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Facile consecutive three-component synthesis of 3,5-disubstituted isoxazoles

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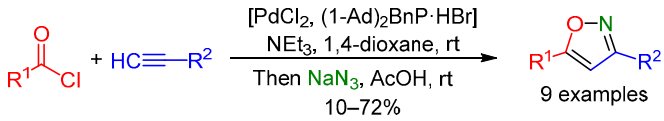


3,5-Di(hetero)aryl-substituted isoxazoles can be rapidly synthesized in a one-pot fashion by a consecutive three-component alkynylation–cyclization sequence starting from (hetero)aroyl chloride, alkynes, and sodium azide/acetic acid under copper-free palladium catalysis as exemplified by 9 different products.

Keywords: alkynes, isoxazoles, azidation, copper-free alkynylation, cyclization, multicomponent reactions.

Isoxazole is a constitutional isomer of oxazole and despite the general importance of isoxazoles in various applications that have been reviewed[1–3] its core structure is relatively seldom found in nature. Ibotenate, an α-amino acid, and its biogenic amine, muscimol (Fig. 1), naturally occur in *Amanita muscaria*, the fly agaric, and the latter represents the principal psychoactive constituent of this mushroom. As a conformationally fixed analog of γ-amino-butyric acid (GABA) muscimol acts as an agonist for $GABA_A$ receptors, displaying powerful neurotoxicity ranging from sedative-hypnotic to hallucinogenic effects.[4–7] Despite its rare occurrence in natural products isoxazole motif is found in many biologically active compounds, which are used as pharmaceuticals,[8] e.g., the antibiotic sulfamethoxazole, the nonsteroidal anti-inflammatory drug isoxicam, and immunosuppressive drug leflunomide.[9] An API containing a 3,5-diaryl-substituted isoxazole moiety as a side chain of echinocandin-derived cyclic lipopeptide is the antifungal drug micafungin (Mycamine®) against *Candida*- and *Aspergillus*-caused dermatomycosis. In fact, the anti-mycotic effect and toxicity are determined by the 3,5-diaryl-isoxazole motif.[10–12] As a consequence of the relevance of biologically active isoxazoles and their application in organic synthesis and natural product synthesis[13,14] the development of isoxazole syntheses has remained unabatedly important and numerous approaches evolved.[1–3,15,16]

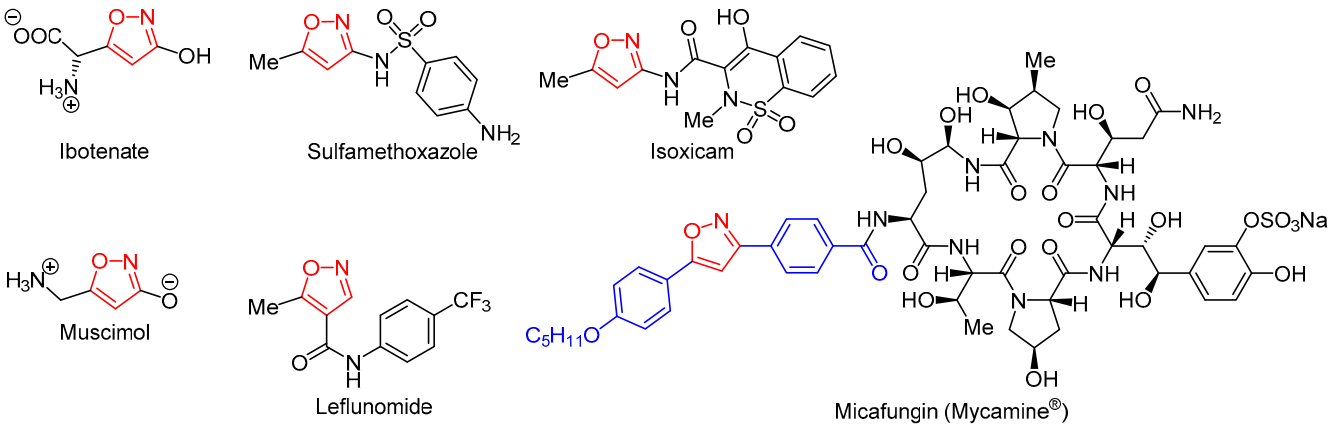


Figure 1. Naturally occurring isoxazoles (ibotenate and muscimol) and isoxazole derivatives as pharmaceuticals (sulfamethoxazole, isoxicam, leflunomide, micafungin).

In the past decade, we have conceptualized consecutive multicomponent syntheses of heterocycles based upon the catalytic formation of alkynones as central intermediates.[17–20] In particular, modified conditions of the Sonogashira alkynylation employing only one stoichiometrically necessary equivalent of NEt_3 enabled a straightforward access to alkynones under mild reaction conditions.[21,22] For accessing isoxazoles, we also employed alkynones, however, not as Michael acceptors but as dipolarophiles, in coupling – 1,3-dipolar cycloaddition sequences to give 4-acylisoxazoles with a broad substitution pattern in a one-pot fashion.[23,24]

One-pot transformations of alkynones into isoxazoles upon cyclocondensation with hydroxylamine as a binucleophilic component have already been exemplified by two different routes.[25,26] However, we reasoned that the Michael addition of azide anions under acidic conditions might lead to β-azidoalkenones, intermediates known to undergo cyclization to isoxazoles upon nitrogen extrusion.[27,28] β-Azidoalkenoates were found to preferentially form 3-alkoxycarbonyl-3*H*-azirines upon photolysis[29] or thermolysis,[30] and only in the presence of α-ester substitution in β-azidoalkenoates 5-ethoxyisoxazoles are formed.[31] Indeed, the transformation of alkynones and hydrazoic acid within 2–6 days to furnish 3,5-disubstituted isoxazoles was reported by Türck and Behringer already in 1965.[32] However, hydrazoic acid cannot be considered to be a safe reactant in this context and, furthermore, the implementation of hydrazoic acid surrogates, such as $TMSN_3$/AcOH or NaN_3/AcOH, never has been probed in the context of concatenating a catalytic alkynone formation, azidation, and cyclization to isoxazoles in a one-pot fashion. Therefore, we report the development of a three-component coupling–azidation–cyclization sequence to furnish isoxazoles in a consecutive one-pot reaction.

First screening reactions indicated that alkynones react with $TMSN_3$/AcOH rather by formation of the isoxazole than by simple Michael addition furnishing the proposed azidoalkenone intermediates. Also with NaN_3/AcOH the isoxazole was the only obtained reaction product. Neither increasing reaction temperature under conductive nor dielectric heating affected the yield of formation of isoxazoles. Therefore, we first performed an optimization study for the cyclization step starting from alkynone **1**, NaN_3, and AcOH as reactants by variation of the solvent system and reaction times to furnish isoxazole **2a** (Scheme1, Table 1).

DCM as a solvent was not effective in comparison to THF or 1,4-dioxane. Interestingly, after 4 h, a complete conversion of alkynone **1** was detected, regardless if a catalytic amount of NEt_3 was present or not (Table 1, entries 4 and 5).

Based upon this quick optimization of the cyclization the concatenation with the modified Sonogashira conditions[21,22] to give isoxazole **2a** was attempted by generation of alkynone **1** from *p*-methoxybenzoyl chloride (**3a**) and 1-hexyne (**4a**) in the presence of catalytic amounts of Pd and Cu catalysts. Indeed the reaction product was not the expected isoxazole **2a** but enaminone **5a** was isolated in 59% yield (Scheme 2).

Scheme 1. Cyclization of alkynone **1**, NaN_3, and AcOH to give isoxazole **2a**

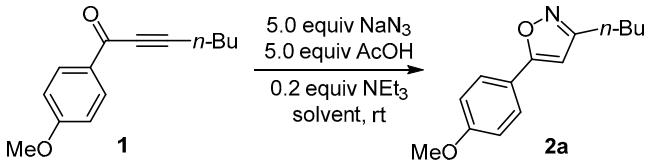
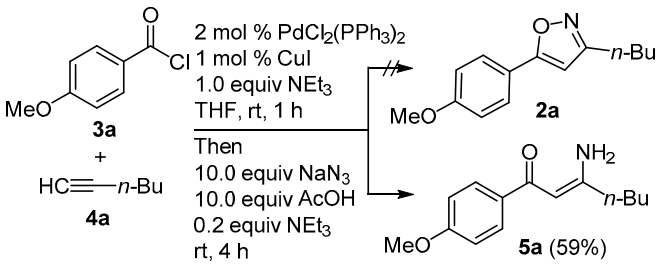


Table 1. Isoxazole **2a** cyclization reaction conditions optimization

Entry	Solvent	Reaction time, h	Yield*, %
1	DCM	6–10	Not isolated**
2***	DCM	6–10	Not isolated**
3	THF	4	72
4	1,4-Dioxane	4	69
5***	1,4-Dioxane	4	69

* Isolated yield after chromatography on silica gel.
** Incomplete conversion (as monitored by TLC).
*** In the absence of NEt_3.

Scheme 2. Attempted concatenation of alkynylation and cyclization under modified Sonogashira conditions

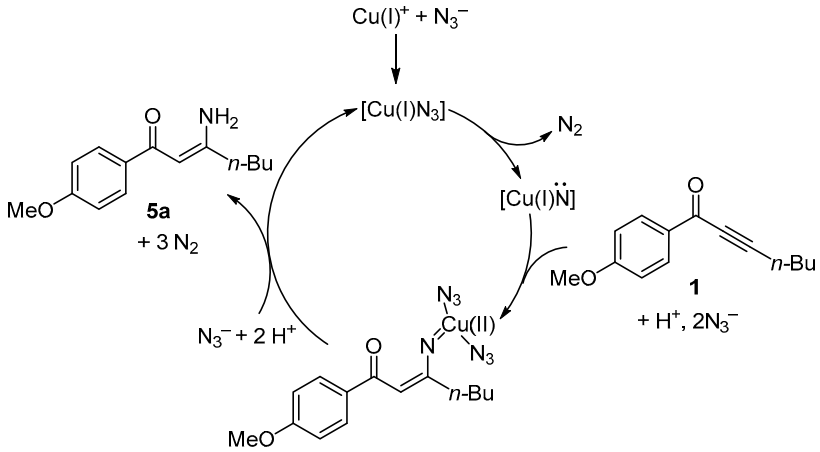


Essentially the same result was obtained upon employing $TMSN_3$ as an azide source furnishing enaminone **5a** in 42% yield. Independently, starting from alkynone **1** in the presence of catalytic amounts of Pd and Cu catalysts furnished enaminone **5a** in 47% yield. However, performing the same reaction only in the presence of the Pd catalyst, i.e., a Cu-free variation, gave rise to the formation of isoxazole **2a** in 77% yield.

For excluding a Cu-catalyzed ring opening–reduction of isoxazole **2a** after its formation, we reacted isoxazole **2a** in the presence of both catalysts, NaN_3, AcOH, and catalytic amounts of NEt_3 in THF. Indeed isoxazole **2a** remained unchanged and no formation of enaminone **5a** was observed.

Although azides have been shown to remain untouched under Sonogashira conditions in the presence of NEt_3 for short reaction times in THF at room temperature[33] it was demonstrated that Cu-mediated Ullmann type arylations of aryl bromide with NaN_3 furnished the corresponding anilines as products at elevated temperatures in DMSO.[34] A closer inspection revealed that Cu(I) complexes were necessary to promote the azidation–reduction.[35] Several related Cu-catalyzed coupling–reduction sequences gave

Scheme 3. Mechanistic rationale for the Cu(I)-catalyzed azidation–reduction of alkynones

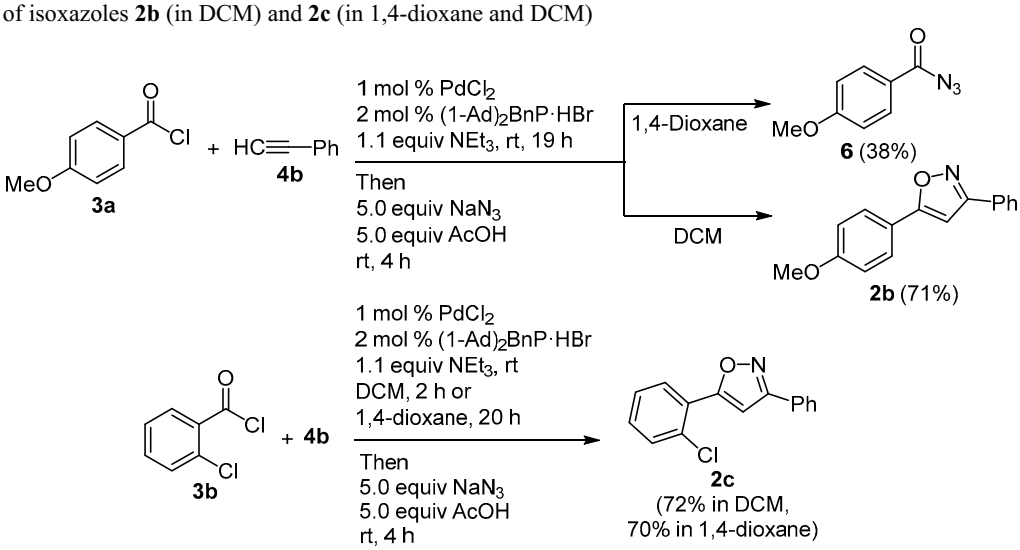


rise to similar results,[36–38] however, the reduction agent was never unambiguously identified. Further studies employing $TMSN_3$ as a nitrogen source indicated that the presence of protic solvents such as 2-aminoethanol was responsible for the successful reduction.[39] This was additionally supported by Ullmann azidation–reduction of aryl bromides with NaN_3 using Cu powder in the presence of 2-aminoethanol.[40] Detailed FTIR studies furthermore indicated the generation and consumption of $Cu(I)N_3$ as a relevant species in the reduction scenario, whereas the presence of aryl azide only affected the reduction process to a minor extent.

Therefore, we reasoned that the unexpected occurrence of enaminone **5a** can be rationalized as follows (Scheme 3). In the presence of azide anions, Cu(I) forms a $Cu(I)N_3$ complex, which loses nitrogen to give a reactive copper nitride. This complex reacts with alkynone **1**, azide ions, and a proton to formally give a Cu(II) nitrene diazido complex. *Via* Cu-mediated decomposition, the two electrons, formally required for a reduction of a nitrene to an amine, are generated by nitrogen formation in the presence of protons. Upon intramolecular electron transfer this simultaneously liberates the enaminone product **5a** and reconstitutes the catalytically active Cu(I) species by coordination of an azide anion.

Therefore, we decided to opt for a Cu-free alkynylative coupling of the acid chloride. Recently, we were able to disclose straightforward Cu-free alkynylation based on Beller's cataCXium® ABn ligand system,[41–44] which was successfully implemented in various consecutive multicomponent heterocycle syntheses.[45–48] Since aliphatic alkynes, such as 1-hexyne (**4a**) only sluggishly undergo the Cu-free alkynylation (alkynone **1** was formed in DCM in 16% and 1,4-dioxane in 40% yield), we decided to slightly alter the test system using phenylacetylene (**4b**) as an alkyne component (Scheme 4). As already observed for attempted coupling–cyclization sequences with 1-hexyne (**4a**) in 1,4-dioxane or DCM as solvents, the incomplete alkynylation caused considerable formation of the corresponding acyl azide. In 1,4-dioxane as a solvent, acyl azide **6** was the only isolable compound. However, changing the solvent to DCM gave an isolated yield of 71% of isoxazole **2b**. The subtle influence of the solvent was additionally underlined by employing 2-chlorobenzoyl

Scheme 4. Consecutive three-component Cu-free alkynylation–cyclization synthesis of isoxazoles **2b** (in DCM) and **2c** (in 1,4-dioxane and DCM)



chloride (**3b**) and phenylacetylene (**4b**) as coupling partners, furnishing comparable yields of isoxazole **2c**, both in 1,4-dioxane and DCM (Scheme 4). The one-pot process is clearly superior to the stepwise process in DCM, where the isolated corresponding alkynone (92% yield) was separately transformed into isoxazole **2c** in 63% yield, giving a combined yield of only 59%.

Due to the better operational handling we finally decided to employ in the most cases 1,4-dioxane as a solvent in the one-pot sequence. The overall sequence for the consecutive three-component synthesis of 3,5-disubstituted isoxazoles **2** from acid chlorides **3**, alkynes **4**, and NaN_3/AcOH proceeds in moderate to good yields and the tested substrate scope are summarized in Scheme 5 and Table 2. Mechanistically this novel one-pot sequence can be rationalized by a Pd-catalyzed alkynylation furnishing an alkynone, which undergoes an (*E*)-selective Michael addition to give an β-azido enone. As shown (Table 1) already at room temperature the concerted electrocyclization–nitrogen extrusion directly furnishes isoxazole **2**.

Exemplarily, the three carbon resonances of the isoxazole core of compound **2b** (numbering according to the systematic nomenclature of isoxazole) were assigned by ^{1}H–^{13}C HSQC and ^{1}H–^{13}C HMBC spectra. The HSQC spectrum allows assigning carbon nucleus C-4 at 96.2 ppm *via* its $^{1}J_{CH}$ coupling of proton (C-4)-H. The cross peaks of the $^{2}J_{CH}$ coupling of (C-4)-H in the HMBC spectra support the assignment of nuclei C-3 and C-5. In addition nucleus C-5 at 170.5 ppm displays a $^{3}J_{CH}$ coupling with the protons of the *p*-anisyl substituent. Therefore, the signal at 63.0 ppm was assigned to nucleus C-3. All isoxazoles **2**, depending on their substitution pattern display carbon resonces for nucleus C-3 at 158.5–164.8 ppm, for nucleus C-4 at 93.2–129.3 ppm, and for nucleus C-5 at 165.5–175.4 ppm. For compound **2e** additionally, the C,F-coupling constants were employed for the assignment of the carbon resonances.

The ESI mass spectra show, besides the molecular peaks, typical cleavages of the substituents R^1 and R^2 from the isoxazole core as well as the $[R^1CO]^+$ fragments arising from a cycloreversion of the isoxazole core of the molecule's radical cation. The IR spectra of isoxazoles **2** display good agreement with the literature[49] typical C=N (1580–1531 cm^{-1}) and C=C stretching vibrations (1443–1414 cm^{-1}) of the isoxazole core.

As a result of this short study on the scope it becomes apparent that aryl-substituted isoxazoles are generally formed in higher yield (Table 2, entries 2–6) than aliphatic (entries 1, 7) or ferrocenyl derivatives (entry 8). The relevance of the methodology is underlined by compound **2f**, which affects as a side chain of the antifungal drug micafungin (Mycamine®) its biological activity.

Finally, we also probed the activation–coupling approach, particularly developed for accessing alkynones starting from delicate *N*-heterocyclic sodium carboxylates for *in situ* generation of acid chlorides,[50] starting from sodium nicotinate, activated by reaction with 1.0 equiv of oxalyl chloride, followed by alkynylation with phenylacetylene (**4b**) and cyclization to furnish 3-phenyl-5-(3-pyridyl)isoxazole (**2i**) in 51% yield after workup and purification (Scheme 6).

Scheme 5. Consecutive three-component alkynylation–cyclization synthesis of isoxazoles **2** and mechanistic rationale

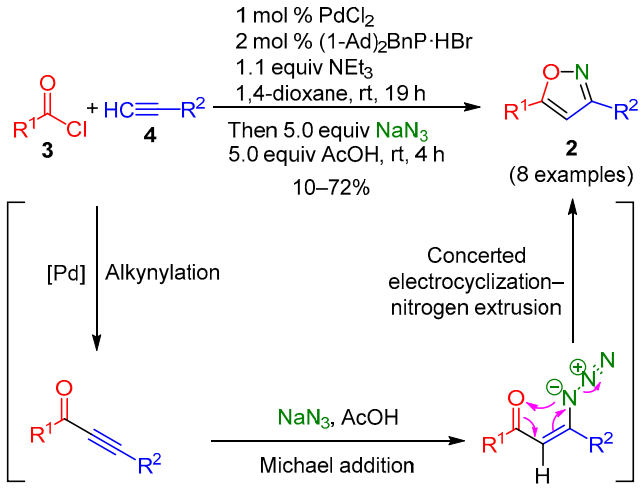
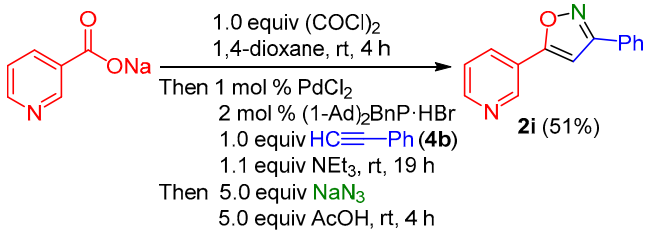


Table 2. One-pot alkynylation–cyclization synthesis of isoxazoles **2**

Entry	Acid chloride	Alkyne	Isoxazole (yield, %)*
1**	**3a** R^1 = *p*-$MeOC_6H_4$	**4a** R^2 = *n*-Bu	**2a** (10)
2***	**3a** R^1 = *p*-$MeOC_6H_4$	**4b** R^2 = Ph	**2b** (71)
3***,*[4]	**3b** R^1 = *o*-ClC_6H_4	**4b** R^2 = Ph	**2c** (72)
4*[5]	**3c** R^1 = 2-thienyl	**4b** R^2 = Ph	**2d** (32)
5*[5]	**3b** R^1 = *o*-ClC_6H_4	**4c** R^2 = *o*-FC_6H_4	**2e** (51)
6	**3a** R^1 = *p*-$MeOC_6H_4$	**4d** R^2 = *p*-$MeO_2CC_6H_4$	**2f** (29)
7	**3d** R^1 = cyclopropyl	**4b** R^2 = Ph	**2g** (42)
8	**3b** R^1 = *o*-ClC_6H_4	**4e** R^2 = ferrocenyl	**2h** (12)

* Isolated yield after chromatography on silica gel.
** The reaction time of the coupling step was 20 h.
*** DCM was used as a solvent.
*[4] The reaction time of the coupling step was 2 h.
*[5] After column chromatography the product was recrystallized from EtOAc.

Scheme 6. Consecutive three-component activation–alkynylation–cyclization synthesis of isoxazole **2i**



In conclusion, we have established a consecutive three-component alkynylation–cyclization synthesis of 3,5-disubstituted isoxazoles starting from the Cu-free catalytic coupling of acid chlorides (or by *in situ* activation of a sodium carboxylate) and terminal alkynes followed by cyclization with NaN_3/AcOH in a one-pot fashion. This room temperature process is particularly efficient for the regioselective synthesis of 3,5-di(hetero)aryl-substituted isoxazoles. Due to their electronical similarity to 3,5-di(hetero)aryl-substituted pyrazoles the elucidation of their

electronic structure and photophysical properties, as well as the extension of the alkynone-based methodology to persubstituted isoxazoles, additional studies are currently underway.

Experimental

IR spectra were obtained on a Shimadzu IRAffinity-1 (ATR) spectrometer. The intensity of the signals is abbreviated as following: s (strong), m (medium), w (weak). ^{1}H, ^{13}C, and 135-DEPT NMR, ^{1}H–^{13}C HSQC and HMBC spectra were recorded on a Bruker AVIII-300 spectrometer (300 and 75 MHz, respectively) in $CDCl_3$. The resonances of $CDCl_3$ were locked as internal standards (^{1}H δ 7.26 ppm, ^{13}C δ 77.0 ppm). The type of carbon nucleus was determined on the basis of 135-DEPT NMR spectra. Mass spectra were measured on a Finnigan MAT 8200 spectrometer (EI, 70 eV). Melting points (uncorrected) were measured on a Büchi Melting Point B-540 apparatus. Elemental analyses were carried out on Perkin Elmer Series II Analyzer 2400 in the Microanalytical laboratory of the Institut für Pharmazeutische und Medizinische Chemie at the Heinrich-Heine-Universität, Düsseldorf. All products were purified by column chromatography on silica gel 60 M (0.04–0.063 mm) from Machery Nagel GmbH & Co KG using flash technique under a pressure of 2 bar. The crude mixtures were absorbed on Celite® 545 (0.02–0.10 mm) from Merck KGaA Darmstadt before chromatographic purification. The reaction progress was observed qualitatively by using TLC Silica gel 60 F254 aluminum sheets. The spots were detected with UV light at 254 nm.

$PdCl_2$, acid chlorides **3**, sodium nicotinate, and alkynes **4a**,**b** were commercially available and used as supplied. Di-(1-adamantyl)benzylphosphonium bromide (cataCXium® ABn·HBr) was prepared recording to literature procedure.[51] Alkynes **4c**–**e** were synthesized by the Sonogashira coupling from the corresponding iodides with (trimethylsilyl)acetylene followed by subsequent disilylation with K_2CO_3/MeOH according to literature procedures.[52-54] 1-(4-Methoxyphenyl)hept-2-yn-1-one (**1**) was prepared according to our published procedure by modified Sonogashira conditions.[21,22]

Qualitative test on the presence of azide ions. At the end of the reaction sequence, i.e., after completion of the cyclization (monitored by TLC), the reaction mixtures were qualitatively checked for the presence of azide (iodine–azide reaction).[55–57] This qualitative test is founded on the following two redox reactions:

(1) $S^{2-} + I_2 \rightarrow S + 2\ I^-$

(2) $S + 2\ N_3^- \rightarrow S^{2-} + 3\ N_2\uparrow$

The presence of azide ions in the reaction mixture causes gas evolution, while the decoloration of the iodine solution is independent of the presence of azide ions.

A spatula tip with ground $Na_2S{\cdot}H_2O$ was placed on a watch glass and a droplet of the reaction mixture was added. Then a few drops of 2 M ethanolic iodine solution were added. Evolution of gas bubbles and a decoloration of the iodine solution were detected. Therefore, not all azide was completely consumed at the end of the terminal cyclization step.

Optimization of the cyclization of alkynone 1 and NaN_3. Alkynone **1** (136 mg, 0.50 mmol) and the corresponding solvent (0.5 ml) were placed under nitrogen into a screw-cap Schlenk tube with magnetic stir bar (for experimental details, see Table 1). Then NaN_3 (162 mg, 2.50 mmol), AcOH (0.14 ml, 2.50 mmol), and dry NEt_3 (8.9 μl, 0.10 mmol) were added, and the reaction mixture was stirred at the temperature and for the time indicated (monitored by TLC). Then the solvents were removed under reduced pressure. The crude product was adsorbed on Celite® and purified by flash chromatography on silica gel (petroleum ether – EtOAc) to give analytically pure isoxazole **2a** with the corresponding yield (Table 1), mp 40°C. R_f 0.11 (petroleum ether – EtOAc, 30:1). IR spectrum, ν, cm^{-1}: 3121 (w), 3013 (w), 2957 (w), 2936 (w), 2874 (w), 1898 (w), 1614 (m), 1591 (w), 1568 (w), 1512 (m), 1464 (w), 1431 (m), 1416 (w), 1381 (w), 1306 (w), 1287 (w), 1256 (m), 1177 (m), 1113 (w), 1092 (w), 1049 (w), 1022 (s), 945 (w), 899 (w), 835 (s), 799 (s), 768 (w), 745 (w), 725 (w), 683 (w), 652 (w). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.95 (3H, t, *J* = 7.3); 1.32–1.52 (2H, m); 1.58–1.80 (2H, m); 2.69 (2H, t, *J* = 7.7); 3.85 (3H, s); 6.25 (1H, s); 6.90–7.04 (2H, m); 7.62–7.78 (2H, m). ^{13}C NMR spectrum, δ, ppm: 13.9 (CH_3); 22.4 (CH_2); 25.9 (CH_2); 30.6 (CH_2); 55.5 (CH_3); 97.9 (CH); 114.4 (CH); 120.7 (C); 127.4 (CH); 161.0 (C); 164.8 (C); 169.6 (C). Mass spectrum, *m*/*z* (I_{rel}, %): 231 $[M]^+$ (19), 230 (14), 202 $[M–C_2H_5]^+$ (8), 190 (13), 189 $[M–C_3H_8]^+$ (100), 174 $[M–C_4H_9]^+$ (7), 161 (18), 135 $[C_8H_7O_2]^+$ (64), 111 (11), 107 $[C_7H_7O]^+$ (10), 97 (17), 95 (11), 85 (23), 83 (16), 81 (11), 77 (16), 71 (28), 69 (18), 57 (38), 55 (21), 43 (27), 41 (18). Found, %: C 72.55; H 7.21; N 6.22. $C_{14}H_{17}NO_2$. Calculated, %: C 72.70; H 7.41; N 6.06.

(*Z*)-3-Amino-1-(4-methoxyphenyl)hept-2-en-1-one (5a), consecutive coupling–azide addition conditions. $PdCl_2(PPh_3)_2$ (14 mg, 20 mmol) and CuI (8 mg, 40 mmol) were placed under nitrogen into a screw-cap Schlenk tube with magnetic stir bar. Then dry THF (2.5 ml), *p*-methoxybenzoyl chloride (**3a**) (176 mg, 1.0 mmol), 1-hexyne (**4a**) (0.12 ml, 1.0 mmol), and NEt_3 (0.14 ml, 1.0 mmol) were successively added, and the reaction mixture was stirred at room temperature for 1 h (monitored by TLC). Then NaN_3 (656 mg, 10.0 mmol), AcOH (0.56 ml, 10.0 mmol), and NEt_3 (17.8 ml, 0.1 mmol) were added, and the reaction mixture was stirred at room temperature for 4 h (monitored by TLC). Then the solvents were removed under reduced pressure. The crude product was adsorbed on Celite® and purified by flash chromatography on silica gel (petroleum ether – EtOAc, 5:1 to 3:1). Yield 138 mg (59%), colorless solid, mp 52°C. R_f 0.13 (petroleum ether – EtOAc, 3:1). IR spectrum, ν, cm^{-1}: 3285 (w), 3142 (w), 3001 (w), 2959 (w), 2932 (w), 2874 (w), 2859 (w), 2835 (w), 1587 (s), 1566 (m), 1526 (s), 1503 (s), 1454 (w), 1439 (w), 1420 (m), 1406 (w), 1377 (w), 1314 (m), 1302 (m), 1285 (m), 1252 (s), 1217 (m), 1204 (w), 1169 (s), 1103 (m), 1063 (w), 1030 (m), 1005 (w), 968 (w), 862 (w), 845 (m), 773 (s), 731 (m), 662 (m), 633 (m), 610 (m). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.94 (3H, t, *J* = 7.3); 1.31–1.48 (2H, m); 1.51–1.68 (2H, m); 2.18–2.30 (2H, m); 3.84 (3H,

s); 5.25 (1H, br. s); 5.71 (1H, s); 6.86–6.96 (2H, m); 7.82–7.92 (2H, m); 10.20 (1H, br). ^{13}C NMR spectrum, δ, ppm: 13.9 (CH_3); 22.4 (CH_2); 30.3 (CH_2); 36.8 (CH_2); 55.4 (CH_3); 91.2 (CH); 113.5 (CH); 129.1 (CH); 133.1 (C); 161.9 (C); 166.8 (C); 188.8 (C). Mass spectrum, *m*/*z* (I_{rel}, %): 233 $[M]^+$ (12), 232 (12), 204 $[M–C_2H_5]^+$ (16), 191 $[M–C_3H_6]^+$ (21), 136 (10), 135 $[C_8H_7O_2]^+$ (100), 96 (12), 85 (11), 77 (11), 57 (13), 43 (16). Found, %: C 72.02; H 7.91; N 6.24. $C_{14}H_{19}NO_2$. Calculated, %: C 72.07; H 8.21; N 6.00.

3,5-Disubstituted isoxazoles 2 (General method, sequential three-component conditions). $PdCl_2$ (3.5 mg, 0.02 mmol) and $(1\text{-Ad})_2$PBn·HBr (18.9 mg, 0.04 mmol) were placed under an atmosphere of argon into a screw-cap Schlenk tube with magnetic stir bar. Then dry 1,4-dioxane (2.0 ml), acid chloride **3** (2.00 mmol), alkyne **4** (2.00 mmol), and dry NEt_3 (0.30 ml, 2.20 mmol) were successively added. The reaction mixture was then stirred at room temperature for 19 h to complete conversion (monitored by TLC). NaN_3 (656 mg, 10.00 mmol) and glacial AcOH (0.56 ml, 10.00 mmol) were then added to this reaction mixture. The mixture was stirred at room temperature for 4 h (monitored by TLC). *CAUTION! Upon releasing nitrogen during the reaction pressure was built up in the reaction vessel.* The reaction mixture was transferred to a round-bottom flask and the solvents were carefully removed *in vacuo*. The crude product was adsorbed on Celite® and purified by flash chromatography on silica gel (petroleum ether – EtOAc) to give the analytically pure isoxazoles **2**.

3-Butyl-5-(4-methoxyphenyl)isoxazole (2a). Purified by flash chromatography on silica gel (petroleum ether – EtOAc, 30:1, R_f 0.11). Yield 47 mg (10%), light-yellow solid, mp 40°C. The spectroscopic data was fully consistent with the analytical data of the previously prepared compound **2a**.

5-(4-Methoxyphenyl)-3-phenylisoxazole (2b). Purified by flash chromatography on silica gel (petroleum ether – EtOAc, 15:1, R_f 0.16). Yield 358 mg (71%), colorless solid, mp 126°C. IR spectrum, ν, cm^{-1}: 3117 (w), 3003 (w), 2967 (w), 2936 (w), 2901 (w), 2839 (w), 1612 (m), 1599 (w), 1578 (w), 1518 (w), 1501 (w), 1464 (m), 1441 (w), 1418 (w), 1400 (m), 1317 (w), 1306 (w), 1248 (m), 1177 (m), 1119 (w), 1072 (w), 1032 (m), 949 (m), 926 (m), 841 (m), 822 (m), 800 (m), 768 (s), 689 (s), 662 (w), 611 (w). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.85 (3H, s); 6.69 (1H, s); 6.93–7.06 (2H, m); 7.39–7.54 (3H, m); 7.71–7.81 (2H, m); 7.28–7.93 (2H, m). ^{13}C NMR spectrum, δ, ppm: 55.5 (CH_3); 96.2 (CH); 114.5 (CH); 120.4 (C); 126.9 (CH); 127.5 (CH); 129.0 (CH); 129.4 (C); 130.0 (CH); 161.2 (C); 163.0 (C); 170.5 (C). Mass spectrum, *m*/*z* (I_{rel}, %): 251 $[M]^+$ (46), 135 $[C_8H_7O_2]^+$ (100), 77 $[C_6H_5]^+$ (15), 40 (10). Found, %: C 76.48; H 4.96; N 5.55. $C_{16}H_{13}NO_2$. Calculated, %: C 76.48; H 5.21; N 5.57.

5-(2-Chlorophenyl)-3-phenylisoxazole (2c). Purified by flash chromatography on silica gel (petroleum ether – EtOAc, 100:1 to 50:1, R_f 0.15 (petroleum ether – EtOAc, 50:1)). Yield 370 mg (72%), yellow solid, mp 60°C. IR spectrum, ν, cm^{-1}: 3067 (w), 2920 (w), 2851 (w), 1601 (w), 1576 (w), 1522 (w), 1479 (w), 1460 (m), 1447 (m), 1420 (w), 1398 (m), 1269 (w), 1213 (w), 1130 (w), 1078 (w), 1032 (m), 949 (m), 916 (w), 810 (w), 758 (s), 733 (m), 725 (w), 683 (s), 646 (w). ^{1}H NMR spectrum, δ, ppm: 7.26 (1H, s); 7.33–7.44 (2H, m); 7.45–7.57 (4H, m); 7.84–7.94 (2H, m); 7.96–8.05 (1H, m). ^{13}C NMR spectrum, δ, ppm: 102.6 (CH); 126.4 (C); 127.0 (CH); 127.4 (CH); 129.1 (CH); 129.2 (C_{quat}); 129.5 (CH); 130.2 (CH); 131.0 (CH); 131.8 (C); 163.1 (C); 166.7 (C). Mass spectrum, *m*/*z* (I_{rel}, %): 257 $[(^{37}Cl)–M]^+$ (16), 256 (10), 255 $[(^{37}Cl)–M]^+$ (45), 254 (10), 212 (11), 202 (20), 144 $[M–C_6H_4Cl]^+$ (26), 141 $[C_7H_4(^{37}Cl)O]^+$ (33), 140 (8), 139 $[C_7H_4(^{35}Cl)O]^+$ (100), 127 (13), 111 (28), 90 (10), 77 $[C_6H_5]^+$ (11), 75 (10). Found, %: C 70.57; H 4.06; N 5.54. $C_{15}H_{10}ClNO$. Calculated, %: C 70.46; H 3.94; N 5.48.

3-Phenyl-5-(thiophen-2-yl)isoxazole (2d). Purified by flash chromatography on silica gel (petroleum ether – EtOAc, 50:1, R_f 0.09), recrystallization from EtOAc. Yield 143 mg (32%), colorless solid, mp 95°C. IR spectrum, ν, cm^{-1}: 3115 (w), 3400 (w), 3082 (w), 1601 (w), 1580 (w), 1466 (w), 1443 (w), 1414 (w), 1400 (m), 1360 (w), 1261 (w), 1202 (w), 1184 (w), 1159 (w), 1053 (w), 1022 (w), 949 (w), 907 (w), 849 (m), 833 (w), 810 (w), 764 (s), 708 (m), 685 (s), 658 (w). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 6.69 (1H, s); 7.13 (1H, dd, *J* = 3.7, *J* = 5.0); 7.41–7.52 (4H, m); 7.55 (1H, dd, *J* = 1.1, *J* = 3.7); 7.79–7.89 (2H, m). ^{13}C NMR spectrum, δ, ppm: 97.4 (CH); 127.0 (CH); 127.2 (CH); 128.1 (CH); 128.2 (CH); 129.0 (CH); 129.0; 129.4 (C); 130.2 (CH); 163.1 (C); 165.5 (C). Mass spectrum, *m*/*z* (I_{rel}, %): 227 $[M]^+$ (31), 199 (10), 111 $[M–C_8H_6N]^+$ (50), 44 (15), 43 (13), 40 (100). Found, %: C 68.93; H 4.04; N 6.11; S 13.86. $C_{13}H_9NOS$. Calculated, %: C 68.70; H 3.99; N 6.16; S 14.11.

5-(2-Chlorophenyl)-3-(2-fluorophenyl)isoxazole (2e). Purified by flash chromatography on silica gel (petroleum ether – EtOAc, 50:1, R_f 0.13), recrystallization from EtOAc. Yield 140 mg (51%), colorless solid, mp 68°C. IR spectrum, ν, cm^{-1}: 3204 (w), 3103 (w), 3059 (w), 3028 (w), 2920 (w), 2851 (w), 1620 (w), 1589 (w), 1564 (w), 1514 (w), 1464 (m), 1443 (m), 1422 (w), 1400 (m), 1273 (w), 1258 (w), 1219 (m), 1157 (w), 1107 (w), 1090 (w), 1076 (w), 1034 (m), 955 (m), 856 (w), 816 (w), 806 (m), 752 (s), 731 (s), 719 (m), 681 (w), 665 (m). ^{1}H NMR spectrum, δ, ppm: 7.15–7.32 (2H, m); 7.33–7.50 (4H, m); 7.50–7.58 (1H, m); 7.94–8.10 (2H, m). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 105.0 (d, J_{CF} = 9, CH); 116.6 (d, J_{CF} = 22, CH); 117.3 (d, J_{CF} = 12, C); 124.8 (d, J_{CF} = 4, CH); 126.4 (C); 127.3 (CH); 129.3 (d, J_{CF} = 3, CH); 129.6 (CH); 131.0 (CH); 131.1 (CH); 131.8 (d, J_{CF} = 9, CH); 158.5 (d, J_{CF} = 2, C); 160.4 (d, J_{CF} = 252, C); 166.7 (d, J_{CF} = 2, C). Mass spectrum, *m*/*z* (I_{rel}, %): 275 $[(^{37}Cl)–M]^+$ (14), 273 $[(^{35}Cl)–M]^+$ (44); 238 $[M–Cl]^+$ (10), 162 $[M–C_6H_4Cl]^+$ (18), 141 $[C_7H_4{}^{37}ClO]^+$ (32), 139 $[C_7H_4(^{35}Cl)O]^+$ (100), 113 $[C_6H_4(^{37}Cl)]^+$ (7), 111 $[C_6H_4(^{35}Cl)]^+$ (22). Found, %: C 65.57; H 3.31; N 5.07. $C_{15}H_9ClFNO$. Calculated, %: C 65.83; H 3.31; N 5.12.

Methyl 4-[5-(4-methoxyphenyl)isoxazol-3-yl]benzoate (2f). Purifed by flash chromatography on silica gel (petroleum ether – EtOAc, 10:1 to 5:1, R_f 0.07 (petroleum ether – EtOAc, 10:1)). Yield 178 mg (29%), light-yellow

solid, mp 185°C. IR spectrum, ν, cm^{-1}: 3115 (w), 3046 (w), 2951 (w), 2922 (w), 2841 (w), 2154 (w), 1709 (m), 1653 (w), 1601 (m), 1572 (w), 1504 (m), 1470 (w), 1452 (w), 1429 (m), 1389 (w), 1371 (w), 1304 (w), 1277 (s), 1254 (s), 1175 (m), 1109 (s), 1018 (m), 962 (w), 949 (m), 918 (w), 864 (m), 835 (m), 812 (s), 795 (w), 775 (s), 708 (s), 692 (w), 662 (w), 631 (w), 615 (m). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.88 (3H, s); 3.95 (3H, s); 6.75 (1H, s); 6.96–7.06 (2H, m); 7.73–7.83 (2H, m); 7.89–7.99 (2H, m); 8.11–8.18 (2H, m). ^{13}C NMR spectrum, δ, ppm: 52.5 (CH_3); 55.6 (CH_3); 96.3 (CH); 114.6 (CH); 120.2 (C); 126.9 (CH); 127.6 (CH); 130.3 (CH); 131.4 (C); 133.6 (C); 161.4 (C); 162.2 (C); 166.7 (C); 171.0 (C). Mass spectrum, *m*/*z* (I_{rel}, %): 309 $[M]^+$ (46), 294 $[M–CH_3]^+$ (5), 278 $[M–OCH_3]^+$ (5), 149 (20), 139 (12), 136 (10), 135 $[C_8H_7O_2]^+$ (100), 129 (26), 111 (17), 107 $[C_7H_7O]^+$ (10), 97 (13), 85 (17), 83 (15), 77 $[C_6H_5]^+$ (13), 71 (26), 70 (11), 69 (12), 57 (32), 55 (15), 43 (18), 41 (10). Found, %: C 69.71; H 5.07; N 4.62. $C_{18}H_{15}NO_4$. Calculated, %: C 69.89; H 4.89; N 4.53.

5-Cyclopropyl-3-phenylisoxazole (2g). Purified by flash chromatography on silica gel (petroleum ether – EtOAc, 100:1 to 50:1, R_f 0.15 (petroleum ether – EtOAc, 50:1)). Yield 155 mg (42%), yellow solid, mp 42°C. IR spectrum, ν, cm^{-1}: 3111 (w), 3005 (w), 2955 (w), 2922 (w), 2851 (w), 1595 (m), 1578 (m), 1510 (w), 1474 (m), 1445 (w), 1416 (m), 1369 (m), 1339 (w), 1287 (w), 1238 (w), 1196 (w), 1150 (w), 1096 (w), 1057 (w), 1028 (w), 984 (m), 953 (w), 918 (m), 887 (m), 816 (m), 793 (w), 773 (s), 692 (s), 669 (m). ^{1}H NMR spectrum, δ, ppm: 0.99–1.15 (4H, m); 1.99–2.15 (1H, m); 6.20 (1H, s); 7.36–7.49 (3H, m); 7.71–7.81 (2H, m). ^{13}C NMR spectrum, δ, ppm: 8.3 (CH); 8.5 (CH_2); 97.0 (CH); 126.8 (CH); 128.9 (CH); 129.5 (C); 129.9 (CH); 162.6 (C); 175.4 (C). Mass spectrum, *m*/*z* (I_{rel}, %): 186 (13), 185 $[M]^+$ (92), 184 (32), 170 $[M–CH_3]^+$ (22), 156 $[M–HNO]^+$ (28), 145 (10), 144 $[M–C_3H_5]^+$ (100), 117 (36), 116 $[M–C_4H_5O]^+$ (33), 89 (15), 82 (17), 77 $[C_6H_5]^+$ (52), 69 (57), 51 (19), 41 (28), 40 (44), 39 (13). Found, %: C 77.91; H 6.07; N 7.30. $C_{12}H_{11}NO$. Calculated, %: C 77.81; H 5.99; N 7.56.

5-(2-Chlorophenyl)-3-ferrocenylisoxazole (2h). Purified by flash chromatography on silica gel (petroleum ether – EtOAc, 25:1, R_f 0.15). Yield 84 mg (12%), red solid, mp 118°C. IR spectrum, ν, cm^{-1}: 3136 (w), 2901 (w), 1601 (w), 1582 (m), 1568 (w), 1530 (w), 1476 (w), 1435 (w), 1425 (w), 1395 (w), 1362 (w), 1269 (w), 1223 (w), 1215 (w), 1107 (w), 1078 (w), 1035 (m), 1022 (w), 1005 (w), 945 (m), 920 (w), 870 (m), 833 (w), 824 (m), 816 (m), 756 (s), 731 (m), 725 (m), 665 (w), 652 (w). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 4.15 (5H, s); 4.41 (2H, t, *J* = 1.6); 4.80 (2H, t, *J* = 1.7); 7.00 (1H, s); 7.30–7.48 (2H, m); 7.49–7.61 (1H, m); 8.00 (1H, dd, *J* = 2.1, *J* = 7.4). ^{13}C NMR spectrum, δ, ppm: 67.8 (CH); 69.9 (CH); 70.0 (CH); 72.7 (C); 103.2 (CH); 126.5 (C); 127.3 (CH); 129.5 (CH); 130.8 (CH); 130.9 (CH); 131.7 (C); 163.3 (C); 165.7 (C). Mass spectrum, *m*/*z* (I_{rel}, %): 365 $[(^{37}Cl)–M]^+$ (32), 364 (23), 363 $[(^{35}Cl)–M]^+$ (100), 185 $[C_{10}H_9Fe]^+$ (13), 153 (11), 152 (14), 129 (11), 121 (21), 89 (14). Found, %: C 62.88; H 4.03; N 3.85. $C_{19}H_{14}ClFeNO$. Calculated, %: C 62.76; H 3.88; N 3.85.

3-Phenyl-5-(pyridin-3-yl)isoxazole (2i), three-component activation–alkynylation–cyclization conditions. Sodium nicotinate (296 mg, 2.00 mmol) and dry 1,4-dioxane (2.0 ml) were placed under an atmosphere of Ar into a screw-cap Schlenk tube with magnetic stir bar. Then oxalyl chloride (0.18 ml, 2.00 mmol) was added dropwise at room temperature, and the reaction mixture was stirred at room temperature for 4 h. Then $PdCl_2$ (3.5 mg, 0.02 mmol), $(1\text{-Ad})_2PBn·HBr$ (18.9 mg, 0.04 mmol), phenylacetylene (**4b**) (0.22 ml, 2.00 mmol), and dry NEt_3 (0.30 ml, 2.20 mmol) were successively added. The reaction mixture was then stirred at room temperature for 19 h to complete conversion (monitored by TLC). NaN_3 (656 mg, 10.00 mmol) and glacial AcOH (0.56 ml, 10.00 mmol) were then added to this reaction mixture. The mixture was stirred at room temperature for 4 h (monitored by TLC). *CAUTION! Upon releasing nitrogen during the reaction, pressure was built up in the reaction vessel.* The reaction mixture was transferred to a round-bottom flask and the solvents were carefully removed *in vacuo*. The crude product was adsorbed on Celite® and purified by flash chromatography on silica gel (petroleum ether – EtOAc, 3:1, R_f 0.08). Yield 225 mg (51%), yellow solid, mp 140–141°C. IR spectrum, ν, cm^{-1}: 3109 (w), 3046 (w), 2955 (w), 2920 (w), 2851 (w), 1611 (m), 1574 (w), 1560 (w), 1483 (w), 1462 (w), 1443 (w), 1412 (m), 1395 (m), 1339 (w), 1273 (w), 1223 (w), 1188 (w), 1126 (w), 1094 (w), 1053 (w), 1020 (w), 1001 (w), 947 (m), 912 (m), 826 (w), 808 (m), 766 (s), 692 (s), 667 (m), 617 (m). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 6.93 (1H, s); 7.39–7.55 (4H, m); 7.81–7.93 (2H, m); 8.09–8.18 (1H, m); 8.69 (1H, dd, *J* = 1.7, *J* = 4.9); 9.08 (1H, s). ^{13}C NMR spectrum, δ, ppm: 98.6 (CH); 123.8 (C); 123.9 (CH); 126.9 (CH); 128.7 (C); 129.1 (CH); 130.4 (CH); 133.0 (CH); 147.1 (CH); 151.1 (CH); 163.2 (C); 167.7 (C). Mass spectrum, *m*/*z* (I_{rel}, %): 223 (12), 222 $[M]^+$ (79), 221 (100), 144 $[M–C_5H_4N]^+$ (38), 116 $[M–C_6H_4NO]^+$ (11), 106 (44), 78 (35), 77 $[C_6H_5]^+$ (13), 51 (15), 40 (32). Found, %: C 75.72; H 4.75; N 12.30. $C_{14}H_{10}N_2O$. Calculated, %: C 75.66; H 4.54; N 12.60.

The Supplementary information file, containing ^{1}H and ^{13}C NMR spectra of compounds **2a**–**i** and **5a**, is available from the journal website at http://link.springer.com/journal/10593.

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