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Synthetic Methods

Competitive Copper Catalysis in the Condensation of Primary Nitro Compounds with Terminal Alkynes: Synthesis of Isoxazoles

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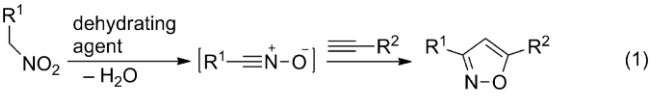
In memory of Paolina Bonari on the 100th anniversary of her birth

Abstract: Isoxazoles, mainly 3,5-disubstituted, are prepared by catalytic condensation of primary nitro compounds with terminal acetylenes by using a copper/base catalytic system. The additional catalytic effect of the copper(II) salts is evidenced by comparing the kinetic profiles. Selectivity dependence on reaction conditions is considered for phenylacetylene in the following competitive processes: oxidative coupling of terminal alkynes to conjugated diynes catalyzed by Cu^{II} and base in the presence of air; production of furazans beside condensation with benzoylnitromethane to 3-benzoylisoxazoles, as a result of the reaction of the dipolarophile with 3,4-dibenzoylfuroxan; addition of electron-poor alkynes (e.g., methyl propiolate) with themselves and with the nitro compound. Thus, oxidative coupling is negligible in reactions with "active" nitro compounds, whereas with nitroalkanes both products are observed: only trace amounts of isoxazoles are detected without copper. Similarly, in the presence of copper, 3-benzoyl-5-phenylisoxazole is predominant over the furazan. Furthermore, condensations of electron-poor alkynes give complex reaction mixtures in the presence of base alone, but cycloadducts are conveniently prepared with copper. The results indicate the practical and general utility of this catalytic method for synthetic practice.

Introduction

Isoxazoles by Condensation of Alkynes with Nitro Compounds

Isoxazoles are not only important building blocks and useful synthons in synthetic organic chemistry,[1,2] but they are also a significant motif in natural products,[3] biologically active compounds,[4–6] investigational pharmaceutical compounds[7] with wide application as drugs,[8–13] and advanced organic materials.[14] The physical properties and the construction of this heterocyclic nucleus has attracted the interest of researchers for decades.[15,16] Among the numerous substrates utilized as starting materials, primary nitro compounds combined with alkynes have received wide attention, as the process builds up isoxazole derivatives directly.[17] Acylating reagents (usually isocyanates) in stoichiometric or excess amounts are used, in general, for the condensation of primary nitro compounds with alkyne (likewise alkene) dipolarophiles, although various other reagents have been reported to serve the purpose.[18] Acylating reagents are assumed to convert the nitro compounds into acylated nitronic acids (or "mixed anhydrides") and thence into nitrile oxides, which undergo cycloaddition with the dipolarophile [Equation (1)].[19–22]



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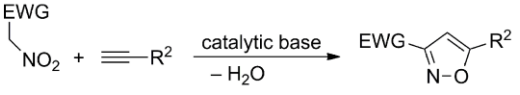

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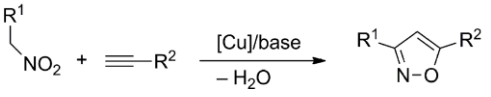

(3)

Furoxans, the products of spontaneous dimerization of nitrile oxides,[23,24] are often detected in the above reactions, which thus supports the role of nitrile oxides as reaction intermediates. Some authors have verified that in the absence of a dipolarophile furoxans are the main reaction products.[25–27]

All these reactions, which use stoichiometric amounts of reagents with unfavorable environmental impact, suffer from additional drawbacks: the formation of byproducts from either the nitro compound or the dehydrating reagent complicates product isolation and purification, which thus affects the yields.

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Moreover several functional groups that would interact with the dehydrating reagent must be left out. Therefore, the above reactions were considerably improved when we established that a catalytic amount of a suitable base was enough to promote condensation of the alkynes (and alkenes) with "active" nitro compounds [those bearing an electron-withdrawing group (EWG) geminal to the nitro group, including phenylnitromethane] and not with nitroalkanes [Equation (2)].[28–31] Condensations occur in chloroform as well as in hydroxylic solvents (e.g., ethanol, water): in chloroform the catalytic effect[28] depends on the nature of the base, whereas in water, any base, either organic or inorganic, has the same catalytic effect.[32] This method avoids the use of excess amounts of highly polluting reagents and the formation of discarded products derived from them; moreover, it tolerates many functional groups (e.g., OH, NH_2, etc.) that would interfere with most of the reagents that were previously used in stoichiometric amounts. The above catalytic method has been referred to as the Machetti–De Sarlo reaction.[33–35] The solvent dependence of the base catalytic effect has been noticed by other authors. Indeed, condensation of dimethyl acetylenedicarboxylate (DMAD) and similar esters with nitroacetates or benzoylnitromethane has been reported to give the expected isoxazole derivatives in aqueous medium under pyridine or *N*-methylimidazole catalysis.[36] On the contrary, in dichloromethane solution with a catalytic amount of pyridine, similar reactions do not give the expected isoxazole derivatives but isomeric products instead.[37] We already observed the lack of catalytic activity of pyridine in chloroform solution in the condensation of benzoylnitromethane.[28] Condensation of benzoylnitromethane with several alkynes has also been reported to occur under poly(phosphoric acid) (PPA)/SiO_2 catalysis in refluxing toluene.[38]

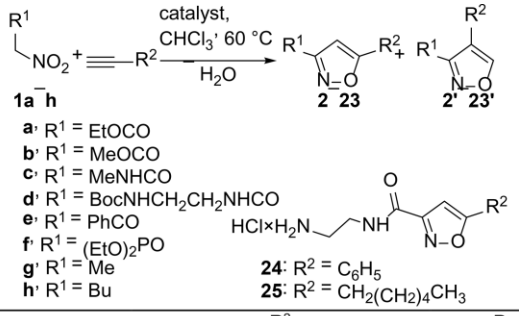
Results and Discussion

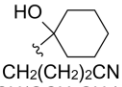
Model Reactions

Copper-Catalyzed Condensation to Isoxazoles

The aim of this paper was to find an effective and selective catalytic system enabling the conversion of primary nitro compounds and alkynes into isoxazoles. Catalyst composition and reaction conditions were carefully investigated to establish favorable selectivity towards condensation to the isoxazole for

Table 1. Reaction of nitro compounds **1a–h** with various alkynes in the presence of a copper/base catalytic system.[a]



Entry	R^1	R^2	Products	Yield (%)[b] Catalyst $Cu(OAc)_2$	Cu
1	EtOCO	Ph	**2a**	87, 94[c]	–
2	EtOCO	$CH_2(CH_2)_4CH_3$	**3a**	82	76
3	EtOCO		**4a**	90	88
4	EtOCO	CH_2OH	**5a**	70	–
5	EtOCO	CH_2CH_2OH	**6a**	77	68
6	EtOCO		**7a**	76	85
7	EtOCO	$CH_2(CH_2)_2CN$	**8a**	94	96
8	EtOCO	$CH(OCH_2CH_3)_2$	**9a**	68	–
9	EtOCO	COOMe	**10a**, **10'a**	40[d,e]	–
10	EtOCO	$CONC_4H_8$	**11a**, **11'a**	73	67
11	MeOCO	$CH_2(CH_2)_4CH_3$	**12b**	70	–
12	MeNHCO	Ph	**13c**	57, 67[c]	–
13	$BocNHCH_2CH_2NHCO$	Ph	**14d**	71	–
14	$BocNHCH_2CH_2NHCO$	$CH_2(CH_2)_4CH_3$	**15d**	58	–
15	PhCO	Ph	**16e**	73, 80[f]	–
16	PhCO	$CH_2(CH_2)_4CH_3$	**17e**	73	–
17	PhCO	$CH_2(CH_2)_2CN$	**18e**	56, 85[f]	–
18	PhCO		**19e**	70	–
19	PhCO	CH_2CH_2OH	**20e**	58[f]	–
20	$(EtO)_2PO$	$CH_2(CH_2)_4CH_3$	**21f**	49	–
21	Me	Ph	**22g**, **22'h**	33[g]	–
22	Bu	Ph	**23h**, **23'h**	39[g], 50[h]	–

[a] Reaction conditions: nitro compound (0.848–1.06 mmol), alkyne (0.424 mmol), NMP (20 mol-%), [Cu] (5 mol-%), unless otherwise indicated. [b] Yield of isolated product after chromatography. [c] With a lower amount of base (10 mol-%) and [Cu] (5 mol-%). [d] Combined yield of the 4-H and 5-H isomers. [e] 4-H/5-H = 66:33. [f] With a lower amount of the catalyst: NMP (10 mol-%), [Cu] (2.5 mol-%). [g] NMP (100 mol-%). [h] TMEDA instead of NMP. See Table 3, entry 17.

each reagent pair. In fact, parallel competitive processes were found to interfere with this condensation: the addition of electron-poor alkynes (e.g., methyl propiolate) to themselves and to the nitro compound; alkyne oxidative coupling, important with sluggish reagents such as nitroalkanes; reaction of the dipolarophile with 3,4-dibenzoylfuroxan derived from benzoylnitromethane, which leads to a furazan derivative. In analogy with the established method for the condensation of nitroalkanes with alkene dipolarophiles, which requires the presence of copper in the catalytic system,[39,40] the condensations of nitro compounds with several terminal alkynes were performed under Cu^{II} and base catalysis in chloroform, and the results are collected in Table 1.[41] The yields for the condensations of phenylacetylene (Table 1 entry 1) and propargyl alcohol (Table 1, entry 4) were compared to those previously reported without Cu^{II} salt,[28–30] but no remarkable differences were ascertained. However, the kinetic profiles for the phenylacetylene condensations (Figure 1) evidenced an additional catalytic effect that may have been due to the presence of the Cu^{II} salt. In fact, the conversion of phenylacetylene into 3-carbethoxy-5-phenylisoxazole (**2a**) was complete within 8 h with Cu^{II} and in 72 h with base alone.

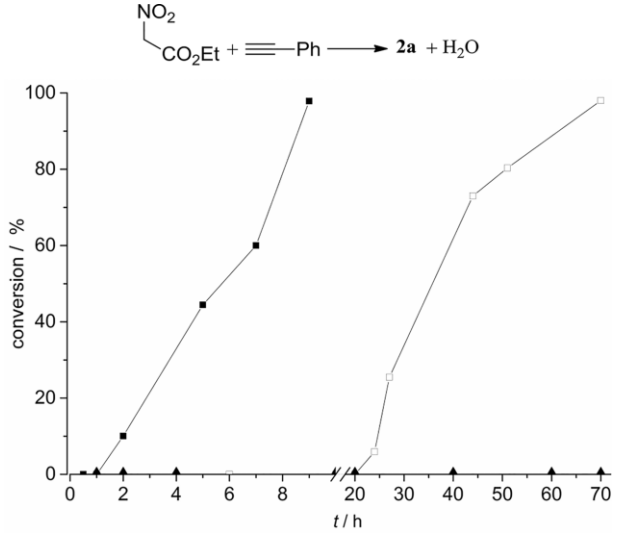


Figure 1. Kinetic profiles for the condensation between ethyl nitroacetate (**1a**) and phenylacetylene to isoxazole **2a** (Table 1, entry 1). In chloroform, no reaction was observed without a catalyst (solid triangles): percentage of the dipolarophile with DABCO (white squares) or DABCO/[Cu] (solid squares) catalysis. See the Experimental Section for details.

Either 1,4-diazabicyclo[2.2.2]octane (DABCO) or *N*-methylpiperidine (NMP) could be used in combination with the Cu salt to catalyze the condensations of ethyl nitroacetate (**1a**); however, the catalytic system NMP + Cu salt was preferred, because it could, in general, be applied with nitroalkanes (see below). Some reactions reported in Table 1 were also performed with metallic Cu (powder) without any significant differences; in fact, the metal was rapidly oxidized by air in an excess amount of the nitroacetate.[40]

Nitroacetate Esters and Amides

Terminal alkynes selectively afforded the 5-substituted isoxazole derivatives, as reported in Table 1, entries 1–8. The result obtained in the condensation of ethyl nitroacetate (**1a**) with 1-octyne (ca. 80 % yield; Table 1, entry 2) favorably compares with the reported result obtained under PPA/SiO_2 catalysis at higher temperature (50 % yield).[38] Notably, some functional groups did not interfere with the condensation (Table 1, entries 4–8). The condensation of ethyl nitroacetate (**1a**) with methyl propiolate was successful only if interaction of the alkyne with the base was avoided; otherwise, fast coupling of methyl propiolate with itself gave the corresponding enyne dioate as the predominant product.[42,43]

Therefore, by controlling the order of reagent addition, it was possible to increase the conversion of methyl propiolate into the cycloadducts. A better result was obtained by using copper/NMP (Table 1, entry 9; 40 % overall yield of isomers **10a** and **10′a**), whereas the use of base alone, such as DABCO, gave a complex mixture containing a very low amount of the desired

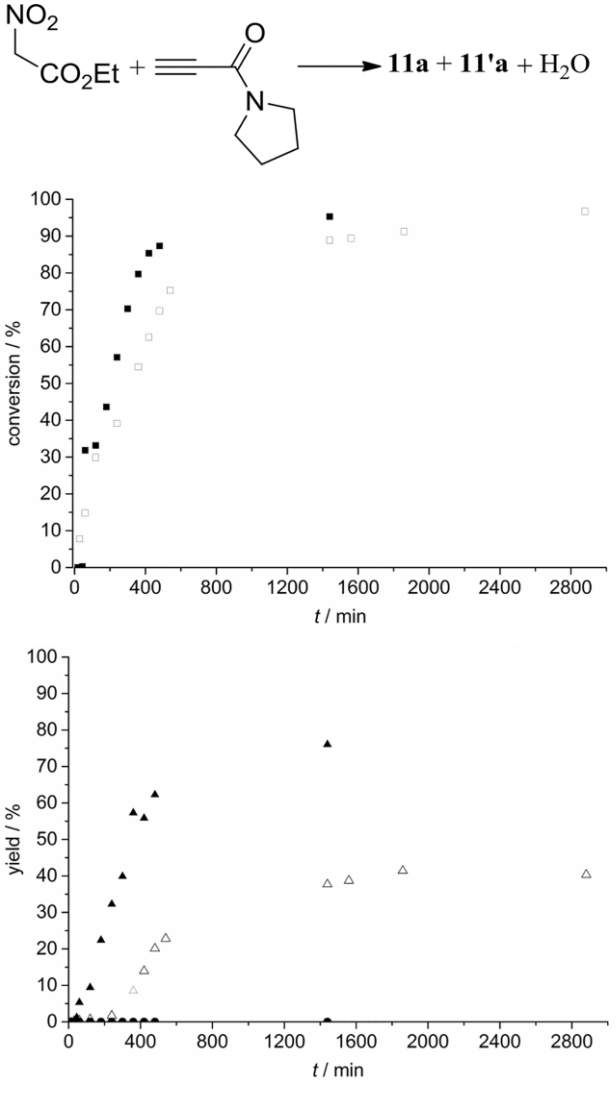


Figure 2. Kinetic profiles for condensation between ethyl nitroacetate (**1a**) and 1-(pyrrolidin-1-yl)prop-2-yn-1-one to mixtures of isoxazoles **11a** and **11′a** (Table 1, entry 10). In chloroform, no reaction was observed without a catalyst (solid circles): conversion of the dipolarophile with DABCO (white squares) or DABCO/[Cu] (solid squares) catalysis (top); yield of isoxazoles **11a** and **11′a** (mixture) with DABCO (white triangles) or DABCO/[Cu] (solid triangles) catalysis (bottom). See the Experimental Section for details.

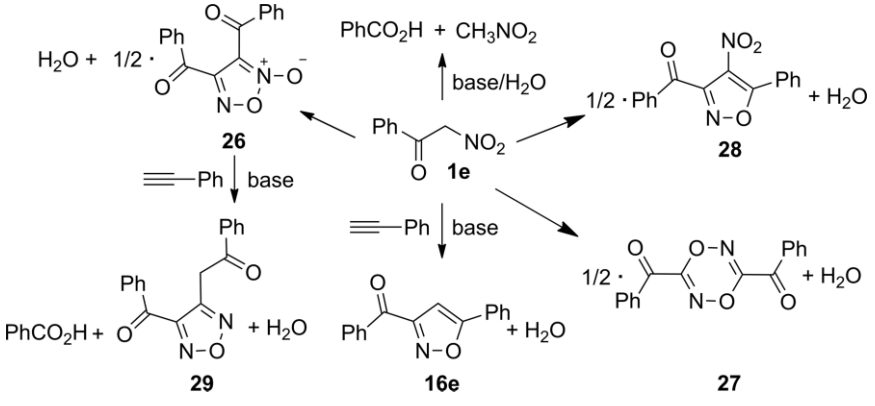
cycloadduct. Notably, the condensation was satisfactory if an acetylenic amide was used (Table 1, entry 10; 73 % yield of **11a** along with a trace amount of **11′a**). The kinetic profiles for the conversions are illustrated in Figure 2 (top): no conversion was observed without a catalyst. The plot of yield versus time (Figure 2, bottom) shows that the addition of copper to the base not only reduced the induction time but also increased the yield. Condensations of ethyl nitroacetate with monosubstituted alkynes containing EWGs were not regioselective, as both isomers were obtained and the 5-substituted isomers (i.e., **10a** and **11a**) predominated.

Nitroacetamides reacted readily with alkynes: amide **1c** gave **13c** in good yield preferably with 10 mol-% of base (Table 1, entry 12). In view of the possible use of these 3-carbamoylisoxazole derivatives, the condensations of nitroacetamide **1d** substituted with a protected amino function were performed with two alkynes (Table 1, entries 13 and 14). The quantitative HCl-mediated removal of the *tert*-butoxycarbonyl (Boc) protecting group gave pendant amine units **24** and **25** as hydrochloride salts.

Benzoylnitromethane

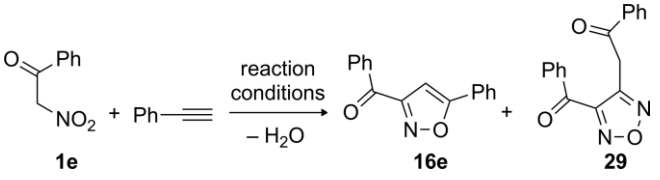
Benzoylnitromethane (**1e**) is known to give several products according to the reaction conditions, with or without dipolarophile implication. Those concerning benzoylnitromethane (**1e**) alone or with phenylacetylene are illustrated in Scheme 1.

Benzoylnitromethane is easily hydrolyzed in the presence of base.[44] Self-condensation occurs spontaneously with any solvent and environmental conditions to furoxan **26**, whereas dioxadiazine isomer **27** was reported to be produced with an excess amount of nitrous acid.[45] A third isomer, isoxazole **28**, becomes the sole self-condensation product upon treatment with the catalytic system DABCO/Cu^{II} in chloroform.[46] In the presence of dipolarophiles, isoxazoline (from alkenes) or isoxazole (from alkynes, e.g., **16e**) cycloadducts are the expected products. However, furoxan **26** in turn reacts with dipolarophiles, owing to its peculiar dipolar reactivity, and this leads to furazans (e.g., **29**) upon hydrolytic loss of benzoic acid from the cycloadducts. This process was previously examined in detail for the reaction with norbornene as a dipolarophile.[47] This picture



Scheme 1. Reactions of benzoylnitromethane alone or with phenylacetylene.

Table 2. Reaction of benzoylnitromethane (**1e**) with phenylacetylene under various reaction conditions.



Entry	Catalyst (mol-%)	*T* [°C]	*t* [h]	Yield [%][a]		Ratio
				16e	**29**	**16e/29**[b]
1	none	60	24	–	–	–
2	NMP (20)	60	4	0.9	–	–
3	NMP (20)	60	8	2	–	–
4	NMP (20)	60	24	73	8.4	9
5	$Cu(OAc)_2$ (5), NMP (20)	60	24	75	3.0	25
6	$Cu(OAc)_2$ (5), NMP (20)	40	24	22	–	–
7	$Cu(OAc)_2$ (5), NMP (20)	40	60	78	4.8	16
8	$Cu(OAc)_2$ (5), NMP (20)	60	4	7	0.7	10
9	$Cu(OAc)_2$ (5), NMP (20)	60	8	78	6	14
10	Cu (5), NMP (20)	60	24	81	4.6	18
11	$Cu(OAc)_2$ (2.5), NMP (10)	60	24	86	4.0	22
12	Cu (2.5), NMP (10)	60	24	82	2.6	32

[a] Yield determined by ^{1}H NMR spectroscopy with the use of an internal standard. [b] Molar ratio determined by analysis of the crude reaction mixture by ^{1}H NMR spectroscopy.

suggests that the results dramatically depend on the reaction conditions. Thus, variations in the NMP/Cu^{II} catalytic system applied to the model reaction of benzoylnitromethane (**1e**) with phenylacetylene gave the results detailed in Table 2 (the ratio between yields of main products **16e** and **29** is reported in the last column). The use of base alone required a reaction time of 24 h to obtain **16e** in 73 % yield (Table 2, entries 2–4), whereas the same result was observed after only 8 h upon the addition of Cu^{II} (Table 2, entry 9), even at a lower temperature in 60 h (Table 2, entry 7). Copper powder catalyzed the reaction as well (Table 2, entry 10 vs. 5). The best results were achieved upon using a lower amount of the catalyst (Table 2, entries 11 and 12), and the highest selectivity was observed towards isoxazole **16e**. Similarly, we previously noticed that with *N*-methylimidazole, isoxazole **16e** was obtained in 97 % yield provided that the amount of the catalyst was far below the stoichiometric value;[30] otherwise, the proportion of furazan **29** formed increased,[47] as also observed by others.[31a] The yields obtained in the latter case (68 %) are in agreement with those obtained in our laboratory. Catalysis as in entries 10 and 12 (Table 2) applied to several terminal alkynes afforded acceptable results in terms of the yield and furazan side-product formation (see Table 1). Corresponding 5-substituted isoxazoles **16e**–**20e** were obtained regioselectively (Table 1) along with trace amounts of byproducts (mainly furazans). The yields of **16e** and **18e** were higher if half the amount of the catalyst was used (Table 1); in other cases, the amount of catalyst could be reduced without worsening the results.

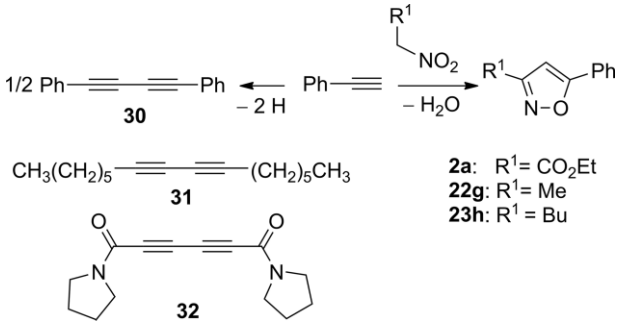
Diethylnitrophosphonate

3-Phosphorylisoxazoles prepared from nitro compound **1f** are rarely reported in the literature and are prepared by using a stoichiometric amount of $POCl_3$.[48] The catalytic direct procedure herein described allows analogous compound **21f** to be obtained in fair yield (Table 1, entry 20).

Nitroalkanes

Catalytic condensations of alkyne dipolarophiles with nitroalkanes such as nitroethane and nitropentane are so far unknown. One attempt with the use of the PPA/SiO_2 catalytic system in refluxing toluene was reported to fail.[49] Under the usual conditions, the [Cu]/NMP catalytic system allows fair yields of the expected condensation products between phenylacetylene and nitroethane (**1g**) or nitropentane (**1h**) to be obtained (33 or 39 % respectively; Table 1, entries 21 and 22). The yields are similar to those previously reported with the use of dehydrating agents.[50–52] Both isomers are observed in the reactions of nitroethane and nitropentane; for the latter, analysis of the crude reaction mixture by ^1H NMR spectroscopy showed the presence of a minor amount of 3-butyl-4-phenylisoxazole

Table 3. Condensation versus oxidative coupling; dependence on reaction conditions.[a]



Entry	R^1	Catalyst, $R^1CH_2NO_2$, time	Yield [%][b]	
			30	Isoxazole
1	–	DABCO (20), 24 h	0	–
2	–	DABCO (20), Cu $(OAc)_2$ (5), 24 h	26	–
3	–	DABCO (20), Cu $(OAc)_2$ (5), 24 h	14[c]	–
4	–	NMP (20), Cu $(OAc)_2$ (5), 24 h	9	–
5	–	NMP (100), Cu $(OAc)_2$ (5), 24 h	16	–
6	CO_2Et	DABCO (20), Cu $(OAc)_2$ (5), **1a** (250), 24 h	7	**2a**, 71
7	CO_2Et	NMP (20), Cu $(OAc)_2$ (5), **1a** (150), 24 h	10	**2a**, 47
8	Me	NMP (100), Cu $(OAc)_2$ (5), **1g** (250), 96 h	14	**22g**, 33
9	Me	NMP (100), Cu $(OAc)_2$ (5), **1g** (250), 96 h	11[c]	**22g**, 11
10	Bu	DABCO (100), Cu $(OAc)_2$ (5), **1h** (250), 120 h	70	**23h**, 0
11	Bu	DABCO (20), Cu $(OAc)_2$ (5), **1h** (150), 96 h	47	**23h**,8
12	Bu	NMP (20), Cu $(OAc)_2$ (5), **1h** (150), 96 h	62	**23h**,12
13	Bu	NMP (100), Cu $(OAc)_2$ (5), **1h** (250) 96 h	28	**23h**,39
14	Bu	NMP (100), Cu $(OAc)_2$ (5), **1h** (250), 96 h	23[c]	**23h**,7
15	Bu	NMP (100), Cu $(OAc)_2$ (20), **1h** (250), 96 h	57[c]	**23h**,10
16	Bu	TMEDA (50), Cu $(OAc)_2$ (5), **1h** (250), 96 h	–	**23h**,31
17	Bu	TMEDA (100), Cu $(OAc)_2$ (5), **1h** (250), 96 h	6	**23h**,50

[a] Reaction conditions: catalyst (mol-%), **1** (mol-%), 60 °C, $CHCl_3$, in air (unless otherwise indicated). [b] Yield of isolated product after chromatography. [c] Under an argon atmosphere.

(**23'h**) (less than 5 %) along with 3-butyl-5-phenylisoxazole (**23h**). Likewise for alkene dipolarophiles,[39,40] the reaction did not occur in the absence of copper or by using DABCO as the base in a stoichiometric amount (Table 3, entry 10). Low yields of 3-alkylisoxazoles **22g** and **23h** were accompanied by nearly complete conversion of phenylacetylene. This suggested that a competitive process was present, owing to the fact that the reactivity of nitroalkanes is lower than that of activated nitro compounds.

Copper-Catalyzed Oxidative Coupling of Terminal Alkynes

The well-known oxidative coupling of terminal alkynes to conjugate diynes in the presence of Cu salts and base was first reported by Glaser on phenylacetylene,[53] and others later slightly modified the reaction conditions;[54] the process is now known as the Glaser–Hay reaction.[55] A wide variety of modified coupling conditions have been described, including variations in the oxidant, ligand, solvent, as well as oxidation state of the added copper catalyst. Among these, copper(II) acetate with an organic base (e.g., DABCO or piperidine) in dichloromethane at room temperature with air admittance was also recently reported.[56,57] These conditions are very similar to those we employed for the condensation of nitro compounds with alkynes; therefore, a possible competition between the two reactions was considered.[58]

Thus, we verified that in the absence of nitro compounds, phenylacetylene gave diyne **30** (Table 3, entries 2–5) in various yields depending on the catalytic system employed. Diyne **30** was not obtained in the absence of copper (Table 3, entry 1). Similar results were obtained from 1-octyne (29 %; conditions as in Table 3, entry 3) and from 1-(pyrrolidin-1-yl)prop-2-yn-1-one (12 %; conditions as in Table 3, entry 4). Only reactions of phenylacetylene with nitro compounds were examined in detail (Table 3, entries 6–17).

The observed yields of the two products for different reactions and conditions, reported in Table 3, show that the condensation of nitroalkanes to isoxazole was favored more with NMP than with DABCO and clearly also by an excess amount of the nitroalkane (Table 3, entries 12 and 13). The presence of air ensured that copper was maintained in the Cu^{II} oxidation state. Thus, experiments performed under an argon atmosphere led to reduced amounts of both products,[59] because Cu^{II} was consumed as a stoichiometric oxidant to **30**,[60] and furthermore, condensation to the isoxazole resulted in loss of the catalyst (Table 3, entries 9 and 14). In fact, the overall yields of the products increased if the amount of Cu^{II} was raised to 20 mol-% (Table 3, entry 15). The yields observed in chloroform for the condensations of alkynes with activated nitro compounds catalyzed by base only[18] or by base and copper (Table 1) did not largely differ.

In reactions of nitroalkanes with phenylacetylene, moderate yields of isoxazoles were obtained only in the presence of copper (Table 1, entries 21 and 22), besides considerable amounts of products resulting from oxidative coupling (Table 3, entries 8 and 13). Given that the kind of base was found to affect both competitive reactions, some experiments were performed by using *N*,*N*,*N'*,*N'*-tetramethylethylenediamine (TMEDA) as the base (Table 3, entries 16 and 17) because this was reported[61] to be unsuited to oxidative coupling. Indeed, the proportion of isoxazole compared to diyne appeared to be higher in these examples (Table 3, entry 17 vs. 13).

Conclusions

Alkyne dipolarophiles are known to condense with active primary nitro compounds to isoxazoles under base catalysis. This paper revealed the advantages of a catalyst containing copper in addition to a base. Thus, active nitro compounds reacted faster with improved yields, and the reaction could be extended to electron-poor alkynes. Even nitroalkanes condensed with phenylacetylene to isoxazoles. However, the most remarkable feature of this catalytic system was the enhanced selectivity towards condensation to isoxazoles over various competitive side reactions. The results indicate the general applicability of this method for the preparation of 3,5-disubstituted isoxazoles.

Experimental Section

General Methods: Melting points were determined in open capillary tubes with a Stuart Scientific SMP3 melting-point apparatus. Chromatographic separations were performed on silica gel 60 (40–6.3 μm) with analytical-grade solvents, driven by a positive pressure of air; R_f values refer to TLC (visualized with UV light and/or by dipping the plates into a solution of anisaldehyde followed by heating with a heat gun) performed on 25 mm silica-gel plates (Merck F254) with the eluent indicated for column chromatography. For gradient column chromatography, the R_f values refer to the more polar eluant. Solvents were removed by evaporation with the use of a rotary evaporator at room temperature. ^{1}H NMR 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. ^{31}P NMR spectra were recorded with a Bruker spectrometer (operating at 162 MHz). The ^{1}H NMR spectroscopic data are reported as [multiplicity, coupling constant(s) in Hz, integration]; the multiplicity is denoted by s = singlet, d = doublet, t = triplet, q = quartet, quint. = quintet, m = multiplet or unresolved, br. = broad signal. The multiplicities of the ^{13}C NMR signals (s, d, t, q; for compound **20e** the multiplicity for C–H are reported along with C–P coupling constants) and the ^{1}H and ^{13}C signals, if possible, were assigned by means of gCOSY, gHSQC, 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). ESI (electrospray ionization) mass spectra were recorded (infusing the sample solution directly into the ESI chamber by syringe pump) with a ThermoFisher LCQ-Fleet ion-trap instrument, and spectra were recorded by using the ESI$^+$ technique. EI (electron impact) mass spectra (at ionization voltage of 70 eV) were obtained by using a Shimadzu QP5050A quadrupole-based mass spectrometer. CI (chemical ionization) mass spectra (MeOH) were obtained by using a Varian Saturn 2200 mass spectrometer interfaced to a Varian CP-3800 gas chromatograph. Ion mass/charge (*m*/*z*) ratios 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. Elemental analyses were performed with a Perkin–Elmer 240C Elemental Analyzer apparatus. All compounds were named by using Autonom (Beilstein Information Systems) and were modified as appropriate.

Materials: Commercially available (Lancaster and Aldrich) ethyl nitroacetate (**1a**), methyl nitroacetate (**1b**), benzoylnitromethane

(**1e**), nitroethane (**1g**), nitropentane (**1h**), and organic bases, 99 %, were used as supplied. Diethyl (nitromethyl)phosphonate (**1f**) was prepared following a previously reported procedure.[62] *N*-Methyl-2-nitroacetamide (**1c**) was prepared following a previously reported procedure.[28] $CHCl_3$ (ethanol-free) was filtered through a short pad of potassium carbonate just before use. Copper(II) acetate and copper powder were used as supplied. Experiments performed under an atmosphere of argon were conducted with degassed $CHCl_3$, which was obtained by three freeze–pump–thaw cycles.

Kinetic Profile for Reactions between Ethyl Nitroacetate (1a) and Phenylacetylene: Different catalysts or none were screened in an apparatus in which 6–8 reactions were performed simultaneously. A mixture of the catalyst (DABCO 0.0424 mmol or Cu 0.0212 mmol/DABCO 0.0424 mmol), phenylacetylene (0.424 mmol), ethyl nitroacetate (**1a**, 1.06 mmol), and $CDCl_3$ (1.4 mL) was stirred at 60 °C in a sealed tube for the indicated time. After the requested time, a portion was withdrawn, diluted with $CDCl_3$ (0.6 mL), and the ^{1}H NMR spectrum was recorded. The percentage of phenylacetylene (as molar ratio) was evaluated by integrating the 4-H proton signal of cycloadduct **2a** [δ = 6.91 (s) ppm] and the acetylenic proton of phenylacetylene [δ = 3.05 (s) ppm]. Without catalyst, no conversion was observed. All experiments were replicated at least once with similar results (Figure 1).

Kinetic Profile for Reactions between Ethyl Nitroacetate (1a) and 1-(Pyrrolidin-1-yl)prop-2-yn-1-one: Conversions and yields were determined by GC and are based on the alkyne used. Gas chromatographic analysis was conducted by using a Shimadzu GC-2010 on a 0.25 mm × 30 m Simplicity-5 capillary column. Typical conditions used for the gas chromatographic analysis were: injector T = 250 °C, constant flow 1.0 mL min^{-1}, initial T = 150 °C, hold time 3 min, 10 °C min^{-1} to 230 °C then hold time 3 min, 5 °C min^{-1} to 250 °C, then hold time 5 min, 5 °C min^{-1} to 280 °C. Retention times (t_R) are referred to the above conditions. Relative response factors were derived from a reference solution obtained by weighing substrate, products, and internal standard. A mixture of the catalyst (NMP 0.0848 mmol or NMP 0.0848 mmol and $Cu(OAc)_2$ 0.0212 mmol or none), ethyl nitroacetate (**1a**, 1.06 mmol), 1-(pyrrolidin-1-yl)prop-2-yn-1-one (0.424 mmol), 2,4-dimethoxyacetophenone (internal standard, 26.1 mg), and $CHCl_3$ (1.4 mL) was stirred at 60 °C in a sealed tube, and the progress of the reaction was monitored by GC analysis. A portion was withdrawn (0.01 mL) at regular intervals, which was diluted with EtOAc (0.1 mL) and then analyzed by GC. The conversion was evaluated by integrating the signals of 1-(pyrrolidin-1-yl)prop-2-yn-1-one (t_R = 5.90) and 2,4-dimethoxyacetophenone (t_R = 9.80). The yield was evaluated by integrating the signals of the internal standard (t_R = 9.80), isoxazole **11′a** (t_R = 13.4), and isoxazole **11a** (t_R = 16.3). Without catalyst, no conversion was observed. All experiments were repeated at least once with similar results (Figure 2).

1-(Pyrrolidin-1-yl)prop-2-yn-1-one: Prepared from methyl propiolate as reported in the literature with slight modification.[63] Methyl propiolate (0.84 mL, 10 mmol) wad added dropwise to a stirred solution of pyrrolidine (0.83 mL, 10 mmol) in water (0.50 mL) and MeOH (0.70 mL) at –50 °C. After 5 h, the mixture was warmed up to room temperature while adding 2 M HCl (40 mL). After 16 h, the mixture was extracted with CH_2Cl_2 (4 × 20 mL). The combined organic layer was washed with aqueous satd. $NaHCO_3$ (20 mL), water (20 mL), and brine (20 mL); dried with Na_2SO_4; filtered; and concentrated in vacuo. The crude solid residue was washed with hexane (3 × 4 mL) to yield the title amide as a yellowish powder (0.558 g, 58 %), m.p. 89–91 °C (ref.[63] 90–91 °C). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.86–1.95 (m, 4 H, 2 CH_2), 3.0 (s, 1 H, C*H*), 3.41–3.48 (m, 2 H, CH_2N), 3.59–3.66 ppm (m, 2 H, CH_2N). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 24.4 (t, CH_2), 25.1 (t, CH_2), 45.1 (t, CH_2N), 47.9 (t, CH_2N), 76.8 (s, *C*CO), 77.1 (d, *C*H), 151.2 ppm (s, *C*O). MS (ESI$^+$): *m/z* (%) = 146 (100) [M + Na]$^+$, 124 (25) [M + H]$^+$. MS (EI): *m/z* (%) = 123 (32) [M]$^+$, 122 (38) [M – H]$^+$, 95 (16), 70 (54), 67 (64), 53 (100) [HCCO]$^+$. IR (KBr): $\tilde{\nu}$ = 3301 (m) [≡C–H], 2976 (m) [C–H], 2955 (m) [C–H], 2883 (m), 2113 (m) [C≡C], 1618 (s) [C=O], 1431 (s), 1340 (m), 1251 (w), 1226 (w), 1191 (w) cm^{-1}. C_7H_9NO (123.15): calcd. C 68.27, H 7.37, N 11.37; found C 68.24, H 7.57, N 10.97.

General Procedure for the Preparation of Isoxazoles: Chloroform (2086 mg, 1.40 mL) was added to a mixture of nitro compound **1a–h** (2.5 equiv.), the catalyst (copper powder or copper acetate 0.05 equiv. and NMP or DABCO 0.2 equiv.), and the alkyne (0.404–0.514 mmol), and then the mixture was maintained at 60 °C whilst stirring in a sealed tube. After the indicated time, the solvent was removed and the crude residue was purified by column chromatography on silica gel. Significant variations in the amounts employed and conditions are mentioned individually (Table 1).

Ethyl 5-Phenylisoxazole-3-carboxylate (2a): From **1a** and phenylacetylene (43.3 mg) in 94 % yield (87.0 mg, yellowish powder) by using DABCO (0.1 equiv.)/$Cu(OAc)_2$ (0.05 equiv.) as catalyst at 60 °C for 23 h. Eluant: hexane/EtOAc = 8:1 (R_f = 0.26), m.p. 48–49 °C (ref.[64] 48–50 °C). $C_{12}H_{11}NO_3$ (217.22): calcd. C 66.35, H 5.10, N 6.44; found C 66.14, H 4.99, N 6.58. The spectroscopic data were identical to those previously reported.[28] The reaction conducted by using NMP (0.2 equiv.)/$Cu(OAc)_2$ (0.05 equiv.) as the catalyst gave **2a** in 87 % yield. The latter sample exhibited spectral and analytical data in agreement with those reported above.

Ethyl 5-Hexylisoxazole-3-carboxylate (3a)

With Cu^{II} Salt: From **1a** and 1-octyne (45.4 mg) in 82 % yield (77.3 mg, clear oil) by using NMP/$Cu(OAc)_2$ as catalyst at 60 °C for 48 h. Eluant: hexane/EtOAc = 20:1 (R_f = 0.22). ^{1}H NMR ($CDCl_3$): δ = 0.87 (t, J = 6.8 Hz, 3 H; CH_3CH$_2$), 1.27–1.34 (m, 6 H, 3 CH_2), 1.38 (t, J = 7.2 Hz, 3 H; OCH$_2$CH_3), 1.68 (quint., J = 7.6 Hz, 2 H; CH_2), 2.77 (t, J = 7.6 Hz, 2 H; C-5CH_2), 4. 40 (q, J = 7.2 Hz, 2 H; OCH_2CH$_3$), 6.37 ppm (s, 1 H, 4-H). ^{13}C NMR ($CDCl_3$): δ = 14.0 (q; CH_3CH$_2$), 14.1 (q; CH_3CH$_2$O), 22.4 (t; CH_2), 26.7 (t; CH_2), 27.3 (t; CH_2), 28.6 (t; CH_2), 31.3 (t; CH_2), 62.0 (t; OCH_2CH$_3$), 101.4 (d; C-4), 156.3 (s; C-3 or *C*O), 160.3 (s; C-3 or *C*O), 175.7 ppm (s; C-5). MS (ESI$^+$, MeOH): *m/z* (%) = 226 (10) [M + H]$^+$, 248 (100) [M + Na]$^+$. IR ($CDCl_3$): $\tilde{\nu}$ = 2958 (s) (C–H), 2931 (s) (C–H), 2871 (m) (C–H), 1732 (s) (C=O), 1591 (m) (C=N), 1462 (s), 1248 (s), 1213 (s) cm^{-1}. $C_{12}H_{19}NO_3$ (225.28): calcd. C 63.98, H 8.50, N 6.22; found C 64.38, H 7.88, N 5.99.

With Cu^0: From **1a** and 1-octyne (45.5 mg) in 76 % yield (71.1 mg, clear oil) by using NMP/Cu powder as catalyst at 60 °C for 24 h. Eluant: as above. $C_{12}H_{19}NO_3$ (225.28): calcd. C 63.98, H 8.50, N 6.22; found C 63.50, H 7.64, N 6.25. The spectroscopic data were identical to those reported above.

Ethyl 5-Cyclopropylisoxazole-3-carboxylate (4a)

With Cu^{II} Salt: From **1a** and cyclopropylacetylene (30.8 mg) in 90 % yield (76.0 mg, clear oil) by using NMP/$Cu(OAc)_2$ as catalyst at 60 °C for 24 h. Eluant: hexane/EtOAc = 7:1 (R_f = 0.30). ^{1}H NMR ($CDCl_3$): δ = 0.96–1.02 (m, 2 H, CHCH_2), 1.06–1.12 (m, 2 H, CHCH_2), 1.38 (t, J = 7.2 Hz, 3 H; CH_3CH$_2$O), 2.02–2.10 (m, 1 H, C*H*CH$_2$), 4.40 (q, J = 7.2 Hz, 2 H; CH$_3$CH_2O), 6.28 ppm (s, 1 H, 4-H). ^{13}C NMR ($CDCl_3$): δ = 8.1 (d; *C*HCH$_2$), 8.8 (t, 2 C; 2 CHCH$_2$), 14.1 (q; CH_3CH$_2$O), 62.0 (t; CH$_3$CH_2O), 99.3 (d; C-4), 156.4 (s; C-3 or *C*O), 160.2 (s; C-3 or *C*O), 176.8 ppm (s; C-5). MS (ESI$^+$, MeOH): *m/z* (%) = 182 (100) [M + H]$^+$. IR ($CDCl_3$): $\tilde{\nu}$ = 2985 (w) [C–H], 2939 (w) [C–H], 1731 (s) [C=O], 1595 (m) [C=N], 1468 (m), 1252 (s), 1228 (s), 1187 (m), 1020 (m) cm^{-1}.

$C_9H_{11}NO_3$ (181.19): calcd. C 59.66, H 6.12, N 7.73; found C 59.51, H 5.64, N 7.59.

With Cu^0: From **1a** and cyclopropylacetylene (28.2 mg) in 88 % yield (67.6 mg, clear oil) by using NMP/Cu powder as catalyst at 60 °C for 24 h. Eluant: as above. $C_9H_{11}NO_3$ (181.19): calcd. C 59.66, H 6.12, N 7.73; found C 59.45, H 5.88, N 7.65. The spectroscopic data were identical to those reported above.

Ethyl 5-Hydroxymethylisoxazole-3-carboxylate (5a): From **1a** and propargyl alcohol (23.8 mg) in 70 % yield (51.0 mg, clear oil) by using NMP/$Cu(OAc)_2$ as catalyst at 60 °C for 24 h. Eluant: hexane/EtOAc = 3:1 (R_f = 0.24). $C_7H_9NO_4$ (171.15): calcd. C 49.12, H 5.30, N 8.18; found C 49.11, H 5.25, N 7.97. The spectroscopic data were identical to those previously reported.[30]

Ethyl 5-(2-Hydroxyethyl)isoxazole-3-carboxylate (6a)

With Cu^{II} Salt: From **1a** and 3-butyn-1-ol (34.9 mg) in 77 % yield (70.9 mg, clear oil) by using NMP/$Cu(OAc)_2$ as catalyst at 60 °C for 46 h. Eluant: hexane/EtOAc = 4:3 (R_f = 0.23). ^{1}H NMR ($CDCl_3$): δ = 1.39 (t, J = 7.2 Hz, 3 H; CH_3CH_2O), 3.06 (t, J = 6.0 Hz, 2 H; CH_2C-5), 3.97 (q, J = 5.3 Hz, 2 H; CH_2OH), 4.41 (q, J = 7.2 Hz, 2 H; CH_3CH_2O), 6.53 ppm (s; 4-H). ^{13}C NMR ($CDCl_3$): δ = 14.1 (q; CH_3CH_2O), 30.2 (t; CH_2C-5), 60.0 (t; CH_2OH), 62.1 (t; CH_3CH_2O), 102.7 (d; C-4), 156.6 (s; C-3 or CO), 160.1 (s; C-3 or CO), 172.5 ppm (s; C-5). MS (ESI^+, MeOH): m/z (%) = 186 (100) $[M + H]^+$. IR ($CDCl_3$): $\tilde{\nu}$ = 3620 (w) [O–H], 2984 (w) [C–H], 2939 (w) [C–H], 2892 (w) [C–H], 1733 (s) [C=O], 1596 (m) [C=N], 1462 (m), 1214 cm^{-1} (s). $C_8H_{11}NO_4$ (185.18): calcd. C 51.89, H 5.99, N 7.56; found C 51.73, H 5.64, N 8.14.

With Cu^0: From **1a** and 3-butyn-1-ol (28.8 mg) in 68 % yield (51.8 mg, clear oil) by using NMP/Cu powder as catalyst at 60 °C for 48 h. Eluant: as above. $C_8H_{11}NO_4$ (185.18): calcd. C 51.89, H 5.99, N 7.56; found C 51.91, H 5.60, N 7.62. The spectroscopic data were identical to those reported above.

Ethyl 5-(1-Hydroxycyclohexyl)isoxazole-3-carboxylate (7a)

With Cu^{II} Salt: From **1a** and 1-ethynyl-cyclohexanol (53.4 mg) in 76 % yield (78.8 mg, clear oil) by using NMP/$Cu(OAc)_2$ as catalyst at 60 °C for 48 h. Eluant: hexane/EtOAc = 9:3 (R_f = 0.30). ^{1}H NMR ($CDCl_3$): δ = 1.38 (t, J = 7.2 Hz, 3 H; CH_3CH_2O), 1.50–1.78 (m, 6 H, 3 CH_2), 1.81–1.90 (m, 2 H, CH_2), 1.91–2.00 (m, 2 H, CH_2), 2.12 (s, 1 H, OH), 4.41 (q, J = 7.2 Hz, 2 H; CH_3CH_2O), 6.56 ppm (s; 4-H). ^{13}C NMR ($CDCl_3$): δ = 14.1 (q; CH_3CH_2O), 21.5 (t, 2 C; 2 CH_2), 25.0 (t; CH_2), 36.5 (t, 2 C; 2 CH_2), 62.1 (t; CH_3CH_2O), 70.4 (s; COH), 100.5 (d; C-4), 156.2 (s; C-3 or CO), 160.0 (s; C-3 or CO), 179.8 ppm (s; C-5). MS (ESI^+, MeOH): m/z (%) = 240 (100) $[M + H]^+$. IR ($CDCl_3$): $\tilde{\nu}$ = 3592 (w) [O–H], 2984 (w) [C–H], 2941 (s) [C–H], 2860 (m) [C–H], 1733 (s) [C=O], 1601 (w) [C=N], 1458 (w), 1449 (w), 1252 (s), 1205 (s), 1020 (w) cm^{-1}. $C_{12}H_{17}NO_4$ (239.12): calcd. C 60.24, H 7.6, N 5.85; found C 60.01, H 7.30, N 5.62.

With Cu^0: From **1a** and 1-ethynyl-cyclohexanol (52.6 mg) in 85 % yield (86.3 mg, greenish oil) by using NMP/Cu powder as catalyst at 60 °C for 120 h. Eluant: hexane/EtOAc = 9:2 (R_f = 0.19). $C_{12}H_{17}NO_4$ (239.12): calcd. C 60.24, H 7.6, N 5.85; found C 60.21, H 7.20, N 6.11. The spectroscopic data were identical to those reported above.

Ethyl 5-(3-Cyanopropyl)isoxazole-3-carboxylate (8a)

With Cu^{II} Salt: From **1a** and hex-5-ynenitrile (38.7 mg) in 94 % yield (82.0 mg, clear oil) by using NMP/$Cu(OAc)_2$ as catalyst at 60 °C for 48 h. Eluant: hexane/EtOAc = 2:1 (R_f = 0.32). $C_{10}H_{12}N_2O_3$ (208.21): calcd. C 57.68, H 5.81, N 13.45; found C 57.57, H 5.59, N 12.61. The spectroscopic data were identical to those reported below.

With Cu^0: From **1a** and hex-5-ynenitrile (37.6 mg) in 96 % yield (80.3 mg, clear oil) by using NMP/Cu powder as catalyst at 60 °C for 72 h. Eluant: hexane/EtOAc = 2:1 (R_f = 0.32). ^{1}H NMR ($CDCl_3$): δ = 1.38 (t, J = 7.2 Hz, 3 H; CH_3CH_2), 2.08 (q, J = 7.2 Hz, 2 H; CH_2), 2.42 (t, J = 6.8 Hz, 2 H; CH_2), 2.98 (t, J = 7.6 Hz, 2 H; C-5CH_2), 4.40 (q, J = 7.2 Hz, 2 H; OCH_2), 6.48 ppm (s, 1 H, 4-H). ^{13}C NMR ($CDCl_3$): δ = 14.1 (q; CH_3CH_2), 16.5 (t; CH_2), 23.2 (t; CH_2), 25.4 (t; CH_2), 62.2 (t; OCH_2), 102.4 (d; C-4), 118.4 (s; CN), 156.5 (s; CO or C-3), 159.8 (s; CO or C-3), 172.5 ppm (s; C-5). MS (ESI^+, MeOH): m/z (%) = 231 (100) $[M + Na]^+$, 439 (30) $[2M + Na]^+$. IR ($CDCl_3$): $\tilde{\nu}$ = 2982 (w) (C–H), 2956 (w) (C–H), 2870 (w) (C–H), 2250 (m) (C≡N), 1800 (w), 1731 (s) (C=O), 1593 (m) (C=N), 1464 (m), 1425 (m), 1296 (m), 1258 (m), 1210 (s), 1098 (m), 1021 (m) cm^{-1}. $C_{10}H_{12}N_2O_3$ (208.21): calcd. C 57.68, H 5.81, N 13.45; found C 57.61, H 5.39, N 12.86.

Ethyl 5-(Diethoxymethyl)isoxazole-3-carboxylate (9a): From **1a** and 3,3-diethoxyprop-1-yne (52.4 mg) in 68 % yield (67.6 mg, clear oil) by using NMP/$Cu(OAc)_2$ as catalyst at 60 °C for 24 h. Eluant: hexane/EtOAc = 9:1 (R_f = 0.38). ^{1}H NMR ($CDCl_3$): δ = 1.25 (t, J = 7.0 Hz, 6 H; 2 CH_3CH_2O), 1.41 (t, J = 7.2 Hz, 3 H; CH_3CH_2OCO), 3.64 (q, J = 7.0 Hz, 4 H; 2 CH_3CH_2O), 4.44 (q, J = 7.2 Hz, 2 H; CH_3CH_2OCO), 5.67 (s, 1 H, CHO), 6.75 ppm (s; 4-H). ^{13}C NMR ($CDCl_3$): δ = 14.1 (q; CH_3CH_2OCO), 15.0 (t, 2 C; 2 CH_3CH_2O), 61.9 (t, 2 C; 2 CH_3CH_2O), 62.2 (t; CH_3CH_2OCO), 94.9 (d; CHO), 103.6 (d; C-4), 156.2 (s; C-3 or CO), 159.8 (s; C-3 or CO), 171.2 ppm (s; C-5). MS (ESI^+, MeOH): m/z (%) = 243 (100) $[M]^+$. IR ($CDCl_3$): $\tilde{\nu}$ = 2982 (m) [C–H], 2932 (w) [C–H], 2898 (w) [C–H], 1734 (s) [C=O], 1600 (w) [C=N], [1472 (w), 1457 (w), 1446 (w), 1251(s) cm^{-1}. $C_{11}H_{17}NO_5$ (243.11): calcd. C 54.31, H 7.04, N 5.76; found C 53.98, H 6.63, N 5.34.

3-Ethyl Isoxazole-3,5-dicarboxylate 5-Methyl Ester (10a) and Isoxazole-3,4-dicarboxylic Acid 3-Ethyl Ester 4-Methyl Ester (10′a): From **1a** and methyl propiolate (35.6 mg) in 40 % overall yield (34 mg, mixture of isomers, yellowish oil) by using NMP/$Cu(OAc)_2$ as catalyst at 60 °C for 60 h. Eluant: hexane/EtOAc = 4:1 (R_f = 0.22). ^{1}H NMR (200 MHz, $CDCl_3$, mixture of isomers): δ = 1.33–1.46 (m, 3 H, CH_3CH_2), 3.98 (s, 3 H, OCH_3), 4.34–4.56 (m, 2 H, OCH_2CH_3), 7.30 (s, 1/2 H; 4-H), 8.91 ppm (s, 1/2 H; 5-H).

Ethyl 5-(Pyrrolidine-1-carbonyl)isoxazole-3-carboxylate (11a) and Ethyl 4-(Pyrrolidine-1-carbonyl)isoxazole-3-carboxylate (11′a)

With Cu^{II} Salt: From **1a** and 1-(pyrrolidin-1-yl)prop-2-yn-1-one (52.6 mg) by using NMP/$Cu(OAc)_2$ as catalyst at 60 °C for 24 h. Purification (hexane/EtOAc = 1:1) gave **11a** (74.0 mg, 73 %, yellowish oil, R_f = 0.33) and diyne **32** (R_f = 0.38) containing trace amounts of **11′a**. Data for **11a**: ^{1}H NMR ($CDCl_3$): δ = 1.39 (t, J = 7.2 Hz, 3 H; CH_3CH_2), 1.88–2.04 (m, 4 H, 2 CH_2), 3.63 (t, J = 6.6 Hz, 2 H; CH_2N), 3.83 (t, J = 6.6 Hz, 2 H; CH_2N), 4.42 (q, J = 7.2 Hz, 2 H; OCH_2CH_3), 7.30 ppm (s, 1 H, 4-H). ^{13}C NMR ($CDCl_3$): δ = 14.1 (q; CH_3CH_2), 23.7 (t; CH_2), 26.0 (t; CH_2), 47.4 (t; CH_2N), 47.8 (t; CH_2N), 62.5 (t; OCH_2), 108.5 (d; C-4), 154.8 (s; CON), 156.3 (s; C-3 or CO_2Et), 159.1 (s; C-3 or CO_2Et), 166.2 ppm (s; C-5). MS (ESI^+, MeOH): m/z (%) = 239 (40) $[M + H]^+$, 261 (100) $[M + Na]^+$. IR ($CDCl_3$): $\tilde{\nu}$ = 2982 (m) (C–H), 2956 (m), 2883 (w), 1736 (s) (C=O), 1628 (s) (C=O), 1414 (m) cm^{-1}. $C_{11}H_{14}N_2O_4$ (238.24): calcd. C 55.46, H 5.92, N 11.76; found C 55.45, H 5.92, N 11.76. Data for **11′a**: ^{1}H NMR ($CDCl_3$, from mixture with **32**): δ = 1.38 (t, J = 7.2 Hz, 3 H; CH_3CH_2), 1.76–2.02 (m, 4 H, 2 CH_2), 3.29 (m, 2 H, CH_2N), 3.61 (m, 2 H, CH_2N), 4.42 (q, J = 7.2 Hz, 2 H; OCH_2CH_3), 8.59 ppm (s, 1 H, 5-H). GC–MS (CI): m/z (%) = 239 (100) $[M + H]^+$.

With Cu^0: From ethyl nitroacetate (**1a**) and 1-(pyrrolidin-1-yl)prop-2-yn-1-one (52.5 mg) by using NMP/Cu powder as catalyst at 60 °C for 24 h. Purification as above gave **11a** (68.2 mg, 67, yellowish oil) and diyne **32** containing trace amounts of **11′a**. Data for **11a**: $C_{11}H_{14}N_2O_4$ (238.24): calcd. C 55.46, H 5.92, N 11.76; found C 55.78,

H 5.71, N 11.39. The spectroscopic data were identical to those reported above.

Methyl 5-Hexylisoxazole-3-carboxylate (12b): From **1b** and 1-octyne (46.7 mg) in 70 % yield (62.0 mg, white powder) by using NMP/$Cu(OAc)_2$ as catalyst at 60 °C for 60 h. Eluant: hexane/EtOAc = 10:1 (R_f = 0.26). M. p. 32–33 °C. ^{1}H NMR ($CDCl_3$): δ = 0.86 (t, J = 6.8 Hz, 3 H; CH_3CH$_2$), 1.24–1.38 (m, 6 H, 3 CH_2), 1.69 (quint., J = 7.6 Hz, 2 H; CH_2), 2.77 (t, J = 7.6 Hz, 2 H; C-5CH_2), 3.94 (s, 3 H, OCH_3), 6.38 ppm (s, 1 H, 4-H). ^{13}C NMR ($CDCl_3$): δ = 14.0 (q, CH_3CH$_2$), 22.4 (t, CH_2), 26.7 (t, CH_2C-5), 27.3 (t, CH_2), 28.6 (t, CH_2C-5), 31.3 (t, CH_2), 52.7 (q, OCH_3), 101.4 (d, C-4), 156.0 (s, CO), 160.7 (s, C-3), 175.8 (s, C-5) ppm. MS (ESI$^+$, MeOH): m/z (%) = 212 (8) [M + H]$^+$, 234 (100) [M + Na]$^+$, 445 (12) [2M + Na]$^+$. IR ($CDCl_3$): $\tilde{\nu}$ = 2957 (s) [C–H], 2932 (s) [C–H], 2860 (m) [C–H], 1736 (s) [C=O], 1592 (m) [C=N], 1471 (m), 1249 (m), 1221 (s), 1004 (m) cm^{-1}. $C_{11}H_{17}NO_3$ (211.26): calcd. C 62.54, H 8.11, N 6.63; found C 62.59, H 8.03, N 6.76.

***N*-Methyl-5-phenylisoxazole-3-carboxamide (13c)**

With Typical Amount of Catalyst: From **1c** (2.5 equiv.) and phenylacetylene (44.6 mg) in 57 % yield (53.3 mg, white powder) by using NMP/$Cu(OAc)_2$ as catalyst at 60 °C for 24 h. Eluant: hexane/EtOAc = 2:1 (R_f = 0.29), m.p. 192–193 °C (ref.[30] 192–193 °C). GC–MS (CI): m/z (%) = 203 (100) [M + H]$^+$. IR (KBr): $\tilde{\nu}$ = 3331 (s) [N–H], 3118 (m), 2981 (w) [C–H], 2945 (w) [C–H], 1669 (s) [C=O], 1566 (s), 1449 (s), 1275 (m), 1269 (m) cm^{-1}. $C_{11}H_{10}N_2O_2$ (202.21): calcd. C 65.34, H 4.98, N 13.85; found C 65.22, H 4.84, N 14.28. The NMR spectroscopic data were identical to those previously reported.[47]

With Lower Amount of Catalyst: From **1c** (2.5 equiv.) and phenylacetylene (43.2 mg) in 67 % yield (56.3 mg, white powder) by using NMP (0.1 equiv./$Cu(OAc)_2$ as catalyst at 60 °C for 24 h then purified as above, m.p. 192–193 °C. $C_{11}H_{10}N_2O_2$ (202.21): calcd. C 65.34, H 4.98, N 13.85; found C 65.43, H 4.89, N 14.32. The NMR spectroscopic data were identical to those previously reported.[47]

5-Phenyl-3-*N*-Boc-aminoethyl Carbamate Isoxazole (14d): From **1d** (2.0 equiv.) and phenylacetylene (44.0 mg) in 71 % yield (101 mg, white powder) by using NMP/$Cu(OAc)_2$ as catalyst at 60 °C for 19 h. Eluant: hexane/EtOAc = 2:1 (R_f = 0.20), m.p. 161–165 °C. ^{1}H NMR ($CDCl_3$): δ = 1.41 (s, 9 H, 3 CH_3), 3.26–3.45 (m, 2 H, CH_2N), 3.48–3.63 (m, 2 H, CH_2N), 4.95 (br. s, 1 H; NHCO), 6.94 (s; 4-H), 7.34 (br. s, 1 H; NHCO_2), 7.40–7.52 (m, 3 H, Ph-H), 7.72–7.81 ppm (m, 2 H, Ph-H). ^{13}C NMR ($CDCl_3$): δ = 28.3 (q, 3 C; 3 CH_3), 40.2 (br. t, 2 C; 2 CH_2NH), 79.8 [s; $C(CH_3)_3$], 99.0 (d; C-4), 125.9 (d, 2 C; Ph-C), 126.8 (s; Ph-C_{ipso}), 129.1 (d, 2 C; Ph-C), 130.7 (d; Ph-C), 156.4 (s; CO_2), 159.0 (s; CO or C-3), 159.5 (s; CO or C-3), 171.6 ppm (s; C-5). MS (ESI$^+$, MeOH): m/z (%) = 354 (100) [M + Na]$^+$, 685 (64) [2M + Na]$^+$. IR (KBr): $\tilde{\nu}$ = 3381 (w) [N–H], 3342 (w) [N–H], 3153 (w), 2981 (m), 2945 (w), 1686 (s) [C=O], 1666 (s), 1609 (w), 1548 (s), 1525 (s), 1446 (m), 1368 (m), 1275 (m), 1262 (m), 1236 (m), 1175 (m) cm^{-1}. $C_{17}H_{21}N_3O_4$ (331.37): calcd. C 61.62, H 6.39, N 12.68; found C 61.78, H 6.34, N 12.65.

5-Hexyl-3-*N*-Boc-aminoethyl Carbamate Isoxazole (15d)

With Cu^{II} Salt: From **1d** (2.0 equiv.) and 1-octyne (49.0 mg) in 58 % yield (88 mg, white powder) by using NMP/$Cu(OAc)_2$ as catalyst at 60 °C for 19 h. Eluant: hexane/EtOAc = 2:1 (R_f = 0.29), m.p. 91–92 °C. $C_{17}H_{29}N_3O_4$ (339.43): calcd. C 60.15, H 8.61, N 12.38; found C 60.12, H 8.33, N 12.52. The spectroscopic data were identical to those reported below.

With Cu^0: From **1d** (2.0 equiv.) and 1-octyne (47.5 mg) in 43 % yield (62 mg, white powder) by using NMP/Cu powder as catalyst at 60 °C for 24 h. Eluant: hexane/EtOAc = 2:1 (R_f = 0.29), m.p. 89–91 °C. ^{1}H NMR ($CDCl_3$): δ = 0. 86 (t, J = 6.8 Hz, 3 H; CH_3), 1.17–1.34 (m, 6 H, 3 CH_2), 1.41 [s, 9 H, C(CH_3)$_3$], 1.67 (quint., J = 7.2 Hz, 2 H; CH_2), 2.75 (t, J = 7.6 Hz, 2 H; C-5CH_2), 3.27–3.38 (m, 2 H, CH_2N), 3.48–3.56 (m, 2 H, CH_2N), 4.88 (br. s, 1 H; NH), 6.38 (s; 4-H), 7.18 ppm (br. s, 1 H; NH). ^{13}C NMR ($CDCl_3$): δ = 14.0 (q; CH_3), 22.4 (t; CH_2CH$_3$), 26.6 (t; CH_2), 27.3 (t; CH_2), 28.3 (q, 3 C; 3 CH_3), 28.6 (t; CH_2), 31.3 (t; CH_2), 40.0 (t; CH_2NHCO), 40.2 (t; CH_2NHCO_2), 79.7 [s; $C(CH_3)_3$], 100.4 (d; C-4), 156.1 (s; CO_2), 158.3 (s; CO or C-3), 159.9 (s; CO or C-3), 175.5 ppm (s; C-5). MS (ESI$^+$, MeOH): m/z (%) = 362 (100) [M + Na]$^+$. IR ($CDCl_3$): $\tilde{\nu}$ = 3457 (w) [N–H], 3418 (w) [N–H], 2932 (m), 2857 (m), 1708 (s) [C=O], 1690 (s), [C=O], 1590 (w) [C=N], 1544 (m), 1506 (s), 1457 (m), 1367 (m), 1252 (m), 1165 (m) cm^{-1}. $C_{17}H_{29}N_3O_4$ (339.43): calcd. C 60.15, H 8.61, N 12.38; found C 60.22, H 8.37, N 12.59.

3-Benzoyl-5-phenylisoxazole (16e)

With Typical Amount of Catalyst: From **1e** and phenylacetylene (41.7 mg) in 73 % yield (74.0 mg, white powder) by using NMP/$Cu(OAc)_2$ as catalyst at 60 °C for 18 h. The residue was dissolved in CH_2Cl_2 (10 mL), silica gel (200 mg) was added to the mixture, and the solvent was evaporated. The silica gel with the adsorbed product was loaded onto the top of a column of silica gel and purified by chromatography. Eluant: hexane/Et_2O = 1:13 (R_f = 0.24), m.p. 84–85 °C (ref.[47] 84–85 °C). $C_{16}H_{11}NO_2$ (249.26): calcd. C 77.10, H 4.45, N 5.62; found C 77.40, H 4.74, N 6.02.

With Lower Amount of Catalyst: From **1e** and phenylacetylene (44.4 mg) in 80 % yield (87.0 mg, white powder) by using NMP (0.1 equiv.)/$Cu(OAc)_2$ (0.025 equiv.) as catalyst at 60 °C for 24 h then purified as above, m.p. 84–85 °C (ref.[47] 84–85 °C). $C_{16}H_{11}NO_2$ (249.26): calcd. C 77.10, H 4.45, N 5.62; found C 76.78, H 4.26, N 5.54. The spectroscopic data of both samples were identical to those previously reported.[47]

3-Benzoyl-5-hexylisoxazole (17e): From **1e** and 1-octyne (46.6 mg) in 73 % yield (79 mg, clear oil) by using NMP/$Cu(OAc)_2$ as catalyst at 60 °C for 24 h. Eluant: hexane/EtOAc = 20:1 (R_f = 0.60). ^{1}H NMR ($CDCl_3$): δ = 0.88 (t, J = 7.4 Hz, 3 H; CH_3), 1.21–1.45 (m, 6 H, 3 CH_2), 1. 73 (quint., J = 7.2 Hz, 2 H; CH_2), 2.81 (t, J = 7.6 Hz, 2 H; CH_2C-5), 6.50 (s, 4-H), 7.44–7.52 (m, 1 H, Ph-H_{para}), 7.56–7.64 (m, 2 H, Ph-H_{meta}), 8.24–8.30 ppm (m, 2 H, COPh-H_{ortho}). ^{13}C NMR ($CDCl_3$): δ = 14.0 (q; CH_3), 22.4 (t; CH_2CH$_3$), 26.6 (t; CH_2), 27.4 (t; CH_2), 28.7 (t; CH_2), 31.3 (t; CH_2), 101.5 (d; C-4), 128.5 (d; 2 C, Ph-C_{meta}), 130.6 (d; 2 C, Ph-C_{ortho}), 133.8 (d, Ph-C_{para}), 135.7 (s; Ph-C_{ipso}), 161.8 (s; C-3), 174.7 (s; C-5), 186.1 ppm (s; COPh). MS (ESI$^+$, MeOH): m/z (%) = 280 (100) [M + Na]$^+$. IR ($CDCl_3$): $\tilde{\nu}$ = 3064 (w) [=C–H], 2956 (s) [C–H], 2932 (s) [C–H], 2860 (m) [C–H], 1662 (s) [C=O], 1599 (m), 1579 (m), 1455 (s), 1281 (w), 1251 (m), 1217 (m), 1182 (w) cm^{-1}. $C_{16}H_{19}NO_2$ (257.33): calcd. C 74.68, H 7.44, N 5.44; found C 74.31, H 7.39, N 5.00.

3-Benzoyl-5-(3-cyanopropyl)isoxazole (18e)

With Typical Amount of Catalyst: From **1e** and hex-5-ynenitrile (40.0 mg) in 56 % yield (58.0 mg, clear oil) by using NMP/$Cu(OAc)_2$ as catalyst at 60 °C for 24 h. Eluant: hexane/EtOAc = 1:4 (R_f = 0.15). After chromatography, isolated **18e** was further washed with hexane. ^{1}H NMR ($CDCl_3$): δ = 2.06–2.16 (m, 2 H, CH_2), 2.46 (t, J = 7.2 Hz, 2 H; CH_2C-5), 3.03 (t, J = 7.2 Hz, 2 H; CH_2CN), 6.59 (s; 4-H), 7.50 (t, J = 7.6 Hz, 2 H; Ph-H_{meta}), 7.63 (t, J = 7.6 Hz, 1 H; Ph-H_{para}), 8.24–8.30 ppm (m, 2 H, COPh-H_{ortho}). ^{13}C NMR ($CDCl_3$): δ = 16.2 (t; CH_2), 23.3 (t; CH_2), 25.4 (t; CH_2), 102.7 (d; C-4), 118.4 (s; CN), 128.6 (d, 2 C; Ph-C_{meta}), 130.6 (d, 2 C; Ph-C_{ortho}), 134.0 (d; Ph-C_{para}), 135.6 (s; Ph-C_{ipso}), 162.0 (s; C-3), 171.6 (s; C-5), 185.6 ppm (s; COPh). MS (ESI$^+$, MeOH): m/z (%) = 263 (100) [M + Na]$^+$. IR ($CDCl_3$): $\tilde{\nu}$ = 3142 (w) [=C–H], 3072 (w) [=C–H], 2956 (w) [C–H], 2250 (m) [C≡N], 1662 (s) [C=O], 1599 (s), 1579 (W), 1456 (s), 1428 (W), 1257 (m), 1218 (m)

1182(m) cm^{-1}. $C_{14}H_{12}N_2O_2$ (240.26): calcd. C 69.99, H 5.03, N 11.66; found C 69.72, H 4.99, N 11.44.

With Lower Amount of Catalyst: From **1d** and hex-5-ynenitrile (40.3 mg) in 85 % yield (88.1 mg, clear oil) by using NMP (0.1 equiv.)/$Cu(OAc)_2$ (0.025 equiv.) as catalyst at 60 °C for 24 h then purified as above. $C_{14}H_{12}N_2O_2$ (240.26): calcd. C 69.99, H 5.03, N 11.66; found C 69.70, H 4.84, N 11.91. The spectroscopic data of both samples were identical to those previously reported.

3-Benzoyl-5-cyclopropylisoxazole (19e): From **1e** and cyclopropylacetylene (30.0 mg) in 70 % yield (67.0 mg, clear oil) by using NMP/$Cu(OAc)_2$ as catalyst at 60 °C for 24 h. Eluant: hexane/ EtOAc = 20:1 (R_f = 0.21). ^1H NMR ($CDCl_3$): δ = 0.99–1.05 (m, 2 H, CH_2), 1.09–1.16 (m, 2 H, CH_2), 2.05–2.16 (m, 1 H, $CHCH_2$), 6.40 (s; 4-H), 7.44–7.52 (m, 2 H, Ph-H_{meta}), 7.56–7.64 (m, 1 H, Ph-H_{para}), 8.24–8.30 ppm (m, 2 H, COPh-H_{ortho}). ^{13}C NMR ($CDCl_3$): δ = 8.04 (d; CH), 8.78 (t, 2 C; CH_2), 99.4 (d, C-4), 128.5 (d, 2 C; Ph-C_{meta}), 130.6 (d, 2 C; Ph-C_{ortho}), 133.9 (d; Ph-C_{para}), 135.7 (s; Ph-C_{ipso}), 161.9 (s; C-3), 175.9 (s; C-5), 186.1 ppm (s; COPh). MS (ESI^+, MeOH): *m/z* (%) = 236 (100) $[M + Na]^+$. IR ($CDCl_3$): $\tilde{\nu}$ = 3143 (w) [=C–H], 3098 (w) [=C–H], 3072 (w) [=C–H], 3018 (w) [=C–H], 2956 (w) [C–H], 1662 (s) [C=O], 1594 (s) 1578 (m), 1456 (s), 1433 (m), 1334 (m), 1282 (m), 1256 (s), 1227 (m) 1181(m) cm^{-1}. $C_{13}H_{11}NO_2$ (213.23): calcd. C 73.23, H 5.20, N 6.57; found C 73.21, H 4.95, N 6.58.

3-Benzoyl-5-hydroxyethylisoxazole (20e): From **1e** and 3-butyn-1-ol (30.2 mg) in 58 % yield (54.0 mg, clear oil) by using NMP (0.1 equiv.)/$Cu(OAc)_2$ (0.025 equiv.) as catalyst at 60 °C for 24 h. Eluant: hexane/ EtOAc = 2:1 (R_f = 0.19). ^1H NMR ($CDCl_3$): δ = 3.10 (t, *J* = 6.0 Hz, 2 H; CH_2C-5), 3.97–4.10 (m, 2 H, CH_2OH), 6.64 (s; 4-H), 7.50 (t, *J* = 7.6 Hz, 2 H; Ph-H_{meta}), 7.62 (m, *J* = 7.6 Hz, 1 H; Ph-H_{para}), 8.24–8.30 ppm (m, 2 H, Ph-H_{ortho}). ^{13}C NMR ($CDCl_3$): δ = 30.2 (t; CH_2C-5), 60.0 (t; CH_2OH), 102.9 (d; C-4), 128.5 (d, 2 C; Ph-C_{meta}), 130.6 (d, 2 C; Ph-C_{ortho}), 134.0 (d; Ph-C_{para}), 135.8 (s; Ph-C_{ipso}), 162.0 (s; C-3), 171.6 (s; C-5), 185.9 ppm (s; COPh). MS (ESI^+, MeOH): *m/z* (%) = 240 (100) $[M + Na]^+$. IR ($CDCl_3$): $\tilde{\nu}$ = 3621 (w) [O–H), 3142 (w) [=C–H], 3072 (w) [=C–H], 2965 (w) [C–H], 2891 (m) [C–H], 1663 (s) [C=O], 1599 (s), 1579 (w), 1455 (s), 1428 (w), 1263 (m), 1219 (m) 1182 (m), 1046 (m) cm^{-1}. $C_{12}H_{11}NO_3$ (217.22): calcd. C 66.35, H 5.10, N 6.45; found C 66.76, H 4.80, N 6.90.

Diethyl (5-Hexylisoxazol-3-yl)phosphonate (21f): From **1f** (2.0 equiv.) and 1-octyne (48 mg) in 49 % yield (62 mg, yellowish oil) by using NMP/$Cu(OAc)_2$ as catalyst at 60 °C for 72 h. Eluant: hexane/EtOAc = 2:1 (R_f = 0.27). ^1H NMR ($CDCl_3$): δ = 0.85–0.93 (m, 3 H, CH_3), 1.22–1.40 (m, 6 H, 3 CH_2), 1.35 (t, *J* = 7.2 Hz, 6 H; 2 OCH_2CH_3), 1.62–1.74 (m, 2 H, CH_2), 2.78 (t, *J* = 7.6 Hz, 2 H; CH_2C-5), 4.16–4.28 (m, 4 H, 2 OCH_2CH_3), 6.27 ppm (s, 1 H, 4-H). ^{13}C NMR ($CDCl_3$): δ = 14.0 (q; CH_3), 16.2 (t, ^3J = 6.4 Hz, 2 C; OCH_2CH_3), 22.4 (t; CH_2), 26.5 (t; CH_2), 27.4 (d; CH_2), 28.7 (t; CH_2 C-5), 31.3 (t; CH_2), 63.5 (t, $^2J_{C,P}$ = 5.8 Hz, 2 C; OCH_2), 103.2 (d, $^2J_{C,P}$ = 21.2 Hz; C-4), 156.5 (s, $^1J_{C,P}$ = 212 Hz; C-3), 174.6 ppm (s, $^3J_{C,P}$ = 10.5 Hz; C-5). ^{31}P NMR ($CDCl_3$): δ = 5.19 ppm. MS (ESI^+, MeOH): *m/z* (%) = 601 (100) $[2M + Na]^+$, 312 (20) $[M + Na]^+$. IR ($CDCl_3$): $\tilde{\nu}$ = 2931 (m), 2861 (w), 1581 (w), 1426 (m), 1394 (w), 1256 (s) [P=O], 1026 (s) cm^{-1}. $C_{13}H_{24}NO_4P$ (289.31): calcd. C 53.97, H 8.36, N 4.84; found C 54.16, H 8.42, N 4.72.

3-Methyl-5-phenylisoxazole (22g): From **1g** and phenylacetylene (43.8 mg) in 33 % yield (22.4 mg, white powder) by using NMP (1.0 equiv.)/$Cu(OAc)_2$ (0.05 equiv.) as catalyst at 60 °C for 96 h. Eluant: hexane/EtOAc = 40:1 (R_f = 0.15). The isolated product contained a trace amount of isoxazole **22'h** [less than 5 %, detected by ^1H NMR spectroscopy: δ= 2.40 (s, CH_3), 8.42 ppm (s, 5-H)]. 1,4-Diphenylbuta-1,3-diyne (**30**) was also isolated (6 mg, 14 %, R_f = 0.70, see below for spectroscopic data), m.p. 64–65 °C (ref.[65] 66–67 °C). ^1H NMR ($CDCl_3$): δ = 2.33 (s, 3 H, CH_3), 6.34 (s; 4-H), 7.37–7.48 (m, 3 H, Ph-H), 7.69–7.75 ppm (m, 2 H, Ph-*H*). ^{13}C NMR ($CDCl_3$): δ = 11.5 (q; CH_3), 100.1 (d; C-4), 125.7 (d, 2 C; Ph-*C*), 127.7 (s; Ph-C_{ipso}), 128.8 (d, 2 C; Ph-*C*), 129.9 (d; Ph-*C*), 160.3 (s; C-3), 169.7 ppm (s; C-5). MS (ESI^+, MeOH): *m/z* (%) = 160 (100) $[M + H]^+$. IR ($CDCl_3$): $\tilde{\nu}$ = 3072 (w) [=C–H], 2933 (w) [C–H], 2860 (w) [C–H], 1618 (m), 1594 (m), 1576 (m), 1471 (m), 1455 (s), 1413 (s), 1373 (w), 1260 (w) cm^{-1}. $C_{10}H_9NO$ (159.18): calcd. C 75.45, H 5.70, N 8.80; found C 75.43, H 5.72, N 8.96.

3-Butyl-5-phenylisoxazole (23h): From **1h** and phenylacetylene (43.8 mg) in 39 % yield (33.6 mg, melting solid) by using NMP (1.0 equiv.)/copper powder (0.05 equiv.) as catalyst at 60 °C for 96 h. Eluant: hexane/EtOAc = 35:1 (R_f = 0.30). The isolated product contained a trace amount of isoxazole **23'h** [less than 5 %, detected by ^1H NMR spectroscopy: δ = 8.37 ppm (5-H)]. 1,4-Diphenylbuta-1,3-diyne (**30**) was also isolated (12.2 mg, 28 %, R_f = 0.70, see below for spectroscopic data), m.p. 27–28 °C. (ref.[66] 27–28 °C). ^1H NMR (200 MHz, $CDCl_3$): δ = 0.94 (t, *J* = 7.4 Hz, 3 H; CH_3), 1.26–1.51 (m, 2 H, CH_2), 1.54–1.78 (m, 2 H, CH_2), 2.70 (t, *J* = 8.0 Hz, 2 H; CH_2C-3), 6.36 (s; 4-H), 7.27–7.49 (m, 3 H, Ph-H), 7.59–7.80 ppm (m, 2 H, Ph-H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.9 (q; CH_3), 22.3 (t; CH_2), 25.8 (t; CH_2), 30.5 (t; CH_2), 99.1 (d; C-4), 125.8 (d, 2 C; Ph-C_{meta}), 128.2 (s; Ph-C_{ipso}), 128.9 (d, 2 C; Ph-C_{ortho}), 129.9 (d; Ph-C_{para}), 164.7 (s; C-3), 169.5 ppm (s; C-5). MS (ESI^+, MeOH): *m/z* (%) = 202 (100) $[M + H]^+$. IR ($CDCl_3$): $\tilde{\nu}$ = 3068 (w) [=C–H], 2960 (w) [C–H], 2933 (w) [C–H], 2874 (w) [C–H], 2864 (w)[C–H], 1616 (m), 1593 (m), 1576 (m), 1466 (m), 1451 (s), 1420 (m), 913 (w), 844 (w), 748 (w) cm^{-1}. $C_{13}H_{15}NO$ (201.26): calcd. C 77.58, H 7.51, N 6.96; found C 77.24, H 7.20, N 6.95. The reaction repeated with the use of TMEDA (1 equiv.) instead of NMP gave **23h** in 50 % yield and **30** in 6 % yield (Table 3).

3-Aminoethyl-5-phenylisoxazole Hydrochloride (24): Boc-amine **14d** (20.1 mg, 0.0607 mmol) was dissolved in MeOH (0.5 mL), and the solution was cooled with ice. 6 M HCl (1 mL) was added dropwise. After stirring for 16 h at room temperature, the mixture was concentrated and the solid residue was triturated with diethyl ether and carefully dried under high vacuum to give product **24** as a white powder (16.0 mg, 98 %), m.p. 245–250 °C (dec.). ^1H NMR (CD_3OD): δ = 3.22 (t, *J* = 6.2 Hz, 2 H; CH_2NCO), 3.73 (t, *J* = 6.2 Hz, 2 H; $CH_2NH_3^+$), 7.16 (s; 4-H), 7.52–7.60 (m, 3 H, Ph-H), 7.89–7.94 ppm (m, 2 H, Ph-H). ^{13}C NMR (CD_3OD): δ = 38.2 (t; $CH_2NH_3^+$), 40.9 (t; CH_2NHCO), 100.0 (d; C-4), 126.9 (d, 2 C; Ph-*C*), 128.1 (s; Ph-C_{ipso}), 130.4 (d, 2 C; Ph-*C*), 132.0 (d; Ph-*C*), 160.3 (s; CO or C-3), 162.4 (s; CO or C-3), 173.0 ppm (s; C-5). MS (ESI^+, MeOH): *m/z* (%) = 232 (100) $[M + H]^+$, 254 (16) $[M + Na]^+$, 463 (20) $[2M + H]^+$, 485 (32) $[2M + Na]^+$. IR (KBr): $\tilde{\nu}$ = 3550–2500 (br.), 3319 (m), 3090 (m)], 1678 (s) [C=O], 1591 (m), 1562 (s), 1494 (s), 1454 (s), 1263 (m), 1170 (m). $C_{12}H_{13}N_3O_2$•HCl (267.72): calcd. C 53.84, H 5.27, N 15.70; found C 53.74, H 5.02, N 15.45.

***N*-(2-Aminoethyl)-5-hexylisoxazole-3-carboxamide Hydrochloride (25):** The same procedure as that reported for **24** was applied to Boc-amine **15d** (20.0 mg) to afford product **25** (16 mg, 98 %) as a white powder, m.p. 154–167 °C (dec.). ^1H NMR ($CD_3OD/CDCl_3$ = 3:1): δ = 0. 88 (t, *J* = 6.8 Hz, 3 H; CH_3), 1.27–1.42 (m, 6 H, 3 CH_2), 1.65–1.75 (m, 2 H, CH_2), 2.80 (t, *J* = 7.6 Hz, 2 H; C-5CH_2), 3.13 (t, *J* = 5.8 Hz, 2 H; CH_2NHCO), 3.64 (t, *J* = 5.8 Hz, 2 H; $CH_2NH_3^+$), 6.45 ppm (s; 4-H). ^{13}C NMR ($CD_3OD/CDCl_3$ = 3:1): δ = 14.3 (q; CH_3), 23.2 (t; CH_2CH_3), 27.2 (t; CH_2), 28.1 (t; CH_2), 29.3 (t; CH_2), 32.1 (t; CH_2), 37.8 (t; $CH_2NH_3^+$), 40.3 (t; CH_2NHCO), 100.9 (d; C-4), 158.9 (s; CO or C-3), 162.2 (s; C-3 or CO), 176.7 ppm (s; C-5). MS (ESI^+, MeOH): *m/z* (%) = 240 (100) $[M + H]^+$, 252 (22) $[M + Na]^+$. IR (KBr): $\tilde{\nu}$ = 3283 (m), 2955 (m) [C–H], 2926 (m) [C–H], 2858 (m) [C–H], 1666 (s) [C=O], 1599

(w) [C=N], 1550 (s), 1520 (m), 1450 (m), 1254 (w), 1169 cm^{-1} (m). $C_{12}H_{22}ClN_3O_2$ (275.77): calcd. C 52.26, H 8.04, N 15.24; found C 52.55, H 8.27, N 15.44.

General Procedure for the Reaction of Benzoylnitromethane with Phenylacetylene: Chloroform (2086 mg, 1.40 mL) was added to the catalyst, benzoylnitromethane (1.05 mmol), and the alkyne (0.424 mmol), and then the mixture was maintained at the indicated temperature whilst stirring in a sealed tube. After the indicated time, the mixture was washed with water (2 2 mL), dried with Na_2SO_4, and then an internal standard (3,4-dimethoxyacetophenone, 24–26 mg) was added. The mixture was concentrated under reduced pressure, and a portion was dissolved in $CDCl_3$ and the ^1H NMR spectrum was registered. Integrating the signal for $COCH_3$ [δ = 2.56 ppm (s)] of the internal standard, the signal for 4-H [δ = 7.04 ppm (s)] of isoxazole **16e**, and the signal for CH_2COPh [δ = 4.84 ppm (s)] of furazan **29** gave the spectroscopic yields (Table 2).

Behavior of Methyl Propiolate in the Presence of NMP: Deuteriochloroform (1.4 mL) was added to methyl propiolate (35.6 mg, 0.424 mmol) and NMP (8.4 mg, 0.084 mmol), and then the dark mixture was maintained at room temperature whilst stirring in a sealed tube controlling the progress of reaction by NMR spectroscopy. After 5 min, the ^1H NMR spectrum showed the complete conversion of methyl propiolate into dimethyl (*E*)-hex-2-en-4-ynedioate. ^1H NMR (200 MHz, $CDCl_3$): δ = 3.77 (s, 3 H, OCH_3), 3.81 (s, 3 H, OCH_3), 6.45 and 7.77 ppm (ABq, *J* = 16 Hz, 2 H; *CH*=CH and *CH*=CH). GC–MS (EI): *m/z* (%) = 168 (16) $[M]^+$, 137 (99) $[M - OMe]^+$, 109 (20) $[M - CO_2Me]^+$, 77 (100) $[C_6H_5]^+$. ^1H NMR spectrum was identical to that previously reported.[67]

General Procedure to Determine the Behavior of Alkynes in the Presence of [Cu]/Base System: Chloroform (2086 mg, 1.40 mL) was added to the catalyst, the nitro compound (if used), and the alkyne (0.418–0.424 mmol), and then the mixture was maintained at 60 °C whilst stirring in a sealed tube. After the indicated time, the solvent was removed and the crude residue was purified by column chromatography on silica gel (with the indicated eluant). Experiments under an atmosphere of argon (Table 3, entries 3, 9, 14, 15) were conducted with degassed chloroform.

1,4-Diphenylbuta-1,3-diyne (30): From phenylacetylene (43.7 mg) in 9 % yield (3.7 mg, white solid) by using NMP/$Cu(OAc)_2$ as catalyst for 24 h (Table 3, entry 4). Eluant: hexane (R_f = 0.30), m.p. 85–86 °C (ref.[68] 82–84 °C). See below for spectroscopic data.

Hexadeca-7,9-diyne (31): From 1-octyne (46.1 mg) in 29 % yield (13.1 mg, clear oil) by using DABCO/$Cu(OAc)_2$ as catalyst for 24 h. Eluant: hexane/EtOAc = 4:1 (R_f = 0.83). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.0 (q, 2 C; 2 CH_3), 19.2 (t, 2 C; 2 CH_2), 22.5 (t, 2 C; 2 CH_2), 28.4 (t, 2 C; 2 CH_2), 28.5 (t, 2 C; 2 CH_2), 31.3 (t, 2 C; 2 CH_2), 65.4 (s, 2 C; 2 C≡C-CH_2), 77.5 ppm (s, 2 C; 2 C≡*C*-CH_2).

1,6-Di(pyrrolidin-1-yl)hexa-2,4-diyne-1,6-dione (32): From 1-(pyrrolidin-1-yl)prop-2-yn-1-one (52.2 mg) in 12 % yield (6.4 mg, white solid) by using NMP/$Cu(OAc)_2$ as catalyst for 24 h. Recovered 21.7 mg of 1-(pyrrolidin-1-yl)prop-2-yn-1-one (R_f = 0.40). Eluant: hexane/EtOAc = 1:1 then hexane/EtOAc = 1:2 (R_f = 0.22), m.p. 105 °C (dec.). ^1H NMR ($CDCl_3$): δ = 1.87–2.00 (m, 4 H, 2 CH_2), 3.48 (t, *J* = 6.8 Hz, 2 H; CH_2N), 3.62 ppm (t, *J* = 6.8 Hz, 2 H; CH_2N). ^{13}C NMR ($CDCl_3$): δ = 24.5 (t; CH_2), 25.3 (t; CH_2), 45.7 (t; CH_2N), 47.9 (t; CH_2N), 71.0 (s; C≡), 74.9 (s; *C*≡), 150.4 ppm (s; *C*O). MS (ESI^+, MeOH): *m/z* (%) = 267 (100) $[M + Na]^+$.

1,4-Diphenylbuta-1,3-diyne (30): Chloroform (2236 mg, 1.5 mL) was added to nitropentane **1h** (125.8 mg, 2.5 equiv.), copper acetate (3.9 mg, 0.021 mmol), DABCO (47.1 mg. 0.420 mmol), and phenylacetylene (44 mg, 0.430 mmol), and then the mixture was maintained at 60 °C whilst stirring in a sealed tube. After 120 h, the solvent was removed and the crude residue was purified by column chromatography on silica gel (hexane/EtOAc = 35:1) to afford 1,4-diphenylbuta-1,3-diyne (**30**) (31 mg, 70 %, R_f = 0.70) (Table 3, entry 10), m.p. 85–86 °C [ref.[68] 82–84 °C (hexane)]. ^1H NMR(200 MHz, $CDCl_3$): δ = 7.26 7.40 (m, 6 H, Ph-H), 7.44–7.58 ppm (m, 4 H, Ph-H_{ortho}). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 74.0 (s, 2 C; 2 C≡*C*-C_6H_5), 81.6 (s, 2 C; 2 C≡*C*-C_6H_5), 121.9 (s, 2 C; 2 Ph-C_{ipso}), 128.4, (d, 4 C; 2 Ph-C_{meta}), 129.2 (d, 2 C; 2 Ph-C_{para}), 132.5 ppm (d, 4 C; 2 Ph-C_{ortho}). GC–MS (CI): *m/z* (%) = 203 (100) $[M + 1]^+$.

Supporting Information (see footnote on the first page of this article): ^1H NMR and ^{13}C NMR spectra for 1-(pyrrolidin-1-yl)prop-2-yn-1-one and compounds **2a**–**11a**, **12b**, **13c**, **14d, 15d, 16e**–**20e**, **21f**, **22g**, **23h**, **24**, **25**, and **30–32**.

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[52] Nitropropane reacted with phenylacetylene in very low yield (6 %) by using ethyl chloroformate. A better yield (31 %) was obtained by using benzenesulfonyl chloride, see ref.[26] A slightly better result (36 %) was reported with the use of di-*tert*-butyl dicarbonate, see ref.[22]
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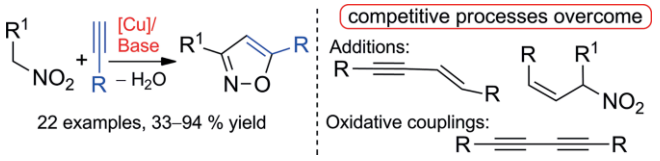
Synthetic Methods



The combination of copper with a suitable base results in a good catalyst for the condensation of nitro compounds with alkynes to isoxazoles. 3,5-Disubstituted isoxazoles bearing various functional groups including alcohols, amines, nitriles, esters, phosphates, and amides are prepared. Competitive processes of the alkynes and nitro compounds alone or in their combination are under control.

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