Available online at www.sciencedirect.com
ScienceDirect
Mendeleev Commun., 2024, **34**, 552–554

Mendeleev Communications

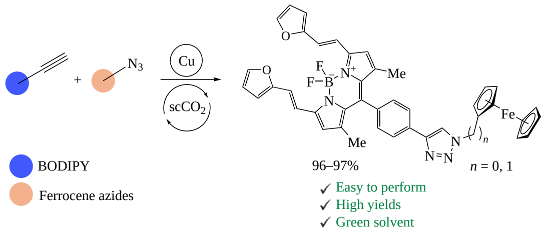
The Huisgen's cycloaddition of BODIPY acetylene and ferrocene azides in supercritical CO_2

Kirill G. Pavlov,[a] **Dmitry A. Guk,**[a] **Roman O. Burlutsky,**[a] **Anna A. Moiseeva,**[a] **Olga O. Krasnovskaya,**[a,b] **Dmitry A. Lemenovskiy,**[a] **Nikolay V. Zyk**[a] **and Elena K. Beloglazkina***[a]

[a] *Department of Chemistry, M. V. Lomonosov Moscow State University, 119991 Moscow, Russian Federation. E-mail: beloglazki@mail.ru*
[b] *National University of Science and Technology 'MISIS', 119049 Moscow, Russian Federation*

DOI: 10.1016/j.mencom.2024.06.027

The copper-catalyzed azide–alkyne cycloaddition of BODIPY acetylene derivative and ferrocene azides in supercritical CO_2 at 80 °C and 81 bar affords the corresponding triazole-containing BODIPY–ferrocene conjugates in high yields. The fluorescent and electrochemical properties of the compounds thus obtained were explored.



Keywords: green chemistry, supercritical fluid, CO_2, copper, azide–alkyne cycloaddition.

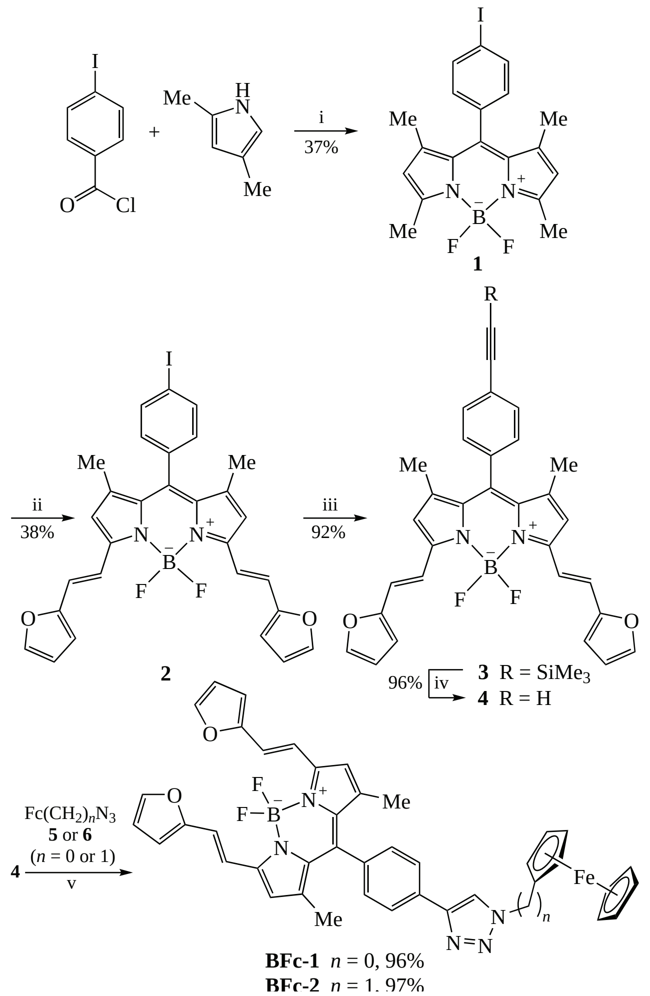
Nowadays, copper-catalysed azide–alkyne cycloaddition (CuAAC) reactions are attracting significant attention due to their simplicity, high selectivity and bioorthogonality.[1,2] However, one of the significant drawbacks of this reaction is the use of organic solvents or mixtures based on water and an organic solvent, typically THF or Bu^tOH.[3] Recycling of the wastes is often a non-trivial task. Since the discovery of supercritical fluid as a state of matter, researchers have attempted to use various gases in a supercritical state as a medium for chemical reactions.[4] Carbon dioxide is a notable supercritical solvent due to its non-toxicity, non-flammability, low cost, and ease of disposal and recycling, and it can be used as a green alternative to classical organic media for the CuAAC reaction.[5,6] Currently, the literature[7–13] presents several versions for performing the CuAAC reaction in supercritical CO_2 ($scCO_2$) media (for the summary, see Online Supplementary Materials, Table S3).

The first example of CuAAC reactions in $scCO_2$ was performed in 2009 by Grignard with the use of CuI as a catalytic agent whose solubility in this non-polar medium was achieved by adding perfluorinated chelating ligands (PFLs).[7,8] Next, Zhang developed an efficient procedure involving $Cu(OAc)_2 \cdot H_2O$ in the absence of PFLs.[9] Recently in 2023, Alcalde proposed the use of a flow reactor with the feeding of components in acetonitrile solutions.[10] Among the described conditions for the CuAAC reactions,[6–14] the most promising looks the use of copper wire as a catalyst due to its simplicity and availability.[11,14] The ability of copper to undergo catalytic transformation in $scCO_2$ may be caused by oxidation of metallic copper with CO_2 forming Cu^I clusters.

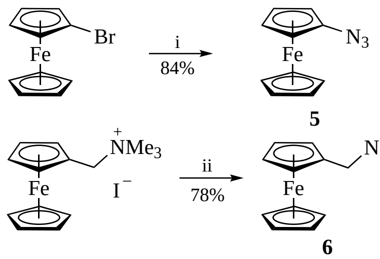
In this work we present modified reaction conditions that allow us to obtain the products of the CuAAC in $scCO_2$ under mild conditions (80 °C and 81 bar) in 96–87% yields; the products are novel conjugates with ferrocene and boron-dipyrromethene (BODIPY) moieties. Structurally, BODIPYs are synthetic analogues of porphyrins, which have great synthetic availability, as well as high photostability and fluorescence quantum yields. Among the photosensitizers of the BODIPY class, compounds with maximum absorption and emission located in the visible light region of the red spectrum, which find their use as dyes for LEDs, stand out. Also, red light in the visible range of the spectrum is less susceptible to scattering and absorption by biological tissues of the body, which makes it possible to obtain biological photodelivery systems and photodynamic therapy agents based on BODIPY.

In this study, the target compounds **BFc-1** and **BFc-2** were obtained as outlined in Scheme 1. The required bis-furanoylstyryl BODIPY **4** containing an acetylene moiety at the phenyl ring in the *meso* position of the BODIPY core along with acidophobic furan rings, was prepared from available starting compounds. First, dipyrromethene was synthesized from 4-iodobenzoyl chloride and 2,4-dimethylpyrrole, which were then reacted with boron trifluoride diethyl etherate to produce 4-iodophenyl BODIPY **1** (see Scheme 1). The latter was modified at the 3,5-methyl groups by the Knoevenagel condensation with furfural to afford compound **2**. The acetylene moiety was introduced by sequential Sonogashira cross-coupling with trimethylsilylacetylene and removal of the TMS protection. Compounds **1–4** were characterized by ^1H, ^{13}C, ^{19}F NMR spectroscopy and HRMS data (see Online Supplementary Materials). The azido ferrocene counterparts **5** and **6** were synthesized according to Scheme 2.

Alkyne **4** was then subjected to CuAAC with azides **5**, **6**, the reaction conditions having been screened for optimization. At 40 °C and 81 bar CO_2 pressure, the expected cycloaddition product was not formed (Table 1, entry 1). Raising the pressure to 101 bar and the temperature to 80 °C (entry 2) led to formation of the products, however, in low yields, possibly due to a decrease in the solubility of BODIPY. Reducing the pressure to 81 bar at 80 °C (entry 3) made it possible to obtain compound **BFc-1** with



Scheme 1 *Reagents and conditions*: i, CH_2Cl_2, 35 °C, 2 h, then Et_3N, $BF_3 \cdot Et_2O$, reflux, 30 min; ii, fufural, MeCN, AcOH, piperidine, MS 3 Å, reflux, 18 h; iii, $Me_3SiC{\equiv}CH$, $Pd(PPh_3)_2Cl_2$ (5 mol%), CuI (5 mol%), Et_3N, THF, room temperature, ~18 h; iv, K_2CO_3, MeOH/THF, room temperature, 1 h; v, **5** or **6**, Cu (wire), $scCO_2$, 80 bar, 80 °C, 8 h.



Scheme 2 *Reagents and conditions*: i, NaN_3, CuCl, EtOH, 0 °C, 24 h; ii, NaN_3, H_2O, reflux, 12 h.

a yield of 96%. Shortening the reaction time to 4 h lowered the conversion to 20% (entry 4).

We also tested the ‘classical’ reaction conditions of CuAAC, *viz*. a heterogeneous system of THF and water for the case of compounds **4** and **5**. The product yield was significantly lower (Table 2, entries 1, 2) than for the reaction in $scCO_2$. With the use of CuI as a catalyst, the yield of **BFc-1** after purification also turned out to be quite low (entry 3). When changing the system to a homogeneous one and using $Cu(MeCN)_4BF_4$ (entry 4) with TBTA as a stabilizer of Cu^I, the complications arose for the reaction realization and additional operations of purification.

Table 1 Optimization of click-reaction conditions of compound **4** with **5**, **6** in $scCO_2$ media.

Entry	Alkyne–azide ratio	*P*/bar	*T*/°C	*t*/h	Yield (%)
1	1.0	81	40	8	–
2	1.0	101	80	8	19–20[a]
3	0.8	81	80	8	96–97[b]
4	1.0	81	80	4	20[a]

[a] From ^1H NMR data. [b] Isolated yield.

Table 2 Comparison of the conditions for the reaction between compounds **4** and **5** in organic solvents.

Entry	Cu catalyst	Solvent system	*T*/°C	Yield (%)
1	Cu (wire)	THF/H_2O	22	<5
2	Cu (wire)	THF/H_2O	64	<5
3	CuI	THF/H_2O	22	25
4	$Cu(MeCN)_4BF_4$ + 0.1% TBTA	THF	22	78

Studying the fluorescent properties of the resulting conjugates, we discovered that treatment of **BFc-2** solution with 1.0 equiv. $Fe(ClO_4)_3$ leads to increasing the fluorescence intensity in the region of 565 nm by a factor of 4.2 (see Online Supplementary Materials, Figures S22–S29). For both compounds **BFc-1** and **BFc-2** complete quenching of fluorescence by Cu^{2+} ions in acetonitrile solution was observed, but in THF for **BFc-1** the quenching was significantly lower than that for **BFc-2**.

The electrochemical characteristics of compounds **BFc-1** and **BFc-2** were determined using cyclic voltammetry. Compound **BFc-1** exhibits an oxidation peak of 0.9 V corresponding to the Fe^{III}/Fe^{II} transition (Figure S30, Table S4). Additionally, the BODIPY system undergoes oxidation at 1.0 V. In contrast, the oxidation potential of the ferrocene moiety in compound **BFc-2** is only 0.68 V (Figure S31, Table S4) due to the absence of conjugation between the ferrocene and triazole fragments. The observed increase in luminescence intensity upon oxidation, and low oxidation potential allow one to consider conjugate **BFc-2** as a potential redox-sensitive (Fenton-type[15,16]) fluorescent sensor for biological applications.

To summarize, a convenient method has been proposed for carrying out the click reaction of BODIPY-containing acetylene and ferrocene-substituted azides in supercritical CO_2 under mild conditions, which makes it possible to obtain their triazole-containing conjugates with high yield. Selective quenching of compound **BFc-2** luminescence in a THF solution by Cu^{2+} ions was demonstrated.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2024.06.027.

References

1 N. J. Agard, J. M. Baskin, J. A. Prescher, A. Lo and C. R. Bertozzi, *ACS Chem. Biol.*, 2006, **1**, 644.
2 L. Li and Z. Zhang, *Molecules*, 2016, **21**, 1393.
3 A. R. Ellanki, A. Islam, V. S. Rama, R. P. Pulipati, D. Rambabu, G. Rama Krishna, C. Malla Reddy, K. Mukkanti, G. R. Vanaja, A. M. Kalle, K. Shiva Kumar and M. Pal, *Bioorg. Med. Chem. Lett.*, 2012, **22**, 3455.
4 E. J. Beckman, *J. Supercrit. Fluids*, 2004, **28**, 121.
5 S. P. Nalawade, F. Picchioni and L. P. B. M. Janssen, *Prog. Polym. Sci.*, 2006, **31**, 19.
6 S. G. Zlotin, K. S. Egorova, V. P. Ananikov, A. A. Akulov, M. V. Varaksin, O. N. Chupakhin, V. N. Charushin, K. P. Bryliakov, A. D. Averin, I. P. Beletskaya, E. L. Dolengovski, Yu. H. Budnikova, O. G. Sinyashin, Z. N. Gafurov, A. O. Kantyukov, D. G. Yakhvarov, A. V. Aksenov, M. N. Elinson, V. G. Nenajdenko, A. M. Chibiryaev, N. S. Nesterov, E. A. Kozlova, O. N. Martyanov, I. A. Balova, V. N. Sorokoumov, D. A. Guk, E. K. Beloglazkina, D. A. Lemenovskii, I. Yu. Chukicheva, L. L. Frolova, E. S. Izmest’ev, I. A. Dvornikova, A. V. Popov, A. V. Kutchin, D. M. Borisova, A. A. Kalinina, A. M. Muzafarov, I. V. Kuchurov, A. L. Maximov and A. V. Zolotukhina, *Russ. Chem. Rev.*, 2023, **92**, RCR5104.

7 B. Grignard, S. Schmeits, R. Riva, C. Detrembleur, P. Lecomte and C. Jérôme, *Green Chem.*, 2009, **11**, 1525.

8 B. Grignard, C. Calberg, C. Jerome and C. Detrembleur, *J. Supercrit. Fluids*, 2010, **53**, 151.

9 W. Zhang, X. He, B. Ren, Y. Jiang and Z. Hu, *Tetrahedron Lett.*, 2015, **56**, 2472.

10 S. Alcalde, R. Porcar, M. L. De La Puente, G. R. Cumming, C. Mateos, P. García-Losada, C. Anta, J. A. Rincón and E. García-Verdugo, *Org. Process Res. Dev.*, 2023, **27**, 276.

11 S. López, J. M. García-Vargas, M. T. García, J. F. Rodríguez, I. Gracia and M. J. Ramos, *Catalysts*, 2022, **12**, 194.

12 E. Gracia, M. T. García, A. De Lucas, J. F. Rodríguez and I. Gracia, *Catal. Today*, 2020, **346**, 65.

13 E. Gracia, M. T. García, A. M. Borreguero, A. De Lucas, I. Gracia and J. F. Rodríguez, *J. CO_2 Util.*, 2017, **20**, 20.

14 C. Chen, X. Yan, Y. Wu, X. Zhang, S. Liu, F. Zhang, X. Sun, Q. Zhu, L. Zheng, J. Zhang, X. Xing, Z. Wu and B. Han, *Nat. Commun.*, 2023, **14**, 1092.

15 A. Singh, I. Lumb, V. Mehra and V. Kumar, *Dalton Trans.*, 2019, **48**, 2840.

16 B. Sharma and V. Kumar, *J. Med. Chem.*, 2021, **64**, 16865.

Received: 20th March 2024; Com. 24/7430