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Microwave assisted cycloaddition of benzonitrile oxides to 1-iodobuta-1,3-diynes

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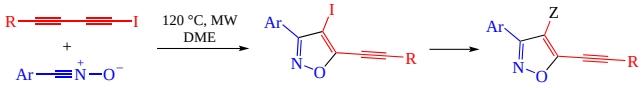
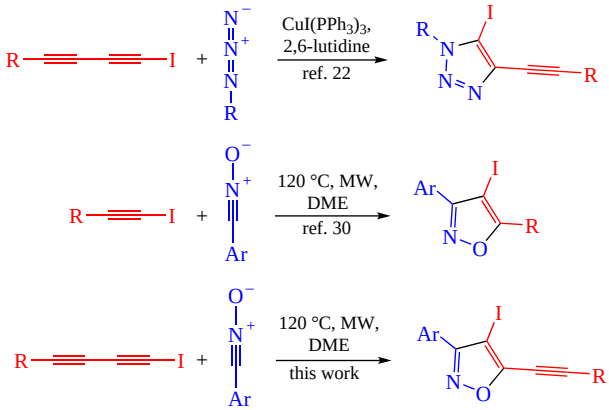
The microwave-assisted cycloaddition of 2,6-disubstituted benzonitrile oxides to 1-iodobuta-1,3-diynes occurs at the iodo-substituted triple bond giving predominantly 5-alkynyl-4-iodo-1,2,3-isoxazoles. The Suzuki–Miyaura and Sonogashira cross-coupling reactions were used for the modification of the thus obtained 4-iodoisoxazoles.



Keywords: 1-iodobuta-1,3-diynes, nitrile oxides, cycloaddition, isoxazoles, Suzuki–Miyaura reaction, Sonogashira cross-coupling, microwave-assisted reaction.

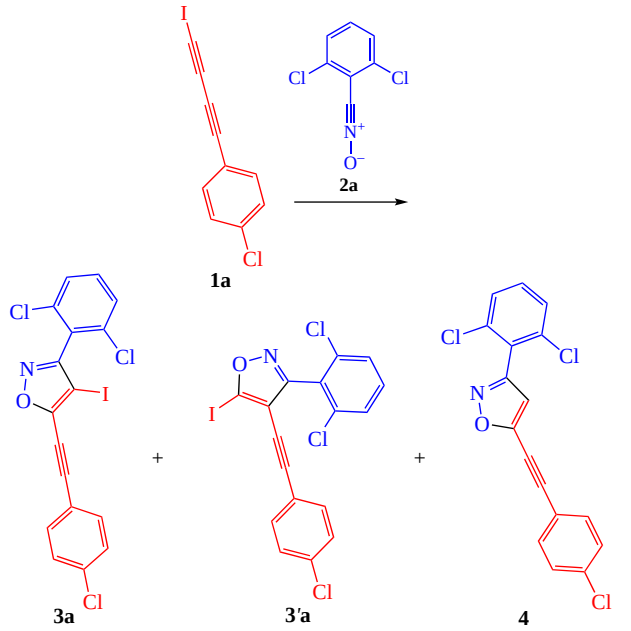
Isoxazoles are of increased interest due to a wide range of their biological properties.[1–5] A number of isoxazole derivatives have valuable photophysical properties.[6–8] Iodoisoxazoles are convenient starting compounds for the introducing various substituents into the isoxazole ring[9–11] and find application in the synthesis of biologically active substances.[12–16] At the same time, isoxazole derivatives containing conjugated alkynyl substituents exhibit valuable pharmacological properties, in particular, antibacterial activity.[17,18] One of the most effective methods for the synthesis of such compounds is the 1,3-dipolar cycloaddition reaction of nitrile oxides to terminal acetylenes.[19–21] The presence of an ethynyl fragment and an iodine atom as substituents in this five-membered heterocycle can provide additional opportunities for modifying the isoxazole structure and creating compounds with potential useful properties. However, synthesis of such compounds using iodination of ethynyltriazoles is difficult due to the lability of the triple bond. Iodobuta-1,3-diynes appear to be promising substrates for the [3+2] cycloaddition reactions, allowing the formation of five-membered heterocycles containing iodine and ethynyl derivatives as substituents. For these unsaturated compounds only Cu-catalyzed [3+2] cycloadditions of azides are described (Scheme 1).[22–25] The regioselectivity, usual for monoacetylene analogues,[26] in this case can be different depending on substitution type in azides: the formation of only 5-iodotriazoles was observed for alkyl azides, and isomeric mixtures of 4-iodo- and 5-iodotriazoles were obtained for aryl azides.[27] The subsequent modification of iodo cycloadducts by the Suzuki–Miyaura and Sonogashira reactions can afford compounds with valuable photophysical properties that are of interest for use in bioimaging. It is known that replacing the triazole ring with an isoxazole one leads to a change in the Stokes shift values and quantum yields.[28,29]



Scheme 1

Reactions of iodo monoacetylenes with nitrile oxides have been reported as a convergent, efficient and selective method for the synthesis of iodoisoxazoles (Scheme 2).[30,31] Moreover, the high reactivity of nitrile oxides in most cases allows cycloaddition reactions to be carried out without the use of catalysts.[32] As far as we know, cycloaddition of iodo diacetylenes to nitrile oxides has not been described. In this paper, we present the results of the study of the cycloaddition reactions between nitrile oxides and iodobuta-1,3-diynes and the possibility of modifying cycloadducts in the cross-coupling reactions (see Scheme 1).

Essentially stable 2,6-disubstituted benzonitrile oxide **2a** and 1-iodobutadiyne **1a** were chosen for initial experiments. An attempt to use the $CuI(PPh_3)_3$/lutidine catalytic system which was the most effective in reactions with azides[22–24] led to a mixture of cycloaddition products **3a** and **3′a**, which is presumably regioisomer of **3a** based on the NMR spectra, in only low yield (see Scheme 2, Table 1, entry 1). In addition, the reaction was accompanied by a protodeiodination process, as evidenced by the formation of product **4**. However, in the absence of catalysts it was possible to improve preparative total yield of compounds **3a** and **3′a** up to 44% (entry 2). Raising the temperature reduced the reaction time, however led to a decrease in the yield of cycloadducts (entry 3). Attempts to use excess of nitrile oxide resulted in the formation of a complex mixture of products that could not be separated by chromatography.



Scheme 2 *Reagents and conditions*: see Table 1.

Table 1 Optimization of the cycloaddition between 1-iodo-1,3-butadiyne **1a** and nitrile oxide **2a**.[a]

Entry	Catalyst	Solvent	*T*/°C	*t*/h	Isolated yield of **3a** + **3′a** (%)
1	$CuI(PPh_3)_3$, lutidine	–	~20	20	28[b]
2	–	Toluene	~20	100	44[c]
3	–	Toluene	60	24	41
4	–	DMF	60	24	10
5	–	DME	120 (MW)	1	45

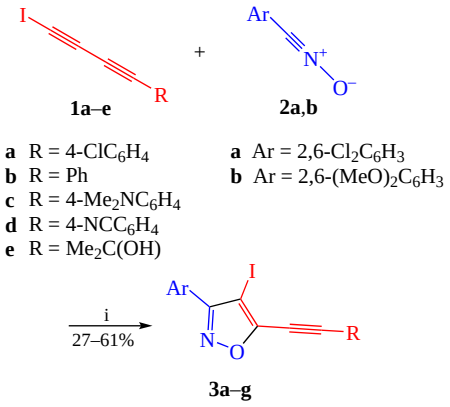
[a] At **1a**/**2a** molar ratio of 1 : 1. [b] Along with compound **4**. [c] When **1a**/**2a** molar ratio 1 : 1.5 was used, complex mixture was formed.

Carrying out the reaction in 1,2-dimethoxyethane (DME) using a microwave heating by analogy with published work[30] led to a slight increase in the yield, but made it possible to significantly reduce the reaction time (entry 5). To determine the yields, products **3a** + **3′a** were isolated as a mixture by column chromatography. The isomer ratio **3a**/**3′a** was approximately 10 : 1 in all cases.

Microwave heating conditions were applied for further investigation of the reaction of iodo diacetylenes **1a–e** with stable nitrile oxides **2a**,**b**. The reaction was shown to proceed with high regioselectivity giving 5-alkynyl-4-iodo-1,2,3-isoxazoles **3a–g** predominantly in moderate to good yields. In addition to cycloadducts, we observed the formation of mixtures of products presumably containing nitrile oxide dimers whose formation was revealed in our previous work.[21] We carried out the reaction with nitrile oxides **2a**,**b** containing either electron-withdrawing (Cl) or electron-donating (MeO) substituents. No significant effect of these substituents on the rate, selectivity, or yield of the reactions was observed. At the same time, electron-withdrawing substituents in the aryl ring of 4-aryl-1-iodobuta-1,3-diynes **1a** and **1d** lead to a slight decrease in the yield of cycloadducts (**3a**,**d**) compared to other iodo diynes (Scheme 3). To confirm the structure of the obtained adducts, X-ray diffraction was performed for compound **3f** (Figure 1). The appropriated crystals were grown from chloroform/hexane mixture.†

To explain the regioselectivity of the cycloaddition, we carried out the quantum chemical calculations. The global electrophilicity and nucleophilicity indices and Fukui functions[33] were calculated for the model structures **1b**, **2a** and **2b** (Table 2). Geometry optimization for all studied species was performed at the b3lyp/(6-31g**, def2TZVP for I) level of theory. The optimized geometries were used for the subsequent electron density calculations that were performed at the b3lyp/(6-311++g**, def2TZVP for I) level of theory. From the calculated data it is clear that all compounds are good nucleophiles and relatively good electrophiles. At the same time, it can be assumed that **1b** is more inclined to act in reactions with **2a** as a nucleophile, and in reactions with **2b** as an electrophile. From considering the values of the Fukui functions it follows that the reaction in both cases should proceed with the formation of 5-iodoisoxazole regioisomer, which is not actually observed. Accordingly, it may be assumed that the regioselectivity is ruled by steric factors.

Next, we investigated the modification of the resulting cycloadducts in the Suzuki–Miyaura reaction with arylboronic acids (Scheme 4). We used the catalytic system $Pd(PPh_3)_4$/K_3PO_4,[38] which was previously successfully used for analogous modification of 4-ethynyl-5-iodo-1,2,3-triazoles.[23] It is noteworthy that products **6a**,**b** exhibited the ability to luminesce when irradiated with a wavelength of 366 nm. In the case of prolonged processing with arylboronic acid **5b**, the formation of hydrodeiodination product **4** (25%) was also observed. When



a R = 4-ClC_6H_4
b R = Ph
c R = 4-$Me_2NC_6H_4$
d R = 4-NCC_6H_4
e R = $Me_2C(OH)$

a Ar = 2,6-$Cl_2C_6H_3$
b Ar = 2,6-$(MeO)_2C_6H_3$

a R = 4-ClC_6H_4, Ar = 2,6-$Cl_2C_6H_3$
b R = Ph, Ar = 2,6-$Cl_2C_6H_3$
c R = 4-$Me_2NC_6H_4$, Ar = 2,6-$Cl_2C_6H_3$
d R = 4-NCC_6H_4, Ar = 2,6-$Cl_2C_6H_3$
e R = $Me_2C(OH)$, Ar = 2,6-$Cl_2C_6H_3$
f R = 4-ClC_6H_4, Ar = 2,6-$(MeO)_2C_6H_3$
g R = Ph, Ar = 2,6-$(MeO)_2C_6H_3$

Scheme 3 *Reagents and conditions*: i, DME, 120 °C, MW, 1 h.

† *Crystal data for* **3f**. $C_{19}H_{13}NO_3ClI$ (M = 465.65), monoclinic, space group $P2_1/n$ at 100.0 K; a = 7.40100(10), b = 14.3259(2) and c = 16.9061(2) Å, α = 90°, β = 95.3010(10)°, γ = 90°, V = 1784.82(4) Å^3, Z = 4, d = 1.733 g cm^{-3}, μ = 15.630 mm^{-1}, $F(000)$ = 912.0. Total of 13275 reflections were collected (3371 independent reflections, R_{int} = 0.0501) and used in the refinement, which converged to wR_2 = 0.0844, GOOF = 1.083 for all independent reflections [R_1 = 0.0318 was calculated for 13275 reflections with $I > 2\sigma(I)$].

X-ray diffraction study of **3f** was performed at 100(2) K on a Rigaku XtaLAB Synergy-S diffractometer (HyPix-6000HE type detector) using Cu Kα (λ = 1.54184 Å) radiation. The structure was solved with the ShelXT[34] structure solution program using Intrinsic Phasing and refined with the ShelXL[35] refinement package incorporated in the OLEX2 program package[36] using Least Squares minimization. Empirical absorption correction was applied in CrysAlisPro[37] program complex using spherical harmonics, implemented in SCALE3 ABSPACK scaling algorithm. The hydrogen atom positions were fixed geometrically at calculated distances and allowed to ride on the parent atoms.

CCDC 2341764 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.

Table 2 Theoretically calculated Fukui functions $f(+)$ and $f(-)$, global electrophilicity (ω) and nucleophilicity (N) indexes for optimized equilibrium model structures in dimethoxyethane [B3LYP/(6-311++G**, I Def2TZVP)//B3LYP/(6-31g**, I Def2TZVP)], $E_{HOMO,\,TCNE}$ = –9.12* eV at the B3LYP/6-31G(d).

Structure	Fukui function	C1[a,b] or O[c]	C2[b] or C[c]	C3	C4	HOMO/eV	LUMO/eV	ω/eV	N/eV
1b	$f(-)$	0.16	0.02	0.14	0.09	–6.22	–1.78	1.80	2.90
	$f(+)$	0.15	–0.01	0.13	0.10				
2a	$f(-)$	0.11	0.06			–6.90	–2.02	2.04	2.22
	$f(+)$	0.25	0.15						
2b	$f(-)$	0.10	0.07			–6.18	–1.37	1.48	2.94
	$f(+)$	0.22	0.09						

[a] C1 is the first carbon atom next to iodine. [b] For structure **1b**. [c] For structures **2a**,**b**.

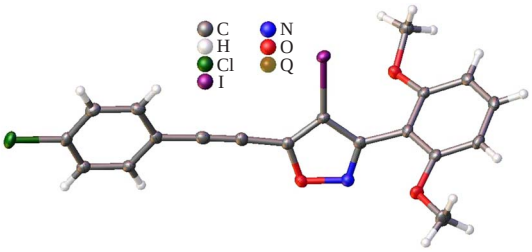
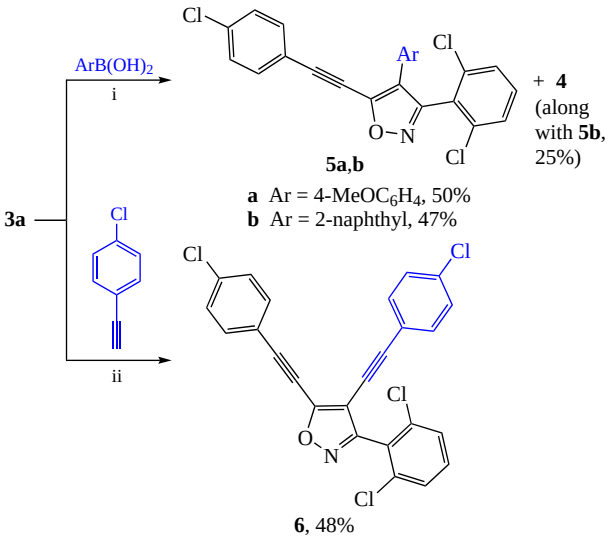


Figure 1 Single-crystal X-ray structure of compound **3f**.



Scheme 4 *Reagents and conditions*: i, $Pd(PPh_3)_4$, K_3PO_4, dioxane, 100 °C, 4–16 h; ii, $Pd(PPh_3)_4$, CuI, Pr^i_2NH, DMF, 40 °C, 30 h.

arylboronic acid with electron-donating substituent was employed, shorter heating (4 h) was required to achieve complete conversion of the starting isoxazole.

Next, we attempted to introduce iodoisoxazole **3a** in the Sonogashira cross-coupling (see Scheme 4). Under conditions previously used for iodotriazoles,[22,24] the formation of a cross-coupling product was not observed and the starting isoxazole predominantly remained in the reaction mixture. However, carrying out the reaction in DMF using diisopropylamine as a base allowed us to obtain product **6** in 48% yield (see Scheme 4).

In summary, iodobutadiynes are capable of reacting with 2,6-disubstituted benzonitrile oxides without using catalysts affording 5-ethynyl-4-iodo-1,2,3-isoxazoles in moderate to good yields. The use of microwave activation made it possible to suggest easily implementable and fast experimental procedure. The regioselectivity of the reaction is probably due to steric factors. The resulting cycloadducts can be modified in the Suzuki–Miyaura and Sonogashira cross-coupling reactions.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2024.06.022.

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