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Base- and Copper-Catalysed Condensation of Primary Activated Nitro Compounds with Enolisable Compounds

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Primary nitro compounds have not been employed as nitrile oxide precursors in reactions with active methylene compounds because the reagents commonly used as dehydrating agents also react with these dipolarophiles. However, the Cu^{II}-catalysed cycloaddition/condensation procedure has been shown to be viable with these substrates, leading directly to the expected polyfunctional isoxazoles provided nitro compounds with enhanced acidity ("activated") were used. In the absence of added dipolarophiles, these nitro compounds underwent self-condensation to the corresponding furoxans. However, as well as 3,4-dibenzoylfuroxan, benzoylnitromethane predominantly gave the isomer 3-benzoyl-4-nitro-5-phenylisoxazole, the structure of which was confirmed by crystallographic analysis.
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Introduction

Active methylene compounds (those with two geminal electron-withdrawing groups: β-diketones, β-keto esters, cyanoacetate, etc.) are known to react with hydroximoyl chlorides in the presence of a base to give isoxazole derivatives.[1] This area was first developed by Quilico and coworkers in the 1930s.[2] They found that benzohydroximoyl chloride reacts with β-diketones and other "active methylene" compounds only in the presence of base, producing isoxazoles. This reaction was later recognised as taking place via the intermediate nitrile oxide derived from the corresponding hydroximoyl chloride.[3] These procedures are still in use today as a convenient approach to highly functionalised isoxazoles, either from hydroximoyl chlorides[4,5] or from isolated nitrile oxides.[6,7] In addition, another protocol is known to lead to isoxazoles and isoxazolines using primary nitro compounds as the starting materials. These are dehydrated to nitrile oxides with various acylating reagents such as aryl isocyanates,[8] acyl chlorides,[9] anhydrides[10] and $POCl_3$[11] among others.[12] In the presence of dipolarophiles, the cycloaddition of nitrile oxide to double or triple bonds leads to isoxazolines or isoxazoles, respectively. However, this protocol has the disadvantage if applied to enolic dipolarophiles that the reagents commonly used as dehydrating agents also react with these dipolarophiles.[13–15] Therefore this approach to the direct preparation of isoxazoles has been largely disregarded. To the best of our knowledge there is only one report describing the treatment of dibenzoylmethane with an excess of phenylnitromethane and acetyl chloride under basic conditions to afford 4-benzoyl-3,5-diphenylisoxazole among other products.[16] To overcome this difficulty, a procedure has been proposed that involves the use of preformed pyrrolidine enamines of substituted β-keto esters[11b,17,18] or β-diketones,[16,19] but this adds a further step to the whole process.

The use of primary nitro compounds as precursors of isoxazole derivatives has recently been improved. Nitro compounds with enhanced acidity and dipolarophiles condense to form the product by organocatalysis.[20–23] 1,4-Diazabicyclo[2.2.2]octane (DABCO) gives the best results if used alone, but the reaction becomes faster on addition of a Cu^{II} salt. With a Cu^{II} salt, other tertiary amines like triethylamine (TEA) or *N*-methylpiperidine (NMP) appear to be more suitable and cycloaddition/condensation reactions occur even with nitroalkanes.[24,25]

In this paper we report the application of this catalytic procedure to "activated" primary nitro compounds using

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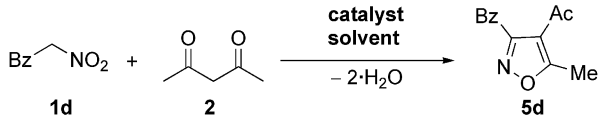
active methylene compounds as dipolarophiles. The reactions of nitroalkanes with these dipolarophiles were unsuccessful.

Results and Discussion

By using the model reaction between benzoylnitromethane (**1d**) and acetylacetone (**2**) we investigated the optimal conditions for isoxazole formation. The reaction was performed with various catalyst compositions and solvents and the spectroscopic yields observed after an established time are reported in Table 1.

Table 1. Optimisation of the reaction conditions of the model reaction between benzoylnitromethane (**1d**) and acetylacetone (**2**).[a]



1d **2** **5d**

Entry	Solvent	Catalyst		Yield [%][b]
		Base [equiv.]	Cu^{II} [equiv.]	
1	$CHCl_3$	DABCO (0.2)	0.1[c]	53 (62)
2	$CHCl_3$	DABCO (0.2)	–	trace (4)
3	$CHCl_3$	NMP (0.2)	0.1[c]	73 (73)
4	$CHCl_3$	NMP (0.1)	0.05[c]	57 (67)
5	$CHCl_3$	NMP (0.2)	–	6 (6)
6	$CHCl_3$	NMP (0.1)	–	14 (20)
7	$CHCl_3$	DABCO (0.1)	0.05[c]	51 (58)
8	$CHCl_3$	DABCO (0.1)	–	6 (6)
9	$CHCl_3$	NMP (0.2)	0.1[d]	54 (62)
10	$CHCl_3$	NMP (0.2)	0.1[c] (1.1)[e]	85[f]
11	$CHCl_3$	NMI[g] (0.2)	0.1[c]	12 (18)
12	$CHCl_3$	TEA (0.2)	0.1[c]	49 (50)
13	$CHCl_3$	–	0.1	0
14	C_2H_5OH	NMP (0.2)	0.1[c]	trace
15	toluene	NMP (0.2)	0.1[c]	78 (90)

[a] Performed at 60 °C, see Exp. Sect. for detailed reaction conditions. [b] Spectroscopic yields evaluated by NMR after 18 h. The spectroscopic yields after 42 h are given in parentheses (but after 72 h for entry 15). [c] $Cu(AcO)_2$. [d] $Cu(acac)_2$. [e] $Cu(acac)_2$ instead of acetylacetone. [f] Possibly an excessive value owing to signal broadening caused by a high copper concentration. [g] *N*-Methylimidazole.

The use of base alone as the catalyst was unsatisfactory as poor yields of the expected isoxazole **5d** were obtained (entries 2, 5, 6 and 8). Higher isoxazole yields were obtained on addition of copper(II) to the base (entries 1, 3, 4 and 7). The best results were achieved with a catalyst loading of 20% base and 10% copper(II) (cf. entries 3 and 4). Of the bases explored, *N*-methylpiperidine (NMP) is to be preferred (cf. entries 1, 3, 11 and 12). Similar results were obtained by using copper(II) acetylacetonate instead of copper(II) acetate (entry 9) or acetylacetone (entry 10). No isoxazole **5d** was produced in the presence of copper(II) alone (entry 13). The use of other solvents showed that a protic solvent (ethanol, entry 14) was not suitable, whereas in toluene the model reaction gave an excellent result (entry 15). However, for other substrates (nitroacetates) chloroform is still to be preferred. Thus, a Cu^{II} salt (0.1 equiv.) with NMP (0.2 equiv.) was employed as the catalyst system in chloroform for the reactions of **1a**, **1b** and **1c**, but for **1d** the reaction was performed in toluene.

The reaction in entry 3 of Table 1 was followed by ^1H NMR spectroscopy. Kinetic profiles, included in the Supporting Information, were prepared by plotting the concentrations versus time of the product **5d** and nitromethane, formed by slow cleavage of benzoylnitromethane (**1d**): nitromethane was produced together with benzoic acid, which reacted with the basic catalyst and thus the rate dropped, even in the presence of excess of the starting material **1d**.

Ethyl nitroacetate (**1a**), methyl nitroacetate (**1b**), *N*-methylnitroacetamide (**1c**) and benzoylnitromethane (**1d**) with acetylacetone (**2**), respectively, afforded the 4-acetylisoxazoles **5a**–**d**. Similarly, reactions of the nitroacetates **1a** and **1b** and the nitro ketone **1d** with benzoylacetone (**3**) gave the regioisomers **6a**, **6b** and **6d**, respectively. Benzoylnitromethane (**1d**) and methyl nitroacetate (**1b**) also reacted with ethyl acetoacetate (**4**) to give the isoxazoles **7d** and **7b**, respectively.

The results are collected in Table 2: no other regioisomers were identified in addition to the products **5**–**7** illustrated. The yields compare favourably with those of previous methods (last column), which, however, require an additional step. Methyl nitroacetate (**1b**) was chosen to obtain simpler ^1H NMR spectra of the crude mixtures. However, it turned out that these reactions gave better results than those of the ethyl ester (compare entries 1 and 2, 5 and 6). Thus, methyl nitroacetate is to be preferred for the preparation of isoxazoles bearing a carboxylate functionality at C-3. The isoxazole **6b** was obtained selectively from four possible isomers. The structure of **6b** was assigned by combined ^{13}C NMR and long-range C–H correlation (gHMBC) NMR analysis.[31] In a previous cycloaddition procedure this isomer was isolated as a minor product (29%) along with 4-acetyl-3-ethoxycarbonyl-5-phenylisoxazole (43%).[27]

This double condensation reaction catalysed by copper(II) was found to proceed smoothly with β-diketones, whereas for ethyl acetoacetate (**4**) the conversions (entries 8 and 9) observed by ^1H NMR were less than 30%. Even by raising the reaction temperature or prolonging the reaction time the ethyl acetoacetate did not react further. Neither changing the solvent (toluene instead of chloroform) nor the addition of further nitro compound and catalyst increased the conversion. Substoichiometric addition of a second base, such as pyrrolidine, only slightly increased the yields.

In addition to the reported isoxazole derivatives **5**–**7**, in the reactions of **1a**, **1b** and **1d**, the furoxans **8a**, **8b** and **8d**, respectively, were detected. In the presence of base and moisture, heating at 60 °C caused the cleavage of all these compounds to some extent, depending on the concentration of the base.[32] For this reason we were unable to detect the furoxan **8a** in our previous experiments[20] on reactions of **1a** with other dipolarophiles and DABCO (0.2 equiv.). The reaction conditions reported herein (0.08 equiv. NMP) have

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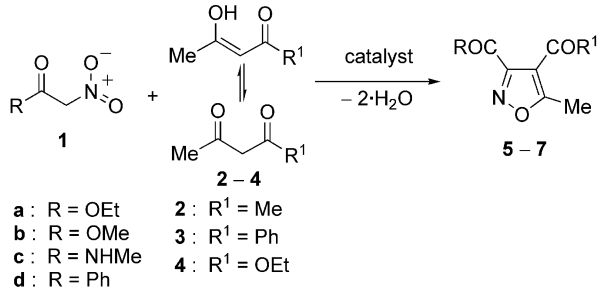
Table 2. Substituted isoxazoles from nitro compounds **1a**–**d** and 1,3-dicarbonyl compounds **2**–**4**.[a]



Entry	R	R^1	Product	Yield [%]	
				Exp.[b]	Lit.
1	OEt	Me	**5a**	48	44[c,d]
2	OMe	Me	**5b**	66	30[e]
3	NHMe	Me	**5c**	35 (41)[f]	–
4	Ph	Me	**5d**	85	–
5	OEt	Ph	**6a**	65 (82)[f]	32[d,g]
6	OMe	Ph	**6b**	75	29[e,h]
7	Ph	Ph	**6d**	93	–
8	OMe	OEt	**7b**	29	25[e]
9	Ph	OEt	**7d**	25	32[d,i]

[a] See the Exp. Sect. for details. [b] Isolated yields were determined for the analytically pure product and are based on the dipolarophile. [c] Ref.[26] [d] The yield includes preparation of the dipole precursor. [e] Ref.[27] [f] The yield considering the recovered diketone is given in parentheses. [g] Ref.[28,29] [h] Another isomer was also present in 43% yield. [i] Ref.[28,30]

allowed the furoxans to be detected. In the absence of other dipolarophiles, fair yields of the furoxans **8a** (43%) and **8b** (68%) were obtained. This procedure appears to be convenient and of synthetic interest in comparison with the known preparation methods of these compounds.[33,34]

In the reactions of the nitro ketone **1d**, an isomer of the furoxan **8d** (Figure 1) was detected and identified as 3-benzoyl-4-nitro-5-phenylisoxazole (**9**) on the basis of spectral evidence and crystallographic analysis. Compound **9** was carefully analysed by NMR spectroscopy and distinguished from the isomer **8d** mainly on the basis of the ^{13}C NMR chemical shifts and long-range C–H connectivity (gHMBC) experiments (Figure 1).

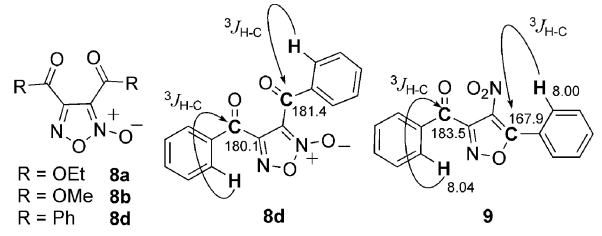


Figure 1. Structures of the self-condensation products and key NMR assignments of the quaternary carbon atoms in **8d** and **9** based on long-range ^{13}C–^{1}H correlations.

The crystal structure of **9** is shown in the ORTEP diagram in Figure 2. The same compound has previously been obtained by reaction of benzoylnitromethane (**1d**) with the appropriate hydroximoyl chloride and triethylamine:[35] the melting point of 100–101 °C and the IR absorption at 1680 cm^{-1} are in agreement with the properties of **9**.

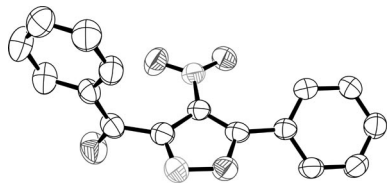


Figure 2. X-ray crystal structure of **9**.

We submitted samples of **8d** and **9** to prolonged treatment under the reaction conditions, thus verifying that the two isomers do not interconvert. When benzoylnitromethane (**1d**) alone was treated with the catalyst, both self-condensation products were obtained: the rate of self-condensation and the molar ratios depend on the composition and concentration of the catalyst (Table 3).

Table 3. Benzoylnitromethane self-condensation.[a]

Entry	Catalyst		**1d/8d/9**[b]
	Base [mmol-%]	Cu^{II} [mmol-%]	
1	DABCO (4)	2	0:37:63
2	DABCO (4)	–	8:30:62
3	NMP (4)	2	0:61:39
4	NMP (4)	–	42:30:28
5	DABCO (8)	4	0:0:100
6	DABCO (8)	–	11:0:89
7	NMP (8)	4	0:34:66

[a] Reaction conditions: 18 h, 60 °C, $CDCl_3$. See Exp. Sect. for more details. [b] Molar ratios evaluated by NMR spectroscopy.

After 18 h, no residual **1d** was observed if Cu^{II} was present: the reactions were slower in the presence of only base. However, the overall yields of the self-condensation products **8d** and **9** were far from quantitative, considerable amounts of benzoic acid and nitromethane being identified in the ^{1}H NMR spectra of the crude reaction mixtures. Moreover, benzoic acid was found in molar excess with respect to nitromethane because it originates from cleavage of not only **1d** but of the furoxan **8d** as well.

The presence of the furoxans **8a**, **8b** and **8d** indicates the formation of their precursors, the corresponding nitrile oxides **10a**, **10b** and **10d**, produced by catalytic dehydration of the nitro compounds **1a**, **1b** and **1d**, respectively (Scheme 1). This view is strongly supported by a theoretical study.[36] The nitro ketone **1d** in its enolic form behaves as a dipolarophile like the other enolisable compounds **2**–**4**, affording the nitroisoxazole **9**[37] either via the nitrile oxide **10d** or by the catalytic cycloaddition/condensation process we reported for other dipolarophiles.[20,25] No 4-nitroisox-

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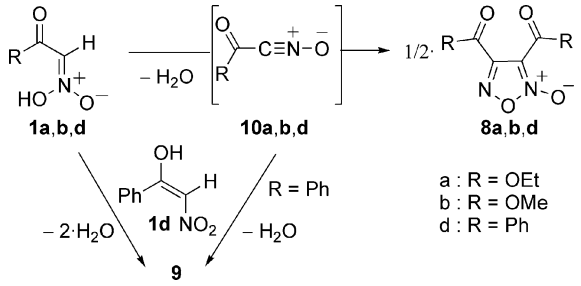
azoles analogous to **9** were found in addition to the furoxans **8a**,**b**: the weaker enolic character of the nitroacetates **1a** and **1b** explains why cycloaddition leading to 4-nitroisoxazoles is not observed.



Scheme 1. Self-condensation of activated nitro compounds.

Conclusions

This study was aimed at the method, rather than at specific targets: only some of the many possible substrates have been reported as selected examples. Functionalised 5-methylisoxazoles were regioselectively obtained by water release using the convenient and economic $Cu(OAc)_2$/NMP catalytic system, thus avoiding the preliminary synthesis of hydroximoyl chlorides.

In addition to the mechanism illustrated in our previous papers,[20] the cycloaddition/condensation process for "activated" primary nitro compounds might even take place, at least in part, via intermediate nitrile oxides because the corresponding dimer furoxans are produced in the absence of dipolarophiles. The nitroalkanes react with other dipolarophiles only in the presence of the Cu^{II}/base catalyst system and no furoxans have been detected so far. The catalytic conversion of primary nitro compounds to furoxans will be the subject of more detailed studies.

Experimental Section

General Methods: Melting points were determined in capillaries with a Büchi 510 apparatus and are uncorrected. Chromatographic separations (column) 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 or anisaldehyde followed by heating with a heat gun) carried out on alumina-backed plates coated with 25 mm silica gel (Merck F254) and the same eluent as indicated for column chromatography. Solvent was removed by evaporation on a rotary evaporator at room temperature. ^1H and ^{13}C NMR spectra were recorded with a Varian Mercuryplus 400 spectrometer (operating at 400 MHz for ^1H NMR and 100.58 MHz for ^{13}C NMR) unless otherwise stated. The ^1H NMR spectroscopic data are reported as follows: s = singlet, d = doublet, t = triplet, m = multiplet or unresolved, br. = broad signal, coupling constant(s) in Hz, integration]. The multiplicity of the ^{13}C NMR signals and their assignments were determined by gHMQC and gHMBC experiments. Chemical shifts were determined relative to the residual solvent peak ($CHCl_3$: 7.24 ppm for ^1H NMR and 77.0 ppm for ^{13}C NMR). EI (electron impact, 70 eV) and CI (chemical ionisation, CH_4) mass spectra were obtained using a Shimadzu QP5050A quadrupole-based mass spectrometer (direct introduction unless otherwise stated). Ion mass/charge ratios (m/z) are reported as values in atomic mass units followed in parentheses by the intensities relative to the base peak. IR spectra were recorded with a Perkin–Elmer 881 spectrometer. Elemental analyses were obtained with an Perkin–Elmer 240C Elemental Analyser. All compounds were named by using Autonom® (Beilstein Information Systems) and modified where appropriate. Commercially available (Lancaster and Aldrich) nitroacetates (**1a** and **1b**), benzoylnitromethane (**1d**), organic bases and enolisable compounds **2**–**4** were used as supplied. $CHCl_3$ (ethanol free) was filtered through a short pad of potassium carbonate just before use. *N*-Methyl-2-nitroacetamide (**1c**) was prepared according to a reported procedure.[21]

Optimisation of Isoxazole Formation from Acetylacetone and Benzoylnitromethane: See Table 1 for the most significant results; various catalytic systems were screened in different solvents. The spectroscopic yields reported in Table 1 refer to reactions performed in an apparatus in which eight reactions were carried out simultaneously. Benzoylnitromethane (**1d**; 1.06 mmol), acetylacetone (**2**) or copper(II) acetylacetonate for entry 10 (0.424 mmol) and dimethyl sulfone (Me_2SO_2) (10–13 mg, 0.106–0.138 mmol) as internal standard were added to the catalyst [base (0.0848 or 0.0424 mmol, 0.2 and 0.1 equiv. respectively) or base (0.0848 or 0.0424 mmol) and copper(II) acetate or copper(II) acetylacetonate for entry 9 (0.0424 or 0.0212 mmol, 0.1 and 0.05 equiv. respectively)] and the mixture dissolved in the indicated solvent (1.4 mL). The mixture was kept at 60 °C. After 18 and 42 h, a portion was withdrawn from the reaction mixture, diluted with $CDCl_3$ (0.6 mL) and the ^1H NMR spectrum recorded. Integration of the methyl proton signal (singlet at δ = 2.99 ppm, 6 H) of the internal standard and the acetyl protons of isoxazole **5d** (singlet at δ = 2.75 ppm, 3 H) gave the spectroscopic yields. The evaluations of the conversions were unreliable and the values are not reported. In the case of an unclear result, a duplicate experiment was run.

Effect of Different Catalyst Compositions on Benzoylnitromethane Self-Condensation Products: See Table 3 for the most significant results; different catalytic systems were screened by using the same apparatus as above.

Copper and Base: Copper(II) acetate (0.021 or 0.042 mmol) was added to a solution of benzoylnitromethane (**1d**; 176 mg, 1.06 mmol, 0.76 M) and base (0.042 or 0.084 mmol; 0.03 and 0.06 M, respectively) in $CDCl_3$ (1.4 mL) and the mixture magnetically stirred in a sealed vessel at 60 °C. After 18 h the molar ratio **1d**/**8d**[38]/**9** was evaluated by ^{13}C NMR (see later).

Base: A solution of benzoylnitromethane (**1d**) (176 mg, 1.06 mmol, 0.76 M) and base (0.042 or 0.084 mmol; 0.03 or 0.06 M, respectively) in $CDCl_3$ (1.4 mL) was magnetically stirred in a sealed vessel at 60 °C. After 18 h the molar ratio **1d**/**8d**/**9** was evaluated by ^{13}C NMR (see later).

Evaluation of the Molar Ratio: A solution of weighed amounts of compounds **1d**, **8d** and **9** was prepared, the ^{13}C NMR spectrum (standard ^{13}C experiment, 100.57 MHz, d_1 = 1 s, $CDCl_3$) recorded and the intensity of selected signals at δ = 186.1 (**1d**), 181.4 (**8d**) and 183.5 ppm (**9**) were compared. Thus the expected molar ratios were obtained with a correction factor of 1.16 for **8d** and this was then applied to evaluate molar ratios from spectra recorded under the same conditions.

Experiments Exploring the Stability of 8d and 9 under the Reaction Conditions: Compounds **8d** and **9** were submitted to several experi-

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ments to establish whether they interconvert or transform into other compounds. Experiments were performed in a septum-sealed 5-mm NMR tube, heating the reaction mixture (0.7 mL, $CDCl_3$) at 60 °C for 18 h in the presence of Me_2SO_2 as the internal standard, and analysed by NMR spectroscopy. Benzoic acid was also identified by MS.

Experiment *a*: A solution of **8d** (12 mg, 0.039 mmol, 0.06 M), NMP (3 μL, 0.021 mmol, 0.03 M) and $Cu(AcO)_2$ (1.95 mg, 0.011 mmol, 0.015 M) showed by spectroscopic analysis a partial decomposition of **8d** in benzoic acid.

Experiment *b*: A solution of **8d** (11 mg, 0.037 mmol, 0.05 M), DABCO (2.2 mg, 0.020 mmol, 0.03 M) and Me_2SO_2 (4 mg, 0.042 mmol) showed by spectroscopic analysis a partial decomposition of **8d** in benzoic acid.

Experiment *c*: A solution of **8d** (5.6 mg, 0.019 mmol), **9** (5.7 mg, 0.019 mmol) and Me_2SO_2 (3.5 mg, 0.037 mmol) showed by spectroscopic analysis a partial transformation in benzoic acid. No interconversion between **8d** and **9** was observed.

Experiment *d*: A solution of **9** (35 mg, 0.119 mmol, 0.17 M), DABCO (4.7 mg, 0.042 mmol, 0.06 M) and Me_2SO_2 (4 mg, 0.042 mmol) showed by ^1H and ^{13}C NMR neither conversion to compound **8d** nor transformation into other compounds.

Experiment *e*: A solution of **9** (35 mg, 0.119 mmol, 0.17 M), NMP (5 μL, 0.042 mmol, 0.06 M), $Cu(AcO)_2$ (3.8 mg, 0.021 mmol, 0.03 M) and Me_2SO_2 (5.2 mg, 0.055 mmol) showed by ^1H and ^{13}C NMR neither conversion to compound **8d** nor transformation into other compounds.

General Procedure for the Preparation of Isoxazoles 5–7: The nitro compound (1.06 mmol), dipolarophile (0.424 mmol) and NMP (10 μL, 0.08 mmol) were added in sequence to a suspension of $Cu(OAc)_2$ (7.8 mg, 0.042 mmol) in the indicated solvent (1.4 mL). The stirred mixture was heated in a sealed tube at 60 °C and stirred for the indicated time. The solvent was then removed under vacuum and the crude material was purified by column chromatography on silica gel with the indicated eluent.

Ethyl 4-Acetyl-5-methylisoxazole-3-carboxylate (5a): Treatment of **2** (43 mg) with **1a** (141 mg) according to the general procedure gave **5a** (40 mg, 48%) as a colourless oil after 72 h ($CHCl_3$) and chromatographic purification (elution with hexane/AcOEt, 5:1; R_f = 0.22). ^1H NMR: δ = 1.39 (t, J = 7.2 Hz, 3 H, OCH_2CH_3), 2.46 (s, 3 H, CH_3CO), 2.63 (s, 3 H, CH_3C-5), 4.44 (q, J = 7.2 Hz, 2 H, OCH_2CH_3) ppm.[27] ^{13}C NMR: δ = 13.2 (q, *C*H$_3$C-5), 13.9 (q, OCH_2CH_3), 30.4 (q, $COCH_3$), 62.9 (t, OCH_2CH_3), 117.0 (s, C-4), 154.3 (s, C-3), 160.4 (s, *C*O$_2$Et), 174.6 (s, C-5), 192.0 (s, *C*OMe) ppm. MS (EI): *m*/*z* (%) = 197 (100) $[M]^+$, 182 (62) $[M - Me]^+$, 169 (32), 168 (6) $[M - Et]^+$, 154 (24), 152 (34), 151 (71), 110 (20), 96 (19), 83 (39), 68 (79). IR ($CDCl_3$): $\tilde{\nu}$ = 1739 (C=O), 1685 (C=O), 1568, 1308, 1208 cm^{-1}. $C_9H_{11}NO_4$ (197.19): calcd. C 54.82, H 5.62, N 7.10; found C 54.76, H 5.79, N 6.94.

Methyl 4-Acetyl-5-methylisoxazole-3-carboxylate (5b): Treatment of **2** (43 mg) with **1b** (126 mg) according to the general procedure gave **5b** (51 mg, 66%) as a colourless oil after 72 h ($CHCl_3$) and chromatographic purification (elution with hexane/AcOEt, 5:1; R_f = 0.16). ^1H NMR: δ = 2.47 (s, 3 H, $COCH_3$), 2.64 (s, 3 H, CH_3C-5), 3.98 (s, 3 H, CO_2CH_3) ppm. ^{13}C NMR: δ = 13.2 (q, *C*H$_3$C-5), 30.4 (q, $COCH_3$), 53.4 (q, OCH_3), 117.2 (s, C-4), 154.0 (s, C-3), 160.8 (s, *C*O$_2$Me), 174.8 (s, C-5), 192.1 (s, *C*OMe) ppm. MS (EI): *m*/*z* (%) = 183 (34) $[M]^+$, 168 (36) $[M - Me]^+$, 151 (34), 124 (4), 82 (19), 59 (100) $[CO_2Me]^+$. IR ($CDCl_3$): $\tilde{\nu}$ = 2957, 1744 (C=O), 1686 (C=O), 1628, 1575, 1457, 1310, 1217 cm^{-1}. $C_8H_9NO_4$ (183.16): calcd. C 52.46, H 4.95, N 7.65; found C 52.20, H 4.98, N 7.61.

4-Acetyl-*N*,5-dimethylisoxazole-3-carboxamide (5c): Treatment of **2** (43 mg) with **1c** (125 mg) according to the general procedure gave unreacted **2** (R_f = 0.68, 6 mg) and **5c** (white solid, R_f = 0.28, 27 mg, 35%) after 38 h ($CHCl_3$) and chromatographic purification (elution first with hexane and then with hexane/diethyl ether, 2:5). The yield based on recovered **2** was 41%; m.p. 108–109 °C (colourless needles, crystallised from diisopropyl ether). ^1H NMR: δ = 2.56 (s, 3 H, $COCH_3$), 2.62 (s, 3 H, CH_3C-5), 3.00 (d, J = 4.8 Hz, 3 H, $CONCH_3$), 6.85 (br. s, 1 H, N*H*) ppm. ^{13}C NMR: δ = 13.3 (q, *C*H$_3$C-5), 26.4 (q, N*C*H$_3$), 31.1 (q, CO*C*H$_3$), 116.8 (s, C-4), 156.1 (s, C-3), 159.6 (s, *C*ONMe), 175.3 (s, C-5), 193.3 (s, *C*OMe) ppm. MS (EI): *m*/*z* (%) = 182 (14) $[M]^+$, 167 (4), 152 (1), 139 (3), 125 (10), 111 (5), 83 (8), 58 (100) $[CONHMe]^+$. IR ($CDCl_3$): $\tilde{\nu}$ 3438, 1689 (C=O), 1573, 1545, 1457, 1415 cm^{-1}. $C_8H_{10}N_2O_3$ (182.18): calcd. C 52.74, H 5.53, N 15.38; found C 52.76, H 5.82, N 15.69.

1-(3-Benzoyl-5-methylisoxazol-4-yl)ethanone (5d): Treatment of **2** (43 mg) with **1d** (175 mg) according to the general procedure gave **5d** (62 mg, 64%) as a colourless oil after 72 h ($CHCl_3$) and chromatographic purification (elution with hexane/AcOEt, 6:1; R_f = 0.31). The same reaction carried out in toluene as above, after column chromatography on silica gel (hexane/diethyl ether/triethylamine 15:1:1, R_f 0.21), gave the pure compound as a yellowish oil (82 mg, 85%). ^1H NMR: δ = 2.32 (s, 3 H, CH_3CO), 2.75 (s, 3 H, CH_3C-5), 7.48–7.53 (m, 2 H, Ph-H_{meta}), 7.63–7.68 (m, 1 H, Ph-H_{para}), 7.99–8.03 (m, 2 H, Ph-H_{ortho}) ppm. ^{13}C NMR: δ = 13.4 (q, *C*H$_3$C-5), 30.2 (q, *C*H$_3$CO), 117.5 (s, C-4), 128.9 (d, 2 C, Ph-C_{meta}), 130.3 (d, 2 C, Ph-C_{ortho}), 134.8 (d, Ph-C_{para}), 135.6 (s, Ph-C_{ipso}), 159.6 (s, C-3), 174.5 (s, C-5), 187.5 (s, *C*OPh), 191.6 (s, *C*OMe) ppm. MS (EI): *m*/*z* (%) = 229 (<1) $[M]^+$, 228 (<1), 199 (14) $[M - Me]^+$, 105 (100) $[PhCO]^+$, 77 (55) $[Ph]^+$, 51 (30). IR ($CDCl_3$): $\tilde{\nu}$ 3069, 1684 (C=O), 1598, 1572, 1457, 1418, 1218 cm^{-1}. $C_{13}H_{11}NO_3$ (229.23): calcd. C 68.11, H 4.84, N 6.11; found C 67.89, H 5.18, N 6.28.

Ethyl 4-Benzoyl-5-methylisoxazole-3-carboxylate (6a): Treatment of **3** (69 mg) with **1a** (141 mg) according to the general procedure gave unreacted **3** (R_f = 0.50, 15 mg) and **6a** (colourless oil, R_f = 0.39, 71 mg, 65%) as a colourless oil after 72 h ($CHCl_3$) and chromatographic purification (elution with hexane/ethyl acetate/Et_3N, 10:1:1). The yield based on recovered **3** was 82%. ^1H NMR: δ = 1.03 (t, J = 6.8 Hz, 3 H, OCH_2CH_3), 2.52 (s, 3 H, CH_3C-5), 4.08 (q, J = 6.8 Hz, 2 H, OCH_2CH_3), 7.41–7.48 (m, 2 H, Ph-H_{meta}), 7.56–7.61 (m, 1 H, Ph-H_{para}), 7.72–7.75 (m, 2 H, Ph-H_{ortho}) ppm. ^{13}C NMR: δ = 12.2 (q, *C*H$_3$C-5), 13.5 (q, OCH_2CH_3), 62.4 (t, OCH_2CH_3), 116.1 (s, C-4), 128.7 (d, 2 C, Ph-C_{meta}), 128.9 (d, 2 C, Ph-C_{ortho}), 133.6 (d, Ph-C_{para}), 137.7 (s, Ph-C_{ipso}), 155.0 (s, C-3), 159.2 (s, *C*O$_2$Et), 173.1 (s, C-5), 188.2 (s, *C*OPh) ppm. MS (EI): *m*/*z* (%) = 259 (25) $[M]^+$, 186 (42) $[M - CO_2Et]^+$, 105 (100), $[PhCO]^+$, 77 (57) $[Ph]^+$, 51 (32). IR ($CDCl_3$): $\tilde{\nu}$ 3067, 2985, 1740 (C=O), 1664 (C=O), 1599, 1449, 1322, 1214 cm^{-1}. $C_{14}H_{13}NO_4$ (259.27): calcd. C 64.86, H 5.05, N 5.40; found C 64.62, H 5.27, N 5.01.

Methyl 4-Benzoyl-5-methylisoxazole-3-carboxylate (6b): Treatment of **3** (69 mg) with **1b** (126 mg) according to the general procedure gave **6b** (78 mg, 75%) as a white powder after 72 h ($CHCl_3$) and chromatographic purification (elution with hexane/diethyl ether/Et_3N, 10:1:1; R_f = 0.23); m.p. 86–88 °C (ref.[27] 82–85 °C, ethanol). ^1H NMR: δ = 2.52 (s, 3 H, CH_3C-5), 3.65 (s, 3 H, OCH_3), 7.43–7.50 (m, 2 H, Ph-H_{meta}), 7.56–7.62 (m, 1 H, Ph-H_{para}), 7.70–7.76 (m, 2 H, Ph-H_{ortho}) ppm. ^{13}C NMR: δ = 12.3 (q, *C*H$_3$C-5), 52.9 (q, OCH_3), 116.3 (s, C-4), 128.8 (d, 2 C, Ph-C_{meta}), 128.9 (d, 2 C, Ph-C_{ortho}), 133.7 (d, Ph-C_{para}), 137.6 (s, Ph-C_{ipso}), 154.8 (s, C-3), 159.7 (s, *C*O$_2$Me), 173.0 (s, C-5), 188.1 (s, *C*OPh) ppm. MS (EI): *m*/*z* (%) = 245 (16) $[M]^+$, 244 (14), 230 (1), 200 (6), 186 (16) [M –

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$CO_2Me]^+$, 105 (62), $[PhCO]^+$, 77 (60) $[Ph]^+$, 59 (62) $[CO_2Me]^+$, 51 (34), 43 (100) $[COMe]^+$. IR ($CDCl_3$): $\tilde{\nu}$ = 3067, 2957, 1745 (C=O), 1664 (C=O), 1600, 1450, 1323, 1221 cm^{-1}. $C_{13}H_{11}NO_4$ (245.23): calcd. C 63.67, H 4.52, N 5.71; found C 63.86, H 4.78, N 5.62.

(4-Benzoyl-5-methylisoxazol-3-yl)phenylmethanone (6d): Treatment of **3** (69 mg) with **1d** (175 mg) according to the general procedure gave **6d** (113 mg, 93%) as a colourless oil[39] after 40 h (toluene) and chromatographic purification (elution with hexane/diethyl ether/Et_3N, 10:1:1; R_f = 0.27). ^1H NMR: δ = 2.56 (s, 3 H, CH_3C-5), 7.31–7.37 (m, 2 H, Ph-*H*), 7.41–7.47 (m, 2 H, Ph-*H*), 7.47–7.53 (m, 1 H, Ph-*H*), 7.57–7.63 (m, 1 H, Ph-H_{para}), 7.64–7.69 (m, 2 H, Ph-H_{ortho} on C-4), 7.99 (m, 1 H, Ph-H_{ortho} on C-3), 8.01 (m, 1 H, Ph-H_{ortho} on C-3) ppm. ^{13}C NMR: δ = 12.5 (q, *C*H_3C-5), 117.1 (s, C-4), 128.6 (d, 4 C, Ph-*C*), 128.8 (d, 2 C, Ph-*C*), 130.2 (d, 2 C, Ph-C_{ortho} on C-3), 133.4 (d, Ph-*C* on C-4), 134.3 (d, Ph-C_{para} on C-3), 135.4 (s, Ph-*C*), 137.5 (s, Ph-*C*), 160.7 (s, C-3), 172.4 (s, C-5), 185.4 (s, *C*OC-4), 188.1 (s, *C*OC-3) ppm. MS (EI): *m*/*z* (%) = 291 (<1) $[M]^+$, 105 (100), $[PhCO]^+$, 77 (58) $[Ph]^+$, 51 (30). IR ($CDCl_3$): $\tilde{\nu}$ = 3067, 1670 (C=O), 1599, 1450, 1323, 1218 cm^{-1}. $C_{18}H_{13}NO_3$ (291.31): calcd. C 74.22, H 4.50, N 4.81; found C 74.24, H 4.57, N 4.88.

4-Ethyl 3-Methyl 5-Methylisoxazole-3,4-dicarboxylate (7b): Treatment of **4** (55 mg) with **1b** (126 mg) according to the general procedure gave **7b** (26 mg, 29%) as a colourless oil after 72 h ($CHCl_3$) and chromatographic purification (elution with hexane/diethyl ether, 5:1; R_f = 0.22). ^1H NMR: δ = 1.31 (t, *J* = 7.2 Hz, 3 H, CH_2CH_3), 2.67 (s, 3 H, CH_3C-5), 3.95 (s, 3 H, OCH_3), 4.28 (q, *J* = 7.2 Hz, 2 H, CH_2CH$_3$) ppm. ^{13}C NMR: δ = 12.7 (q, *C*H_3C-5), 14.0 (q, *C*H_3CH$_2$), 53.2 (q, O*C*H$_3$), 61.3 (t, CH$_3$*C*H$_2$), 108.7 (s, C-4), 155.4 (s, C-3), 160.4 (s, *C*O_2Me), 160.5 (s, *C*O_2Et), 175.2 (s, C-5) ppm. MS (EI): *m*/*z* (%) = 213 (2) $[M]^+$, 198 (1) $[M - Me]^+$, 182 (2) $[M - OMe]^+$, 168 (8), 167 (8), 82 (22), 59 (75) $[CO_2Me]^+$, 43 (100). IR ($CDCl_3$): $\tilde{\nu}$ = 2957, 1750 (C=O), 1723 (C=O), 1607, 1457 cm^{-1}. $C_9H_{11}NO_5$ (213.19): calcd. C 50.70, H 5.20, N 6.57; found C 50.84, H 4.98, N 6.32.

Ethyl 3-Benzoyl-5-methylisoxazole-4-carboxylate (7d): Treatment of **4** (55 mg) with **1d** (175 mg) according to the general procedure gave **7d** (11 mg, 10%) as a colourless oil after 72 h (toluene) and chromatographic purification (elution with hexane/diethyl ether/triethylamine, 15:1:1; R_f = 0.21). The same reaction carried out as above, but with added pyrrolidine (15 mg, 0.214 mmol) gave **7d** as a yellowish oil (28 mg, 25%). ^1H NMR: δ = 1.00 (t, *J* = 7.2 Hz, 3 H, CH_2CH_3), 2.75 (s, 3 H, CH_3C-5), 4.09 (q, *J* = 7.2 Hz, 2 H, CH_2CH$_3$), 7.45–7.50 (m, 2 H, Ph-H_{meta}), 7.59–7.64 (m, 1 H, Ph-H_{para}), 7.87–7.92 (m, 2 H, Ph-H_{ortho}) ppm. ^{13}C NMR: δ = 12.8 (q, *C*H_3C-5), 13.6 (q, *C*H_3CH$_2$), 61.1 (t, CH$_3$*C*H$_2$), 109.2 (s, C-4), 128.7 (d, 2 C, Ph-C_{meta}), 129.8 (d, 2 C, Ph-C_{ortho}), 134.4 (d, Ph-C_{para}), 135.7 (s, Ph-C_{ipso}), 160.4 (s, *C*O_2Et or C-3), 160.6 (s, *C*O_2Et or C-3), 175.2 (s, C-5), 186.8 (s, Ph*C*O) ppm. GC–MS (CI): *m*/*z* (%) = 260 (<1) $[M + H]^+$, 105 (100) $[PhCO]^+$, 77 (19) $[Ph]^+$, 51 (14). IR ($CDCl_3$): $\tilde{\nu}$ = 3068, 2964, 1724 (C=O), 1682, 1449 (C=O), 1599 cm^{-1}. $C_{14}H_{13}NO_4$ (259.26): calcd. C 64.86, H 5.05, N 5.40; found C 65.12, H 5.38, N 5.48.

(4-Nitro-5-phenylisoxazol-3-yl)phenylmethanone (9): Copper(II) acetate (7.8 mg, 0.0414 mmol) was added to a mixture of benzoylnitromethane (**1d**; 175 mg, 1.06 mmol) and DABCO (9.6 mg, 0.0848 mmol) in chloroform or toluene (1.4 mL) and the mixture was magnetically stirred in a sealed vessel at 60 °C. After 18 h the reaction mixture was concentrated and the residue was purified by chromatography on silica gel, eluting first with hexane/diethyl ether/triethylamine (15:1:1) to afford benzoylnitromethane (**1d**; R_f = 0.50, 16 mg, 0.097 mmol) and **9** (R_f = 0.21, 46 mg, 29%) and then with hexane/diethyl ether/triethylamine/MeOH (15:1:1:1) to afford triethylammonium benzoate (119 mg, 0.721 mmol).

9: M.p. 100–101 °C (ref.[35] 100–101 °C, from methanol). ^1H NMR: δ = 7.52–7.62 (m, 4 H, Ph-H_{meta}), 7.64–7.72 (m, 2 H, Ph-H_{para}), 7.98–8.02 (m, 2 H, Ph-H_{ortho} on C-5), 8.02–8.06 (m, 2 H, Ph-H_{ortho} on C-3) ppm. ^{13}C NMR: δ = 123.7 (s), 129.0 (d, 2 C, Ph-C_{meta}), 129.1 (d, 2 C, Ph-C_{meta}), 129.4 (d, 2 C, Ph-C_{ortho} on C-5), 130.1 [d, 2 C, C(O)-Ph-C_{ortho}], 133.4 (d, Ph-C_{para} on C-5), 134.8 (s), 135.2 [d, C(O)Ph-C_{para}], 156.9 (s, C-3), 167.9 (s, C-5), 183.5 (s, *C*OPh) ppm. One carbon atom was not detected. MS (EI): *m*/*z* (%)[40] = 147 (10) $[PhC(O)C{\equiv}N{-}O]^+$, 131 (34) $[PhC(O)C{\equiv}N]^+$, 105 (100) $[PhCO]^+$, 77 (80) $[Ph]^+$, 51 (38). IR ($CDCl_3$): $\tilde{\nu}$ = 3069, 1687 (C=O), 1600, 1575, 1527, 1468, 1360, 1265, 1233 cm^{-1}. $C_{16}H_{10}N_2O_4$ (294.26): calcd. C 65.31, H 3.43, N 9.52; found C 65.04, H 3.76, N 9.63.

Triethylammonium Benzoate: ^1H NMR (200 MHz): δ = 1.29 (t, *J* = 6.0 Hz, 3 H, CH_3CH$_2$), 3.14 (q, *J* = 6.0 Hz, 3 H, CH$_3$CH_2), 6.77 (br. s, 1 H, N*H*), 7.42–7.52 (m, 3 H, Ph-*H*), 7.85 –8.20 (m, 2 H, Ph-*H*) ppm.

Diethyl 1,2,5-Oxadiazole-3,4-dicarboxylate 2-Oxide (8a): Copper(II) acetate (22 mg, 0.12 mmol) was added to a mixture of ethyl nitroacetate (**1a**; 399 mg, 3.0 mmol) and 1-methylpiperidine (24 mg, 0.24 mmol) in chloroform (2 mL) and the mixture was magnetically stirred in a sealed vessel at 60 °C. After 96 h the reaction mixture was diluted in chloroform (25 mL) and washed with H_2O (2 × 20 mL), 0.05 N NaOH (3 × 20 mL) and H_2O (3 × 20 mL). The organic layer was dried with Na_2SO_4 and filtered. The chloroform was removed under vacuum to give the furoxan **8a** as a pale-yellow oil (0.15 g, 43% yield). An analytical sample was obtained as a colourless oil by using a sublimator at 0.4 Torr and 60 °C. ^1H NMR: δ = 1.36 (t, *J* = 7.2 Hz, 3 H, $CO_2CH_2CH_3$), 1.40 (t, *J* = 6.8 Hz, 2 H, $CO_2CH_2CH_3$), 4.42 (q, *J* = 6.8 Hz, 2 H, $CO_2CH_2CH_3$), 4.47 (q, *J* = 7.2 Hz, 2 H, $CO_2CH_2CH_3$) ppm. ^{13}C NMR: δ = 13.8 (q, *C*H_3), 13.9 (q, *C*H_3), 63.1 (t, 2 C, 2 CO*C*H$_2$), 106.7 (s, C-3), 148.3 (s, C-4), 155.1 (s, *C*O_2Et), 156.6 (s, *C*O_2Et) ppm. MS (EI): *m*/*z* (%) = 231 (9) $[M + 1]^+$, 230 (4) $[M]^+$, 200 (9), 185 (73), 169 (20), 168 (18), 159 (19), 158 (100), 157 (28), 141 (25), 130 (96), 111 (18), 100 (32). IR (film): $\tilde{\nu}$ = 2987, 1748 (C=O), 1626, 1480, 1374, 1333, 1246 cm^{-1}.

Dimethyl 1,2,5-Oxadiazole-3,4-dicarboxylate 2-Oxide (8b): Methyl nitroacetate (**1b**; 126 mg, 1.062 mmol) was added to a mixture of copper(II) acetate (3.9 mg, 0.0212 mmol) and 1-methylpiperidine (8.4 mg, 0.0849 mmol) in chloroform (1.4 mL) and the mixture was magnetically stirred in a sealed vessel at 60 °C. After 96 h the reaction mixture was concentrated and the residue purified by chromatography on silica gel with hexane/ethyl acetate (8:1; R_f = 0.19) to afford the furoxan **8b** as a colourless oil (73 mg, 68%). ^1H NMR: δ = 3.97 (s, 3 H, CO_2CH_3), 4.02 (s, 3 H, CO_2CH_3) ppm. ^{13}C NMR: δ = 53.9 (q, 2 C, 2 CO_2CH_3), 106.6 (s, C-3), 148.0 (s, C-4), 155.0 (s, *C*O_2Me), 157.0 (s, *C*O_2Me) ppm. MS (EI): *m*/*z* (%) = 202 (1) $[M]^+$, 172 (8), 171 (6) $[M - OMe]^+$, 128 (11), 111 (12), 100 (6), 98 (12), 59 (100) $[CO_2Me]^+$. IR (film): $\tilde{\nu}$ = 2958, 1752 (C=O), 1628, 1483, 1342, 1312, 1252 cm^{-1}.

Crystallisation and X-ray Structural Analysis of Compound 9: A suitable crystal of isoxazole **9** (colourless needle) for X-ray diffraction analysis was obtained by recrystallisation from methanol/diethyl ether (3:1). X-ray analysis was carried out with a Siemens P4 diffractometer at room temperature using graphite-monochromated Mo-K_α radiation. The integrated intensities, measured by using the ω scan mode, were corrected for Lorentzian and polarisation effects.[41] The structure was solved by direct methods using SIR97[42] and refined by using the full-matrix least-squares on F^2

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provided by SHELXL97.[43] The non-hydrogen atoms were refined anisotropically whereas hydrogen atoms were assigned to calculated positions and refined isotropically.

$C_{16}H_{10}N_2O_4$, M = 294.26, monoclinic, space group $P2_1/n$, a = 5.7370(10), b = 12.1950(10), c = 19.844(3) Å, β = 95.940(10)°, V = 1380.9(3) Å^3, Z = 4, D_c = 1.415, μ = 0.104 mm^{-1}, $F(000)$ = 608. 12191 reflections were collected in a $1.96 \leq \theta \leq 25.0$ range; 2414 were independent, the number of parameters was 239 and the final R index 0.0399 for reflections having $I \geq 2\sigma I$.

CCDC-721723 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supporting Information (see also the footnote on the first page of this article): ^{1}H and ^{13}C NMR data for isoxazoles **5**–**7**, a plot of concentration versus time for the reaction between **1d** and **2**, ^{1}H and gHMBC NMR spectra for compounds **6b** and **9**.

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