contrast, using **ammonium nitrate and trifluoroacetic anhydride** at rt, under the conditions reported by Crivello,[9] we obtained moderate to good yields of nitration of **1–3** in preliminary experiments. Provided that sufficient amounts of the reagent mixture in CH_2Cl_2 were employed, even *N*-cyclohexylacetamide (**4**) and *N*-cyclohexylpentanamide were nitrated in acceptable yields.[15] Thus, we realized that *this was the method of choice.* The probable reactive species is the mixed anhydride CF_3COONO_2,[5,9] which appears to have appropriate "stability" and nitrating power.

Finally, we have studied the reactivity of some amides, in CH_3CN at −30 °C, with **(*N*-methyl)phenylimidoyl nitrate**, $PhC(=NCH_3)ONO_2$, prepared from the imidoyl chloride of **2**, with the purpose of evaluating whether a transnitration could take place in good yield or not. A representative result is shown in Scheme II, in which, from 1 equiv of **3**, a mixture of nitro and nitroso derivatives, besides ca. 0.5 equiv of **2** and **3**, was isolated. When 3 equiv of **3** was added, **3a** and **3b** were obtained in 12% and 36% yields, respectively, while **2a** and **2b** were hardly observed. Thus, with an excess of **3**, transnitrosation and transnitration takes mainly place.[16] From a practical point of view, *simple imidoyl nitrates cannot be recommended as nitrating agents for complex amides, lactams, or peptides, due to the concomitant nitrosation.* From a mechanistic point of view, our results confirm qualitatively those of Carvalho et al.[4c,6] but introduce new insights into the subject because of the clear *intermolecular transfer of* NO_2

(10) Masci, B. *J. Org. Chem.* **1985**, *50*, 4081.

(11) (a) Jones, J.; Jones, J. *Tetrahedron Lett.* **1964**, 2117. (b) Olah, G. A.; Olah, J. A.; Overchuk, N. A. *J. Org. Chem.* **1965**, *30*, 3373. (c) Cupas, C. A.; Pearson, R. L. *J. Am. Chem. Soc.* **1968**, *90*, 4742. (d) Olah, G. A.; Narang, S. C.; Olah, J. A.; Pearson, R. L.; Cupas, C. A. *J. Am. Chem. Soc.* **1980**, *102*, 3507. (e) Olah, G. A.; Laali, K.; Farooq, O.; Olah, J. A. *J. Org. Chem.* **1990**, *55*, 5179; while treatment of 2,6-dimethylpyridine with NO_2BF_4 gives rise to N-nitration, it is shown in this report that 2,6-di-*tert*-butylpyridine undergoes C-nitration.

(12) In TFA/CH_2Cl_2 at 0 °C no reaction occurred either between amide **1** and NO_2BF_4 (although it may be due to the scarce solubility of the nitronium salt in the medium). The same mixture, *after 18 h at rt*, afforded 54% of nonanoic acid, the cleavage product, 28% of the starting amide, and 4% of its nitroso derivative. Nitrolyses of amides by NO_2BF_4, even of simple *N*-alkylcarboxamides, have been reported: Andreev, S. A.; Lebedev, B. A.; Tselinskii, I. V. *Zh. Org. Khim.* **1978**, *14*, 909. Also see ref 4b. Nitrolysis is reasonably attributed to the formation of species such as $RCON^+H(NO_2)R'$ that may give rise to $RCO^+ + O_2NNHR'$; after the workup, RCOOH and nitramines are obtained.

(13) The low yields of nitroamides and moderate yields of nitrosoamides that are obtained in many attempted nitrations cannot be attributed to a lack of purity of NO_2BF_4 (ref 4a) as we have proved it to lie around 95% (ref 1f). Another possible explanation of the striking behavior of the nitronium ion, a peculiar cation of linear structure, may lie on its oxidizing properties (see, e.g.: Olah G. A.; Gupta, B. G. B.; Narang, S. C. *J. Am. Chem. Soc.* **1979**, *101*, 5317. Boughriet, A.; Wartel, M. *J. Chem. Soc., Chem. Commun.* **1989**, 809). In fact, if a redox process took place between the substrate and reagent, NO_2^+ could be converted to NO_2, a good nitrosating agent. However, no ESR signals were observed, from −60 °C to rt, in mixing degassed CH_3CN solutions of **2** and NO_2BF_4; thus, it seems that radicals are hardly formed in the first step of these nitrations.

(14) It is known that many electrophilic attacks to carboxamides initially take place at the oxygen atom. For example, nitrosation occurs at the oxygen (although it is followed by a slow proton transfer and then by a fast O-to-N rearrangement): Castro, A.; Iglesias, E.; Leis, J. R.; Peña, M. E.; Vázquez, J. *J. Chem. Soc., Perkin Trans. 2*, **1986**, 1725 and references cited therein. Also, protonation of amides in strong acid media, in cold, takes place mainly at the carbonyl oxygen atom; see, e.g.: Gillespie, R. J.; Birchall, T. *Can. J. Chem.* **1963**, *41*, 148.

(15) By the way, the HNO_3/Ac_2O mixture did not nitrate **4**, at 0 °C for 12 h. After 2 h at rt, 12% of *N*-cyclohexyl-*N*-nitroacetamide (**4a**) and 5% of its analogous nitroso derivative (**4b**) were isolated, 40% of **4** being recovered; the rest was decomposition product(s).

(16) In another illustrative experiment, the imidoyl chloride arising from *N*-cyclohexylpivalamide was analogously treated with $AgNO_3$ in the presence of 3 equiv of **3**; compound **3b** was again obtained as the major product, but now almost quantitatively, only traces of **3a** being detected.

Table I. Reaction of Amides and Lactams with NH_4NO_3 and TFAA[a]

amide or lactam	NH_4NO_3 (mmol)	TFAA (mmol)	reactn time	product(s)	yield (%)
N-methylnonanamide, 1	1.5	3	25 min	$CH_3(CH_2)_7CON(NO_2)Me$, 1a	86
PhCONHMe, 2	1.5	3	15 min	$PhCON(NO_2)Me$, 2a	94
2-pyrrolidinone, 3	1.5	3	15 min	*N*-nitro-2-pyrrolidinone, 3a	95
MeCONHCy, 4	3	6	2 h	$MeCON(NO_2)Cy$, 4a	94[b]
$Pr^iCONHBu$, 5	2	4	45 min	$Pr^iCON(NO_2)Bu$, 5a	92
BuCONHBu, 6	2	4	15 min	$BuCON(NO_2)Bu$, 6a	92
caprolactam, 7	1.5	3	15 min	*N*-nitrocaprolactam, 7a	95
dodecanelactam, 8	2	4	45 min	*N*-nitrododecanelactam, 8a	90
PhCONHMe, 2	4.5	9	35 min	$NO_2PhCON(NO_2)Me$[c]	98
4-NO_2PhCONHMe, 9	1.5	3	15 min	4-$NO_2PhCON(NO_2)Me$, 9a″	93
AcLeuOMe, 10	4	8	2.5 h	$Ac(NO_2)LeuOMe$, 10a	85

[a] 1 mmol of the amide or lactam was added at 0 °C, after a delay of 45–60 min at rt, to a vigorously stirred mixture of NH_4NO_3 and TFAA in 5 mL of anhydrous CH_2Cl_2. [b] This is the crude yield, since the product undergoes a partial decomposition to ester and N_2O during its isolation. *N*-Cyclohexylpentanamide behaves identically to 4. [c] Similar amounts of ortho, meta, and para isomers (9a/9a′/9a″) were obtained. Methyl *N*-benzoylglycylglycinate gave similarly a mixture (not separated) of *o*-, *m*-, and *p*-nitrobenzoyl derivatives of di-N-nitrated GlyGlyOMe in 92% yield by treatment with 4 equiv of NH_4NO_3 and 8 equiv of TFAA for 3.5 h; see ref 1b for the benzoyl derivative of di-N-nitrated GlyGlyOMe.

and NO groups. It would be of interest to determine whether transnitration takes place mainly via an O-to-O nitro transfer followed by an O-to-N internal migration or via a direct nitro transfer from the imidoyl nitrate to the nitrogen atom of **3**, as well as to elucidate what is the fate of the oxygen atom which is "lost" in the transnitrosation,[17] but the study of these questions is outside the scope of the present work.

Optimization of the Crivello Method. Having established that NH_4NO_3/TFAA was the most promising reagent for the N-nitration of amides, it was carried out an optimization of the NH_4NO_3/TFAA molar relationship, with regard to the nitration of *N*-butyl-2-methylpropanamide (**5**) and *N*-butylpentanamide (**6**). The best yields were obtained with a reagent prepared from NH_4NO_3 and TFAA in CH_2Cl_2[18] in a 1:2 molar ratio, adding the amides after dissolution of most of the solid. Higher amounts of TFAA and/or premature addition of the amide gave partial, competitive trifluoroacetylation of **5** and **6**. It is also worth noting that with a 1:1 molar ratio of NH_4NO_3 and TFAA, i.e., with smaller amounts of TFAA, the nitration yields decreased.

To evaluate the importance of the relative solubility of the amide salt and steric hinderance, we treated amide **1** with different ammonium nitrates and TFAA. The results are collected in a table given as supplementary material. Tertiary and quaternary ammonium nitrates did not act as good nitrating reagents, whereas the salts of morpholine, ethylamine, *tert*-butylamine, and ammonia gave encouraging results. Moreover, in these last cases, isolation of byproducts like trifluoroacetylmorpholine and trifluoroacetamide suggested that the amine was involved as a reagent, consuming 1 equiv of TFAA according to the following equation: $R_2NH_2^+\ NO_3^- + 2\ (CF_3CO)_2O \rightarrow CF_3COONO_2 + CF_3CONR_2 + 2\ CF_3COOH$. In fact, we supposed that the reaction took place in two steps and that the irreversible reaction of R_2NH with the second molecule of TFAA aided to shift the equilibrium to the right.

This overall reaction could be easily demonstrated to be general by treating NH_4NO_3 with 2 equiv of TFAA in CH_2Cl_2 at rt for 90 min, since pure CF_3CONH_2 was isolated in 66% yield. The reaction has also been monitored by

Scheme III

$$^{15}NH_4{}^{15}NO_3 + (CF_3CO)_2O \rightleftharpoons CF_3COO{}^{15}NO_2 + {}^{15}NH_4OOCCF_3$$

$$^{15}NH_4OOCCF_3 + (CF_3CO)_2O \longrightarrow CF_3CO{}^{15}NH_2 + 2CF_3COOH$$

$$CF_3COO{}^{15}NO_2 + CF_3CO{}^{15}NH_2 \longrightarrow CF_3COOH + [CF_3CO{}^{15}NH{}^{15}NO_2]$$

$$\downarrow$$

$$2CF_3COOH + {}^{15}N{}^{15}NO$$

^{15}N NMR spectroscopy: TFAA and doubly labeled ammonium nitrate ($^{15}NH_4{}^{15}NO_3$) were mixed in the 2:1 molar ratio in a cold 8:2 mixture of $CDCl_3$ and CD_3CN, and spectra were recorded every 10 min; there appeared quite rapidly a broad peak at δ 294.1 (which we attribute to $CF_3COO{}^{15}NO_2$), while a peak at δ 99.0, a triplet of $J = 95$ Hz in the undecoupled spectra (which must be attributed to $CF_3CO{}^{15}NH_2$) began to increase; later on, a pair of doublets at δ 230.8 and 146.4, with $J = 9.6$ Hz (which can only be ascribed to N_2O)[19] appeared and increased more and more at expenses of the peaks at δ 294 and 99. We interpret these observations according to the reaction sequence of Scheme III.

Formally, the process may be viewed as the dehydration of NH_4NO_3 by an anhydride, without heating. It explains that the timing is so important to achieve good yields of nitration: if the amide to be nitrated is added too early, when an excess of TFAA is still present, trifluoroacetylated amide is obtained; if too much time is allowed for the formation of the nitrating mixture before adding the amide, poor yields of nitration are observed since most CF_3COONO_2 has disappeared to give N_2O.

The nitration of different substrates with NH_4NO_3 and TFAA was then carried out. The best results using the appropriate reagent ratios and conditions are shown in Table I. Benzamides and the less hindered aliphatic amides were nitrated within several minutes, though others required few hours, in excellent isolated yields (crude yields were usually quantitative). We should recall, for the sake of comparison, the long reaction times needed when the nitrating agent is CH_3COONO_2 instead of CF_3COONO_2. The minor problem lies in the fact that aromatic rings (benzoyl groups) were also nitrated when an excess of nitrating mixture was employed; it indicates, e.g., that polynitration of amide bonds of protected peptides could be accompanied in practice by extensive nitration of those aromatic side chains and N-protective groups that are more reactive towards nitration than benzoyl groups.

(17) It seems that the homolytic cleavage of the imidate O–N bond gives nitrogen dioxide, which mainly through its dimer would act as the nitrosating agent, but the stoichiometry of the reaction with nitrogen dioxide does require the appearance of oxidized byproducts (HNO_3 and, maybe, oxidation products of the amides) accompanying the nitroso derivatives (see Scheme I).

(18) In CH_3CN, the yields were lower; in CH_3NO_2, nitro/nitroso mixtures were obtained.

(19) Battacharyya, P. K.; Dailey, B. P. *J. Chem. Phys.* **1973**, *59*, 5820.

Table II. Nitration of Amides Using Morpholinium Nitrate (MN)[a]

amide	MN (mmol)	mmol, anhydride	reactn time	product	yield (%)
1	1.5	3, TFAA	25 min	1a	90
4	3	6, TFAA	2 h	4a	94[b]
5	2	4, TFAA	45 min	5a	92
5	2	4, $(C_3F_7CO)_2O$	45 min	5a	98
6	2	4, TFAA	15 min	6a	92
6	2	4, $(C_3F_7CO)_2O$	15 min	6a	96

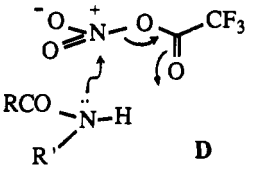
[a] 1 mmol of the amide was added at 0 °C, after a delay of 30 min at rt, to the mixture of MN and the anhydride in 5 mL of anhydrous CH_2Cl_2. [b] This is the crude yield, since the product undergoes a partial decomposition to ester and N_2O during its isolation.

Nitration Using Morpholinium Nitrate (MN). The optimized N-nitration yields, using morpholinium nitrate (MN) instead of NH_4NO_3, are summarized in Table II. The advantages that we envisaged for nitrates such as this one[20] were that they are much more soluble in CH_2Cl_2 and other organic solvents than NH_4NO_3, so that the active species could be more rapidly observed, and furthermore we believed that trifluoroacetylmorpholine, being a deactivated N,N-disubstituted amide,[21] would not react with CF_3COONO_2, or at least would consume less CF_3COONO_2 than trifluoroacetamide.[22]

In comparing Tables I and II, it appears that the performance of MN and TFAA, and that of MN and heptafluorobutyric anhydride, $(C_3F_7CO)_2O$, are slightly better than that of the NH_4NO_3/TFAA mixture. Really, MN was rapidly solubilized and it was observed that the nitration agent was formed earlier, but in practice, when enough time for the dissolution of NH_4NO_3 was provided before adding the amide, the differences were not significant. Therefore, in most cases the use of MN and $(C_3F_7CO)_2O$ does not compensate for the availability and lower cost of NH_4NO_3 and TFAA.

Mechanistic Considerations. A last question to be discussed is the mechanism of the reaction of CF_3COONO_2 (and of $RCOONO_2$ in general[23]) with the amides. Two hypotheses were considered reasonable at first sight. The first one was that, *after the O-nitration of the amide group, the presence of TFA and CF_3CONR_2 in the reaction medium*, when CF_3COONO_2 is produced from $R_2NH_2^+NO_3^-$ and TFAA, *could avoid the formation of nitrosoamides*, the undesired byproducts; for example, the reaction of the amide group with NO_2/N_2O_4 (see Scheme I) could not be so shifted to the right in the presence of an excess of CF_3COOH; moreover, in the case in which CF_3CONH_2 appears in the medium, this amide could also react with NO_2/N_2O_4 so that part of these nitrogen oxides would be eliminated.[24] We ruled out this hypothesis readily by carrying out the nitrosation of amide **6** in the presence of an excess of TFA (4–6 equiv) and/or of CF_3CONH_2, either in CH_2Cl_2 (with a defect of nitrogen oxides as nitrosating agents) or in CH_3CN (with 1 equiv of $NOBF_4$, with or without pyridine, as nitrosating agent). In practice, no differences were observed with regard to control experiments. In other words, moderate amounts of TFA and/or CF_3CONH_2 do not prevent the nitrosation of nonhindered *N*-alkylcarboxamides like **6**. Thus, the nitrating power of the $R_2NH_2^+NO_3^-$/TFAA mixtures must be inherent in the mixed anhydride CF_3COONO_2.

A second hypothesis was that *reagents like CF_3COONO_2 give rise to the direct N-nitration rather than the O-nitration* of the amide group. Really, if O-nitration took place, poorer yields of nitroamides and significant amounts of nitrosoamides would be obtained, as it happens when many other nitrating agents are employed. In fact, it was expected that CF_3COONO_2 behaved as a softer electrophile than NO_2^+ or H^+, so that its preferred interaction with the softer nucleophilic center seemed us reasonable; however, other NO_2X reagents with covalent N–X bonds that have been studied in this work should or might have proceeded analogously. Therefore, as an explanation of the performance of $RCOONO_2$ vs other NO_2X species, we suggest the possibility of a cyclic, six-membered transition state arising from the reagent approach pointed by D.



D

From the reasonings posed in the two last paragraphs it appeared to us that any method of generation of CF_3COONO_2 ($RCOONO_2$ in general) below rt could afford excellent percentages of N-nitration, provided that: (i) the equilibria involved in their formation were enough shifted to the right; (ii) the resulting solutions were free of other species that could compete for the amides (like an excess of TFAA) or could react prematurely with these mixed anhydrides; and (iii) the dielectric constant of the medium was sufficiently low to prevent the ionization of CF_3COONO_2 to give CF_3COO^- and NO_2^+. Regarding this last point, it has been already commented[8,18] that higher yields of nitroamides have been obtained in CH_2Cl_2 than in CH_3CN and CH_3NO_2. The detrimental effect of polar media has been corroborated by preparing solutions of CF_3COONO_2 in CH_2Cl_2 in the presence of quaternary ammonium salts, since in all cases the yields of nitroamide decreased in relation to those indicated in Table I ($2NH_4NO_3$/4 TFAA/$Bu_4N^+CF_3COO^-$/**6**, 74%; $2NH_4NO_3$/4TFAA/$2Bu_4N^+CF_3COO^-$/**6**, 50%; $2NH_4NO_3$/4TFAA/$Bu_4N^+NO_3^-$/**6**, 71%; $2NH_4NO_3$/4TFAA/$2Bu_4N^+BF_4^-$/**1**, 42%; $2NO_2^+BF_4^-$/$2Bu_4N^+CF_3COO^-$/**3**, 15%; $2NO_2^+BF_4^-$/$2Bu_4N^+CF_3COO^-$/2TFA/**6**, ca. 5%). This can explain the success of the nitrating mixtures used in Tables I and II, since in these cases the salts, such as ammonium trifluoroacetate or morpholinium trifluoroacetate, disappear rapidly from the solution.

(20) Pyrrolidinium nitrate was also prepared but it appeared to be too hygroscopic. Piperidinium nitrate gave lower yields than morpholinium nitrate.

(21) It is known that *N,N*-dialkylacetamides undergo nitrolysis to give nitramines, but amides with electronegative substituents on the acyl moiety do not; see: Robson, J. H.; Reinhart, J. *J. Am. Chem. Soc.* **1955**, *77*, 2453 and references cited therein. In our case (trifluoroacetylmorpholine) we did not observe the nitrolysis of the CO–N bond to yield *N*-nitromorpholine but a slow, partial cleavage of the ether linkage.

(22) We have followed the reaction of morpholinium nitrate with TFAA in $CDCl_3$ by ^1H and ^{19}F NMR spectroscopy. At the normal probe temperature, the methylene protons of morpholinium ion, which appear at δ 4.00 and 3.38, began to diminish in few minutes, and the signals of *N*-trifluoroacetylmorpholine at δ 3.85–3.70 increased more and more; within 35 min all the morpholinium ions had been converted into *N*-(trifluoroacetyl)morpholine. By ^{19}F NMR, after few min it was clearly observed the signal corresponding to *N*-(trifluoroacetyl)morpholine at δ 6.2; when the amide **6** was then introduced into the NMR tube, changes were rapidly observed, but that signal was maintained.

(23) Such as acetyl nitrate (ref 3). For the use of benzoyl nitrate for the nitration of alkylbenzenes, see: Smith, K.; Fry, K.; Butters, M.; Nay, B. *Tetrahedron Lett.* **1989**, *30*, 5333. Also see: Kurz, M. E.; Yang, L. T. A.; Zahora, E. P.; Adams, R. C. *J. Org. Chem.* **1973**, *38*, 2271 and references cited therein. With regard to the structure of acyl nitrates, see: Burton, H.; Praill, P. F. G. *J. Chem. Soc.* **1955**, 729.

(24) Due to the electron-withdrawing nature of CF_3, it is believed that trifluoroacetamides should react with nitrosating agents more slowly than most carboxamides. Nevertheless, some trifluoroacetylamides can be nitrosated; see: Nikolaides, N.; Ganem, B. *J. Org. Chem.* **1989**, *54*, 5996.

Conclusions

Among the several nitrating agents of general formula NO_2X that have been evaluated, ranging from those which involve almost unsolvated nitronium ion (NO_2^+) to others with practically covalent N–X bonds, it turns out that the species of intermediate polarity, the mixed anhydrides CF_3COONO_2 and $C_3F_7COONO_2$, afford the best yields of *N*-nitroamides, with practically no evidence of the corresponding *N*-nitrosoamides in the crude product.

Nitric trifluoroacetic and heptafluorobutyric nitric anhydrides, when properly prepared, by treatment of either ammonium nitrate or morpholinium nitrate with TFAA and $(C_3F_7CO)_2O$, respectively, in the 1:2 molar ratio, are the reagents of choice since they give excellent N-nitration yields in all cases, including some hindered amides which are unreactive towards CH_3COONO_2 and other nitrating agents.

It has been shown that the process begins with the two-step reaction $R_2NH_2^+ NO_3^- + 2(CF_3CO)_2O \rightarrow CF_3COONO_2 + CF_3CONR_2 + 2CF_3COOH$, and then the nitrating species attacks predominantly the nitrogen atom of the amide group. In view of the effect of the medium polarity on the relative N-nitration percentages and that nitroso derivatives are not obtained under these conditions, it is believed that a double H/NO_2 transfer between the amide and CF_3COONO_2 through a six-membered transition state may explain the better performance of this reagent.

Experimental Section

Melting points are uncorrected. The NMR spectra were obtained in $CDCl_3$ (unless otherwise indicated) at 200 MHz for ^1H, at 50.3 MHz for ^{13}C, at 50.7 MHz for ^{15}N, or at 56.4 MHz for ^{19}F NMR; ^{15}N chemical shifts are referred to NH_3, and ^{19}F are given with respect to external TFA. *J* values are given in Hz. All the starting amides, lactams, and protected amino acids were known: those which are not commercial products were prepared by standard procedures (reaction of acid chlorides with amines or oxime rearrangement). Nitronium tetrafluoroborate and triflic anhydride were purchased from Fluka, and 2,6-di-*tert*-butyl-4-methylpyridine and heptafluorobutyric anhydride from Sigma. Imidoyl chlorides were prepared by treatment of the amides with an excess of $SOCl_2$ in CH_2Cl_2 at reflux overnight and evaporation of the solvent; reaction of the residues, without further purification, with $AgNO_3$ in CH_3CN was carried out at −30 °C, according to refs 4c and 6. Tetrabutylammonium trifluoroacetate was prepared according to ref 25. Commercial samples of tetrabutylammonium tetrafluoroborate and tetrabutylammonium nitrate were also employed in some experiments.

Nitration of Amides with NH_4NO_3 and TFAA. Typical procedure: A suspension of 160 mg (2 mmol) of NH_4NO_3 and 560 μL (4 mmol) of TFAA in 5 mL of dry CH_2Cl_2 under Ar was vigorously stirred at rt until most of the solid was dissolved (ca. 1 h). The mixture was cooled to 0 °C, and 157 mg (1 mmol) of amide **6** in 1 mL of CH_2Cl_2 was added by syringe through the septum. After 15 min, the cooling bath was removed, and 50–100 mL of CH_2Cl_2 was added; the solution was then washed with cold phosphate buffer (pH 7; 2 × 25 mL), dried, and evaporated without heating to afford 180 mg (90%) of *N*-butyl-*N*-nitropentanamide (**6a**): oil; ^1H NMR δ 4.10 (t, 2 H, *J* = 7.4), 2.95 (t, 2 H, *J* = 7.4), 1.65 (m, 4 H), 1.37 (m, 4 H), 0.94 (t, 6 H, *J* = 7.2); ^{13}C NMR δ 172.8, 46.6 (NCH_2), 37.8 (CH_2CO), 28.7, 26.6, 21.9, 19.6, 13.5, 13.3; IR ($CHCl_3$) 1715, 1570 cm^{-1}. Anal. Calcd for $C_9H_{18}N_2O_3$: C, 53.45; H, 8.97; N, 13.85. Found: C, 53.40; H, 8.96; N, 13.69.

Alternatively, the reaction mixture was concentrated under vacuum, without heating, added to a silica gel column, and separated by using CH_2Cl_2 as the eluent, to afford 186 mg (92%) of **6a**.[26]

***N*-Butyl-*N*-nitro-2-methylpropanamide (5a)**: oil; ^1H NMR δ 4.06 (t, 2 H, *J* = 7.3), 3.52 (h, 1 H, *J* = 6.7), 1.59 (m, 2 H), 1.32 (m, 2 H), 1.23 (d, 6 H, *J* = 6.7), 0.94 (t, 3 H, *J* = 7.2); ^{13}C NMR δ 178.1, 47.6 (NCH_2), 35.7 (CHCO), 29.3, 20.0, 19.8, 19.8, 13.7; IR ($CHCl_3$) 1720, 1570. Anal. Calcd for $C_8H_{16}N_2O_3$: C, 51.05; H, 8.58; N, 14.88. Found: C, 51.42; H, 8.80; N, 14.02.[27]

***N*-Methyl-*N*,2-dinitrobenzamide (9a), *N*-methyl-*N*,3-dinitrobenzamide (9a′), and *N*-methyl-*N*,4-dinitrobenzamide (9a″) mixture**: oil; ^1H NMR δ 8.24 (br dd, *J* = 8.0, 1.2, 1 H), 7.76 (td, *J* = 7.5, 1.2, 1 H), 7.62 (ddd, *J* = 8.0, 7.5, 1.5, 1 H), 7.38 (br dd, *J* = 7.5, 1.5, 1 H), 3.79 (s, 3 H) (**9a**); 8.45 (ddd, *J* = 2.2, 1.7, 0.5, 1 H), 8.39 (ddd, *J* = 8.2, 2.2, 1.2, 1 H), 7.93 (ddd, *J* = 7.8, 1.7, 1.2, 1 H), 7.66 (td, *J* = 8.0 ± 0.2, 0.5, 1 H), 3.70 (s, 3 H), (**9a′**); 8.28 (AA′ moiety of an AA′XX′ system, J_{AX} = 9.0, 2 H), 7.76 (XX′ moiety, 2 H), 3.70 (s, 3 H), (**9a″**).[28]

N-Methyl-*N*-nitrononanamide (**1a**), *N*-methyl-*N*-nitrobenzamide (**2a**), *N*-nitro-2-pyrrolidinone (**3a**), *N*-cyclohexyl-*N*-nitroacetamide (**4a**), *N*-nitrocaprolactam (**7a**), *N*-nitrododecanelactam (**8a**), *N*-methyl-*N*,4-dinitrobenzamide (**9a″**), and methyl *N*-acetyl-*N*-nitroleucinate (**10a**) were similarly prepared (see Table I). Their physical and spectral data were exactly coincident with those of authentic samples which we have obtained by other methods (according to refs 1b and 4c).

Nitration of Amides with Morpholinium Nitrate and TFAA. Typical procedure: 450 μL (3.2 mmol) of TFAA were added with a syringe to a solution of 240 mg (1.6 mmol) of morpholinium nitrate in 4 mL of dry CH_2Cl_2 at 0 °C, under Ar. The cooling bath was removed, and the solution was stirred at rt. Thirty min later, the solution was cooled with an ice–water bath, and 126 mg (0.8 mmols) of amide **6** in 1 mL of dry CH_2Cl_2 was added. Stirring was maintained for 15 min, and then the mixture was separated by column chromatography (silica gel) with CH_2Cl_2 to give 186 mg (92%) of nitroamide **6a**. See Table II for related experiments.

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Registry No. 1, 6212-93-7; **1a**, 91083-84-0; **2**, 613-93-4; **2a**, 59476-39-0; **3**, 616-45-5; **3a**, 4391-52-0; **4**, 1124-53-4; **4a**, 97661-73-9; **5**, 6282-85-5; **5a**, 136805-92-0; **6**, 2763-67-9; **6a**, 136805-93-1; **7**, 105-60-2; **7a**, 91083-87-3; **8**, 947-04-6; **8a**, 91083-89-5; **9**, 2585-23-1; **9a**, 136805-94-2; **9a′**, 90110-79-5; **9a″**, 59476-41-4; **10**, 1492-11-1; **10a**, 91083-95-3.

Supplementary Material Available: Experimental procedure for the nitration of **2** in the presence of 2,6-di-*tert*-butyl-4-methylpyridine; results of the reaction of **1** with different ammonium nitrates and TFAA (Table); ^{15}N NMR spectra of the $^{15}NH_4{}^{15}NO_3$/TFAA mixture in $CDCl_3/CD_3CN$; ^1H NMR spectrum of the aromatic region of the mixture of **9a**/**9a′**/**9a″**; and ^1H NMR spectrum of the aromatic region of **9a′** (6 pages). Ordering information is given on any current masthead page.

(25) Clark, J. H.; Emsley, J. *J. Chem. Soc., Dalton Trans.* **1974**, 1125.

(26) For the more unstable nitroamides, direct separation by column chromatography using cold CH_2Cl_2 in recommended.

(27) The nitrogen percentages of different samples of **5a** submitted to microanalyses were sistematically lower than required, indicating that partial decomposition occurred on standing. This product (as well as other branched nitroamides) is best characterized by allowing it to decompose: the resulting residue is identical with a sample of butyl 2-methylpropanoate (butyl isobutyrate) prepared independently.

(28) Assignations were confirmed by decoupling experiments and by NMR comparison with pure samples of **9a′**, prepared from *N*-methyl-3-nitrobenzamide (see supplementary material), and of **9a″**, a known compound (ref 4c).