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Acid–Base-Catalysed Condensation Reaction in Water: Isoxazolines and Isoxazoles from Nitroacetates and Dipolarophiles

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Dedicated to Professor Alberto Brandi on the occasion of his 60th birthday

Abstract: Base-catalysed condensation reactions of nitroacetic esters with dipolarophiles to give isoxazole derivatives proceed faster, and often with higher yields, in the presence of water than in organic solvents such as chloroform. Kinetic profiles show that induction times are greatly reduced when the reaction is performed "in water" or "on water". Any specificity of the base related to H-bonding ability observed in chloroform is lost in water: all bases either organic or inorganic give the same result that is simply depending on concentration. A 0.1 molar ratio of base to nucleophile gives the best conversion, whereas addition of one equivalent of base or strong acid prevents the reaction from occurring. These results fit into a reaction sequence in which reversible addition to a dipolarophile is followed by acid-catalysed irreversible dehydration of the cycloadduct. This is a remarkable example of a condensation reaction occurring in water because of irreversible acid-catalysed water elimination. The reaction has been successfully applied to dipolarophiles containing a wide variety of functional groups, including carboxylic acids and ammonium salts, under mild conditions. This new click-style reaction is expected to be compatible with biological environments.

Keywords: cycloaddition · homogeneous catalysis · isoxazoles · nitrogen heterocycles · water

Introduction

Water is the cheapest and most environmentally benign solvent. It is the medium in which the chemistry of life takes place.[1] Early studies of the use of water for organic reactions were likely encouraged by these facts. However many other features of organic reactions carried out in water have created considerable interest in this subject during the last 30 years.[2,3] In many cases considerable rate enhancements are observed in water relative to same reactions in organic solvents.[4] This effect is often caused by the simple presence of water, because sparingly soluble reagents participate in the reaction as a separate phase. In these cases stirring is helpful and a faster reaction of liquid than solid reagents has been reported.[5] These reactions have been defined as "on water"[6–9] or "in the presence of water" rather than "in water" reactions.[10] If the products are water insoluble the reaction work-up is made easier.[11] However, when the product needs to be extracted from the aqueous solution the primary benefit of avoiding organic solvents is lost.[12] Diels—Alder reactions, both catalysed and uncatalysed,[13] 1,3-dipolar cycloaddition reactions,[14] Claisen rearrangements,[15] nucleophilic substitutions or additions,[16] Michael reactions and aldol-type reactions are among the transformations that have been successfully carried out in water. Both the rates and selectivities[17] of reactions have been shown to be affected by the presence of water relative to the same reactions in organic solvents. The extensive literature on organic reactions in water has been the object of many reviews.[18]

Isoxazole and its derivatives have received much attention during the past century.[19] Isoxazoles continue to be used as intermediates in organic synthesis or in the preparation of different classes of compounds that have the isoxazole skeleton embedded.[20–23]

Previous procedures for the synthesis of these heterocycles have been based on the dehydration of primary nitro compounds to give intermediate nitrile oxides followed by cycloaddition to dipolarophiles [Eq. (1)].[24,25] To serve the purpose, we have recently developed an improved protocol by catalysed condensation of the same nitro compounds with dipolarophiles [Eq. (2)].[26–31] Whereas the former method requires anhydrous conditions and dehydrating reagents in stoichiometric amounts,[32,33] the latter condensation reaction in chloroform relies on the acid-catalysed de-

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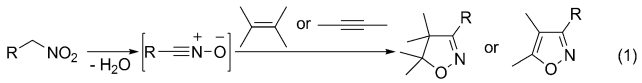
hydration of the intermediate cycloadduct.[30] Importantly, the final irreversible step is compatible with the presence of water.

Condensation reactions in water require a driving force capable of shifting the equilibrium in favour of the desired product. For example, removal of the product in a separate phase, owing to low solubility. Similarly, a "micellar effect" has been reported that displaces the equilibria towards the condensation product, even in aqueous medium.[34,35] In Equation (2), water elimination with formation of the C=N double bond provides the driving force for dehydration. Water elimination from aldoximes to nitriles is well known,[36,37] whereas only a few examples of water elimination from N-substituted hydroxylamines have been reported: imines are obtained by thermolysis,[38] with $KHSO_4$,[39] or under Ti^{III}[40] catalysis.

In the present paper we report the catalysed condensation reaction of nitroacetic esters with a variety of dipolarophiles (alkenes or alkynes) in aqueous medium [Eq. (3)]. In this medium the reaction course and the catalytic system are modified relative to those in organic solvent.



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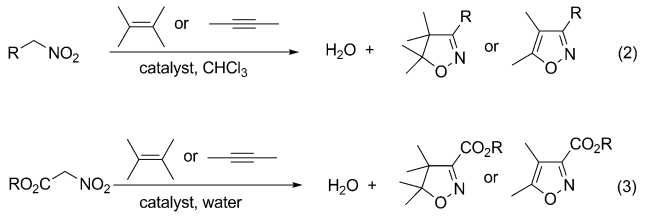
Abstract in Italian: *La condensazione tra nitroacetati e dipolarofili a derivati isossazolici con catalisi basica è più veloce e spesso dà rese migliori in presenza di acqua che in solventi organici come il clorofomio. Il tempo di induzione della reazione è ridotto sensibilmente quando la reazione è condotta in sistemi acquosi sia omogenei che eterogenei, come mostrato dai profili cinetici. La specificità della base legata alla sua capacità di formare legami ad idrogeno, osservata nella reazione condotta in cloroformio, scompare nella reazione condotta in acqua. In questo solvente ogni base, sia organica che inorganica, porta agli stessi risultati a parità di concentrazione. I migliori risultati si ottengono con un rapporto molare base/dipolarofilo di 0.1, mentre la reazione non procede per aggiunta di 1 equiv di base, né in presenza di acido forte. Questi risultati sono spiegabili con un pre-equilibrio di cicloaddizione fra nitronato o acido nitronico e dipolarofilo, seguito da eliminazione irreversibile di acqua con catalisi acida. Si tratta di un notevole esempio di condensazione in ambiente acquoso, in virtù dell'eliminazione irreversibile di acqua catalizzata da acidi. Il processo è stato applicato con successo a dipolarofili recanti i più svariati gruppi funzionali, tra cui il carbossilico e l'ammonico. Perciò, tenuto conto delle miti condizioni richieste, si può pensare di utilizzare la condensazione tra esteri nitroacetici e dipolarofili come un nuovo ed efficiente processo di trasformazione molecolare compatibile con sistemi biologici.*



(2)
(3)

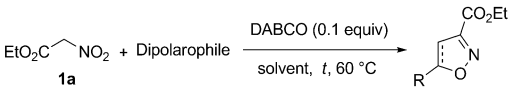
Results and Discussion

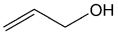
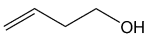
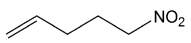
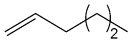
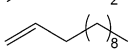
Reaction in water/reaction on water: As reported in our previous papers,[27,28] ethyl nitroacetate reacts with various dipolarophiles under base catalysis to afford 3-ethoxycarbonylisoxazolines by a cycloaddition–condensation reaction process. To date, these reactions have been conveniently and successfully carried out in chloroform. Many reagents are only sparingly soluble in water and, as such, water was disregarded as a reaction medium. However, condensation reactions of ethyl nitroacetate with several dipolarophiles in water, regardless of solubility, favourably compare with the results of the same reactions performed in chloroform.

The extents of conversion of dipolarophiles into products observed after set times are reported in Table 1.

Ethyl nitroacetate (1.06 mmol), dipolarophile (0.424 mmol) and DABCO (1,4-diazabicyclo[2.2.2]octane, 0.0424 mmol) forms only a partially soluble reaction mixture in 1.4 mL of water, although the same reagents would be completely soluble in the same volume of chloroform. In fact, a saturated solution of ethyl nitroacetate in water is

Table 1. Condensation reactions of ethyl nitroacetate with various dipolarophiles under base catalysed conditions. Comparison between water and chloroform as solvent.

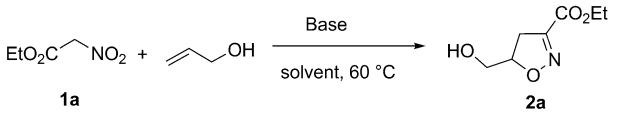


	Dipolarophile	Product yield [%][a]		
		H_2O	$CHCl_3$	
		18 h	18 h	80 h
1		83	0	16
2		88	0	57
3		52 (64)[b]	0	25
4		63 (95)[b]	0	96
5		96	0	91
6		69	4	74
7		61	2	65
8		40	0	84
9		65 (84)[c]	0	61

[a] Spectroscopic yield calculated by ^1H NMR after the indicated time. [b] In parentheses the spectroscopic yield calculated after 66 h. [c] In parentheses the spectroscopic yield calculated after 80 h.

about 0.17 M at room temperature. If a base (DABCO, 0.03 M) is added, the resulting solubility increases to 0.19 M overall of nitroacetate and its salt (nitronate). These values are not significantly different at 60 °C. Therefore, in our reaction conditions, the excess of nitroacetate gives rise to an organic layer and the reaction takes place partly in water and partly under heterogeneous conditions.

The spectroscopic yields reported in Table 1, observed after 18 h, are significantly higher in water than in chloroform. However, the values in parentheses that refer to longer reaction times (66 or 80 h) show comparable results in either media. Kinetic profiles of the reactions under both conditions provide a deeper insight. The reaction progress was followed by plotting time versus the conversion of dipolarophile to product for two model condensation reactions with ethyl nitroacetate; the first reaction used a water-soluble dipolarophile (allyl alcohol, solubility > 0.3 M) and the second, used styrene, which is water insoluble (Table 1, entries 1 and 3). The graphs in Figure 1 refer to the reaction with allyl alcohol and show a very long induction period in chloroform (solid squares): a 52 % spectroscopic yield of cycloadduct **2a** is obtained after 10 days. During the induction period the nitroacetate undergoes partial hydrolytic cleavage to give ethanol, carbon dioxide and nitromethane. When performed neat, the reaction (Figure 1, solid triangles) begins after a 3 h induction period, whereas in the presence of water the induction time is even shorter and the reaction is almost complete after 8 h. The conversion in the presence of water could not be monitored directly by NMR spectroscopy and was evaluated either by extraction (Figure 1, solid circles) or by concentrating each sample at the time indicated and recording the spectrum of the residue after dissolution in deuterochloroform (Figure 1, open circles). The dramatic drop of the induction period and the enhanced rate observed is attributed, in part, to the neat reaction, but mainly to the reaction occurring "in water" or "on water".



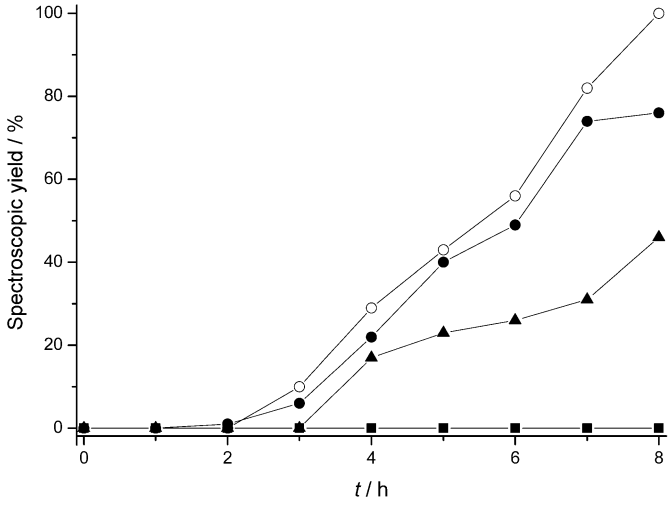


Figure 1. Reaction profiles for the condensation reaction of ethyl nitroacetate (**1a**) and allyl alcohol in water or chloroform as solvent or neat. Reaction in water with extraction in chloroform (solid circles); reaction in water followed by concentration (open circles); reaction in chloroform (solid squares) and neat (solid triangles).

Figure 2 illustrates the progress of the reaction with styrene. The reaction to form product **3a** in the presence of water (open circles) begins after 6 h and attains 75 % conversion after 12 h, whereas the reaction in chloroform (solid squares) requires a much longer induction time (48 h). Complete conversion is not achieved in either reaction owing to nitroacetate hydrolysis affecting the pH of the medium. This effect is discussed in more detail later in this article.

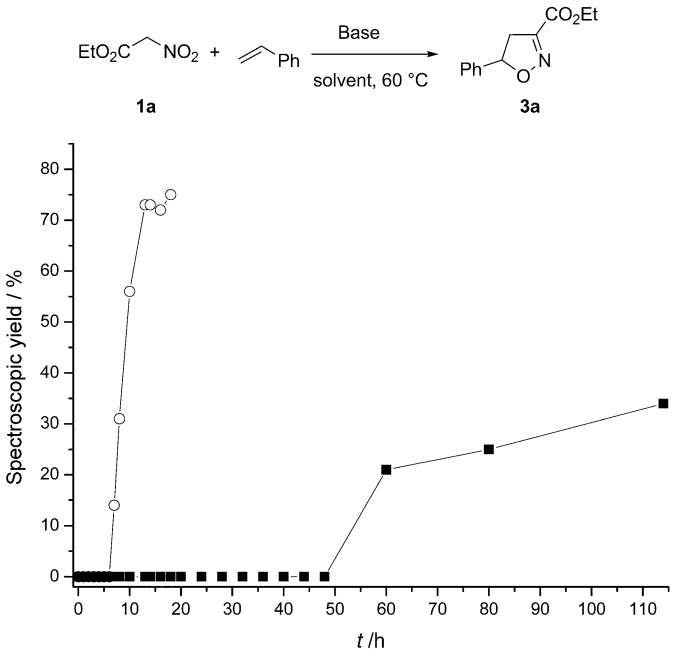


Figure 2. Kinetic profiles of reactions of **1a** with styrene in $CHCl_3$ (solid squares) and in water (open circles).

The above reactions were carried out in water at 60 °C with or without stirring. After 18 h the reaction with allyl alcohol reached 76 and 74 % conversion with and without stirring, respectively. The reaction with styrene reached 73 and 25 % conversion with and without stirring, respectively. We consider the reaction with allyl alcohol to take place mainly "in water" because stirring does not significantly modify the reaction rate. In contrast, stirring improves the reaction with styrene, therefore we consider this reaction to take place mainly "on water".

To obtain accurate kinetic profiles the reactions needed to be carried out under homogeneous conditions. By performing the reaction in heavy water (D_2O) it could be monitored directly by NMR spectroscopy. Solutions of methyl nitroacetate (0.256 M), which is more soluble than the ethyl ester, in

water, D_2O or chloroform were treated with water-soluble dipolarophiles and DABCO under the same conditions as those described above. The influence of isotopic composition of water on condensation reaction of allyl alcohol with methyl nitroacetate (**1b**) is illustrated in Figure 3. The kinetic profiles for the reaction in D_2O (solid squares) and in mixtures of D_2O and H_2O (ratio 1:1, open squares; ratio 1:2, open circles), obtained by direct NMR monitoring, did not show significant differences due to the solvent isotope composition. Evaluation of NMR spectroscopic signals is more accurate in D_2O than in the presence of water. In this case a constant rate was seen after less than 1 h and conversion almost complete within 2.5 h.

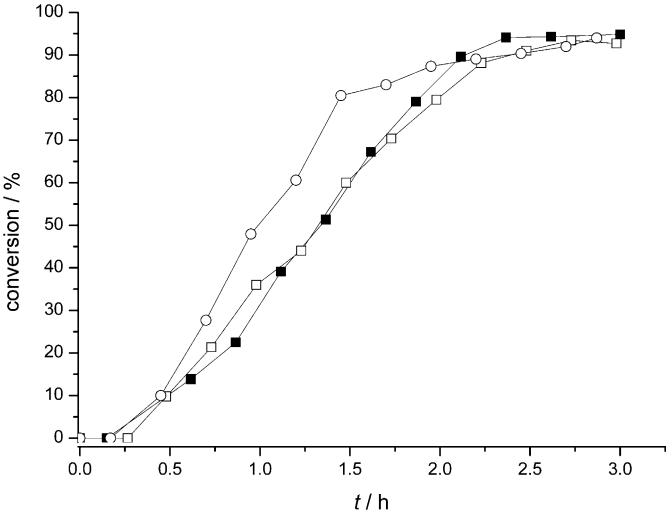


Figure 3. Condensation reaction of methyl nitroacetate (**1b**) with allyl alcohol catalysed by DABCO at 60 °C. Effect of solvent isotope composition on the conversion of dipolarophile to cycloadduct. Heavy water (solid squares); heavy water/water 1:2 (open squares); heavy water/water 1:1 (open circles).

The reaction profiles of **1b** with allyl alcohol (Figure 4) and with its water-soluble homologues (Figure 5) in D_2O and $CDCl_3$ are dramatically different. In deuterochloroform complete conversion is only achieved after 10 days following a very long induction period. Similarly, for the homologues of allyl alcohol, conversion is completed in water within 3 h. After the same time in chloroform, no product is observed under the same conditions (Figure 5).

Base catalysis: The model reactions with allyl alcohol and with styrene, carried out under various experimental conditions, gave the results reported in Table 2. Without the addition of base, no reaction is observed in the "neat" mixture of nitroacetate with styrene, whereas low conversion was found in the neat reaction with allyl alcohol (Table 2, entry 4). In the case of allyl alcohol, the hydroxy group might be providing a small catalytic effect. On addition of water both reactions were successful, although long reaction times were required (Table 2, entries 6, 7 and 8). Addition of a catalytic amount of base (DABCO) resulted in a faster

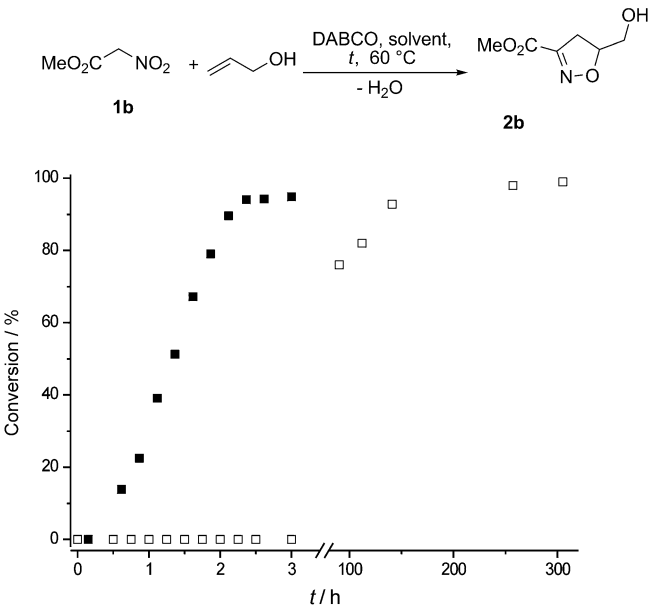


Figure 4. Condensation reaction of methyl nitroacetate (**1b**) with allyl alcohol catalysed by DABCO at 60 °C. Effect of solvent on the conversion of dipolarophile to cycloadduct **2b**. Heavy water (solid squares); deuterochloroform (open squares).[41]

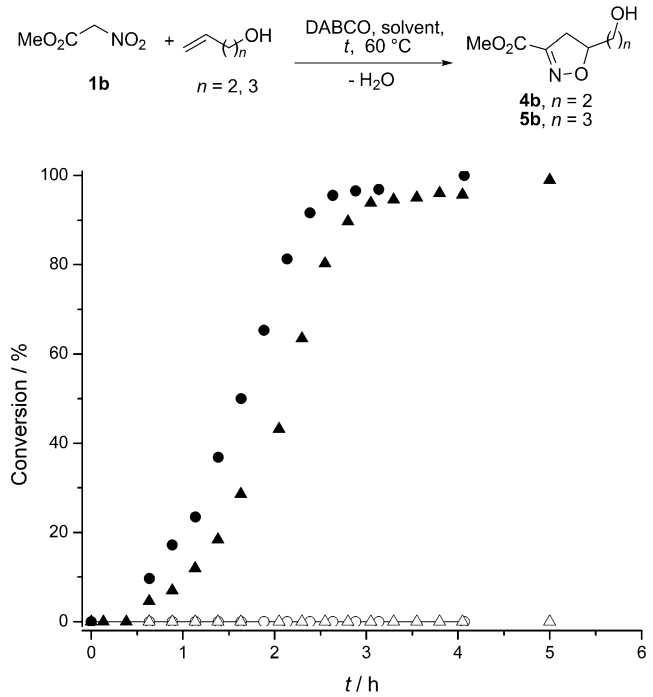
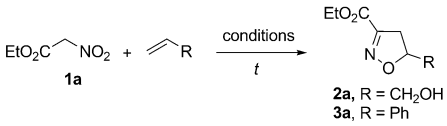


Figure 5. Condensation reaction of methyl nitroacetate (**1b**) with 3-buten-1-ol (circles) and 4-penten-1-ol (triangles) catalysed by DABCO at 60 °C. Effect of solvent on the conversion of the dipolarophiles to the cycloadducts **4b** and **5b**, respectively. Heavy water (solid markers) deuterochloroform (open markers).

condensation reaction under neat conditions as well as with water.[42] The conversion enhancement caused by both base and water is dramatic for the "in water" reaction of allyl al-

Table 2. Condensation reaction of ethyl nitroacetate with allyl alcohol or styrene either neat or in water and various bases.



	Conditions	*t* [h]	**2a** Yield [%][a]	**3a** Yield [%][a]
1	neat, 60 °C	18	0	0
2	neat, 60 °C	65	0	0
3	neat, 100 °C	18	0	0
4	neat, 100 °C	65	10	0
5	water, 60 °C	18	0	0
6	water, 60 °C	48	10	0
7	water, 60 °C	216	35	24
8	water, 100 °C	18	43	6
9	neat, DABCO 0.1 equiv, 60 °C	18	49	62
10	water, DABCO 0.1 equiv, 60 °C	18	83	52
11	water, DABCO 0.1 equiv, 30 °C	95	35	0
12	water, pyridine 0.1 equiv, 60 °C	18	74	73
13	water, triethylamine 0.1 equiv, 60 °C	18	83	75
14	water, butylamine 0.1 equiv, 60 °C	18	70	72
15	water, piperidine 0.1 equiv, 60 °C	18	79	72
16	water, NaOH 0.1 equiv, 60 °C	18	80	69
17	water, Na_2CO_3 0.1equiv, 60 °C	18	68	64
18	water, KF 0.1 equiv, 60 °C	18	67	68
19	phosphate buffer solution,[b] 60 °C	18	66 (0)	63 (0)
20	HCl solution,[c] 60 °C	18	0	0
21	HCl solution,[c] DABCO 0.1 equiv, 60 °C	18	0	0

[a] Spectroscopic yield calculated by ^{1}H NMR with an internal standard. [b] 0.1 M (0.33 equiv) phosphate. In parentheses 0.5 M (1.66 equiv) phosphate buffer, (pH 7.0). [c] 0.6 M (pH < 1).

cohol (Table 2, entry 10) and occurs even at a lower temperature (Table 2, entry 11). The base specificity observed in chlorofom[27] is lost in reactions carried out either "in water" or "on water". The results of the reactions are scarcely affected irrespective of whether DABCO, pyridine, triethylamine, sodium hydroxide, or sodium carbonate are used (0.1 equiv with respect to dipolarophile: Table 2, entries 10–18). On the other hand, condensation reactions are observed in water alone (though slower, Table 2, entries 6 and 7), although no reaction takes place in the presence of excess hydrochloric acid (Table 2, entries 20 and 21), in which the concentration of nitronate becomes negligible. The effect of a phosphate solution (Table 2, entry 19) is discussed below.

Slow reactions, like the condensation reaction with styrene (Figure 2), do not achieve complete conversion of the dipolarophile owing to the parallel hydrolysis of nitroacetate to nitroacetic acid ($pK_a = 1.63$).[43] When the reaction was performed in D_2O at 60 °C with 0.1 equivalents of base, 0.1 equivalents of nitroacetate are hydrolysed after 12 h; with exceedingly long reaction times, nitromethane was also detected as a result of cleavage of nitroacetic acid.[44–46]

Furthermore, the reactivity of dipolarophiles with ethyl nitroacetate depends on the amount of added base (the excess of nitroacetate forms as a separate phase and acts as a buffer, to some extent, for the aqueous solution). For the same model reactions with allyl alcohol and with styrene shows a maximum conversion at 0.1 equivalents of base after 18 h (Figure 6).

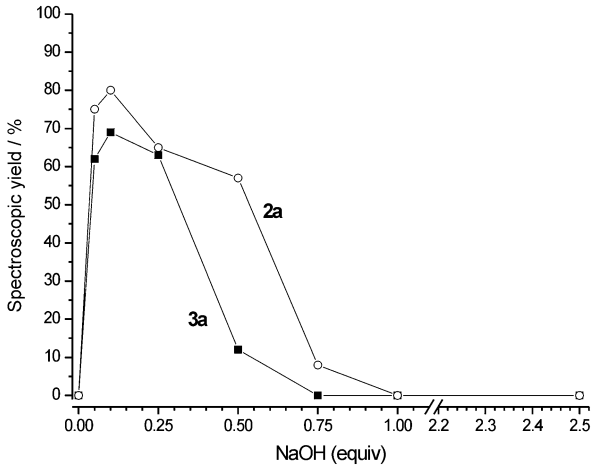


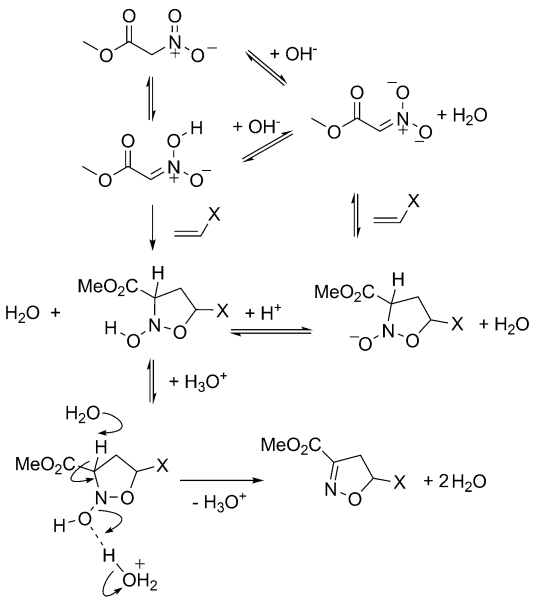
Figure 6. Profiles of the reaction between ethyl nitroacetate (**1a**) and allyl alcohol (open circles) or styrene (solid squares). The data shows the calculated yield after 18 h depending on the amount of sodium hydroxide used in the reaction.

The reactions with 1 equivalent or more of sodium hydroxide failed due to the lack of or drop in acidity necessary for water release. In buffer solution (0.1 M, pH 7) corresponding to 0.33 equivalent of base the result was not significantly modified (Table 2, entry 19).

By using phosphate buffer (0.5 M) corresponding to 1.66 equivalent of base, the condensation reaction is prevented (Table 2, entry 19, values in parentheses). We may conclude therefore that a catalytic amount of base is required for the condensation reaction to take place. However, the success of the reaction rests on the excess of nitroacetate that keeps the pH of the medium low enough to allow the release of water in the final irreversible, rate-determining step (Scheme 1).

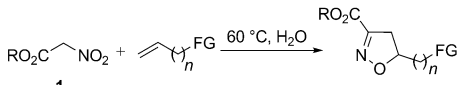
Synthetic applications: We then tested the scope of the reaction. Comparison between dipolarophiles with the same functional group, but different chain lengths, indicates that the water solubility of the dipolarophile does not affect the efficiency of the reactions (Table 3, entries 1–8). Both short- and long-chain dipolarophiles give the cycloadducts in good to excellent yield.

By using the reaction conditions described above the scope of the reaction was explored. Challenging substrates, which may interfere both with the catalytic system and nitroacetate reagents, were included (Tables 3 and 4). Good chemoselectivity and broad functional group tolerance on the dipolarophiles was noted when screening condensation reactions of nitroacetates to give 4,5-dihydroisoxazoles and isoxazoles. Compounds that contained a labile proton such as carboxylic acids and ammonium salts were also included. Moreover, in view of the mild conditions, this reaction



Scheme 1. Reaction mechanism between dipolarophile and nitroacetate.

Table 3. Condensation reaction of nitroacetates with alkenes bearing various functional groups (FG).[a]



a: R = Et; **b**: R = Me

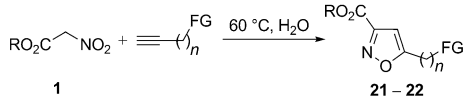
	FG	*n*	Product	Yield [%][b]
1	H	10	**6a**	74
2	OH	2	**4a**	84
3	OH	9	**7a**	93
4	$C(Me)_2CHO$	1	**8a**	73
5	CHO	8	**9a**	90
6	CO_2H	1	**10a**	81
7	CO_2H	1	**10b**	91
8	CO_2H	8	**11a**	83
9	C_6H_5	1	**12a**	62
10	2-OH-C_6H_4	1	**13a**	70
11	NH_3^+	2	**14a**	89
12	NH_3^+	2	**14b**	88
13	NO_2	3	**15a**	95
14	COMe	2	**16a**	94
15	Br	2	**17a**	74
16	OEt	1	**18b**	46
17	SMe	1	**19a**	53
18	CN	3	**20a**	99

[a] See the Experimental Section for details. [b] Analytically pure, isolated product yield (yields were not optimised).

might prove valuable in a biological context.[47,48] The substrates reported in Tables 3 and 4 mainly react either "in" and/or "on" water depending on their solubility.

Hydrocarbons (see Table 3, entries 1, 9; Table 4 entry 2): 1-Dodecene, and allylbenzene are insoluble in water, therefore these reactions are considered to occur "on water".

Table 4. Condensation reaction of nitroacetates with alkynes bearing various functional groups (FG).[a]



a: R = Et

	FG	*n*	Product	Yield [%][b]
1	OH	1	**21a**	77
2	Ph	0	**22a**	88

[a] See the Experimental Section for details. [b] Analytically pure, isolated product yield (yields were not optimised).

Similarly phenylacetylene reacts "on water" to give an excellent product yield.

Alcohols and phenol (see Table 3, entries 2, 3, 10; Table 4 entry 1): Both 3-buten-1-ol and 10-undecen-1-ol react in solution to give excellent results. However, 2-allylphenol, which is sparingly soluble in water, reacts to give a fair product yield. Similarly, propargyl alcohol affords 3-carbethoxy-5-hydroxymethylisoxazole in fair yield.

Nitro, bromo, ether, methylthio and cyanide groups (see Table 3, entries 13, 15, 16, 17 and 18, respectively): When the functional group is unconjugated with the reacting double bond fair to excellent results are obtained. Note the chemoselective behaviour shown when two nitro groups are present (Table 3, entry 13). Nitroalkanes are unreactive under these reaction conditions.

Aldehydes and ketones (see Table 3, entries 4, 5 and 14): The aldehyde 2,2-dimethylheptenal, which is sparingly soluble in water, reacts with good results. 1-Undecenal, which is almost insoluble, reacts very well "on water". It should be noted that cycloaddition reactions with nitro compounds as precursors of dipoles on unprotected olefinic aldehydes have been rarely reported.[49] Usually, to overcome lower yields, the aldehyde function is protected prior to cycloaddition[50] or masked with a suitable functional group.[20c,51] 1-Hexen-5-one reacts with ethyl nitroacetate in excellent yield (Table 3, entry 14).

The use of water can expand the scope of this reaction to give excellent results with carboxylic acids and amines.

Carboxylic acids (see Table 3, entries 6–8): Carboxylic acids give condensation products in excellent yields irrespective of chain length and solubility (Table 3, entry 6 vs. entry 8). It is worth noting that dipolarophiles bearing carboxylic acids have never been used in a dehydration reaction to give the intermediate nitrile oxides. Isoxazole carboxylic acids are generally prepared from the corresponding esters as intermediates.[52]

Amines (see Table 3, entries 11 and 12):. Amines react as ammonium salts without the need of protection. 4-Amino-1-butene undergoes the reaction as the hydrochloride salt.

The alkylammonium group is a weaker acid than the nitroacetic ester, thus the amount of nitronate is not affected. However, conversion is only partial when reacting the free amine. The result is not improved when methyl nitroacetate (**1b**), which is more soluble in water, is used (Table 3, entry 12). It is worth noting that dipolarophiles bearing unprotected amino groups have never been used to prepare isoxazoles from nitrocompounds. Preparation of isoxazolines from the nitrile oxides generated from nitro compounds has been rarely reported even with protected amines[53] or compounds obtained through functional group interconversion.[54]

Conclusion

The success of the reported condensation reaction depends on a number of parameters.

- A catalytic amount of base is required to produce a concentration of adduct that is sufficient to push the final irreversible step to release water.
- The elimination of water requires a catalytic amount of acid. This is ensured by using an excess of nitroacetate.
- However, if the reaction is exceedingly slow yields are not quantitative because hydrolysis of nitroacetate competes with the condensation reaction. The resulting nitroacetic acid ($pK_a = 1.63$) reacts with the catalyst—in these cases yields are not quantitative for this reason, rather than due to consumption of nitroacetate;
- With very long reaction times decomposition of nitroacetate occurs resulting in cleavage of the nitroacetic acid to give carbon dioxide and nitromethane.
- The excess of nitroacetate, which sits as a separate phase, helps the aqueous solution to be buffered; hydrolysis is slower than in solution.
- Heating the reaction mixture is favourable for the condensation reaction, particularly when this reaction is in competition with the conjugate addition.[31] This suggests that the release of the water is the rate-determining step and not the cycloaddition. However, at 100 °C the decomposition of nitroacetate is detrimental.

The best results are obtained by using an excess of nitroacetate and 0.1 equivalents of any base. Since the reaction requires much shorter induction periods than in organic solvents, hydrolysis of nitroacetate, in most cases, does not limit the yield of the condensation reaction. The condensation reactions occur easily in water with dipolarophiles containing acidic protons such as carboxylic acids and ammonium salts. Importantly, the synthesis of isoxazole derivatives from nitro compounds containing these functional groups as well as aldehydes has been rarely reported to date, and often with poor results. This method requires a ratio of dipolarophile to reagent of less than 1. Previous methods, based on nitrile oxides as intermediates (either from nitro compounds or from hydroxamoyl chlorides), have required a ratio greater than 1.[32,55] Here the aim is to favour the cycloaddition reaction by reducing as much as possible dimerisation of nitrile oxide to furoxan. A synthesis involving a silyl nitronate intermediate would require an additional step.[56]

Finally, in view of the mild aqueous conditions, compatible with a biological environment, this condensation can be envisaged as a new protocol reminiscent of the analogous "click process" with azides.[47b,57]

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 (visualised with UV light and/or by dipping the plates into a solution of permanganate followed by heating with a heat gun). TLC was carried out on alumina backed plates coated with 25 mm silica gel (Merck F_{254}) with the same eluant as indicated for the column chromatography. For gradient column chromatography R_f values refer to the more polar eluant. Solvent removal was performed by evaporation under reduced pressure at room temperature. ^{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 (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 gHMQC and gHMBC experiments. Chemical shifts were determined relative to the residual solvent peak ($CHCl_3$: 7.24 ppm for ^{1}H NMR and 77.0 ppm for ^{13}C NMR; H_2O: 4.74 ppm for ^{1}H NMR). Chemical shifts for ^{13}C NMR in D_2O are relative to CH_3CN (1.47 ppm) as internal reference. EI (electron impact) mass spectra were recorded with a Shimadzu QP5050 A quadrupole-based mass spectrometer (direct introduction unless otherwise stated, at ionising voltage of 70 eV). ESI (electrospray ionisation) mass spectra were recorded with a ThermoFisher LCQ-Fleet ion trap instrument and spectra were registered with either ESI^+ or ESI^- technique. Ion mass/charge ratios (m/z) are reported as values in atomic mass units followed by the intensities relative to the base peak in parentheses. IR spectra were recorded with a Perkin–Elmer 881 spectrophotometer; bands are characterised as broad (br), strong (s), medium (m) and weak (w). Elemental analyses were recorded with an Elemental Analyser Perkin–Elmer 240C apparatus.

Solubility in water at 25 °C of dipolarophiles (M):[58] Very soluble: 2-propen-1-ol (allyl alcohol)[59] (2.13), 2-propyn-1-ol (propargyl alcohol)[60] (3.62), 3-buten-1-amine (1.04); Soluble: 3-buten-1-ol (0.82), 4-penten-1-ol (0.45), 3-butenoic acid (0.83), 5-hexenenitrile (0.13), 3-ethoxy-1-propene (allyl ethyl ether)[61] (0.29), 5-hexen-2-one (0.19), allyl methyl sulphide (0.20); Slightly soluble: 2,2-dimethyl-4-pentenal (0.028), 2-(prop-2-enyl)-phenol (0.022), 5-nitropent-1-ene (0.074); Sparingly soluble: styrene[62] (2.98×10^{-3}), 10-undecenal (6.9×10^{-4}), 10-undecen-1-ol (3.6×10^{-4}), 1-hexene (4.98×10^{-4}), phenylacetylene (4.2×10^{-3}), 1-dodecene (4.1×10^{-8}), allylbenzene (1.0×10^{-3}), 4-bromobut-1-ene (6.8×10^{-3}), norbornene (2.4×10^{-3}), 10-undecenoic acid[63] (1.8×10^{-3}).

All compounds were named with Autonom® (Beilstein Information Systems) and modified where appropriate.

Materials: All alkenes and alkynes are liquid at room temperature except norbornene (m.p. 44–46 °C) and but-3-enylammonium chloride (m.p. 176–180 °C) . Commercially available (Lancaster and Aldrich) ethyl nitroacetate (**1a**), methylnitroacetate (**1b**), organic bases, olefins and alkynes were used as supplied. $CHCl_3$ (ethanol free) was filtered through a short pad of potassium carbonate just before use. Water (deionised) was twice distilled from $KMnO_4$ before use.

Condensation reaction of ethyl nitroacetate with different dipolarophiles under base catalysis—comparison between water and chloroform (Table 1): A mixture of ethyl nitroacetate (1.06 mmol), alkene or alkyne

(0.424 mmol), DABCO (0.0424 mmol) and water or chloroform (1.4 mL) was heated to 60 °C with vigorous stirring in a sealed tube. After a given amount of time, the reaction mixture was concentrated and the crude residue was dissolved in deuterochloroform with 2,4-dimethoxy-acetophenone (14–21 mg, 0.078–0.12 mmol) as the internal standard and the ^{1}H NMR spectra was recorded. The spectroscopic yields and reaction times are reported in Table 1. Integration of the 3′ and 5′-proton signals of the internal standard (m, 6.40–6.58) and the signal of one proton (4-H or 5-H) of the cycloadduct on the NMR spectra were used to calculate the spectroscopic yields. The following signals were used: Table 1, entry 1: 4.88 ppm (m, 5-H); entry 2: 4.98 ppm (m, 5-H); entry 3: 3.20 ppm (dd, 4-H); entry 4: 4.64 ppm (d, C*H*ON); entry 5: 4.80 ppm (m, 5-H); entry 6: 6.81 ppm (s, 4-H); entry 7: 6.62 ppm (brs, 4-H); entry 8: 3.21 ppm (dd, 4-H) or 4.67 ppm (m, 5-H); entry 9: 3.20 ppm (dd, 4-H) or 2.81 ppm (dd, 4-H)].

Condensation reaction of allyl alcohol with ethyl nitroacetate in water, chloroform or neat (Figure 1), and condensation of styrene with ethyl nitroacetate in water and chloroform (Figure 2)

$CDCl_3$

Sample preparation: Reaction mixtures were prepared by dissolving DABCO (4.8 mg, 0.0425 mmol), ethyl nitroacetate (141 mg, 1.062 mmol), allyl alcohol (24 mg, 0.424 mmol) or styrene (44 mg, 0.424 mmol), and $(CH_3)_2SO_2$ (11–15 mg, 0.1169–0.1594 mmol) as the internal standard in $CDCl_3$ (1.4 mL, freshly filtered through K_2CO_3). A sample from each reaction (550 μL) were transferred to a septum-sealed NMR spectroscopy tube, spinning (20 Hz) in the probe of the spectrometer, and the spectra were recorded at 60 °C. Duplicate reactions were run if unclear results were obtained.

Spectroscopic yield: ^{1}H NMR spectra were recorded at intervals of 30 or 60 min for each reaction and the spectroscopic yields were calculated by integrating the C*H*$_3$ protons signals (2.93 ppm) of the internal standard and the 4-H protons signals of cycloadduct **2a** (3.05–3.28 ppm, m, 2H) or cycloadduct **3a** (3.20 ppm, dd, 1H).

H_2O

Preparation of sample: Reaction mixtures (without internal standard) were prepared as above but with H_2O (1.4 mL) as solvent. The mixtures were stirred vigorously and maintained at 60 °C in a thermostatic bath in sealed tubes .

Spectroscopic yield: At appropriate time intervals, each reaction mixture was either extracted into $CDCl_3$ (3×0.6 mL) or concentrated and the residue dissolved in $CDCl_3$ and 2,4-dimethoxy-acetophenone (14–21 mg, 0.078–0.12 mmol) added as internal standard. The ^{1}H NMR spectra were then recorded and the spectroscopic yields calculated as described above.

Neat

Preparation of samples. Reaction mixtures were prepared by mixing DABCO (4.8 mg, 0.0425 mmol), ethyl nitroacetate (**1a**) (141 mg, 1.062 mmol) and allyl alcohol (24 mg, 0.425 mmol) in sealed tubes at 60 °C under stirring.

Spectroscopic yield: Every hour one reaction mixture was dissolved in $CDCl_3$ (1 mL). 2,4-Dimethoxy-acetophenone (14–21 mg, 0.078–0.12 mmol) was added as an internal standard and the ^{1}H NMR spectrum was recorded. The spectroscopic yields were calculated as described above.

Effect of water isotope composition (Figure 3): Reactions were run in septa-sealed 5 mm NMR tubes spinning (20 Hz) in the probe of the spectrophotometer at 60 °C.

Preparation of samples: DABCO (2.4 mg, 0.0212 mmol), methyl nitroacetate (**1b**) (63 mg, 0.529 mmol), allyl alcohol (12 mg, 0.212 mmol) and Me_2SO_2 (5.1–5.5 mg) as internal standard, were dissolved in heavy water (2.24 g, 2.00 mL) or heavy water (1.12 g, 1.00 mL) and water (1.00 g, 1 mL), or heavy water (0.762 g, 0.68 mL) and water (1.32 g, 1.32 mL). A clear solution was obtained after stirring a few minutes at room temperature and a portion (550 μL) was transferred to an septum-sealed 5 mm NMR tube set to spin (20 Hz) in the probe of the spectrometer maintained at 60 °C. ^{1}H NMR spectra were recorded at intervals of 15 min until no further spectral changes were observed. The conversion was calculated by integrating one of the olefinic proton signals of allyl alcohol (6.34–6.48 ppm, m, 2H) and the 5-H proton signal for the cycloadduct **2b**. The spectroscopic yield of the final reaction mixture appeared to be quantitative, thus the formation of the cycloadduct was assumed to be the only process involving allyl alcohol. Signals for Me_2SO_2 were recorded as: ^{1}H NMR (D_2O, 26 °C): $\delta = 3.16$ ppm; ^{1}H NMR (D_2O, 60 °C): $\delta =$ 3.52 ppm.

Methyl ester of 5-hydroxymethyl-4,5-dihydroisoxazole-3-carboxylic acid (2b): ^{1}H NMR (D_2O, 26 °C): $\delta = 3.11$ (dd, $J = 8.0$ and 18.0 Hz, 1H; 4-H), 3.39 (dd, $J = 11.6$ and 18.0 Hz, 1H; 4-H), 3.66–3.71 (m, 2H; CH_2OH), 3.91 (s, 3H; OCH_3), 5.01–5.08 ppm (m, 1H; 5-H); ^{1}H NMR (D_2O, 60 °C): $\delta = 3.47$ (dd, $J = 8.4$, 18.0 Hz, 1H; 4-H), 3.74 (dd, $J = 11.2$, 18.0 Hz, 1H; 4-H), 4.05 (dd, $J = 5.2$, 12.4 Hz, 1H; CH_2OH), 4.18 (dd, $J = 3.6$, 12.4 Hz, 1H; CH_2OH), 4.28 (s, 3H; OCH_3), 5.35–5.43 ppm (m, 1H; 5-H).

Progress of the condensation reaction of methyl nitroacetate with alcoholic dipolarophiles in water or in chloroform (homogeneous solutions; Figures 4 and 5)

Preparation of samples: DABCO (2.4 mg, 0.0212 mmol), methyl nitroacetate **1b** (63 mg, 0.529 mmol), dipolarophile (0.212 mmol: allyl alcohol (12 mg); 3-buten-1-ol (15 mg), 4-penten-1-ol (18 mg)) and Me_2SO_2 (5.0–8.0 mg, internal standard) were mixed with heavy water (2.24 g, 2 mL) or deuterochloroform (3.0 g, 2 mL), freshly filtered through K_2CO_3, at room temperature. A clear solution was obtained after stirring a few minutes at room temperature and an aliquot (550 μL) was transferred to a septum-sealed 5 mm NMR tube set to spin (20 Hz) in the probe of the spectrometer maintained at 60 °C. After a few hours, the reactions in heavy water were complete, whereas those in deuterochloroform, which were subject to very long induction periods, were maintained in a thermostatic bath at 60 °C and checked at appropriate time intervals.

Spectroscopic yield: ^{1}H NMR spectra for the D_2O reaction were recorded at time intervals of 15 min until no further spectral changes were observed. The extent of conversion was calculated by integrating one of the olefinic protons signals of the dipolarophile (allyl alcohol 6.34–6.48 ppm, m, 2H; 3-buten-1-ol 5.48–5.58 ppm, m, 2H; 4-penten-1-ol 6.4 ppm, m, 1H) and the 5-H proton signal of the cycloadducts **2b**, **4b** and **5b**. The spectroscopic yield of the final reaction mixture appeared to be quantitative, thus the formation of the cycloadducts was assumed to be the only process involving the dipolarophiles.

Methyl ester of 5-(2-hydroxyethyl)-4,5-dihydroisoxazole-3-carboxylic acid (4b): ^{1}H NMR (D_2O, 26 °C): $\delta = 1.88$–2.07 (m, 2H; CH_2C-5), 3.05 (dd, $J =$ 8.0, 18.0 Hz, 1H; 4-H), 3.44 (dd, $J = 11.2$ and 18.0 Hz, 1H; 4-H), 3.76 (td, $J = 1.2$, 6.0 Hz, 2H; CH_2OH), 3.91 (s, 3H, OCH_3), 5.02–5.11 ppm (m, 1H; 5-H); ^{1}H NMR (D_2O, 60 °C): $\delta = 2.23$–2.43 (m, 2H; CH_2C-5), 3.39 (dd, $J = 8.4$, 18.0 Hz, 1H; 4-H), 3.78 (dd, $J = 10.8$, 18.0 Hz, 1H; 4-H), 4.09 (t, $J = 6.4$ Hz, 2H; CH_2OH), 4.27 (s, 3H; OCH_3), 5.35–5.45 ppm (m, 1H; 5-H).

Methyl ester of 5-(3-hydroxypropyl)-4,5-dihydroisoxazole-3-carboxylic acid (5b): ^{1}H NMR (D_2O, 26 °C): $\delta = 1.55$–1.65 (m, 4H; CH_2CH_2C-5), 3.00 (dd, $J = 8.4$, 18.0 Hz, 1H; 4-H), 3.40 (dd, $J = 11.2$, 18.0 Hz, 1H; 4-H), 3.66 (t, $J = 6.4$ Hz, 2H; CH_2OH), 3.91 (s, 3H; OCH_3), 4.94–5.40 ppm (m, 1H; 5-H); ^{1}H NMR (D_2O, 60 °C): $\delta = 1.92$–2.20 (m, 4H; CH_2CH_2C-5), 3.34 (dd, $J = 8.4$, 18.0 Hz, 1H; 4-H), 3.75 (dd, $J = 11.2$, 18.0 Hz, 1H; 4-H), 4.00 (t, $J = 6.4$ Hz, 2H; CH_2OH), 4.27 (s, 3H; OCH_3), 5.29–5.39 ppm (m, 1H; 5-H).

Spectroscopic yield: The conversion of the reactions in $CDCl_3$ was calculated, similarly to the experiments in D_2O, by integrating one of the olefinic proton signals of the dipolarophile (allyl alcohol at 27 °C 5.92–6.02 ppm, m, 1H and at 60 °C 5.93–6.03 ppm, m, 1H; 3-buten-1-ol at 27 °C 5.70–5.83 ppm, m, 1H and at 60 °C 5.73–5.83 ppm, m, 1H; 4-penten-1-ol 5.74–5.86 ppm, m, 1H) and the 5-H proton signal of the cycloadducts **2b**, **4b** and **5b**. Signals for Me_2SO_2 were recorded as: ^{1}H NMR ($CDCl_3$, 27 °C): $\delta = 2.94$ ppm; ^{1}H NMR ($CDCl_3$, 60 °C): $\delta =$ 2.93 ppm.

Methyl ester of 5-hydroxymethyl-4,5-dihydroisoxazole-3-carboxylic acid (2b): ^{1}H NMR ($CDCl_3$, 27 °C): $\delta = 2.22$ (brs, 1H; O*H*), 3.08–3.26 (m, 2H; 4-H), 3.61 (dd, $J = 4.4$, 12.4 Hz, 1H; C*H*OH), 3.83 (dd, $J = 3.2$, 12.4 Hz, 1H; C*H*OH), 3.84 (s, 3H; OCH_3), 4.85–4.92 ppm (m, 1H; 5-H); ^{1}H NMR

($CDCl_3$, 60 °C): $\delta = 2.21$ (br s, 1H; O*H*), 3.07–3.24 (m, 2H; 4-H), 3.63 (dd, $J = 4.4$, 12.4 Hz, 1H; C*H*OH), 3.82 (dd, $J = 3.2$, 12.4 Hz, 1H; C*H*OH), 3.84 (s, 3H; CH_3O), 4.83–4.90 ppm (m, 1H; 5-H).

Methyl ester of 5-(2-hydroxyethyl)-4,5-dihydroisoxazole-3-carboxylic acid (4b): The spectroscopic yield for this product was calculated as 54% after 66 h and 79% after 5 days (not reported in Figure 5). ^{1}H NMR ($CDCl_3$, 27 °C): $\delta = 1.79$–1.88 (m, 1H; CH_2C-5), 1.90–2.00 (m, 1H; CH_2C-5), 2.25 (br s, 1H; O*H*), 2.91 (dd, $J = 8.4$, 17.6.0 Hz, 1H; 4-H), 3.28 (dd, $J = 11.0$, 17.6 Hz, 1H; 4-H), 3.75–3.79 (m, 2H; CH_2OH), 3.83 (s, 3H; CH_3O), 4.91–5.01 ppm (m, 1H; 5-H); ^{1}H NMR ($CDCl_3$, 60 °C): $\delta = 1.81$–1.90 (m, 1H; CH_2C-5), 1.92–2.01 (m, 1H; CH_2C-5), 2.04 (br s, 1H; O*H*), 2.91 (dd, $J = 8.4$, 17.6.0 Hz, 1H; 4-H), 3.28 (dd, $J = 11.0$, 17.6 Hz, 1H; 4-H), 3.76–3.80 (m, 2H; CH_2OH), 3.84 (s, 3H; OCH_3), 4.90–4.99 ppm (m, 1H; 5-H).

Methyl ester of 5-(3-hydroxypropyl)-4,5-dihydroisoxazole-3-carboxylic acid (5b): Maximum conversion for this reaction was reached after 5 days and resulted in 50% spectroscopic yield (not reported in Figure 5). ^{1}H NMR ($CDCl_3$, 27 °C): $\delta = 1.65$–1.75 (m, 4H; CH_2CH_2C-5), 2.82 (dd, $J = 8.4$, 17.6 Hz, 1H; 4-H), 3.24 (dd, $J = 10.8$, 17.6 Hz, 1H; 4-H), 3.65 (t, $J = 5.6$ Hz, 2H; CH_2OH), 3.84 (s, 3H; OCH_3), 4.78–4.88 ppm (m, 1H; 5-H).

Reaction conditions affecting the condensation reaction of ethyl nitroacetate with allyl alcohol or styrene either neat or in water media: The conversions and spectroscopic yields reported in Table 2 refer to conditions where eight reactions were carried out simultaneously. A mixture of ethyl nitroacetate (1.06 mmol), allyl alcohol or styrene (0.424 mmol), with base (0.0424 mmol) and water, buffer or $HCl_{(aq)}$ (1.4 mL) was prepared in a sealed tube and left to react for the desired time period. The reaction mixture was then extracted with $CDCl_3$ (3 × 0.6 mL). 2,4-Dimethoxyacetophenone (14–21 mg, 0.078–0.12 mmol) was added as the internal standard and the ^{1}H NMR spectrum recorded. Integration of the 3′-H and 5′-H proton signals of the internal standard (6.40–6.58, m) and the signals of the 4-H protons of products from allyl alcohol and styrene (3.16 ppm, m, and 3.20 ppm, dd, respectively) allowed the spectroscopic yield to be calculated. Duplicate reactions were run if unclear results were obtained.

Condensation reaction of allyl alcohol and styrene with ethyl nitroacetate in water, with different amounts of NaOH (Figure 6): All reactions were carried out in sealed tubes. Different volumes of aqueous 4.24 M NaOH (100, 75, 50, 25, 10, 5 μL) corresponding to a variable base/alkene molar ratio (1.0, 0.75, 0.5, 0.25, 0.1, 0.05, respectively) were added to a mixture of ethyl nitroacetate (1.06 mmol), allyl alcohol (0.424 mmol), or styrene (0.424 mmol). Each mixture was then dissolved in a complementary volume of heavy water (1.3, 1.325, 1.350, 1.375, 1.390, 1.395 mL, respectively) to give an overall volume of 1.4 mL. Each mixture was vigorously stirred at 60 °C. After 18 h each reaction mixture was concentrated, and dissolved in $CDCl_3$. Me_2SO_2 (14–20 mg) was added as the internal standard. The ^{1}H NMR spectrum was then recorded and the spectroscopic yield calculated as follows. Allyl alcohol: by integrating 4-H proton signals of the cycloadduct **2a** ($\delta = 3.05$–3.28 ppm, m, 2H) and the CH_3 proton signal of the internal standard ($\delta = 2.57$ ppm, s, 6H). Styrene: by integrating 4-H proton signals of the cycloadduct **3a** ($\delta = 3.2$ ppm, dd, 1H) and the CH_3 proton signal of the internal standard as above. No conversion was seen without the addition of base. Duplicate reactions were run if unclear results were obtained.

Determination of ethyl nitroacetate solubilities in water and in the reaction mixture: The solubility of **1a** in water and in the reaction mixture at room temperature and 60 °C were determined by measuring the integration values from the ^{1}H NMR spectra as described above.

In water: $(CH_3)_2SO_2$ (16.7 mg) as internal standard was dissolved in heavy water (0.7 mL). This solution was saturated with ethyl nitroacetate (**1a**) and the mixture was transferred to a septum-sealed 5 mm NMR tube and placed in the probe of the spectrometer at 26 °C. The ^{1}H NMR spectra was recorded and the amount of dissolved **1a** was calculated by integrating the CH_3 proton signal of the internal standard ($\delta = 3.16$ ppm, s, 6H) and the CH_2O proton signal for **1a** ($\delta = 4.22$ ppm, q, 2H). The concentration of **1a** was calculated to be 0.17 M.

As a reaction mixture: $(CH_3)_2SO_2$ (16.7 mg) as internal standard and DABCO (2.4 mg, 0.03 M) were dissolved in heavy water (0.7 mL). This solution was saturated with ethyl nitroacetate (**1a**) and the mixture was transferred to a septum-sealed 5 mm NMR tube and placed in the probe of the spectrometer at 26 °C. The ^{1}H NMR spectra were recorded and the amount of dissolved **1a** was calculated by integrating the CH_3 proton signal of the internal standard ($\delta = 3.16$ ppm, s, 6H) and the CH_2O proton signal for **1a** ($\delta = 4.22$ ppm, q, 2H) at 26 °C. The concentration of **1a** was calculated to be 0.19 M. A pH of 4.4 for this solution is in agreement with the pK_a value (5.82)[64] of **1a**. The concentration of **1a** was calculated by using the procedure described above, at 60 °C to be 0.22 M.

General preparation method for the products reported in Tables 3 and 4: A solution of NaOH (4.24 M, 0.010 mL, 0.0424 mmol) was added to a mixture of nitroacetic ester **1a** (141 mg, 1.06 mmol), or **1b** (126.2 mg, 1.06 mmol), dipolarophile (see individual reactions below) and water (1390 mg) and the mixture vigorously stirred in a sealed tube at 60 °C for the indicated time. The reaction mixture was concentrated and the residue was subject to flash chromatography on silica gel to give the desired products. Different work-up were followed for **10a**, for **10b**, for **14a**, for **14b** and for **16a**.

Condensation reaction of ethyl nitroacetate with 1-dodecene to give ethyl 5-decyl-4,5-dihydro-3-isoxazolecarboxylate (6a): The reaction of 1-dodecene (71.4 mg, 0.424 mmol) with **1a** after 48 h gave **6a** (91 mg, 76%) after chromatography (petroleum ether/diethyl ether 6:1) as a colourless oil. $R_f = 0.34$; ^{1}H NMR: $\delta = 0.85$ (t, $J = 6.4$ Hz, 3H; CH_3), 1.18–1.40, (m, 16H; C$H_2 \times 8$), 1.33 (t, $J = 7.2$ Hz, 3H; OCH$_2$CH_3), 1.50–1.62 (m, 1H; CH_2C-5), 1.68–1.78 (m, 1H; CH_2C-5), 2.81 (dd, $J = 8.6$, 17.5 Hz, 1H; 4-H), 3.20 (dd, $J = 10.9$, 17.5 Hz, 1H; 4-H), 4.32 (q, $J = 7.2$ Hz, 2H; OCH_2CH$_3$), 4.71–4.80 ppm (m, 1H; 5-H); ^{13}C NMR: $\delta = 14.0$ (q, *C*H$_3$), 14.1 (q, OCH$_2$*C*H$_3$), 22.6 (t, *C*H$_2$), 25.0 (t, *C*H$_2$), 29.2 (t, *C*H$_2$), 29.3 (t, *C*H$_2$), 29.4 (t, *C*H$_2$), 29.5 (t, 2C, *C*H$_2$), 31.8 (t, *C*H$_2$), 35.0 (t, *C*H$_2$C-5), 38.3, (t, C-4), 61.9 (t, O*C*H$_2$CH$_3$), 84.1, (d, C-5), 151.3 (s, C-3), 160.9 ppm (s, *C*=O); IR ($CDCl_3$): $\tilde{\nu} = 2927$ (s), 2855 (s), 1716 (s; C=O), 1588 (m; C=N), 1466 (m), 1380 (m), 1256 cm^{-1} (s); MS (EI): *m*/*z* (%): 283 (2) $[M]^+$, 266 (4), 254 (4) $[M-Et]^+$, 238 (2) $[M-OEt]^+$, 210 (26) $[M-CO_2Et]^+$, 142 (54) $[M-(CH_2)_9CH_3]^+$, 116 (22), 43 (92), 41 (100); elemental analysis calcd (%) for $C_{16}H_{29}NO_3$ (283.41): C 67.81, H 10.31, N 4.94; found: C 67.69, H 10.61 N 4.82.

Condensation reaction of ethyl nitroacetate with 3-buten-1-ol to give ethyl 5-(2-hydroethyl)-4,5-dihydro-3-isoxazolecarboxylate (4a): The reaction of 3-buten-1-ol (30 mg, 0.416 mmol) with **1a** after 16 h gave **4a** (66 mg, 84%) after chromatography (petroleum ether/diethyl ether 6:1, then diethyl ether) as a colourless oil. $R_f = 0.41$; elemental analysis calcd (%) for $C_8H_{13}NO_4$ (187.19): C 51.33, H 7.00, N 7.48; found: C 51.14, H 7.22, N 7.71. The spectral data are identical to those previously reported.[28]

Condensation reaction of ethyl nitroacetate with 10-undecen-1-ol to give ethyl 5-(2-hydroxynonyl)-4,5-dihydro-3-isoxazolecarboxylate (7a): The reaction of 10-undecen-1-ol (72 mg, 0.423 mmol) with **1a** after 72 h gave unreacted alcohol (12 mg, $R_f = 0.64$) and **7a** (93 mg, 93% calculated taking into account recovered 10-undecen-1-ol) after chromatography (petroleum ether/ethyl acetate 4:1, then petroleum ether/ethyl acetate 3:1) as a white solid. $R_f = 0.18$; m.p. 36–37 °C; ^{1}H NMR: $\delta = 1.18$–1.40 (m, 12H; C$H_2 \times 6$), 1.34 (t, $J = 7.2$ Hz, 3H; OCH$_2$CH_3), 1.50–1.62 (m, 3H; CH_2C-5, CH_2CH$_2$OH), 1.70–1.81 (m, 1H; CH_2C-5), 2.81 (dd, $J = 8.8$, 17.6 Hz, 1H; 4-H), 3.22 (dd, $J = 10.8$, 17.6 Hz, 1H; 4-H), 3.62 (t, $J = 6.8$ Hz, CH_2OH, 2H), 4.32 (q, $J = 7.2$ Hz, 2H; OCH_2CH$_3$), 4.72–4.81 ppm (m, 1H; 5-H); ^{13}C NMR: $\delta = 14.1$ (q, OCH$_2$*C*H$_3$), 25.1 (t, *C*H$_2$), 25.7 (t, *C*H$_2$), 29.2 (t, *C*H$_2$), 29.3 (t, 2C, *C*H$_2$), 29.4 (t, *C*H$_2$), 32.8 (t, *C*H$_2$CH$_2$OH), 35.0, (t, *C*H$_2$C-5), 38.4 (t, C-4), 62.0 (t, O*C*H$_2$CH$_3$), 63.1 (t, *C*H$_2$OH), 84.2, (d, C-5), 151.4 (s, C-3), 160.9 ppm (s, *C*O$_2$Et); IR ($CDCl_3$): $\tilde{\nu} = 2930$ (s), 2856 (m), 1714(s; C=O), 1588 (w; C=N), 1256(m), 1127 cm^{-1} (w); MS (EI): *m*/*z* (%): 268 (<1) $[M-OH]^+$, 212 (4) $[M-CO_2Et]^+$, 182 (9), 142 (100) $[M-(CH_2)_9OH]^+$, 114 (27), 86 (12), 81(12), 69 (24), 55 (44), 41 (48); elemental analysis calcd (%) for $C_{15}H_{27}NO_4$ (285.38): C 63.13, H 9.54, N 4.91; found: C 63.47, H 9.75, N 4.53.

Condensation reaction of ethyl nitroacetate with 2,2-dimethyl-4-pentenal to give ethyl 5-(2,2-dimethyl-3-oxopropyl)-4,5-dihydro-3-isoxazolecarboxylate (8a): The reaction of 2,2-dimethyl-4-pentenal (48 mg, 0.424 mmol) with **1a** after 42 h gave **8a** (44–70 mg, 46–73%) after chromatography (petroleum ether/ethyl acetate 4:1, then petroleum ether/ethyl acetate 3:1) as a yellowish oil. $R_f=0.21$; ^{1}H NMR: $\delta=1.10$ (s, 3H; CCH_3), 1.14 (s, 3H; CCH_3), 1.32 (t, $J=7.2$ Hz, 3H; OCH$_2$CH_3), 1.73 (dd, $J=3.6$, 14.8 Hz, 1H; CHC-5), 2.00 (t, $J=9.2$, 14.8 Hz, 1H; CHC-5), 2.79 (dd, $J=8.0$, 17.6 Hz, 1H; 4-H), 3.30 (dd, $J=11.2$, 17.6 Hz, 1H; 4-H), 4.32 (q, $J=7.2$ Hz, 2H; OCH_2CH$_3$), 4.76–4.86 (m, 1H; 5-H), 9.44 ppm (s, 1H; CHO); ^{13}C NMR: $\delta=14.0$ (q, OCH$_2$CH_3), 21.4 (q, CCH_3), 22.3 (q, CCH_3), 40.0, (t, C-4), 42.9 (t, CHC-5), 44.8 (s, CCH_3), 62.0 (t, OCH_2CH$_3$), 80.6 (d, C-5), 151.5 (s, C-3), 160.6 (s, CO_2Et), 204.6 ppm (d, CHO); IR (CDCl$_3$): $\tilde{\nu}=2981$ (s), 2934 (s), 1724 (s; C=O), 1590 (m; C=N), 1469 (m), 1380 (s), 1258 (s), 1129 cm^{-1} (s); MS (EI): m/z (%): 198 (12) $[M-$CHO$]^+$, 182 (34), 156 (100), 142 (74) $[M-$CH$_2$CH-(CH$_3$)$_2$CHO$]^+$, 128 (32), 114 (54), 85 (42), 72 (30); elemental analysis calcd (%) for $C_{11}H_{17}NO_4$ (227.26): C 58.14, H 7.54, N 6.16; found: C 57.74, H 7.84, N 6.09.

Condensation reaction of ethyl nitroacetate with 10-undecenal to give ethyl 5-(3-oxononyl)-4,5-dihydro-3-isoxazolecarboxylate (9a): The reaction of 10-undecenal (70 mg, 0.416 mmol) with **1a** after 48 h gave **9a** (106 mg, 90%) after chromatography (petroleum ether/ethyl acetate 5:1, then petroleum ether/ethyl acetate 4:1) as a colourless oil that became yellowish on standing. $R_f=0.23$; ^{1}H NMR: $\delta=1.18$–1.40 (m, 10H; C$H_2\times$ 5), 1.34 (t, $J=7.2$ Hz, 3H; OCH$_2$CH_3), 1.50–1.62 (m, 3H; CH_2C-5, CH_2CH$_2$CHO), 1.70–1.81 (m, 1H; CHC-5), 2.40 (t, $J=7.4$ Hz, 2H; CH_2CHO), 2.80 (dd, $J=8.0$, 17.6 Hz, 1H; 4-H), 3.23 (dd, $J=11.2$, 17.6 Hz, 1H; 4-H), 4.32 (q, $J=7.2$ Hz, 2H; OCH_2CH$_3$), 4.68–4.86 (m, 1H; 5-H), 9.74 ppm (s, 1H; CHO); ^{13}C NMR: $\delta=14.1$ (q, OCH$_2$CH_3), 22.0 (t, CH_2CH$_2$CHO), 25.0 (t, CH_2), 29.1 (t, CH_2), 29.2 (t, 2C, CH_2), 29.5 (t, CH_2), 35.0 (t, CH_2C-5), 38.3 (t, C-4), 43.8 (t, CH_2CHO), 62.0 (t, OCH_2CH$_3$), 84.1, (d, C-5), 151.3 (s, C-3), 160.9 (s, CO_2Et), 202.9 ppm (d, CHO); IR (CDCl$_3$): $\tilde{\nu}=2930$ (s), 2857 (m), 1717 (s; C=O), 1590 (w), 1255 cm^{-1} (m); MS (EI): m/z (%): 282 (4) $[M-$H$]^+$, 254 (6) $[M-$CHO$]^+$, 208 (4), 193 (8), 168 (9), 155 (80), 142 (100) $[M-$(CH$_2$)CHO$]^+$, 114, (41). The ^{1}H NMR spectra showed the presence of traces of hydrate **9a**. Selected signal: $\delta=5.08$–5.18 ppm (m, CH(OH)$_2$).[65]

Condensation reaction of ethyl nitroacetate with 3-butenoic acid to give (3-ethoxycarbonyl-4,5-dihydro-5-isoxazolyl)acetic acid (10a): 3-Butenoic acid (42.5 mg, 0.494 mmol) with **1a** was reacted together for 48 h. After this time the reaction mixture was concentrated and the solid residue was triturated and washed twice with diisopropyl ether (2×2 mL) to afford the final product as a white powder. Alternatively the reaction mixture was treated with water (10 mL), washed with hexane (3×5 mL) and carefully concentrated under reduced pressure. The solid residue was passed through a short pad of silica gel (dichloromethane/MeOH 20:1) to afford the acid **10a** (80 mg, 81%) as a white solid. M.p. 111–112°C; ^{1}H NMR: $\delta=1.35$ (*t*, $J=7.2$ Hz, 3H; CH_3), 2.68 (dd, $J=7.2$, 16.6 Hz, 1H; CH_2CO$_2$H), 2.87 (dd, $J=6.4$, 16.6 Hz, 1H; CH_2CO$_2$H), 2.99 (dd, $J=7.6$, 18.0 Hz, 1H; 4-H), 3.40 (dd, $J=10.8$, 18.0 Hz, 1H; 4-H), 4.33 (q, $J=$ 7.2 Hz, 2H; OCH_2CH$_3$), 5.10–5.20 ppm (m, 1H; 5-H); ^{13}C NMR: $\delta=14.1$ (q, OCH$_2$CH_3), 38.8 (t, C-4), 39.0 (t, CH_2CO$_2$H), 62.2 (t, OCH_2CH$_3$), 79.0 (d, C-5), 151.6 (s, C-3), 160.4 (s, CO_2Et), 173.9 ppm (s, CO_2H); IR (KBr): $\tilde{\nu}=2988$ (w), 2929 (w) 1724 (s; C=O), 1705 (s; C=O), 1593 (w; C=N), 1258 cm^{-1} (m); MS (ESI$^-$, MeOH): m/z (%): 200 (100) $[M-1]^+$; elemental analysis calcd (%) for $C_8H_{11}NO_5$ (201.18): C 47.76, H 5.51, N 6.96; found: C 47.71 H 5.77, N 7.17.

Condensation reaction of methyl nitroacetate with 3-butenoic acid to give (3-methoxycarbonyl-4,5-dihydro-5-isoxazolyl)acetic acid (10b): 3-Butenoic acid (39.3 mg, 0.456 mmol) was treated with **1b** as described previously. After 12 h the reaction mixture was diluted with water (10 mL), and worked-up as described above to afford acid **10b** (78 mg, 91%) as a white solid. M.p. 108–109°C; ^{1}H NMR: $\delta=2.68$ (dd, $J=7.2$, 16.8 Hz, 1H; CH_2CO$_2$H), 2.87 (dd, $J=6.4$, 16.8 Hz, 1H; CH_2CO$_2$H), 3.00 (dd, $J=8.0$, 18.0 Hz, 1H; 4-H), 3.41 (dd, $J=11.2$, 18.0 Hz, 1H; 4-H), 3.87 (s, 3H; OCH_3), 5.10–5.20 ppm (m, 1H; 5-H); ^{13}C NMR: $\delta=38.7$ (t, C-4), 39.0 (t, CH_2CO$_2$H), 52.9 (q, OCH_3), 79.1 (d, C-5), 151.3 (s, C-3), 160.8 (s, CO_2Me), 174.1 ppm (s, CO_2H); IR (KBr): $\tilde{\nu}=3000$ (br; OH), 2957 (w), 1718 (s; C=O), 1591 (w; C=N), 1444 (m), 1260 cm^{-1} (m); MS (ESI$^-$, MeOH): m/z (%): 186 (100) $[M-1]^+$; elemental analysis calcd (%) for $C_7H_9NO_5$ (187.15): C 44.92, H 4.85, N 7.48; found: C 44.90, H 4.55, N 7.49.

Condensation reaction of ethyl nitroacetate with 10-undecenoic acid to give 9-(3-ethoxycarbonyl-4,5-dihydro-5-isoxazolyl)nonanoic acid (11a): The reaction of 10-undecenoic acid (78 mg, 0.423 mmol) with **1a** after 65 h gave **11a** (105 mg, 83%) after chromatography (petroleum ether/ethyl acetate 2:1) as a white powder. $R_f=0.30$; m.p. 59–63°C; ^{1}H NMR: $\delta=1.34$ (*t*, $J=7.2$ Hz, 3H; CH_3), 1.24–1.40 (m, 10H; C$H_2\times$5), 1.50–1.64 (m, 3H; CH_2C-5, CH_2CH$_2$CO$_2$H), 1.69–1.80 (m, 1H; CHC-5), 2.32 (t, $J=7.6$ Hz, 2H; CH_2CO$_2$H), 2.81(dd, J=8.4, 17.6 Hz, 1H; 4-H), 3.22 (dd, $J=10.8$, 17.6 Hz, 1H; 4-H), 4.32 (q, $J=7.2$ Hz, 2H; OCH_2CH$_3$), 4.71–4.81 ppm (m, 1H; 5-H); ^{13}C NMR: $\delta=14.1$ (q, CH_3), 24.6 (t, CH_2CH$_2$CO$_2$H), 25.0 (t, CH_2), 28.9 (t, CH_2), 29.0 (t, CH_2), 29.2 (t, 2 C, CH_2), 33.9 (t, CH_2CO$_2$H), 35.0 (t, CH_2C-5), 38.4 (t, C-4), 62.0 (t, OCH_2CH$_3$), 84.1 (d, C-5), 151.3 (s, C-3), 160.9 (s, CO_2Et), 179.3 ppm (s, CO_2H); IR (CDCl$_3$): $\tilde{\nu}=2932$ (m), 2860 (w), 1713 (s; C=O), 1590 (w; C=N), 1254 (m), 1129 cm^{-1} (m); MS (ESI$^-$, MeOH): m/z (%): 298 (100) $[M-1]^+$; elemental analysis calcd (%) for $C_{15}H_{25}NO_5$ (299.36): C 60.18, H 8.42, N 4.68; found: C 60.36 , H 8.37, N 4.32.

Condensation reaction of ethyl nitroacetate with allylbenzene to give ethyl 5-benzyl-4,5-dihydro-3-isoxazolecarboxylate (12a): The reaction of allylbenzene (50 mg, 0.422 mmol) with **1a** after 72 h gave **12a** (62 mg, 62%) after chromatography (petroleum ether/ethyl acetate 5:1) as a colourless oil. $R_f=0.50$; ^{1}H NMR: $\delta=1.34$ (t, $J=7.2$ Hz, 3H; OCH$_2$CH_3), 2.88 (dd, $J=6.8$, 14.0 Hz, 1H; CHC-5), 2.92 (dd, $J=8.4$, 17.8 Hz, 1H; 4-H), 3.11 (dd, $J=6.0$, 14.0 Hz, 1H; CH_2C-5), 3.18 (dd, $J=10.8$, 17.8 Hz, 1H; 4-H), 4.31 (q, $J=7.2$ Hz, 2H; OCH_2CH$_3$), 5.00–5.08 (m, 1H; 5-H), 7.19–7.28 (m, 3H; Ph-H), 7.28–7.35 ppm (m, 2H; Ph-H); ^{13}C NMR: $\delta=$ 14.1 (q, OCH$_2$CH_3), 37.8 (t, CH_2C-5), 40.7, (t, C-4), 62.0 (t, OCH_2CH$_3$), 84.3, (d, C-5), 126.9 (d, C$_6$H$_5$-C$_{para}$), 128.7 (d, 2 C, C$_6$H$_5$-C), 129.4 (d, 2 C, C$_6$H$_5$-C), 135.9 (s, C$_6$H$_5$-C$_{ipso}$), 151.4 (s, C-3), 160.7 ppm (s, C=O); IR (CDCl$_3$): $\tilde{\nu}=3023$ (w), 2984 (w), 2930 (w), 1718 (s; C=O), 1589 (w; C=N), 1254 cm^{-1} (s); MS (EI): m/z (%): 142 (6) $[M-$CH$_2$C$_6$H$_5]^+$, 91 (100) [CH$_2$Ph]$^+$, 77 (7) [Ph]$^+$, 65 (28); elemental analysis calcd (%) for $C_{13}H_{15}NO_3$ (233.26): C 66.94, H 6.48, N 6.00; found: C 66.97, H 6.57, N 6.02.

Condensation reaction of ethyl nitroacetate with 2-allylphenol to give ethyl 5-(2-hydroxybenzyl)-4,5-dihydro-3-isoxazolecarboxylate (13a): The reaction of 2-prop-2-enylphenol (58 mg, 0.429 mmol) with **1a** after 72 h gave **13a** (74 mg, 70%) after chromatography (petroleum ether/ethyl acetate 5:1) as a colourless oil. $R_f=0.23$; ^{1}H NMR: $\delta=1.32$ (t, $J=7.2$ Hz, 3H; OCH$_2$CH_3), 2.94–3.05 (m, 3H; CH_2C-5 and 4-H), 3.19 (dd, $J=10.8$, 17.6 Hz, 1H; 4-H), 4.30 (q, $J=7.2$ Hz, 2H; OCH_2CH$_3$), 5.08–5.18 (m, 1H; 5-H), 5.84 (br s, OH, 1H), 6.77–6.90 (m, 2H; Ph-H), 7.05–7.16 ppm (m, 2H; Ph-H); ^{13}C NMR: $\delta=14.0$ (q, OCH$_2$CH_3), 35.5 (t, CH_2C-5), 37.8, (t, C-4), 62.1 (t, OCH_2CH$_3$), 84.0 (d, C-5), 116.3 (d, Ph-C), 120.9 (d, Ph-C), 122.5 (s, Ph-C), 128.6 (d, Ph-C), 131.7 (d, Ph-C), 152.2 (s, C-3), 154.3 (s, Ph-COH), 160.6 ppm (s, C=O); IR (CDCl$_3$): $\tilde{\nu}=3600$ (m), 3560 (br), 1724 (s; C=O), 1590 (w), 1375 (m), 1256 cm^{-1} (s); MS (EI): m/z (%): 249 (4) $[M]^+$, 232 (2), 204 (4), 142 (21) $[M-$CH$_2$C$_6$H$_4$OH$]^+$, 131 (33), 107 (100), 91 (8) [CH$_2$Ph]$^+$, 77(32) [Ph]$^+$; elemental analysis calcd (%) for $C_{13}H_{15}NO_4$ (249.26): C 62.64, H 6.07, N 5.62; found: C 61.85, H 6.03, N 5.30.

Condensation reaction of ethyl nitroacetate with butenylamine hydrochloride to give ethyl 5-(2-aminoethyl)-4,5-dihydro-3-isoxazolecarboxylate hydrochloride (14a): But-3-enylammonium chloride (46 mg, 0.424 mmol) was treated with **1a** as described previously. After 42 h the reaction mixture was diluted with water (5 mL) and washed with hexane (3×5 mL) before purification by using Chromabond C8 (Macherey–Nagel) column (water, then with 10% methanol in water). Concentration of the eluant gave **14a** (84 mg, 89%) as a semisolid residue. ^{1}H NMR (D$_2$O): $\delta=1.31$ (t, $J=7.2$ Hz, 3H; OCH$_2$CH_3), 2.01–2.11 (m, 2H; CH_2C-5), 3.02 (dd, $J=7.6$, 18.0, 1H; 4-H), 3.15 (m, 2H; CH_2NH$_2$), 3.44 (dd, $J=$ 10.8, 18.0, 1H; 4-H), 4.33 (q, $J=7.2$ Hz, 2H; OCH_2CH$_3$), 4.97–5.07 ppm (m, 1H; 5-H); ^{13}C NMR (D$_2$O): $\delta=13.8$ (q, OCH$_2$CH_3), 32.5 (t, CH_2C-5),

36.9 (t, $CH_2NH_3^+$), 38.8 (t, C-4), 63.8 (t, OCH_2CH_3), 82.5 (d, C-5), 154.0 (s, C-3), 162.1 ppm (s, CO_2Me); IR (KBr): $\tilde{\nu}$ = 2986 (s), 2933 (s), 1722 (s) (C=O), 1598 (m; C=N), 1505 (m), 1262 cm^{-1} (s); MS (ESI^+, MeOH): *m/z* (%): 209 (6) $[M+Na]^+$, 187 (100) $[M+H]^+$; elemental analysis calcd (%) for $C_8H_{14}N_2O_3$·HCl (222.67): C 43.16, H 6.79, N 12.58; found: C 43.56, H 6.40, N 12.28.

Alternatively the reaction mixture was diluted with water (15 mL), washed with diethyl ether (3×15 mL) and then the pH adjusted to about 10 by addition of aqueous NaOH (1 M). This solution was extracted with chloroform (3×15 mL) and the combined organic extracts were dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford the free amine conjugate base of **14a** (28 mg, 35%) as a colourless oil. ^1H NMR: δ = 1.34 (t, *J* = 7.1 Hz, 3H; OCH_2CH_3), 1.80–1.91 (m, 1H; CH_2C-5), 1.92–2.03 (m, 1H; CH_2C-5), 2.88 (dd, *J* = 8.0, 17.6, 1H; 4-H), 3.33 (dd, *J* = 10.8, 17.6, 1H; 4-H), 3.45–3.58 (m, 2H; CH_2NH_2), 4.33 (q, *J* = 7.1 Hz, 2H; OCH_2CH_3), 4.85–4.95 ppm (m, 1H; 5-H); ^{13}C NMR: δ = 14.1 (q, OCH_2CH_3), 36.4 (t, CH_2C-5), 38.7 (t, C-4), 39.3 (t, CH_2NH_2), 62.2 (t, OCH_2), 80.4 (d, C-5), 151.5 (s, C-3), 160.5 ppm (s, CO_2Et); IR ($CDCl_3$): $\tilde{\nu}$ = 2983 (w), 2962 (w), 2928 (w), 1718 (s; C=O), 1590 (w; C=N), 1253 cm^{-1} (s).

Condensation reaction of methyl nitroacetate with butenylamine to give methyl 5-(2-aminoethyl)-4,5-dihydro-3-isoxazolecarboxylate hydrochloride (14b): Aqueous NaOH (4.24 M, 0.010 mL, 0.0424 mmol) was added to a solution of **1b** (62 mg, 0.518 mmol), but-3-enylammonium chloride (22 mg, 0.207 mmol) and water (2.000 g) and the mixture vigorously stirred in a sealed vessel at 60 °C. After 3 h the reaction mixture was washed with hexane (3×5 mL) before purification by using a Chromabond C8 (Macherey–Nagel) column (water, then with 10% methanol in water). Evaporation of the eluant gave **14b** (38 mg, 88%) as a semisolid residue. ^1H NMR (D_2O): δ = 2.06–2.14 (m, 2H; CH_2C-5), 3.06 (dd, *J* = 7.6, 18.0, 1H; 4-H), 3.19 (m, 2H; CH_2NH_2), 3.49 (dd, *J* = 10.8, 18.0, 1H; 4-H), 3.91 (s, 3H; OCH_3), 5.03–5.12 ppm (m, 1H; 5-H); ^{13}C NMR (D_2O): δ = 32.5 (t, CH_2C-5), 37.0 (t, $CH_2NH_3^+$), 38.8 (t, C-4), 53.8 (q, OCH_3), 82.6 (d, C-5), 153.8 (s, C-3), 162.6 ppm (s, CO_2Me); IR (KBr): $\tilde{\nu}$ = 3430 (br), 1729 (s; C=O), 1646 (m) 1599 (w; C=N), 1144 (w), 1259 cm^{-1} (m); MS (ESI^+, MeOH): *m/z* (%): 195 (14) $[M+Na]^+$, 173 (100) $[M+H]^+$; elemental analysis calcd (%) for $C_7H_{12}N_2O_3$·HCl (208.64): C 40.30, H 6.28, N 13.43; found: C 34.82, H 5.21, N 11.49.

Condensation reaction of ethyl nitroacetate with 5-nitro-1-pentene to give ethyl 5-(3-nitropropyl)-4,5-dihydro-3-isoxazolecarboxylate (15a): The reaction of 5-nitro-pent-1-ene (48.8 mg, 0.424 mmol) with **1a** after 18 h gave **15a** (93 mg, 95%) after chromatography (petroleum ether/diethyl ether 1:1) as a colourless oil. The spectral data are identical to those previously reported.[28] R_f = 0.25; elemental analysis calcd (%) for $C_9H_{14}N_2O_5$ (230.22): C 46.95, H 6.13, N 12.17; found: C 46.65, H 5.90, N 12.24.

Condensation reaction of ethyl nitroacetate with 5-hexen-2-one to give ethyl 5-(3-oxobutyl)-4,5-dihydro-3-isoxazolecarboxylate (16a): The reaction of 5-Hexen-2-one (42 mg, 0.424 mmol) with **1a** after 72 h gave **16a** (85 mg, 94%) after chromatography (petroleum ether/ethyl acetate 5:1) as a colourless oil. R_f = 0.12; ^1H NMR: δ = 1.33 (t, *J* = 7.2 Hz, 3H; OCH_2CH_3), 1.78–1.98 (m, 2H; CH_2C-5), 2.14 (s, 3H; $COCH_3$), 2.60 (t, *J* = 7.2 Hz, 2H; CH_2CO), 2.81 (dd, *J* = 8.0, 17.6 Hz, 1H; 4-H), 3.25 (dd, *J* = 10.8, 17.6, 1H; 4-H), 4.31 (q, *J* = 7.2 Hz, 2H; OCH_2CH_3), 4.75–4.84 ppm (m, 1H; 5-H);[66] ^{13}C NMR: δ = 14.1 (q, OCH_2CH_3), 28.9 (t, CH_2C-5), 30.0 (q, $COCH_3$), 38.6 (t, CH_2CO), 38.7 (t, C-4), 62.0 (t, OCH_2), 82.6 (d, C-5), 151.5 (s, C-3), 160.6 (s, CO_2Et), 207.4 ppm (s, $COCH_3$); IR ($CDCl_3$): $\tilde{\nu}$ = 2983 (m), 2939 (m), 1736 (s; C=O), 1716 (s; C=O), 1589 (w; C=N), 1256 cm^{-1} (s); MS (EI): *m/z* (%): 170 (2) $[M-COMe]^+$, 168 (2), 156 (2), 155 (16), 142 (10), 140 (10) $[M-(CH_2)_2COMe]^+$, 114 (35), 99 (60), 71 (100) $[(CH_2)_2COMe]^+$; elemental analysis calcd (%) for $C_{10}H_{15}NO_4$ (213.23): C 56.33, H 7.09, N 6.57; found: C 56.04, H 7.22, N 6.78.

Condensation reaction of ethyl nitroacetate with 4-bromobut-1-ene to give ethyl 5-(2-bromoethyl)-4,5-dihydro-3-isoxazolecarboxylate (17a): The reaction of 4-bromobut-1-ene (57 mg, 0.424 mmol) with **1a** after 72 h gave **17a** (79 mg, 74%) after chromatography (petroleum ether/ethyl acetate 6:1) as a colourless oil. R_f = 0.17; ^1H NMR: δ = 1.34 (t, *J* = 7.0 Hz, 3H; OCH_2CH_3), 2.02–2.10 (m, 1H; CH_2C-5), 2.22–2.32 (m, 1H; CH_2C-5), 2.86 (dd, *J* = 7.6, 17.6 Hz, 1H; 4-H), 3.33 (dd, *J* = 10.9, 17.6 Hz, 1H; 4-H), 3.44–3.52 (m, 2H; CH_2Br), 4.32 (q, *J* = 7.0 Hz, 2H; OCH_2CH_3), 4.94–5.30 ppm (m, 1H; 5-H); ^{13}C NMR: δ = 14.1 (q, OCH_2CH_3), 28.2 (t, CH_2Br), 38.0 (t, CH_2C-5), 38.5 (t, C-4), 62.1 (t, OCH_2CH_3), 81.4 (d, C-5), 151.5 (s, C-3), 160.5 ppm (s, CO_2Et); IR ($CDCl_3$): $\tilde{\nu}$ = 2984 (m), 2939 (m), 1720 (s; C=O), 1590 (m; C=N), 1257 cm^{-1} (s); MS (EI): *m/z* (%): 251 (2) $[M+2]^+$, 249 (2) $[M]^+$, 206 (5) $[M+2-OEt]^+$, 204 (5) $[M-OEt]^+$, 143 (9), 142 (68) $[M-(CH_2)_2Br]^+$, 124 (10), 114 (12), 109 (8), 107 (8), 96 (16), 88 (16), 70 (44), 42 (100); elemental analysis calcd (%) for $C_8H_{12}NO_3Br$ (250.09): C 38.42, H 4.84, N 5.60; found: C 38.64, H 4.72, N 5.24.

Condensation reaction of methyl nitroacetate with ethyl allyl ether to give 5-the methyl ester of ethoxymethyl-4,5-dihydro-isoxazole-3-carboxylic acid (18b): The reaction of 3-ethoxy-propene (36.5 mg, 0.424 mmol) with **1b** after 48 h gave **18b** (36 mg, 46%) after chromatography (dichloromethane then dichloromethane/methanol 40:1) as a colourless oil. R_f = 0.57; ^1H NMR: δ = 1.17 (t, *J* = 6.8 Hz, 3H; OCH_2CH_3), 3.07–3.14 (m, 1H; 4-H), 3.17–3.24 (m, 1H; 4-H), 3.53 (q, *J* = 6.8 Hz, 2H; OCH_2CH_3), 3.54–3.56 (m, 2H; CH_2C-5), 3.86 (s, 3H; OCH_3), 4.88–4.96 ppm (m, 1H; 5-H); ^{13}C NMR: δ = 15.0 (q, OCH_2CH_3), 35.5 (t, C-4), 52.7 (q, OCH_3), 67.2 (t, OCH_2CH_3), 70.8 (t, CH_2C-5), 82.6 (d, C-5), 151.2 (s, C-3), 161.1 ppm (s, CO_2Me); IR ($CDCl_3$): $\tilde{\nu}$ = 2978 (m), 2956 (m), 2931 (m), 2872 (m), 1724 (s; C=O), 1591 (w; C=N), 1444 (m), 1260 cm^{-1} (s); MS (EI): *m/z* (%): 187 (<1), $[M]^+$, 156 (2) $[M-OMe]^+$, 128 (14), 59 (100) $[CO_2Me]^+$; elemental analysis calcd (%) for $C_8H_{13}NO_4$ (187.19): C 51.33, H 7.00, N 7.48; found: C 51.63 H 7.16, N 6.99.

Condensation reaction of ethyl nitroacetate with allyl methyl sulfide to give thyl 5-[(methylsulfanyl)methyl]-4,5-dihydro-3-isoxazolecarboxylate (19a): Allyl methyl sulfide (37 mg, 0.424 mmol) was treated with **1a** as described previously. After 16 h the reaction mixture was concentrated, the residue dissolved in diethyl ether (15 mL) and washed with brine (3×15 mL), saturated aqueous Na_2CO_3 (3×15 mL), and brine again (3×15 mL). The organic layer was dried with sodium sulphate and concentrated to afford **19a** (46 mg, 53%) as a colourless oil. ^1H NMR: δ = 1.33 (t, *J* = 7.0 Hz, 3H; OCH_2CH_3), 2.16 (s, 3H; SCH_3), 2.67 (dd, *J* = 7.2, 14.0 Hz, 1H; CH_2S), 2.77 (dd, *J* = 4.8, 14.0 Hz, 1H; CH_2S), 3.10 (dd, *J* = 7.6, 18.0 Hz, 1H; 4-H), 3.28 (dd, *J* = 11.2, 18.0 Hz, 1H; 4-H), 4.31 (q, *J* = 7.0 Hz, 2H; OCH_2CH_3), 4.93–5.20 ppm (m, 1H; 5-H); ^{13}C NMR: δ = 14.1 (q, OCH_2CH_3), 16.3 (q, SCH_3), 37.7 (t, CH_2S), 38.1 (t, C-4), 62.1 (t, OCH_2CH_3), 83.0 (d, C-5), 151.4 (s, C-3), 160.5 ppm (s, CO_2Et); IR ($CDCl_3$): $\tilde{\nu}$ = 2984 (m), 2922 (m), 1716 (s; C=O), 1591 (m; C=N), 1260 cm^{-1} (s); MS (EI): *m/z* (%) = 203 (<1), $[M]^+$, 158 (2) $[M-OEt]^+$, 142 (10) $[M-MeSCH_2]^+$, 114(1), 62 (35), 61 (100) $[MeSCH_2]^+$; elemental analysis calcd (%) for $C_8H_{13}NO_3S$(203.26): C 47.27, H 6.45, N 6.89; found: C 47.58, H 6.85, N 6.69.

Condensation reaction of ethyl nitroacetate with 5-hexenenitrile to give 5-(4,5-dihydro-5-isoxazolyl)butanenitrile (20a): The reaction of 5-hexenenitrile (40 mg, 0.424 mmol) with **1a** after 16 h gave **20a** (89 mg, 99%) after chromatography (petroleum ether/ethyl acetate 5:1 then petroleum ether/ethyl acetate 3:1) as a colourless oil. R_f = 0.15; ^1H NMR: δ = 1.33 (t, *J* = 7.0 Hz, 3H; OCH_2CH_3), 1.70–1.90 (m, 4H; 2×CH_2), 2.34–2.46 (m, 2H; CH_2CN), 2.83 (dd, *J* = 8.0, 17.6 Hz, 1H; 4-H), 3.28 (dd, *J* = 11.2, 17.6 Hz, 1H; 4-H), 4.31 (q, *J* = 7.0 Hz, 2H; OCH_2CH_3), 4.74–4.84 ppm (m, 1H; 5-H); ^{13}C NMR: δ = 14.0 (q, OCH_2CH_3), 16.9 (t, CH_2CN), 21.4 (t, CH_2), 33.9 (t, CH_2C-5), 38.6 (t, C-4), 62.1 (t, OCH_2CH_3), 82.6 (d, C-5), 119.0 (s, CN), 151.4 (s, C-3), 160.5 ppm (s, CO_2Et); IR (neat): $\tilde{\nu}$ = 2983 (s), 2939 (s), 2244 (m; C≡N), 1716 (s; C=O), 1589 (m, C=N), 1295 (s), 1127 cm^{-1} (s); MS (EI): *m/z* (%): 211 (3) $[M+1]^+$, 165 (10), 142 (48) $[M-(CH_2)_2CN]^+$, 114 (38), 96 (18), 41 (100); elemental analysis calcd (%) for $C_{10}H_{14}N_2O_3$ (210.23): C 57.13, H 6.71, N 13.33; found: C 56.80, H 6.89, N 12.92.

Condensation reaction of ethyl nitroacetate with propargyl alcohol to give the ethyl ester of 5-hydroxymethylisoxazole-3-carboxylic acid (21a): The reaction of propargyl alcohol (23.7 mg, 0.424 mmol) with **1a** after 48 h gave **21a** (56.3 mg, 77%) after chromatography (dichloromethane then dichloromethane/methanol 50:1) as a colourless oil. The spectral data are identical to those previously reported.[28] R_f = 0.22; elemental

analysis calcd (%) for $C_7H_9NO_4$ (171.15): C 49.12, H 5.30, N 8.18; found: C 48.75, H 4.91, N 8.10.

Condensation reaction of ethyl nitroacetate with phenylacetylene to give the ethyl ester of phenylisoxazole-3-carboxylic acid (22a): Phenylacetylene (51.5 mg, 0.504 mmol) was treated with **1a** as described previously. After 48 h the reaction mixture was concentrated and the residue dissolved in diethyl ether (10 mL), then washed with brine (3×10 mL), sat. aqueous Na_2CO_3 (3×10 mL) and brine again (3×10 mL). The organic layer was dried with sodium sulphate and concentrated to afford **22a** (95.6 mg, 88%) as white solid. The spectral data are identical to those previously reported.[27] M.p. 48–49°C (ethanol) (Reference [27] 49°C); elemental analysis calcd (%) for $C_{12}H_{11}NO_3$ (217.22): C 66.35, H 5.10, N 6.45; found: C 66.06, H 5.13, N 6.51.

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