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Conjugate Addition versus Cycloaddition/Condensation of Nitro Compounds in Water: Selectivity, Acid–Base Catalysis, and Induction Period

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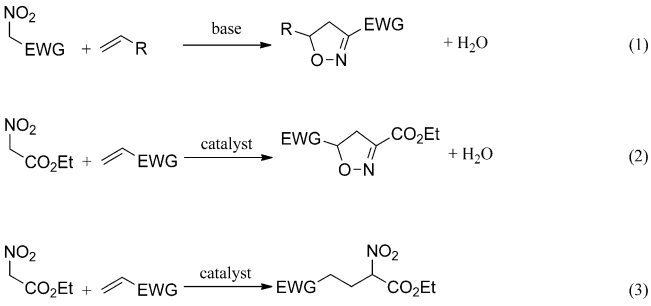
Abstract: Nitroacetates and nitroacetamides react in water as in chloroform with electron-deficient dipolarophiles to give condensation or conjugate addition products under base catalysis. In general, high selectivity towards condensation is observed in water, with shorter induction periods than in chloroform. In water, condensations slowly occur even without base; kinetic profiles evidence the catalytic effect of the base, which should be related to the conversion into the tautomer nitronic acid. Condensations in water provide convenient access to isoxazole derivatives bearing various functional groups including ammonium, carboxy, and carboxyamide.

Keywords: cycloaddition · homogeneous catalysis · Michael addition · nitrogen heterocycles · water

Introduction

Nitro compounds are a useful source of carbon nucleophiles; the corresponding nitronate anions[1] react with electron-poor alkenes or alkynes (Michael acceptors)[2] and the resulting conjugate addition has been extensively employed for the formation of carbon–carbon bonds.[3] An ultimate goal is to perform the reaction in water with an efficient catalyst.[4]

On the other hand, activated primary nitro compounds have been shown to undergo base-catalyzed condensations with unsaturated substrates (dipolarophiles) to give isoxazole derivatives [Equation (1)]. When these reactions are carried out in chloroform, a certain specificity of the base is observed; the best results, obtained in general with biprotic tertiary amines {e.g., 1,4-diazabicyclo[2.2.2]octane (DABCO)}, have been related to their ability to establish hydrogen bonds.[5,6]



In reactions of ethyl nitroacetate (**1**) in chloroform solution with dipolarophiles that are Michael acceptors, condensations [Eq. (2)] compete, as expected, with the conjugate addition [Eq. (3)]. The ratio between the two products (variable during the reaction) was found to depend on the base employed and on its concentration. The results were rationalized by considering that condensations to isoxazolines occur after considerable induction times. Condensations, in general, predominate when a Cu^{II} salt is added to the catalytic system.[7]

Water as a reaction medium is known to dramatically modify reaction selectivity and rate in comparison to the same reaction performed in organic solvents.[8–10] This was the case for condensations in water between nitroacetates and dipolarophiles, in which a drop in the induction time and rate enhancement in comparison with those observed with chloroform solvent were evidenced. Under these conditions no specificity of the base was observed; any organic or inorganic base, at the appropriate concentration, had the same effect provided its strength was higher than or comparable to that of the nitronate (see below).[11]

In the present study we wish to examine how selectivity and rates are modified in water compared with chloroform and to gain insight into the mechanism of condensations in water. To this end, kinetic profiles of several reactions either

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in chloroform or in water are compared, with or without base catalysis. We thus attempt to address the question concerning the formation of nitrile oxide[12] as intermediates in this condensation, or, in other words, determine whether dehydration precedes or follows cycloaddition.[13] Induction periods,[14,15] a common feature of these reactions, are often observed in multistep reactions,[16] therefore, observed changes might be related to changes in reaction mechanism. Moreover, the selectivity observed in chloroform between condensation and conjugate addition with dipolarophiles that are Michael acceptors might be modified when the same reactions are carried out in water.

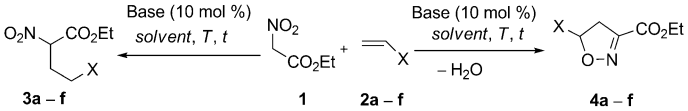
Results and Discussion

The previously reported reactions in chloroform have been repeated in water under similar conditions; the results are collected in Table 1, together with those in chloroform, which are included for comparison.[7]

The occurrence of reactions in water, even without added base, previously reported for allyl alcohol and styrene, is extended to electron-poor dipolarophiles (Table 1, entries 8, 9, 22, and 25).[11] Conjugate additions without base catalysis are well known,[17] whereas condensations are new. Moreover, in the absence of base, condensations predominate over additions, with the exception of vinyl ketone **2e**; in this case, the minor condensation product **4e** is detectable. It should be noted that no condensations are observed in chloroform without base addition.[18]

Among the examples given in Table 1, high selectivity was observed towards condensation only with dimethylacrylamide in water rather than in chloroform (**2b**; Table 1, entries 5–7). In contrast, addition selectively occurs in the reaction with ketone **2e** in chloroform (Table 1, entry 23). The products of condensations with methyl acrylate (Table 1, entries 1–4), with acrylonitrile (Table 1, entries 10–16) and with phenyl vinyl sulfone (Table 1, entries 17–22) occur as mixtures with the respective addition products. Experiments conducted over a range of temperatures confirmed that condensations are favored as the temperature increases (Table 1, cf. entries 2–4, 12–14, and 19–20).[7]

Table 1. Effect of solvent and temperature on the competition between adducts **3** and condensed cycloadducts **4**.[a]



a: X = CO_2Me; **b**: X = $CONMe_2$; **c**: X = CN; **d**: X = SO_2Ph; **e**: X = COMe; **f**: X = CO_2H

Entry	2	Base[b]	T [°C]	t [h]	Conv. [%][c]	Solvent	Yield 3 [%][d]	Yield 4 [%][d]
1[e]	**a**	DABCO	60	48	100	$CHCl_3$	59	41
2	**a**	NaOH	10	168	41	H_2O	42	0
3[f]	**a**	NaOH	30	168	100	H_2O	31	19
4[f]	**a**	NaOH	60	20	100	H_2O	23	21
5[e]	**b**	DABCO	60	48	100	$CHCl_3$	18	82
6	**b**	DABCO	60	20	100	H_2O	0	90
7	**b**	NaOH	60	20	100	H_2O	0	95
8	**b**	None	60	20	53	H_2O	0	34[g]
9	**b**	None	60	72	100	H_2O	0	58[g]
10[e]	**c**	DABCO	30	240	100	$CHCl_3$	64	36
11[e]	**c**	DABCO	60	168	86	$CHCl_3$	41	36
12	**c**	NaOH	10	168	25	H_2O	19	0
13	**c**	NaOH	30	168	97	H_2O	4	26
14	**c**	NaOH	60	20	100	H_2O	20	52
15	**c**	NaOH	100	5	68	H_2O	11	37
16	**c**	DABCO	60	20	93	H_2O	5	34
17[e]	**d**	DABCO	60	20	100	$CHCl_3$	80	19
18	**d**	NaOH	10	168	26	H_2O	10	0
19	**d**	NaOH	30	168	88	H_2O	84	0
20	**d**	NaOH	60	20	100	H_2O	91	6
21	**d**	NaOH	100	5	72	H_2O	42	29
22	**d**	None	60	72	33	H_2O	4	24
23[e]	**e**	DABCO	60	48	100	$CHCl_3$	97	0
24	**e**	NaOH	60	21	100	H_2O	53	0
25	**e**	none	60	20	100	H_2O	69	6
26[h]	**f**	DABCO	60	48	20	$CHCl_3$	20	0
27	**f**	NaOH	60	20	100	H_2O	0	50

[a] See the Experimental Section for details. [b] DABCO: 1,4-diazabicyclo[2.2.2]octane. [c] Conversion based on the consumption of dipolarophile determined by ^{1}H NMR spectroscopic analysis. [d] Spectroscopic yield determined by ^{1}H NMR spectroscopic analysis with the use of an internal standard. [e] From ref. [7]. [f] Spectroscopic yields are lower than conversions as a result of partial methyl ester hydrolysis. [g] Partial hydrolysis of the ethyl ester was observed. [h] Compound **3f** was isolated and characterized, see the Experimental Section.

The ester groups undergo slow hydrolysis, particularly when they are on the isoxazoline ring and for long reaction times. The yields of products **4** are therefore severely reduced in some cases (Table 1, entries 4, 8, and 9), whereas amides are less liable to this drawback. Reactions with acrylic acid (**2f**), also included in Table 1, show sluggish conversion into the addition product (**3f**) in chloroform (Table 1, entry 26), whereas in water (Table 1, entry 27) selective condensation to the isoxazoline **4f** was observed.

Chloroform, the standard solvent used in previously reported reactions, contains about 90 ppm water. The model reaction between ethyl nitroacetate (**1**) and dimethylacrylamide (**2b**) was repeated in chloroform saturated with water (containing ca. 800 ppm of water). The results obtained in

Abstract in Italian: *Nitroacetati e nitroacetammidi reagiscono in acqua o cloroformio con dipolarofili elettronpoveri per dare prodotti di cicloaddizione-condensazione o di addizione coniugata. La reazione è catalizzata da basi. In generale la condensazione avviene con un'elevata selettività in acqua, con periodi di induzione più brevi rispetto al cloroformio. La condensazione in acqua avviene, seppur in maniera più lenta, anche in assenza di base. I profili cinetici evidenziano l'effetto catalitico della base che è stato correlato all'equilibrio di tautomerizzazione del nitrocomposto nel corrispondente acido nitronico. La condensazione in acqua è un'utile e conveniente procedura sintetica per la preparazione di derivati isossazolici contenenti vari gruppi funzionali tra cui ammonio, carbossilico, carbossiammide.*

the two cases do not differ significantly, the final proportion being about 84% condensation to **4b** versus 16% addition to **3b** in either reaction. As reported before,[11] condensations exhibit a dramatic shortening of induction times in water compared with chloroform. To compare the kinetic profiles in water and in chloroform, model reactions (methyl nitroacetate with amides) were selected on the basis of complete solubility in either deuterated solvents for direct NMR monitoring.

Methyl nitroacetate (**5**) in chloroform undergoes conjugate addition with acrylamide (**2g**) after a long induction time (Figure 1, some condensation product being detected later), whereas use of methacrylamide (**8g**) in the same solvent gave only the condensation product (Figure 2). However, after short induction times in water both reactions go to completion within 3 h to selectively give the condensation products **6** (Figure 1) and **9** (Figure 2), respectively. It should be noted that the two reaction profiles are almost identical. As already pointed out,[11] no significant dependence on the kind of base employed was observed in water (Table 1, entries 6 vs. 7 and 14 vs. 16).

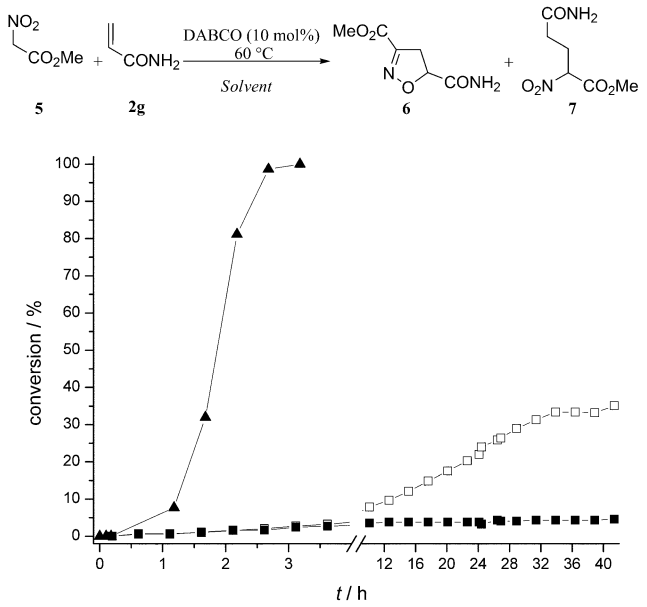


Figure 1. Kinetic profile for reactions between methyl nitroacetate (**5**) and acrylamide (**2g**) catalyzed by DABCO in water or chloroform. Effect of solvent on the conversion of the dipolarophile: D_2O (▲ **6**), $CDCl_3$ (□ **7** and ■ **6**). The reaction was performed in a septum-sealed NMR tube in the probe of the spectrometer at 60 °C: methyl nitroacetate (0.265 M), acrylamide (0.106 M), and DABCO (0.0106 M). See the Experimental Section for details.

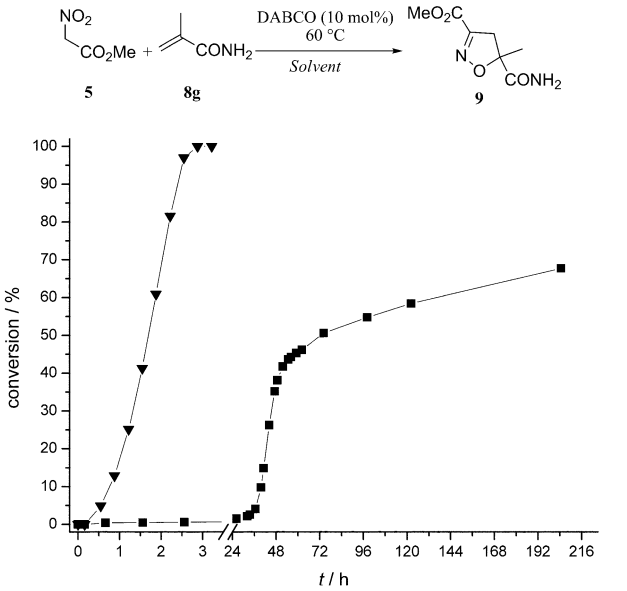


Figure 2. Kinetic profile for reactions between methyl nitroacetate (**5**) and methacrylamide (**8g**) catalyzed by DABCO in water or chloroform. Effect of solvent on the conversion of the dipolarophile: D_2O (▼), $CDCl_3$ (■). The reaction was performed in a septum-sealed NMR tube in the probe of the spectrometer at 60 °C: methyl nitroacetate (0.265 M), methacrylamide (0.106 M), and DABCO (0.0106 M). See the Experimental Section for details.

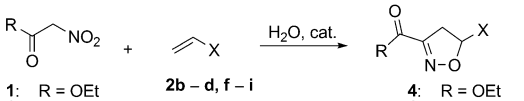
Useful preparations: Several reactions that selectively afford condensation products in water, reported hereinafter, involve nitro compounds with ester, amide, or ammonium functional groups and dipolarophiles with ester, amide, phosphonate, carboxylic, cyano, ammonium, or sulfonyl groups. The model reactions illustrated in Figure 1 and Figure 2 are repeated using the ethyl ester, as incomplete solubility does not hamper the success of the reaction. Several other reagents have limited solubility in water, particularly phenylvinylsulfone (**2d**) and *N*-butyl nitroacetamide (**11**), nevertheless, the condensations are successful.[11,19] Therefore, the method appears to be of general preparative value, using inexpensive catalyst and a straightforward procedure to deliver good to excellent yields. Examples of the reaction performed on a larger scale (products **14g** and **15g**) are described in the Experimental Section.

Reaction times up to 24 h are indicated for convenience even though the dipolarophile was used up after a few hours in many cases; only the 5-substituted 4,5-dihydroisoxazoles (**4** and **13**; Table 2) were observed by ^1H NMR spectroscopic analysis of crude reaction mixtures, with negligible amounts of by-products. Similarly, condensations with methacrylic acid or its ester or amide selectively give the 5-disubstituted regioisomers (**14**–**17**; Table 3).

From condensations of methyl nitroacetamide with methyl propiolate and with propiolic acid, minor amounts (**20a**) or traces (**20f**) of the 3,4-disubstituted regioisomers were obtained in addition to the 3,5-disubstituted regioisomers (Table 4).

Dipolarophiles bearing a carboxyl group have been employed in the past to directly prepare isoxazole derivatives by cycloaddition with nitrile oxides.[20] However, reactions of nitro compounds with carboxylic dipolarophiles such as **2f** (Table 2, entries 2, and 9), **8f** (Table 2, entries 2, and 5), or **18f** (Table 4, entry 2) are reported here for the first time because the dehydrating agents previously used would interact

Table 2. 4,5-Dihydroisoxazoles from nitro compounds and terminal olefins.[a]



1: R = OEt
10: R = NHMe

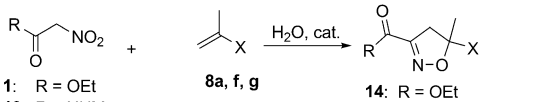
2b – d, f – i
b: X = $CONMe_2$
c: X = CN
d: X = SO_2Ph
f: X = CO_2H
g: X = $CONH_2$
h: X = $CONH(CH_2)_2NH_3^+$
i: X = $P(O)(OEt)_2$

4: R = OEt
13: R = NHMe

Entry	Product	R	X	Yield [%][b]
1	**4b**	OEt	$CONMe_2$	72
2	**4f**	OEt	CO_2H	60
3	**4g**	OEt	$CONH_2$	84
4	**4h**	OEt	$CONH(CH_2)_2NH_3^+$	94
5	**4i**	OEt	$P(O)(OEt)_2$	62
6	**13b**	NHMe	$CONMe_2$	79
7	**13c**	NHMe	CN	78
8	**13d**	NHMe	SO_2Ph	87
9	**13f**	NHMe	CO_2H	76
10	**13g**	NHMe	$CONH_2$	77
11	**13h**	NHMe	$CONH(CH_2)_2NH_3^+$	99
12	**13i**	NHMe	$P(O)(OEt)_2$	94

[a] Reaction conditions: water, 60 °C, NaOH (10 mol %). [b] Yield of isolated product.

Table 3. 4,5-Dihydroisoxazoles from nitro compounds and methacrylic derivatives.[a]



1: R = OEt
10: R = NHMe
11: R = NHBu
12: R = $NH(CH_2)_2NH_3^+$

8a, f, g
a: X = CO_2Me
f: X = CO_2H
g: X = $CONH_2$

14: R = OEt
15: R = NHMe
16: R = NHBu
17: R = $NH(CH_2)_2NH_3^+$

Entry[a]	Product	R	X	Yield [%][b]
1	**14a**	OEt	CO_2Me	73
2	**14f**	OEt	CO_2H	65
3	**14g**	OEt	$CONH_2$	78
4	**15a**	NHMe	CO_2Me	77
5	**15f**	NHMe	CO_2H	88
6	**15g**	NHMe	$CONH_2$	98
7	**16a**	NH*n*Bu	CO_2Me	65
8	**17g**	$NH(CH_2)_2NH_3^+$	$CONH_2$	92

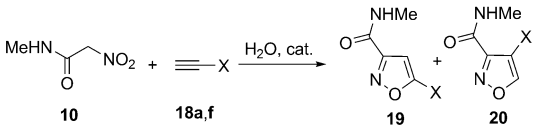
[a] Reaction conditions: water, 60 °C, NaOH (10 mol %). [b] Yield of isolated product.

with the carboxylic function. Syntheses from unsaturated esters or nitriles are commonly reported, but require an additional step to convert the adducts into carboxylic acids.[21,22]

The above carboxylic acids are challenging substrates that may interfere with the catalytic system (acrylic acid: pK_a [25 °C, H_2O] 4.26,[23] propiolic acid: pK_a [25 °C, H_2O] 1.85[24,25]).

The presence of an ammonium ion in the dipolarophile does not modify the reactivity (Table 2, entries 4 and 11), nevertheless, the ammonium group as inner salt of nitroacetamide **12** (Table 3, entry 8) deserves some comment (see below).

Table 4. Isoxazoles from nitro compounds and alkynes.[a]



10

18a,f
a: X = CO_2Me
f: X = CO_2H

19

20

Entry	Product	X	Yield [%][b,c]
1	**19a** and **20a**	CO_2Me	71 (8:1)
2	**19f** and **20f**	CO_2H	75[d]

[a] Reaction conditions: water, 60 °C, NaOH (10 mol %). [b] Yield of isolated product. [c] Regioisomeric ratio given in parentheses. [d] Traces of **20f**.

Attempted condensations with 1,2-disubstituted ethylenic esters (dimethyl maleate, dimethyl fumarate, methyl crotonate) did not show different selectivities in water compared to chloroform.[7] However, the yields were significantly affected by ester hydrolysis. Because condensation reactions with carboxylic dipolarophiles in water are practical, reactions have been carried out directly on fumaric, maleic, and *E*-crotonic acids with ethyl nitroacetate and *N*-methyl nitroacetamide. Refining these preparative methods was beyond the scope of the current study at this stage. As an example, the condensation of *N*-methyl nitroacetamide (**10**) with fumaric acid (**21**)[21b,26] is reported in the experimental section; the main product (*trans*-dicarboxylic acid **22**, ca. 65 %) contains approximately 10 % of the *cis*-isomer **23** and traces of the decarboxylated product **13f**.[27]

Acid-base catalysis and induction period: As pointed out above, condensations of nitroacetic ester **1** occur slowly even without base catalysis. *N*-Methyl nitroacetamide (**10**) behaves similarly, thus suggesting that this might be the rule, at least for reactions that are not exceedingly slow. Some condensations showing this behavior have been selected as model reactions with the aim of investigating the role of acid-base catalysis and the origin of induction time.

N-Methyl nitroacetamide (**10**) in aqueous solution without base or dipolarophile was almost unaffected after 24 h. Under the same reaction conditions, **10** reacted with acrylamide (**2g**) to give the expected dihydroisoxazole derivative **13g** without added base; both reagents are quite soluble in water, and the medium is weakly acidic due to the presence of *N*-methyl nitroacetamide (**10**) in excess (the pK_a of *N*-methylnitroacetamide was evaluated by potentiometric titration[28] to be 5.46). The kinetic profile in D_2O,[29] illustrated in Figure 3 (top), exhibits a very long induction time (15 to 20 h), then the condensation is complete within 26 h. The same reaction, carried out with addition of 0.1 equiv of base (Table 2, entry 10), followed the kinetic profile illustrated in Figure 3 (bottom); after a much shorter induction time, a constant rate was attained at approximately 60 % reaction progress and the condensation was complete after 105 min.

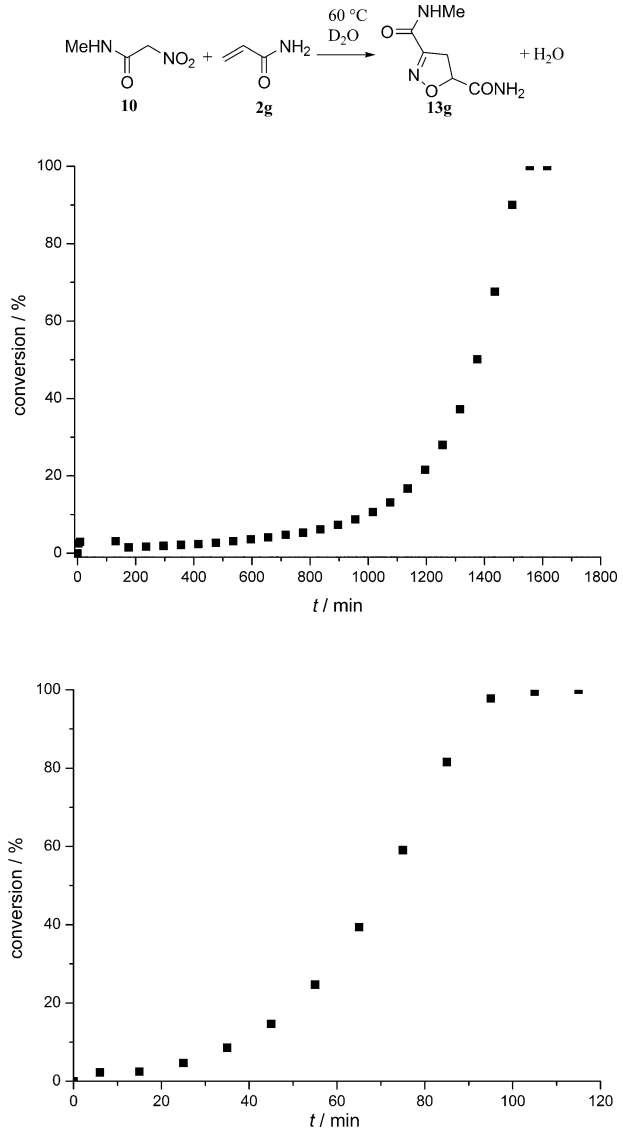


Figure 3. Reaction profile of reactions of *N*-methyl nitroacetamide (**10**) and acrylamide (**2g**) without addition of base (top) and with 0.1 equiv of base (bottom). See the Experimental Section for details.

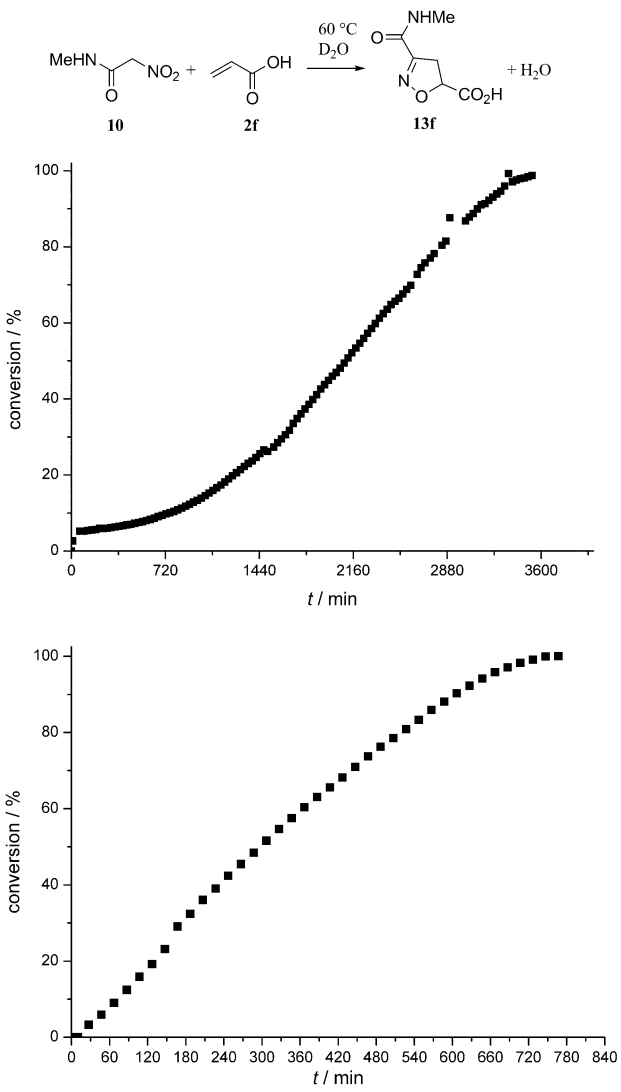


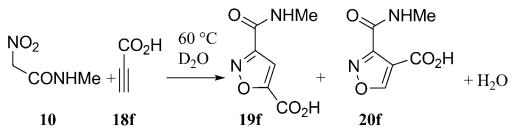
Figure 4. Reaction profile of reactions of *N*-methyl nitroacetamide (**10**) and acrylic acid (**2f**) without addition of base (top) and with 0.1 equiv of base (bottom). See the Experimental Section for details.

Aqueous *N*-methyl nitroacetamide, under the same conditions with base but without dipolarophile, decomposed within 2 h into a mixture containing residual *N*-methyl nitroacetamide and N^3,N^5-dimethyl-3,4-bis-carbamoylfuroxan (**26**; 15%) in addition to other unidentified products.

Any base, as already pointed out,[11] had the same catalytic effect provided its strength was higher or comparable to that of the nitronate. However, the best results were achieved with 0.1 equiv of base. Increasing the proportion of added base has been shown to reduce the condensation rate in two model reactions of ethyl nitroacetate. After 18 h, no condensation product was detected when 1 equiv of base was added.[11]

No base was needed for *N*-methyl nitroacetamide (**10**) to react with dipolarophiles containing a carboxylic function; the kinetic profiles are illustrated in Figure 4 (top) for acrylic acid (pK_a 4.26,[23] 4.25[30]) and in Figure 5 (□) for propiolic acid (pK_a 1.85[24]). The usual pattern can be observed, with long induction times and constant rates being observed during the central part of the reactions. On addition of a strong base (NaOH, 0.1 equiv), in fact this is converted into weaker bases (nitronate and carboxylates) in amounts depending on strength and concentration, and changing as the reactions proceed.

In the reaction with acrylic acid, even in the presence of the product **13f** (pK_a 3.73, see the Experimental Section), there was enough nitronate to ensure a considerable catalytic effect; the reaction profile of the catalyzed reaction is illustrated in Figure 4 (bottom). However, in the presence of acids much stronger than the nitronic acid, such as propiolic acid and its condensation product, the isoxazole-5-carboxylic acid derivative (pK_a 2.04 is reported for the unsubstituted



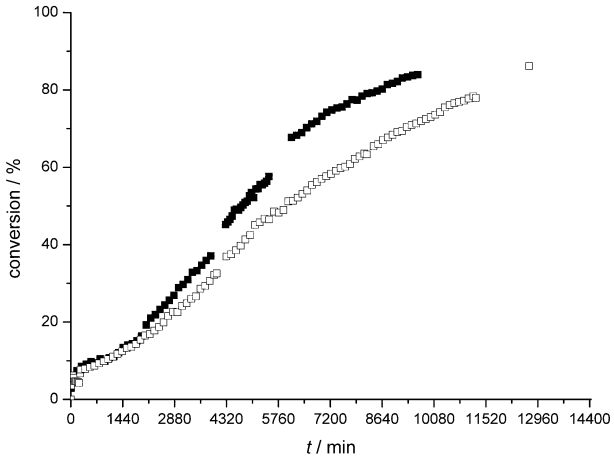
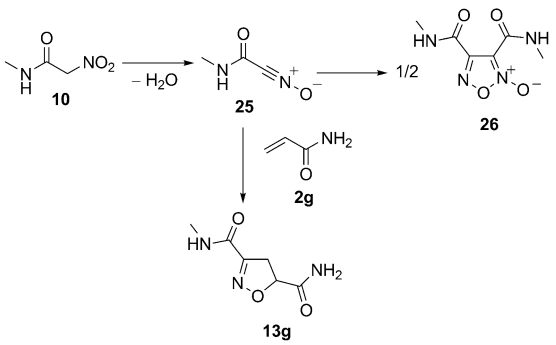


Figure 5. Reaction profile for the condensation of methyl nitroacetamide (**10**) and propiolic acid (**18 f**) with base (■) and without (□). N.B., 1440 min = 1 day. See the Experimental Section for details.

isoxazole-5-carboxylic acid),[31] the amount of nitronate becomes negligible. In fact, the kinetic profile of the reaction, illustrated in Figure 5 (■), does not differ significantly from that of the same reaction without base (□). These results, indicating that the nitronate is the actual catalytic species, suggest that tautomerization is the key step subject to basic catalysis. However, because condensation is hampered by high base concentrations (1 equiv),[11] nitronate is not the reacting species in this reaction, unlike conjugate addition occurring with dipolarophiles that are Michael acceptors.

On the other hand, when the nitro compound bears an amino group, and therefore exists as an inner salt, this slowly reacts with acrylamide to give addition rather than condensation products. However, the corresponding hydrochloride reacted as usual upon addition of 0.1 equiv of base (Table 3, entry 8). Constant reaction rates observed during the central part of some reactions indicate that the steady-state approximation appears to be effective in these cases.[32]

The above pieces of evidence provide some hints concerning the mechanism. The observed stability of *N*-methyl nitroacetamide (**10**) in water and its almost quantitative conversion (without base) into the condensation product with acrylamide (**2 g**) allows a path that operates through nitrile oxide intermediate **25** in this case, to be ruled out (Scheme 1). The presence of furoxan **26**, detected in the experiments in the presence of base, indicates that nitrile oxide **25** might be an intermediate in a minor route in the catalyzed condensation (Scheme 1). If the role of nitrile oxide is negligible as an intermediate in this reaction, the condensation should be reasonably ascribed to a 1,3-dipolar cycloaddition preceding dehydration. In fact, a base-catalyzed monopolar addition to electron-poor dipolarophiles



Scheme 1. Reaction pathway via nitrile oxide.

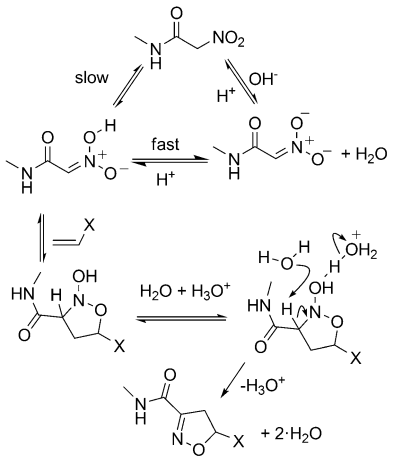
competes with the condensation, as shown before, and the addition products cannot be converted into isoxazoles.

The occurrence of condensations even without base catalysis suggests that nitronic acid is the 1,3-dipole reacting with dipolarophiles and the catalytic effect of a base should be related to the equilibrium between nitro compound and nitronic acid. In fact, tautomeric equilibria of nitro compounds are known to be attained faster under base catalysis, whereas acid catalysis does not seem actual.[33–36] A particular example of acid-catalyzed conversion into nitronic acid was reported,[37,38] due to the presence of the tropylium ion as an electrofuge instead of H^+. It seems reasonable that a sufficiently strong base is required to produce a catalytic effect by substantially increasing the amount of nitronate.

In some cases (see Figure 4 and Figure 5), before the induction period, a small amount of product (5–10 %) was detected. However, this does not seem to depend on the small interval preceding reaction monitoring. On the other hand, previous studies on the tautomerism of methyl nitroacetate[39,40] report a concentration of the nitronic acid tautomer at equilibrium too low to be invoked as an explanation, whereas, to the best of our knowledge, the tautomerism of *N*-methyl nitroacetamide has not been investigated so far.[41]

The dramatic induction times observed in these reactions are compatible with a multistep process, including tautomerization to nitronic acid,[42] cycloaddition, and dehydration, as illustrated for *N*-methyl nitroacetamide in Scheme 2. The induction period in consecutive reactions has been discussed in detail[16] and shown to depend on relative rates of the steps involved. The cycloaddition might be reversible or not, whereas the final acid-catalyzed dehydration step occurs irreversibly, possibly through the illustrated transition state.

Additional kinetic data would be required to identify the rate-determining step. The reported experiments at different temperatures indicate that condensations are favored by temperature increases and this result would be consistent with dehydration rather than cycloaddition as the rate-determining step.[43]



Scheme 2. Plausible mechanism.

Conclusions

Reactions of nitroacetic esters or amides with electron-deficient dipolarophiles in water selectively produce isoxazole derivatives as a result of cycloaddition-condensation, whereas in chloroform, Cu^{II} catalysis is required for the same purpose. The method appears to be of preparative value, with good to excellent yields and compatibility with many functional groups. Slow condensations occur even without base catalysis; long induction periods are ascribed to pre-equilibria that are followed by acid-catalyzed irreversible water elimination.

Experimental Section

General methods: Melting points were determined in capillaries with a Büchi 510 apparatus and are uncorrected. Chromatographic separations were performed on silica gel 60 (40–6.3 μm) with analytical grade solvents, driven by a positive pressure of air; R_f values refer to TLC (visualized with UV light and/or by dipping the plates into a solution of permanganate followed by heating with a heat gun) carried out on alumina-backed plates coated with 25 mm silica gel (Merck F_{254}), with the same eluant indicated for the column chromatography. For gradient column chromatography R_f values refer to the more polar eluant. Solvent removal was performed by evaporation on a rotavap at RT. ^{1}H and ^{13}C NMR spectra were recorded with a Varian Mercuryplus 400 spectrometer (operating at 400 MHz for ^{1}H and 100.58 MHz for ^{13}C) unless otherwise stated. The ^{1}H NMR data are reported as multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet or unresolved, br = broad signal), coupling constant(s) in Hz, integration). Multiplicity of the ^{13}C NMR signals and assignments were determined by means of gHSQC and gHMBC experiments. Chemical shifts were determined relative to the residual solvent peak ($CHCl_3$: $\delta = 7.24$ ppm for ^{1}H NMR and $\delta = 77.0$ ppm for ^{13}C NMR; H_2O: $\delta = 4.79$ ppm for ^{1}H NMR). Chemical shifts for ^{13}C NMR in D_2O are given relative to CH_3CN ($\delta = 1.47$ ppm) as internal reference. EI (electron impact) mass spectra were obtained with a Shimadzu QP5050A quadrupole based mass spectrometer (direct introduction unless otherwise stated, at ionizing voltage of 70 eV). Ion mass/charge ratios (m/z) are reported as values in atomic mass units followed by the intensities relative to the base peak in parenthesis. ESI (electronspray ionization) mass spectra were obtained with a ThermoFisher LCQ-Fleet ion trap instrument and spectra were registered with either ESI^+ or ESI^- techniques. IR spectra were recorded with a Perkin–Elmer 881 spectrophotometer; bands are characterized as broad (br), strong (s), medium (m), or weak (w). Elemental analyses were obtained with an Elemental Analyser Perkin–Elmer 240C apparatus. Water content of chloroform was evaluated by Karl Fisher coulometric titration with a 831 KF Metrohm coulometer. The pH values were determined with a CyberScan510 pH meter produced by Eutech instruments. Solubility in water at 25 °C of dipolarophiles (mol/dm^3):[44] very soluble *N,N*-dimethylacrylamide (**2b**; 5.38), acrylonitrile (**2c**; 1.87 from literature[45]), acrylamide (**2g**; 30.3, from literature at 30 °C[46]), soluble methacrylamide (**8g**; 0.27), methyl acrylate (**2a**; 0.46), methyl methacrylate (**8a**; 0.25), acrylic acid (**2f**; 0.55), methacrilic acid (**8f**; 0.30), methyl vinylketone (**2e**; 0.58), diethylvinylphosphonate (**2i**; 0.20), fumaric acid (**21**; 0.32 mol/L), slightly soluble: phenylvinylsulfone (**2d**; 0.013). All compounds were named with Autonom (Beilstein Information Systems) and modified where appropriate.

Materials: All alkenes and alkynes are liquid at RT, except acryl amide (**2g**; m.p. 84.5–85[47]), phenylvinylsulfone (**2d**; m. p. 70–71 °C[48]), and methacrylamide (**8g**; m.p. 111.5–112 °C[49]). Commercially available (Lancaster and Aldrich) ethyl nitroacetate (**1**), methylnitroacetate (**5**), organic bases, olefins, and alkynes were used as supplied except acrylic acid, which was purified by vacuum distillation before use. NaOH volumetric standard 0.100 N water solution was supplied from Aldrich. $CHCl_3$ (ethanol free) was filtered through a short pad of potassium carbonate just before use and its water-content was determined to be 80–100 ppm. Chloroform saturated with water contains 780 ppm of water. Water (deionized) was twice distilled from $KMnO_4$ before use. *N*-Methyl nitroacetamide (**10**) was prepared by following a previously reported procedure.[5b] (2-Acryloylaminoethyl)carbamic acid *tert*-butyl ester was prepared by following a previously reported procedure.[50] Ambersept 900 anionic resin was washed with deionized water until neutral pH before use.

Determination of ionization constants: The ionization constant of nitro compound **10** was determined in water by potentiometric titration. The procedure is described in the Supporting Information.

The pK_a values in water for methyl nitroacetate (**5**) and 3-(methylcarbamoyl)-4,5-dihydroisoxazole-5-carboxylic acid (**13f**) were determined with identical procedures. pK_a (**5**) 5.68 ($T = 23$ °C) (Lit. 5.56,[39] 5.82[51]); pK_a (**13f**) 3.73 ($T = 22$ °C).

Screening of reaction conditions (Table 1): The conversions and spectroscopic yields reported in Table 1 refer to reactions performed in an apparatus in which eight reactions were carried out simultaneously. A mixture of ethyl nitroacetate (**1**; 1.06 mmol), base (0.0424 mmol or none), and olefin (0.424 mmol) in water or chloroform (1.4 mL) was kept at the indicated temperature. For each dipolarophile, details of experiments are described in the Supporting Information. Compound **3f** (2-nitro-pentanedioic acid 1-ethyl ester) was prepared for reference as reported in the Supporting Information. Spectroscopic data are in agreement with those previously reported.[52]

Condensation of acrylamide (2g; Figure 1) and of methacrylamide (8g; Figure 2) with methyl nitroacetate (5) in water: Reactions were run in a septum-sealed 5 mm NMR tube spinning (20 Hz) in the probe of the spectrophotometer at 60 °C for reaction times less than 24 h. For longer experiments, reactions were run in a thermostated oil bath at 60 °C. See the Supporting Information for details and spectroscopic data for compounds **6**, **7**, and **9**.

Kinetic profiles: General procedure for data reported in Figures 3–5 are described in the Supporting Information.

Behavior of *N*-methyl nitroacetamide (10) in water in the absence of dipolarophile:

a) Without added base: The ^{1}H NMR spectrum of a solution of **10** (37.5 mg, 0.318 mmol) and CH_3CN (10 mg) in D_2O (0.755 g, 0.70 mL) heated at 60 °C was registered after 10 min and after 24 h: no difference was observed.

b) With added base: The ^{1}H NMR spectrum of a solution of **10** (37.5 mg, 0.318 mmol), 4.24 M NaOH (0.005 mL, 0.0212 mmol), and CH_3CN (10 mg) in D_2O (0.750 g, 0.695 mL) heated at 60 °C was registered at intervals of 10 min. After 2 h, the signals of furoxan **26** were observed in addition to other unidentified signals. After 24 h, no residual signal of *N*-methyl nitroacetamide (**10**) was detected.

Compound 26: Data from crude reaction mixture evaporated to dryness. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.02$ (d, $J = 4.8$ Hz, 3H; CH_3NH), 3.04 (d, $J = 4.8$ Hz, 3H; CH_3NH), 8.62 (br s, 1H; N*H*), 9.60 ppm (br s, 1H; N*H*);[53] ^{13}C NMR (100.58 MHz, $CDCl_3$): $\delta = 26.6$ (q, 2 C; $NHCH_3$), 110.1 (s, $C{=}N^+O^-$), 150. 5 (s, *C*=N), 155.6 (s, *C*O), 156.0 ppm (s, *C*O); MS (ESI$^+$): *m*/*z*: 201 $[M + H]^+$.

***N*-Butyl-2-nitroacetamide (11)**: A mixture of methyl nitroacetate (**5**; 0.33 g, 2.8 mmol) and *N*-butylamine (2.02 g, 28 mmol) was stirred at RT for 2 days. After this time, excess amine was removed under reduced pressure. The residue was cooled, acidified with 3 N HCl to pH 3–4 and extracted with EtOAc (4×10 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give **11** (0.440 g, 98%) as a low-melting solid.[54] ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.91$ (t, $J = 7.2$ Hz, 3H; CH_3), 1.28–1.40 (m, 2H; $CH_2CH_2CH_3$), 1.46–1.58 (m, 2H; $CH_2CH_2CH_3$), 3.22–3.38 (m, 2H; CH_2NHCO), 5.06 (s, 2H; CH_2NO_2), 6.52 ppm (br s; N*H*); ^{13}C NMR (100.58 MHz, $CDCl_3$): $\delta = 13.6$ (q, CH_3), 19.9 (t, CH_2CH_3), 31.1 (t, $CH_2CH_2CH_3$), 39.9 (t, CH_2NHCO), 77.9 (t, CH_2NO_2), 159.9 ppm (s, *C*O); IR ($CHCl_3$): $\tilde{\nu} = 3417$ (w), 2962 (m), 2933 (m), 2873 (w), 1622 (s) (C=O), 1560 (s), 1533 (s), 1465 (w), 1377 cm^{-1} (w); MS (ESI$^-$): *m*/*z* (%): 159 $(M-1)^-$; elemental analysis calcd (%) for $C_6H_{12}N_2O_3$ (160.17): C 44.99, H 7.55, N 17.49; found: C 44.96, H 7.84, N 17.69.

2-(2-Nitro-acetylamino)ethylammonium chloride (12·Cl): Prepared as previously reported.[55] Ethylenediamine (0.673 mg, 11.2 mmol) was added to a mixture of methyl nitroacetate (**5**; 1.33 g, 11.2 mmol), pyridine (1.4 mL), water (1.4 mL), and the reaction mixture was stirred at 100 °C. After 45 min, the reaction mixture was cooled and concentrated under reduced pressure. The residue was treated with MeOH and the precipitate was filtered, washed with MeOH, and dried to give *N*-nitroacetyl-1,2-ethylenediamine (1.1 g, 66%) as a yellowish solid; m.p. 140–142 °C (dec.) [Lit.[55] 140–142 °C (dec.)]; ^{1}H NMR (400 MHz, D_2O): $\delta = 3.23$ (t, $J = 5.9$ Hz, 2H; CH_2NH_2), 3.66 (t, $J = 5.9$ Hz, 2H; CH_2CONH), 6.52 ppm (s, 1H; $CH{=}NO_2^-$; ^{1}H NMR (400 MHz, 60 °C, D_2O): $\delta = 3.55$ (t, $J = 6.4$ Hz, 2H; CH_2NH_2), 3.97 ppm (t, $J = 6.4$ Hz, 2H; CH_2CONH); $CH{=}NO_2^-$ not detected; ^{13}C NMR (100.58 MHz, D_2O): $\delta = 37.1$ (t, CH_2CONH), 40.1 (t, CH_2NH_2), 166.9 ppm (s, *C*O), CH_2NO_2 not detected; elemental analysis calcd (%) for $C_4H_9N_3O_3$ (147.13): C 32.65, H 6.17, N 28.56; found: C 32.23, H 6.47, N 28.85.

The inner salt was dissolved in aqueous 5% HCl (pH 1) then dried to give the chloride of **12** (1.37 g, 99%); m.p. 118–121 °C (dec.); ^{1}H NMR (400 MHz, D_2O): $\delta = 3.26$ (t, $J = 18$ Hz, 2H; $CH_2NH_3^+$), 3.66 (t, $J = 18$ Hz, 2H; CH_2CONH), 5.41 ppm (m, exchange with D_2O, CH_2NO_2); ^{13}C NMR (100.58 MHz, D_2O): $\delta = 37.8$ (t, CH_2CONH), 39.4 (t, $CH_2NH_3^+$), 165.0 ppm (s, *C*O), $CHNO_2$ not detected; IR (KBr): $\tilde{\nu} = 3600$–2400 (br), 1670 (s), 1578 (s), 1561 (s), 1494 (m), 1435 (w), 1385 (w), 1276 (w), 1176 cm^{-1} (w). MS (ESI$^+$): *m*/*z* (%): 148 $[M+H]^+$; elemental analysis calcd (%) for $C_4H_{10}N_3O_3{\cdot}HCl$ (183.59): C 26.17, H 5.49, N 22.89; found: C 26.26, H 5.63, N 22.75.

***N*-(2-Aminoethyl)acrylamide hydrochloride (2h·Cl)**: 2-Acryloylaminoethylcarbamic acid *tert*-butyl ester (214 mg, 1 mmol) was dissolved in a cooled solution of 3 N HCl (0.5 mL) and MeOH (1.5 mL). The mixture was then stirred for 30 min at r.t., the solvent was removed under reduced pressure, and the residue was carefully triturated with diethyl ether to afford **2h·Cl** (148 mg, 99%) as a white powder; m.p. 79–81 °C (dec.); ^{1}H NMR (400 MHz, D_2O): $\delta = 3.24$ (t, $J = 6.0$ Hz, 2H; $CH_2NH_3^+$), 3.63 (t, $J = 5.2$ Hz, 2H; CH_2NHCO), 5.84 (dd, $J = 2.0$, 9.6 Hz, 1H; $CH{=}CH_2$), 6.23–6.28 (m, 1H; $CH{=}CH_2$), 6.29–6.35 ppm (m, 1H; $CH{=}CH_2$); ^{13}C NMR (100.59 MHz, D_2O): $\delta = 37.4$ (t, CH_2NHCO), 39.8 (t, $CH_2NH_3^+$), 128.6 (t, $CH{=}CH_2$), 130.1 (d, $CH{=}CH_2$), 170.0 ppm (s, *C*ONH); IR ($CDCl_3$): $\tilde{\nu} = 3600$–2400 cm^{-1} (br); MS (ESI$^+$): *m*/*z* (%): 115 $[M+H]^+$; elemental analysis calcd (%) for $C_5H_{10}N_2O{\cdot}HCl$ (150.06): C 39.87, H 7.36, N 18.60; found: C 39.93, H 7.43, N 19.02.

***N*-(2-Aminoethyl)acrylamide trifluoroacetic acid salt (2h trifluoroacetate)**: 2-Acryloylamino-ethyl-carbamic acid *tert*-butyl ester (214 mg, 1 mmol) was treated with trifluoroacetic acid (3 mL, 39 mmol) in CH_2Cl_2 (2 mL) at r.t. for 1 h. After this time, the solvent was removed under reduced pressure and the residue was carefully triturated with diethyl ether to afford **2h** trifluoroacetate (224 mg, 99%) as a dark-yellow oil. ^{1}H NMR (400 MHz, D_2O): $\delta = 3.22$ (t, $J = 6.0$ Hz, 2H; $CH_2NH_3^+$), 3.62 (t, $J = 5.2$ Hz, 2H; CH_2NHCO), 5.83 (dd, $J = 2.4$, 9.2 Hz, 1H; $CH<C=>CH_2$), 6.23–6.28 (m, 1H; $CH<C=>CH_2$), 6.29–6.35 ppm (m, 1H; $CH<C=>CH_2$); ^{13}C NMR (100.59 MHz, D_2O): $\delta = 37.4$ (t, CH_2NHCO), 39.8 (t, $CH_2NH_3^+$), 117.0 (q, ^1J(C,F) = 291.4 Hz, CF_3CO), 128.6 (t, $CH<C=>CH_2$), 130.2 (d, $CH<C=>CH_2$), 163.6 (q, ^2J(C,F) = 36.0 Hz, CF_3CO), 170.0 ppm (s, *C*ONH); IR ($CDCl_3$): $\tilde{\nu} = 3600$–2400 (br), 1766 (w), 1667 cm^{-1} (m); MS (ESI$^+$): *m*/*z* (%): 115 $[M+H]^+$.

Preparation of isoxazolines (Table 2, Table 3) and isoxazoles (Table 4):

General procedure: Aqueous 4.24 M NaOH (0.010 mL, 0.0424 mmol) was added to a mixture of nitro compound (0.636 mmol, unless otherwise stated) **1**, **10**, **11** or **12** with alkene or alkyne (0.424 mmol) and water (1390 mg), and the mixture was vigorously stirred in a sealed tube at 60 °C. After the indicated time, the reaction mixture was worked-up and, if necessary, the residue was purified by chromatography on silica gel with the indicated eluant.

*Ethyl 5-[(dimethylamino)carbonyl]-4,5-dihydroisoxazole-3-carboxylate (**4b**)*: From *N*,*N*-dimethylacrylamide (**2b**; 42 mg, 0.424 mmol, 44 μL) and ethyl nitroacetate (**1**; 85 mg, 0.636 mmol, 70 μL). After 20 h, the reaction mixture was concentrated under reduced pressure and the residue was purified by chromatography on silica gel (hexane/ethyl acetate, 1:1; $R_f = 0.15$) to give **4b** (65 mg, 72%) as a colorless oil. Elemental analysis calcd (%) for $C_9H_{14}N_2O_4$ (214.22): C 50.46, H 6.59, N 13.08; found: C 50.27, H 6.61, N 13.33. The spectral data are identical to those previously reported.[7]

*Compound **4f***: From acrylic acid (**2f**; 30.6 mg, 0.424 mmol, 29.1 μL) and ethyl nitroacetate (**1**; 85 mg, 0.636 mmol, 70 μL). After 20 h, the reaction mixture was neutralized with aqueous 4 M NaOH and washed with diethyl ether (4×1.5 mL). The aqueous phase was acidified to pH 1 with aqueous 3 M HCl and washed with hexane (2×2 mL) then extracted with ethyl acetate (4×2 mL). The combined ethyl acetate phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford **4f** (48 mg, 60%) as a colorless oil.[22] Alternatively, the reaction mixture was carefully concentrated under reduced pressure and the residue was purified by chromatography on silica gel (elution first with $CHCl_3$ and then with $CHCl_3$/*i*PrOH/AcOH, 9:1:0.1; $R_f = 0.36$) to give **4f** as a colorless oil (yield as above). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.37$ (t, $J = 7.2$ Hz, 3H; CH_2CH_3), 3.52–3.53 (m, 1H; 4-H), 3.54–3.56 (m, 1H; 4-H), 4.36 (q, $J = 7.2$ Hz, 2H; CH_2CH_3), 5.24 ppm (dd, $J = 8.6$, 10.7 Hz, 1H; H-5); ^{1}H NMR (400 MHz, D_2O): $\delta = 1.37$ (t, $J = 7.2$ Hz, 3H; CH_2CH_3), 3.52 (unsymmetrical dd, $J = 7.2$, 18.0 Hz, 1H; 4-H), 3.70 (unsymmetrical dd, $J = 12.8$, 18.0 Hz, 1H; 4-H), 4.40 (q, $J = 7.2$ Hz, 2H; CH_2CH_3), 5.40 ppm (dd, $J = 7.2$, 12.8 Hz, 1H; H-5); ^{13}C NMR (100.58 MHz, $CDCl_3$): $\delta = 14.0$ (q, CH_3), 37.8 (t, C-4), 62.6 (t, CH_2O), 79.1 (d, C-5), 151.2 (s, C-3), 159.7 (s, CO_2Et), 173.1 ppm (s, CO_2H); IR (neat): $\tilde{\nu} = 3400$–2200 (broad signal), 2985 (m), 1730 (s), 1601 (w) (C=N), 1562 (w), 1257 cm^{-1} (m); MS (ESI$^-$, MeOH): *m*/*z*: 186 $[M-H]^-$; elemental analysis calcd (%) for $C_7H_9NO_5$ (187.15): C 44.92, H 4.85, N 7.48; found: C 44.77, H 4.70, N 7.10.

*Ethyl 5-carbamoyl-4,5-dihydroisoxazole-3-carboxylate (**4g**)*: From acrylamide (**2g**; 30.1 mg, 0.424 mmol) and ethyl nitroacetate (**1**; 85 mg, 0.636 mmol, 70 μL). The reaction mixture was cooled after 6 h and kept at 4 °C overnight. The liquid was removed and the precipitate was washed with cold H_2O (1 mL) and then warmed at 60 °C in an oven to give **4g** (52.7 mg) as a white powder. The aqueous fractions were combined and evaporated to dryness. The residue was dissolved in $CHCl_3$ and filtered through a short pad of silica gel. The solution was concentrated to afford additional **4g** (13.3 mg) as a white powder. Overall yield 84%; m.p. 123–124 °C;[56] ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.36$ (t, $J = 7.2$ Hz, 3H; CH_2CH_3), 3.52 (d, $J = 4.4$ Hz, 1H; 4-H), 3.54 (d, $J = 1.2$ Hz, 1H; 4-H), 4.34 (q, $J = 7.2$ Hz, 2H; CH_2CH_3), 5.17 (dd, $J = 7.6$, 10.8 Hz, 1H; 5-H), 5.82 (br. s, 1H; N*H*), 6.58 ppm (br. s, 1H; N*H*); ^{13}C NMR (100.59 MHz, $CDCl_3$): $\delta = 14.0$ (q, CH_3), 38.2 (t, C-4), 62.5 (t, CH_2O), 80.4 (d, C-5), 152.2 (s, C-3), 159.5 (s, CO_2Et), 172.1 ppm (s, $CONH_2$); IR (KBr): $\tilde{\nu} = 3427$ (m) (N-H), 3192 (m), 2987 (w), 1725 (s) (OC=O), 1654 (s) (NC=O), 1634 (m), 1605 (w) (C=N), 1423 (w), 1326 (w), 1264 cm^{-1} (m); MS (EI): *m*/*z* (%): 186 (3) $[M]^+$, 142 (57) $[M-CONH_2]^+$, 114 (14), 70 (33), 44 (100) $[CONH_2]^+$; elemental analysis calcd (%) for $C_7H_{10}N_2O_4$ (186.17): C 45.16; H 5.41; N 15.05; found: C 45.10; H 5.19; N 14.75.

*5-(2-Amino-ethylcarbamoyl)-4,5-dihydroisoxazole-3-carboxylic acid ethyl ester trifluoroacetic salt (**4h** trifluoroacetate)*: From **2h** trifluoroacetate (97 mg, 0.424 mmol) and ethyl nitroacetate (**1**; 85 mg, 0.636 mmol, 70 μL). After 24 h, the mixture was diluted with H_2O (5 mL) and washed with $CHCl_3$ (3×5 mL). The aqueous phase was evaporated under reduced pressure to give the product **4h** trifluoroacetate (150 mg, 94%) as a yellow oil. ^{1}H NMR (400 MHz, D_2O): δ=1.36 (t, J=6.9 Hz, 3H; CH_2CH_3), 3.21 (t, J=6.0 Hz, 2H; $CH_2NH_3^+$), 3.50 (unsymmetrical dd, J=6.8, 18.4 Hz, 1H, 4-H), 3.52–3.67 (m, 2H; CH_2NCO), 3.69 (unsymmetrical dd, J=12.4, 18.4 Hz, 1H; 4-H), 4.35 (q, J=6.9 Hz, 2H; CH_2CH_3), 5.40 ppm (dd, J=6.8, 12.4 Hz, 1H; 5-H); ^{13}C NMR (100.58 MHz, D_2O): δ=13.8 (q, CH_3), 37.4 (t, $CH_2NH_3^+$), 38.4 (t, C-4), 39.6 (t, CH_2NCO), 64.1 (t, CH_2O), 81.3 (d, C-5), 117.0 (q, J(C,F)=291.5 Hz, CF_3CO), 153.9 (s, C-3), 161.4 (s, CO_2Et), 163.6 (q, ^2J(C,F)=36.2 Hz, CF_3CO), 173.6 ppm (s, CONH); IR (MeOH): $\tilde{\nu}$=1729 (s) (OC=O), 1680 (s) (NC=O), 1601 (w) (C=N), 1543 cm^{-1} (w); MS (ESI$^+$): m/z (%): 230 [M+H]$^+$ (100); elemental analysis calcd (%) for $C_9H_{15}N_3O_4{\cdot}CF_3CO_2H$ (343.26): C 38.49; H 4.70; N 12.24; found: C 38.80; H 4.86; N 11.41.

*5-(Diethoxy-phosphoryl)-4,5-dihydro-isoxazole-3-carboxylic acid ethyl ester (**4i**)*: From diethyl vinyl phosphonate (**2i**; 69.6 mg, 0.424 mmol) and ethyl nitroacetate (**1**; 85 mg, 0.636 mmol, 70 μL). After 15 h, the reaction mixture was cooled and extracted with EtOAc (5×1.5 mL), the organic phases were combined, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by chromatography on silica gel (Et_2O; R_f= 0.27) to give **4i** (73.7 mg, 62%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.30–1.35 (m, 9H; 3×CH_2CH_3), 3.42–3.52 (m, 2H; 4-H), 4.16–4.26 (m, 4H; 2×$POCH_2CH_3$), 4.32 (q, J=6.8 Hz, 2H; $COCH_2CH_3$), 4.86 ppm (t, J=10.8 Hz, 1H; 5-H); ^{13}C NMR (100.58 MHz, $CDCl_3$): δ= 14.0 (q, $COCH_2CH_3$), 16.4 (q, $POCH_2CH_3$), 16.5 (q, $POCH_2CH_3$), 36.4 (t, C-4), 62.3 (t, $COCH_2$), 63.4 (t, J(C,P)=7.6 Hz, $POCH_2$), 63.7 (t, J(C,P)= 7.6 Hz, $POCH_2$), 77.2 (d, J(C,P)=168.0 Hz, C-5), 151.4 (s, ^3J(C,P)= 6.9 Hz, C-3), 159.8 ppm (s, CO); ^{31}P (80.96 MHz, $CDCl_3$): δ=17.4 ppm; IR ($CDCl_3$): $\tilde{\nu}$=2984 (m), 2939 (w), 2909 (w), 1722 (s) (C=O), 1599 (w) (C=N), 1253 cm^{-1} (s) (P=O); MS (ESI$^+$): m/z (%): 302 [M+Na]$^+$; elemental analysis calcd (%) for $C_{10}H_{18}NO_6P$ (279.23): C 43.01, H 6.50, N 5.02; found: C 42.84, H 6.75, N 5.94.

*N^3,N^5,N^5-Trimethyl-4,5-dihydroisoxazole-3,5-dicarboxamide (**13b**)*: From *N*,*N*-dimethylacrylamide (**2b**; 42 mg, 0.424 mmol) and *N*-methyl nitroacetamide (**10**; 75.1 mg, 0.636 mmol). After 20 h, the mixture was cooled and treated with Ambersep 900 OH and concentrated under reduced pressure to give **13b** (67 mg, 79%) as a pale-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ=2.85 (d, J=5.2 Hz, 3H; $NHCH_3$), 2.94 (s, 3H; NCH_3), 3.10 (s, 3H; NCH_3), 3.34 (dd, J=11.7, 17.9 Hz, 1H; 4-H), 3.85 (dd, J=7.8, 17.9 Hz, 1H; 4-H), 5.35 (dd, J=7.7, 11.7 Hz, 1H; 5-H), 6.66 ppm (br. s, 1H; NH); ^{13}C NMR (100.58 MHz, $CDCl_3$): δ=26.0 (q, $NHCH_3$), 36.0 (t, C-4), 36.0 (q, NCH_3), 37.1 (q, NCH_3), 79.2 (d, C-5), 154.3 (s, C-3), 159.6 (s, CONHMe), 166.7 ppm (s, $CONMe_2$); IR ($CDCl_3$): $\tilde{\nu}$=3434 (m) (N-H), 2941 (w), 1662 (s) (C=O), 1602 (w) (C=N), 1543 (m), 1417 cm^{-1} (m); MS (EI): m/z (%)=199 (1) [M]$^+$, 169 (4), 127 (37) [M−$CONMe_2$]$^+$, 72 (100) [$CONMe_2$]$^+$, 58 (97) [CONHMe]$^+$; elemental analysis calcd (%) for $C_8H_{13}N_3O_3$ (199.21): C 48.23, H 6.58, N 21.09; found: C 46.34, H 6.71, N 21.09.

*5-Cyano-4,5-dihydro-N-methylisoxazole-3-carboxamide (**13c**)*: From acrylonitrile (**2c**; 22.5 mg, 0.424 mmol) and *N*-methyl nitroacetamide (**10**; 125.1 mg, 1.06 mmol). After 24 h, aqueous 4.24 M NaOH was added to pH 8, and the mixture was washed with hexane (4×1.5 mL). The aqueous phase was acidified to pH 1 with 3 M HCl, washed with hexane (4× 1.5 mL) and then extracted with ethyl acetate (5×1.5 mL). The combined extracts were dried (sodium sulfate), filtered, and concentrated under reduced pressure to give a yellow oil residue that was purified by chromatography on silica gel (hexane/Et_2O, 1:4; R_f=0.19) to yield **13c** (50.6 mg, 0.330 mmol, 78%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ= 2.92 (d, J=5.0 Hz, 3H; $NHCH_3$), 3.62 (s, 1H; 4-H), 3.64 (d, J=2.7 Hz, 1H; 4-H), 5.33 (dd, J=5.6, 6.6 Hz, 1H; 5-H), 6.62 ppm (br. s, 1H; NH); ^{13}C NMR (100.58 MHz, $CDCl_3$): δ=26.3 (q, NCH_3), 40.0 (t, C-4), 67.8 (d, C-5), 116.0 (s, CN), 153.4 (s, C-3), 158.2 ppm (s, CONHMe); MS (EI): m/z (%): 153 (2) [M]$^+$, 123 (8) [M−NHMe]$^+$, 98 (12), 70 (5), 58 (48) [$CONHCH_3$]$^+$, 30 (100) [$NHCH_3$]$^+$; IR ($CDCl_3$): $\tilde{\nu}$=3434 (m) (N-H), 2945 (w) (C−H), 2245 (w) (C≡N), 1685 (s) (C=O), 1604 (w) (C=N), 1544 (m), 1418 (w), 1267 cm^{-1} (w); elemental analysis calcd (%) for $C_6H_7N_3O_2$ (153.14): C 47.06, H 4.61, N 27.44; found: C 46.71, H 4.75, N 27.30.

*4,5-Dihydro-N-methyl-5-(phenylsulfonyl)isoxazole-3-carboxamide (**13d**)*: From phenylvinylsulfone (**2d**; 71.3 mg, 0.424 mmol) and *N*-methyl nitroacetamide (**10**; 125.1 mg, 1.06 mmol). After 5 h, **13d** began to precipitate out of the solution as a fine white powder. After 22 h, the reaction mixture was cooled and the white precipitate was collected by centrifugation, washed with cold water (0.7 mL), and oven-dried at 50 °C to afford pure **13d** (99 mg, 87%) as a white powder; m.p. 99–101 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=2.87 (d, J=4.8 Hz; $NHCH_3$), 3.67 (unsymmetrical dd, J=11.4, 19.6 Hz, 1H; 4-H), 3.93 (unsymmetrical dd, J=5.2, 19.6 Hz, 1H; 4-H), 5.50 (dd, J=5.2, 11.0 Hz, 1H; 5-H), 6.48 (br. s, 1H; NH), 7.56–7.62 (m, 2H; Ph-H), 7.68–7.73 (m, 1H; Ph-H), 7.93–7.97 ppm (m, 2H; Ph-H); ^{13}C NMR (100.58 MHz, $CDCl_3$): δ=26.2 (q, $NHCH_3$), 35.9 (t, C-4), 93.9 (d, C-5), 129.4 (d, 2 C; Ph-C_{ortho}), 129.7 (d, 2 C; Ph-C), 134.8 (d, Ph-C), 135.0 (s, Ph-C_{ipso}), 154.2 (s, C-3), 158.2 ppm (s, CONHMe); MS (EI): m/z (%): 142 (25), 127 (20) [M−SO_2Ph]$^+$, 77 (30) [C_6H_5]$^+$, 70 (9), 58 (100) [CONHMe]$^+$; IR ($CDCl_3$): $\tilde{\nu}$=3402 (s) (N-H), 3070 (w), 2980 (w), 1676 (s) (C=O), 1609 (m) (C=N), 1539 (m), 1447 (w), 1318 cm^{-1} (w); elemental analysis calcd (%) for $C_{11}H_{12}N_2O_4S$ (268.29): C 49.24, H 4.51, N 10.44; found: C 48.846, H 4.334, N 10.81.

*3-(Methylcarbamoyl)-4,5-dihydroisoxazole-5-carboxylic acid (**13f**)*: From acrylic acid (**2f**; 30.5 mg, 0.424 mmol) and *N*-methyl nitroacetamide (**10**; 75.1 mg, 0.636 mmol). After 18 h, the reaction mixture was neutralized with aqueous 4 M NaOH, and washed with diethyl ether (4×1.5 mL). The aqueous phase was acidified to pH 1 with aqueous 3 M HCl, washed with diethyl ether (4×1.5 mL), then extracted with ethyl acetate (5×1.5 mL). The combined ethyl acetate extracts were dried (sodium sulfate), filtered, and concentrated under reduced pressure to afford **13f** (55 mg, 76%) as a clear oil that solidified on standing; m.p. 157 °C (dec.); ^{1}H NMR (400 MHz, D_2O): δ=2.84 (s, 3H; CH_3), 3.47 (unsymmetrical dd, J=6.8, 18.0 Hz, 1H; 4-H), 3.66 (unsymmetrical dd, J=12.3, 18.0 Hz, 1H; 4-H), 5.16 ppm (dd, J=6.8, 12.3 Hz, 1H; 5-H); ^{13}C NMR (100.58 MHz, D_2O): δ=26.4 (q, CH_3), 38.4 (t, C-4), 79.8 (d, C-5), 154.8 (s, C-3), 161.8 (s, $CONH_2$), 174.6 ppm (s, CO_2H); IR (KBr): $\tilde{\nu}$=3700–2300 (br), 3345 (N-H), 2622 (w), 1721 (s) (C=O), 1652 (s) (C=O), 1596 (w) (C=N), 1566 (w), 1421 (w), 1275 (w), 1248 (w), 1230 cm^{-1} (w); MS (EI): m/z (%): 142 (2), 127 (9) [M−CO_2H]$^+$, 70 (8), 58 (100) [CONHMe]$^+$; elemental analysis calcd (%) for $C_6H_8N_2O_4$ (172.14): C 41.86, H 4.68, N 16.27; found: C 41.46, H 4.74, N 16.44.

*N^3-Methyl-4,5-dihydroisoxazole-3,5-dicarboxamide (**13g**)*: From acrylamide (**2g**; 30.1 mg, 0.424 mmol) and *N*-methyl nitroacetamide (**10**; 75.1 mg, 0.636 mmol). After 20 h, on cooling, the precipitated product **13g** was collected, washed with cold H_2O (1 mL), and oven-dried at 80 °C (1 h). The product (56 mg, 77%) was obtained as a white powder; m.p. 192–194 °C; ^{1}H NMR (400 MHz, D_2O): δ=2.89 (s, 3H; $NHCH_3$), 3.46 (unsymmetrical dd, J=6.8, 18.4 Hz, 1H; 4-H), 3.70 (unsymmetrical dd, J=12.4, 18.4 Hz, 1H; 4-H), 5.32 ppm (dd, J=6.8, 12.4 Hz, 1H; 5-H); ^{13}C NMR (100.59 MHz, D_2O): δ=26.5 (q, $NHCH_3$), 38.8 (t, C-4), 80.4 (d, C-5), 155.0 (s, C-3), 161.7 (s, CONHMe), 175.7 ppm (s, $CONH_2$); IR (KBr): $\tilde{\nu}$=3402 (N−H), 3328 (N−H), 3206 (N-H), 2978, 1659 (C=O), 1597 (C=N), 1547, 1439 cm^{-1}; MS (EI): m/z (%): 127 (14) [M−$CONH_2$]$^+$, 70 (10), 58 (100) [CONHMe]$^+$, 44 (36) [$CONH_2$]$^+$; elemental analysis calcd (%) for $C_6H_9N_3O_3$ (171.15): C 42.10, H 5.30, N 24.55; found: C 41.89, H 5.57, N 24.31.

*4,5-Dihydro-isoxazole-3,5-dicarboxylic acid 5-[(2-amino-ethyl)-amide] 3-methylamide hydrochloride (**13h**·Cl)*: From 2-acryloylaminoethylammonium **2h**·Cl (63.8 mg, 0.424 mmol) and *N*-methyl nitroacetamide (**10**; 75.1 mg, 0.636 mmol). After 5 h, the mixture was filtered through a glass Pasteur pipette filled with Ambersep 900 OH^- resin (1 mL). The resin was washed with H_2O (3 mL) and the aqueous fractions were combined and evaporated under reduced pressure. The residue was triturated with Et_2O, affording 4,5-dihydro-isoxazole-3,5-dicarboxylic acid 5-[(2-amino-ethyl)-amide] 3-methylamide (88 mg, 99%) as a white powder. M.p. 140–144 °C (dec); ^{1}H NMR (400 MHz, D_2O): δ=2.80–2.86 (m, 2H; CH_2NH_2), 2.88 (s, 3H; $NHCH_3$), 3.30–3.49 (m, 3H; CH_2NHCO and H-4), 5.32 ppm

(dd, $J=7.2$, 12.4 Hz, 1H; 5-H); ^{13}C NMR (100.58 MHz, D_2O): $\delta=26.4$ (q, NCH_3), 38.8 (t, C-4), 40.2 (t, CH_2NH_2), 41.5 (t, CH_2NCO), 80.8 (d, C-5), 155.1 (s, C-3), 161.7 (s, CONHMe), 173.0 ppm (s, CONHCH$_2$); IR (KBr): $\tilde{\nu}=1667$ (m), 1600 cm^{-1} (w); MS (ESI$^+$): m/z (%): 215 $[M+H]^+$ (100); elemental analysis calcd (%) for $C_8H_{14}N_4O_3$·(214.22): C 44.85, H 6.59, N 26.15; found: C 44.46, H 6.58, N 29.49.

The above amine (35 mg, 0.164 mmol) was dissolved in H_2O (1 mL) and 3 N HCl (0.25 mL) was added. The mixture was evaporated and the residue was triturated with Et_2O, affording **13h**·Cl (41 mg, 99%) as a white powder. M.p. 170–175 °C (dec); ^{1}H NMR (400 MHz, D_2O): $\delta=2.88$ (s, 3H; NHCH_3), 3.48 (unsymmetrical dd, $J=6.8$, 18.4 Hz, 1H; 4-H), 3.22 (t, $J=5.6$ Hz, 2H; $CH_2NH_3^+$), 3.53–3.68 (m, 2H; CH_2NHCO), 3.69 (unsymmetrical dd, $J=12.8$, 18.4 Hz, 1H; 4-H), 5.36 ppm (dd, $J=6.8$, 12.4 Hz, 1H; 5-H); ^{13}C NMR (100.58 MHz, D_2O): $\delta=26.5$ (q, NCH_3), 37.4 (t, $CH_2NH_3^+$), 38.7 (t, C-4), 39.6 (t, CH_2NCO), 80.7 (d, C-5), 155.2 (s, C-3), 161.6 (s, CONHMe), 173.8 ppm (s, CONHCH$_2$); IR (KBr): $\tilde{\nu}=3600$–2660 (br), 1660 (s), 1596 (w), 1534 cm^{-1}.

*Diethyl 3-(methylcarbamoyl)-4,5-dihydroisoxazol-5-ylphosphonate (**13i**)*: From diethyl vinylphosphonate (**2i**; 69.6 mg, 0.424 mmol) and *N*-methyl nitroacetamide (**10**; 75.1 mg, 0.636 mmol). After 15 h, the reaction mixture was cooled, concentrated, and the residue was purified by chromatography on silica gel ($CHCl_3$/MeOH, 95:5; $R_f=0.43$) to give **13i** (106 mg, 94%) as a colorless oil. ^{1}H NMR (400 MHz, D_2O): $\delta=1.39$ (t, ^1J(H,H)=6.9 Hz, 6H; 2×POCH$_2$CH_3), 2.90 (s, 3H; NHCH_3), 3.46–3.58 (m, 1H; 4-H), 3.66–3.78 (m, 1H; 4-H), 4.26–4.36 (m, 4H; 2×POCH_2CH$_3$), 4.86 ppm (ddd, ^2J(H,P)=12.4 Hz, ^3J(H,H)=9.2, 3.2 Hz, 1H; 5-H); ^{13}C NMR (100.58 MHz, D_2O): $\delta=16.2$ (q, POCH$_2$CH_3), 16.3 (q, POCH_2CH$_3$), 26.5 (q, CONHCH_3), 36.4 (t, C-4), 65.7 (t, ^2J(C,P)=4.6 Hz; POCH_2), 65.8 (t, ^2J(C,P)=4.6 Hz; POCH_2), 76.6 (d, J(C,P)=168.6 Hz; C-5), 155.2 (s, ^3J(C,P)=4.1 Hz; C-3), 161.4 ppm (s, CO); ^{31}P (80.95 MHz, D_2O): $\delta=19.3$ ppm; IR (KBr): $\tilde{\nu}=3434$ (m) (N–H), 2984 (w), 2941 (w), 2910 (w), 1680 (s) (C=O), 1603 (w) (C=N), 1541 (m), 1251 cm^{-1} (s) (P=O); MS (ESI$^+$): m/z (%): 287 $[M+Na]^+$; elemental analysis calcd (%) for $C_9H_{17}N_2O_5P$ (264.22): C 40.91, H 6.49, N 10.60; found: C 40.52, H 6.62, N 10.72.

*5-Methyl-4,5-dihydro-isoxazole-3,5-dicarboxylic acid 3-ethyl ester 5-methyl ester (**14a**)*: From methyl methacrylate (**8a**; 42.5 mg, 0.424 mmol, 45 μL) and ethyl nitroacetate (**1**; 85 mg, 0.636 mmol, 70 μL). After 20 h, the reaction mixture was extracted with Et_2O (4×1.5 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the product **14a** (67 mg, 73%) as a yellow oil. Elemental analysis calcd (%) for $C_9H_{13}NO_5$ (215.20): C 50.23, H 6.09, N 6.51; found: C 49.85, H 5.92, N 6.95. The spectral data are identical to those previously reported.[7]

*3-(Ethoxycarbonyl)-5-methyl-4,5-dihydroisoxazole-5-carboxylic acid (**14f**)*: From methacrylic acid (**8f**; 36.5 mg, 0.424 mmol, 36 μL) and ethyl nitroacetate (**1**; 85 mg, 0.636 mmol, 70 μL). After 72 h, the reaction mixture was concentrated under reduced pressure and the residue was mixed with EtOAc (6 mL). The obtained suspension was stirred for a few minutes at RT. After filtration, the organic phase was concentrated under reduced pressure to give **14f** (55 mg, 65%) as a yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=1.33$ (t, $J=6.9$ Hz, 3H; CH$_2$CH_3), 1.69 (s, 3H; CCH_3), 3.10 and 3.69 (ABq, $J=18.0$ Hz, 2H; 4-H), 4.35 ppm (q, $J=6.9$ Hz, 2H; CH_2CH$_3$); ^{13}C NMR (100.58 MHz, $CDCl_3$): $\delta=14.0$ (q, CH$_2$CH_3), 23.2 (q, C-5CH_3), 43.4 (t, C-4), 62.4 (t, CH_2CH$_3$), 88.1 (s, C-5), 151.2 (s, C-3), 159.9 (s, CO$_2$Et), 174.8 ppm (s, CO$_2$H); MS (EI): m/z (%): 156 (54) $[M-CO_2H]^+$, 84 (39), 69 (28), 45 (49), 42 (100); IR (neat): $\tilde{\nu}=$ 3600–2400 (broad signal), 2985 (w), 2939 (w), 1728 (s) (C=O), 1597 (w) (C=N), 1380 (w), 1269 cm^{-1} (m); elemental analysis calcd (%) for $C_8H_{11}NO_5$ (201.18): C 47.76; H 5.51, N 6.96; found: C 48.03, H 5.94, N 7.16.

*Ethyl 5-carbamoyl-5-methyl-4,5-dihydroisoxazole-3-carboxylate (**14g**)*: From methacrylamide (**8g**; 36.1 mg, 0.424 mmol) and ethyl nitroacetate (**1**; 85 mg, 0.636 mmol, 70 μL). After 6 h, the reaction mixture was cooled and kept at 4 °C overnight. The precipitate was collected, washed with cold H_2O (1 mL), and then oven dried at 80 °C (3 h) to give **14g** (47.4 mg) as a white powder. The aqueous fractions were combined and evaporated to dryness. The residue was dissolved in $CHCl_3$ and filtered through a short pad of silica gel. On concentration, further **14g** (19.1 mg) was recovered as a white powder. Combined yield: 78%; m.p. 148–150 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=1.34$ (t, $J=7.2$ Hz, 3H; CH$_2$CH_3), 1.69 (s, 3H; CCH_3), 3.10 and 3.65 (ABq, $J=18.8$ Hz, 2H; 4-H), 4.34 (q, $J=7.2$ Hz, 2H; CH_2CH$_3$), 5.58 (br. s, 1H; NH_2), 6.60 ppm (br. s, 1H; NH_2); ^{13}C NMR (100.59 MHz, $CDCl_3$): $\delta=14.0$ (q, CH_2CH_3), 23.8 (q, C-5CH_3), 43.9 (t, C-4), 62.4 (t, CH_2CH_3), 89.7 (s, C-5), 152.5 (s, C-3), 159.8 (s, CO_2Et), 174.9 ppm (s, CONH$_2$); IR (KBr): $\tilde{\nu}=3373$ (s) (N-H), 3178 (m) (N-H), 2996 (w), 2983 (w), 1726 (s) (C=O), 1693(s) (C=O), 1599 (m) (C=N), 1479 (w), 1411 (m), 1390 (m), 1271 cm^{-1} (s); MS (EI): m/z (%): 200 (1) $[M]^+$, 156 (13) $[M-CONH_2]^+$, 155 (12) $[M-OEt]^+$, 84 (14), 73 (6) $[CO_2Et]^+$, 44 (42) $[CONH_2]^+$, 42 (100); elemental analysis calcd (%) for $C_8H_{12}N_2O_4$ (200.19): C 48.00, H 6.04, N 13.99; found: C 47.83, H 5.91, N 13.85.

*Methyl 3-(methylcarbamoyl)-4,5-dihydro-5-methylisoxazole-5-carboxylate (**15a**)*: From methyl methacrylate (**2a**; 42.4 mg, 0.424 mmol) and *N*-methyl nitroacetamide (**10**; 75.1 mg mg, 0.636 mmol). After 16 h, the mixture was extracted with EtOAc (4×1.5 mL), the combined extracts were dried (sodium sulfate), filtered, and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (2 mL) and washed with sat. $NaHCO_3$ (1×1.5 mL), dried over Na_2SO_4, filtered, and evaporated under reduced pressure to afford **15a** (66 mg, 77%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=1.64$ (s, 3H; C-5CH_3), 2. 89 (d, $J=4.8$ Hz, 3H; NHCH_3), 3.12 and 3.69 (ABq, $J=18.2$ Hz, 2H; 4-H), 3.77 (s, 3H; OCH_3), 6.66 ppm (br. s, 1H; NH); ^{13}C NMR (100.56 Mz, $CDCl_3$): $\delta=23.3$ (q, C-5CH_3), 26.0 (q, NCH_3), 43.5 (t, C-4), 53.0 (s, OCH_3), 88.0 (s, C-5), 153.4 (s, C-3), 159.7 (s, CONHMe), 171.4 ppm (s, CO_2Me); MS (EI): m/z (%): 200 (<1) $[M]^+$, 141 (6), 84 (15), 58 (100) $[CONHCH_3]^+$; IR: $\tilde{\nu}=3434$ (m) (N-H), 2995 (w), 1742 (s) (C=O), 1671 (s) (C=O), 1600 (w) (C=N), 1542 (m), 1262 (m), 1202 cm^{-1} (m); elemental analysis calcd (%) for $C_8H_{12}N_2O_4$ (200.19): C 48.00, H 6.04, N 13.99; found C 48.16, H 6.24, N 13.62.

*3-(Methylcarbamoyl)-4,5-dihydro-5-methylisoxazole-5-carboxylic acid (**15f**)*: From methacrylic acid (**8f**; 36.5 mg, 0.424 mmol) and *N*-methyl nitroacetamide (**10**; 75.1 mg, 0.636 mmol). After 24 h, the reaction mixture was made alkaline (pH 8) with 4.24 M NaOH, and washed with Et_2O (4×1.5 mL); the aqueous phase was acidified to pH 1 with 3 N HCl and washed with hexane (4×1.5 mL). The aqueous phase was evaporated to dryness and purified by chromatography on silica gel ($CHCl_3$/MeOH/AcOH, 9:0.9:0.1; $R_f=0.09$) to give **15f** (69 mg, 88%) as a white powder; m.p. 133–135 °C. ^{1}H NMR (300 MHz, D_2O): $\delta=1.61$ (s, 3H; C-5CH_3), 2.79 (s, 3H; CH_3NH), 3.21 and 3.61 ppm (ABq, $J=18.4$ Hz, 2H; H-4); ^{13}C NMR (50.29 MHz, D_2O): $\delta=23.3$ (q, C-5CH_3), 26.4 (q, NCH_3), 43.7 (t, C-4), 89.1 (s, C-5), 154.9 (s, C-3), 161.9 (s, CONHMe), 176.4 ppm (s, CO_2H); IR (KBr): $\tilde{\nu}=3600$–2300 (br), 2981 (m), 2943 (m), 1734 (m) (C=O), 1670 (s) (C=O), 1597 (w) (C=N), 1558 (m), 1413 (w), 1272 cm^{-1}; MS (EI): m/z (%): 156 (2) $[M-NHMe]^+$, 141 (8) $[M-CO_2H]^+$, 84 (15), 58 (100) $[CONHMe]^+$, 45 (10) $[CO_2H]^+$, 43 (55); MS (ESI$^-$): m/z (%): 185 (100) $[M-H]^-$; elemental analysis calcd (%) for $C_7H_{10}N_2O_4$ (186.17): C 45.16, H 5.41, N 15.05; found: C 45.40, H 5.12, N 15.24.

*N^3,5-Dimethyl-4,5-dihydroisoxazole-3,5-dicarboxamide (**15g**)*: From methacrylamide (**8g**; 36.1 mg, 0.424 mmol) and *N*-methyl nitroacetamide (**10**; 75.1 mg, 0.636 mmol). After 20 h, the reaction mixture was cooled and kept at 4 °C overnight. The precipitate was collected and washed with cold H_2O (1 mL) then oven-dried at 50 °C to afford the product **15g** (44.7 mg). The aqueous fractions were combined and evaporated to dryness. The residue was dissolved in $CHCl_3$ and filtered through a short pad of silica gel. The solvent was evaporated under reduced pressure to give further **15g** (31.6 mg) as a white solid. Combined yield: 98%; m.p. 209–212 °C. ^{1}H NMR (400 MHz, D_2O): $\delta=1.70$ (s, 3H; C-5CH_3), 2.88 (s, 3H; CH_3NH), 3.32 and 3.62 ppm (ABq, $J=18.2$ Hz, 2H; 4-H); ^{13}C NMR (D_2O): $\delta=23.6$ (C-5CH_3), 26.5 (NHCH_3), 44.1 (t, C-4), 89.6 (s, C-5), 155.5 (s, C-3), 162.0 (s, CONHMe), 178.5 ppm (s, CONH$_2$); IR: $\tilde{\nu}=3404$ (N-H), 3369 (N–H), 2984, 1658 and 1636 (C=O), 1608 cm^{-1} (C=N); MS (EI): m/z (%): 141 (8) $[M-CONH_2]^+$, 84 (15), 58 (100) $[CONHMe]^+$, 44 (36) $[CONH_2]^+$; elemental analysis calcd (%) for $C_7H_{11}N_3O_3$ (185.18): C 45.40, H 5.99, N 22.69; found: C 45.05, H 6.22, N 22.93.

*3-Butylcarbamoyl-5-methyl-4,5-dihydro-isoxazole-5-carboxylic acid methyl ester (**16a**)*: From methyl methacrylate (**8a**; 42.5 mg, 0.424 mmol, 44 μL) and *N*-butylnitroacetamide (**11**; 101.8 mg, 0.636 mmol, 70 μL). After 24 h, the reaction mixture was cooled and extracted with EtOAc (4×10 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (2 mL) and washed with sat. $NaHCO_3$ (1×1.5 mL), dried over Na_2SO_4, filtered, and evaporated under reduced pressure to afford **16a** (66 mg, 65%) as a pale-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.90 (t, J=7.4 Hz, 3H; CH_2CH_3), 1.28–1.38 (m, 2H; CH_2CH_3), 1.46–1.55 (m, 2H; $NHCH_2CH_2$), 1.63 (s, 3H; C-5CH_3), 3.12 and 3.71 (ABq, J=18.3 Hz, 2H; H-4), 3.30 (q, J=5.8 Hz, 1H; $CONHCH_2$), 3.76 (s, 3H; OCH_3), 6.59 ppm (br. s, 1H; N*H*); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=13.6 (q, CH_3), 19.9 (t, CH_3CH_2), 23.4 (q, C-5CH_3), 31.4 (t, $NHCH_2CH_2$), 39.2 (t, $CONHCH_2$), 43.6 (t, C-4), 53.0 (q, OCH_3), 88.0 (s, C-5), 153.6 (s, C-3), 159.0 (s, *C*ONHBu), 171.4 ppm (s, CO_2Me); IR ($CDCl_3$): $\tilde{\nu}$=3421 (m) (N–H), 2958 (m), 2934 (m), 1742 (s) (OC=O), 1676 (s) (NC=O), 1599 (w) (C=N), 1202 cm^{-1} (w); MS (EI): *m/z* (%): 242 (<1) $[M]^+$, 199, (2) $[M-Pr]^+$, 183 (4) $[M-CO_2Me]^+$, 170 (6), 84 (8), 100 (22) $[CONHBu]^+$, 57 (100); elemental analysis calcd (%) for $C_{11}H_{18}N_2O_4$ (242.27): C 54.53, H 7.49, N 11.56; found: C 54.21, H 7.76, N 11.99.

*5-Methyl-4,5-dihydro-isoxazole-3,5-dicarboxylic acid 5-amide 3-[(2-aminoethyl)amide] hydrochloride (**17g**·Cl)*: From methacrylamide (**8g**; 36.1 mg, 0.424 mmol) and *N*-aminoethyl nitroacetamide hydrochloride (**12**·Cl; 116.4 mg, 0.636 mmol). After 24 h, the reaction mixture was cooled, washed with diethyl ether (4×1.5 mL), and the aqueous phase was concentrated. The residue was dissolved in MeOH (12 mL) and treated with ambersep 900. After evaporation of the methanolic solution, 5-methyl-4,5-dihydro-isoxazole-3,5-dicarboxylic acid 5-amide 3-[(2-aminoethyl)amide] (83 mg, 92%) was obtained as a colorless oil. ^{1}H NMR (200 MHz, D_2O): δ=1.69 (s, 3H; CH_3), 2.85 (t, J=6.2 Hz, 2H; NH_2CH_2), 3.42 (t, J=6.2 Hz, 2H; $CONHCH_2$), 3.29 and 3.62 ppm (ABq, J=18.4 Hz, 2H, 4-H); ^{13}C NMR (100.58 MHz, D_2O): δ=23.4 (q, CH_3), 39.4 (t, $CONHCH_2$), 39.8 (t, NH_2CH_2), 43.9 (t, C-4), 89.7 (s, C-5), 155.3 (s, C-3), 162.1 (s, *C*ONH), 178.3 ppm (s, $CONH_2$); MS (ESI^+): *m/z* (%): 237 (100) $[M+Na]^+$, 215 (74) $[M+H]^+$; elemental analysis calcd (%) for $C_8H_{14}N_4O_3$ (214.22): C 44.85, H 6.59, N 26.15; found: C 45.13, H 6.34, N 25.94.

The above amine (78 mg) was treated with 3 N HCl to give **17g** Cl in quantitative yield; m.p. 205°C (dec.). ^{1}H NMR (400 MHz, D_2O): δ=1.70 (s, 3H; CH_3), 3.25 (t, J=6.2 Hz, 2H; NH_2CH_2), 3.67 (t, J=6.2 Hz, 2H; $CONHCH_2$), 3.32 and 3.63 ppm (ABq, J=17.2 Hz, 2H; 4-H); ^{13}C NMR (100.58 MHz, D_2O): δ=23.5 (q, CH_3), 40.2 (t,$CONHCH_2$), 41.8 (t, NH_2CH_2), 43.9 (t, C-4), 89.5 (s, C-5), 155.2 (s, C-3), 161.5 (s, *C*ONH), 178.0 ppm (s, $CONH_2$); IR (KBr): $\tilde{\nu}$=3500–2500 (br), 1668 cm^{-1} (C=O) (s); elemental analysis calcd (%) for $C_8H_{14}N_4O_3$·HCl (250.68): C 38.33, H 6.03, N 22.35; found: C 38.46, H 5.99, N 22.59.

*3-Methylcarbamoyl-isoxazole-5-carboxylic acid methyl ester (**19a**) and 3-methylcarbamoyl-isoxazole-4-carboxylic acid methyl ester (**20a**)*: From methyl propiolate (**18a**; 35.6 mg, 0.424 mmol) and *N*-methyl nitroacetamide (**10**; 75.1 mg, 0.636 mmol). After 22 h, the reaction mixture was cooled to 4°C for 4 h. The precipitate was separated by centrifugation and oven-dried at 80°C to afford **19a** (31 mg, 0.168 mmol, 39%) as a white powder. The water supernatant was extracted with $CHCl_3$ (5×1.5 mL) and the combined organic phases were dried over Na_2SO_4, filtered, and evaporated to yield the two regioisomers (**19a**/**20a**, 3:7; 25 mg, 0.136 mmol, 32%). Overall yield 71%.

Compound **19a**: White powder; m.p. 158–160°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=3.00 (d, J=5.2 Hz, 3H; NCH_3), 3.97 (s, 3H; OCH_3), 6.84 (br. s, 1H; N*H*), 7.32 ppm (s, 1H, 4-H); ^{13}C NMR (100.58 MHz, $CDCl_3$): δ=26.2 (q, NCH_3), 53.1 (q, OCH_3), 108.9 (s, C-4), 156.6 (s, CO_2CH_3), 158.3. (s, $CONHCH_3$), 159.0 (s, C-3 or C-5), 161.4 ppm (s, C-3 or C-5); IR (KBr): $\tilde{\nu}$=3271 (br), 3114 (m), 2960 (m), 1731 (OC=O) (s), 1650 (NC=O) (s), 1605 (C=N) (w), 1573 (m), 1289 cm^{-1} (br, s); MS (EI): *m/z* (%): 154 (2) $[M-NHMe]^+$, 125 (13) $[M-CO_2Me]^+$, 68 (19), 58 (100) $[CONHMe]^+$; elemental analysis calcd (%) for $C_7H_8N_2O_4$ (184.15): C 45.66, H 4.38, N 15.21; found: C 45.44, H 4.29, N 15.23.

Compound **20a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ (selected signals from the mixture)=3.02 (d, J=5.2 Hz, 3H; NCH_3), 3.91 (s, 3H; OCH_3), 9.00 ppm (s, 1H; 5-H).

*3-Methylcarbamoyl-isoxazole-5-carboxylic acid (19f) and 3-methylcarbamoyl-isoxazole-4-carboxylic acid (**20f**)*: From propiolic acid (**18f**; 29.7 mg, 0.424 mmol) and *N*-methyl nitroacetamide (**10**; 75.1 mg, 0.636 mmol). After 168 h, the reaction mixture was cooled and concentrated under reduced pressure and the residue was purified by chromatography on silica gel ($CHCl_3$/MeOH/AcOH, 8:1.8:0.2) to give a first fraction (12 mg; R_f=0.2) containing traces of isoxazole **20f**, and a second fraction containing pure isoxazole **19f** (54 mg, 75%; R_f=0.08).

Compound **19f**: White powder; m.p. 185°C (dec.). ^{1}H NMR (400 MHz, D_2O): δ=2.97 (s, 3H; $NHCH_3$), 7.10 ppm (s, 1H; 4-H); ^{13}C NMR (100.58 MHz, D_2O): δ=26.6 (q, NCH_3), 105.9 (s, C-4), 159.4 (s), 161.9 (s), 163.0 (s), 168.0 ppm (s, CO_2H); IR (KBr): $\tilde{\nu}$=3600–2600 (br), 1678, 1622 cm^{-1}; MS (ESI^-): *m/z* (%): 169 (100) $[M-H]^-$; elemental analysis calcd (%) for $C_6H_6N_2O_4$ (170.12): C 42.36, H 3.55, N 16.47; found: C 42.68, H 3.55, N 16.33.

Compound **20f**: ^{1}H NMR (200 MHz, D_2O): δ (selected signals from the mixture)=2.95 (s, 3H; $NHCH_3$), 9.05 ppm (s, 1H; 5-H).

Scale up for the reactions between methacrylamide (8g) and ethyl nitroacetate (1) or *N*-methyl nitroacetamide (10):

*Ethyl 5-carbamoyl-4,5-dihydro-5-methylisoxazole-3-carboxylate (**14g**)*: Methacrylamide (**8g**; 361 mg, 4.24 mmol) was added to a mixture of aqueous 4.24 M NaOH (0.10 mL, 0.424 mmol), ethyl nitroacetate (**1**; 678 mg, 5.09 mmol) and water (13.9 mL), and the reaction mixture was vigorously stirred in a sealed tube at 60°C. After 22 h, the reaction mixture was cooled and kept in the refrigerator (4°C) overnight. The precipitate was collected, washed with H_2O (3×5 mL) and oven-dried at 80°C, affording **14g** (549 mg) as white powder. The mother solution combined with washings was extracted with $CHCl_3$ (3×10 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and evaporated to dryness. The residue was washed with Et_2O (5 mL), giving further **14g** (101 mg) as a white powder. Overall yield 77%. Elemental analysis calcd (%) for $C_8H_{12}N_2O_4$ (200.19): C 48.00, H 6.04, N 13.99; found: C 47.83, H 5.91, N 13.85. The spectral data are identical to those reported above.

*4,5-Dihydro-N^3,5-dimethylisoxazole-3,5-dicarboxamide (**15g**)*: The same procedure applied to *N*-methyl nitroacetamide (**10**; 600 mg, 5.09 mmol) afforded **15g** (531 mg) as a white powder. The mother solution combined with washings was evaporated to dryness. The residue was washed with EtOAc (5 mL) and $CHCl_3$ (5 mL) to give further **15g** (109 mg). Overall yield 82%. Elemental analysis calcd (%) for $C_7H_{11}N_3O_3$ (185.18): C 45.40, H 5.99, N 22.69; found: C 45.05, H 6.22, N 22.93. The spectral data are identical to those reported above.

Condensation of Fumaric acid (21) with *N*-methyl nitroacetamide (10):

*trans-3-Methylcarbamoyl-4,5-dihydroisoxazole-4,5-dicarboxylic acid (**22**), cis-3-methylcarbamoyl-4,5-dihydroisoxazole-4,5-dicarboxylic acid (**23**), and 3-methylcarbamoyl-4,5-dihydroisoxazole-5-carboxylic acid (**13f**)*: From fumaric acid (**21**; 49.2 mg, 0.424 mmol) and *N*-methyl nitroacetamide (**10**; 125.1 mg, 1.06 mmol) and NaOH 4.24 M (10 μL, 0.0424 mmol). After 7 days, the reaction mixture was cooled and concentrated under reduced pressure and the residue was purified by chromatography on silica gel ($CHCl_3$/*i*PrOH 95:5 to $CHCl_3$/*i*PrOH/AcOH 48:48:2). The main *trans* isomer **22**, collected at about R_f=0.19, contained in the head fractions (23 mg, ca. 25%) the decarboxylated isoxazoline **13f** (detected by ^{1}H NMR spectroscopic analysis, less than 4%) and in the tail fractions (36 mg, 40%) the *cis* isomer **23** (detected by ^{1}H NMR spectroscopic analysis, less than 10%).

Compound **22**: Sticky oil; ^{1}H NMR (400 MHz, D_2O): δ=2.90 (s, 3H; $NHCH_3$), 4.30 (d, J=5.6 Hz, 1H; 4-H), 5.21 ppm (d, J=5.6 Hz, 1H; 5-H); ^{13}C NMR (50 MHz, D_2O): δ=26.4 (q, NCH_3), 60.1 (d, C-4), 86.5 (d, C-5), 153.9 (s, C-3), 161.7 (s, *C*ONH), 175.0 (s, C-5CO_2H), 176.6 ppm (s, C-4CO_2H); IR (KBr): $\tilde{\nu}$=3600–2800 (br), 1730 (s), 1660 cm^{-1} (s); MS (ESI^-): *m/z* (%): 215 $[M-H]^-$; elemental analysis (with **23**) calcd (%) for $C_7H_8N_2O_6$ (216.15): C 38.90, H 3.73, N 12.96; found: C 38.64, H 3.93, N 12.74.

Compound **23**: Identified signals. ^{1}H NMR (400 MHz, D_2O): $\delta = 2.89$ (s, 3H; $NHCH_3$), 4.46 (d, $J = 12.0$ Hz, 1H; 4-H), 5.30 ppm (d, $J = 12.0$ Hz, 1H; 5-H).

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