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$R_4NHal/NOHSO_4$: A Usable System for Halogenation of Isoxazoles, Pyrazoles, and Beyond

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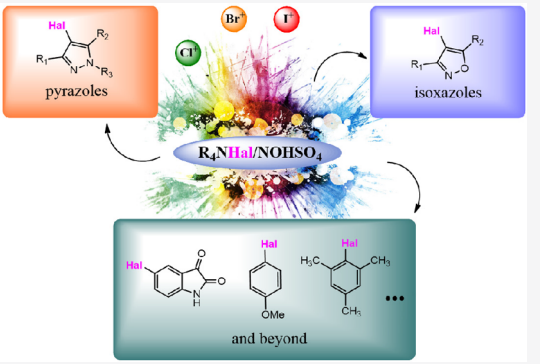
ABSTRACT: A new convenient and versatile halogenating system ($R_4NHal/NOHSO_4$), giving straightforward and general access to halogenated 3,5-diaryl- and alkylarylisoxazoles, pyrazoles and electron-rich benzenes from the corresponding scaffolds, is suggested. The method provides excellent regioselectivity, scalability to the gram scale, and a broad scope for both aromatics and halogens. A three-step, one-pot reaction protocol was developed, and a series of 3,5-diaryl-4-haloisoxazoles has been efficiently synthesized from 1,2-diarylcyclopropanes under suggested nitrosating−halogenating conditions.



INTRODUCTION

Halogenated aromatic compounds are valuable synthetic scaffolds that can be applied as precursors for direct coupling,[1] selective preparation of either arylboronic esters or acids, or for further functionalization of arenes via Grignard reaction[2] or the aromatic nucleophilic substitution. The same methods are used for the synthesis of substituted hetarenes including isoxazoles starting from their halogenated precursors.[3−5] Haloisoxazoles and 4-haloisoxazoles, in particular, are widely applied for functionalization of the isoxazole ring[6,7] and for construction of combinatorial libraries of this heterocycle.[8,9] 4-Haloisoxazoles are obtained by electrophilic cyclization of α-alkynyl oximes[10,11] and 1,3-dipolar cycloadditions of 1-halo- or 1-aluminoalkynes with nitrile oxides;[12,13] nevertheless, direct electrophilic aromatic halogenation of 4*H*-isoxazoles is the most available one. A wide range of halogenating agents have been suggested for the direct synthesis of arylhalogenides; however, only a few of them are mild.[14−16] Most halogenating systems prescribe rather rigid conditions and have limited application. Thus, screening literature revealed that the use of a strongly acidic medium or oxidizing agents is necessary for the synthesis of 4-haloisoxazoles.[17]

In our previous investigations dealt with the synthesis of 5-haloisoxazoles, we found that nitrosonium cation readily oxidizes bromide anion formed during the reaction, thus generating electrophilic species that in situ brominate the isoxazole ring.[18,19] This result was put at the core of the study dealing with the development of new convenient halogenating systems for electron-rich aromatics.[20]

RESULTS AND DISCUSSIONS

We began our experiments with the bromination of a model 3,5-diphenylisoxazole **1**. Searching for optimal reaction conditions, we varied the source of halogen and tried several nitrosating reagents, as well as solvents. We primarily selected a range of bromides as bromine surrogates, namely, gaseous hydrogen bromide, as well as potassium, ammonium, and tetramethylammonium bromides. The reaction of **1** with either hydrogen or potassium bromides in combination with nitrosonium chlorosulfate in nitromethane was inefficient, obviously due to the low solubility of the reactants. However, the same reaction with ammonium or tetramethylammonium bromides gave excellent results: isoxazole **1** was smoothly, quantitatively, and selectively brominated at the C-4 carbon of the isoxazole ring in reaction with 3 equiv of both $Me_4NBr/NOSO_3Cl$ at 20 °C for 20 min. We also screened other nitrosating reagents including nitrosonium tetrafluoroborate and nitrosylsulfuric acid. Though all of them provided good results, we revealed nitrosylsulfuric acid as an oxidant of choice due to its availability, cheapness, and relative stability. At the next stage, we examined the influence of temperature, reaction duration, and the reagent ratio on the transformation of

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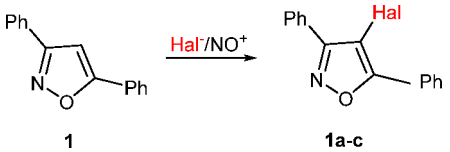
Table 1. Halogenation of 3,5-Diphenylisoxazole 1 with $R_4NHal/NOHSO_4$: Optimization of the Reaction Conditions



1 1a-c

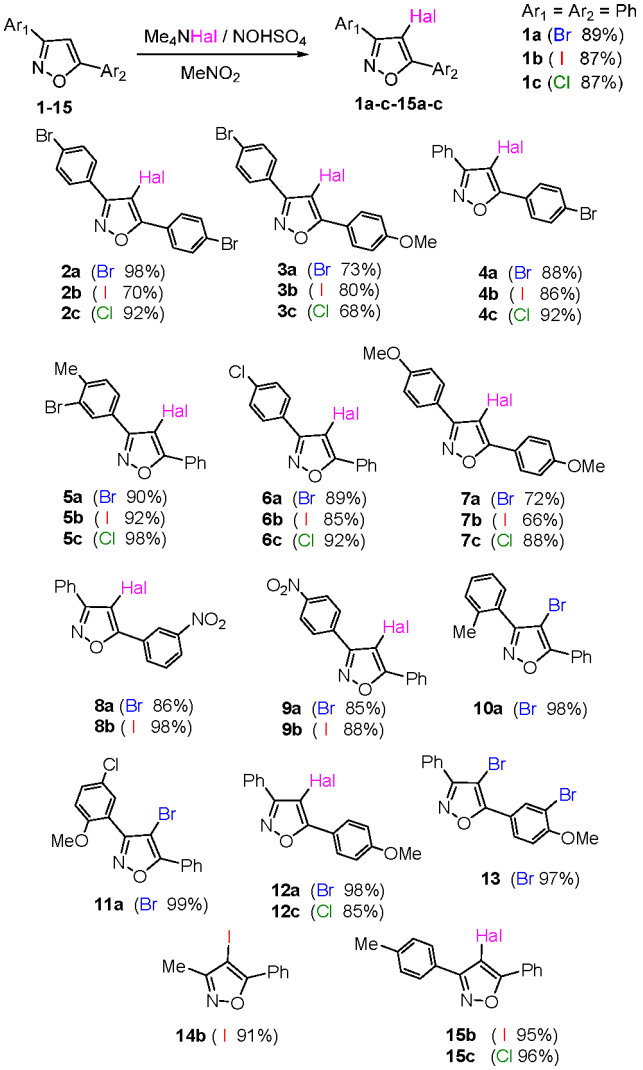
entry	halogen source (equiv)	$NOHSO_4$, equiv	T (°C)	t (h)	product	Hal	conversion	isolated yield (%)
1	Me_4NBr (1.1)	1.1	20	1	**1a**	Br	30	
2	Me_4NBr (1.2)	3	20	1	**1a**	Br	100	89
3	NH_4Br (1.2)	3	20	3	**1a**	Br	100	70
4	Me_4NI (1.2)	3	20	1	**1b**	I	100	87
5	NH_4I (1.2)	3	20	3	**1b**	I	100	89
6	I_2 (0.6)	3	20	2	**1b**	I	100	82
7	Me_4NCl (1.2)	3	20	24	**1c**	Cl	45	
8	NH_4Cl (1.5)	4	20	24	**1c**	Cl	20	
9	Me_4NCl (3.0)	3	20	24	**1c**	Cl	100	87

isoxazole **1** to 4-bromoisoxazole **1a**. It was shown that the excess of both components of the brominating system or even only the excess of nitrosylsulfuric acid significantly accelerates the reaction (Table 1, entries 1 and 2): $Me_4NBr/NOHSO_4$ taken in a ratio of 1.2:3 equiv per 1 equiv of **1** ensured 100% conversion of **1** at 20 °C for 1 h and produced 4-bromoisoxazole **1a** in an 89% isolated yield. Changing Me_4NBr for NH_4Br under the same reaction conditions gave 100% conversion of **1** in 3 h. Though, in nitromethane, the reaction proceeds faster and cleaner, DCM, carbon tetrachloride, and acetonitrile also can be applied. An important peculiarity of this reaction process is the workup, in which the use of successive treatment of the resultant mixture with aqueous Na_2SO_3 and water gave the products not requiring any purification.

We next studied the reaction scope against the change of substitution at the benzene rings. Most of the isoxazoles **1**–**12** presented at Scheme 1 were smoothly brominated at room temperature within 1–5 h, depending on the reactivity of the substrates. Enhancing the temperature accelerates the reactions. For example, the reaction of isoxazoles **8** and **9**, bearing electron-deficient aromatics with 3 equiv of $Me_4NBr/NOHSO_4$, could be completed at 20 °C in 24 h or at 60 °C in 3 h. Note that, for all studied isoxazoles, we observed high regioselectivity of halogenation for the isoxazole ring in spite of the excess of halogenating reagents. An exception is compounds with strongly electron-donating substituents in the benzene rings. Thus, in the case of isoxazole **12**, 100% bromination for the isoxazole ring has been already achieved in 30 min of the reaction with 1.2 equiv of both $Me_4NBr/NOHSO_4$ at 20 °C. Treatment of **12** with 3-fold excess of the reagents for 20 h afforded only double brominated product **13** with a nearly quantitative yield.

We next evaluated the generality of the reaction toward other halogens. In order to get direct access to 4-iodoisoxazoles, we changed ammonium bromides for the corresponding iodine salts. Both ammonium and tetramethylammonium iodides in the presence of nitrosylsulfuric acid afforded 4-iodo-3,5-diphenylisoxazole **1b** with equal success (Table 1, entries 4 and 5). The excess of nitrosylsulfuric acid in relation to iodine surrogate is strongly recommended, especially in the case of EWG-substituted benzene rings (isoxazoles **6**, **8**, and **9**). The fact is that the deactivated isoxazole ring is less reactive toward electrophilic halogenation, and a part of I^+ species formed during the redox reaction

Scheme 1. Halogenation of 3,5-Diarylisoxazoles



recombines with iodide anions of the ammonium salt and is discarded out of the solution in the form of elemental iodine. Elevating the temperature slightly promotes the iodination, unlike the bromination, apparently due to the fact that elemental bromine itself can be used for the bromination of isoxazoles.[21] However, using an excess of nitrosylsulfuric acid

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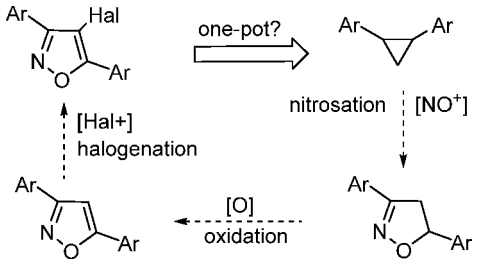
provides some constant amount of I^+ species in the reaction medium, thus making it possible to rectify the situation and consequently to afford high yields of 4-iodoisoxazoles (Scheme 1). Due to the low equilibrium concentration of electrophilic iodine, the $Me_4NI/NOHSO_4$ system is very gentle and selective even for isoxazoles bearing electron-rich benzene rings. Thus, alkyl-substituted isoxazole **14** was found to be an equally viable substrate for the reaction to furnish the product **14b** in 91% yield. Elemental iodine also can be applied for the iodination of isoxazoles, and in combination with $NOHSO_4$, it forms a more active iodinating system. In this case, both iodine atoms participate in the process; hence, 0.5−0.6 mol of iodine per mole of isoxazole is enough to complete the reaction (Table 1, entry 6). This is a notable difference from the NIS reactions when a large excess of NIS was required for complete iodination of 3,5-diarylisoxazoles.[17] The system $I_2/NOHSO_4$ ensures excellent results for isoxazoles with deactivated benzene rings. The reaction of isoxazole **6** with $I_2/NOHSO_4$ taken in a molar ration 1:1.2:3 was completed in 1 h at room temperature, and the corresponding 4-iodoisoxazole **6b** was obtained in 85% isolated yield, for comparison, conversion of **6** in reaction with $Me_4NI/NOHSO_4$ (molar ration 1:1.2:3) for the same period of time constituted 60%. To test the ability to scale up the synthesis, gram-scale reactions of isoxazoles **1**, **5**, and **6** with either $Me_4NI/NOHSO_4$ or $I_2/NOHSO_4$ were also carried out, giving the corresponding 4-iodoisoxazoles **1b**, **5b**, and **6b** in 72−83% yields.

We were also pleased to discover a general chlorination procedure for the synthesis of 3,5-diaryl-4-chloroisoxazoles using ammonium or tetramethytlammonium chlorides. In detail, the chlorination of isoxazoles proceeds slower in comparison with the bromination and iodination, apparently due to the higher oxidation potential of a chloride ion (Table 1, entry 7). In a common case, the reactions should be performed with 3 equiv of both nitrosylsulfuric acid and chlorine surrogate relative to isoxazole at room temperature for an extended reaction time (about 20−24 h), especially for deactivated substrates. Short-term rather than prolonged heating of the reaction mixture (30 min at 60 °C then 20 °C) accelerates the reaction resulting in 30% conversion in 3 h and full completion of the reaction in 20 h. Prolonged heating may provoke the emission of gaseous chlorine out of the solution (yellow-green fumes in a reaction vessel), thus preventing the reaction to complete. As a result of our study, a series of 3,5-diaryl-4-chloroisoxazoles **1c**−**7c**, **12c**, and **15c** was obtained with the same excellent regioselectivity and good-to-excellent yields (Scheme 1).

One of the routes for the construction of five-membered *N,O*-heterocyclic scaffolds, isoxazolines, or isoxazoles is nitrosation of cyclopropanes.[22−25] Recently, we have shown that nitrosylsulfuric acid can be successfully used in the synthesis of 3,5-diarylisoxazoles from the corresponding 1,2-diarylcyclopropanes.[26,27] We envisioned the scenario depicted in Scheme 2

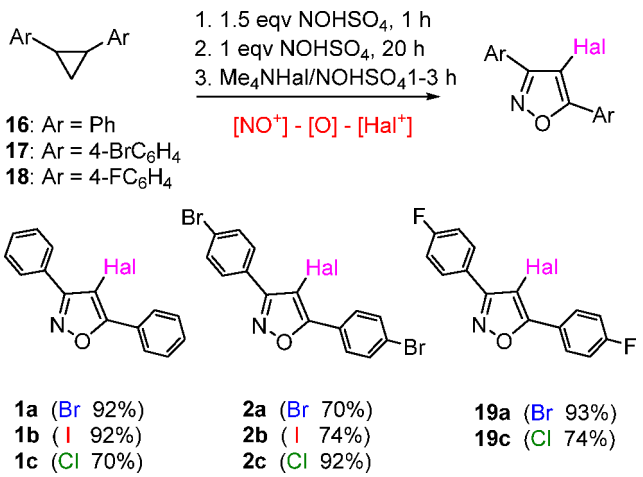
Indeed, the portion-wise addition of 1.5 followed by 1 equiv of nitrosylsulfuric acid in an hour or two to a solution of 1,2-diarylcyclopropane in $MeNO_2$ resulted in the sequential formation of the corresponding 3,5-diaryl-4,5-dihydroisoxazole followed by 3,5-diarylisoxazole that can be monitored by TLC. Finally, the introduction of an additional portion of nitrosylsulfuric acid and tetramethylammonium halide into the resulting mixture afforded the targeted 4-haloisoxazole.

Scheme 2. Envisioned Scenario for the Synthesis of 3,5-Diaryl-4-haloisoxazoles Starting from Symmetric 1,2-Diarylcyclopropanes



It is important to note that the last stage, halogenation of the isoxazole ring, should be initiated only after full completion of the previous nitrosation−oxidation processes (TLC control). The question is that nitrosation of 1,2-diarylcyclopropanes is a rate-limiting stage in these reaction sequences. The oxidation of 4,5-dihydroisoxazole to the corresponding isoxazole, as well as the oxidation of halide anions to the electrophilic species, proceeds much more vigorously. As a result, the hasty addition of tetramethylammonium halide into the reaction medium leads to the foremost consumption of nitrosylsulfuric acid for halide ion oxidation rather than cyclopropane nitrosation. Thus, starting from the corresponding 1,2-diarylcyclopropanes **16**−**18**, the full one-pot nitrosation−oxidation−halogenation reaction sequence afforded direct access to the targeted isoxazoles **1a**−**c**, **2a**−**c**, and **19a**,**c**, respectively, in 70−93% overall yields (Scheme 3), and the nitrosylsulfuric acid can be viewed as a tandem nitrosation−oxidation process agent.

Scheme 3. One-Pot Synthesis of 3,5-Diaryl-4-haloisoxazoles from 1,2-Diarylcyclopropanes



The first results prompted our further investigations with a variety of substances. A series of pyrazoles **20**−**22** was halogenated under the standard conditions in uniformly good yields of the corresponding 4-halopyrazoles **20a**, **21a**,**b**, and **22a**−**c** (Scheme 4).

Finally, we tested some other aromatic systems for their ability toward halogenation under suggested conditions. Compounds **23**−**30** depicted at Scheme 5 were obtained in good yields (for details of the experiments, see Supporting Information). Benzenes with electron-withdrawing groups, namely, nitrobenzene, bromobenzene, and 4-nitrotoluene, occur inactively and were recovered intact. Since for

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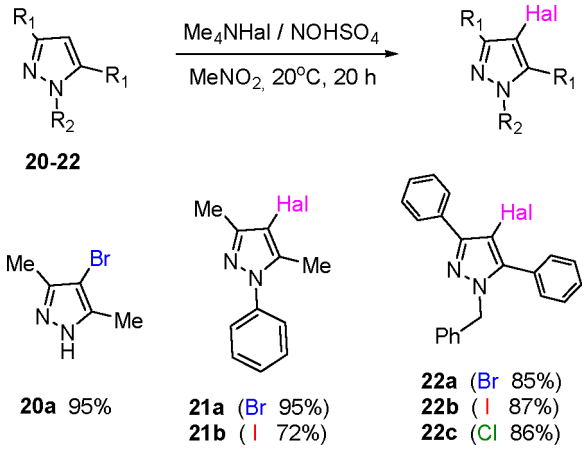
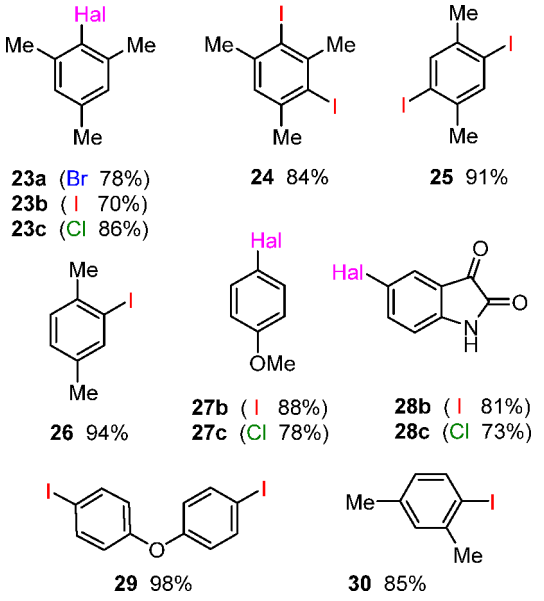
Scheme 4. Halogenation of 3,5-Disubstituted Pyrazoles

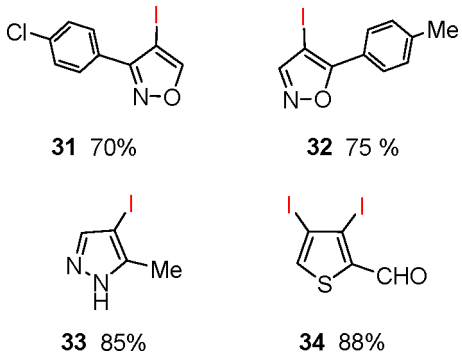


Scheme 5



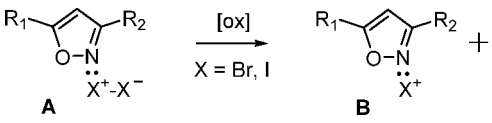
mesitylene and *p*-xylene, bis-iodination products **24** and **25** were easily formed when the excess of an iodine surrogate was used, we tried several monosubstituted five-membered heterocycles with more than one C−H bond in the heteroring. In all cases, except 2-thiophenecarbaldehyde, we obtained monoiodinated products **31**−**33** (Scheme 6).

Scheme 6



Although we did not specially investigate the mechanism of halogenation when using the $R_4NHal/NOHSO_4$ system, we can express some considerations on this issue based on the literature and the facts at our disposal. As the common feature of 1,2-azoles, S_EAr reactions occur at the 4-position of the isoxazole ring.[28] The latest report on the electrophilic halogenation of isoxazole confirms the following: treatment of unsubstituted isoxazole with NIS/TFA under microwave irradiation conditions (120 °C) afforded only 4-iodoisoxazole in 70% yield.[29] The specific rules of the orientation in the azole series are determined by heteroatoms of two types in the azole molecules. A reaction is directed preferentially to that position of the heterocycle that is the least deactivated by the "pyridine" nitrogen atom (the *β*-position relative to N_{pyrid}).[30] Our data on the reactivity of substrates, depending on the electronic properties of substituents in the aromatic/heteroaromatic rings and the orientation of the substituents in halogenation with the $R_4NHal/NOHSO_4$ system, also testify in favor of the electrophilic substitution reaction. So the question is as follows: what is an electrophilic particle "Hal^+", and how is it formed?

Early assumptions about the processes occurring during the halogenation of isoxazoles were expressed in the works of Sokolov et al., which successfully carried out bromination and iodination of isoxazoles in the presence of an oxidizing agent (HNO_3 d = 1.5).[31] It is known that nitrogen-containing heterocycles form complexes of various compositions with halogens, which are used for the halogenation of donor aromatics, and in some cases, they are intermediates in halogenation of the heterocycles their selves. An example is the autohalogenation of pyridine.[32] The same complexes are known for the oxazole series.[33] Sokolov et al. suggested that isoxazole complexes with bromine or iodine (**A**) are halogenating agents in the halogenation reactions.[31] In the absence of any additive (oxidants, catalysts), complexes of type **A** carry out intermolecular electrophilic substitution.[21] In their opinion, the action of an oxidizing agent in the halogenation reaction is apparently reduced to facilitating the appearance of cation **B** from complex **A** by oxidation of the halide anion (eq 1).



The assumption that the halogenating agent appears to be a complex cation **B** is confirmed by the absence of substitution in aryl rings of arylated isoxazoles and is explained by the additional deactivation of aromatic rings in the complex cation **B**. It is obvious that the additional effect of a positively charged halogen bound to nitrogen is quite large that, even with an excess of the halogenating reagent, only 4-haloisoxazoles are formed without any traces of the halogenation at benzene rings.

In 1988, Radner F. suggested a simple method for the iodination of aromatic compounds, using I^- as the iodine source and O_2 and catalytic amounts of $NOBF_4$ as the oxidant.[34] In this work, the formation of "I^+" was discussed in terms of possible outer-sphere and inner-sphere electron-transfer steps. Some data concerning the mechanism of direct iodination of aromatic compounds are presented in the review by Merkushev E., where it was emphasized that the existence of

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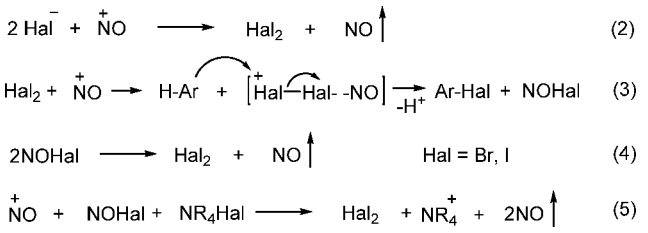
the iodine cation as a kinetically independent species is possible only in highly acid media.[35]

Taking into account these considerations, we can suggest a rational scheme of the transformations proceeding in the reaction medium during the halogenation of aromatic compounds by the $R_4NHal/NOHSO_4$ system (eqs 2−5).At



the initial stage, we observe the oxidation of halide anions to halogens accompanying by intense coloring of the solution (eq 2). The next step is the generation of effective electrophilic species in which the nitrosonium cation can play the role of a Lewis acid followed by the S_EAr reaction with an aromatic compound (eq 3). At this stage, in the case of isoxazoles, we do not exclude the possibility of the transformation shown by eq 1. The final step is regeneration of Hal_2 schematically presented by eqs 4 and 5. In conclusion, we must note that, in all cases of halogenation, the halogenating agent is a complex cation that is in agreement with the high selectivity and mild character of the $R_4NHal/NOHSO_4$ system. The key role of NO^+ is to promote the formation of some positive halide species. This is consistent with the fact that chlorination is more difficult than bromination, and the latter is more difficult than iodination, which can be explained by the higher oxidation potential of chlorine and bromine compared to the potential of iodine.

Quoting Radner F., we want to say that "despite the many uncertainties regarding the mechanism discussed above, the synthetic value of the reaction is considerable." Table 2 illustrates this statement.

The data on the yields of halogenated 3,5-diarylisoxazoles, pyrazoles, and beyond obtained by this method and others given in Table 2 demonstrate the high competitiveness of the $R_4NHal/NOHSO_4$ system: the yields of the products are usually comparable or superior to that obtained by the other methods. Some of these methods suffer from the disadvantage of the drastic conditions employed. Elevated temperatures and strongly acidic media are used in reactions with *N*-halosuccinimides. To achieve high yields in iodination, a significant excess of NIS is required, which is rather an expensive reagent. Using silver salts as a hydrogen iodide trap also has some disadvantages, namely, the high cost of silver salts and the loss of one equivalent of the halogenating reagent in the form of silver halide. The use of the $R_4NHal/NOHSO_4$ system offers a number of advantages in terms of the reagent availability, ease of handling, and reaction workup in comparison to other methods. All reaction wastes are water-soluble and meet the challenges of green chemistry.

CONCLUSIONS

We suggested a new convenient and versatile halogenating system, $R_4NHal/NOHSO_4$, which opens a straightforward and general access to halogenated 3,5-diaryl- and alkylarylisoxazoles, pyrazoles, and electron-rich benzenes from the corresponding scaffolds. The method offers a broad scope for both halogens and aromatics and provides excellent regioselectivity of the halogenation. The products can be produced on a gram scale without chromatographic purification. We also developed a three-step, one-pot protocol for the synthesis of 3,5-diaryl-4-haloisoxazoles starting from available 1,2-diarylcyclopropanes. The suggested sequence of the reactions in which isoxazoline formation, followed by its oxidation to isoxazole, and subsequent isoxazole halogenation performed by sequential addition of the reagents, makes it possible to reduce the number of the workup and purification step. The most significant features of the one-pot synthesis of 3,5-diaryl-4-haloisoxazoles are mild conditions and high productivity. Thus, using the dual nitrosating and oxidative character of nitrosylsulfuric acid, we performed a multistep process as a simple synthetic procedure.

Table 2. Comparative Data on the Yields of Haloisoxazoles, Pyrazoles, and beyond Obtained by This Method and Others

comp	Hal. system	yield (%)	Hal. system	yield (%)	ref	comp	Hal. system	yield (%)	Hal. system	yield (%)	ref
1a	$Me_4NBr/NOHSO_4$	89	NBS[a]	80	11	**21b**	$Me_4NI/NOHSO_4$	72	NIS	92	43
1b	$Me_4NI/NOHSO_4$	87	NIS[a]	85	17	**22b**	$Me_4NI/NOHSO_4$	87		*c*	44
1c	$Me_4NCl/NOHSO_4$	87	NCS	99	11	**23a**	$Me_4NBr/NOHSO_4$	78	PhSSPh/NBS	35	45
4a	$Me_4NBr/NOHSO_4$	88	NBS	86	17	**23b**	$Me_4NI/NOHSO_4$	70	$I_2/H_2O_2/HCl$	97	46
4b	$Me_4NI/NOHSO_4$	86	NIS	59	17	**23c**	$Me_4NCl/NOHSO_4$	86	NCS	60	47
4c	$Me_4NCl/NOHSO_4$	92	NCS	88	17	**24**	$Me_4NI/NOHSO_4$	84	I_2/mCPBA[d]	53	48
6a	$Me_4NBr/NOHSO_4$	89	NBS	71	38	**25**	$Me_4NI/NOHSO_4$	91	I_2/mCPBA[d]	78	48
6b	$Me_4NI/NOHSO_4$	85	ICl[a]	94	39	**26**	$Me_4NI/NOHSO_4$	94	*c*	62	49
6c	$Me_4NCl/NOHSO_4$	92	NCS	75	11	**27b**	$Me_4NI/NOHSO_4$	88	I_2/CF_3COOAg	75	50
7a	$Me_4NBr/NOHSO_4$	72		*b*	40	**27c**	$Me_4NCl/NOHSO_4$	78	$NaIO_4/Cl_2$	83	51
7b	$Me_4NI/NOHSO_4$	66	NIS	45	41	**28b**	$Me_4NI/NOHSO_4$	81	$KICl_2$	86	52
12a	$Me_4NBr/NOHSO_4$	98	NBS	52	17	**28c**	$Me_4NCl/NOHSO_4$	73	Cl_2/AcOH	72	53
12c	$Me_4NCl/NOHSO_4$	85	NCS	37	17	**29**	$Me_4NI/NOHSO_4$	98	IBX/I_2	95	54
14b	$Me_4NI/NOHSO_4$	91	NIS[a]	89	11	**30**	$Me_4NI/NOHSO_4$	85	NIS/TFA	94	55
15c	$Me_4NCl/NOHSO_4$	96		*c*	42	**31**	$Me_4NI/NOHSO_4$	70	NIS/TFA	76	56
20a	$Me_4NBr/NOHSO_4$	95	NBS	98	43	**33**	$Me_4NI/NOHSO_4$	85	I_2/CAN	90	57
21a	$Me_4NBr/NOHSO_4$	95	NBS	96	43						

[a]Indirect halogenation: haloisoxazoles were obtained via halogenative cyclization of alkynyl-*O*-methyl oximes. [b]The yield is not specified. [c]Indirect halogenation. [d]Indirect halogenation: compound was obtained via desulfonyloxyiodiation of the corresponding arenesulfonic acid.

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EXPERIMENTAL SECTION

General Information. The ^{1}H and ^{13}C NMR spectra were recorded on Bruker Avance 400 and Agilent spectrometers with working frequencies of 400.13 and 100.61 MHz in $CDCl_3$ with TMS as an internal standard. The mass spectra were registered on a Finnigan MAT SSQ 7000 GC−MS instrument equipped with a 25 m quartz capillary OV-1 column in the electron-impact ionization mode at an ionization energy of 70 eV with temperature programming from 70 (2 min) to 280 °C (10 min) at a rate of 20 K min^{-1}. Electrospray ionization (ESI) high-resolution mass spectra were recorded on a Bruker microTOF II instrument (direct input). The melting points were measured in a block in an open capillary.

3,5-Diarylisoxazoles **1**−**8**, **12**, and **15** were obtained according to well-known experimental procedures.[36] Isoxazoles **9**−**11** and **14** as well as cyclopropane **18** were kindly provided by L. G. Saginova (M.V. Lomonosov Moscow State University). *trans*-1,2-Bis(4-bromophenyl)cyclopropane **17** was obtained by the reaction of *trans*-1,2-diphenylcyclopropane with NBS according to the LaLonde procedure.[37] Pyrazoles **20**−**22** were kindly provided by L. A. Sviridova (M.V. Lomonosov Moscow State University). Other initials were commercially available.

*Halogenation of 3,5-diarylisoxazoles **1**−**12**, **14**, and **15**, Pyrasoles **20**−**22**, and beyond (General Procedure).* A thoroughly dried 50 mL round-bottom flask equipped with a tightly fitted stopper and a magnetic rod was sequentially charged with crystalline nitrosylsulfuric acid, 10 mL of dry nitromethane, tetramethylammonium salt, and 1 mmol of arene/hetarene, and the resultant mixture was stirred on a magnetic stirrer (for experimental details, see Tables S1−S3). The reaction progress was monitored by TLC. After completion of the reaction, the resultant mixture was quenched with 10% $NaHCO_3$ aqueous solution (10 mL), and organic substances were extracted with CH_2Cl_2 (3 × 15 mL). Combined organic layers were washed with 10% Na_2SO_3 aqueous solution (10 mL) and then water (15 mL) and dried over Na_2SO_4. The solvent was evaporated in vacuo to give the crude product, which, if necessary, was purified by recrystallization from ethanol for solid compounds or by flash chromatography for liquid compounds.

*4-Bromo-3,5-diphenylisoxazole (**1a**):*[11] 133 mg (89% yield), white crystalline solid; mp 130 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.08−8.13 (m, 2H), 7.88−7.92 (m, 2H), 7.49−7.56 (m, 6H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 165.8, 162.1, 130.7, 130.2, 128.9, 128.7, 128.6, 127.9, 127.1, 126.8, 89.6.

*4-Iodo-3,5-diphenylisoxazole (**1b**):*[11] 75 mg (87% yield), yellowish solid; mp 172 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.06−8.12 (m, 2H), 7.80−7.84 (m, 2H), 7.50−7.57 (m, 6H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 169.0, 164.8, 130.8, 130.1, 129.1, 128.8, 128.7, 128.6, 127.8, 127.3, 56.2.

*4-Chloro-3,5-diphenylisoxazole (**1c**):*[11] 66 mg (87% yield), white solid; mp 84 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.07−8.10 (m, 2H), 7.88−7.96 (m, 2H), 7.49−7.57 (m, 6H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 164.1, 160.8, 130.6, 130.3, 128.9, 128.8, 128.3, 127.4, 126.57, 126.52, 104.6.

*4-Bromo-3,5-bis(4-bromophenyl)isoxazole (**2a**):* 118 mg (98% yield), white crystalline solid; mp 180°C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.97 (d, 2H, J = 8.6 Hz), 7.76 (d, 2H, J = 8.4 Hz), 7.65−7.72 (m, 4H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 165.1, 161.3, 132.2, 132.0, 130.0, 128.4, 126.5, 125.4, 124.9, 89.6. One signal is overlapped. Calcd for $C_{15}H_8Br_3NO$, %: C, 39.34; H, 1.76; N, 3.06. Found, %: C, 39.46; H, 1.84; N, 3.15.

*3,5-Bis(4-bromophenyl)-4-iodoisoxazole (**2b**):* 140 mg (70% yield), yellowish crystalline solid; mp 151 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.94 (d, 2H, J = 8.6 Hz), 7.66 (m, 6H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 168.2, 164.0, 132.1, 131.9, 130.5, 129.1, 127.4, 125.9, 125.5, 124.9, 56.2. Calcd for $C_{15}H_8Br_2INO$, %: C, 35.68; H, 1.60; N, 2.77. Found, %: C, 35.67; H, 1.63; N, 2.77.

*3,5-Bis(4-bromophenyl)-4-chloroisoxazole (**2c**):* 155 mg (92% yield), white crystalline solid; mp 122 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.93 (d, 2H, J = 8.6 Hz), 7.78 (d, 2H, J = 8.4 Hz), 7.67 (m, 4H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 163.0, 159.5, 131.9, 131.7, 129.3, 127.5, 125.7, 124.9, 124.7, 124.6, 104.4; HRMS (ESI) m/z [M$^+$] calcd for $C_{15}H_8Br_2ClNO$ 410.8656, 412.8634, 414.8615, 416.8585; found 410.8664, 412.8639, 414.8622, 416.8587.

*4-Bromo-3-(4-bromophenyl)-5-(4-methoxyphenyl)isoxazole (**3a**):* 90 mg (73% yield), colorless crystals; mp 138 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.02 (d, 2H, J = 8.8 Hz), 7.74 (d, 2H, J = 8.3 Hz), 7.64 (d, 2H, J = 8.3 Hz), 7.03 (d, 2H, J = 8.8 Hz), 3.88 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 166.1, 161.4, 161.1, 131.9, 130.1, 128.7, 126.9, 124.7, 119.2, 114.3, 87.8, 55.5; GC−MS (EI, 70 eV, m/z (I_{rel} (%)) cluster 407 (10), 409 (17), 411 (9) [M$^+$]; cluster 300 (3), 302 (4) [M − Br − CO]$^+$; 249 (10) [M − 2Br]$^+$; 135 (100) [$MeOC_6H_4CO$]$^+$; 107 (12) [$MeOC_6H_4$]$^+$; 77 (15) [Ph]$^+$; 76 (9) [C_6H_4]$^+$. Calcd for $C_{16}H_{11}Br_2NO_2$, %: C, 46.98; H, 2.71; N, 3.42. Found, %: C, 46.93; H, 2.67; N, 3.45.

*3-(4-Bromophenyl)-4-iodo-5-(4-methoxyphenyl)isoxazole (**3b**):* 110 mg (80% yield), cream crystalline solid; mp 142 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.02 (d, 2H, J = 8.6 Hz), 7.65 (m, 4H), 7.03 (d, 2H, J = 8.6 Hz), 3.88 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 169.2, 163.7, 161.5, 131.8, 130.5, 129.4, 127.8, 124.6, 119.6, 114.2, 55.5, 54.3; GC−MS (EI, 70 eV, m/z (I_{rel} (%)) cluster 455 (16), 457 (14) [M$^+$]; 249 (8) [M − Br − I]$^+$; 135 (100) [$MeOC_6H_4CO$]$^+$; 107 (10) [$MeOC_6H_4$]$^+$; 77 (12) [Ph]$^+$. Calcd for $C_{16}H_{11}BrINO_2$, %: C, 42.14; H, 2.43; N, 3.07. Found, %: C, 42.08; H, 2.37; N, 3.05.

*3-(4-Bromophenyl)-4-chloro-5-(4-methoxyphenyl)isoxazole (**3c**):* 75 mg (68% yield); white amorphous solid; mp 118 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.99 (d, 2H, J = 8.7 Hz), 7.77 (d, 2H, J = 8.4 Hz), 7.64 (d, 2H, J = 8.4 Hz), 7.03 (d, 2H, J = 8.7 Hz), 3.87 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 164.5, 161.4, 159.7, 132.0, 129.7, 128.2, 126.5, 124.8, 118.9, 114.4, 102.9, 55.4. Calcd for $C_{16}H_{11}BrClNO_2$, %: C, 52.70; H, 3.04; N, 3.84. Found, %: C, 52.85; H, 3.17; N, 3.75.

*4-Bromo-5-(4-bromophenyl)-3-phenylisoxazole (**4a**):*[17] 167 mg (88% yield), white crystalline solid; mp 118−119 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.96 (d, 2H, J = 8.6 Hz), 7.84−7.88 (m, 2H), 7.65 (d, 2H, J = 8.6 Hz), 7.49−7.56 (m, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 164.8, 162.2, 132.2, 130.3, 128.7, 128.6, 128.4, 127.6, 125.6, 125.3, 90.0; GC−MS (EI, 70 eV, m/z (I_{rel} (%)) cluster 377 (11), 379 (22), 381 (11) [M$^+$]; cluster 298 (14), 300 (14) [M − Br]$^+$; cluster 270 (12), 272 (11) [M − CO − Br]$^+$; cluster 258 (16), 260 (18); 219 (19) [M − 2Br]$^+$; cluster 183 (100), 185 (90) [BrC_6H_4CO]$^+$; cluster 155 (69), 157 (64) [BrC_6H_4]$^+$, 77 (59) [Ph]$^+$, 76 (72) [C_6H_4]$^+$, 75 (60).

*5-(4-Bromophenyl)-4-iodo-3-phenylisoxazole (**4b**):*[17] 128 mg (86% yield), white amorphous solid; mp 151−152 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.96 (d, 2H, J = 8.6 Hz), 7.77−7.81 (m, 2H), 7.66 (d, 2H, J = 8.6 Hz), 7.50−7.55 (m, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 167.9, 164.9, 132.1, 130.2, 129.2, 129.0, 128.6, 128.5, 126.1, 125.3, 56.6; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{15}H_{10}BrINO$ 425.8985, 427.8964; found 425.9017, 427.8976.

*5-(4-Bromophenyl)-4-chloro-3-phenylisoxazole (**4c**):*[17] 154 mg (92% yield), white crystalline solid; mp 110−111 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.92 (d, 2H, J = 8.6 Hz), 7.88 (m, 2H), 7.65 (d, 2H, J = 8.6 Hz), 7.49−7.55 (m, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 162.7, 160.4, 131.8, 130.0, 128.4, 127.8, 127.5, 126.8, 124.9, 124.7, 104.6.

*4-Bromo-3-(3-bromo-4-methylphenyl)-5-phenylisoxazole (**5a**):* 225 mg (90% yield), white crystalline solid; mp 110 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.05−8.11 (m, 3H), 7.73 (dd, 1H, J = 1.6, J = 7.9 Hz), 7.51−7.57 (m, 3H), 7.38 (d, 1H, J = 7.9 Hz), 2.49 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 166.0, 160.7, 140.3, 132.2, 131.0, 130.8, 128.9, 127.4, 127.1, 126.6, 125.1, 89.3, 23.0. One signal is overlapped. GC−MS (EI, 70 eV, m/z (I_{rel} (%)) cluster 391 (9), 393 (16), 395 (8) [M$^+$]; cluster 284 (5), 286 (5) [M$^+$ − Br − CO]; cluster 272 (4), 274 (4); 233 (21) [M − 2Br]$^+$; 105(100) [PhCO]$^+$; 77(41) [C_6H_5]$^+$; 51 (5) [C_4H_3]$^+$. Calcd for $C_{16}H_{11}Br_2NO$, %: C, 48.89; H, 2.82. Found, %: C, 49.04; H, 3.20.

*3-(3-Bromo-4-methylphenyl)-4-iodo-5-phenylisoxazole (**5b**):* 202 mg (92% yield), pale yellow solid; mp 122 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.04−8.11 (m, 2H), 8.01 (s, 1H), 7.66 (d, 1H, J = 8.5 Hz), 7.48−7.59 (m, 3H), 7.38 (d, 1H, J = 8.5 Hz), 2.49 (s, 3H); ^{13}C{^{1}H}

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NMR (101 MHz, $CDCl_3$) δ 169.1, 163.3, 140.0, 132.6, 130.81, 130.8, 128.8, 127.9, 127.8, 127.7, 127.1, 124.9, 55.8, 23.0; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{16}H_{12}BrINO$ 439.9141, 441.9122; found 439.9128, 441.9114.

*3-(3-Bromo-4-methylphenyl)-4-chloro-5-phenylisoxazole (**5c**):* 103 mg (98% yield), white solid; mp 114 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.10 (s, 1H), 8.03−8.08 (m, 2H), 7.76 (d, 1H, J = 7.9 Hz), 7.53 (m, 3H), 7.38 (d, 1H, J = 7.9 Hz), 2.48 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 163.9, 159.0, 139.9, 131.4, 130.6, 130.3, 128.5, 126.6, 126.2, 126.1, 125.9, 124.8, 104.0, 22.6; GC−MS (EI, 70 eV, m/z (I_{rel} (%)) cluster 347 (12), 349 (19), 351 (3) $[M^+]$; cluster 312 (2), 314 (2) $[M^+ - Cl]$; cluster 272 (5), 274 (5); cluster 240 (16), 242 (5) $[M^+ - Br - CO]$; 233 (14) $[M^+ - Cl - Br]$; 105(100) $[PhCO]^+$; 89 (11) $[C_7H_5]^+$; 77(43) $[C_6H_5]^+$. Calcd for $C_{16}H_{11}BrClNO$, %: C, 55.12; H, 3.18. Found, %: C, 55.74; H, 3.43.

*4-Bromo-3-(4-chlorophenyl)-5-phenylisoxazole (**6a**):*[38] 175 mg (89% yield), colorless crystals; mp 126−127 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.08 (m, 2H), 7.83 (d, 2H, J = 8.4 Hz), 7.53 (m, 3H), 7.50 (d, 2H, J = 8.4 Hz); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 166.1, 161.1, 136.5, 130.8, 129.9, 129.0, 128.9, 127.1, 126.6, 126.3, 89.3.

*3-(4-Chlorophenyl)-4-iodo-5-phenylisoxazole (**6b**):*[39] 190 mg (85% yield), white crystals; mp 165 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.09 (m, 2H), 7.76 (d, 2H, J = 8.1 Hz), 7.51 (m, 5H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 169.3, 163.8, 136.4, 130.9, 130.3, 128.9, 128.8, 127.8, 127.2, 127.1, 55.8; GC−MS (EI, 70 eV, m/z (I_{rel} (%)) cluster 381 (4), 383 (1) $[M^+]$; cluster 137 (3), 139 (1) $[ClC_6H_4CN]^+$; 114 (5) $[M - I - PhCO - Cl]^+$; 105 (100) $[PhCO]^+$; 77 (54) $[Ph]^+$.

*4-Chloro-3-(4-chlorophenyl)-5-phenylisoxazole (**6c**):*[11] 157 mg (92% yield), white crystalline solid; mp 95 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.06 (m, 2H), 7.86 (d, 2H, J = 8.4 Hz), 7.52−7.58 (m, 3H), 7.50 (d, 2H, J = 8.4 Hz); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 164.4, 159.8, 136.6, 130.8, 129.5, 129.1, 129.0, 126.6, 126.3, 125.9, 104.4; GC−MS (EI, 70 eV, m/z (I_{rel} (%)) cluster 289 (6), 291 (4), 293 (0.8) $[M^+]$; cluster 254 (3), 256 (1) $[M - Cl]^+$; cluster 214 (3), 216 (1); cluster 137 (3), 139 (1) $[ClC_6H_4CN]^+$; 105 (100) $[PhCO]^+$; 77 (68) $[Ph]^+$.

*4-Bromo-3,5-bis(4-methoxyphenyl)isoxazole (**7a**):*[40] 129 mg (72% yield), white solid; mp 128 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.02 (d, 2H, J = 8.8 Hz), 7.81 (d, 2H, J = 8.8 Hz), 7.02 (d, 4H, J = 8.8 Hz), 3.86 (s, 6H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 165.6, 161.6, 161.3, 161.0, 129.9, 128.6, 120.3, 119.4, 114.2, 114.1, 88.1, 55.42, 55.36.

*4-Iodo-3,5-bis(4-methoxyphenyl)isoxazole (**7b**):*[41] 134 mg (66% yield), yellowish solid; mp 163 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.04 (d, 2H, J = 8.3 Hz), 7.75 (d, 2H, J = 8.3 Hz), 7.04 (m, 4H), 3.89 (s, 3H), 3.88 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 168.8, 164.2, 161.3, 161.0, 130.4, 129.4, 121.1, 119.9, 114.1, 114.0, 55.44, 55.37, 54.8.

*4-Chloro-3,5-bis(4-methoxyphenyl)isoxazole (**7c**):* 138 mg (88% yield), white crystalline solid; mp 123 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.00 (d, 2H, J = 8.8 Hz), 7.85 (d, 2H, J = 8.8 Hz), 7.03 (d, 4H, J = 8.8 Hz), 3.87 (s, 6H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 163.9, 161.2, 161.1, 160.2, 129.6, 128.2, 119.9, 119.2, 114.3, 114.2, 103.0, 55.41, 55.36. Calcd for $C_{17}H_{14}ClNO_3$, %: C, 64.67; H, 4.47; N, 4.44. Found, %: C, 64.35; H, 4.42; N, 4.51.

*4-Bromo-5-(3-nitrophenyl)-3-phenylisoxazole (**8a**):* 117 mg (86% yield), white amorphous solid; mp 119−120 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 9.02 (br s, 1H), 8.43 (d, 1H, J = 8.0 Hz), 8.38 (d, 1H, J = 8.0 Hz), 7.87 (m, 2H), 7.76 (t, 1H, J = 8.0 Hz), 7.55 (m, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 162.8, 162.0, 148.1, 132.0, 130.1, 129.8, 128.4, 128.2, 127.8, 126.8, 124.7, 121.4, 91.0; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{15}H_{10}BrN_2O_3$ 344.9869, 346.9849; found 344.9869, 346.9854.

*4-Iodo-5-(3-nitrophenyl)-3-phenylisoxazole (**8b**):* 245 mg (98% yield), cream amorphous solid; mp 144−145 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 9.02 (s, 1H), 8.42 (d, 1H, J = 8.1 Hz), 8.37 (d, 1H, J = 8.1 Hz), 7.78 (m, 2H), 7.75 (t, 1H, J = 8.1 Hz), 7.51−7.56 (m, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 165.8, 164.7, 147.9, 132.8, 130.0, 129.7, 128.6, 128.31, 128.3, 127.7, 124.8, 122.2, 57.7. Calcd for $C_{15}H_9IN_2O_3$, %: C, 45.94; H, 2.31; N, 7.14. Found, %: C, 46.07; H, 2.04; N, 7.13.

*4-Bromo-3-(4-nitrophenyl)-5-phenylisoxazole (**9a**):* 60 mg (85% yield), white crystalline solid; mp 157 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.39 (d, 2H, J = 8.7 Hz), 8.08−8.12 (m, 4H), 7.56−7.58 (m, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 166.8, 160.3, 148.8, 134.1, 131.1, 129.6, 129.0, 127.1, 126.3, 123.9, 89.1; GC−MS (EI, 70 eV, m/z (I_{rel} (%)) 266 (52) $[M^+]$, 105 (100) $[PhCO]^+$. Calcd for $C_{15}H_9BrN_2O_3$, %: C, 52.20; H, 2.63; N, 8.12. Found, %: C, 51.95; H, 3.07; N, 8.15.

*4-Iodo-3-(4-nitrophenyl)-5-phenylisoxazole (**9b**):* 35 mg (88% yield), cream crystals; mp 139 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.39 (d, 2H, J = 8.9 Hz), 8.04−8.13 (m, 2H), 8.02 (d, 2H, J = 8.9 Hz), 7.50−7.60 (m, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 169.5, 162.6, 148.4, 134.6, 130.7, 129.7, 128.5, 127.4, 126.3, 123.4, 54.7; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{15}H_{10}IN_2O_3$ 392.9731, found 392.9734.

*4-Bromo-3-(2-methylphenyl)-5-phenylisoxazole (**10a**):* 130 mg (98% yield), purified by flash chromatography (eluent, ethyl acetate/light petroleum ether = 1:10), yellow oil; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.14−8.17 (m, 2H), 7.54−7.58 (m, 3H), 7.32−7.46 (m, 4H), 2.39 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 164.9, 163.9, 137.6, 130.7, 130.5, 130.1, 130.0, 128.9, 127.2, 126.9, 126.8, 125.8, 91.3, 20.0. Calcd for $C_{16}H_{12}BrNO$, %: C, 61.17; H, 3.85; N, 4.46. Found, %: C, 61.52; H, 4.09; N, 4.56.

*4-Bromo-3-(2-methoxy-5-chlorophenyl)-5-phenylisoxazole (**11a**):* 126 mg (99% yield), purified by flash chromatography (eluent, ethyl acetate/light petroleum ether = 1:10), yellowish oil; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.11−8.14 (m, 2H), 7.54−7.55 (m, 3H), 7.47 (dd, 1H, J = 8.8, J = 2.7 Hz), 7.44 (d, 1H, J = 2.7 Hz), 6.99 (d, 1H, J = 8.8 Hz), 3.88 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 164.6, 160.8, 155.8, 131.0, 130.6, 130.2, 128.4, 126.5, 126.3, 125.1, 117.9, 112.1, 91.3, 55.6. Calcd for $C_{16}H_{11}BrClNO_2$, %: C, 52.70; H, 3.04; N, 3.84. Found, %: C, 52.48; H, 3.35; N, 3.93.

*4-Bromo-5-(4-methoxyphenyl)-3-phenylisoxazole (**12a**):*[17] 193 mg (98% yield), white solid; mp 140 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.06 (d, 2H, J = 8.7 Hz) 7.87 (m, 2H), 7.53 (m, 3H), 7.05 (d, 2H, J = 8.7 Hz), 3.89 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 165.4, 161.6, 160.9, 129.7, 128.3, 128.2, 128.17, 127.6, 119.0, 113.8, 87.7, 55.0.

*4-Chloro-5-(4-methoxyphenyl)-3-phenylisoxazole (**12c**):*[17] 24 mg (85% yield), white solid; mp 101 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.03 (d, 2H, J = 8.0 Hz), 7.83−7.95 (m, 2H), 7.43−7.57 (m, 3H), 7.05 (d, 2H, J = 8.0 Hz), 3.89 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 163.7, 160.9, 160.2, 129.8, 128.3, 127.83, 127.8, 127.2, 118.8, 113.9, 102.7, 55.0.

*4-Bromo-5-(3-bromo-4-methoxyphenyl)-3-phenylisoxazole (**13**):* 158 mg (97% yield), colorless crystals; mp 153 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.33 (d, 1H, J = 2.1), 8.06 (dd, 1H, J = 8.6, J = 2.1 Hz), 7.87 (m, 2H), 7.52−7.56 (m, 3H), 7.06 (d, 1H, J = 8.6 Hz), 4.00 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 164.2, 162.0, 157.4, 131.7, 130.1, 128.6, 128.4, 127.6, 127.5, 120.4, 112.0, 111.6, 88.7, 56.3. Calcd for $C_{16}H_{11}Br_2NO_2$, %: C, 46.98; H, 2.71; N, 3.42. Found, %: C, 47.04; H, 3.10; N, 3.64.

*4-Iodo-3-methyl-5-phenylisoxazole (**14b**):*[11] 78 mg (91% yield), purified by flash chromatography (eluent, ethyl acetate/light petroleum ether = 1:10), yellow oil; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.03 (m, 2H), 7.48 (m, 3H), 2.35 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 167.4, 163.0, 130.6, 128.7, 127.3, 127.2, 57.9, 12.7.

*4-Iodo-3-(4-methylphenyl)-5-phenylisoxazole (**15b**):* 145 mg (95% yield), cream crystalline solid; mp 92 °C; ^1H NMR (400 MHz, $CDCl_3$) δ ^1H NMR ($CDCl_3$, 400 MHz) δ 8.09 (m, 2H), 7.71 (d, 2H, J = 7.9 Hz), 7.49−7.58 (m, 3H), 7.34 (d, 2H, J = 7.9 Hz), 2.45 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 168.9, 164.7, 140.2, 130.7, 129.3, 128.9, 128.7, 127.8, 127.4, 125.8, 56.2, 21.5; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{16}H_{13}INO$ 362.0036, found 362.0040.

*4-Chloro-3-(4-methylphenyl)-5-phenylisoxazole (**15c**):*[42] 55 mg (96% yield), white amorphous solid; mp 104 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.04−8.12 (m, 2H), 7.81 (d, 2H, J = 6.5 Hz), 7.49−7.59

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(m, 3H), 7.34 (d, 2H, J = 6.5 Hz), 2.45 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 163.6, 160.3, 140.1, 130.1, 129.1, 128.5, 127.7, 126.1, 124.1, 104.2, 21.1. One signal is overlapped.

*4-Bromo-3,5-dimethyl-1H-pyrazole (**20a**):*[43] 173 mg (95% yield), colorless crystals; mp 123 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 12.5 (br s, 1H), 2.25 (s); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 142.7, 94.2, 11.2.

*4-Bromo-3,5-dimethyl-1-phenyl-1H-pyrazole (**21a**):*[43] 145 mg (95% yield), purified by flash chromatography (eluent, ethyl acetate/light petroleum ether = 1:10); yellow oil: ^1H NMR ($CDCl_3$, 400 MHz) δ 7.30−7.48 (m, 5H), 2.29 (s, 3H), 2.28 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ, 147.5, 139.8, 137.4, 129.2, 127.8, 124.6, 96.4, 12.4, 11.8.

*4-Iodo-3,5-dimethyl-1-phenyl-1H-pyrazole (**21b**):*[43] 130 mg (72% yield), purified by flash chromatography (eluent, ethyl acetate/light petroleum ether = 1:10), yellow oil; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.31−7.48 (m, 5H), 2.30 (s, 3H), 2.29 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 150.7, 140.8, 139.9, 129.2, 127.9, 124.8, 65.5, 14.2, 13.5; GC−MS (EI, 70 eV, m/z (I_{rel} (%)) 298 (50) $[M^+]$; 297 (16) $[M - H]^+$; 170 (18) $[M - I - H]^+$; 130 (19); 127 (14); 118 (17); 77 (100) $[Ph^+]$.

*1-Benzyl-4-bromo-3,5-diphenyl-1H-pyrazole (**22a**):* 165 mg (85% yield), white crystalline solid; mp 112 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.02 (m, 2H), 7.46−7.54 (m, 5H), 7.42 (m, 1H), 7.37 (m, 2H), 7.26−7.33 (m, 3H), 7.10 (m, 2H), 5.35 (s, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 148.5, 143.3, 136.9, 132.3, 130.1, 129.4, 128.8, 128.7, 128.6, 128.4, 128.2, 127.9, 127.7, 127.1, 92.9, 54.4. Calcd for $C_{22}H_{17}BrN_2$, %: C, 67.88; H, 4.40; N, 7.20. Found, %: C, 68.14; H, 4.34; N, 7.52.

*1-Benzyl-4-iodo-3,5-diphenyl-1H-pyrazole (**22b**):*[44] 190 mg (87% yield), yellow crystalline solid; mp 120 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.99 (m, 2H), 7.42−7.53 (m, 6H), 7.35 (m, 2H), 7.26−7.32 (m, 3H), 7.10 (m, 2H), 5.36 (s, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 151.8, 146.8, 136.9, 133.1, 130.4, 130.0, 129.5, 128.73, 128.65, 128.5, 128.34, 128.30, 127.8, 127.2, 61.3, 54.6.

*1-Benzyl-4-chloro-3,5-diphenyl-1H-pyrazole (**22c**):* 90 mg (86% yield), white amorphous solid; mp 104 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.03 (m, 2H), 7.46−7.53 (m, 5H), 7.42 (m, 1H), 7.36−7.40 (m, 2H), 7.26−7.34 (m, 3H), 7.11 (m, 2H), 5.34 (s, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 146.5, 141.1, 136.5, 131.5, 129.5, 129.0, 128.3, 128.2, 128.0, 127.7, 127.3, 127.1, 126.6, 106.7, 53.8. One signal is overlapped. GC−MS (EI, 70 eV, m/z (I_{rel} (%)) cluster 344 (70), 346 (23) $[M^+]$; cluster 343 (56), 345 (19) $[M - H]^+$; cluster 267 (40), 269 (13) $[M - Ph]^+$; 189 (22), 91 (100). Calcd for $C_{22}H_{17}ClN_2$, %: C, 76.63; H, 4.97; N, 8.12. Found, %: C, 76.45; H, 4.80; N, 8.24.

*2-Bromo-1,3,5-trimethylbenzene (**23a**):*[45] 233 mg (78% yield), purified by flash chromatography (eluent, ethyl acetate/light petroleum ether = 1:20), colorless liquid; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.91 (s, 2H), 2.39 (s, 6H), 2.26 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 137.9, 136.3, 129.1, 124.2, 23.7, 20.7.

*2-Iodo-1,3,5-trimethylbenzene (**23b**):*[46] 72 mg (70% yield), colorless amorphous solid; mp 28−30 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.90 (s, 2H), 2.45 (s, 6H), 2.25 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 141.3, 136.9, 127.6, 103.9, 29.1, 20.3.

*2-Chloro-1,3,5-trimethylbenzene (**23c**):*[47] 66 mg (86% yield), purified by flash chromatography (eluent, ethyl acetate/light petroleum ether = 1:20), colorless liquid; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.93 (s, 2H), 2.38 (s, 6H), 2.29 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 135.4, 135.1, 133.7, 128.8, 20.3, 20.2.

*2,4-Diiodo-1,3,5-trimethylbenzene (**24**):*[48] 130 mg (84% yield), colorless crystals; mp 82 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.99 (s, 1H), 2.93 (s, 3H), 2.42 (s, 6H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 143.0, 141.4, 127.5, 102.8, 37.1, 29.6.

*1,4-Diiodo-2,5-dimethylbenzene (**25**):*[48] 306 mg (91% yield), white solid; mp 101 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.64 (s, 2H), 2.34 (s, 6H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 140.2, 138.8, 100.3, 26.6.

*2-Iodo-1,4-dimethylbenzene (**26**):*[49] 727 mg (94%), yellow oil; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.68 (s, 1H), 7.14 (d, 1H, J = 7.7 Hz), 7.07 (d, 1H, J = 7.7 Hz), 2.42 (s, 3H), 2.30 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 138.9, 137.7, 136.8, 129.0, 128.6, 100.7, 27.2, 19.9

*1-Iodo-4-methoxybenzene (**27b**):*[50] 190 mg (88% yield), cream solid; mp 50−52 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.56 (d, 2H, J = 8.7 Hz), 6.69 (d, 2H, J = 8.7 Hz), 3.77 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 159.0, 137.8, 116.0, 82.3, 54.9.

*1-Chloro-4-methoxybenzene (**27c**):*[51] 103 mg (78% yield), purified by flash chromatography (eluent, ethyl acetate/light petroleum ether = 1:20), colorless liquid; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.24 (d, 2H, J = 9.0 Hz), 6.83 (d, 2H, J = 9.0 Hz), 3.79 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 157.8, 128.9, 125.1, 114.8, 55.1.

*5-Iodoisatine (**28b**):*[52] 117 mg (81% yield), red solid; mp 274 °C; ^1H NMR (DMSO-d_6, 400 MHz) δ 11.09 (s, 1H), 7.86 (dd, 1H, J = 8.2, J = 1.6 Hz), 7.74 (d, 1H, J = 1.6 Hz), 6.73 (d, 1H, J = 8.2 Hz); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ 183.1, 158.7, 150.0, 145.8, 132.4, 120.0, 114.6, 85.4.

*5-Chloroisatine (**28c**):*[53] 45 mg (73% yield), orange solid; mp 256 °C; ^1H NMR (DMSO-d_6, 400 MHz) δ 11.13 (s, 1H), 7.59 (dd, 1H, J = 8.3, J = 2.2 Hz), 7.52 (d, 1H, J = 2.2 Hz), 6.91 (d, 1H, J = 8.3 Hz); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ 183.4, 159.2, 149.3, 137.3, 126.8, 124.1, 119.1, 113.9.

*4,4′-Diiododiphenyl ether (**29**);*[54] 170 mg (98% yield), cream crystalline solid; mp 140 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.63 (d, 4H, J = 8.9 Hz), 6.77 (d, 4H, J = 8.9 Hz); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 156.3, 138.4, 120.7, 86.2.

*1-Iodo-2,4-dimethylbenzene (**30**):*[55] 93 mg (85% yield), purified by flash chromatography (eluent, ethyl acetate/light petroleum ether = 1:20), yellowish oil; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.69 (d, 1H, J = 8.0 Hz), 7.09 (s, 1H), 6.72 (d, 1H, J = 8.0 Hz), 2.42 (s, 3H), 2.30 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 140.8, 138.3, 137.7, 130.4, 128.0, 96.7, 27.5, 20.5.

*3-(4-Chlorophenyl)-4-iodoisoxazole (**31**):*[56] purified by flash chromatography (eluent, ethyl acetate/light petroleum ether = 1:10), 37 mg (70%), white crystals; mp 99−100 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.48 (s, 1H), 7.78 (d, 2H, J = 8.6 Hz), 7.48 (d, 2H, J = 8.6 Hz); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 162.4, 160.8, 136.1, 129.5, 129.3, 128.6, 57.4.

*4-Iodo-5-(4-methylphenyl)ioxazole (**32**):* purified by flash chromatography (eluent, ethyl acetate/light petroleum ether = 1:10), 40 mg (75%), white crystals; mp 105−106 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.27 (s, 1H), 7.94 (d, 2H, J = 8.2 Hz), 7.31 (d, 2H, J = 8.2 Hz), 2.42 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 167.0, 156.4, 140.7, 129.1, 126.9, 123.6, 51.0, 21.2; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{10}H_9INO$ 285.9723, found 285.9719.

*4-Iodo-5-methyl-1H-pyrazole (**33**):*[57] 647 mg (85%), yellowish solid; mp 110 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 11.41 (s, 1H), 7.55 (s, 1H), 2.33 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 144.9, 140.1, 59.3, 12.0.

*3,4-Diiodothiophen-2-ylcarbaldehyde (**34**):* 171 mg (88% yield), yellowish crystalline solid; mp 145 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 9.75 (s, 1H), 7.53 (s, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 180.3, 150.3, 143.2, 98.0, 95.0; GC−MS (EI, 70 eV, m/z (I_{rel} (%)) 364 (100) $[M^+]$, 363 (58) $[M - H]^+$, 208 (17) $[M - I - CHO]^+$, 127 (16) $[I^+]$, 81 (25) $[C_4HS]^+$. Calcd for $C_5H_2I_2OS$, %: C, 16.50; H, 0.55. Found, %: C, 16.53; H, 0.57.

Gram-Scale Procedure for Iodination of 3,5-Diarylisoxazoles. A thoroughly dried 250 mL round-bottom flask equipped with a tightly fitted stopper and a magnetic rod was sequentially charged with 4.5 g (0.035 mol) of crystalline nitrosylsulfuric acid, 100 mL of dry nitromethane, 2.5 g (0.012 mol) of tetramethylammonium iodide, and 2.21 g (0.01 mol) of isoxazole **1**, and the resultant mixture was stirred on a magnetic stirrer at room temperature for 1−2 h. Over this period of time, a precipitate appeared in the flask. Then the flask was placed into a water bath, and the reaction mixture was heated at 55−60 °C for 15−60 min to complete the reaction (monitoring by TLC). After completion of the reaction, the resultant mixture was sequentially shaken with $NaHCO_3$ and Na_2SO_3 aqueous solutions, the organic layer was separated and evaporated in vacuo to regenerate

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nitromethane, and the residue was dissolved in CH_2Cl_2. The water layers were treated with CH_2Cl_2. Combined organic fractions were additionally washed with water and dried over anhydrous Na_2SO_4. The solvent was evaporated in vacuo to give 2.98 g of a pale yellow crude product, which was washed with cold ether to afford 2.78 g (80%) of **1b** as a white solid.

Isoxazole **5b** was prepared according to the gram-scale procedure from 2.20 g (0.007 mol) of **5**, 1.09 g (0.004 mol) of I_2, and 3.20 g (0.025 mol) of $NOHSO_4$ in 72% yield (2.22 g).

Isoxazole **6b** was prepared according to the gram-scale procedure from 1.55 g (0.006 mol) of **6**, 1.80 g (0.009 mol) of Me_4NI, and 3.05 g (0.024 mol) of $NOHSO_4$ in 83% yield (1.92 g).

*One-Pot Synthesis of 3,5-Diaryl-4-haloisoxazoles **1a−c**, **2a−c**, **19a**, and **19c**, from 1,2-Diarylcyclopropanes **16−18** (General Procedure).* Cyclopropane (1 mmol), nitromethane (10 mL), and $NOHSO_4$ (0.176 g, 1.5 mmol) were loaded into a thoroughly dried 50 mL round-bottom flask equipped with a tightly fitted stopper and a magnetic stirrer. The reaction mixture was stirred at room temperature for 1.0−1.5 h; then an additional amount of $NOHSO_4$ (0.117 g, 1 mmol) was added, and stirring was continued until full consumption of the corresponding 3,5-diaryl-4,5-dihydroisoxazole (TLC monitoring). Then, the required tetramethylammonium halide and an additional amount of $NOHSO_4$ were added in agreement with Table 1. After completion of the reaction, the mixture was neutralized with a 0.1 M solution of $NaHCO_3$, and the organic compounds were extracted with chloroform (3 × 20 mL). The organic extracts were combined, washed in series with 10% Na_2SO_3 water solution, water, and dried over sodium sulfate. The solvent was evaporated using a rotary evaporator. The products were purified by recrystallization from ethanol to afford the following compounds: **1a**, 259 mg (92% yield); **1b**, 329 mg (92% yield); **1c**, 252 mg (70% yield); **2a**, 90 mg (70% yield); **2b**, 159 mg (74% yield); **2c**, 42 mg (92% yield).

*4-Bromo-3,5-bis(4-fluorophenyl)isoxazole (**19a**):* 136 mg (93% yield), white crystalline solid; mp 184−185 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.12 (dd, 2H, J_{H-H} = 8.9, J_{H-F} = 5.3 Hz), 7.88 (dd, 2H, J_{H-H} = 8.9, J_{H-F} = 5.3 Hz), 7.22−7.28 (m, 4H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 164.7, 163.6 (d, $^1J_{C-F}$ = 250.3 Hz), 163.5 (d, $^1J_{C-F}$ = 253.2 Hz), 160.9, 130.2 (d, $^3J_{C-F}$ = 8.5 Hz), 128.8 (d, $^3J_{C-F}$ = 8.7 Hz), 123.4 (d, $^4J_{C-F}$ = 3.3 Hz), 122.5 (d, $^4J_{C-F}$ = 3.5 Hz), 115.7 (d, $^2J_{C-F}$ = 25.6 Hz), 115.4 (d, $^2J_{C-F}$ = 26.5 Hz), 88.7. Calcd for $C_{15}H_8BrF_2NO$, %: C, 53.57; H, 2.38; N, 4.17. Found, %: C, 53.68; H, 2.55; N, 4.22.

*3,5-Bis(4-fluorophenyl)-4-chloroisoxazole (**19c**):* 94 mg (74% yield), white crystalline solid; mp 93 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.05 (dd, 2H, J_{H-H} = 8.7, J_{H-F} = 5.3 Hz), 7.90 (dd, 2H, J_{H-H} = 8.7, J_{H-F} = 5.3 Hz), 7.23 (t, 2H, J = 8.7 Hz), 7.22 (t, 2H, J = 8.7 Hz); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 163.6 (d, $^1J_{C-F}$ = 250.8 Hz), 163.5 (d, $^1J_{C-F}$ = 252.7 Hz), 163.0, 159.5, 129.9 (d, $^3J_{C-F}$ = 8.5 Hz), 128.3 (d, $^3J_{C-F}$ = 8.7 Hz), 123.0 (d, $^4J_{C-F}$ = 3.3 Hz), 122.3 (d, $^4J_{C-F}$ = 3.3 Hz), 115.8 (d, $^2J_{C-F}$ = 22.1 Hz), 115.6 (d, $^2J_{C-F}$ = 21.9 Hz), 103.7; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{15}H_9ClF_2NO$ 292.0335, 294.0306; found 292.0338, 294.0308.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c02106.

^{1}H and ^{13}C NMR spectra (PDF)

FAIR data, including the primary NMR FID files, for compounds **1a−1c**, **2a−2c**, **3a−3c**, **4a−4c**, **5a−5c**, **6a−6c**, **7a−7c**, **8a**, **8b**, **9a**, **9b**, **10a**, **11a**, **12a**, **12c**, **13**, **14b**, **15b**, **15c**, **19a**, **19c**, **20a**, **21a**, **21b**, **22a−22c**, **23a−23c**, **24**, **25**, **26**, **27b**, **27c**, **28b**, **28c**, **29**, **30**, **31**, **32**, **33**, and **34** (ZIP)

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Notes

The authors declare no competing financial interest.

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