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Multicomponent Synthesis of Biologically Relevant *S*-Aryl Dithiocarbamates Using Diaryliodonium Salts

Sushanta K. Parida, Sonal Jaiswal, Priyanka Singh,* and Sandip Murarka*

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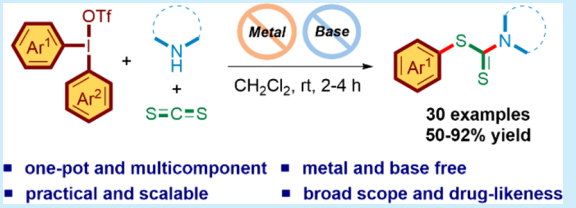
ABSTRACT: A transition-metal-free one-pot three-component annulation between diaryliodonium triflates, cyclic and acyclic aliphatic amines, and carbon disulfide providing a convenient and efficient access to biologically relevant *S*-aryl dithiocarbamates is developed. The reaction does not require metal, base, or any other additive and operates under mild and ambient conditions. This methodology is robust, scalable, and exhibits a broad substrate scope. The *in silico* analysis revealed that the majority of the compounds have a drug-likeness and good ADMET characteristics.

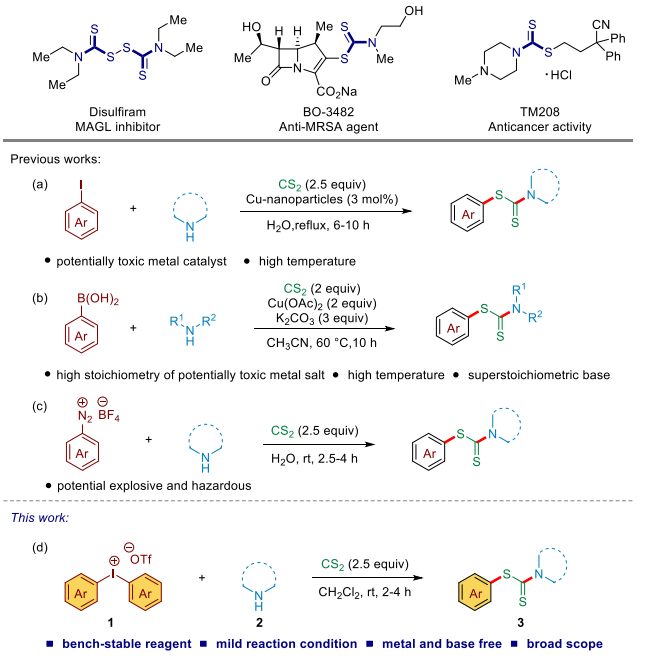


Over the years organic dithiocarbamates have received much attention owing to their diverse applications across the fields. They serve as linkers in solid phase synthesis,[1] important intermediates in the synthesis of a variety of building blocks,[2] and protecting groups in peptide synthesis.[3] Moreover, several biologically active compounds and pharmaceuticals embedded with this structural framework have been reported to act as anticancer agents,[4] antimethicillin-resistant *Staphylococcus aureus* (MRSA) agents,[5] and monoacylglycerol lipase (MAGL) inhibitors,[6] to name a few (Scheme 1). Accordingly, their synthesis has attracted interest of the synthetic community and several methods allowing access to this class of compounds have been developed.

Conventional methods for the synthesis of aryl dithiocarbamates either involve use of stoichiometric and toxic organometallic reagents with tetramethylthiuram disulfide[7] or are driven by copper-catalyzed cross-coupling between iodoarenes[8] or aryl boronic acids[9] with sodium salt of dithiocarbamic acid. Recently, copper-catalyzed *S*-arylation of tetraalkylthiuram disulfides using iodoarenes,[10] aryl boronic acids,[11] and diaryliodonium salts[12] was reported. All these transition-metal-catalyzed methods were carried out in the presence of expensive and toxic copper catalysts, and at elevated temperature. The presence of a strong base and an expensive ligand was indispensable for the success of some of these transformations. The corresponding transition-metal-free two component couplings involving sodium salt of dithiocarbamic acid with either aryldiazonium chloride[13] or hypervalent iodine[14] have been developed as well. However, sodium salt of dithiocarbamic acid is potentially toxic, is difficult to prepare, and limits the substrate scope with regard to amines.[13,15]

In this regard multicomponent reaction (MCR) is noteworthy and desirable, as it represents step economic and cost-efficient tool and enables rapid construction of structurally diverse compound library.[16] Additionally, a MCR obviating the

Scheme 1. Biologically Active Dithiocarbamates and Multicomponent Methods for the Synthesis of Aryl Dithiocarbamates



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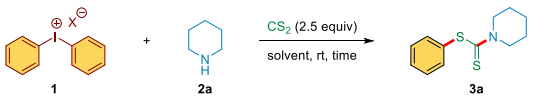
need of any transition metal is even more beneficial as it reduces toxicity, improves cost efficiency, sidelines the hassle during purification, and enables smooth scale-up of the process. A one-pot method for the preparation of alkyl dithiocarbamate through reaction of amines with carbon disulfide and alkyl halide was reported.[17] But this method is mostly restricted to alkyl dithiocarbamates. A strongly activated arene system, such as pentafluorobenzonitrile that is suitable for a S_NAr-type reaction was required for such a reaction to be applicable for the preparation of corresponding aryl counterpart.[18] A three-component one-pot coupling reaction between amines, carbon disulfide, and aryl/styryl halide catalyzed by a copper nanoparticle at high temperature was reported (Scheme 1a).[19] A similar copper-mediated process utilizing (hetero)aryl/alkyl boronic acids was also documented (Scheme 1b).[20] The Ranu group described a metal-free coupling between amines, carbon disulfide and aryl diazonium tetrafluoroborates allowing access to the corresponding aryl dithiocarbamates (Scheme 1c).[26] However, the hazardous and explosive nature of the diazonium salts limited the applicability of the process. Therefore, considering diverse applications of aryl dithiocarbamates, it is highly desirable to develop straightforward, easily diversifiable, metal-free, and environmentally benign reaction technologies utilizing bench-stable and nontoxic reagents for the synthesis of this scaffold.

Lately, hypervalent iodine(III) (HVI) reagents have emerged as easily available, nontoxic, bench-stable, and high functional group tolerant powerful synthetic tool enabling construction of a range of carbon−carbon and carbon-heteroatom bonds.[21] Diaryliodonium salts have often been utilized as electrophilic reagents[22] and are reported to react with a range of carbon- and heteroatom-centered nucleophiles under transition-metal-free conditions.[23] We were intrigued by the possibility of utilizing diaryl iodonium salts as the aryl source in the three-component coupling with amines and using carbon disulfide under metal-free conditions. Such a cascade strategy would be novel, highly efficient, and fascinating from the perspective of green chemistry and sustainable synthesis. As part of our program to develop metal-free cascade annulations[24] and driven by our interest in hypervalent iodine(III) reagents,[21c,d] we herein disclose a hitherto unknown metal-free one-pot multicomponent coupling between diaryliodonium salts, carbon disulfide, and amines to provide biologically relevant *S*-aryl dithiocarbamates in an efficient fashion (Scheme 1d).

We embarked on optimization studies through reacting diaryl iodonium triflate **1** (1 equiv), piperidine **2a** (1.2 equiv), and carbon disulfide (CS_2, 2.5 equiv) in DMF at room temperature for 2 h (Table 1). To our delight, the desired aryl dithiocarbmate **3a** was obtained in 48% yield (entry 1). Typically, an amine **2** was added to a solution/suspension of CS_2 in a given solvent at room temperature and the solution was stirred for 5 min. Then diaryl iodonium salt **1** was added over a period of 10−15 min and the reaction mixture was continued to stir until completion. Importantly, the reactions were carried out in a screw-cap vial and inert atmosphere or Schlenck techniques were not required to perform these reactions. The structure of **3a** was confirmed by single-crystal X-ray analysis (see SI for details). Nevertheless, the yield increased to 57% upon switching the solvent from DMF to acetone (entry 2). No product formation was observed in 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) solvent (entry 3). Pleasingly, the yield of **3a** jumped to 92% in CH_2Cl_2 (entry 4).

Table 1. Optimization of the Reaction Conditions[a]



1 2a 3a

entry	X	solvent	time (h)	yield (%)[b]
1	OTf	DMF	2	48
2	OTf	Acetone	2	57
3	OTf	HFIP	2	ND
4	OTf	CH_2Cl_2	2	92
5	OTf	DCE	2	80
6	OTf	H_2O	2	55
7	OTs	CH_2Cl_2	2	56
8	Br	CH_2Cl_2	2	72
9	BF_4	CH_2Cl_2	2	68
10	OTf	CH_2Cl_2	0.5	80
11	OTf	CH_2Cl_2	1	84
12	OTf	CH_2Cl_2	4	91
13[c]	OTf	CH_2Cl_2	2	80

[a]Reaction conditions: 0.1 mmol scale using **1** (1 equiv), **2a** (1.2 equiv), and CS_2 (2.5 equiv) in solvent (1 mL). [b]Isolated yield. [c]Using 1.5 equiv of CS_2.

Among the other solvents tested (DCE, H_2O), CH_2Cl_2 remained to be the optimal one (entries 5 and 6). Then we decided to investigate the role of diaryl iodonium counterion on the efficacy of the reaction. Notably, the yield plummeted to 56% upon utilizing tosylate as an counterion (entry 7), whereas, in case of bromide and tetrafluoroborate, 72% and 68% yields were obtained in a respective manner (entries 8 and 9). Reducing the reaction time to either 0.5 or 1 h delivered inferior results (entries 10 and 11), and prolonging the reaction time to 4 h did not improve the yield (entry 12). Moreover, decreasing the amount of CS_2 from 2.5 equiv to 1.5 equiv led to reduced yield (entry 13).

With optimized conditions in hand, we set out to explore the scope of the three-component reaction manifold through reacting diphenyliodonium triflate **1a** with an array of electronically and structurally diverse amines **2** (Figure 1). Pleasingly, a range of cyclic aliphatic amines, such as piperidine, pyrrolidine, morpholine, *N*-Boc-protected piperazine, tetrahydroisoquinoline, and azepane that are diverse with regard to ring size and heteroatoms, participated in the

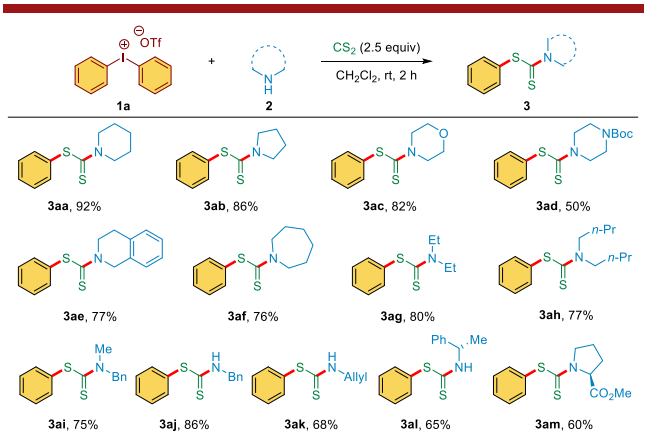


Figure 1. Substrate scope with regard to amines. Reactions were performed on 0.25 mmol scale using **1a** (1 equiv), **2** (1.2 equiv), and CS_2 (2.5 equiv) in CH_2Cl_2 (2.5 mL).

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transformation providing the corresponding products (**3aa**–**3af**) in moderate to excellent yields (50%–92% yields). The method was found to be quite robust for several acyclic secondary aliphatic amines to furnish the corresponding aryl dithiocarbamates (**3ag**–**3ai**) in good yields. Pleasingly, primary aliphatic amines, which could not be accommodated in earlier methods,[10a,19,20,25] underwent smooth transformation under the present protocol. Accordingly, benzyl amine and allyl amine afforded the desired products **3aj** and **3ak** in 86% and 68% yields, respectively. Unfortunately, the attempt to prepare phenyl carbamodithioate through MCR of **1a** with aqueous ammonia and CS_2 was unsuccessful. Importantly, chiral primary and secondary amines were tolerated to give the corresponding coupled products **3al** (65%) and **3am** (60%) in good yields.

Next, we explored the scope of symmetrical diaryliodonium triflates **1** by varying substitution pattern on the phenyl ring (Figure 2). The diaryliodonium triflates containing 4-Me and

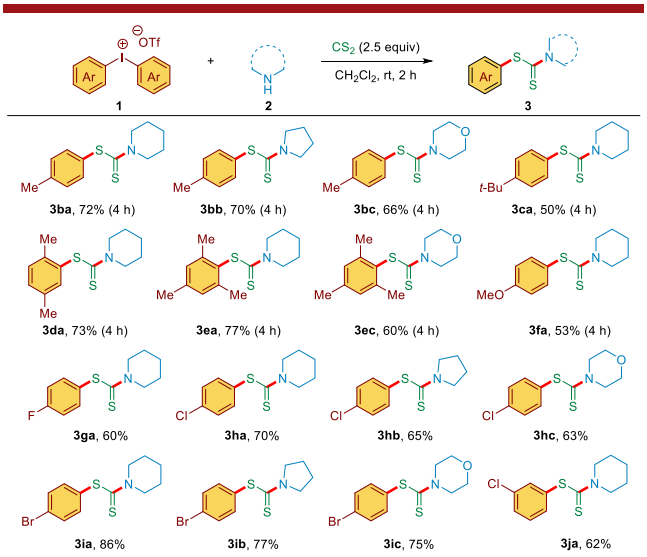
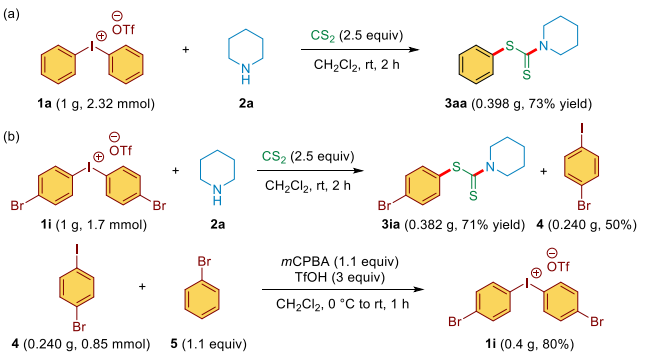


Figure 2. Substrate scope with regard to diaryl iodonium salts. Reactions were performed on 0.25 mmol scale using **1** (1 equiv), **2** (1.2 equiv), and CS_2 (2.5 equiv) in CH_2Cl_2 (2.5 mL).

4-*t*-Bu substituents on the phenyl ring underwent smooth transformation providing the corresponding products (**3ba**–**3ca**) in moderate to good yields (50%–72%). Pleasingly, the reaction was feasible in case of iodine(III) reagents containing 2,5-dimethyl (**3da**, 73%) and sterically encumbered 2,4,6-trimethyl substitution pattern on the phenyl ring (**3ea**, 77% and **3ec**, 60%). Notably, aryl dithiocarbamates containing such a sterically congested aryl moiety could not be prepared through earlier metal-free or copper-catalyzed/mediated protocols.[9–12,19,20,26] An electron-rich methoxy functionality could be accommodated on the phenyl ring to furnish the desired product (**3fa**) in 53% yield. Expectedly, the MCR was found to be quite efficient in case of HVI reagents containing electron-withdrawing substituents (4-F, 4-Cl, 4-Br, 3-Cl) on the phenyl ring furnishing the corresponding coupled products (**3ga**–**3ja**) in good yields (60%–86%). Notably, diheteroaryl iodonium salts, such as di-2-thienyl iodonium trilflate could not be accommodated in this MCR. In general, the reaction was faster in the case of HVI reagents with electron-withdrawing substituents on the phenyl ring and a longer reaction time (4 h) was required where the aromatic ring was embedded with electron-rich substituents.

In order to demonstrate the robustness and practicality of the process, large scale reactions were carried out (Scheme 2).

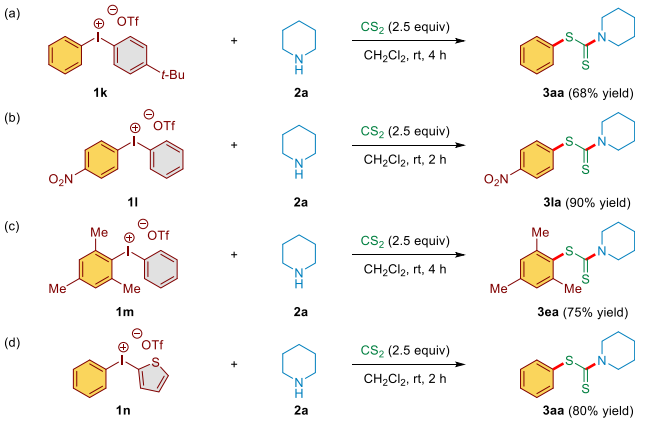
Scheme 2. Scale-up Synthesis of *S*-Aryl Dithiocarbamates



We were pleased to note that 1 g of HVI reagents **1a** and **1i** participated in the three-component coupling through reacting with piperidine **2a** and CS_2 to provide the coupling products **3aa** and **3ia** in 73% and 71% yields, respectively. Importantly, to address the concern of atom economy of the process, we decided to isolate the liberated iodoarene derivative. Pleasingly, as shown in Scheme 2b, besides 71% of desired **3ia**, iodoarene derivative **4** was recovered in 50% yield in the scale-up reaction. Moreover, the recycled **4** was utilized to prepare the HVI reagent **1i** in 80% yield.[27]

Subsequently, we intended to evaluate the scope of the process with regard to nonsymmetrical diaryliodonium triflates (Scheme 3). Importantly, reaction of unsymmetrical diary-

Scheme 3. Chemoselectivity Trends for Unsymmetrical Diaryliodonium Triflates



liodonium salts with nucleophiles is controlled by the electronic and steric nature as well as the type of nucleophile plays a crucial role in the chemoselective outcome of the process.[23a] In general, it has been observed that under transition-metal-free conditions, transfer of more electron-withdrawing and sterically hindered aryl group is preferred.[23a,c,d] Accordingly, to explore the chemoselectivity of the transformation, we synthesized four different electronically and sterically diverse nonsymmetrical diaryliodonium triflates (**1k**–**1n**) and reacted those with piperidine **2a** and CS_2 under the standard reaction conditions. When diaryliodonium salts **1k**

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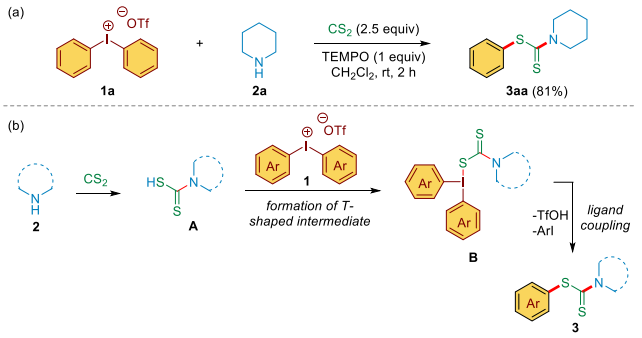
and **1l** were reacted, the selective transfer of phenyl group over 4-*t*-Bu-Ph group in case of **1k**, and 4-nitrophenyl group instead of the phenyl ring in the latter case (**1l**) was observed (Scheme 3a and 3b). These facts explicitly demonstrates that transfer of electron-deficient aryl ring is strongly preferred in this reaction. When mesityliodonium salt **1m** was used, an exclusive transfer of the sterically congested mesityl group giving rise to the product **3ea** (75%) along the line of so-called "*ortho*-effect" was observed (Scheme 3c). In corroboration with previous reports,[23b,c] we observed that the thienyl group imparts strong directing ability and behaved as a perfect "spectator" group allowing selective transfer of the phenyl ring in case of iodonium salt **1n** (Scheme 3d).

It is well-documented that transition-metal-free arylations using diaryliodonium salts either proceed through a SET (single electron transfer) mechanism[28] or *via* formation of a T-shaped intermediate,[23a,29] which then collapses to the product by ligand coupling between the nucleophile and the equatorial aryl group. In order to investigate the possibility of a radical mechanism, **1a**, **2a**, and CS_2 were reacted under optimized conditions in the presence of TEMPO as the radical scavenger (Scheme 4a). The multicomponent reaction was found to be

Scheme 4. Control Experiment and Proposed Mechanism



insensitive toward the radical scavenger and the product **3a** was formed in 81% yield. This experiment ruled out the possibility of an underlying SET mechanism. Based on our control experiment and previous reports,[23a,d,30] we propose that an initial reaction between amines **2a** and CS_2 leads to the generation of dithiocarbamic acids **A**, which upon reaction with diaryliodonium salts **1** form a T-shaped intermediate **B** (Scheme 4b). Finally, a ligand coupling between dithiocarbamate moiety and the equatorial aryl functionality furnishes the desired *S*-aryl dithiocarbmates **3**.

Since dithiocarbamates impart diverse biological properties, we decided to perform *in silico* studies of the synthesized *S*-aryl dithiocarbamates to predict their drug-likeness and lead-like pharmacokinetic properties. Pleasingly, the compounds were found to be in good compliance (75%−100%) with different drug-likeness filters (Lipinski, Ghose, Veber, Egan, and Muegge) (Figure 3a and SI Tables 1−3). Furthermore, to our delight, all compounds showed a good range of average ADMET score (0.76−0.84) with regard to human intestinal absorption, blood-brain barrier penetration, Caco-2 permeability, Ames mutagenicity, carcinogenicity, and acute oral toxicity class (Figure 3b and SI Table 4).

In summary, we have developed an efficient, robust, and scalable multicomponent coupling between symmetrical and unsymmetrical diaryliodonium triflates, cyclic and acyclic primary and secondary amines and carbon disulfide enabling

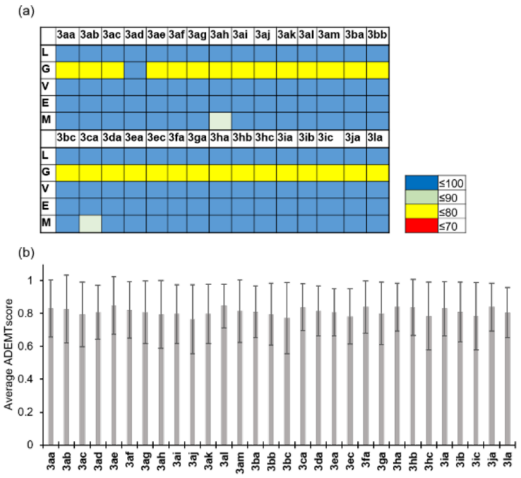


Figure 3. *In silico* analysis of drug-likeness (a) and ADMET (b) prediction. (a) Color map indicating percentage compliance of each drug for L = Lipinski, G = Ghose, V = Veber, E = Egan, and M = Muegge drug-likeness filters. (b) Bar graph represents average ADMET-score for each drug. The error bars indicate standard deviation.

an easy access to a diverse range of *S*-aryl dithiocarbamates. The method does not require any expensive and toxic transition metal, strong base, and high temperature. The reactions were carried out under environmentally benign conditions using nonhazardous, bench-stable, easily available, and inexpensive reacting partners. Furthermore, the present method is noteworthy as it allows rapid construction of a potentially biologically active compound library that is diversified with regard to both the aryl as well the amine part. This is a major improvement over the earlier protocols, especially those utilizing either sodium salt of dithiocarbamic acid or thiuram disulfide reagents as coupling partners, which drastically limited the scope of the reaction. Importantly, *in silico* analysis revealed that the synthesized compounds accomplished drug-likeness and lead-like properties that are requisite for drug potency, in turn making them promising candidates for further exploration of their efficacy using biological assays.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c02220.

Experimental procedures, crystal data, tables of SMILES notations, physiochemical properties, drug-likeness percentage compliance, and ADMET scores, and NMR spectral data of all new compounds (PDF)

Accession Codes

CCDC 2083980 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge *via* www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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AUTHOR INFORMATION

Corresponding Authors

Priyanka Singh − *Department of Bioscience and Bioengineering, Indian Institute of Technology Jodhpur, Karwar 342037 Rajasthan, India*; Email: priyankasingh@iitj.ac.in

Sandip Murarka − *Department of Chemistry, Indian Institute of Technology Jodhpur, Karwar 342037 Rajasthan, India*; orcid.org/0000-0003-1692-0939; Email: sandipmurarka@iitj.ac.in

Authors

Sushanta K. Parida − *Department of Chemistry, Indian Institute of Technology Jodhpur, Karwar 342037 Rajasthan, India*

Sonal Jaiswal − *Department of Bioscience and Bioengineering, Indian Institute of Technology Jodhpur, Karwar 342037 Rajasthan, India*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.1c02220

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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