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Advanced Synthesis & Catalysis

Copper-Catalyzed Selective N-Arylation of Oxadiazolones by Diaryliodonium Salts

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Abstract: Here, we report the method for copper-catalyzed N-arylation of diverse oxadiazolones by diaryliodonium salts under mild conditions in high yields (up to 92%) using available CuI as a catalyst. The developed method allows utilizing both symmetric and unsymmetric diaryliodonium salts bearing auxiliary groups such as 2,4,6-trimethoxyphenyl (TMP). We found that the steric effects in aryl moieties determined the chemoselectivity of N- and O-arylation of the 1,2,4-oxadiazol-5(4*H*)-ones. Mesityl-substituted diaryliodonium salts demonstrated the high potential as a selective arylation reagent. The structural study suggests that steric accessibility of N-atom in 1,2,4-oxadiazol-5(4*H*)-ones impact to arylation with sterically hindered diaryliodonium salts. The synthetic application of proposed method was also demonstrated on selective arylation of 1,3,4-oxadiazol-2(3*H*)-ones and 1,2,4-oxadiazole-5-thiol.

Keywords: Iodonium salts; Arylation; Amides; Heterocycles; Chemoselectivity

Introduction

Heterocyclic compounds are a pivotal class of organic substances, which widely spread among natural and artificial products. Nitrogen-containing heterocyclic compounds are found in such substances as α-amino acids and peptides, DNA, RNA, while the high affinity of N-heterocyclic compounds to biological molecules allows implementing it in drug design, pharmacology, and medicinal chemistry.[1–4] Due to this reason, the development of new approaches and methods to the synthesis of heterocyclic core and its modification can be considered as an essential task for organic chemistry.[5]

One of the promising classes of heterocyclic organic compounds is oxadiazolones, revealing versatile biological activity (Figure 1). For instance, 1,3,4-oxadiazol-2(3*H*)-one based compounds have been

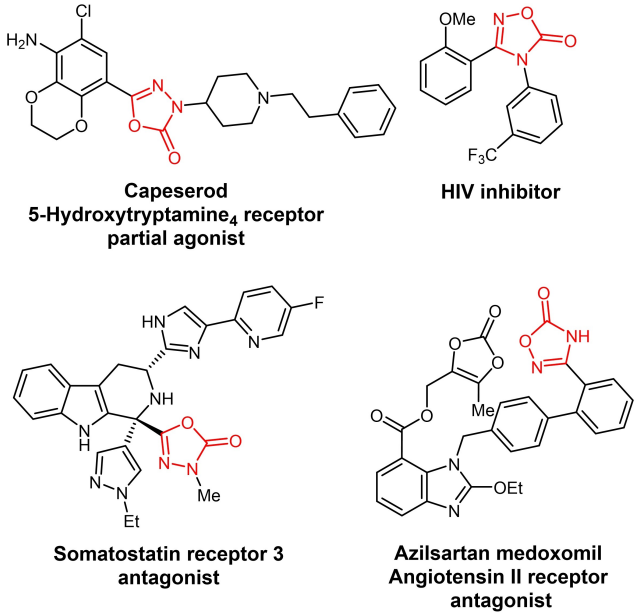
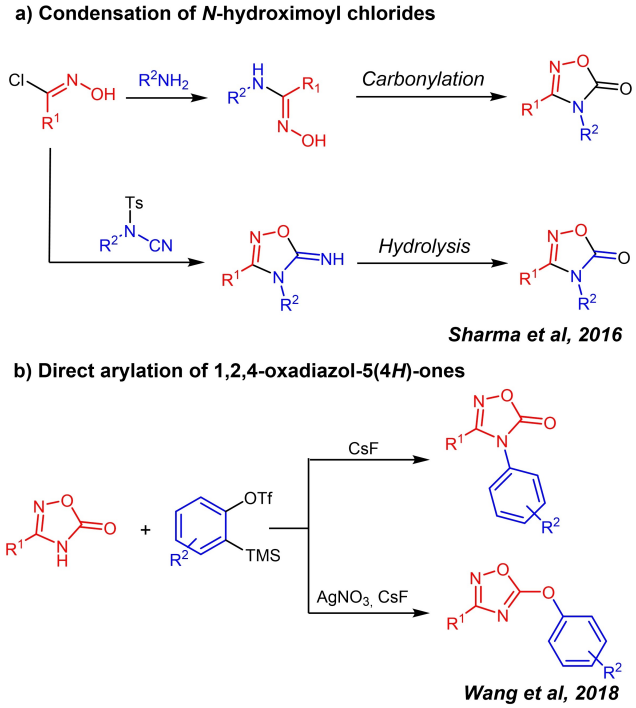
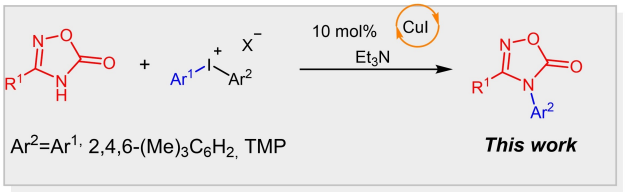


Figure 1. Examples of biologically active oxadiazolones.





Scheme 1. Synthetic pathways to N-arylated 1,2,4-oxadiazol-5(4*H*)-ones.

applied for the treatment of type 2 diabetes and dementia (Capeserod).[6,7] The derivative of 1,2,4-oxadiazol-4(5*H*)-ones, Azilsartan medoxomil, is registered as a drug for the therapy of hypertonia.[8] Another example of perspective targets is 3-(2-methoxyphenyl)-4-(3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5(4*H*)-one demonstrating HIV inhibition activity.[9] Despite the broad applicability of oxadiazolones, the further evaluation of the biological activity of these compounds can be hampered due to limited numbers of synthetic approaches and methods of late-stage modification, including N-arylation of 1,2,4-oxadiazol-4(5*H*)-ones.

The reported synthesis of N-arylated 1,2,4-oxadiazol-5(4*H*)-one can be separated into two main approaches: a) condensation of N-hydroximoyl chlorides; and b) direct arylation of 1,2,4-oxadiazol-5(4*H*)-one core (Scheme 1). The first approach was reported in the XIX century and consumed condensation of N-hydroximoyl chlorides and anilines with the formation of *N*′-hydroxy-N-arylbenzimidamide following carboxylation with phosgene, ethyl chloroformate, or 1,1′-carbonyldiimidazole.[10–12] Recently, Sharma et al. reported a convenient way for the construction of 1,2,4-oxadiazol-5(4*H*)-one core *via* interaction of cyanamides and N-hydroximoyl chlorides with the formation of 1,2,4-oxadiazol-5(4*H*)-imine, which was readily converted to 1,2,4-oxadiazol-5(4*H*)-one by simple hydrolysis.[13]

To the best of our knowledge, the direct arylation of 1,2,4-oxadiazol-5(4*H*)-ones is investigated poorly. The formation of arylated derivatives was demonstrated by Wang et al. in 2018[14] in the reaction between aryne precursor and 1,2,4-oxadiazol-5(4*H*)-ones. This approach has notably high chemoselectivity of N/O-arylation in dependence on the presence of Ag-catalyst. Despite this, the main drawbacks of this method are the low regioselectivity of arylation by substituted aryne precursors, low synthetic availability and relatively high cost of *ortho*-(trimethylsilyl)phenyl triflates.

We proposed that diaryliodonium salts are able to be a source of electrophilic aryl intermediates in the reaction with 1,2,4-oxadiazol-5(4*H*)-ones similarly to arylation of various nucleophiles demonstrated previously.[15–17] The hypervalent iodine reagents are widely used for the transfer of alkynyl-,[16,18–20] alkenyl-,[16,21,22] aryl groups,[16,23–26] etc.[27] Particularly important the direct arylation of various nucleophiles by diaryliodonium salts. Thus, the strong nucleophiles are able to react with electron-poor aryl electrophile without the addition of transition metals (for instance, amines,[28–31] alkoxides,[32–34] *S*-nucleophiles,[35,36] etc.). The weaker nucleophiles require higher temperatures or the addition of transition metals, especially

copper.[24] The particular interest has been appealed by the N-arylation of heterocycles. The electron-rich heterocycles can be arylated by iodonium salts in relatively mild conditions,[37–40] while electron-poor (especially cyclic amides and related compounds) require the addition of catalyst.[41–46] Also, the synthetic procedures for preparing diaryliodonium salts make available the versatile scope of these compounds with high yields from common laboratory reagents.[47–54]

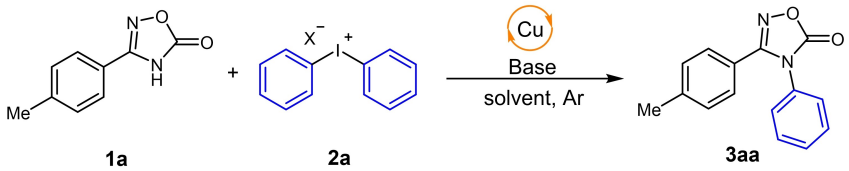
Nevertheless, the chemoselectivity of arylation of N,O-containing heterocycles presents a challenging task in hypervalent iodine chemistry. For instance, selective N- and O-arylation of pyridine-2-ones was problematic[58,59] until a recent report, where base-tuned chemoselectivity has been applied.[60] It should also be noted that the arylation of weak nucleophiles by iodonium salts represents a complex task, which affects the synthetic applicability of hypervalent iodine reagents.

In the proposed contribution, we report a mild and effective arylation procedure of oxadiazolones by symmetrical and unsymmetrical diaryliodonium salts. The developed approach displays the high applicability for the functionalization of both 1,2,4-oxadiazol-5(4*H*)-ones and 1,3,4-oxadiazol-2(3*H*)-ones bearing various substituents. Moreover, the evaluation of auxiliary group effects in unsymmetrical iodoniums salts demonstrated the high regioselectivity of interaction with readily available aryl(mesityl)iodonium salts.

Results and Discussion

We initially evaluated prospects of the arylation of **1a** employing diphenyliodonium triflate **2a**. Indeed, the current trends in the arylation of N-centered nucleophiles consume metal-free conditions, but the low nucleophilicity of **1a** did not favor the direct arylation (Table 1, Entries 1–4). In order to find suitable conditions, we added CuI as a cheap and available catalyst, which has been already applied for the arylation of hydantoins,[42] 2,7-naphthyridin-1(2*H*)-one,[43] and other weak N-centered nucleophiles.[15,61] The addition of 10 mol% CuI in the presence of

Table 1. Optimization of the arylation of 3-(*p*-tolyl)-1,2,4-oxadiazol-5-one with diphenyliodonium salts.[a]



1a **2a** **3aa**

Entry	X^-	Base, (1.5 equiv.)	Solvent	T, °C	Cat., (mol%)	Yield,[b] %
1	TfO^-	^tBuONa	1,2-DCE	rt.	None	NR[c]
2	TfO^-	aq. NH_3	1,2-DCE	rt	None	NR[c]
3	TfO^-	Cs_2CO_3	1,2-DCE	rt	None	NR[c]
4	TfO^-	NaOH	1,2-DCE	rt	None	NR[c]
5	TfO^-	^tBuONa	1,2-DCE	rt	CuI, (10)	NR[c]
6	TfO^-	aq. NH_3	1,2-DCE	rt	CuI, (10)	NR[c]
7	TfO^-	Cs_2CO_3	1,2-DCE	rt	CuI, (10)	2
8	TfO^-	NaOH	1,2-DCE	rt	CuI, (10)	6
9	TfO^-	NaOH	1,2-DCE	60	CuI, (10)	77(59)[d]
10	TfO^-	NaOH	1,2-DCE	80	CuI, (10)	44
11	**TfO^-**	**Et_3N**	**1,2-DCE**	**60**	**CuI, (10)**	**83**
12	TfO^-	Et_3N	1,2-DCE	60	CuBr, (10)	76
13	TfO^-	Et_3N	1,2-DCE	60	$CuBF_4$ $(MeCN)_4$	82
14	TfO^-	Et_3N	1,2-DCE	60	$Cu(OTf)_2$	65
15	TfO^-	Et_3N	MeCN	60	CuI, (10)	80
16	CF_3COO^-	Et_3N	1,2-DCE	60	CuI, (10)	77
17	BF_4^-	Et_3N	1,2-DCE	60	CuI, (10)	83
18	Br^-	Et_3N	1,2-DCE	60	CuI, (10)	19
19	TfO^-	Et_3N	1,2-DCE	60	CuI, (10)	58[e]
20	TfO^-	Et_3N	1,2-DCE	60	CuI, (5)	52

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.75 mmol), of **2a**, base (0.75 mmol) in 5 mL of solvent for 24 h in Ar.
[b] Isolated yield.
[c] According to TLC.
[d] Reaction performed in air.
[e] 0.625 mmol of **2a** was used.

Cs_2CO_3 or NaOH furnished **3** in low yields (Table 1, Entries 5–8). The increase of reaction temperature up to 60 °C allowed the isolation of **3** in a better yield (77%, Table 1, Entry 9), but a further increase of temperature (up to 80 °C) led to the decrease the yield (44%; Table 1, Entry 10). In view of that, the heating of the reaction mixture up to 60 °C was considered as an optimal. Under such conditions, we attempted to avoid the use of argon, but the reaction conducted in air resulted in a significant yield drop (59%; Table 1, Entry 9). In the next stage, we changed the NaOH to the triethylamine, which allowed the isolation of target **3** in 83% yield (Table 1, Entry 11). The reaction was not sensitive to solvent and the anion in the catalyst (Table 1, Entries 12–13, 15). An only slight decrease of the yield (approximately 5%) was observed in the case of CuBr (Table 1, Entry 12). However, utilization of Cu(II)-catalyst decrease the yield down to 65% (Table 1, Entry 14). The reaction was tolerant of the non-coordinating anions in diaryliodonium salt (Table 1, Entries 16–17). However, in the case of diphenyliodonium bromide, the yield dramatically drops to 19% due to competitive arylation of bromide-anion (Table 1, Entry 18). The proposed method was sensitive to the amounts of reacting compounds. Thus, the addition of 5 mol% of the catalyst (Table 1, Entry 20) or decreased amount of **2a** (Table 1, Entry 19) led to a sufficient decrease the yield of **3**.

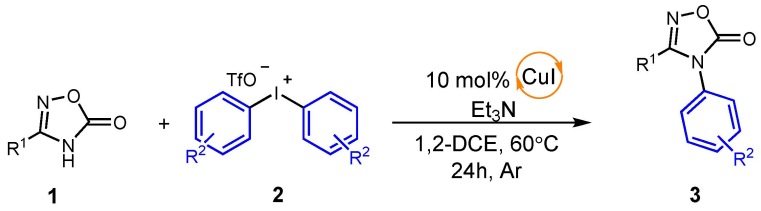
The best result was achieved (Table 1, Entries 11 and 17) when **2a** or **2aBF$_4$** were used as the aryl-source. In a further study, we used diaryliodonium triflates due to the convenience of its preparation using Oxone[53,54] or *m*CPBA[62,63] as oxidants.

With optimized conditions in hands, we evaluated the scope and limitations of the proposed method using 1,2,4-oxadiazol-5(4*H*)-ones **1a–o** and symmetric diaryliodonium salts **2a–f** (Scheme 2). The arylation of **1a–o** by **2a** demonstrated the good tolerance to electronic and steric effect of substituents in 1,2,4-oxadiazol-5(4*H*)-one. 3-Aryl-1,2,4-oxadiazol-5(4*H*)-ones **1a–g**,**i**,**k** bearing moderate electron-withdrawing and electron-donating substituents reacted with **2a** to give high yields of arylation products **3aa–ga**,**ia**,**ka** (> 82%). Only for the NO_2-substituent we observed a slight decrease of product yield (70%), probably, due to the limited solubility of **1h**. Particularly important, the reaction involving sterically-hindered *ortho*-substituted oxadiazolones **1c**,**f** as reactants proceeded smoothly to provide **3ca** and **3fa** in high to excellent yields (86% and 92% correspondingly). The sufficient decrease of yield was observed only for *ortho*-OMe substituted **1l**, and product **3la** was isolated in 63% yield. Looking ahead, we consider that *ortho*-OMe substituted oxadiazolone **1l** demonstrated lower reactivity in the reaction with other iodonium salts (**3lb**,**ld**,**lf**).

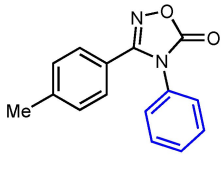
The reaction proceeded smoothly with oxadiazolone **1j** bearing competitive nucleophilic center as the AcNH-group. We did not observe the arylation of acetamido group, which evidenced high chemoselectivity of reaction. Nevertheless, the yield of target **3ja** was slightly lower (61%). The suggested approach was also applicable for the functionalization of oxadiazolones containing heterocyclic (**1m**) and alkyl moieties (**1n–o**). In both cases, the desired products were isolated in good yields (**3ma** 77%, **3na** 85%, and **3oa** 82%).

The evaluation of scope using symmetrical iodonium salts displays high acceptability toward halo-substituted diaryliodonium salts **2b–c** provided **3** in higher yield for most substrates compared with **2a** (the only exception **3gc**). In contrast, reaction with diaryliodonium salt **2d** bearing electron-withdrawing groups (CF_3) proceeded with lowered yield (**3dd**, 67%; **3ld**, 30%). Unsuccessful arylation was observed for dibenziodolium triflate that resulted in the decomposition of iodonium salt with the formation of 2-iodobiphenyl. Besides the electronic effect in diaryliodonium salts **2**, the steric accessibility affects both reaction pathways and product yields. In the case of sterically hindered **2e** having 2,5-xylyl-group, yields of **3** decreased by approximately 10–20%. The bulkier mesityl-derived iodonium salts **2f** reacted differently depend on steric effects in **1**. Notable that for *ortho*-substituted **1c**,**f**,**l** the corresponding product was prepared selectively in high yield for **3cf** (82%) and moderate yield for **3ff** and **3lf** (62% and 43% correspondingly). In contrast, the interaction of less sterically hindered **1** with **2f**, afforded both N-arylated and O-arylated products with low yields (< 27%) (Scheme 3). Evaluation of results does not reveal any dependence of yield and products ratio on electron effects of substituents in **1**.

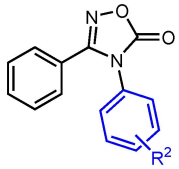
Notably, the molecular structure of seven compounds **3** was confidently confirmed by single-crystal XRD analysis. The obtained crystal structure of **3** can indirectly explain observed selectivity for *ortho*-substituted **1c**,**f**,**l** that exhibited larger angle between plane normals (∠α) of aryl ring (belong to **1**), and 1,2,4-oxadiazol-5-one rings in **3**. For instance, in *ortho*-substituted **3fa**,**ff**,**lb** it is more than 55°, while in *para*-substituted **3ea** and **3ka**, and in reported structure **3ba** (CDS code: FOVVUH01)[13] the ∠α less 36°. The plane angles in the product can explain the steric hindrance for bulky mesityl species (Figure 2, a–b). Notably, that in cases when the phenyl ring rotated oppositely, the determined ∠α is more than 90° we used for comparison calculated adjacent angle (180°–∠α) (Figure 2, c–d). Moreover, observed selectivity N,O-arylation of *para*-substituted with **2f** can be explained by lower steric hindrance of O-atom compared to N-atom in combination with kinetic features of reaction to lower nucleophilicity of oxygen than nitrogen.



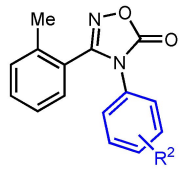
1 2 3



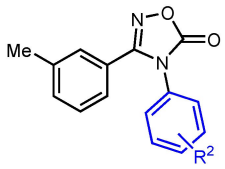
3aa, 83%



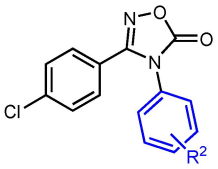
3ba, R^2=H 88%
3bc, R^2=4-Br 90%



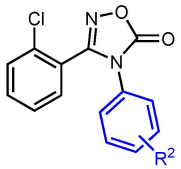
3ca, R^2=H 86%
3cf, R^2=2,4,6-$(Me)_3$ 82%



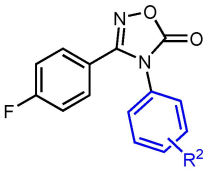
3da, R^2=H 82%
3db, R^2=4-Cl 87%
3dd, R^2=3-CF_3 67%



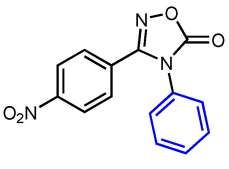
3ea, R^2=H 84%
3eb, R^2=4-Cl 85%



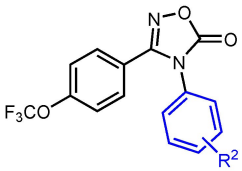
3fa, R^2=H 92%
3fe, R^2=2,5-$(Me)_2$ 83%
3ff, R^2=2,4,6-$(Me)_3$ 62%



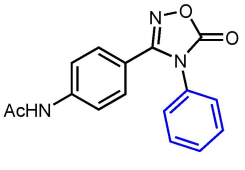
3ga, R^2=H 88%
3gc, R^2=4-Br 76%



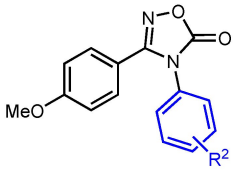
3ha, 70%



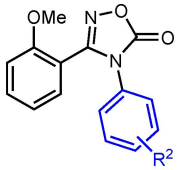
3ia, R^2=H 87%
3ie, R^2=2,5-$(Me)_2$ 76%



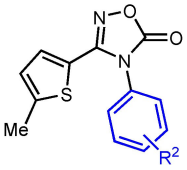
3ja, 61%



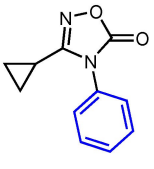
3ka, R^2=H 85%
3kc, R^2=4-Br 91%



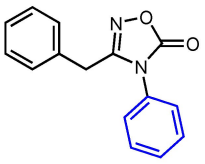
3la, R^2=H 63%
3lb, R^2=4-Cl 72%
3ld, R^2=3-CF_3 30%
3lf, R^2=2,4,6-$(Me)_3$ 43%



3ma, R^2=H 77%
3me, R^2=2,5-$(Me)_2$ 55%

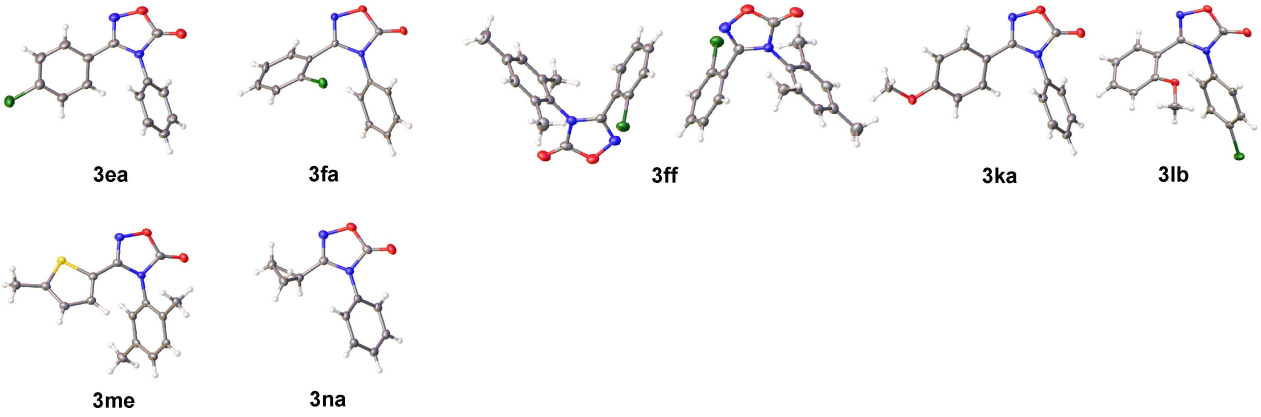


3na, 85%



3oa, 82%

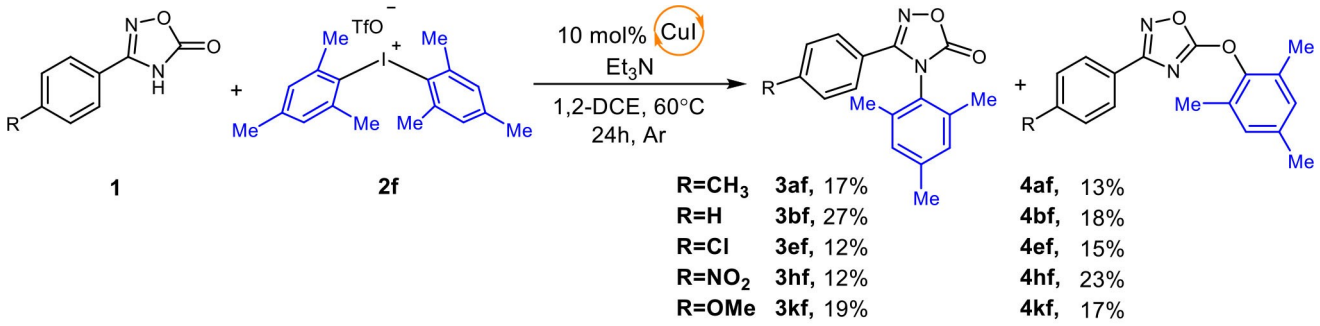
X-Ray structures



3ea 3fa 3ff 3ka 3lb

3me 3na

Scheme 2. Scope of arylation of 1,2,4-oxadiazol-5(4*H*)-ones **1a–o** by symmetric diaryliodonium salts **2a–f** (Top panel); single crystal XRD structures of products **3** (Top panel, the detailed description is provided in SI).[a,b]



[a)] Conditions: 0.5 mmol of 1, 0.75 mmol of 2f, 0.75 mmol of Et3N, 10 mol% CuI in 5 mL of 1,2-DCE for 24 h in Ar atmosphere; b) Isolated yield.

Scheme 3. Arylation of 1,2,4-oxadiazol-5(4*H*)-one **1** with **2f**.[a,b]

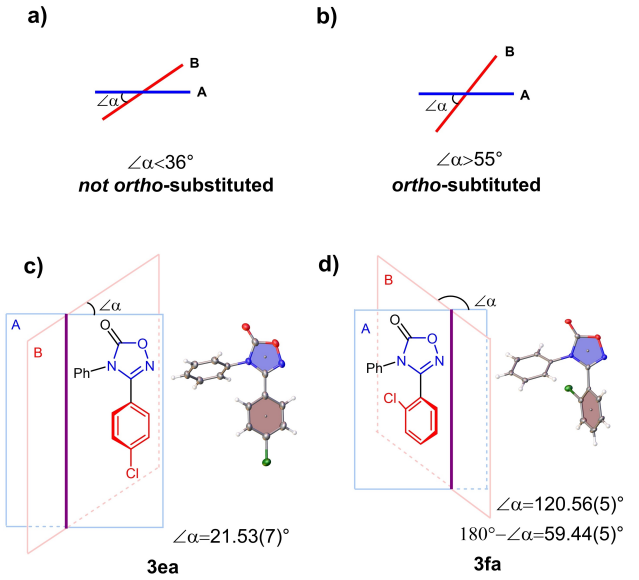


Figure 2. Steric accessibility of N-atom in dependence on angles between plane normals.

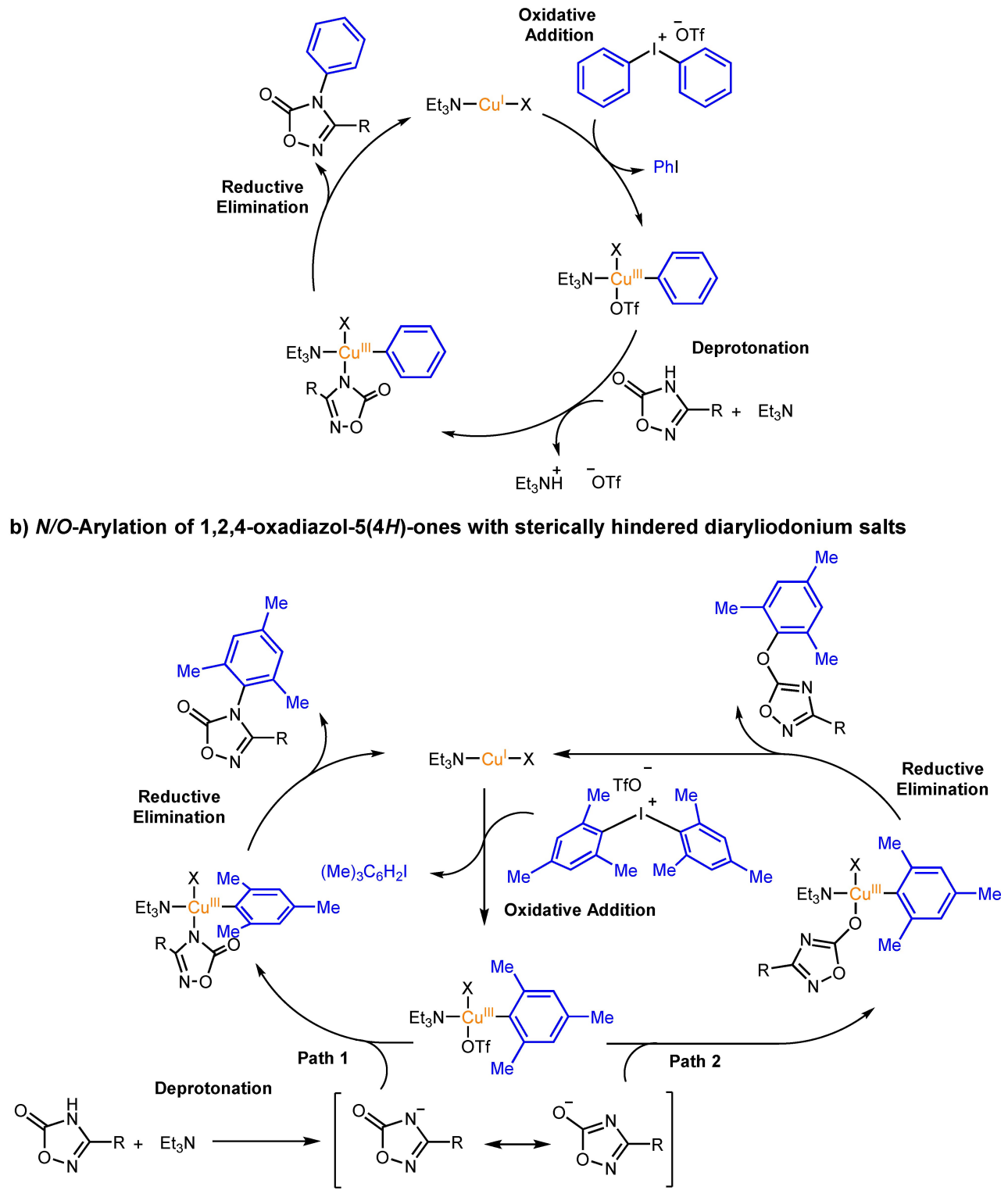
Based on experimental results and previous reports[24,42,46] we proposed the mechanism of the N- and N/O-arylation of 1,2,4-oxadiazol-5-ones (Scheme 4,a). Plausible mechanism includes the oxidative addition of CuI complex with Et_3N to diaryliodonium salt following ligand exchange with deprotonated oxadiazolone and reductive elimination (Scheme 4,a). In the case of N/O-arylation of **1**, we suppose that the attack of product of oxidative addition is hampered for N-nucleophilic site due to steric hindrance. Thus, the kinetically controlled product of O-arylation has been formed in the more considerable amount (Scheme 4,b)

In the next step, we tested the applicability of the unsymmetrical iodonium salts in the arylation of **1a** under optimized conditions (Table 2, Entries 1–4). The main drawback of unsymmetrical iodonium salts is connected with regioselectivity issues controlled by steric or electronic effects in iodonium salts[64] or external physical triggers such as plasmon resonance.[65] However, the application of unsymmetrical iodonium salts can access arylation products, which are difficult to prepare using symmetrical iodonium salts due to synthetic limitations. For instance, preparation of symmetrical iodonium salts bearing electron-withdrawing groups proceed in low yields and often required expensive reagents as corresponding boronic acid.[66,67] Similar issues are revealed in the case of challenging regiospecific synthesis of symmetrical iodonium salts.

Previously, Stuart et al. reported the preparation and synthetic applicability of aryl(2,4,6-trimethoxyphenyl) iodonium salts as selective arylation agents for various nucleophiles (C, N, O, and S).[50,51,68] We tested readily accessed phenyl(2,4,6-trimethoxyphenyl)iodonium tosylates and trifluoroacetates for arylation of **1a**. In both cases, we succeeded in isolation of desired products with a slightly higher yield of **3aa** (85%) (Table 2, Entries 1–3). Our previous results in arylation by bis(mesityl)iodonium salt **2f** were promising for aryl(mesityl)iodonium salts as a selective reagent for arylation of **1**. Indeed, utilization of **2i** leads to selective formation of **3aa** in the highest yields (87%).

Further comparison of iodonium salts reactivity demonstrated that utilization of unsymmetrical iodonium salts bearing electron-withdrawing substituent as CF_3-group was more efficient and led to the sufficient increase of yields up to 86% (reaction of **2d** gave **3dd** only in 67% yield – (Scheme 2)). Nevertheless, the application of mesityl-substituted iodonium salts (such as **2k**) led to the formation of O-arylated product in low yield (compound **B**, Table 2), hampering the isolation of **A**.

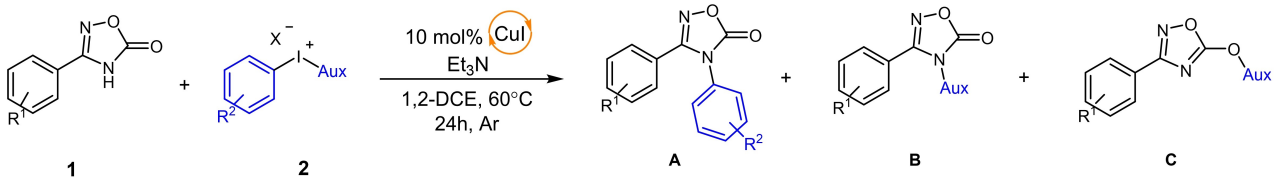
We found a few more reasons for the preferable utilization of 2,4,6-trimethoxyphenyl-substituted (TMP-substituted) iodonium salts instead of mesityl ones. First of all, TMP-substituted iodonium salt bearing NO_2-group **2l** was more reactive over mesityl-



Scheme 4. Plausible mechanism of arylation of 1,2,4-oxadiazol-5-ones with diaryliodonium salts.

analog **2 m** (80% vs. 53% yield of **3 al**). Similar behavior has been demonstrated in the arylation of oxadiazolone **1 l** by **2 j** and **2 k** with the formation of **3 ld** product. 3-(2-Methoxyphenyl)-4-(3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5(4*H*)-one **3 ld** has been proved as a potent anti-human immunodeficiency virus

Table 2. Optimization and initial evaluation of arylation of 1,2,4-oxadiazol-5(4*H*)-one **1** by unsymmetrical iodonium salts.[a]

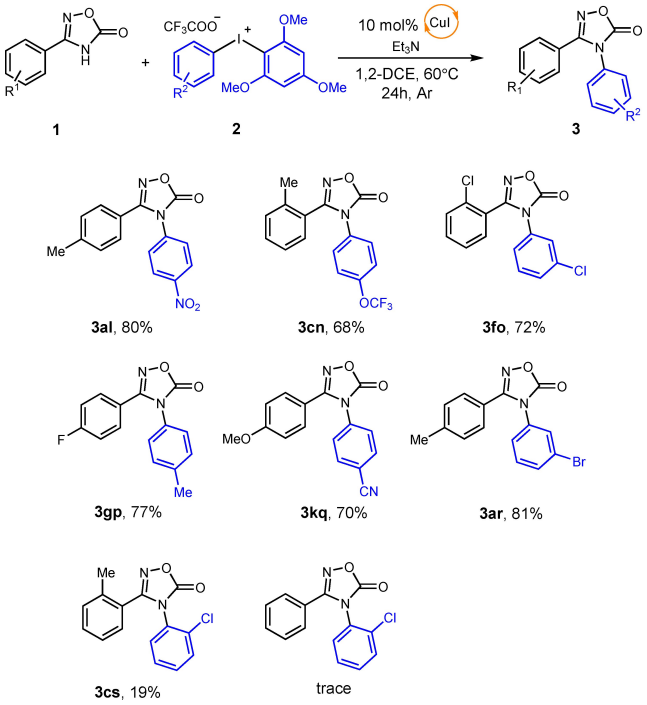


Entry	Substrates 1, R^1	2, R^2	Aux	X^-	Time, h	Yield of A,[b] %	Yield of B, %	Yield of C, %
1	**1a**, 4-Me	**2g**, H	TMP	TsO^-	5	**3aa**, 74	–	-
2		**2h**, H	TMP	CF_3COO^-	5	**3aa**, 78	–	–
3		**2h**, H	TMP	CF_3COO^-	24	**3aa**, 85	–	–
4		**2i**, H	2,4,6-$(Me)_3C_6H_2$	TfO^-	24	**3aa**, 87	–	–
5	**1d**, 3-Me	**2j**, 3-CF_3	TMP	CF_3COO^-	24	**3dd**, 82	–	–
6		**2k**, 3-CF_3	2,4,6-$(Me)_3C_6H_2$	TfO^-	24	**3dd**, 86[c]	9[c]	–
7	**1l**, 2-OMe	**2j**, 3-CF_3	TMP	CF_3COO^-	24	**3ld**, 75	–	–
8		**2k**, 3-CF_3	2,4,6-$(Me)_3C_6H_2$	TfO^-	24	**3ld**, 43[c]	7[c]	–
9	**1a**, 4-Me	**2l**, 4-NO_2	TMP	CF_3COO^-	24	**3al**, 80	–	–
10		**2m**, 4-NO_2	2,4,6-$(Me)_3C_6H_2$	TfO^-	24	**3al**, 53[c]	6[c]	4[b]

[a] Conditions: 0.5 mmol of **1**, 0.75 mmol of **2**, 0.75 mmol of Et_3N, 10 mol% CuI in 5 mL of 1,2-DCE in Ar atmosphere.
[b] Isolated yield.
[c] According to the NMR experiments.

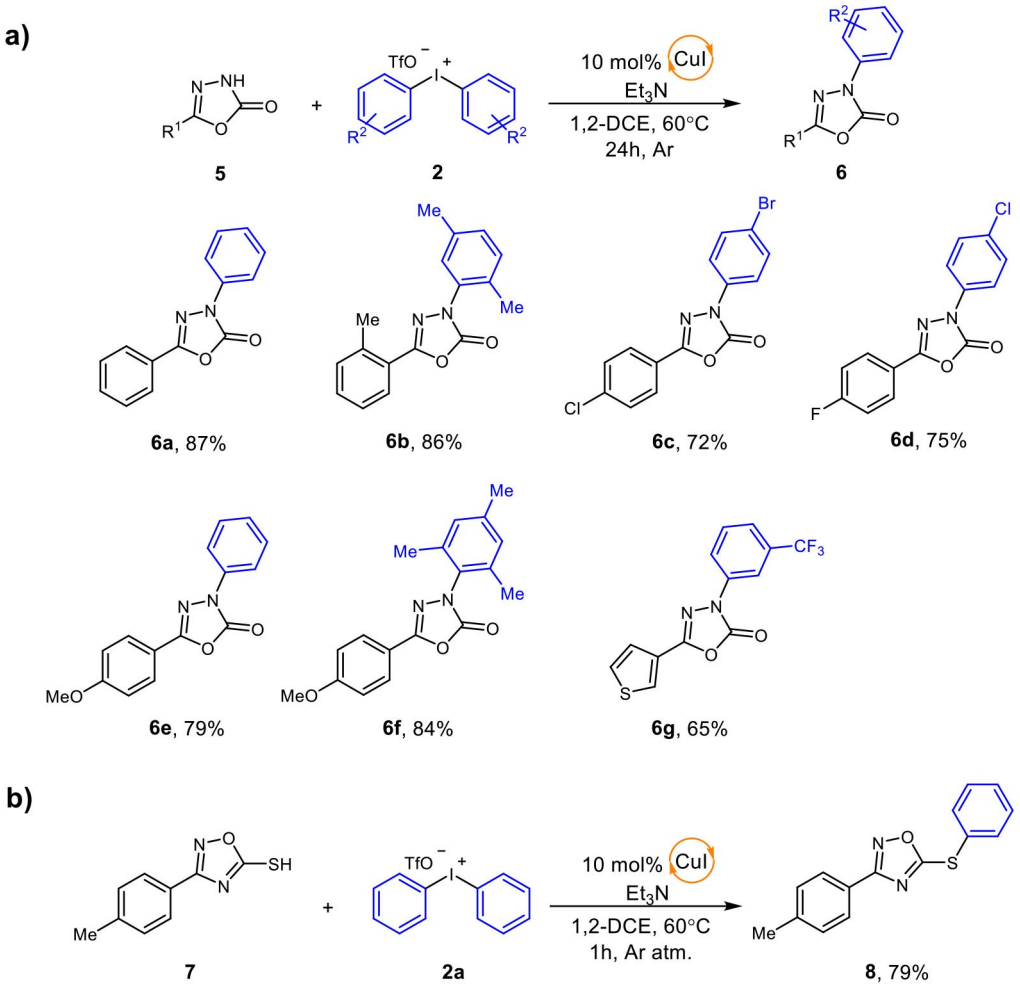
(HIV) molecule.[9] Our initial experiments with symmetric iodonium salts allowed to isolate **3ld** in 30% yields (Scheme 2). Implementation of TMP-substituted iodonium salt **2j** resulted only in 43% (Table 2, Entries 7 and 8). Overall, albeit mesityl-substituted iodonium salt in some cases demonstrated better yield than TMP-substituted iodonium salt, the utilization of the last ones sufficiently increased the yield of **3ld** up to 75%, while the use of mesityl-substituted iodonium salt **2k** ones led to more sustainable results in both selectivity and yield of arylation.

The evaluation of iodonium salts reactivity allowed us to sufficiently improve the yields of products **3** compared to symmetrical iodonium salts. Thus, we successfully prepared the arylated oxadiazolones **3al–ks** using unsymmetrical **2l,n–s** with better yields (68–88%) (Scheme 5). The yield of product does not depend on the electronic effects of substituents in the *para*-position of diaryliodonium salts The reaction proceeded smoothly with electron-withdrawing (**3al**, 80%; **3kq**, 70%) and electron-donating groups (**3cn**, 68%; **3gp** 77%). The reaction with *meta*-substituted iodonium salts **2j**,**o**,**r** give good yields (**3fo**, 72%; **3ar** 81%). However, in the case of sterically hindered *ortho*-chlorophenyl-substituted iodonium salt **2s**, the desired product **3cs** was isolated in lower yield 19% for *ortho*-substituted oxadiazolone **1c** and in trace amount for **1b**. The decrease of yield is in agreement with the behavior of sterically hindered diaryliodonium salt **2f** and reported data about arylation of N-nucleophiles with TMP-substituted iodonium salts.[37,39,42]



Scheme 5. Arylation of 1,2,4-oxadiazol-5(4*H*)-one **1** by unsymmetrical diaryliodonium salts **2**.[a,b]

To our delight, the reaction's scope could be extended to 1,3,4-oxadiazol-2(3*H*)-ones **5** (Scheme 6, a). The published approaches to arylation of 1,3,4-oxadiazol-2(3*H*)-ones limited only to corresponding 5-alkyl-derivatives prepared by interaction with haloar-



[a] Conditions: 0.5 mmol of **5** or **7**, 0.75 mmol of **2**, 0.75 mmol of Et_3N, 10 mol% CuI in 5 mL of 1,2-DCE in Ar atmosphere; [b] Isolated yield;

Scheme 6. Arylation of 1,3,4-oxadiazol-2(3*H*)-ones **5** and 3-(*p*-tolyl)-1,2,4-oxadiazole-5-thiol **7** by symmetric diaryliodonium salts.[a,b]

enes under harsh conditions.[69,70] The application of the developed procedure allowed to isolate the appropriate derivatives **6** in good yields (>65%) independently from the electronic and steric effect of substituents in **5** The products **6b** and **6f** was obtained selectively in high yield (86 and 84% correspondingly) albeit the use of sterically hindered iodonium salts **2e** and **2f**. Obviously, the efficiency of reaction with **5** revealed a similar to **1** pattern and proceeded smoothly for most substrates. In further experiments, we examined the synthetic applicability of the method for arylation of 3-(*p*-tolyl)-1,2,4-oxadiazole-5-thiol **7** (Scheme 6, b). The soft nucleophilic nature of *S*-center in **7** sufficiently changed the reaction selectivity towards *S*-arylation.[35] The reaction proceeded smoothly, and product **8** was formed after 1 h of stirring. Notable, that arylation of 3-(aryl)-1,2,4-oxadiazole-5-thiol is unknown and proposed procedure can be effective tool for synthesis of 5-(arylthio)-3-(aryl)-1,2,4-oxadiazoles.

Conclusion

In conclusion, we have developed the method for the N-arylation of oxadiazolones derivatives with symmetric and unsymmetric diaryliodonium salts under mild conditions using inexpensive CuI as a catalyst. The utilization of symmetric and unsymmetric diaryliodonium salts sufficiently facilitates access to valuable arylated cyclic amides. Impact of steric effects in

diaryliodonium salts and 1,2,4-oxadiazol-5(4*H*)-ones allow to utilize ready available mesityl-substituted iodonium salts as an alternative to highly selective aryl (TMP)iodonium salts. The proposed method facilitates access to novel derivatives of oxadiazolones, including N-arylated 1,2,4-oxadiazol-5(4*H*)-ones and 1,3,4-oxadiazol-2(3*H*)-ones, and *S*-arylated 1,2,4-oxadiazole-5-thiols. We believe that the proposed approach is able to increase the synthetic applicability of iodonium salts and, moreover, provide a novel way for the design of heterocycles based on oxadiazolones.[56]

Experimental Section

General procedure for the preparation of **3**, **4**, **6**. The solution of triethylamine (0.75 mmol, 104 μL) in 1,2-DCE (5 mL) was added to mixture of oxadiazolone (**1** or **5**, 0.5 mmol, prepared by slightly modified reported procedures),[71,72] diaryliodonium salt (**2**, 0.75 mmol) and CuI (10 mol%, 9.5 mg) under Ar atmosphere. The resulted mixture was heated at 60 °C for 24 hours. Then the solvent was removed under reduced pressure, and the product was purified by silica gel column chromatography (eluent hexane : EtOAc, EtOAc 0→20% or hexane : DCM, DCM 0→50% for the synthesis with TMP-substituted iodonium salts).

Acknowledgements

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[73] The initial manuscript has been uploaded as the preprint: N. Soldatova, A. Semenov, K. Geyl, S. Baykov, A. Shetnev, A. Konstantinova, M. Korsakov, M. Yusubov, P. Postnikov, *ChemRxiv.* **2021**, DOI: 10.26434/chemrxiv.14368985.v1.
[74] Supplementary crystallographic data for this paper have been deposited at Cambridge Crystallographic Data Centre (CCDC numbers 2075081–2075087) and can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif.

RESEARCH ARTICLE

Copper-Catalyzed Selective N-Arylation of Oxadiazolones by Diaryliodonium Salts

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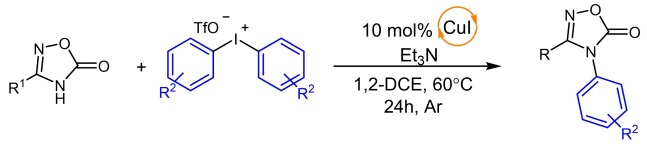
N. S. Soldatova*, A. V. Semenov, K. K. Geyl, S. V. Baykov*, A. A. Shetnev, A. S. Konstantinova, M. M. Korsakov, M. S. Yusubov, P. S. Postnikov*



- **mild conditions**
- **high regio- and chemoselectivity**
- **available catalyst**
- **wide reaction scope**

up to 92%