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Short Communication

Synergistic effect of dual-frequency ultrasound irradiation in the one-pot synthesis of 3,5-disubstituted isoxazoles

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ABSTRACT

Herein is reported a one-pot three-step process for the regioselective synthesis of 3,5-disubstituted isoxazoles based on copper(I)-catalyzed cycloaddition reaction between *in situ* generated nitrile oxides (from the corresponding aldehydes) and alkynes, using ultrasound irradiation, avoiding toxic reagents and solvents and isolation/purification of intermediates.

The combined use of 40 kHz ultrasonic bath and 20 kHz probe in the presence of copper turnings reduced reaction time to 1 h and resulted in only one final purification step with increased yields, clearly indicating that there is a dual-frequency synergistic effect.

In addition, under metal free conditions, the 1,3-dipolar cycloaddition was regioselective giving low to modest yields.

1. Introduction

Isoxazoles, a major class of five-membered nitrogen heterocycles, have been widely used as key building blocks for drugs. A number of analogues based on the isoxazole pharmacophore have been reported to exhibit a wide range of biological activities including, antiviral [1], antiapoptotic [2], antiparasitic [3] and anticancer [4] properties.

The method employed generally to prepare isoxazole derivatives is the 1,3-dipolar cycloaddition of alkynes with nitrile oxides (from the dehydrohalogenation of hydroximoyl chlorides in the presence of triethylamine). Thermal nitrile oxide–alkyne cycloadditions typically give low yields, side-reactions and poor regioselectivity [5]. Fokin and co-workers have described an elegant approach to the regioselective formation of 3,5-disubstituted isoxazoles based on "click" methodology. Copper(I) acetylides react regioselectively with nitrile oxides to generate 3,5-disubstituted isoxazoles [6]. The reaction is attractive because nitrile oxides are obtained directly from oximes, without isolation and handling of potentially harmful and unstable hydroximoyl chlorides, while chloramine-T as dipole generating agent is compatible with biological systems [7]. Moreover, the *in situ* generation of the highly reactive nitrile oxides avoids dimerization from the corresponding hydroximoyl chlorides [8].

We have recently reported the synthesis of isoxazole substituted chromans of high neuroprotective activity, using the copper(I)-catalyzed cycloaddition reaction between *in situ* generated nitrile oxides and terminal acetylenes. In this paper, the aldehydes were reacted with hydroxylamine in the presence of pyridine and the corresponding aldoximes were isolated [9].

Herein we report our efforts towards the one-pot synthesis of isoxazoles from *in situ* generated nitrile oxides (from the corresponding aldehydes) and alkynes using ultrasound irradiation. Ultrasound (US) activation has emerged as a powerful technique to enhance reaction rates of a variety of chemical transformations while ultrasound reactions using green catalysts such as copper are attractive in the growing field of green and more sustainable chemistry.

Ultrasound has been successfully employed as non-conventional technique, to promote 1,3-dipolar cycloadditions [10]. The synthesis of 1,2,3-triazoles, performed in a common US cleaning bath, was first described in 2007 [11]. Recently, an ultrasound-assisted methodology for the synthesis of chrysin derivatives linked with 1,2,3-triazoles, using *t*-BuOH/H_2O (1:1 v/v) as reaction solvents and $CuSO_4 \cdot 5H_2O$/sodium ascorbate as the catalyst, was reported for which a 40 kHz ultrasonic bath was employed. The ultrasound irradiation accelerated greatly the reaction rate and enhanced the yields [12]. Additionally, sonication and iron/copper catalysis improved rates and yields of modified 1,2,3-triazole nucleosides using a sequential one-pot acetylation-azidation-cycloaddition procedure in a 40 kHz ultrasonic bath [13]. To our knowledge, the one-pot synthesis of isoxazoles from aldehydes and alkynes using ultrasound irradiation has not yet been reported.

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2. Experimental

2.1. Material and methods

All starting materials and common laboratory chemicals were purchased from commercial sources and used without further purification. ^{1}H NMR spectra were recorded on Varian spectrometers operating at 300 MHz or 600 MHz and ^{13}C spectra were recorded at 75 MHz using $CDCl_3$ as solvent. Silica gel plates Macherey–Nagel Sil G-25 UV_{254} were used for thin layer chromatography. Chromatographic purification was performed with silica gel (200–400 mesh). Mass spectra were obtained on HPLC–MS^n Fleet-Thermo, in the ESI mode. HRMS spectra were recorded, in the ESI mode, on UPLC-MS^n Orbitrap Velos-Thermo.The ultrasound-assisted reactions were carried out in a FALC INSTRUMENTS s.r.l, bath cleaner LBS2, 4.5 Lt, (40 kHz, 59 kHz, 250 W) and a Sonics & Material INC. Vibra-Cell VCX130 Titanium alloy Ti-6Al-4 V probe (20 kHz, 130 W) with 2 mm tip diameter. The reaction tube was located in the maximum energy area in the bath and the temperature was 60 °C. When combined ultrasound experiments were performed, the probe was immerged in the tube, which was placed in the ultrasonic bath (Fig. 1).

2.2. General procedure for preparation of 3,5-disubstituted isoxazoles

To a solution of aldehyde (1 eq) and hydroxylamine hydrochloride (1.05 eq) in a mixture of *t*-BuOH and H_2O (1:1) was added 1 M aqueous NaOH (1.05 eq). The reaction mixture was stirred at ambient temperature until thin-layer chromatography indicated consumption of the aldehyde. After oxime formation was complete, 1.05 eq of chloramine-T [*N*-chloro-4-methylbenzenesulfonamide sodium salt, TsN(Cl)Na·$3H_2O$], was added, followed by $CuSO_4$·$5H_2O$ (0.3 eq)/sodium ascorbate (0.6 eq) or $CuSO_4$·$5H_2O$ (0.3 eq)/Cu turnings (0.6 eq) or Cu turnings (0.6 eq). Terminal alkyne (1.05 eq) was then added, the pH of the reaction medium was adjusted to 6 by addition of few drops of 1 M aqueous NaOH and the mixture was stirred/heated or irradiated with US as indicated in the Table 1. The reaction mixture was poured into ice/water and after addition of 1 M aqueous NH_4OH (1 ml), (to remove all copper salts), it was extracted with AcOEt. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue was purified by column chromatography (pet. ether/ethyl acetate, 90:10).

Fig. 1. Experimental system (bath + probe).

When only copper turnings were used, copper was filtered off, the solvent was evaporated *in vacuo* and the crude product was purified by column chromatography.

2.2.1. 3-(4-Methoxyphenyl)-5-phenyl-isoxazole [14]

White solid. TLC (pet. ether/ethyl acetate, 90:10) R_f = 0.5, ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.83–7.80 (m, 4H, Ar*H*), 7.48–7.44 (m, 3H, Ar*H*), 6.99 (d, *J* = 8.7 Hz, 2H, Ar*H*), 6.77 (s, 1H, *H*-isoxazole), 3.86 (s, 1H, OCH_3), ^{13}C NMR (75 MHz, $CDCl_3$) δ: 170.1, 162.6, 161.0, 130.1,129.0, 128.2, 127.5, 125.8, 121.6, 114.3, 97.3, 55.4, MS m/z: 524.60 (2 M + Na)$^+$.

2.2.2. 3-(4-Methoxyphenyl)-5-propyl-isoxazole [15]

Yellowish oil, TLC (pet. ether/ethyl acetate, 90:10) R_f = 0.6, ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.73 (d, *J* = 8.8 Hz, 2H, Ar*H*), 6.96 (d, *J* = 8.8 Hz, 2H, Ar*H*), 6.23 (s, 1H, *H*-isoxazole), 3.85 (s, 1H, OCH_3), 2.75 (t, *J* = 7.5 Hz, 2H, $CH_3CH_2CH_2$-), 1.83–1.71 (m, 2H, $CH_3CH_2CH_2$-), 1.02 (t, *J* = 7.4 Hz, 3H, $CH_3CH_2CH_2$-), ^{13}C NMR (75 MHz, $CDCl_3$) δ: 173.8, 161.9, 160.8, 128.1, 121.9, 114.2, 98.6, 55.3, 28.7, 21.0, 13.7, MS m/z: 218.11 (M + H)$^+$, 456.62 (2 M + Na)$^+$.

2.2.3. 3-(4-Fluorophenyl)-5-phenylisoxazole [16]

White solid, TLC (pet. ether/ethyl acetate, 90:10) R_f = 0.5, ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.86–7.82 (m, 4H, Ar*H*), 7.50–7.45 (m, 3H, Ar*H*), 7.16 (t, *J* = 8.6 Hz, 2H, Ar*H*), 6.78 (s, 1H, *H*-isoxazole), ^{13}C NMR (75 MHz, $CDCl_3$) δ: 170.6, 165.5, 162.0, 130.3, 129.0, 128.7, 127.3, 125.8, 116.2, 115.9, 97.3, MS m/z: 240.08 (M + H)$^+$.

2.2.4. 5-{[(3,4-Dihydro-6-methoxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)methoxy] methyl-3-(4-methoxyphenyl)-isoxazole [9]

Yellowish oil, TLC (pet. ether/ethyl acetate, 90:10) R_f = 0.3, ^{1}H NMR (600 MHz, $CDCl_3$) δ: δ: 7.72 (d, *J* = 8.7 Hz, 2H, Ar*H*), 6.96 (d, *J* = 8.7 Hz, 2H, Ar*H*), 6.47 (s, 1H, *H*-isoxazole), 4.76–4.70 (m, 2H), 3.84 (s, 3H, OCH_3), 3.62 (s, 3H, OCH_3), 3.63–3.55 (m, 2H), 2.60 (t, *J* = 6.8 Hz, 2H), 2.18 (s, 3H), 2.13 (s, 3H), 2.09 (s, 3H), 2.04–1.98 (m, 1H), 1.79–1.75 (m, 1H), 1.30 (s, 3H), ^{13}C NMR (75 MHz, $CDCl_3$) δ: 169.7, 161.9, 161.0, 149.7, 147.3, 128.2, 128.0, 125.9, 122.8, 121.4, 117.5, 114.3,114.2, 100.7, 74.9, 64.6, 60.4, 55.3, 28.3, 22.1, 20.2, 12.6, 11.9, 11.7 MS m/z: 438.10 (M + H)$^+$, 460.25 (M + Na)$^+$, 896.67 (2 M + Na)$^+$.

2.2.5. 5-{[(3,4-Dihydro-6-methoxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)methoxy] methyl-3-(3,4-dimethoxyphenyl)-isoxazole

Colorless oil, TLC (pet. ether/ethyl acetate, 90:10) R_f = 0.2, ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.40 (s, 1H, Ar*H*), 7.72 (dd, 1H, Ar*H*), 6.91 (d, *J* = 8.3 Hz, 1H, Ar*H*), 6.48 (s, 1H, *H*-isoxazole), 4.76–4.68 (m, 2H), 3.94 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 3.61 (s, 3H, OCH_3), 3.62–3.55 (dd, 2H), 2.59 (t, *J* = 6.8 Hz, 2H), 2.17 (s, 3H), 2.12 (s, 3H), 2.08 (s, 3H), 2.01–1.97 (m, 1H), 1.78–1.76 (m, 1H), 1.29 (s, 3H), ^{13}C NMR (75 MHz, $CDCl_3$) δ: 169.8, 162.1, 150.6, 149.7, 149.3, 147.3, 128.0, 125.9, 122.8, 121.6, 119.9, 117.4, 111.0, 109.2, 100.7, 74.9, 64.6, 60.4, 56.0, 55.9, 28.3, 22.0, 20.2, 12.6, 11.9, 11.7, MS m/z: 468.08 (M + H)$^+$, 490.25 (M + Na)$^+$, 956.6 (2 M + Na)$^+$ HRMS: calcd for $C_{27}H_{34}NO_6$ (M + H$^+$) 468.2381; found: 468.2375.

3. Results and discussion

Initially, we investigated the 1,3-dipolar cycloaddition of highly energetic nitrile oxide to alkyne using *in situ* generation of Cu(I) moiety from $CuSO_4$·$5H_2O$ and sodium ascorbate in a mixture of *tert*-butanol/water in a ratio of 1:1. Thus, commercially available 4-methoxy-benzaldehyde reacted with hydroxylamine hydrochlo-

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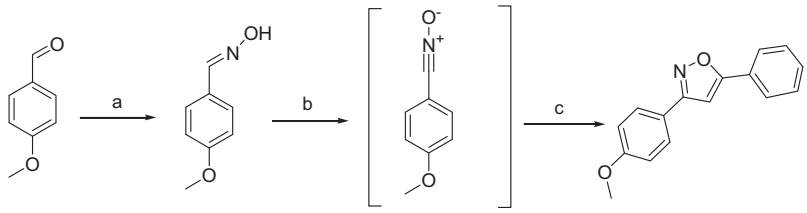

Scheme 1. One-pot isoxazole synthesis. *Reagents and Conditions:* a: $NH_2OH{\cdot}HCl$, *t*-BuOH:H_2O (1:1), NaOH 1 N, rt, b: chloramine-T [TsN(Cl)Na·$3H_2O$], rt, c: $CuSO_4{\cdot}5H_2O$/Sodium ascorbate or $CuSO_4{\cdot}5H_2O$/Cu turnings or Cu turnings, phenylacetylene, US irradiation.

Table 1
Reaction conditions for the synthesis of 3-(4-methoxyphenyl)-5-phenyl-isoxazole.[a]

Entry	Catalyst	Method	Time	Yield (%)[b]
1	a	Room temperature	24 h	45
2	a	Convent. Heat. 90 °C	24 h	55
3	a	US bath	30 min	43
4	a	US probe	30 min	53
5	a	US bath + probe	30 min	60
6	b	Room temperature	24 h	50
7	b	US probe	30 min	60
8	b	US bath + probe	30 min	70
9	c	Room temperature	3 days	65
10	c	Convent. Heat. 60 °C	60 min	58
11	c	US bath	60 min	46
12	c	US bath*	60 min	42
13	c	US probe	60 min	58
14	c	US bath* + probe	30 min	42
15	c	US bath + probe	30 min	59
16	c	US bath + probe	45 min	61
17	c	US bath + probe	60 min	75
18	c	US bath + probe	120 min	51

The temperature in all the ultrasonic experiments was 60 °C.
US bath: Freq. 40 kHz, Power 100%, US bath*: Freq. 59 kHz, Power 100%,
US probe: 20 kHz, 130 W, Ampl. 80%.
[a] Solvent: *t*-BuOH:H_2O (1:1), (a) $CuSO_4{\cdot}5H_2O$/Sodium ascorbate (0.3 eq/0.6 eq), (b) $CuSO_4{\cdot}5H_2O$/Cu turnings, (c) Cu turnings (0.6eq).
[b] Isolated yield, based on 4-methoxy-benzaldehyde.

ride in the presence of sodium hydroxide to afford the -4-methoxy-benzaldoxime which, without isolation and through reaction with chloramine-T gave *in situ* the corresponding nitrile oxide (Scheme 1). For the oxime synthesis we used $NH_2OH{\cdot}HCl$, *t*-BuOH:H_2O (1:1), NaOH 1 N (instead of pyridine) and chloramine-T as dipole generating agent avoiding toxic reagents or solvents as well as the use of *N*-chlorosuccinimide (NCS), pyridine [17] or NaOCl in chloroform. Formation of furoxan, due to the dimerization of nitrile oxide was not observed, probably because the fast generation of the arylnitrile oxide, disfavored the competitive dimerization process [18].

Since excess of nitrile oxides may cause side reactions leading to a decrease in yields of the desired products, the transient dipole was trapped with 1.05 eq of phenylacetylene (Scheme 1) and following stirring overnight at room temperature, the cycloaddition product was obtained in 45% yield. The yields are based on aldehydes. When, the reaction was carried out at 90 °C the desired product was obtained in 55% yield after 24 h. Using copper turnings and $CuSO_4{\cdot}5H_2O$ for the generation of Cu(I) and following the same procedure, 3,5-substituted isoxazole was obtained in 50% yield.

The ultrasound-assisted reactions were carried out using a bath cleaner, (40 kHz or 59 kHz) and a probe (20 kHz). The results and the conditions of the reactions under ultrasound irradiation, catalysed by $CuSO_4$/ascorbate or copper turnings/$CuSO_4$ are summarized in Table 1. Sonication under 20 kHz increased reaction rate (entries 4 and 7) whereas the yield of the reaction was further increased to 60% when an ultrasonic bath (40 kHz) and a probe (20 kHz) were used simultaneously (entries 5 and 8). It has been reported that the application of multi-frequency irradiation, can disturb and break the surface continuity of a solution more stronger, compared to the single-frequency ultrasound, thus resulting in an enhancement of mass transfer and cavitation nuclei in the solution [19].

The recent report of Cravotto et al. of a process in which metallic copper efficiently catalyzes azide-alkyne cycloadditions under US or simultaneous US/MW irradiation, prompted us to explore this methodology in nitrile oxide/alkyne cycloaddition reactions. US irradiation activates the redox process between metallic copper and Cu_2O on the metal surface generating the Cu(I) species. Moreover, metallic copper is a simple and inexpensive catalyst, which can be used in aqueous solution and easily removed [20].

Application of US in the synthesis of isoxazole from 4-methoxy-benzaldehyde and phenyl acetylene in the presence of Cu turnings significantly decreased the reaction time from 3 days to 60 min (Table 1). The reaction at 60 °C without sonication gave the desired product in 58% yield after 60 min. Using an ultrasound bath gave isoxazole with 46% yield (40 kHz) and 42% (59 kHz) after 60 min, while the yield was increased to 58% (60 min) when an ultrasound probe was employed.

The advantage of using copper turnings was that workup (addition of dilute NH_4OH to remove all copper salts, extraction with AcOEt) was not necessary. Copper was filtered off and the crude product was purified by column chromatography.

Interestingly, simultaneous use of ultrasonic bath and probe gave isoxazole with 75% yield in 60 min (entry 17). Shorter or prolonged reaction times (30, 45 and 120 min) resulted in lower yields, 59%, 61% and 51%, respectively. Moreover, the reaction yield decreased (42%) when the 59 kHz bath was used.

The data of Table 1 reveal that the use of bath (40 or 59 kHz) gives lower yields compared to classic heating (entries 10, 11 and 12), while the probe (20 kHz) gives similar yields (entries 10 and 13). The combined use of a bath 59 kHz and the probe 20 kHz gave the same yield in 30 min (entry 14) as the use of bath alone in 60 min (entry 12). Clearly, from entries 5, 8, 15, 16 and 17, there is evidence of a synergistic effect when dual-frequency ultrasound (20 and 40 kHz) is applied in this reaction.

In our experiments the *in situ* generation hydroximoyl chlorides and their conversion to nitrile oxides is very fast, followed by addition of terminal alkynes which are trapping agents to avoid the dimerization of nitrile oxides to furoxans. Although the dimerization of aryl nitrile oxides is possible at 60 °C, both NMR and MS spectra of crude mixtures (after 30 min or 60 min) indicated the presence of the isoxazole, traces of unreacted oxime, the *p*-toluenesulfonamide (Me–Ph–SO_2NH_2, common end product in the oxidation reactions with chloramine-T) and unreacted alkyne. In addition NMR spectra indicated the formation of the 3,5-isoxazole isomer.

As shown in Table 2, aromatic aldehydes with electron-deficient or electron-rich groups and aromatic or aliphatic alkynes, were converted to 3,5-disubstituted isoxazoles in good yields based on the aldehyde used. Aliphatic alkynes were less reactive than

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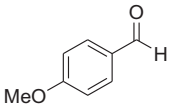
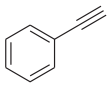
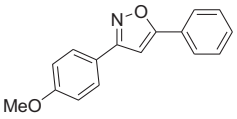
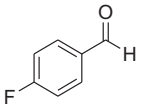
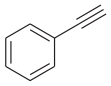
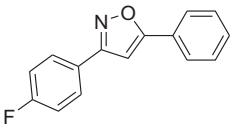
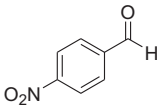
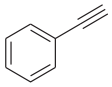
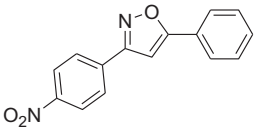
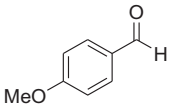
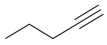
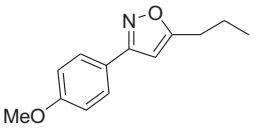
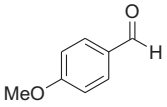
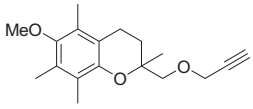
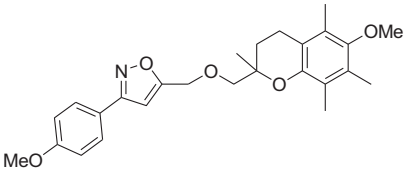
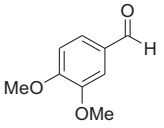
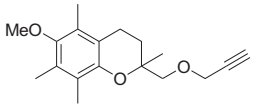
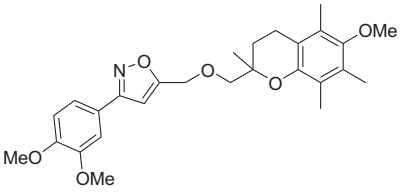
Table 2
Synthesis of isoxazoles using 40 kHz US bath and 20 kHz US probe in the presence of Cu turnings.[a]

Aldehyde	Alkyne	Isoxazole	Yield (%)
			75(58)
			52(34)
			30(9)
			30(24)
			20(8)
			35(10)

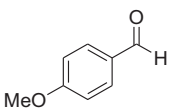
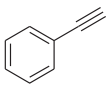
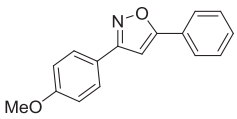
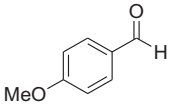
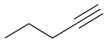
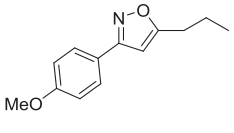
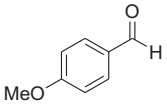
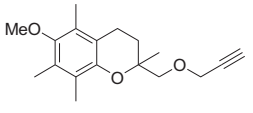
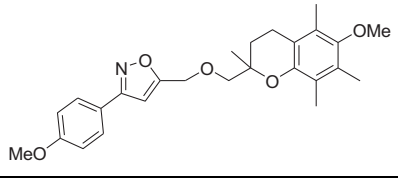
[a] In parentheses are the yields without sonication at 60 °C.

aromatic alkynes giving 30% of product. The presence of electron donating groups on the aldehydes resulted in higher yields. The yields in parentheses are without sonication. The data show that the yields significantly increase by simultaneous use of ultrasonic bath and probe.

Recently, 1,3-cycloadditions using aromatic nitrile-oxides and aliphatic alkynes without catalyst have been reported giving isoxazoles in modest to good yields [21–23]. However the formation of the 4-substituted isomer was not avoided [24]. Thus, we examined the feasibility of metal free 1,3-dipolar cycloaddition reactions for the construction of isoxazole rings, using ultrasound irradiation. The results are reported in Table 3.

The data show that using ultrasound bath and probe simultaneously in the absence of copper catalyst gave isoxazoles

Table 3
Metal free synthesis of isoxazoles.

Aldehyde	Alkyne	Isoxazole	Yield (%)
			61
			40
			18

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with low to modest yields. Interestingly, under metal free conditions, aliphatic alkynes gave better yields than using Cu turnings. Moreover, formation of 4-substituted isomer was not detected.

4. Conclusions

In summary, we have developed an effective procedure for the one pot synthesis of derivatives bearing the isoxazole pharmacophore avoiding toxic reagents and solvents, isolation/purification of intermediates and workups. The method is based on the use of ultrasound irradiation and copper turnings for 1,3-dipolar cycloaddition of different aromatic nitrile oxides to functionalized acetylenes. The synergistic effect of the combined use of 40 kHz ultrasonic bath and 20 kHz probe reduced reaction time to 1 h, resulted in only one final purification step and increased yields.In addition, under metal free conditions, the 1,3-dipolar cycloaddition was regioselective giving modest yields.

A potential application of the method is the rapid synthesis of resveratrol or combretastatin derivatives, in which the olefinic bridge is replaced by five-membered heterocyclic rings such as isoxazoles [25–27].

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