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Synthesis and Aminolysis of 2,4-Dinitrophenyl and 5-Nitropyridine *N*-Hydroxy Oxime Derivatives

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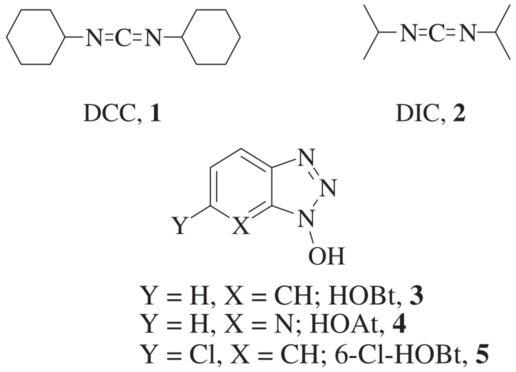
The 2,4-dinitrophenoxy derivatives **12**–**16** and the 5-nitro-2-pyridyloxy derivatives **18**–**22** were prepared. The products were identified by elemental analysis, IR, and NMR. The reaction of **12**–**16** and **18**–**22** with morpholine as nucleophile in CH_3CN occurs through nucleophilic aromatic substitutions to give *N*-(2,4-dinitrophenyl)morpholine (**23**) and *N*-(5-nitro-2-pyridyl)morpholine (**24**) respectively. Spectrophotometric measurements of the kinetics of these reactions in CH_3CN at a range of temperatures indicated that they are not morpholine-catalyzed. The Brønsted-type plots for the reactions of **12**–**16** and **18**–**22** with morpholine are linear with slopes, $\beta_{12\text{–}16} = -1.58 \pm 0.1$ and $\beta_{18\text{–}22} = -1.15 \pm 0.25$ respectively. The relative rate constants compared to the least reactive substrate, as well as the low negative β values, supported that the decomposition of the zwitterionic intermediate is a slow process. The low activation parameters ($\Delta H^{\#}$ and $\Delta S^{\#}$) are in accordance with the proposed transition state ($T^{\#}$). The expulsion of RO^- anion in the rate-determining step is assisted by intramolecular hydrogen-bonding with the ammonio-hydrogen present in the intermediate $T^{\#}$.

Amide bond formation is the main goal in the synthesis of a huge array of organic compounds of biological interest[1–5] such as peptides, peptoids, oligocarbamates, oligoamides, β-lactams, polyenamides, benzodiazepines, diketopiperazines, and hydantoins. The ester group is another crucial functionality and can be prepared from a carboxylic acid and a corresponding alcohol using peptide coupling reagents.

The coupling technique can be performed in solution or solid phase by in situ activation of the carboxylic acid. The method used should be efficient and reliable, especially when long sequences of amino acids are built up in solid-phase peptide synthesis.[6,7] The maintenance of configuration, especially in amino acids, is also important. Thus the main challenge in the development of coupling reagents is to achieve a combination of high yield and optical purity.

Carbodiimides such as DCC **1** and DIC **2**, which have been used previously as coupling reagents, gained their importance as useful reagents when used in the presence of several additives with an X–OH structure.[8]

The use of these kinds of additives to fine-tune coupling reagents is common during peptide bond formation (Figure 1). Thus, the addition 1-hydroxybenzotriazole (HOBt, **3**) minimizes the loss of configuration during coupling.[8] Later, 1-hydroxy-7-azabenzotriazole (HOAt, **4**) was described as a more favorable coupling additive for both solution[9] and solid-phase synthesis.[10] Recently, 6-Cl-HOBt (**5**) has been introduced into solid-phase synthesis. This additive is a good compromise between HOAt and HOBt in terms of reactivity and price.[11]



DCC, **1** DIC, **2**

Y = H, X = CH; HOBt, **3**
Y = H, X = N; HOAt, **4**
Y = Cl, X = CH; 6-Cl-HOBt, **5**

Figure 1. Coupling additives.

As a result of the explosive properties of HOBt derivatives,[12] they have been reclassified as class 1 explosives, thus increasing difficulties for their transportation.

In our search for safe and efficient additives, we came across a family of acidic oximes reported earlier by Itoh.[13] Some of the *N*-hydroxyamine derivatives, such as diethyl (hydroxyimino)malonate (**6**), ethyl cyano(hydroxyimino)acetate (oxyma, **7**), (hydroxyimino)malononitrile (**8**), (hydroxyimino)-2-pyridylacetonitrile (**9**), and 1-hydroxypyridin-2(1*H*)-one (**10**) (Figure 2), reported as alcoholic components of active esters perform well as leaving groups.[13] Thus, it was expected that strongly acidic and nucleophilic oximes, which include

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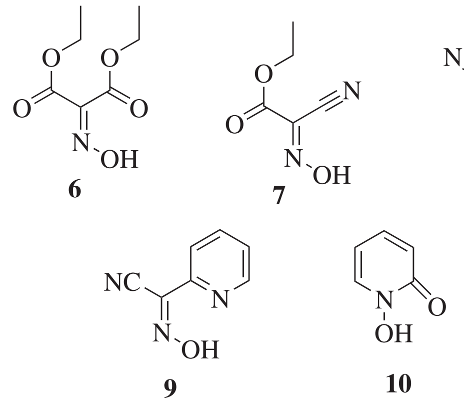


Figure 2. *N*-Hydroxyamine derivatives.

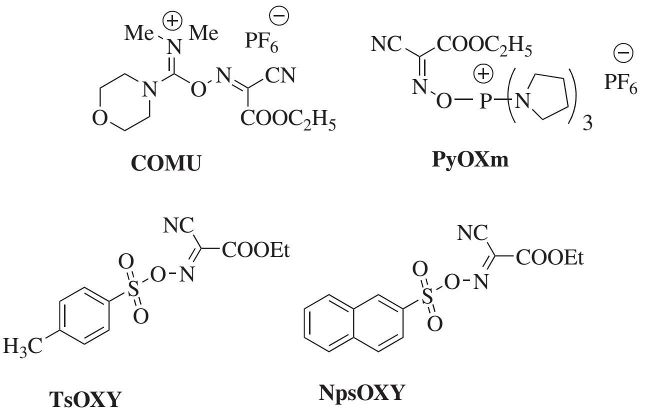
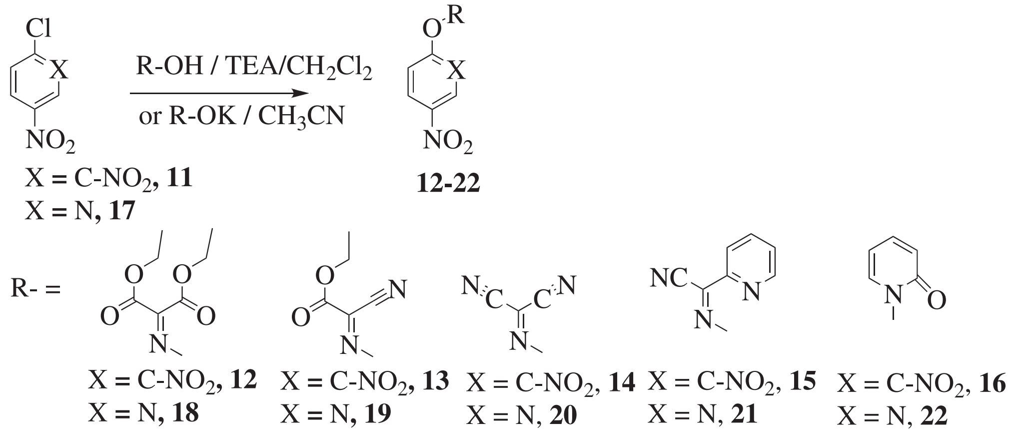


Figure 3. Uronium-, phosphonium-, and sulfonate-type coupling reagents derived from oxyma.



Scheme 1. Synthesis of 2,4-dinitrophenyl and 5-nitropyridine oxime derivatives.

electron-withdrawing groups in the molecule, would be suitable as additives.

Ethyl cyano(hydroxyimino)acetate (oxyma, **7**), one of the oximes studied, has been tested by our research group as an additive for use in the carbodiimide and TFFH approaches for the formation of peptide bonds. Oxyma **7** displayed a remarkable capacity to inhibit racemization, together with impressive coupling efficiency in both automated and manual synthesis, superior to the performance of HOBt and HOAt.[14] In addition, calorimetry assays (DSC and ARC) indicated a lower risk of explosion for oxyma **7**.[14]

Thus, a third generation of uronium-[14b,14c] and phosphonium-type[15] coupling reagents derived from oxyma **7** (Figure 3) were also studied. In addition, a new family of sulfonate ester coupling reagents derived from **7** (Figure 3) has been reported.[16]

As a continuation of our work in the field of nucleophilic aryl and acyl reactions,[17–19] we addressed kinetic studies of the leaving group ability of oximes **6**–**10** (Figure 2). For this purpose, we used the nucleophilic aromatic substitution of 2,4-dinitrophenoxy and 5-nitro-2-pyridyloxy derivatives by morpholine in acetonitrile (ACN) involving the departure of various leaving groups as models. Morpholine was selected as nucleophile because it posses a comparable pK_a value to those reported for many amino acids. To extend our previous work,[19] 2,4-dinitrophenoxy and 5-nitro-2-pyridyloxy derivatives were used as reactive spieces to compare their effect on the leaving ability of different leaving groups (oximino derivatives), recently used for preparation of different coupling reagents.[14–16]

Results and Discussion

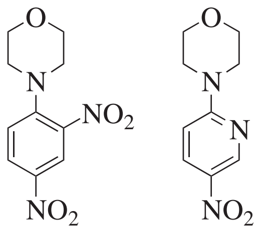
The 2,4-dinitrophenoxy derivatives **12**, **14** and the 5-nitro-2-pyridyloxy derivatives **18**, **20** were prepared via the reaction of 1-chloro-2,4-dinitrobenzene or 2-chloro-5-nitropyridine with the potassium salt of **6** or **8** in anhydrous ACN (Scheme 1). The 2,4-dinitrophenoxy derivatives **15**, **16** and the 5-nitropyridin-2-yloxy derivatives **21**, **22** were prepared via the reaction of 1-chloro-2,4-dinitrobenzene or 2-chloro-5-nitropyridine with **9** or **10** in the presence of Et_3N in anhydrous CH_2Cl_2 (Scheme 1). In contrast, the 2,4-dinitrophenoxy derivative **13** and the 5-nitropyridin-2-yloxy derivative **19** were prepared via the reaction of 1-chloro-2,4-dinitrobenzene or 2-chloro-5-nitropyridine with **7** in the presence of NaOH in anhydrous ACN (Scheme 1). The structures of compounds **12**–**16** and **18**–**22** were confirmed by IR, ^{1}H NMR, ^{13}C NMR spectroscopy and elemental analysis.

The reactions of **12**–**16** and **18**–**22** with morpholine gave *N*-(2,4-dinitrophenyl)morpholine (**23**) and *N*-(5-nitro-2-pyridyl)morpholine (**24**) respectively (Figure 4). The rate of the reactions of these compounds in ACN were followed spectrophotometrically, with maximum absorption of the products **23** and **24** at $\lambda = 375$ and 370 nm respectively. The UV absorption of the starting materials and the products did not overlap.

The rate of the reactions of **12–16** and **18–22** with morpholine in ACN may depend on the following: (i) the electron-withdrawing power of the substituent in the substrate; (ii) the stabilization of the formed intermediate by intra- or intermolecular hydrogen bonding; and (iii) the basicity of the leaving group anion. Also, the rate constants for the morpholino-dealkoxylation can be obtained by applying first-order conditions. The optical densities of solutions measured after the completion of the reactions were consistent with the authentic sample of the corresponding products with the same concentration. Pseudo-first-order rate constants (k_Ψ/s^{-1}) were determined from eq 1.

$$\ln(A_\infty - A_t) = -k_\Psi t + C \tag{1}$$

In general, the correlation coefficients for the linear regressions were almost 0.99. The plots of k_Ψ vs. morpholine concentrations were linear and passed through the origin, thus indicating that catalysis by morpholine is absent and the reactions are first order with respect to each reactant. The apparent second-order rate constants (k_A/L mol^{-1} s^{-1}) were determined from the slope of the linear plots of k_Ψ vs. morpholine concentrations. The uncertainty in the rate constants was estimated to be less than 3% from replicate runs. Table 1 provides the apparent rate constant k_A values calculated at four temperatures from 30 to 45 °C and activation parameters ($\Delta H^\#$ and $\Delta S^\#$) calculated from the Arrhenius equation for the reactions of **12–16** and **18–22** with morpholine.



23 **24**

Figure 4. *N*-(2,4-Dinitrophenyl)morpholine (**23**) and *N*-(5-nitro-2-pyridyl)morpholine (**24**).

To obtain information on the reaction mechanism, we dissected the apparent second-order rate constants for the reactions of **12–16** and **18–22** with morpholine on the assumption that the reactions proceed through initial nucleophilic attack to form the zwitterionic intermediate (**I**), which undergoes deprotonation to form a Meisenheimer intermediate (**II**). The formation of substitution products **23** or **24** is achieved from the expulsion of the alkoxy group from the Meisenheimer intermediate (**II**) (catalyzed pathway, where the proton transfer is rate limiting and the reaction is second order in morpholine) or directly from the zwitterionic intermediate (**I**) (uncatalyzed pathway, where it is first order in morpholine), Scheme 2.

Many aromatic substitutions of activated or moderately activated aryl ethers or aryl thioethers by amine nucleophiles are subjected to catalysis.[20–23] The base-catalyzed pathway involves either rate-limiting proton transfer from the zwitterionic intermediate to base for substrates carrying good leaving groups[24–29] (Scheme 2), or general acid catalysis by conjugate acid for substrates with poor leaving groups.[26,27] The uncatalyzed pathway either proceeds by initial attack of morpholine on substrates **12–16** and **18–22** in a slow step followed by rapid expulsion of the leaving group or by fast attack on these substrates to form the zwitterionic intermediate **I** followed by a slow expulsion of the leaving group (Scheme 2).

In order to predict the reaction mechanism, the first-order dependence on morpholine concentration is compatible with a rate limiting nucleophilic attack and also with an intermediate decomposition without base catalysis. One of the methods to determine the rate determining step of the reaction is by changing the nature of the leaving group i.e., "element-effect like" as well as the significance of coefficient β values of Brønsted plots.

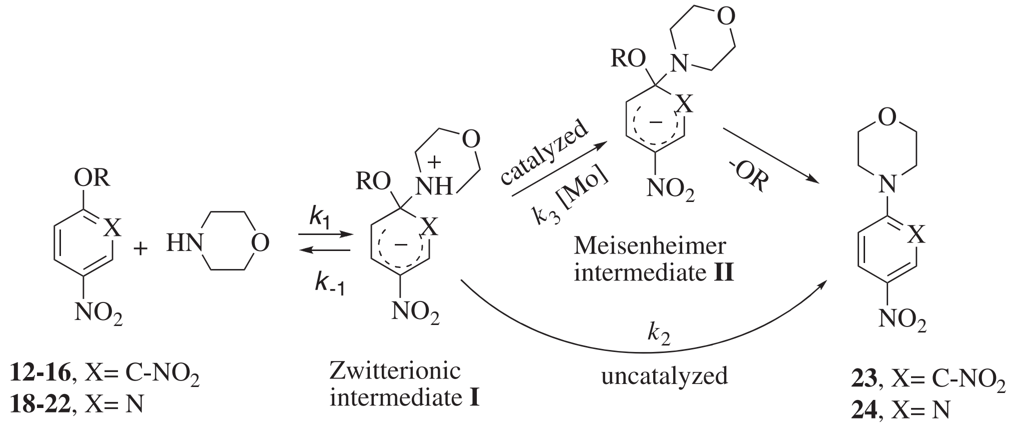
Based on the reactions of **12–16** and **18–22** with morpholine, similar to several nucleophilic aromatic substitution reactions,[24,30,31] which are not morpholine-catalyzed, the kinetic eq 2 is derived with reference to the uncatalyzed mechanism in Scheme 2 on the basis of the steady state assumption.

$$k_\Psi = k_1 k_2[\mathrm{Mo}]/(k_{-1} + k_2) \tag{2}$$

Table 1. Specific Rate Constants[a)] and Activation Parameters for the Reactions of **12–16** and **18–22** with Morpholine in ACN

Compd	$k_2 \times 10^3$/L mol^{-1} s^{-1}				$\Delta H^\#$ /kcal mol^{-1}	$-\Delta S^\#$ /e.u.
	30 °C	35 °C	40 °C	45 °C		
12	11.01 ± 0.18	12.96 ± 0.14	14.35 ± 0.07	16.42 ± 0.20	4.37 ± 0.28	53.03 ± 3.01
13	1050.89 ± 19.08	1222.96 ± 20.46	1378.57 ± 20.38	1521.83 ± 11.06	4.10 ± 0.28	44.87 ± 2.60
14	2509.33 ± 13.77	2976.53 ± 30.37	3261.45 ± 45.82	3572.51 ± 20.22	3.80 ± 0.48	44.14 ± 4.79
15	66.08 ± 0.22	73.07 ± 0.42	83.52 ± 0.5	97.22 ± 1.5	4.32 ± 0.36	49.72 ± 3.62
16	129.71 ± 0.27	145.47 ± 3.42	162.33 ± 2.98	188.35 ± 1.82	4.08 ± 0.28	49.14 ± 2.93
18	2.02 ± 0.01	2.37 ± 0.05	2.83 ± 0.01	3.32 ± 0.02	5.76 ± 0.11	51.86 ± 0.94
19	29.57 ± 0.67	35.46 ± 0.79	40.60 ± 0.41	48.44 ± 0.28	5.58 ± 0.24	47.09 ± 1.81
20	138.24 ± 0.56	162.92 ± 1.13	190.74 ± 0.84	223.87 ± 1.92	5.53 ± 0.04	44.20 ± 0.19
21	3.72 ± 0.01	4.50 ± 0.04	5.15 ± 0.05	6.15 ± 0.05	5.674 ± 0.26	50.87 ± 2.06
22	10.60 ± 0.20	12.98 ± 0.15	14.65 ± 0.13	17.59 ± 0.24	5.669 ± 0.40	48.82 ± 3.07

a) $k_2 = k_{\mathrm{obs}}$/[morpholine]. Rate constants were calculated by the least-squares method and the correlation coefficient was 0.99 in most cases.



Scheme 2. Reaction mechanism of oxime derivatives with morpholine.

The kinetic results showed a measurable difference in rates with changing in the nature of the leaving groups, Table 1. It shows that k_A values are greatly enhanced for the leaving group containing two cyano groups and the least reactive is that containing two ethoxycarbonyl groups. The ratios of **14**/**12**, **13**/**12**, **16**/**12**, and **15**/**12** are 227, 95, 11, and 6 respectively for the reactions of **12**–**16** with morpholine while they are 68, 14, 5, and 1.8 for the reactions of **18**–**22**. These ratios indicate that the order of rate enhancement is **14** > **13** > **16** > **15** > **12** and **20** > **19** > **22** > **21** > **18** for the reactions of **11** and **17** with morpholine respectively. This order is in harmony with the pK_a values of the free leaving groups.[32] These results, in addition to the observation that our reaction is not catalyzed by morpholine, suggest that the departure of the leaving group in reactions of **12**–**16** and **18**–**22** with morpholine in ACN at all temperatures is the rate-determining step, unlike most nucleophilic aromatic substitution reactions.[24,30,31]

Therefore $k_{-1} \gg k_2$

and

$$k_\Psi = k_1 k_2[\mathrm{Mo}]/k_{-1} = K_1 k_2[\mathrm{Mo}]$$

where $K_1 = k_1/k_{-1}$

The formation of k_A yields

$$k_A = k_\Psi/[\mathrm{Mo}] = K_1 k_2 \tag{3}$$

The eq 3 resembles a bimolecular reaction with a corresponding pseudo-first-order rate constant $k_\Psi/[\mathrm{Mo}]$ where $\upsilon = k_2[\mathrm{S}][\mathrm{Mo}]$ and υ is the rate of the reaction, while [S] and [Mo] are the concentrations of the substrates and morpholine respectively.

The Brønsted type plots for the reactions of **12**–**16** and **18**–**22** with morpholine are linear with slopes $\beta_{12\text{–}16} = -1.58 \pm 0.1$ (Figure 5) and $\beta_{18\text{–}22} = -1.15 \pm 0.25$ (Figure 6) respectively. However, the β values obtained from the nucleophilic aromatic substitution reactions gave positive values ranged between 1.08–0.45, with different nucleophiles.[18a,33–36] Accordingly, the lower values of β in our case are presumably due to the change in position of the rate-determining step and are consistent with the slow departure of the leaving groups. These observations lead us to hypothesize that the positive value of β is due to the association of the bond formation in the transition state, which leads to the formation of the zwitterionic intermediate in a slow process,[18a] while the negative value of β reflects the bond dissociation in the transition state, i.e., where the decomposition of the intermediate **I** is a slow process, as in our reaction. This notion is consistent with the fact that the absolute value of β indicates the degree of formation or bond cleavage in the rate-determining step.

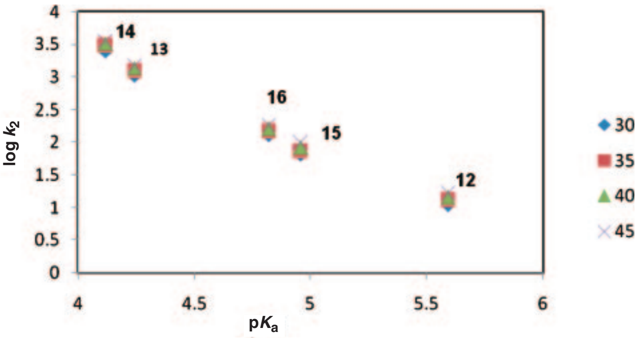


Figure 5. Brønsted like plot for the reaction of the oxime derivatives **12**–**16** with morpholine at 30, 35, 40, and 45 °C.

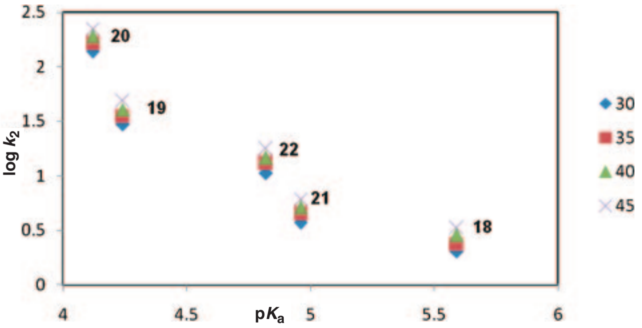


Figure 6. Brønsted like plot for the reaction of the oxime derivatives **18**–**22** with morpholine at 30, 35, 40, and 45 °C.

The low activation enthalpies $\Delta H^{\#}$ and the highly negative activation entropies $\Delta S^{\#}$, Table 1, are in accordance with the proposed transition states ($\mathrm{T}^{\#}_{a\text{–}c}$, Figure 7). They involve a possible intramolecular hydrogen bonding between the ammonium hydrogen atom and the etheric linkage ($\mathrm{T}^{\#}_{a}$), the aza

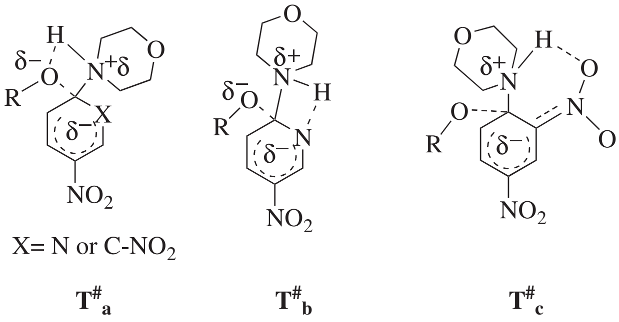


Figure 7.

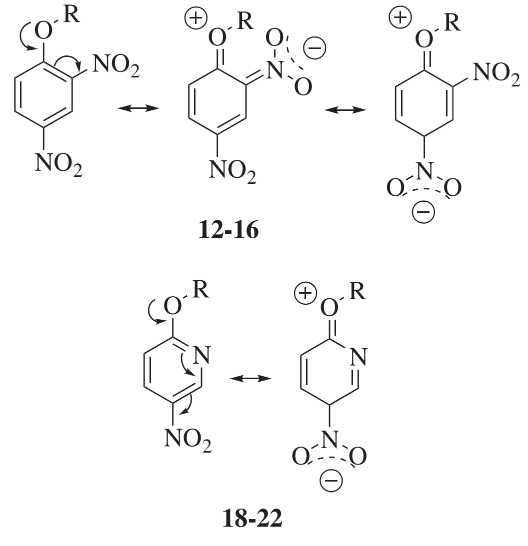


Figure 8.

group ($T^{\#}_{b}$) in compounds **18–22** whereas compounds **12–16** exhibit $T^{\#}_{c}$ (hydrogen bond to the *o*-nitro group).[17c] Such hydrogen bonding facilitates the attack of the morpholine to form zwitterionic intermediate **I** rather than its decomposition. Actually, the energy of formation of the N–H···O bond is ≈2000 cal and that of N–H···N is ≈1930 cal.[17c] The expulsion of RO^- anion in the rate-determining step is assisted by the intramolecular hydrogen-bonding with the ammonio hydrogen present in $T^{\#}_{a}$, which accordingly will lower the $\Delta H^{\#}$ value, whereas the structured and rigid $T^{\#}$ reflects the observed large negative $\Delta S^{\#}$ value.

For compounds **12–16** and **18–22**, the bulk of the 2-substituent as well as its activating effect clearly have to be considered. The effect of changing the nature of the ring substituents on the rate constants k_A is given in Table 1. The results show that the activating effects of the ortho substituents is in the order $NO_2 >$ ring aza. The effect of ring activation may be due to the ground state stabilization[18a] (Figure 8), the thermodynamic stabilities of the zwitterionic intermediate **I** or the transition states $T^{\#}_{a\text{–}c}$ leading to the products. This is because of the negligible steric effect of the 2-NO_2 and the aza ring.[18d] Since the rate constants depend on the pK_a of the leaving group, the transition state $T^{\#}_{c}$ has greater thermodynamic stability than that of $T^{\#}_{b}$. This reflects the higher reactivity of compounds **12–16** than **18–22**.

Conclusion

The aminolysis of *O*-(2,4-dinitrophenyl) derivatives **12–16** and *O*-(5-nitro-2-pyridyl) derivatives **18–22** of the oximes is not catalyzed by morpholine. Unlike most nucleophilic aromatic substitution reactions, the departure of the leaving group in reactions of **12–16** and **18–22** with morpholine in ACN at all the temperatures tested is the rate-determining step. The neighboring group effect is not relevant in these systems. This observation thus gives a clear picture of the reactivity of the different additives in peptide synthesis in terms of racemization and leaving ability. The proposed mechanism is supported by the low negative value of β, which reflects the bond dissociation in the transition state, i.e., when decomposition of the intermediate **I** is slow. The low activation parameters are in accordance with the proposed transition states ($T^{\#}_{a\text{–}c}$). The expulsion of RO^- anion in the rate-determining step is assisted by intramolecular hydrogen-bonding with the ammonio hydrogen present in the intermediate $T^{\#}_{a,b}$.

Experimental

Materials. The solvents used for kinetic runs were of reagent grade (BDH), and further purifications were performed. Acetonitrile (ACN) was used after distillation from anhydrous K_2CO_3. Morpholine (99%) was used after distillation. Melting points were determined with a Mel-Temp apparatus and are uncorrected. Magnetic resonance spectra (^{1}H NMR and ^{13}C NMR spectra) were recorded on a JEOL 500 MHz or on a Mercury 400 MHz spectrometer with chemical shift values reported in δ units (part per million) relative to an internal standard. Infrared (IR) data were obtained on a Perkin-Elmer 1600 series Fourier transform instrument as KBr pellets. Ultraviolet (UV) data were recorded on a SHIMADZU (UV-160A) UV–visible recording spectrophotometer. Elemental analyses were performed on Perkin-Elmer 2400 elemental analyzer, and the values measured were within ±0.3% of the theoretical values. Follow up of the reactions and checking the purity of the compounds were made by TLC on silica gel-protected aluminium sheets (Type 60 GF254, Merck) and the spots were detected by exposure to UV-lamp at λ 254 nm for a few seconds. The compounds were named using Chem. Draw Ultra version 10, Cambridge soft Corporation.

General Procedure for the Preparation of 15, 16, 21, and 22. (Hydroxyimino)-2-pyridylacetonitrile (1 mmol) or 1-hydroxypyridin-2(1*H*)-one (1 mmol) was dissolved in 3 mL anhydrous methylene chloride, TEA (2 mmol) was added, then 1 mmol of 1-chloro-2,4-dinitrobenzene or 2-chloro-5-nitropyridine was added to the reaction mixture. The reaction mixture was stirred overnight at room temperature and then filtered and washed with water. The crude product was recrystallized from ethanol.

(2,4-Dinitrophenoxyimino)-2-pyridylacetonitrile (15): This compound was obtained as white crystals, 0.26 g (83.07%) yield, mp 210–211 °C; IR (KBr): 2367 (CN), 1604 (C=N), 1535 and 1345 (NO_2) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.56 (dt, 1H, Py-H-5, $J = 6.4$, 0.8 Hz), 7.91 (dt, 1H, Py-H-4, $J = 7.6$, 1.6 Hz), 7.97 (d, 1H, Ar-H, $J = 9.2$ Hz), 8.06 (d, 1H, Py-H-3, $J = 7.6$ Hz), 8.54 (dd, 1H, Ar-H, $J = 9.2$, 2.8 Hz), 8.85 (d, 1H, Py-H-6, $J = 4.4$ Hz), 8.95 (d, 1H, Ar-H,

$J = 2.4$ Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 118.34, 122.33, 122.43, 127.22, 129.39, 137.61, 146.79, 146.84, 146.88, 151.00. Elemental analysis Calcd for $C_{13}H_7N_5O_5$: C, 49.85; H, 2.25; N, 22.36%. Found: C, 50.12; H, 2.43; N, 22.55%.

1-(2,4-Dinitrophenoxy)pyridin-2(1*H*)-one (16): This compound was obtained as white crystals, 0.24 g (86.64%) yield, mp 161–162 °C; IR (KBr): 1671 (C=O), 1538 and 1350 (NO_2) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.35 (dt, 1H, Py-H-5, $J = 7.2$, 2.0 Hz), 6.81 (dd, 1H, Py-H-3, $J = 9.2$, 1.6 Hz), 7.04 (d, 1H, Ar-H, $J = 9.2$ Hz), 7.50 (dt, 1H, Py-H-4, $J = 6.8$, 2.0 Hz), 7.68 (dd, 1H, Py-H-6, $J = 7.2$, 2.0 Hz), 8.41 (dd, 1H, Ar-H, $J = 9.2$, 2.8 Hz), 8.96 (d, 1H, Ar-H, $J = 2.8$ Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 106.59, 116.00, 116.05, 122.82, 122.87, 124.01, 125.24, 129.58, 129.70, 135.12, 140.41, 155.58, 157.01. Elemental analysis Calcd for $C_{11}H_7N_3O_6$: C, 47.66; H, 2.55; N, 15.16%. Found: C, 47.41; H, 2.68; N, 14.97%.

(5-Nitro-2-pyridyloxyimino)-2-pyridylacetonitrile (21): This compound was obtained as white crystals, 0.23 g (85.43%) yield, mp 199–200 °C; IR (KBr): 2371 (CN), 1525 and 1360 (NO_2) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.47 (d, 1H, Ar-H, $J = 9.2$ Hz), 7.53 (dt, 1H, Ar-H, $J = 4.8$, 1.2 Hz), 7.90 (t, 1H, Ar-H, $J = 7.6$ Hz), 8.14 (d, 1H, Ar-H, $J = 8.0$ Hz), 8.63 (dd, 1H, Ar-H, $J = 9.2$, 1.2 Hz), 8.83 (d, 1H, Py-H, $J = 4.8$ Hz), 9.26 (d, 1H, Ar-H, $J = 2.4$ Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 108.37, 109.75, 122.20, 126.89, 126.97, 135.68, 135.74, 137.50, 145.38, 145.44, 147.40, 150.77. Elemental analysis Calcd for $C_{12}H_7N_5O_3$: C, 53.54; H, 2.62; N, 26.01%. Found: C, 53.81; H, 2.48; N, 25.75%.

1-(5-Nitro-2-pyridyloxy)pyridin-2(1*H*)-one (22): This compound was obtained as white crystals, 0.21 g (90.13%) yield, mp 144–145 °C; IR (KBr): 1671 (C=O), 1525 and 1360 (NO_2) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.28 (dt, 1H, Ar-H, $J = 7.2$, 1.6 Hz), 6.78 (dd, 1H, Ar-H, $J = 9.2$, 1.6 Hz), 7.26 (d, 1H, Ar-H, $J = 9.2$ Hz), 7.46 (dt, 1H, Ar-H, $J = 6.8$, 2.0 Hz), 7.55 (dd, 1H, Ar-H, $J = 7.2$, 2.0 Hz), 8.58 (dd, 1H, Ar-H, $J = 9.2$, 2.8 Hz), 9.01 (d, 1H, Ar-H, $J = 2.4$ Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 105.51, 109.63, 123.58, 135.83, 135.92, 135.99, 139.82, 144.73, 157.50, 165.17. Elemental analysis Calcd for $C_{10}H_7N_3O_4$: C, 51.51; H, 3.03; N, 18.02%. Found: C, 51.78; H; 3.29; N, 17.81%.

General Procedure for the Preparation of 12, 14, 18, and 20. 1 mmol of the potassium salt of diethyl (hydroxyimino)malonate or (hydroxyimino)malononitrile was dissolved in 3 mL anhydrous ACN, and then 1 mmol of 1-chloro-2,4-dinitrobenzene or 2-chloro-5-nitropyridine was added to the reaction mixture. The reaction mixture was stirred overnight at room temperature and then allowed to reflux for 1 h. A white precipitate (KCl) was formed, which was then filtered. The solvent was evaporated under vacuo to obtain an oily residue. The crude product was recrystallized from ethanol.

Diethyl 2-(2,4-Dinitrophenoxyimino)malonate (12): This compound was obtained as white crystals, 0.29 g (81.69%) yield, mp 64–65 °C; IR (KBr): 1755, 1726 (C=O), 1539 and 1350 (NO_2) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.42, 1.44 (t, 6H, $2CH_3$, $J = 7.2$ Hz), 4.45, 4.52 (quart, 4H, $2CH_2$, $J = 7.2$ Hz), 8.02 (d, 1H, Ar-H, $J = 9.6$ Hz), 8.50 (dd, 1H, Ar-H, $J = 9.6$, 2.8 Hz), 8.92 (d, 1H, Ar-H, $J = 2.4$ Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.14, 14.20, 63.96, 64.01, 117.82, 122.30, 129.62, 142.84, 150.29, 155.42, 158.30, 158.89. Elemental analysis Calcd for $C_{13}H_{13}N_3O_9$: C, 43.95; H, 3.69; N, 11.83%. Found: C, 44.22; H, 3.91; N, 11.58%.

(2,4-Dinitrophenoxyimino)malononitrile (14): This compound was obtained as white crystals, 0.21 g (80.46%) yield, mp 107–108 °C; IR (KBr): 2367, 2246 (CN), 1542 and 1350 (NO_2) cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.89 (d, 1H, Ar-H, $J = 9.2$ Hz), 8.60 (dd, 1H, Ar-H, $J = 9.2$, 2.3 Hz), 8.99 (d, 1H, Ar-H, $J = 3.1$ Hz). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 104.70, 107.58, 115.27, 118.58, 122.60, 129.78, 137.61, 144.83, 153.33. Elemental analysis Calcd for $C_9H_3N_5O_5$: C, 41.39; H, 1.16; N, 26.82%. Found: C, 41.11; H, 1.45; N, 27.10%.

Diethyl (5-Nitro-2-pyridyloxyimino)malonate (18): This compound was obtained as a colorless oil and was solidified in a refrigerator to obtain a white solid, 0.27 g (86.79%) yield; IR (KBr): 1754, 1725 (C=O), 1539 and 1349 (NO_2) cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.39–1.41 (m, 6H, $2CH_3$), 4.42, 4.47 (quart, 4H, $2CH_2$, $J = 6.9$ Hz), 7.47 (d, 1H, Ar-H, $J = 9.2$ Hz), 8.56 (dd, 1H, Ar-H, $J = 9.2$, 2.3 Hz), 9.17 (d, 1H, Ar-H, $J = 3.1$ Hz). Elemental analysis Calcd for $C_{12}H_{13}N_3O_7$: C, 46.31; H, 4.21; N, 13.50%. Found: C, 46.06; H, 3.97; N, 13.78%.

(5-Nitro-2-pyridyloxyimino)malononitrile (20): This compound was obtained as beige crystals, 0.19 g (87.56%) yield, mp 83–84 °C; IR (KBr): 2367, 2246 (CN), 1540 and 1349 (NO_2) cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.43 (d, 1H, Ar-H, $J = 9.2$ Hz), 8.56 (dd, 1H, Ar-H, $J = 9.2$, 3.1 Hz), 9.16 (d, 1H, Ar-H, $J = 3.1$ Hz). Elemental analysis Calcd for $C_8H_3N_5O_3$: C, 44.25; H, 1.39; N, 32.25%. Found: C, 44.01; H, 1.63; N, 31.98%.

General Procedure for the Preparation of 13 and 19. 1 mmol of ethyl cyano(hydroxyimino)acetate was dissolved in 3 mL of ACN, then 2 mmol of NaOH was added, and the reaction mixture was heated until the NaOH was dissolved. 1 mmol of 1-chloro-2,4-dinitrobenzene or 2-chloro-5-nitropyridine was then added to the reaction mixture. The mixture was stirred overnight at room temperature. A white precipitate (NaCl) was formed, which was then filtered. The solvent was evaporated under vacuo to yield the crude product, which was recrystallized from ethanol.

Ethyl Cyano(2,4-dinitrophenoxyimino)acetate (13): This compound was obtained as pale yellow crystals, 0.28 g (90.90%) yield, mp 122–123 °C; IR (KBr): 2367 (CN), 1752 (CO), 1535 and 1346 (NO_2) cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.45 (t, 3H, CH_3, $J = 7.7$ Hz), 4.51 (quart, 2H, CH_2, $J = 7.7$ Hz), 7.95 (d, 1H, Ar-H, $J = 9.2$ Hz), 8.55 (dd, 1H, Ar-H, $J = 9.2$, 3.1 Hz), 8.94 (d, 1H, Ar-H, $J = 3.1$ Hz). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 14.09, 64.99, 106.63, 118.66, 122.35, 129.54, 131.73, 137.54, 144.02, 154.23, 156.09. Elemental analysis Calcd for $C_{11}H_8N_4O_7$: C, 42.87; H, 2.62; N, 18.18%. Found: C, 43.12; H, 2.96; N, 17.89%.

Ethyl Cyano(5-nitro-2-pyridyloxyimino)acetate (19): This compound was obtained as a white powder, 0.23 g (87.06%) yield, mp 105–106 °C; IR (KBr): 2371 (CN), 1753 (CO), 1525 and 1360 (NO_2) cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.45 (t, 3H, CH_3, $J = 6.9$ Hz), 4.51 (quart, 2H, CH_2, $J = 6.9$ Hz), 7.49 (d, 1H, Ar-H, $J = 9.2$ Hz), 8.64 (dd, 1H, Ar-H, $J = 9.2$, 3.1 Hz), 9.23 (d, 1H, Ar-H, $J = 2.3$ Hz).

^{13}C NMR ($CDCl_3$): δ 14.11, 64.75, 100.00, 109.85, 135.94, 142.66, 145.23, 158.30. Elemental analysis Calcd for $C_{10}H_8N_4O_5$: C, 45.46; H, 3.05; N, 21.21%. Found: C, 45.21; H, 2.77; N, 21.49%.

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Supporting Information

Kinetic calculations, ^{1}H and ^{13}C NMR spectra of compounds **12–16**, ^{1}H and ^{13}C NMR spectra of compounds **18–22**. This material is available free of charge on the web at http://www.csj.jp/journals/bcsj/.

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