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Isoxazoles and Isoxazolines by 1,3-Dipolar Cycloaddition: Base-Catalysed Condensation of Primary Nitro Compounds with Dipolarophiles

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1,4-Diazabicyclo[2.2.2]octane (DABCO) or other suitable N-bases cause primary activated nitro compounds to condense with alkenes to yield isoxazolines or with alkynes to give isoxazoles. As the molar ratio of the base with respect to the dipolarophile decreased, the reaction became slower, but the nitro compound became more resistant to hydrolytic cleavage. The best results were achieved with a molar ratio of base in the range of 0.05–0.1. The reactions were carried out in chloroform at 60 °C; for ethyl nitroacetate and phenylnitromethane, ethanol at 80 °C can be employed with better results and shorter reaction times. A catalytic cycle is proposed: in chloroform the hydrogen-bonded ion pair formed between the nitronate and the protonated base undergoes reversible cycloaddition with the dipolarophile and then the hydrogen-bonded intermediate adduct releases water by reaction with a second nitro molecule to give the product and the hydrogen-bonded nitronate.

Introduction

The importance of isoxazole derivatives has stimulated the development of many methods for their synthesis,[1,2] including the use of primary nitro compounds as precursors of 1,3-dipoles, affording isoxazoles and isoxazolines by 1,3-dipolar cycloaddition (1,3-DC).[3] By this retrosynthetic approach, alkyl-, acyl- or silylnitronates or nitrile oxides can be used as 1,3-dipoles depending on the reagents employed.

Acidic dehydrating agents[4] have been utilised at high temperatures, while acylating or alkylating reagents have been utilised with a base.[5] These methods have in general an unfavourable environmental impact and in addition suffer from drawbacks arising from the dipole (dimerisation or polymerisation) or the dehydrating agent (byproducts) and limitations derived from interference by other functional groups present in the reagents. Consequently, product isolation and purification is often complicated by these contaminants and yields may be low.

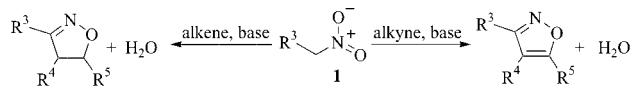
Considering that the loss of water is irreversible in the above processes, a dehydrating reagent appears not to be an essential component of the reaction. Thus, we investigated which kinds of reagents (nitro compound, base and dipolarophile) and solvents would allow the reaction to occur.

We recently reported[6–8] that the dehydration of "activated" primary nitro compounds, including phenylnitromethane, is achieved with 1,4-diazabicyclo[2.2.2]octane (DABCO) or other bases provided dipolarophiles are present, thus leading directly to the expected cycloadducts. No dehydrating agents are required: the reaction proceeds even in the presence of water. A major drawback of water, combined with the presence of a base, concerns the facile decomposition of the activated nitro compounds (**1a**–**e**).

The mechanism we have proposed for the reaction implies that the base behaves as a catalyst. Therefore we consider here how the reaction is affected when the amount of base is lowered to catalytic quantities.[9,10]

Results and Discussion

The title reactions are illustrated in Scheme 1: dipolarophiles bearing functional groups such as OH or NO_2 have been included with the aim of illustrating the substrate scope of the method.



1

2: R^4- R^5 = 
3: R^4 = H, R^5 = CH_2OH
4: R^4 = CH_2OH, R^5 = H
5: R^4 = H, R^5 = CH_2CH_2OH
6: R^4 = H, R^5 = $CH_2CH_2CH_2NO_2$

a: R^3 = PhCO
b: R^3 = EtOCO
c: R^3 = MeNHCO
d: R^3 = $PhCH_2NHCO$
e: R^3 = Ph

7: R^4 = H, R^5 = Ph
8: R^4 = H, R^5 = CH_2OH
9: R^4 = R^5 = CH_2OH

Scheme 1. Synthetic approach and nitro compounds/dipolarophiles used in this study.

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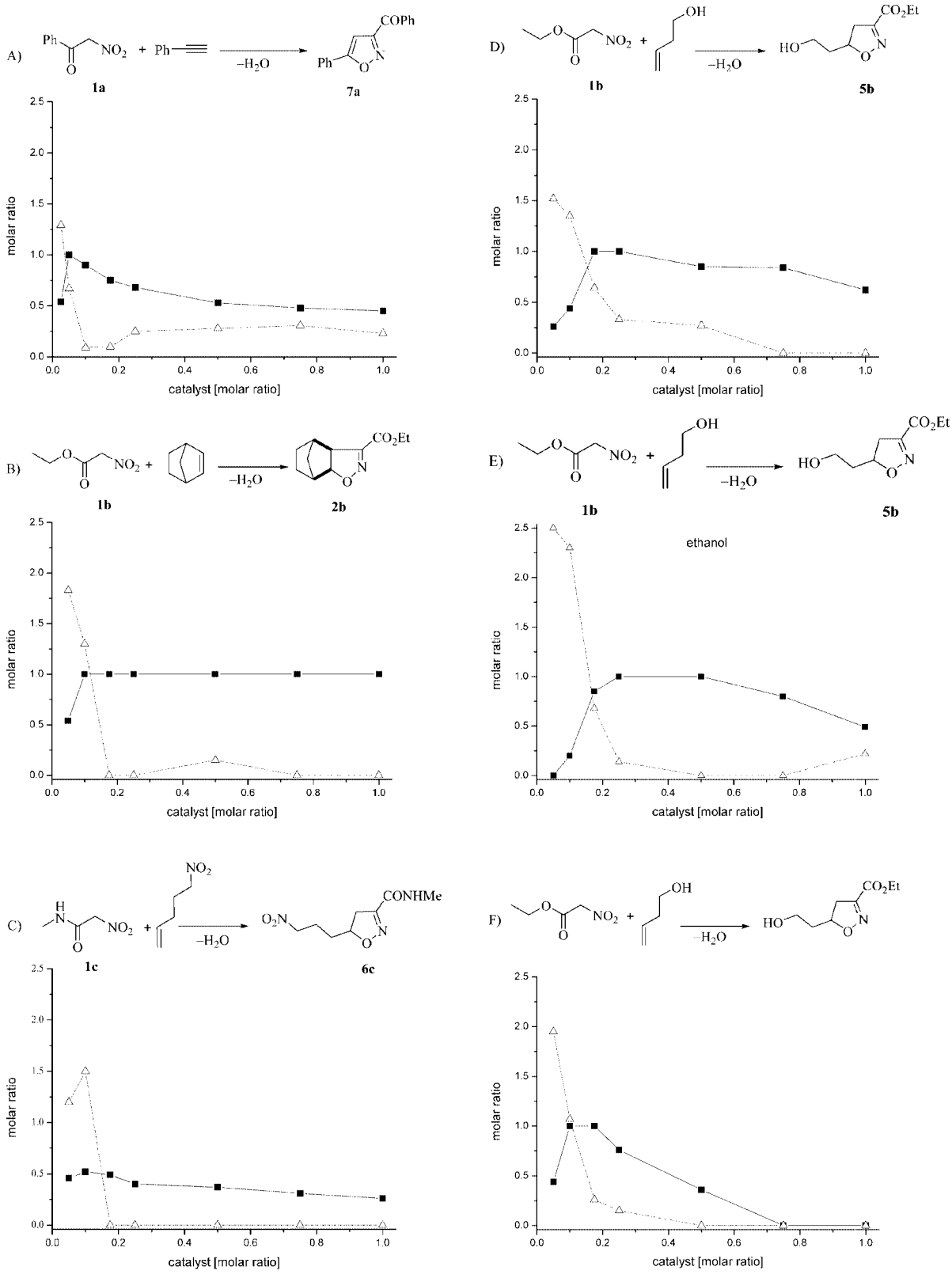


Figure 1. Condensation of nitro compounds with dipolarophiles catalysed by organic bases. Effect of the base/dipolarophile ratio on the conversion of the dipolarophile into the cycloadduct and on the decomposition of the nitro compound (**1a**–**1d**, **1f** in chloroform, **1e** in ethanol). The molar ratios of the product (solid squares) and of the residual nitro compound (white triangles) (with respect to the dipolarophile and detected by ^{1}H NMR spectroscopy after the established time) are reported as a function of the molar ratio of the base. Nitro compound (0.75 M) + dipolarophile (0.30 M) at 60 °C: (A)–(D) and (F) in chloroform, (E) in ethanol. (A) NMI, 20 h; B) DABCO, 40 h; C) DABCO, 20 h; D) DABCO, 40 h; E) DABCO, 40 h; F) 4-DMAP, 40 h.

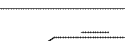
Several reactions were chosen as models for this study (Figure 1A–F). These were carried out under the usual conditions: nitro compound **1** + dipolarophile + base (molar ratios: 2.5:1:variable, ranging from 0.025 to 1) at 60 °C in chloroform except for one example carried out in ethanol (**5b**, Figure 1E). The base employed was *N*-methylimidazole (NMI) for the reaction leading to the adduct **7a** in order to avoid a side-reaction leading to furazan derivatives from the reagents benzoylnitromethane (**1a**) and the dipolarophile in the molar ratio 2:1.[7] In the other reactions (Figure 1B–D), DABCO was used as the base. For comparison, the reaction leading to **5b** was also studied with 4-(dimethylamino)pyridine (4-DMAP) as the base (Figure 1F).

After the time indicated, the reacting mixtures were analysed by ^{1}H NMR spectroscopy and the molar ratios between the product, nitro compound and dipolarophile evaluated relative to the dipolarophile (residual + amount converted into adduct). For each molar ratio of base (with respect to the dipolarophile employed) we report (Figure 1A–F) the molar ratios of the dipolarophile converted into the product (solid squares) and the residual nitro compound (white triangles).

The presence of the base (with the water produced in the reaction) causes considerable decomposition[11] of the nitro compounds (**1a**, **1b** and **1c**): in fact, the total amount (residual + converted into adduct) detected at the end is largely below the amount engaged in the reaction (2.5 molar fraction with respect to the dipolarophile). However, as the amount of base is lowered, the decomposition of the nitro compounds is less severe: some minor variations depend on which base, nitro compound or solvent is involved. The conversion into products observed after the established time results from a balance between the reaction rate (increasing with the molar ratio of the base) and the stability of the starting nitro compound (decreasing as the molar ratio of the base increases). When the conversion is incomplete, a longer reaction time might ensure an increased yield only if some nitro compound is still present (e.g., **6c**, at a molar ratio of 0.1 DABCO, Figure 1C): the excess of the nitro compound (2.5 times the dipolarophile) we employed in our experiments was aimed at enhancing the conversion of the dipolarophile into the product. The use of ethanol as the solvent gave good results with ethyl nitroacetate (**1a**) and phenylnitromethane (**1e**), whereas the other nitro compounds were more rapidly cleaved in this solvent.

The reaction conditions were selected on the basis of the above results and the compounds prepared are reported in Table 1. Compared with previous results (when available)

Table 1. Base-catalysed synthesis of isoxazolines and isoxazoles by condensation of primary nitro compounds and dipolarophiles.[a]

Entry	R^3	Dipolarophile	Solvent	T (°C)	Base (mol-%)[b]	t (h)	Product	%[c]	%[d]
1	EtOCO	norbornene	$CHCl_3$	60	DABCO (10)	40	**2b**	100	100
2	Ph	norbornene	$CHCl_3$	60	DABCO (10)	72	**2e**	100	98
3	EtOCO		$CHCl_3$	60	DABCO (10)	60	**3b**	60	...
4	EtOCO		EtOH	80	DABCO (10)	37		100	95
5	EtOCO		$CHCl_3$	60	DABCO (17.5)	40	**5b**	100	97
6	EtOCO				4-DMAP (10)	40		100	96
7	EtOCO		EtOH	80	DABCO (17.5)	16		100	97
8	Ph		$CHCl_3$	60	DABCO (10)	40	**5c**	61	49
9	Ph		EtOH	80				100	94
10	PhCO		$CHCl_3$	60	NMI (5)	72	**6a**	100	83
11	EtOCO		$CHCl_3$	60	DABCO (10)	72	**6b**	100	98
12	MeNHCO		$CHCl_3$	60	DABCO (5)	120	**6c**	100	88
13	PhCO		$CHCl_3$	60	NMI (5)	20	**7a**	100	97
14	MeNHCO		$CHCl_3$	60	DABCO (5)	72	**7c**	nd[e]	84
15	MeNHCO				DABCO (10)			nd[e]	75
16	BnNHCO		$CHCl_3$	60	DABCO (5)	72	**7d**	97	68
17	EtOCO		$CHCl_3$	60	DABCO (10)	72	**8b**	100	74
18	EtOCO		EtOH	60	DABCO (10)	72		29	–
19	EtOCO			80				100	98
20	EtOCO		EtOH	80	DABCO (10)	72	**9b**	50	29, 46[f]
21	EtOCO				4-DMAP (10)			nd[e]	21

[a] See the Experimental Section for details. [b] Relative to the dipolarophile. [c] Conversion of dipolarophiles, determined by ^{1}H NMR spectroscopy. [d] Isolated yield, determined on the analytically pure product and based on the dipolarophile. [e] Not determined: signals are not well resolved in the ^{1}H NMR spectra. [f] Obtained with 5 equiv. of ethyl nitroacetate instead of 2.5 equiv. and in a longer time of 90 h.

the yields are higher [products **2b** (83%),[12] **7a** (34%),[13] **8b** (61%),[14] **5e** (54%)[15] and **5b** (70%)[16]] or similar [products **2e** (98%)[17] and **7c** (85%)[18]].

All the reactions were carried out in chloroform except for that of 2-butyne-1,4-diol which was carried out in ethanol (Entries 20 and 21) because of the low solubility of this dipolarophile in chloroform. From dipolarophiles containing monosubstituted multiple bonds, only the 5-substituted regioisomers were detected by ^{1}H NMR spectroscopy. However, in the reaction of ethyl nitroacetate (**1b**) with allyl alcohol, carried out on a larger scale, besides the 5-hydroxymethyl regioisomer **3b**, a minor amount of the 4-hydroxymethyl regioisomer **4b** was detected and isolated by repeated chromatography.

For the reactions of benzoylnitromethane (**1a**, Entries 10 and 13), *N*-methylimidazole (NMI) was employed for the above-mentioned reason, with excellent results.

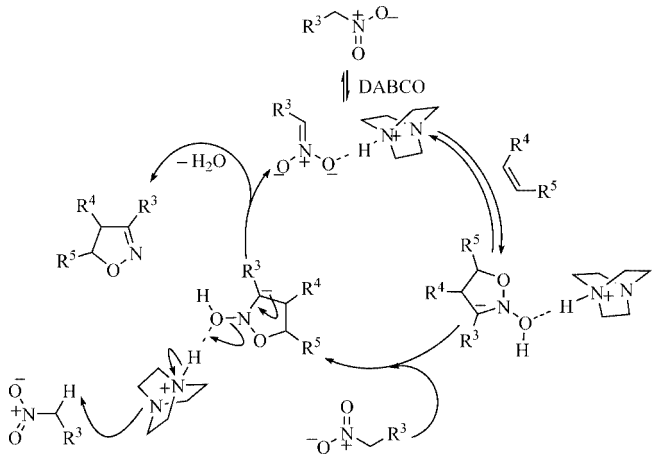
The reactions of benzoylnitromethane (**1a**) and of nitroacetamides (**1c** and **1d**) could not be carried out in ethanol as cleavage is easier than in chloroform. However, reactions of ethyl nitroacetate (**1b**), leading to **3b**, **5b**, **8b** and **9b** (Entries 4, 7, 19 and 20), and of phenylnitromethane (**1e**), leading to **5e** (Entry 9), could be profitably performed in ethanol (Figure 1E): the reaction temperature can be raised to 80 °C with considerable reduction of reaction time and enhancement of conversion (Entries 4, 9 and 19). The presence of a hydroxy group in the dipolarophile does not interfere with the reaction (100% conversion observed: Entries 4, 7, 9 and 19). The reduced yield of **8b** observed in $CHCl_3$, in spite of a quantitative conversion (Entry 17), is ascribed to partial intermolecular transesterification: the product is protected when ethanol is the solvent (Entry 19).

The catalytic use of 4-(dimethylamino)pyridine (see Figure 1F), applied in two cases (Table 1, Entries 6 and 21), gave the same results as those obtained with DABCO, but required a lower concentration of the base (Entry 5 vs. Entry 6), while for the sluggish reaction with 2-butyne-1,4-diol no improvement was observed (Entry 21).

The preparation of **3b** from ethyl nitroacetate (**1b**) and allyl alcohol in ethanol was repeated on a larger scale (0.349 g of dipolarophile converted) with no significant difference to the result reported in Table 1 (Entry 4), but the minor regioisomer **4b** was identified.

Conclusions

The illustrated examples unequivocally show that primary activated nitro compounds condense with dipolarophiles to form isoxazole derivatives under organic catalysis by DABCO or other suitable N-bases. An attempted rationalisation of the mechanism is depicted in Scheme 2: in chloroform the hydrogen-bonded ion pair formed between the nitronate and the protonated base undergoes reversible cycloaddition with the dipolarophile and then the hydrogen-bonded intermediate adduct releases water by reaction with a second nitro molecule to give the product and the hydrogen-bonded nitronate.



Scheme 2. Plausible mechanism for the catalysed condensation of nitro compounds and dipolarophiles.

The illustrated catalytic cycle, relevant to a solvent of low polarity such as chloroform, rests upon the following evidence. (i) nitro compounds **1a**–**e**, having $pK_{HB} \leq 7$, on mixing with DABCO react to give ammonium salts either as separate ions or as hydrogen-bonded complexes depending on the solvent polarity; (ii) these nitro compounds are unaffected by dipolarophiles in the absence of a base or other reagents; (iii) from nitro compounds and a catalytic amount of base, isoxazoles are produced from alkynes and 4,5-dihydroisoxazoles from alkenes; (iv) changing the base has shown that its efficiency is related to the stability of the hydrogen bond between the nitronate and the protonated base. Indeed, in other solvents the reaction is not favoured when ion separation is caused by highly polar solvents (DMSO, acetonitrile) unless a hydroxy group (ethanol) ensures hydrogen-bonding to the anion.[8]

Experimental Section

General: Melting points were recorded 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 carried out on 25-mm silica gel plates (Merck F254) with the eluent indicated for the column chromatography. For gradient column chromatography R_f values refer to the more polar eluent. ^{1}H and ^{13}C NMR spectra were recorded with a Mercuryplus 400 spectrometer (operating at 400 MHz for ^{1}H and 100.58 MHz for ^{13}C). The multiplicities of the ^{13}C NMR signals and assignments were determined by means of HMQC and gHMBC experiments. Chemical shifts were determined relative to the residual solvent peak ($CHCl_3$: δ = 7.24 ppm for ^{1}H NMR and δ = 77.0 ppm for ^{13}C NMR). EI (electron impact) mass spectra (at an ionising voltage of 70 eV) were obtained using a Shimadzu QP5050A quadrupole-based mass spectrometer. Ion mass/charge ratios (*m*/*z*) are reported in atomic mass units followed by the intensities relative to the base peak in parentheses. IR spectra were recorded with a Perkin-Elmer 881 spectrometer. Elemental analyses were obtained with an Elemental Analyser Perkin-Elmer 240C apparatus. Phenylnitromethane and *N*-methyl-2-nitroacetamide were prepared according to reported procedures.[8] Commercially available (Lancaster and Aldrich) benzoylnitromethane and

ethyl nitroacetate, were used as supplied. DABCO, 4-DMAP and NMI are commercially available and used as supplied. $CHCl_3$ (ethanol-free) was filtered through a short pad of potassium carbonate just before use. Allyl alcohol and propargyl alcohol were distilled before use. 2-Butyne-1,4-diol was crystallised (AcOEt) before use.

Effect of the Amount of Base on the Conversion of the Dipolarophile (Figure 1A–F): Different amounts of base were screened in an apparatus in which 6–8 reactions were carried out simultaneously. The base (DABCO, NMI or 4-DMAP), in a variable base/dipolarophile molar ratio (1, 0.75, 0.5, 0.25, 0.175, 0.10, 0.05, 0.025), dipolarophile (0.424 mmol), nitro compound (1.06 mmol) and solvent (chloroform or ethanol, 1.4 mL) were stirred at 60 °C in a sealed tube for the indicated time. For the 0.025 base/dipolarophile molar ratio, twice the amount of reagents and solvent was used. After the requested time, an aliquot portion was withdrawn and diluted with $CDCl_3$ (0.6 mL). After addition of TFA (4×10^{-3} mL), the ^{1}H NMR spectrum was recorded and the conversion (as a molar ratio) was evaluated as follows. Benzoylnitromethane and phenylacetylene (Figure 1A): by integrating the 4-H proton signal of the cycloadduct **7a** [δ = 7.03 (s) ppm] and the acetylenic proton of phenylacetylene [δ = 3.05 (s) ppm]. Ethyl nitroacetate and norbornene (Figure 1B): by integrating the C*H*ON proton signal [δ = 4.64 (d) ppm] of the cycloadduct **2b** and the ethylene protons of norbornene [δ = 5.98 (s) ppm]. *N*-Methyl-2-nitroacetamide and 5-nitro-1-pentene (Figure 1C): by integrating the 5-H proton signal [δ = 4.70–4.80 (m) ppm] of the cycloadduct **6c** and an ethylene proton of 5-nitro-1-pentene [δ = 5.64–5.88 (m) ppm]. Ethyl nitroacetate and 3-buten-1-ol (Figure 1D): by integrating the 5-H proton signal [δ = 4.78–5.08 (m) ppm] of the cycloadduct **5b** and an ethylene proton of 3-buten-1-ol [δ = 5.68–5.88 (m) ppm]. The residual nitro compound was evaluated by integrating its methylene protons (δ = 5.88, 5.19, 5.08 ppm for **1a**, **1b** and **1c**, respectively). Without base no conversion was observed. In the case of an unclear result a duplicate experiment was run.

Preparation of *N*-Benzyl-2-nitroacetamide (1d): A mixture of ethyl nitroacetate (**1b**) (1.33 g, 10 mmol) and benzylamine (10.9 mL, 10 equiv.) was heated whilst stirring at 60 °C. After 16 h, the mixture was cooled and 3 N HCl was added to pH = 3. The mixture was then extracted with diethyl ether (2 × 30 mL). The combined organic layers were washed with 5% HCl (2 × 15 mL), dried with Na_2SO_4, filtered and concentrated in vacuo. Trituration of the resultant solid with cold Et_2O afforded the amide **1d** as a white solid. Yield: 0.970 g, 50%. M.p. 97–98 °C (ref.[19] 87–89 °C). ^{1}H NMR: δ = 4.48 (d, *J* = 5.6 Hz, 2 H, C*H*$_2$Ph), 5.08 (s, 2 H, C*H*$_2$NO$_2$), 6.77 (br. s, 1 H, N*H*), 7.26–7.38 (m, 5 H, Ph-*H*) ppm. ^{13}C NMR: δ = 44.1 (t, *C*H$_2$Ph), 77.7 (t, *C*H$_2$NO$_2$), 127.8 (d, 2 C, Ph-*C*), 128.1 (d, Ph-*C*), 128.9 (d, 2 C, Ph-*C*), 136.6 (s, Ph-*C*), 159.8 (s, *C*=O) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 3419 (NH), 1692 (C=O), 1564, 1527 cm^{-1}. MS (EI): *m*/*z* (%) = 194 (1) $[M]^+$, 148 (100) $[M - NO_2]^+$, 133 (6) $[PhCH_2NCO]^+$, 107 (81), 91 (89) $[PhCH_2]^+$. $C_9H_{10}N_2O_3$ (194.19): calcd. C 55.67, H 5.19, N 14.43; found C 55.85, H 5.10, N 14.28.

General Procedure for the Preparation of Isoxazolines 1–6 and Isoxazoles 7–9: A solution of nitro compound (**1a**–**e**) (1.06 mmol unless otherwise stated, 2.5 equiv.), base (0.05–0.175 equiv.) and dipolarophile (0.424 mmol, 1 equiv.) in chloroform or ethanol (1.4 mL) was stirred for the indicated time in a sealed vessel (Schlenk) at 60 or 80 °C. The solvent was then removed and the residue purified by chromatography directly or after the reported workup.

Isoxazoline 2b (Ethyl 3-Oxa-4-azatricyclo[5.2.1.0^{2,6}]dec-4-ene-5-carboxylate): Isoxazoline **2b** was prepared according to the general procedure from **1b** and norbornene in chloroform at 60 °C (40 h) using DABCO (0.1 equiv.) as the base. The residue was dissolved in diethyl ether (15 mL), washed with brine (3 × 15 mL portions), satd. Na_2CO_3 solution (3 × 15 mL portions), and brine again (3 × 15 mL portions). The organic layer was dried (sodium sulfate), filtered and concentrated. Clear oil. Yield: 89 mg, 100%. $C_{11}H_{15}NO_3$ (209.2): calcd. C 63.14, H 7.23, N 6.69; found C 63.36, H 7.52, N 6.40. The spectral data are identical to those previously reported.[8]

Isoxazoline 2e (5-Phenyl-3-oxa-4-azatricyclo[5.2.1.0^{2,6}]dec-4-ene): Isoxazoline **2e** was prepared according to the general procedure from **1e** and norbornene in chloroform at 60 °C (72 h) using DABCO (0.1 equiv.) as the base. The residue was dissolved in diethyl ether (15 mL), washed with water (3 × 15 mL portions), 1 M NaOH (3 × 15 mL portions) and brine (3 × 15 mL portions) in sequence. The organic layer was dried (sodium sulfate), filtered and concentrated. The crude product was triturated in ice-cold diethyl ether and then filtered. Yellowish solid. Yield: 89 mg, 98%. M.p. 95–97 °C (ref.[8] 98–99 °C). $C_{14}H_{15}NO$ (213.28): calcd. C 78.84, H 7.09, N 6.57; found C 78.87, H 7.09, N 6.42. The spectral data are identical to those previously reported.

Isoxazoline 3b [Ethyl 5-(Hydroxymethyl)-4,5-dihydro-3-isoxazolecarboxylate]: Isoxazoline **3b** was prepared according to the general procedure from **1b** and allyl alcohol in ethanol at 80 °C (36 h) using DABCO (0.10 equiv.) as the base. The residue was dissolved in dichloromethane (10 mL), silica gel (200 mg) was added to the mixture and the solvent evaporated. The silica gel with the adsorbed product was loaded onto the top of a column of silica gel and purified by chromatography. Eluent: hexane/diethyl ether, 6:1, then diethyl ether, R_f = 0.31. Clear liquid. Yield: 70 mg, 95%. ^{1}H NMR: δ = 1.34 (t, *J* = 7.2 Hz, 3 H, C*H*$_3$CH$_2$O), 1.96 (br. s, 1 H, O*H*), 3.05–3.28 (m, 2 H, 4-H), 3.62 (dd, *J* = 4.4 and 12.4 Hz, 1 H, C*H*OH), 3.84 (dd, *J* = 3.2 and 12.4 Hz, 1 H, C*H*OH), 4.33 (q, *J* = 7.2 Hz, 2 H, CH$_3$C*H*$_2$O), 4.84–4.93 (m, 1 H, 5-H) ppm. ^{13}C NMR: δ = 14.1 (q, *C*H$_3$CH$_2$O), 34.8 (t, C-4), 62.1 (t, CH$_3$*C*H$_2$O), 63.3 (t, *C*H$_2$OH), 83.8 (d, C-5), 152.1 (s, C-3), 160.4 (s, *C*=O) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 3600 (OH), 2985, 1720 (C=O), 1593 (C=N), 1258 cm^{-1}. MS (EI): *m*/*z* (%) = 173 (4) $[M]^+$, 142 (39), 128 (27), 70 (100). $C_7H_{11}NO_4$ (173.17): calcd. C 48.55, H 6.40, N 8.09; found C 48.26, H 6.39, N 7.88.

Isoxazoline 5b [Ethyl 5-(2-Hydroxyethyl)-4,5-dihydro-3-isoxazolecarboxylate]: Isoxazoline **5b** was prepared according to the general procedure from **1b** (4.24 mmol) and 3-buten-1-ol in chloroform at 60 °C (40 h) using DABCO (0.175 equiv.) as the base. The residue was purified by chromatography to afford 310 mg (97%) of **5b**. In other experiments carried out according to the general procedure the reaction carried out in chloroform at 60 °C using 4-DMAP (0.1 equiv.) as the base or in ethanol at 80 °C using DABCO (0.175 equiv.) as the base afforded the isoxazoline **5b** in 96 and 97% yields, respectively. Eluent: dichloromethane then dichloromethane/methanol, 20:1, R_f = 0.27. Clear oil. ^{1}H NMR: δ = 1.32 (t, *J* = 7.1 Hz, 3 H, C*H*$_3$CH$_2$O), 1.81–1.87 (m, 1 H, C*H*$_2$C-5), 1.91–1.99 (m, 1 H, C*H*$_2$C-5), 2.04 (br. s, 1 H, O*H*), 2.89 (dd, *J* = 8.0 and 18.0 Hz, 1 H, 4-H), 3.28 (dd, *J* = 11.2 and 18.0 Hz, 1 H, 4-H), 3.72–3.82 (m, 2 H, C*H*$_2$OH), 4.29 (q, *J* = 7.1 Hz, 2 H, CH$_3$C*H*$_2$O), 4.90–5.00 (m, 1 H, 5-H) ppm. ^{13}C NMR: δ = 14.2 (q, *C*H$_3$CH$_2$O), 37.7 (t, *C*H$_2$C-5), 38.9 (t, C-4), 59.1 (t, *C*H$_2$OH), 62.1 (t, CH$_3$*C*H$_2$O), 81.7 (d, C-5), 151.5 (s, C-3), 160.5 (s, *C*=O) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 3625 (OH), 1720 (C=O), 1589 (C=N), 1381, 1257 cm^{-1}. MS (EI): *m*/*z* (%) = 187 (1) $[M]^+$, 142 (100) $[M - OEt]^+$, 114 (66) $[M - CO_2Et]^+$, 96 (28). $C_8H_{13}NO_4$ (187.19): calcd. C 51.33, H 7.00, N 7.48; found C 51.65, H 6.97, N 7.70.

Isoxazoline 5e [(3-Phenyl-4,5-dihydroisoxazol-5-yl)ethanol]: Isoxazoline **5e** was prepared according to the general procedure from

1e and 3-buten-1-ol in ethanol at 80 °C (40 h) using DABCO (0.10 equiv.) as the base. The residue was purified by chromatography to afford 76 mg (94%) of **5e**. In another experiment carried out according to the general procedure, the reaction in chloroform at 60 °C (40 h) using DABCO (0.10 equiv.) as the base afforded the isoxazoline **5e** in 49% yield. Eluent: hexane then hexane/ethyl acetate, 2:3, R_f = 0.28. White solid. M.p. 78–79 °C (ref.[20] 78 °C). ^{1}H NMR: δ = 1.86–1.95 (m, 1 H, CH_2C-5), 1.96–2.05 (m, 1 H, CH_2C-5), 3.06 (dd, J = 8.0 and 16.4 Hz, 1 H, 4-H), 3.46 (dd, J = 10.4 and 16.4 Hz, 1 H, 4-H), 3.82–3.92 (m, 2 H, CH_2OH), 4.88–4.96 (m, 1 H, 5-H), 7.36–7.42 (m, 3 H, Ph-H), 7.62–7.68 (m, 2 H, Ph-H) ppm. ^{13}C NMR: δ = 37.8 (t, CH$_2$C-5), 40.5 (t, C-4), 59.9 (t, CH$_2$OH), 79.5 (d, C-5), 126.6 (d, 2 C, Ph-C), 128.7 (d, 2 C, Ph-C), 129.5 (s, Ph-C), 130.1 (d, Ph-C), 156.8 (s, C-3) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 3623 (OH), 1601, 1356 cm^{-1}. MS (EI): m/z (%) = 191 (13) [M]$^+$, 146 (100) [M – CH_2CH_2OH]$^+$, 118 (29), 77 (75) [Ph]$^+$. $C_{11}H_{13}NO_2$ (191.23): calcd. C 69.09, H 6.85, N 7.32; found C 68.80, H 6.55, N 7.15.

Isoxazoline 6a {[5-(3-Nitropropyl)-4,5-dihydro-3-isoxazolyl](phenyl)-methanone}: Isoxazoline **6a** was prepared according to the general procedure from **1a** and 5-nitro-1-pentene in chloroform at 60 °C (72 h) using NMI (0.05 equiv.) as the base. The residue was dissolved in diethyl ether (15 mL), washed with brine (3 × 15 mL portions), 3 M NaOH (3 × 15 mL portions) and brine again (3 × 15 mL portions). The organic layer was dried (sodium sulfate), filtered and concentrated. The residue was dissolved in dichloromethane (10 mL), silica gel (200 mg) was added to the mixture and the solvent evaporated. The silica gel with the adsorbed product was loaded onto the top of a column of silica gel and purified by chromatography. Eluent: hexane/diethyl ether, 6:1, then hexane/diethyl ether, 3:2, R_f = 0.15. Clear oil. Yield: 93 mg, 83%. ^{1}H NMR: δ = 1.73–1.88 (m, 2 H, CH_2C-5), 2.10–2.30 (m, 2 H, CH_2CH$_2$C-5), 3.02 (dd, J = 8.0 and 17.8 Hz, 1 H, 4-H), 3.43 (dd, J = 10.8 and 17.8 Hz, 1 H, 4-H), 4.39–4.52 (m, 2 H, CH_2NO$_2$), 4.77–4.86 (m, 1 H, 5-H), 7.42–7.50 (m, 2 H, Ph-H_{meta}), 7.56–7.62 (m, 1 H, Ph-H_{para}), 8.14–8.21 (m, 2 H, Ph-H_{ortho}) ppm. ^{13}C NMR: δ = 23.4 (t, CH$_2$CH$_2$C-5), 32.0 (t, CH$_2$C-5), 39.2 (t, C-4), 74.9 (t, CH$_2$NO$_2$), 81.9 (d, C-5), 128.2 (d, 2 C, Ph-C_{meta}), 130.1 (d, 2 C, Ph-C_{ortho}), 133.5 (d, Ph-C_{para}), 135.4 (s, Ph-C_{ipso}) 157.5 (s, C-3), 185.9 (s, C=O) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 2936, 1652 (C=O), 1598 (C=N) 1555 (ON–O), 1365 (ON–O) cm^{-1}. MS (EI): m/z (%) = 262 (7) [M]$^+$, 174 (42), 105 (100) [PhCO]$^+$, 77 (83) [Ph]$^+$. $C_{13}H_{14}N_2O_4$ (262.26): calcd. C 59.54, H 5.38, N 10.68; found C 59.34, H 4.92, N 10.33.

Isoxazoline 6b [Ethyl 5-(3-Nitropropyl)-4,5-dihydro-3-isoxazolecarboxylate]: Isoxazoline **6b** was prepared according to the general procedure from **1b** and 5-nitro-1-pentene in chloroform at 60 °C (72 h) using DABCO (0.10 equiv.) as the base. The residue was purified by chromatography. Eluent: hexane/diethyl ether, 1:1, R_f = 0.30. Clear liquid. Yield: 96 mg, 98%. ^{1}H NMR: δ = 1.32 (t, J = 7.0 Hz, 3 H, CH_3CH$_2$), 1.68–1.82 (m, 2 H, CH_2C-5), 2.04–2.22 (m, 2 H, CH_2CH$_2$C-5), 2.83 (dd, J = 8.0 and 17.8 Hz, 1 H, 4-H), 3.29 (dd, J = 10.9 and 17.8 Hz, 1 H, 4-H), 4.30 (q, J = 7.0 Hz, 2 H, CH$_3$CH_2), 4.36–4.48 (m, 2 H, CH_2NO$_2$), 4.76–4.84 (m, 1 H, 5-H) ppm. ^{13}C NMR: δ = 14.0 (q, CH$_3$CH$_2$), 23.1 (t, CH$_2$CH$_2$C-5), 31.8 (t, CH$_2$C-5), 38.6 (t, C-4), 62.1 (t, CH$_3$$CH_2$), 74.8 (t, CH$_2NO_2$), 82.5 (d, C-5), 151.4 (s, C-3), 160.4 (s, C=O) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 1720 (C=O), 1590 (C=N) 1555 (ON–O), 1379, (ON–O) cm^{-1}. MS (EI): m/z (%) = 231 (6) [MH]$^+$, 213 (4), 185 (33) [MH – NO_2]$^+$, 155 (64), 142 (100) 114 (92) [MH – NO$_2$(CH$_2$)$_3$CHO]$^+$. $C_9H_{14}N_2O_5$ (230.22): calcd. C 46.95, H 6.13, N 12.17; found C 47.29, H 6.16, N 12.19.

Isoxazoline 6c [*N*-Methyl-5-(3-nitropropyl)-4,5-dihydro-3-isoxazolecarboxamide]: Isoxazoline **6c** was prepared according to the general procedure from **1c** and 5-nitro-1-pentene in chloroform at 60 °C (120 h) using DABCO (0.05 equiv.) as the base. The residue was dissolved in ethyl acetate (15 mL) and washed with brine (3 × 15 mL portions), 1 M NaOH (3 × 15 mL portions), and brine again (3 × 15 mL portions). The organic layer was dried (sodium sulfate), filtered and concentrated to afford **6c** (70 mg). More **6c** was obtained by back-extraction of the combined aqueous layers with ethyl acetate (3 × 30 mL) and concentration of the extracts (10 mg). White solid. Yield: 80 mg, 88%. M.p. 75–76 °C. ^{1}H NMR: δ = 1.62–1.78 (m, 2 H, CH_2C-5), 2.02–2.20 (m, 2 H, CH_2CH$_2$C-5), 2.87 (d, J = 5.2 Hz, 3 H, CH_3), 2.88 (dd, J = 8.0 and 17.9 Hz, 1 H, 4-H), 3.30 (dd, J = 10.9 and 17.9 Hz, 1 H, 4-H), 4.36–4.48 (m, 2 H, CH_2NO$_2$), 4.70–4.80 (m, 1 H, 5-H), 6.64 (br. s, 1 H, NH) ppm. ^{13}C NMR: δ = 23.3 (t, CH$_2$CH$_2$C-5), 26.1 (q, CH$_3$N), 31.8 (t, CH$_2$C-5), 38.6 (t, C-4), 74.9 (t, CH$_2$NO$_2$), 82.3 (d, C-5), 153.9 (s, C-3), 160.1 (s, C=O) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 3434 (N-H), 2941, 1678 (C=O), 1595, 1555 cm^{-1}. MS (EI): m/z (%) = 215 (1) [M]$^+$, 185 (1) [M – $NHCH_3$]$^+$, 58 (100) [CONHMe]$^+$. $C_8H_{13}N_3O_4$ (215.21): calcd. C 44.65, H 6.09, N 19.53; found C 44.35, H 6.10, N 19.68.

Isoxazole 7a [(Phenyl)(5-phenyl-3-isoxazolyl)methanone]: Isoxazole **7a** was prepared according to the general procedure from **1a** and phenylacetylene in chloroform at 60 °C (20 h) using 1-methylimidazole (0.05 equiv.) as the base. The solvent was then removed and the residue dissolved in diethyl ether (15 mL), washed with brine (3 × 15 mL portions), 1 M NaOH (3 × 15 mL portions) and brine again (3 × 15 mL portions). The organic layer was dried (sodium sulfate), filtered and concentrated. When necessary the workup was repeated. White solid. Yield: 103 mg, 97%. M.p. 77–78 °C (ref.[21] 78–79 °C). $C_{16}H_{11}NO_2$ (249.27): calcd. C 77.10, H 4.45, N 5.62; found C 77.31, H 4.69, N 6.01. The spectral data are identical to those previously reported.[7]

Isoxazole 7c (*N*-Methyl-5-phenyl-3-isoxazolecarboxamide): Isoxazole **7c** was prepared according to the general procedure from **1c** and phenylacetylene in chloroform at 60 °C (72 h) using DABCO (0.05 equiv.) as the base. The residue was dissolved in diethyl ether (15 mL) and washed with brine (3 × 15 mL portions), 1 M NaOH (3 × 15 mL portions) and brine again (3 × 15 mL portions) in sequence. The organic layer was dried (sodium sulfate), filtered and concentrated. White solid. Yield: 73 mg, 84%. M.p. 192–193 °C (ref.[8] 198–199 °C). $C_{11}H_{10}N_2O_2$ (202.21): calcd. C 65.34, H 4.98, N 13.85; found C 64.95, H 5.21, N 13.95. The spectral data are identical to those previously reported.[7]

Isoxazole 7d (*N*-Benzyl-5-phenyl-3-isoxazolecarboxamide): Isoxazole **7d** was prepared according to the general procedure from **1d** and phenylacetylene in chloroform at 60 °C (72 h) using DABCO (0.05 equiv.) as the base. The residue was dissolved in diethyl ether (15 mL) and washed with water (3 × 15 mL portions), 1 M NaOH (3 × 15 mL portions) and brine (3 × 15 mL portions) in sequence. The organic layer was dried (sodium sulfate), concentrated and the residue dissolved in dichloromethane (6 mL). Silica gel (200 mg) was added to the mixture and the solvent evaporated. The silica gel with the adsorbed product was loaded onto the top of a column of silica gel and purified by chromatography. Eluent: hexane/diethyl ether, 3:1, R_f = 0.25. White solid. Yield: 77 mg, 68%. M.p. 151–152 °C (ref.[22] 152 °C). ^{1}H NMR: δ = 4.64 (d, J = 5.8 Hz, 2 H, CH_2Ph), 6.98 (s, 1 H, 4-H), 7.10–7.19 (br. s, 1 H, NH), 7.27–7.32 (m, 1 H, Bn-H), 7.33–7.36 (m, 4 H, Bn-H), 7.44–7.50 (m, 3 H, Ph-H_{meta} and Ph-H_{para}), 7.78–7.80 (m, 2 H, Ph-H_{ortho}) ppm. ^{13}C NMR: δ = 43.5 (t, NCH$_2$Ph), 99.2 (d, C-4), 125.9 (d, 2 C, Ph-C_{ortho}), 126.8 (s, Ph-C_{ipso}), 127.8 (d, Bn-C), 127.9 (d, 2 C, Bn-C), 128.8 (d, 2 C, Bn-C), 129.1 (d, 2 C, Ph-C_{meta}), 130.7 (d, Ph-C_{para}), 137.3 (s, Bn-

C_{ipso}), 158.8 (s, C-3)*, 159.0 (s, *C*=O)*, 171.7 (s, C-5) ppm; * may be exchanged. IR: ṽ = 3416 (NH), 1683 (C=O), 1541, 1447 cm^{-1}. MS (EI): *m*/*z* (%) = 278 (37) $[M]^+$, 277 (90) $[M - 1]^+$, 201 (10), 173 (22), 146 (54), 105 (83) $[PhCO]^+$, 91 (100) $[PhCH_2]^+$, 77 (60) $[Ph]^+$. $C_{17}H_{14}N_2O_2$ (278.31): calcd. C 73.37, H 5.07, N 10.07; found C 73.40, H 5.36, N 10.02.

Isoxazole 8b [Ethyl 5-(Hydroxymethyl)-3-isoxazolecarboxylate]: Isoxazole **8b** was prepared according to the general procedure from **1b** and propargyl alcohol in ethanol at 80 °C (72 h) using DABCO (0.10 equiv.) as the base. The solvent was then removed and the residue purified by chromatography to afford 72 mg (98%) of **8b**. In another experiment carried out according to the general procedure, the reaction in chloroform at 60 °C (72 h) using DABCO (0.10 equiv.) as the base afforded the isoxazole **8b** in 74% yield. Eluent: dichloromethane and then dichloromethane/methanol, 40:1, R_f = 0.29. Clear liquid. ^{1}H NMR: δ = 1.40 (t, *J* = 6.8 Hz, 3 H, C*H*$_3$), 2.19 (br. s, 1 H, O*H*), 4.42 (q, *J* = 6.8 Hz, 2 H, OC*H*$_2$), 4.81 (s, 2 H, C*H*$_2$OH), 6.66 (t, ^4J = 0.8 Hz, 1 H, 4-H) ppm. ^{13}C NMR: δ = 14.1 (q, *C*H$_3$), 56.4 (t, *C*H$_2$OH), 62.3 (t, OCH$_2$), 102.6 (d, C-4), 156.4 (s, C-3), 159.8 (s, *C*=O), 173.1 (s, C-5) ppm. IR: ṽ = 3609 (OH), 1734 (C=O), 1600, 1470 cm^{-1}. MS (EI):[23] *m*/*z* (%) = 171 (4) $[M]^+$, 126 (30) $[M - OEt]^+$, 68 (100). $C_7H_9NO_4$ (171.15): calcd. C 49.12, H 5.30, N 8.18; found C 49.22, H 5.44, N 7.96.

Isoxazole 9b [Ethyl 4,5-Bis(hydroxymethyl)-3-isoxazolecarboxylate]: Isoxazole **9b** was prepared according to the general procedure from **1b** and 2-butyne-1,4-diol in ethanol at 80 °C (72 h) using DABCO (0.1 equiv.) as the base. The residue was purified by chromatography to afford **9b** (25 mg, 29%). The reaction repeated with a larger excess of ethyl nitroacetate (282 mg, 2.124 mmol, 5 equiv.) for 90 h afforded 39 mg (46%) of **9b**. In another experiment, according to the general procedure, the reaction carried out in ethanol at 80 °C (72 h) using 4-DMAP (0.10 equiv.) as the base afforded the isoxazole **9b** in 21% yield. Eluent: dichloromethane then dichloromethane/methanol, 50:1, then dichloromethane/methanol, 20:1, R_f = 0.22. Clear oil. ^{1}H NMR: δ = 1.42 (t, *J* = 7.2 Hz, 3 H, CH$_2$C*H*$_3$), 3.20–3.48 (br. s, 2 H, 2 × CH$_2$O*H*), 4.45 (q, *J* = 7.2 Hz, 2 H, C*H*$_2$CH$_3$), 4.75 (s, 2 H, C*H*$_2$OH), 4.80 (s, 2 H, C*H*$_2$OH) ppm. ^{13}C NMR: δ = 14.1 (q, *C*H$_3$CH$_2$), 53.8 (t, *C*H$_2$OH), 55.3 (t, *C*H$_2$OH), 62.7 (t, CH$_3$*C*H$_2$), 117.3 (s, C-4), 154.3 (s, C-3), 161.09 (s, *C*=O), 169.9 (s, C-5) ppm. IR: ṽ = 3608 (OH), 1719 (C=O), 1555 cm^{-1}. MS (EI): *m*/*z* (%) = 200 (2) $[M - H]^+$, 184 (10) $[M - OH]^+$, 170 (13), 142 (100), 128 (28), 114 (52), 110 (95). $C_8H_{11}NO_5$ (201.18): calcd. C 47.76, H 5.51, N 6.96; found C 47.47, H 5.28, N 7.21.

Scale-Up of the Preparation of Isoxazoline 3b [Ethyl 5-(Hydroxymethyl)-4,5-dihydro-3-isoxazolecarboxylate]: In a sealed 50 mL Schlenk flask DABCO (67 mg, 0.601 mmol, 0.1 equiv.) was dissolved in anhydrous ethanol (20 mL). Ethyl nitroacetate (**1b**) (2.00 g, 15.0 mmol, 2.5 equiv.) was added to this solution followed by allyl alcohol (0.349 g, 6.01 mmol). The flask was placed in an oil bath heated at 80 °C and the mixture stirred (gentle reflux) for 24 h. The solvent was then removed under reduced pressure and the residue purified by chromatography eluting with diethyl ether/petroleum ether, 10:1, to yield 874 mg (R_f = 0.94, 1.1 equiv. corresponding to 73% of the expected recovery) of recovered nitroacetate (**1b**) and 968 mg (93% yield, R_f = 0.32) of isoxazoline **3b** as a clear oil containing less than 5% of the corresponding 4-substituted regioisomer **4b** as a clear liquid. A further chromatographic separation, under the same conditions, allowed the two regioisomers to be separated. Isoxazole **4b** [ethyl 4-(hydroxymethyl)-4,5-dihydro-3-isoxazolecarboxylate]: ^{1}H NMR: δ = 1.37 (t, *J* = 7.2 Hz, 3 H, C*H*$_3$CH$_2$O), 2.53 (br. s, 1 H, O*H*), 3.64–3.74 (m, 1 H, 4-H), 3.80–3.86 (m, 2 H, C*H*$_2$OH), 4.28–4.44 (m, 3 H, CH$_3$C*H*$_2$O, 5-H), 4.64 (dd, *J* = 8.8 and 11.2 Hz, 1 H, 5-H) ppm. ^{13}C NMR: δ = 14.0 (q, *C*H$_3$CH$_2$O), 49.7 (d, C-4), 62.0 (t, *C*H$_2$OH), 62.5 (t, CH$_3$*C*H$_2$O), 74.6 (t, C-5), 152.1 (s, C-3), 161.6 (s, *C*=O) ppm. IR ($CDCl_3$): ṽ = 1716 (C=O) cm^{-1}. MS (EI): *m*/*z* (%) 173 (4) $[M]^+$, 142 (65), 128 (23), 115 (87), 97 (100). $C_7H_{11}NO_4$ (173.17): calcd. C 48.55, H 6.40, N 8.09; found C 48.22, H 6.06, N 7.76. The spectral data of **3b** are identical to those reported above.

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