JOC The Journal of Organic Chemistry

pubs.acs.org/joc Article

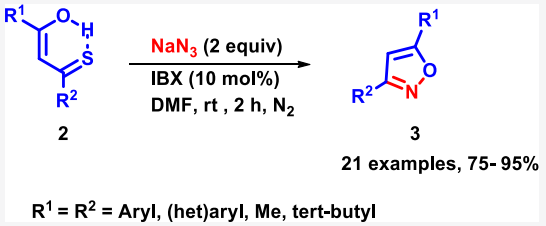
Reaction of 1,3-Bis(het)arylmonothio-1,3-diketones with Sodium Azide: Regioselective Synthesis of 3,5-Bis(het)arylisoxazoles via Intramolecular N−O Bond Formation

Mary Antony P, Gantala L. Balaji, Pethaperumal Iniyavan, and Hiriyakkanavar Ila*

Cite This: https://dx.doi.org/10.1021/acs.joc.0c02216 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: An efficient new synthesis of 3,5-bis(het)arylisoxazoles, involving the reaction of 1,3-bis(het)arylmonothio-1,3-diketones with sodium azide in the presence of IBX catalyst, has been reported. The reaction proceeds at room temperature in high yields and is applicable to a broad range of substrates including the synthesis of 5-methyl-3-arylisoxazoles, a key subunit present in several β-lactamase-resistant antibiotics. A probable mechanism for the formation of isoxazoles has been suggested. A few of the 5-styryl/arylbutadienyl-3-(het)arylisoxazoles have also been synthesized by reacting the corresponding 1-(het)aryl-1-(methylthio)-4-(het)arylidene-but-1-en-3-ones with sodium azide at higher temperatures. The reaction of β-ketodithioesters with sodium azide is shown to furnish β-ketonitriles in good yields.



INTRODUCTION

The isoxazole motif is a privileged heterocyclic scaffold present in a plethora of natural products (ibotenic acid, muscimol, isoxazole-4-carboxylic acid) and synthetic compounds,[1,2] displaying a broad range of biological and pharmacological activities,[3] thus emerging as a key structure in drug discovery, agrochemicals, as well as in material science. The isoxazole framework constitutes the core structure of many marketed drugs such as valdecoxib/parecoxib (COX2 inhibitor, antiinflammatory), sulfamethoxazole (antibacterial), leflunomide (antirheumatic), isocarboxazid (antidepressant), antibiotics oxacillin, cloxacillin, flucoxacillin, and micafungin (antifungal) (Figure 1).[3,4] Isoxazole derivatives also serve as versatile building blocks in organic synthesis,[3e,5] as they can be converted into several useful functionalities such as β-hydroxyketones, β-hydroxynitriles, γ-aminoalcohols, and α,β-unsaturated oximes. Therefore, given the relevance of these class of compounds in organic and medicinal chemistry, the development of new synthetic methods for substituted isoxazoles from readily accessible, starting materials under mild conditions is an important and useful endeavor.

Although numerous methods have been reported for the synthesis of isoxazoles,[1,2,3e] [3 + 2] dipolar cycloaddition of nitrile oxides with alkynes is probably the most direct route to access these heterocycles.[3c,6] However, the nitrile oxides themselves are typically prepared, sometimes from unstable hydroximinoyl chloride, oximes, or by dehydration of nitroalkanes under frequently harsh conditions.[1a,b] Besides, the uncatalyzed thermal cycloaddition of nitrile oxides with alkynes is neither chemo- nor regioselective, and as a consequence, leads to the formation of multiple products. Regioselectivity in these [3 + 2] cycloaddition reactions has been achieved using copper[7a−c] or ruthenium catalysts.[7d] There also exist few metal-free protocols for the synthesis of isoxazoles involving the use of hypervalent iodine reagents for in situ generation of nitrile oxides from oximes.[8] Another typical general approach for these heterocycles involves cyclocondensation of hydroxylamine with β-diketones or their equivalents, three carbon 1,3-electrophilic units[3e,9] bearing sp or sp^2 carbons such as propargyl ketones, α,β-unsaturated ketones, enaminones, β-chloro/alkylthioenones, α,β-unsaturated nitriles, or α-oxoketenedithioacetals, which also suffer from regioselectivity problems, yielding sometimes regioisomeric mixtures of isoxazoles. In recent years, halonium-ion-mediated or transition-metal-catalyzed, electrophilic cycloisomerization of several acetylenic hydroxylamine derivatives such as 2-alkyn-1-one-*O*-alkyloximes[10] or *O*-propargylic-*N*-tosyl/alkylhydroxylamine derivatives[11] to substituted isoxazoles has also been reported.

However, all these useful synthesis of isoxazoles originate from starting materials with a pre-existing N−O bond, such as nitrile oxides, hydroxylamine, oximes, and their derivatives. On the other hand, an alternative synthetic protocol involving direct intramolecular construction of the N−O bond provides an attractive approach for the synthesis of isoxazoles. There are

Received: September 15, 2020

https://dx.doi.org/10.1021/acs.joc.0c02216
J. Org. Chem. XXXX, XXX, XXX−XXX

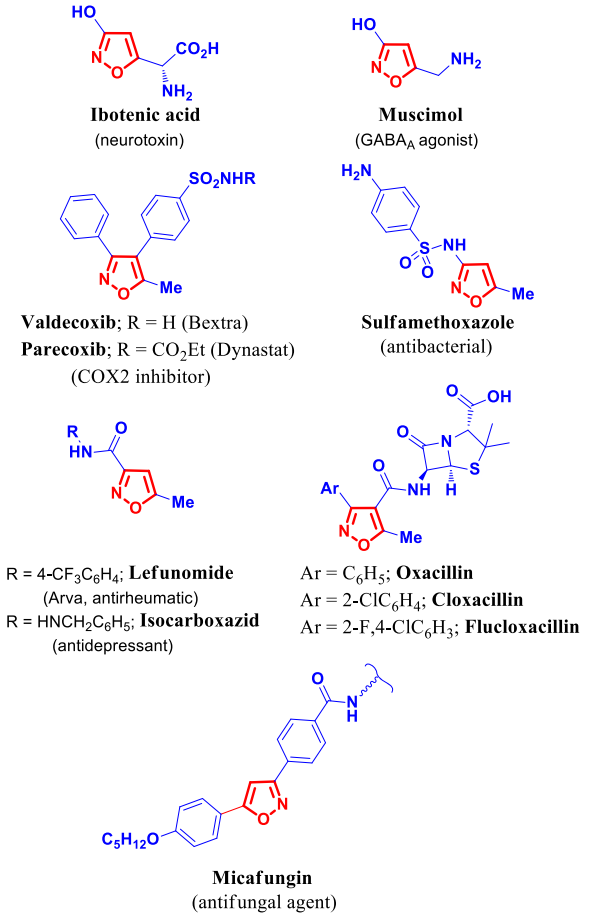


Figure 1. Examples of bioactive isoxazoles.

few previous reports for the synthesis of 2,1-benzoisoxazoles via intramolecular N−O bond formation involving either hypervalent-iodine-mediated[12a,b]/transition-metal-catalyzed intramolecular oxidative cyclization of *o*-aminocarbonyl compounds[12c] or thermal decomposition of *o*-azidocarbonyl compounds.[12d] However, examples of such approaches for the construction of isoxazole ring are only few in the literature and less explored (Scheme 1). Among them, photochemical or thermal isomerization of 2*H*-acylazirines is an old example,[13a,b] whereas recently these transformations have also been achieved by some metal catalysts such as Grubb's ruthenium−carbene complex[13c] or rhodium acetate dimer ($Rh_2(OAc)_4$) (Scheme 1a).[13d] Interestingly, these acylazirines themselves have been obtained previously via photochemical isomerization of appropriate isoxazoles in the presence of light of particular wavelengths.[13b] Recently, Zhao and co-workers have reported a one-pot procedure for substituted isoxazoles involving $PhI(OAc)_2$-mediated oxidation of enaminone to acylazirines and their in situ isomerization to trisubstituted isoxazoles mediated by Fe(II) chloride (Scheme 1b).[13a] On the other hand, Auricchio and co-workers have demonstrated previously the $FeCl_2$ catalyzed isomerization of isoxazoles to 2*H*-azirines or enaminones (Scheme 1b) and have shown that, in the presence of this catalyst, both the isoxazoles and azirines exist in equilibrium.[14a,b] Therefore, these methods cannot be considered useful for a general synthesis of substituted isoxazoles via intramolecular N−O bond formation. A few of the 5-anilino-4-acylisoxazoles have also been reported to be formed by oxidative N−O bond formation of *β*-aminoacrylamide in the presence of iodosobenzene, with only limited examples.[14c] Recently, Reddy and co-workers have reported the synthesis of 3,5-substituted isoxazoles via denitrogenative cyclization of substituted alkynones with trimethylsilyl azide in a specific solvent, that is, trichloroethylene (Scheme 1c).[15a] Although the authors have shown a broad substrate scope for this cyclization reaction, considering the cost and hazardousness of trimethylsilyl azide, as well as the use of carcinogenic solvent and not so easily accessible alkynones, development of an alternative new method for isoxazole synthesis via intramolecular N−O bond formation employing cheaper reagents and readily available starting materials will be much more attractive and desirable.[15b,c]

During the course of our ongoing research program directed toward design and development of new synthetic routes for five- and six-membered heterocycles from various organosulfur building blocks, we have recently reported the synthesis and application of unsymmetrically substituted 1,3-bis(het)arylmonothio-1,3-diketones of the general structure **2**, a new class of versatile organosulfur synthons, which are readily available in good yields by base-mediated condensation of active methylene ketones with (het)aryldithioesters **1** (Table 2).[16a] These 1,3-monothiodiketones **2** can be considered as 1,3-diketone surrogates, displaying significant different reactivity and electronic properties of carbonyl and thiocarbonyl groups. By employing these monothiodiketones, we have previously developed efficient regioselective synthesis of 1-aryl-3,5-bis(het)arylpyrazoles,[16a] substituted thiophenes/push−pull thiophene acrylates,[16b] trisubstituted imidazoles,[16c] and substituted benzo[*b*]thiophenes by transition-metal-catalyzed coupling-cyclization with *o*-bromoiodoarenes.[16d] We had also described previously a regioselective synthesis of 3,5-bis(het)arylisoxazoles by cyclocondensation of 1,3-monothiodiketones as three carbon 1,3-biselectrophilic components with hydroxylamine under controlled reaction conditions (Scheme 2a).[3e] In continuation of these studies, we further envisaged to explore synthetic applications and reactivity of these intermediates, and we now report an alternate novel high-yield regioselective synthesis of 3,5-disubstituted isoxazoles by reaction of 1,3-monothiodiketones with sodium azide in the presence of a catalytic amount of IBX (Scheme 2b). The key feature of this new isoxazole synthesis is that it involves an intramolecular ring closure via formation of the N−O bond and proceeds under mild conditions at room temperature, employing easily accessible reagents and starting materials.

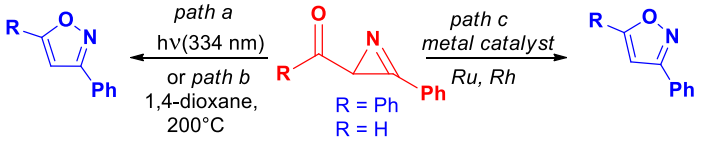
RESULTS AND DISCUSSION

The desired 1,3-bis(het)arylmonothio-1,3-diketones **2a−v** were synthesized in good yields according to our earlier reported procedure[16a] by reacting the respective active methylene ketones with appropriate (het)aryldithioesters **1** in the presence of sodium hydride (Table 2). We selected 1,3-monothiodiketone **2a** as the model substrate for examining its reaction with sodium azide (or trimethylsilyl azide) under a variety of reaction conditions (Table 1). Thus, when **2a** was reacted with sodium azide (2 equiv) in DMF as solvent for 24 h at room temperature, no reaction was observed (entry 1). However, when the reaction mixture was heated at 90 °C for 12 h, the work-up of the reaction mixture furnished a product (58%) (entry 2), which was characterized as 3-(4-methoxyphenyl)-5-phenylisoxazole **3a** on the basis of comparison of its spectral and analytical data with that of the reported one.[3e] A dramatic improvement in the yield of **3a** was observed when

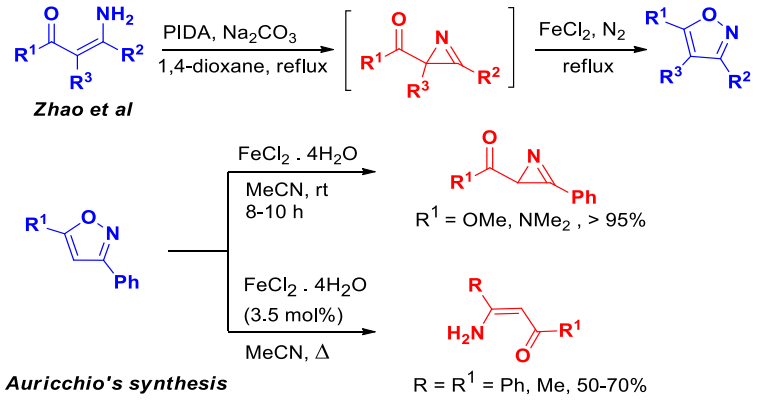
https://dx.doi.org/10.1021/acs.joc.0c02216
J. Org. Chem. XXXX, XXX, XXX−XXX

Scheme 1. Synthesis of Isoxazoles via Intramolecular N−O Bond Formation

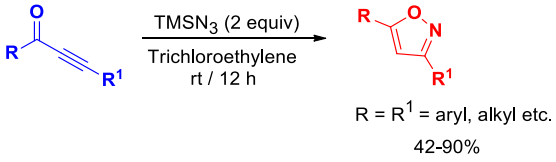
a). Rearrangement of 2*H*-acylazirines into isoxazoles[13b-d]



b). $FeCl_2$ Mediated formation of isoxazoles from 2*H*-acylazirines and conversion of isoxazoles into azirines[13a,14a]



c). Synthesis of 3,5-disubstituted isoxazoles from alkynones and trimethylsilyl azide[15a]



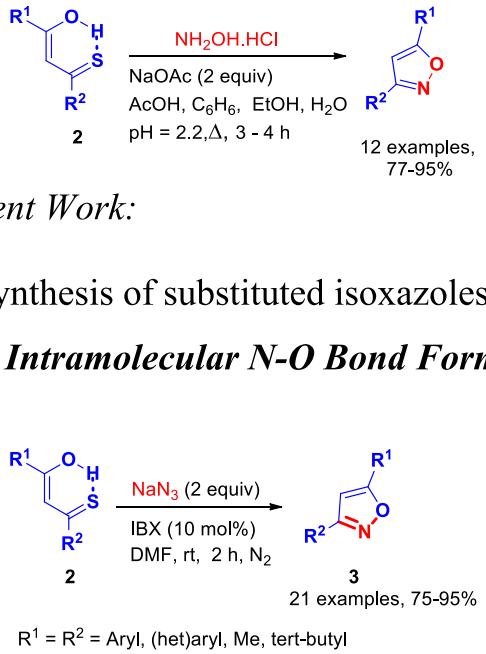
2a was reacted with sodium azide in the presence of IBX (20 mol %) for 2 h at room temperature (entry 3). Reducing the catalytic loading to 10 mol % did not affect the yield of **3a** (entry 4). Use of DMP (Dess−Martin periodinane) or CuI as catalyst, instead of IBX, under identical conditions also furnished isoxazole **3a** however, in decreased yields (entries 5−7). Similarly, DMF was found to be the best solvent and reduced yields of **3a** were obtained in other solvents such as THF, CH_3CN, or DMSO (entries 8−10), or when 1 equiv of sodium azide was employed (entry 11). Interestingly, **2a** was found to be completely inert toward trimethylsilyl azide even at higher temperatures or in the presence of catalysts such as Ag_2CO_3, $AgNO_3$, IBX, and CuI, or in solvents such as DMF, DMSO, or even trichloroethylene,[15a] yielding only the starting material or an intractable reaction mixture (Table 1, entries 12−19). We therefore selected reaction of **2a** with 2 equiv of sodium azide in DMF in the presence of 10 mol % of IBX at room temperature for 2 h as the standard reaction conditions for our further studies (Table 1, entry 4).

Having established the optimized reaction conditions for the conversion of 1,3-monothiodiketone **2a** to isoxazole **3a** (Table 1, entry 4), we next examined the substrate scope of this new reaction for direct synthesis of isoxazoles from various 1,3-monothiodiketones **2** bearing different substituents (Table 2). Thus 1,3-monothiodiketones **2b−f** bearing either electron-donating or -withdrawing substituents on the phenyl rings attached to thiocarbonyl or carbonyl moieties reacted smoothly with sodium azide under identical conditions in the presence of the IBX catalyst, affording the corresponding isoxazoles **3b−f** in excellent yields (Table 2, entries 2−6). The presence of an ortho substituent on the aryl ring, attached to either carbonyl (**2f**) or thiocarbonyl group (**2g**), also did not affect the yields of product isoxazoles **3f−g** (entries 6−7). The isoxazole **3g** bearing the (4-methoxybenzyloxyphenyl) group at the 3-position could be transformed into 3-(2-hydroxyphenyl)-isoxazole **3g′** on treatment with trifluoroacetic acid (Table 2, entry 7).

Versatility of the reaction was further evident by synthesis of various (het)aryl-substituted isoxazoles (entries 7−17). Thus,

https://dx.doi.org/10.1021/acs.joc.0c02216
J. Org. Chem. XXXX, XXX, XXX−XXX

Scheme 2. Synthesis of Substituted Isoxazoles from 1,3-Monothio-β-diketones



by appropriate choice of (het)aryl groups in the starting 1,3-monothiodiketones **2**, it was possible to introduce various five- or six-membered heterocyclic substituents such as 2-thienyl- (entries 8−11), 2-furyl-(entry 11), 2-(*N*-methylpyrrolyl-) (entry 12), (2-thiazolyl-) (entry 13), 3-(*N*-methylindolyl-) (entries 14−15), and 3- or 4-pyridyl groups (entries 7, 15−17) at either 3- or 5-positions of isoxazoles **3h−q** in a highly regioselective fashion in excellent yields (Table 2, entries 7−17). Entry 10 shows the introduction of a sterically crowded *t*-butyl group in the isoxazole ring. The structures and regiochemistry of all these new isoxazoles **3b−q** were confirmed by their spectral and analytical data and also by X-ray crystallographic data of isoxazole **3l** (Supporting Information, Figure S1).

We also synthesized few 5-methyl-3-(het)arylisoxazoles (**3r−t**) (entries 18−20) as this outstanding subunit is present in many marketed drugs, such as valdecoxib and parecoxib, oxacillin, cloxacillin, and flucloxacillin, a group of β-lactamase-resistant antibiotics, which are widely used clinically to treat infections caused by penicillin-resistant *Staphylococcus aureus* (Figure 1).[4b] Thus, the 5-methyl-3-(het)arylisoxazoles **3r−t** were synthesized in high yields from the respective 1-methyl-3-(het)aryl monothiodiketones **2r−t** under optimized reaction conditions (Table 2, entries 18−20). We also reacted thioketones **2u** derived from butyrophenone and cyclic thioketone **2v** obtained from α-tetralone with sodium azide under optimized reaction conditions with a view to synthesize trisubstituted isoxazole **3u** and bicyclic isoxazole **3v** (Table 2, entries 21−22). However, these reactions failed to furnish the desired isoxazoles **3u−v**, yielding either a starting material or a complex reaction mixture even at higher temperature, which is probably due to steric crowding in the starting monothio-1,3-diketones **2u−v** (Scheme 6). We also carried out gram-scale synthesis by reacting **2a** and sodium azide under optimized conditions, affording isoxazole **3a** in 85% yield (Scheme S1 in the Supporting Information).

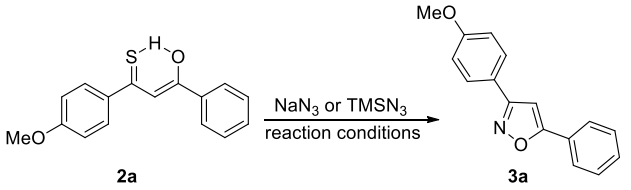
To further extend the scope of this novel isoxazole synthesis, we undertook the preparation of 3-(het)aryl-5-enylisoxazoles **8a−d** by employing a similar strategy (Scheme 4). However, attempted synthesis of 1-(styryl)-3-(4-methoxyphenyl)-monothio-1,3-diketone **5a** by reacting benzylideneacetone **4** with dithioesters **2a** in the presence of sodium hydride under standard reaction conditions was not successful and only a complex mixture of products was formed (Scheme 3).

We therefore intended to synthesize the desired isoxazoles **8** via an alternate route by the reaction of the corresponding 1-(het)aryl-1-(methylthio)-4-(het)arylidene-but-1-en-3-ones **7** with sodium azide (Schemes 3 and 4).The desired β-(methylthio) enones **7a−d** were obtained in good yields by Aldol condensation of various aldehydes with 1-(het)aryl-1-(methylthio)-but-1-en-3-ones **6a−b** (obtained by in situ S-methylation of 1,3-monothiodiketones **1s** or **1t** with methyl iodide) in the presence of sodium hydroxide (Scheme 3).

We next examined the reaction of **7a** with sodium azide under various reaction conditions, with a view to synthesizing 5-styrylisoxazole **8a** (Table 3). Thus, **7a** remained unchanged when reacted with sodium azide in DMF at rt either in the absence or in the presence of IBX (entries 1−2); however, at

https://dx.doi.org/10.1021/acs.joc.0c02216
J. Org. Chem. XXXX, XXX, XXX−XXX

Table 1. Optimization of the Reaction Conditions for the Reaction of 2a with Azides[a]



2a 3a

entry	azide	catalyst (mol %)	solvent	temp (°C)	time (h)	yield (%)[b]
1	NaN_3		DMF	rt	24	
2	NaN_3		DMF	90	12	58
3[c]	NaN_3	IBX	DMF	rt	2	90
4[d]	NaN_3	IBX	DMF	rt	2	89
5[c]	NaN_3	DMP	DMF	rt	5	75
6[c]	NaN_3	CuI	DMF	rt	6	70
7[c]	NaN_3	CuI	DMF	rt	12	65
8	NaN_3	IBX	THF	rt	10	48
9	NaN_3	IBX	CH_3CN	rt	6	70
10	NaN_3	IBX	DMSO	rt	6	73
11	NaN_3	IBX	DMF	rt	10	60
12	$TMSN_3$		DMF	rt	24	[f]
13	$TMSN_3$		DMF	100	12	[g]
14	$TMSN_3$		DMSO	100	12	[g]
15	$TMSN_3$	Ag_2CO_3	DMSO	rt	12	[f]
16	$TMSN_3$	$AgNO_3$	DMSO	rt	12	[f]
17	$TMSN_3$		C_2HCl_3	rt	12	[f]
18	$TMSN_3$	IBX	DMF	rt	12	[f]
19	$TMSN_3$	CuI	DMF	rt	24	[f]

[a]Standard conditions: **2a** (1.0 mmol), NaN_3 or $TMSN_3$ (2.0 equiv), solvent (5 mL), catalyst (10 or 20 mol %). [b]Isolated yield. [c]20 mol % catalyst. [d]10 mol % catalyst. [e]1 equiv of NaN_3. [f]Starting material. [g]Intractable reaction mixture.

100 °C, **8a** was obtained in improved yield under relatively drastic conditions on prolonged heating (entry 3). The best yield of **8a** was obtained when the reaction was conducted at a higher temperature in DMSO instead of DMF for 12 h (Table 3, entry 4), while the reaction in the presence of IBX afforded only lower yields of **8a** under identical conditions (entry 5).

Following these optimal conditions (entry 4), the other substituted 3-(het)aryl-5-styryl (**8b-c**) and 5-(4-phenylbuta-1,3-dien-1-yl)isoxazole **8d** were obtained in good yields (Scheme 4). The inertness of 1-(methylthio)-1-(het)aryl-4-(het)arylidene-but-1-en-3-ones **7** toward conjugate addition with sodium azide at room temperature requiring higher temperature appears to be probably due the steric hindrance created by the presence of two substituents at the 1-position of the enone moiety in **7**.

With the successful synthesis of 1,3-disubstituted isoxazoles **3** from 1,3-monothiodiketones **2**, we further became interested in exploring the reaction of other thiocarbonyl compounds such as β-ketodithioesters **9** with sodium azide under various reaction conditions (Scheme 5). Thus, when **9a** was reacted with sodium azide in DMF either at room temperature or at a higher temperature (or in the presence of IBX), the expected 3-(methylthio)-5-(4-methoxyphenyl)isoxazole **10** could not be isolated from the reaction mixture. The only product isolated in varying yields was identified as (4-methoxybenzoyl)-acetonitrile **11a** (Scheme 5). The best yield of **11a** (80%) was obtained when **9a** was reacted with 2 equiv of sodium azide in DMF at 90 °C for 3 h (Scheme 5).

The other substituted β-oxodithioesters **9b−e** also furnished the corresponding β-ketoacetonitriles **11b−e** in high yields (Scheme 5). It should be noted that Wang and co-workers have recently reported the formation of β-ketonitriles during reaction of β-ketodithioesters with hydroxylamine in EtOH at room temperature in daylight.[17]

Mechanism. A plausible mechanism for the formation of isoxazoles **3** from 1,3-monothiodiketones **2** and sodium azide is depicted in Scheme 6. Thus, nucleophilic attack of the thiocarbonyl group on IBX results in the formation of intermediate **A**, which undergoes conjugate addition−elimination with sodium azide furnishing β-azidoenone intermediate **C**. Subsequent intramolecular electrocyclization of intermediate **C**, with concurrent N−O bond formation and extrusion of nitrogen, provides isoxazoles **3** in high yields. An alternative mechanism involving acylazirine intermediate **E** is ruled out as acylazirines are reported to yield isoxazoles either under drastic thermal or photolytic conditions or in the presence various transition-metal catalysts.[13,14] The failure of sterically congested monothio-1,3-diketone **2u** and cyclic ketone **2v** to furnish trisubstituted isoxazoles **3u−v** (Table 2, entries 21−22) suggests that N−O bond formation occurs through a planar reactive intermediate such as **C** by electrocyclization and the presence of substituents (R^1) at the 2-position in intermediate **C′** causes a destabilizing interaction during planarization (Scheme 6). The probable mechanism for the regeneration of the IBX catalyst in the absence of any oxidizing agent[18] is not very clear; however, it seems that the thiolated IBX intermediate **D** formed during the reaction appears to lose thiolate anions, regenerating back the IBX catalyst.

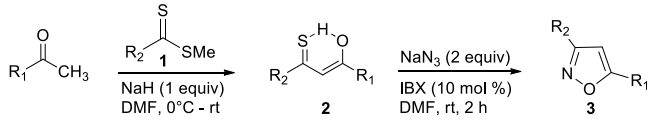
The probable mechanism for the formation of β-ketonitriles **11** from the reaction of sodium azide with β-ketodithioesters **9** is depicted in Scheme 7. Thus, nucleophilic addition of azide anion on the thiocarbonyl group of a dithioester affords intermediate **D**, which, on sequential extrusion of the methylthio group and nitrogen via intermediates **D−E**, affords thiazirine intermediate **F**, which, on subsequent extrusion of sulfur, yields β-ketonitriles **11** in high yields. Unlike the reaction of β-ketodithioesters with hydroxylamine in the presence of daylight to give β-ketonitriles,[17] the present reaction proceeds even under the dark.

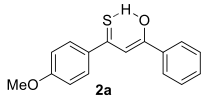
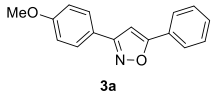
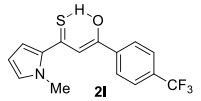
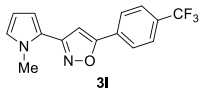
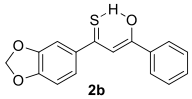
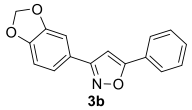
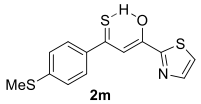
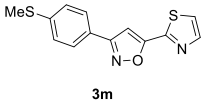
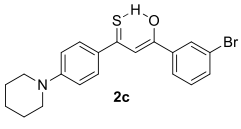
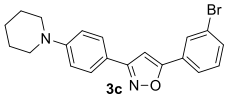
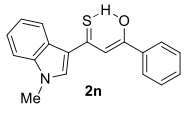
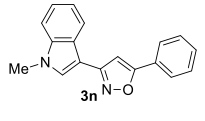
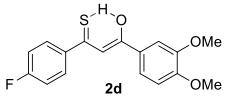
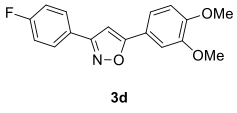
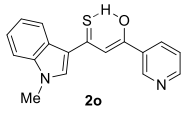
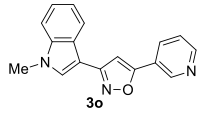
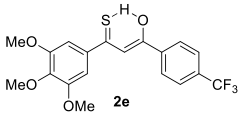
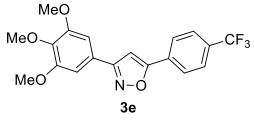
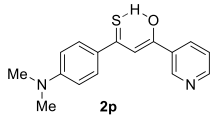
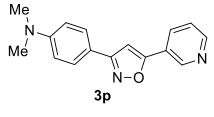
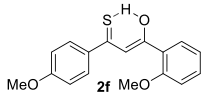
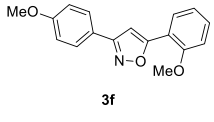
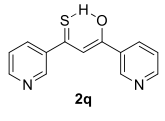
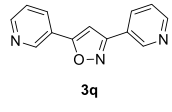
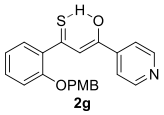
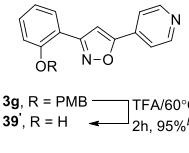
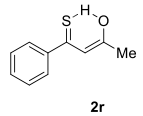
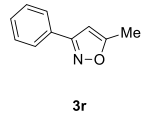
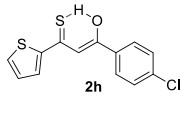
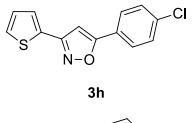
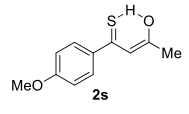
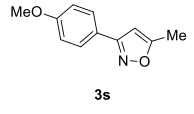
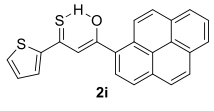
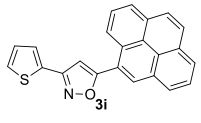
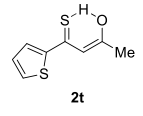
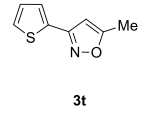
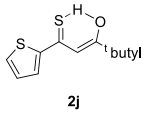
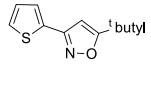
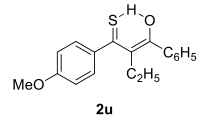
CONCLUSIONS

In summary, we have developed a highly efficient, novel synthetic approach for substituted isoxazoles involving IBX-catalyzed reaction of sodium azide with 1,3-bis(het)-arylmonothiol-1,3-diketones under very mild conditions. The methodology is applicable to a broad range of substrates and is also appropriate for the synthesis of 5-methyl-3-arylisoxazoles, a key subunit present in several β-lactamase-resistant antibiotics. Unlike previously known widely applicable synthetic approaches for isoxazoles, the present synthesis provides a new set of disconnection involving tandem intermolecular C−N and intramolecular N−O bond formation. The examples of such kind of synthetic sequences for isoxazole synthesis are very few in literature (Scheme 1). The ready availability of starting materials, namely, 1,3-monothiodiketones, mild reaction conditions, operational simplicity, and good yields of the product isoxazoles along with high regioselectivity, must make the present methodology more useful and particularly attractive in organic synthesis. We believe that this kind of

https://dx.doi.org/10.1021/acs.joc.0c02216
J. Org. Chem. XXXX, XXX, XXX−XXX

Table 2. Substrate Scope of Isoxazole Synthesis



entry	2	% yield 2[a]	3	% yield 3[a]	entry	2	% yield 2[a]	3	% yield 3[a]
1		85		90	12		76		80
2		79		75	13		78		80
3		76		85	14		85		82
4		80		90	15		79		84
5		86		79	16		80		88
6		75		77	17		85		79
7		78		84	18		78		86
8		69		78	19		82		92
9		78		90	20		64		79
10		81		92	21		61		0
11		80		85	22		55		0

[a]Yields of isolated products. [b]Obtained by heating **3g** with TFA at 60 °C for 2 h.

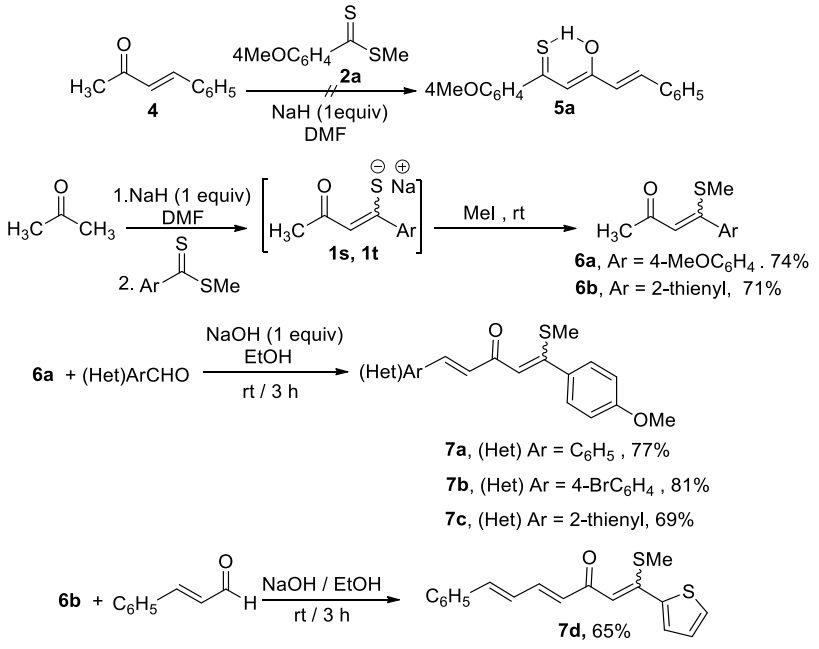
approach could find application in future for designing synthesis of other new heterocycles.

EXPERIMENTAL SECTION

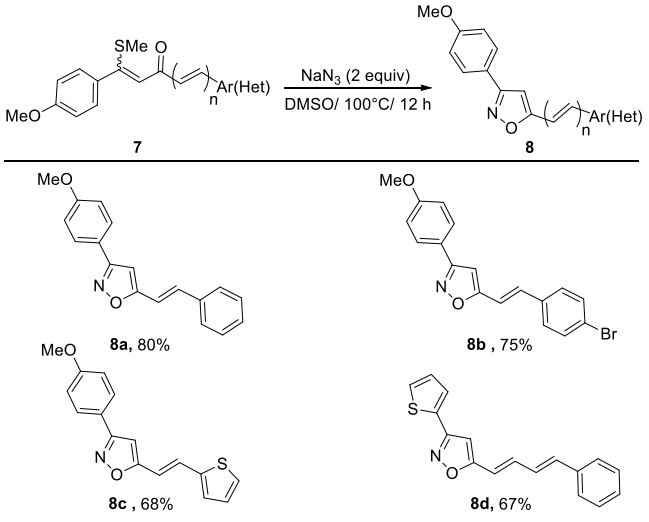
General Information. All the reagents were purchased from commercial suppliers and used without further purification. Solvents were dried according to the standard procedures. All the reactions were monitored by thin layer chromatography (TLC) using standard TLC silica gel plates and visualized with UV light. Column chromatography was performed using Merck silica gel (100−200 mesh). Nuclear magnetic resonance spectra were recorded on Bruker (400 MHz) ultra shield plus and Jeol (600 MHz) ECZ 600R FT-NMR spectrometer with $CDCl_3$, DMSO-d_6 as solvent. Chemical shifts

https://dx.doi.org/10.1021/acs.joc.0c02216
J. Org. Chem. XXXX, XXX, XXX−XXX

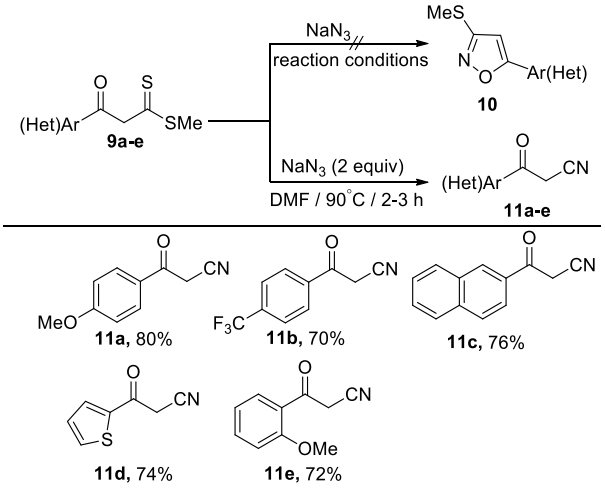
Scheme 3. Synthesis of 1-(Methylthio)-1-(het)aryl-4-(het)arylidene-but-1-en-3-ones 7a−d



Scheme 4. Synthesis of 3-(Het)aryl-5-styryl/(Arylbutadienyl)isoxazoles 8a−d



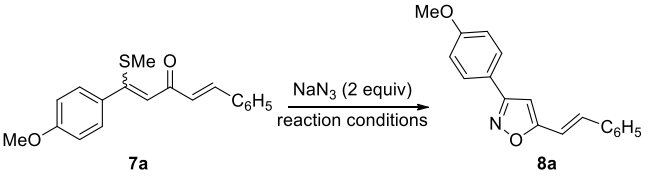
Scheme 5. Synthesis of β-Ketonitriles by Reaction of β-Oxodithioesters with NaN_3



were reported in δ (ppm) using residual solvent protons as the internal standard (δ 7.26 for $CDCl_3$ and δ 2.50 for DMSO-d_6, in ^{1}H NMR, δ 77.16 for $CDCl_3$, and δ 39.52 for DMSO-d_6 in ^{13}C NMR spectra). Coupling constants were reported as *J* values in hertz (Hz). Splitting patterns are designated as s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublet), dt (doublet of triplet), td (triplet of doublet), m (multiplet), and br (broad). Infrared spectra of neat samples were recorded in attenuated total reflectance mode using an FT-IR instrument (Agilent Technologies), and HRMS spectra on a 6538 UYHD accurate mass Q-TOF LC/MS spectrometer through electro spray ionization (ESI) mode. Melting points were recorded using an electro thermal capillary melting point apparatus and are uncorrected.

All the 1,3-bis(het)arylmonothiodiketones **2a−v** were prepared by base-induced condensation of various active methylene ketones with appropriate dithioesters **1** according to our earlier reported procedure.[16a] The known 1,3-bis(het)arylmonothiodiketones **2a**, **2r**, **2v** were characterized by comparison of their spectral and analytical data with the reported one,[16a,19] whereas the spectral and analytical

Table 3. Optimization of Reaction Conditions for the Synthesis of 8a from 7a

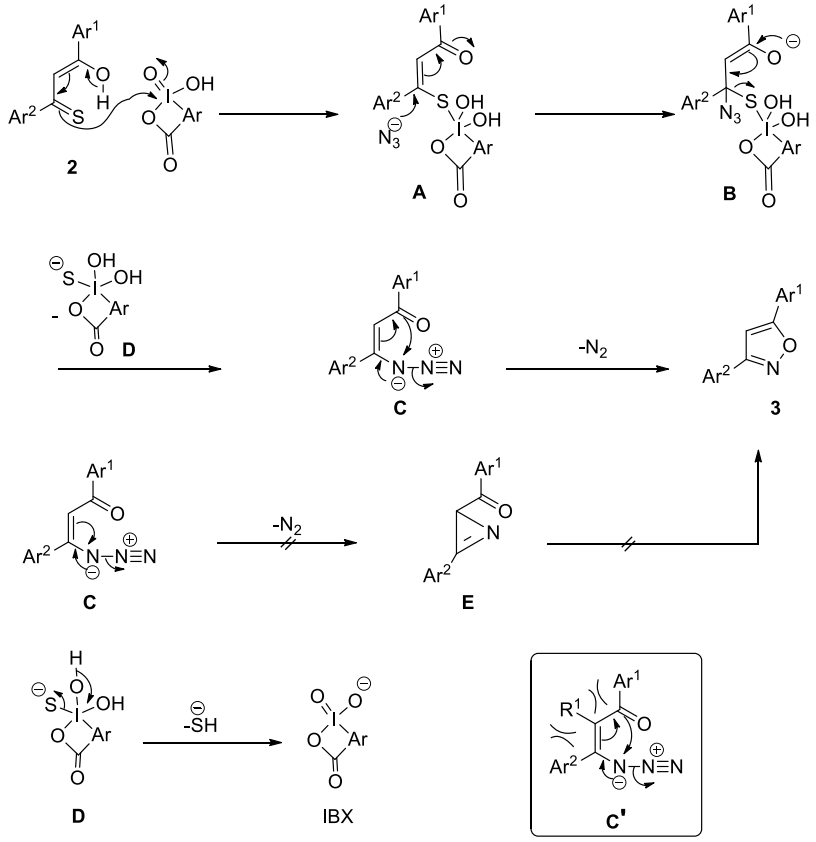


entry	catalyst	solvent	temp (°C)	time (h)	product	yield (%)[a]
1		DMF	RT	24	**8a**	
2[b]	IBX	DMF	RT	15	**8a**	
3		DMF	100	12	**8a**	60
4		DMSO	100	12	**8a**	80
5[b]	IBX	DMSO	100	12	**8a**	68

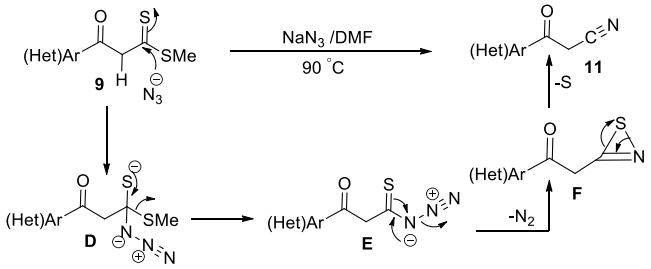
[a]Yield of isolated product. [b]IBX (10 mol %).

https://dx.doi.org/10.1021/acs.joc.0c02216
J. Org. Chem. XXXX, XXX, XXX−XXX

Scheme 6. Plausible Mechanism for the Formation of Isoxazole 3 from 2 and NaN_3



Scheme 7. Plausible Mechanism for the Formation of β-Ketonitriles 11 from β-Oxodithioester 9



data of unknown 1,3-monothiodiketones **2b–q** and **2s–u** are given below. All the known β-ketodithioesters **9a–d** and the unknown **9e** were prepared according to an earlier reported procedure.[20] The spectral and analytical data of **9e** are given below.

3-(Benzo[*d*][1,3]dioxol-5-yl)-1-phenyl-3-thioxopropan-1-one (2b). Red solid (237 mg, 79%); mp 65–67 °C; R_f 0.53 (1:9 EtOAc/hexane); IR (neat, cm^{-1}): 3525, 3010, 2912, 1703, 1253, 1050; ^1H NMR (400 MHz, $CDCl_3$): δ 15.93 (br, 1H), 7.99 (d, *J* = 7.6 Hz, 2H), 7.56 (t, *J* = 7.2 Hz, 1H), 7.51–7.46 (m, 3H), 7.43 (d, *J* = 2.0 Hz, 1H), 7.39 (s, 1H), 6.84 (d, *J* = 8.0 Hz, 1H), 6.04 (s, 2H); $^{13}C\{H\}$ NMR (100 MHz, $CDCl_3$): δ 205.9, 178.1, 150.7, 148.1, 140.2, 135.5, 132.5, 128.8, 127.1, 121.9, 109.1, 107.9, 107.7, 101.9; HRMS (ESI) *m*/*z*: calcd for $C_{16}H_{13}O_3S$ $[M + H]^+$, 285.0585; found, 285.0589.

1-(3-Bromophenyl)-3-(4-(piperidin-1-yl)phenyl)-3-thioxopropan-1-one (2c). Red solid (220 mg, 76%); mp 102–104 °C; R_f 0.34 (1:9 EtOAc/hexane); IR (neat, cm^{-1}): 3584, 3101, 2941, 1721, 1465, 685; ^1H NMR (400 MHz, $CDCl_3$): δ 16.23 (br, 1H), 8.09 (t, *J* = 1.8 Hz 1H), 7.94 (d, *J* = 9.2 Hz, 2H), 7.88 (d, *J* = 7.6 Hz, 1H), 7.64 (d, *J* = 8.0 Hz, 1H), 7.36–7.32 (m, 2H), 6.84 (d, *J* = 9.2 Hz, 2H), 3.38 (s, 4H), 1.68 (s, 6H); $^{13}C\{H\}$ NMR (100 MHz, $CDCl_3$): δ 206.4, 175.8, 153.4, 138.2, 134.5, 134.3, 130.3, 129.7, 129.4, 125.3, 122.9, 113.2, 106.6, 48.6, 25.4, 24.4; HRMS (ESI) *m*/*z*: calcd for $C_{20}H_{21}BrNOS$ $[M + H]^+$, 402.0527 and $[M + H + 2]^+$, 404.0527; found, 402.0502 and 404.0484.

1-(3,4-Dimethoxyphenyl)-3-(4-fluorophenyl)-3-thioxopropan-1-one (2d). Red solid (210 mg, 80%); mp 112–114 °C; R_f 0.46 (1:9 EtOAc/hexane); IR (neat, cm^{-1}): 3555, 2927, 2309, 1703, 1257, 1020; ^1H NMR (400 MHz, $CDCl_3$): δ 15.48 (br, 1H), 7.82 (dd, *J* = 8.2, 5.4 Hz, 2H), 7.64 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.55 (d, *J* = 2.0 Hz, 1H), 7.38 (s, 1H), 7.11 (t, *J* = 8.4 Hz, 2H), 6.94 (d, *J* = 8.4 Hz, 1H), 3.99 (s, 6H); $^{13}C\{H\}$ NMR (100 MHz, $CDCl_3$): δ 199.9, 179.6, 165.8, 163.3, 153.3, 149.3, 141.8, 141.7, 129.0, 128.9, 128.1, 121.4, 115.6, 115.3, 110.8, 109.9, 109.8, 56.14, 56.11; HRMS (ESI) *m*/*z*: calcd for $C_{17}H_{16}FO_3S$ $[M + H]^+$, 319.0804; found, 319.0800.

3-Thioxo-1-(4-(trifluoromethyl)phenyl)-3-(3,4,5-trimethoxyphenyl)propan-1-one (2e). Red solid (230 mg, 86%); mp 109–111 °C; R_f 0.45 (1:9 EtOAc/hexane); IR (neat, cm^{-1}): 3300, 3109, 2845, 1750, 1012, 1054; ^1H NMR (400 MHz, $CDCl_3$): δ 15.34 (br, 1H), 8.08 (d, *J* = 8.4 Hz, 2H), 7.76 (d, *J* = 8.0 Hz, 2H), 7.37 (s, 1H), 7.07 (s, 2H), 3.95 (s, 6H), 3.93 (s, 3H); $^{13}C\{H\}$ NMR (100 MHz, $CDCl_3$): δ 205.8, 176.9, 153.0, 141.6, 140.9, 139.1, 133.9, 133.6, 127.4, 125.93, 125.89, 125.86, 125.83, 124.9, 122.3, 110.1, 104.7, 61.0, 56.4; HRMS (ESI) *m*/*z*: calcd for $C_{19}H_{18}F_3O_4S$ $[M + H]^+$, 399.0872; found, 399.0857.

1-(2-Methoxyphenyl)-3-(4-methoxyphenyl)-3-thioxopropan-1-one (2f). Red liquid (200 mg, 75%); R_f 0.52 (1:9 EtOAc/hexane); IR (neat, cm^{-1}): 3655, 2947, 2509, 1733, 1558, 1227; ^1H NMR (600 MHz, $CDCl_3$): δ 16.02 (br, 1H), 7.93 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.89 (dd, *J* = 6.9, 2.1 Hz, 2H), 7.75 (s, 1H), 7.47 (td, *J* = 8.7, 1.8 Hz, 1H), 7.07 (t, *J* = 7.5 Hz, 1H), 6.99 (d, *J* = 8.4 Hz, 1H), 6.92 (dd, *J* = 6.6, 2.4 Hz, 2H), 3.93 (s, 3H), 3.85 (s, 3H); $^{13}C\{H\}$ NMR (150 MHz, $CDCl_3$): δ 204.9, 177.3, 162.6, 158.2, 138.5, 133.2, 130.5, 129.1, 125.1, 121.1, 114.3, 113.8, 112.0, 56.0, 55.6; HRMS (ESI) *m*/*z*: calcd for $C_{17}H_{16}KO_3S$ $[M + K]^+$, 339.0452; found, 339.0449.

3-(2-((4-Methoxybenzyl)oxy)phenyl)-1-(pyridin-4-yl)-3-thioxopropan-1-one (2g). Red solid (224 mg, 78%); mp 101–103 °C; R_f 0.38 (3:7 EtOAc/hexane); IR (neat, cm^{-1}): 3150, 3109, 2945,

https://dx.doi.org/10.1021/acs.joc.0c02216
J. Org. Chem. XXXX, XXX, XXX–XXX

1740, 1675, 1213; ^{1}H NMR (400 MHz, $CDCl_3$): δ 13.92 (br, 1H), 8.63 (d, J = 6.0 Hz, 2H), 7.67 (dd, J = 7.8, 1.8 Hz, 1H), 7.51 (s, 1H), 7.45−7.40 (m, 3H), 7.32 (d, J = 8.8 Hz, 2H), 7.08−7.03 (m, 2H), 6.81 (d, J = 8.8 Hz, 2H), 5.06 (s, 2H), 3.76 (s, 3H); ^{13}C{H} NMR (100 MHz, $CDCl_3$): δ 201.4, 176.1, 159.7, 154.1, 150.5, 143.4, 135.2, 132.2, 131.3, 129.5, 128.1, 121.3, 120.4, 114.6, 114.0, 113.1, 70.7, 55.3; HRMS (ESI) m/z: calcd for $C_{22}H_{20}NO_3S$ $[M + H]^+$, 378.1158; found, 378.1148.

1-(4-Chlorophenyl)-3-(thiophen-2-yl)-3-thioxopropan-1-one (2h). Orange solid (215 mg, 69%); mp 112−114 °C; R_f 0.52 (1:9 EtOAc/hexane); IR (neat, cm^{-1}): 3650, 3111, 2952, 1737, 1081, 704; ^{1}H NMR (400 MHz, $CDCl_3$): δ 16.02 (br, 1H), 7.89 (d, J = 6.4 Hz, 2H), 7.78 (d, J = 4.0 Hz, 1H), 7.65 (d, J = 5.2 Hz, 1H) 7.46 (d, J = 8.8 Hz, 2H), 7.38 (s, 1H), 7.15 (t, J = 4.4, Hz, 1H); ^{13}C{H} NMR (100 MHz, $CDCl_3$): δ 200.7, 174.6, 152.3, 138.7, 134.4, 133.4, 129.2, 128.8, 128.2, 127.7, 106.4; HRMS (ESI) m/z: calcd for $C_{13}H_{10}ClOS_2$ $[M + H]^+$, 280.9856; found, 280.9841.

1-(Pyren-1-yl)-3-(thiophen-2-yl)-3-thioxopropan-1-one (2i). Yellow solid (234 mg, 78%); mp 98−99 °C; R_f 0.56 (2:8 EtOAc/hexane); IR (neat, cm^{-1}): 3650, 3100, 2885, 1790, 1650, 1049; ^{1}H NMR (600 MHz, $CDCl_3$): δ 16.34 (br, 1H), 8.71 (d, J = 9.0 Hz, 1H), 8.28−8.16 (m, 6H), 8.09−8.05 (m, 2H), 7.76 (dd, J = 4.2, 1.2 Hz, 1H), 7.65 (dd, J = 5.4, 1.2 Hz, 1H), 7.42 (s, 1H), 7.14 (t, J = 5.4 Hz, 1H); ^{13}C{H} NMR (150 MHz, $CDCl_3$): δ 199.6, 179.5, 152.5, 134.6, 133.5, 131.3, 130.7, 130.6, 129.5, 129.1, 128.9, 127.9, 127.3, 127.2, 126.6, 126.4, 126.3, 126.2, 125.1, 124.8, 124.6, 124.5, 112.7; HRMS (ESI) m/z: calcd for $C_{23}H_{15}OS_2$ $[M + H]^+$, 371.0564; found, 371.0534.

4,4-Dimethyl-1-(thiophen-2-yl)-1-thioxopentan-3-one (2j). Yellow liquid (256 mg, 81%); R_f 0.46 (1:9 EtOAc/hexane); IR (neat, cm^{-1}): 3715, 3109, 2905, 1699, 1060, 1453; ^{1}H NMR (400 MHz, $CDCl_3$): δ 15.78 (br, 1H), 7.69 (dd, J = 4.0, 1.2 Hz, 1H), 7.59 (dd, J = 5.0, 1.4 Hz, 1H), 7.11 (dd, J = 5.0, 3.8 Hz, 1H), 6.93 (s, 1H), 1.29 (s, 9H); ^{13}C{H} NMR (100 MHz, $CDCl_3$): δ 199.1, 192.9, 152.0, 133.6, 128.5, 127.4, 105.8, 38.9, 27.7; HRMS (ESI) m/z: calcd for $C_{11}H_{14}OS_2$ $[M + H]^+$, 227.0559; found, 227.0540.

1-(Furan-2-yl)-3-(thiophen-2-yl)-3-thioxopropan-1-one (2k). Red solid (243 mg, 80%); mp 97−98 °C; R_f 0.41 (1:9 EtOAc/hexane); IR (neat, cm^{-1}): 3720, 3201, 2885, 1730, 1200, 1050; ^{1}H NMR (400 MHz, $CDCl_3$): δ 15.52 (br, 1H), 7.76 (dd, J = 4.0, 1.2 Hz, 1H), 7.64 (d, J = 2.0 Hz, 1H), 7.62 (dd, J = 5.2, 1.2 Hz, 1H), 7.38 (s, 1H), 7.25 (d, J = 3.6 Hz, 1H), 7.13 (dd, J = 5.0, 3.8 Hz, 1H), 6.61 (dd, J = 3.6, 1.6 Hz, 1H); ^{13}C{H} NMR (100 MHz, $CDCl_3$): δ 198.5, 165.9, 152.2, 149.6, 146.4, 134.2, 128.7, 127.5, 116.3, 113.2, 105.5; HRMS (ESI) m/z: calcd for $C_{11}H_9O_2S_2$ $[M + H]^+$, 237.0038; found, 237.0025.

3-(1-Methyl-1*H*-pyrrol-3-yl)-3-thioxo-1-(4-(trifluoromethyl)-phenyl)propan-1-one (2l). Orange solid (231 mg, 76%); mp 52−54 °C; R_f 0.34 (2:9 EtOAc/hexane); IR (neat, cm^{-1}): 3729, 3078, 2927, 1055, 1069, 1296; ^{1}H NMR (400 MHz, $CDCl_3$): δ 15.96 (br, 1H), 8.00 (d, J = 8.0 Hz, 2H), 7.71 (d, J = 8.4 Hz, 2H), 7.25 (s, 1H), 6.97 (d, J = 3.2 Hz, 2H), 6.22 (t, J = 3.4 Hz, 1H), 4.08 (s, 3H); ^{13}C{H} NMR (100 MHz, $CDCl_3$): δ 199.5, 170.9, 140.7, 139.2, 134.5, 133.3, 133.0, 132.7, 132.4, 127.9, 127.6, 126.8, 125.72, 125.69, 125.65, 125.61, 125.17, 122.5, 119.7, 115.5, 108.8, 107.4, 38.9; HRMS (ESI) m/z: calcd for $C_{15}H_{13}F_3NOS$ $[M + H]^+$, 312.0670; found, 312.0654.

3-(4-(Methylthio)phenyl)-1-(thiazol-2-yl)-3-thioxopropan-1-one (2m). Red solid (208 mg, 78%); mp 89−90 °C; R_f 0.46 (1:9 EtOAc/hexane); IR (neat, cm^{-1}): 3729, 3078, 2927, 1055, 1069, 1296; ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.39 (br, 1H), 8.02 (d, J = 2.8 Hz, 1H), 7.91 (s, 1H), 7.81 (d, J = 8.4 Hz, 2H), 7.68 (d, J = 2.8 Hz, 1H), 7.26 (d, J = 8.8 Hz, 2H), 1.87 (s, 3H); ^{13}C{H} NMR (100 MHz, $CDCl_3$): δ 189.5, 174.1, 166.9, 144.8, 144.2, 139.3, 127.4, 125.5, 125.2, 109.4, 15.0; HRMS (ESI) m/z: calcd for $C_{13}H_{12}NOS_3$ $[M + H]^+$, 294.0081; found, 294.0062.

3-(1-Methyl-1*H*-indol-3-yl)-1-phenyl-3-thioxopropan-1-one (2n). Orange solid (256 mg, 85%); mp 121−123 °C; R_f 0.54 (2:8 EtOAc/hexane); IR (neat, cm^{-1}): 3742, 3101, 2323, 1745, 1360, 1235; ^{1}H NMR (400 MHz, $CDCl_3$): δ 16.41 (s, 1H), 8.55 (d, J = 7.2 Hz, 1H), 7.95 (dd, J = 7.8, 1.8 Hz, 2H), 7.84 (s, 1H), 7.54−7.45 (m, 3H), 7.37 (s, 1H), 7.35−7.28 (m, 3H), 3.75 (s, 3H); ^{13}C{H} NMR (100 MHz, $CDCl_3$): δ 203.4, 173.9, 138.3, 135.8, 133.6, 131.7, 128.8, 126.6, 125.7, 125.3, 123.4, 122.9, 122.3, 110.3, 106.5, 33.6; HRMS (ESI) m/z: calcd for $C_{18}H_{16}NOS$ $[M + H]^+$, 294.0947; found, 294.0935.

3-(1-Methyl-1*H*-indol-3-yl)-1-(pyridin-3-yl)-3-thioxopropan-1-one (2o). Orange solid (238 mg, 79%); mp 124−126 °C; R_f 0.53 (3:7 EtOAc/hexane); IR (neat, cm^{-1}): 3739, 3208, 2981, 1752, 1358, 1200; ^{1}H NMR (400 MHz, $CDCl_3$): δ 16.18 (br, 1H), 9.12 (d, J = 2.4 Hz, 1H), 8.71 (dd, J = 4.8, 1.6 Hz, 1H), 8.59 (dd, J = 7.2, 1.6 Hz, 1H), 8.15 (td, J = 8.0, 2.0 Hz, 1H), 7.85 (s, 1H), 7.39 (dd, J = 8.0 Hz, 4.8 Hz, 1H), 7.36−7.28 (m, 3H), 7.26 (s, 1H), 3.77 (s, 3H); ^{13}C{H} NMR (100 MHz, $CDCl_3$): δ 203.9, 170.4, 151.8, 147.7, 138.3, 133.9, 133.6, 131.7, 125.8, 125.3, 123.6, 123.5, 123.2, 122.4, 110.3, 106.2, 33.6; HRMS (ESI) m/z: calcd for $C_{17}H_{15}N_2OS$ $[M + H]^+$, 295.0900; found, 295.0914.

3-(4-(Dimethylamino)phenyl)-1-(pyridin-3-yl)-3-thioxopropan-1-one (2p). Reddish brown solid (220 mg, 80%); 118−120 °C; R_f 0.31 (2:8 EtOAc/hexane); IR (neat, cm^{-1}): 3715, 2932, 2856, 2323, 1050, 1018; ^{1}H NMR (400 MHz, $CDCl_3$): δ 16.30 (br, 1H), 9.17 (d, J = 2.4 Hz, 1H), 8.78 (dd, J = 4.8, 1.6 Hz, 1H), 8.23 (d, J = 8.4 Hz, 1H), 7.99 (d, J = 9.2 Hz, 2H), 7.41 (dd, J = 8.0, 4.8 Hz, 1H), 7.37 (s, 1H), 6.65 (d, J = 8.4 Hz, 2H), 3.08 (s, 6H); ^{13}C {H} NMR (100 MHz, $CDCl_3$): δ 208.3, 172.2, 153.4, 152.0, 147.9, 134.1, 133.0, 132.0, 129.1, 123.6, 110.9, 106.2, 40.1; HRMS (ESI) m/z: calcd for $C_{16}H_{17}N_2OS$ $[M + H]^+$, 285.1062; found, 285.1033.

1,3-Dsi(pyridin-3-yl)-3-thioxopropan-1-one (2q). Red solid (217 mg, 78%); mp 99−100 °C; R_f 0.56 (4:6 EtOAc/hexane); IR (neat, cm^{-1}): 3705, 3081, 2869, 1708, 1089, 1665; ^{1}H NMR (400 MHz, $CDCl_3$): δ 14.88 (br, 1H), 9.22 (s, 1H), 9.01 (s, 1H), 8.79 (s, 1H), 8.73 (s, 1H), 8.26 (d, J = 7.2 Hz, 1H), 8.09 (d, J = 7.6 Hz, 1H), 7.45 (dd, J = 7.8, 4.6 Hz, 1H), 7.41 (s, 2H); ^{13}C{H} NMR (100 MHz, $CDCl_3$): δ 200.9, 177.9, 153.2, 151.9, 148.4, 146.9, 140.5, 134.6, 134.4, 131.2, 123.8, 123.5, 110.6; HRMS (ESI) m/z: calcd for $C_{13}H_{11}N_2OS$ $[M + H]^+$, 243.0592; found, 243.0569.

4-(4-Methoxyphenyl)-4-thioxobutan-2-one (2s). Yellow solid (205 mg, 82%); mp 80−82 °C; R_f 0.32 (1:9 EtOAc/hexane); IR (neat, cm^{-1}): 3525, 3201, 2869, 1745, 1225, 1068; ^{1}H NMR (400 MHz, $CDCl_3$): δ 14.98 (br, 1H), 7.79 (d, J = 8.8 Hz, 2H), 6.89 (d, J = 8.8 Hz, 2H), 6.74 (s, 1H), 3.84 (s, 3H), 2.22 (s, 3H); ^{13}C{H} NMR (100 MHz, $CDCl_3$): δ 200.8, 185.9, 162.6, 136.9, 128.8, 113.7, 111.9, 55.5, 25.9; HRMS (ESI) m/z: calcd for $C_{11}H_{13}O_2S$ $[M + H]^+$, 209.0636; found, 209.0614.

4-(Thiophen-2-yl)-4-thioxobutan-2-one (2t). Red solid (260 mg, 64%); mp 84−86 °C; R_f 0.41 (1:9 EtOAc/hexane); IR (neat, cm^{-1}): 3400, 2900, 2895, 1704, 1205, 1075; ^{1}H NMR (400 MHz, $CDCl_3$): δ 15.55 (br, 1H), 7.68 (d, J = 4.0 Hz, 1H), 7.60 (d, J = 5.2 Hz, 1H), 7.12 (t, J = 4.4 Hz, 1H), 6.77 (s, 1H), 2.20 (s, 3H); ^{13}C{H} NMR (100 MHz, $CDCl_3$): δ 199.1, 182.6, 151.5, 134.0, 128.6, 127.6, 109.6, 24.6; HRMS (ESI) m/z: calcd for $C_8H_9OS_2$ $[M + H]^+$, 185.0095; found, 185.0073.

General Procedure for the Synthesis of 1-(Methylthio)-1-(het)aryl-1-buten-3-one 6a−b. To a stirred suspension of NaH (34 mg, 1.0 mmol, 100%) in DMF (10 mL) under an N_2 atmosphere, a solution of acetone (70 mg, 1.2 mmol) and (het)aryl dithioesters **1** (1.0 mmol) in DMF (5 mL) was added at 0 °C, and the reaction mixture was further stirred at room temperature for 1 h. It was then cooled (monitored by TLC), followed by dropwise addition of methyl iodide (170 mg, 1.2 mmol) and stirring was further continued at room temperature for 1 h (monitored by TLC). The reaction mixture was then poured into water (50 mL) and extracted with EtOAc (3 × 50 mL). The combined organic extracts were washed with H_2O (3 × 50 mL) and brine (1 × 50 mL), dried (Na_2SO_4), and evaporated under reduced pressure to give crude products **6**, which were purified by column chromatography using EtOAc/hexane as eluent.

(E/Z)-1-(4-Methoxyphenyl)-1-(methylthio)but-1-en-3-one (6a). E/Z = 67:33; yellow viscous liquid (204 mg, 74%); R_f 0.41 (1:9 EtOAc/hexane); IR (neat, cm^{-1}): 3200, 2900, 2895, 1711, 1212; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.13 (dd, J = 6.6, 1.8 Hz, 0.67H), 7.08

https://dx.doi.org/10.1021/acs.joc.0c02216
J. Org. Chem. XXXX, XXX, XXX−XXX

(dd, J = 6.6, 1.8 Hz, 1.25H), 6.80 (dd, J = 6.6, 2.4 Hz, 1.33H), 6.78 (dd, J = 6.6, 1.8 Hz, 0.68H), 6.22 (s, 0.58H), 5.81 (s, 0.38H), 3.69 (s, 2.05H), 3.68 (s, 1.06H), 2.21 (s, 1.06H), 2.11 (s, 2H), 1.79 (s, 2H), 1.69 (s, 1.04H); $^{13}C\{H\}$ NMR (150 MHz, $CDCl_3$): δ 195.9, 195.8, 161.3, 160.7, 160.1, 159.6, 130.5, 129.9, 129.6, 129.4, 122.7, 120.9, 113.9, 113.8, 60.3, 55.3, 30.5, 30.1, 16.3, 14.2; HRMS (ESI) m/z: calcd for $C_{12}H_{15}O_2S$ $[M + H]^+$, 223.0793; found, 223.0778.

*(E/Z)-1-(Methylthio)-1-(thiophen-2-yl)but-1-en-3-one (**6b**).* E/Z = 67:33; brown viscous liquid (214 mg, 71%); R_f 0.41 (1:9 EtOAc/hexane); IR (neat, cm^{-1}): 3200, 2900, 2895, 1711, 1212; ^1H NMR (600 MHz, $CDCl_3$): δ 7.42 (d, J = 4.8 Hz, 0.34H), 7.34 (d, J = 4.8 Hz, 0.60H), 7.19 (d, J = 3.0 Hz, 0.37H), 7.10 (d, J = 3.6 Hz, 0.67H), 7.03 (dd, J = 5.1, 3.3 Hz, 0.67H), 7.01 (dd, J = 3.6, 1.8 Hz, 0.34H), 2.35 (s, 1.02H), 2.24 (s, 2.08H), 2.12 (s, 2.07H), 1.95 (s, 1.01H); $^{13}C\{H\}$ NMR (150 MHz, $CDCl_3$): δ 196.4, 195.8, 152.1, 150.7, 139.8, 137.7, 129.7, 128.9, 128.3, 127.6, 127.4, 124.2, 122.0, 30.9, 29.9, 17.2, 16.9; HRMS (ESI) m/z: calcd for $C_9H_{11}OS_2$ $[M + H]^+$, 199.0251; found, 199.0233.

General Procedure for the Synthesis of 1-(Methylthio)-1-(het)aryl-4-(het)arylidene-but-1-en-3-one 7a−c. To a stirred suspension of NaOH (40 mg, 1.0 mmol) in ethanol (3 mL), a solution of 1-(methylthio)-1-(het)aryl-1-buten-3-one **6** (1.0 mmol) in ethanol (3 mL) was added dropwise at room temperature, followed by addition of a solution of (het)arylaldehyde (1.0 mmol) in ethanol (3 mL). After further stirring for 1−2 h (monitored by TLC), the reaction mixture was evaporated under reduced pressure, and the residue was dissolved in EtOAc (10 mL), diluted with water (10 mL), and further extracted with EtOAc (3 × 10 mL); the combined organic layer was washed with water (3 × 25 mL) and brine (25 mL), dried (Na_2SO_4), and evaporated under vacuum to give crude products **7**, which were further purified by column chromatography using EtOAc/hexane as eluent.

*(1Z,4E)-1-(4-Methoxyphenyl)-1-(methylthio)-5-phenylpenta-1,4-dien-3-one (**7a**).* E/Z = 67:33; brown viscous liquid (200 mg, 77%); R_f 0.41 (1:9 EtOAc/hexane); IR (neat, cm^{-1}): 3425, 2932, 2892, 1704, 1200, 1068; ^1H NMR (600 MHz, $CDCl_3$): δ 7.62 (d, J = 16.2 Hz, 0.66H), 7.55 (d, J = 7.2 Hz, 1.34 H), 7.42 (d, J = 15.6 Hz, 0.35H), 7.37−7.34 (m, 2.21H), 7.28−7.25 (m, 2.07H), 7.20 (d, J = 7.2 Hz, 1.04H), 6.94 (d, J = 9.0 Hz, 1.33H), 6.89 (d, J = 8.4 Hz, 1.09H), 6.86 (d, J = 16.2 Hz, 0.66H), 6.59 (s, 1.90H), 6.36 (d, J = 15.6 Hz, 1.70H), 6.10 (s, 0.69H), 3.81 (s, 2.25H), 3.75 (s, 1.28H), 2.37 (s, 1.31H), 1.95 (s, 2.04H); $^{13}C\{H\}$ NMR (150 MHz, $CDCl_3$): δ 187.8, 187.3, 163.5, 161.0, 160.2, 160.1, 141.8, 140.8, 135.2, 131.1, 130.6, 130.1, 129.93, 129.90, 129.59, 129.54, 128.9, 128.8, 128.3, 128.1, 127.5, 126.6, 122.9, 122.5, 120.9, 113.9, 55.5, 16.9, 16.6; HRMS (ESI) m/z: calcd for $C_{19}H_{19}O_2S$ $[M + H]^+$, 311.1106; found, 311.1089.

*(1Z,4E)-5-(4-Bromophenyl)-1-(4-methoxyphenyl)-1-(methylthio)-penta-1,4-dien-3-one (**7b**).* E/Z = 69:31; yellow solid (208 mg, 81%); mp 100−102 °C; R_f 0.45 (1:9 EtOAc/hexane); IR (neat, cm^{-1}): 2941, 2902, 1700, 1200, 1068; ^1H NMR (600 MHz, $CDCl_3$): δ 7.48 (d, J = 16.2 Hz, 0.62H), 7.41 (d, J = 8.4 Hz, 1.37H), 7.33 (d, J = 9.0 Hz, 2.05H), 7.28 (t, J = 8.1 Hz, 1.06H), 7.19 (d, J = 7.8 Hz, 1.38H), 6.99 (d, J = 8.4 Hz, 0.62H), 6.88 (d, J = 7.8 Hz, 1.39H), 6.83 (d, J = 8.4 Hz, 0.63H), 6.79 (d, J = 15.6 Hz, 0.62H), 6.52 (s, 0.69H), 6.28 (d, J = 15.6 Hz, 0.31H), 6.04 (s, 0.30H), 3.77 (s, 2.08H), 3.72 (s, 0.94H), 2.34 (s, 0.93H), 1.91 (s, 2.06H); $^{13}C\{H\}$ NMR (150 MHz, $CDCl_3$): δ 187.3, 186.7, 164.0, 161.1, 160.6, 160.2, 140.2, 139.1, 134.2, 134.1, 132.1, 131.9, 130.8, 130.7, 129.8, 129.7, 129.6, 129.4, 127.9, 127.2, 124.2, 124.0, 122.5, 120.8, 114.0, 113.9, 55.5, 16.9, 16.7; HRMS (ESI) m/z: calcd for $C_{19}H_{18}BrO_2S$ $[M + H]^+$, 389.0211 and $[M + H + 2]^+$, 291.0211; found, 389.0231, 391.0213.

*(1Z,4E)-1-(4-Methoxyphenyl)-1-(methylthio)-5-(thiophen-2-yl)-penta-1,4-dien-3-one (**7c**).* E/Z = 60:40; yellow viscous liquid (230 mg, 69%); R_f 0.56 (1:9 EtOAc/hexane); IR (neat, cm^{-1}): 2900, 2782, 1690, 1230, 699; ^1H NMR (600 MHz, $CDCl_3$): δ 7.72 (d, J = 15.6 Hz, 0.61H), 7.52 (d, J = 15.6 Hz, 0.33H), 7.31 (d, J = 7.8 Hz, 1.25H), 7.24−7.21 (m, 2.15H), 7.06 (d, J = 3.6 Hz, 0.42H), 7.01 (d, J = 4.2 Hz, 0.62H), 6.93 (d, J = 4.2 Hz, 0.43H), 6.91 (d, J = 8.4 Hz, 1.34H), 6.87 (d, J = 8.4 Hz, 0.85H), 6.64 (d, J = 15.0 Hz, 0.62H), 6.49 (s, 0.63H), 6.14 (d, J = 15.0 Hz, 0.34H), 6.04 (s, 0.40H), 3.81 (s, 1.88H), 3.76 (s, 1.25H), 2.37 (s, 1.24H), 1.94 (s, 1.87H); $^{13}C\{H\}$ NMR (150 MHz, $CDCl_3$): δ 187.1, 186.6, 163.4, 161.0, 160.2, 140.8, 140.7, 134.3, 133.3, 131.2, 130.99, 130.95, 130.55, 130.15, 129.7, 129.6, 129.5, 128.3, 128.1, 128.0, 126.4, 125.7, 122.7, 120.8, 114.0, 55.5, 55.4, 16.9, 16.6; HRMS (ESI) m/z: calcd for $C_{17}H_{17}O_2S_2$ $[M + H]^+$, 317.0670; found, 317.0616.

*(1Z,4E,6E)-1-(Methylthio)-7-phenyl-1-(thiophen-2-yl)hepta-1,4,6-trien-3-one (**7d**).* Trienone **7d** was obtained following the above general procedure for **7a−c** using cinnamaldehyde (132 mg, 1.0 mmol) and **6b** (198 mg, 1.0 mmol), E/Z = 66:34; yellow viscous liquid (231 mg, 65%); R_f 0.52 (1:9 EtOAc/hexane); IR (neat, cm^{-1}): 2952, 2808, 1703, 1620, 1050; ^1H NMR (400 MHz, $CDCl_3$): δ 7.47−7.44 (m, 1.41H), 7.42−7.40 (m, 0.96H), 7.39−7.38 (m, 1.0H), 7.37−7.36 (m, 0.64H), 7.34−7.32 (m, 1.43H), 7.29 (dd, J = 5.6, 1.6 Hz, 1.36H), 7.26 (dd, J = 3.4, 1.4 Hz, 0.68H), 7.16 (dd, J = 3.6, 1.2 Hz, 0.72H), 7.07 (dd, J = 5.2, 3.6 Hz, 0.71H), 7.01 (dd, J = 5.2, 3.6 Hz, 0.33H), 6.92 (s, 1.05H), 6.89 (s, 0.33H), 6.85 (d, J = 15.6 Hz, 0.36H), 6.73 (s, 0.71H), 6.43 (d, J = 15.2 Hz, 0.71H), 6.09 (d, J = 10.4 Hz, 0.67H), 2.41 (s, 0.98H), 2.18 (s, 2.12H); $^{13}C\{H\}$ NMR (100 MHz, $CDCl_3$): δ 188.4, 187.1, 153.1, 149.8, 142.2, 141.8, 140.9, 140.6, 140.2, 136.3, 130.9, 130.1, 129.9, 129.0, 128.96, 128.82, 128.77, 128.18, 127.50, 127.41, 127.31, 127.20, 127.15, 127.07, 126.9, 123.8, 121.4, 17.4, 16.9; HRMS (ESI) m/z: calcd for $C_{18}H_{17}OS_2$ $[M + H]^+$, 313.0715; found, 313.0727.

General Procedure for the Synthesis of 3-(Het)aryl-5-(het)aryl/alkylisoxazoles 3. To a stirred solution of 1,3-monothiodiketone **2** (1.0 mmol) in DMF (3 mL), a solution of IBX (50 mg, 10 mol %) in DMF (3 mL) was added dropwise at room temperature under an N_2 atmosphere, and after stirring for 5 min, sodium azide (45 mg, 2.0 mmol) was added and stirring was continued at room temperature for further 1−2 h (monitored by TLC). The reaction mixture was then quenched with saturated NH_4Cl solution (25 mL) and extracted with EtOAc (3 × 25 mL), and the combined organic layer was washed with water (3 × 25 mL) and brine (25 mL), dried (Na_2SO_4), and evaporated under vacuum to give crude isoxazoles **3**, which were further purified by column chromatography using hexane/ethyl acetate as eluent.

*3-(4-Methoxyphenyl)-5-phenylisoxazole (**3a**).* White solid (215 mg, 90%); mp 120−122 °C (reported 120 °C);[13c] R_f 0.52 (1:9 EtOAc/hexane); IR (neat, cm^{-1}): 3018, 2879, 1764, 1501, 1018: ^1H NMR (400 MHz, $CDCl_3$): δ 7.85−7.79 (m, 4H), 7.50−7.45 (m, 3H), 7.00 (d, J = 8.8 Hz, 2H), 6.78 (s, 1H), 3.87 (s, 3H); $^{13}C\{H\}$ NMR (100 MHz, $CDCl_3$): δ 170.2, 162.6, 161.0, 130.1, 128.9, 128.2, 127.6, 125.8, 121.7, 114.3, 97.3, 55.4; HRMS (ESI): calcd for $C_{16}H_{14}NO_2$ $[M + H]^+$, 252.1025; found, 252.1015.

*3-(Benzo[d][1,3]dioxol-5-yl)-5-phenylisoxazole (**3b**).* Pale yellow solid (200 mg, 75%); mp 92−94 °C; R_f 0.47 (1:9 EtOAc/hexane); IR (neat, cm^{-1}): 3010, 2912, 1690, 1550, 1000; ^1H NMR (400 MHz, $CDCl_3$): δ 7.83 (dd, J = 7.8, 1.8 Hz, 2H), 7.51−7.45 (m, 3H), 7.38 (d, J = 2.0 Hz, 1H), 7.34 (dd, J = 8.0, 1.6 Hz, 1H), 6.91 (d, J = 8.0 Hz, 1H), 6.75 (s, 1H), 6.04 (s, 2H); $^{13}C\{H\}$ NMR (100 MHz, $CDCl_3$): δ 170.3, 162.6, 149.2, 148.3, 130.2, 128.9, 127.5, 125.8, 123.1, 121.2, 108.6, 107.0, 101.5, 97.3; HRMS (ESI) m/z: calcd for $C_{16}H_{12}NO_3$ $[M + H]^+$, 266.0817; found, 266.0803.

*5-(3-Bromophenyl)-3-(4-(piperidin-1-yl)phenyl)isoxazole (**3c**).* White solid (218 mg, 85%) mp 103−105 °C; R_f 0.46 (1:9 EtOAc/hexane); IR (neat, cm^{-1}): 3101, 2941, 1665, 980, 685; ^1H NMR (400 MHz, $CDCl_3$): δ 7.97 (s, 1H), 7.77−7.71 (m, 3H), 7.56 (d, J = 8.0 Hz, 1H), 7.35 (t, J = 7.8 Hz, 1H), 6.97 (d, J = 8.4 Hz, 2H), 6.78 (s, 1H), 3.28 (t, J = 5.4 Hz, 4H), 1.71 (d, J = 5.6 Hz, 4H), 1.63 (d, J = 4.8 Hz, 2H); $^{13}C\{H\}$ NMR (100 MHz, $CDCl_3$): δ 168.2, 162.9, 153.0, 132.9, 130.5, 129.6, 128.8, 127.8, 124.3, 123.0, 118.4, 115.5, 98.0, 49.6, 25.5, 24.3; HRMS (ESI) m/z: calcd for $C_{20}H_{20}BrN_2O$ $[M + H]^+$, 383.0759 and $[M + H + 2]^+$, 385.0759; found, 383.0691 and 385.0674.

5-(3,4-Dimethoxyphenyl)-3-(4-fluorophenyl)isoxazole (3d). White solid (250 mg, 90%); mp 98−99 °C; R_f 0.48 (1:9 EtOAc/hexane); IR (neat, cm^{-1}): 2927, 2309, 1557, 1205, 755; ^1H NMR (400 MHz, $CDCl_3$): δ 7.85 (dd, J = 6.0, 3.6 Hz, 2H), 7.41 (dd, J =

https://dx.doi.org/10.1021/acs.joc.0c02216
J. Org. Chem. XXXX, XXX, XXX−XXX

5.6, 1.2 Hz, 1H), 7.34 (d, J = 1.6 Hz, 1H), 7.17 (t, J = 5.8 Hz, 2H), 6.96 (d, J = 5.6 Hz, 1H), 6.69 (s, 1H), 3.98 (s, 3H), 3.95 (s, 3H); $^{13}C\{H\}$ NMR (100 MHz, $CDCl_3$): δ 170.6, 164.7, 163.1, 162.2, 150.9, 149.4, 128.84, 128.79, 125.6, 125.5, 120.4, 119.3, 116.2, 116.0, 111.4, 108.8, 96.3, 56.2, 56.1; HRMS (ESI) m/z: calcd for $C_{17}H_{15}FNO_3$ $[M + H]^+$, 300.1036; found, 300.1030.

*5-(4-(Trifluoromethyl)phenyl)-3-(3,4,5-trimethoxyphenyl)-isoxazole (**3e**).* White solid (234 mg, 79%), mp 108−109 °C; R_f 0.42 (1:9 EtOAc/hexane); IR (neat, cm^{-1}): 3109, 2845, 1512, 1450, 1054; ^1H NMR (400 MHz, $CDCl_3$): δ 7.96 (d, J = 8.4 Hz, 2H), 7.75 (d, J = 8.4 Hz, 2H), 7.09 (s, 2H), 6.90 (s, 1H), 3.95 (s, 6H), 3.92 (s, 3H); $^{13}C\{H\}$ NMR (100 MHz, $CDCl_3$): δ 168.8, 163.1, 153.7, 139.9, 132.1, 131.8, 130.5, 126.15, 126.10, 126.07, 126.04, 125.1, 124.1, 122.4, 104.2, 98.9, 60.9, 56.3; HRMS (ESI) m/z: calcd for $C_{19}H_{17}F_3NO_4$ $[M + H]^+$, 380.1110; found, 380.1017.

*5-(2-Methoxyphenyl)-3-(4-methoxyphenyl)isoxazole (**3f**).* Yellow liquid (270 mg, 77%); R_f 0.35 (1:9 EtOAc/hexane); IR (neat, cm^{-1}): 2947, 2509, 1733, 1558, 980; ^1H NMR (600 MHz, $CDCl_3$): δ 8.01 (d, J = 8.4 Hz, 1H), 7.83 (d, J = 7.8 Hz, 2H), 7.41 (t, J = 7.5 Hz. 1H), 7.08 (t, J = 7.5 Hz, 1H), 7.04 (s, 1H), 7.02 (d, J = 7.8 Hz, 1H), 6.99 (d, J = 7.8 Hz, 2H), 3.99 (s, 3H), 3.86 (s, 3H); $^{13}C\{H\}$ NMR (150 MHz, $CDCl_3$): δ 170.9, 161.8, 161.4, 132.9, 131.4, 130.5, 129.9, 127.6, 125.4, 123.1, 120.1, 114.6, 96.1, 56.4, 55.9; HRMS (ESI) m/z: calcd for $C_{17}H_{16}NO_3$ $[M + H]^+$, 282.1130; found, 282.1106.

*3-(2-((4-Methoxybenzyl)oxy)phenyl)-5-(pyridin-4-yl)isoxazole (**3g**).* Yellow solid (230 mg, 84%); mp 130−131 °C; R_f 0.45 (2:8 EtOAc/hexane); IR (neat, cm^{-1}): 3109, 2945, 1675, 1558, 1213; ^1H NMR (400 MHz, $CDCl_3$): δ 8.71 (dd, J = 4.6, 1.8 Hz, 2H), 8.01 (dd, J = 7.6, 1.6 Hz, 1H), 7.55 (dd, J = 4.6, 1.8 Hz, 2H), 7.43−7.41 (m, 1H), 7.39 (d, J = 8.8 Hz, 2H), 7.37 (s, 1H), 7.18−7.09 (m, 2H), 7.07−6.93 (m, 2H), 5.12 (s, 2H), 3.83 (s, 3H); $^{13}C\{H\}$ NMR (100 MHz, $CDCl_3$): δ 166.4, 160.7, 159.7, 156.5, 150.7, 134.5, 131.5, 129.3, 129.2, 128.5, 121.4, 119.4, 117.8, 114.1, 113.2, 103.9, 70.7, 55.3; HRMS (ESI) m/z: calcd for $C_{22}H_{19}N_2O_3$ $[M + H]^+$, 359.1396; found, 359.0688.

*2-(5-(Pyridin-4-yl)isoxazol-3-yl)phenol (**3g′**).* Orange solid (250 mg, 95%); mp 127−128 °C; R_f 0.62 (2:8 EtOAc/hexane); IR (neat, cm^{-1}): 3540, 3109, 2945, 1675, 1558; ^1H NMR (400 MHz, $CDCl_3$): δ 10.33 (br s, 1H), 8.88 (s, 2H), 8.06 (d, J = 5.6 Hz, 2H), 7.76 (s, 1H), 7.78 (dd, J = 7.8, 6.2 Hz, 1H), 7.36 (td, J = 8.6, 1.8 Hz, 1H), 7.06 (d, J = 8.0 Hz, 1H), 6.95 (t, J = 7.6 Hz, 1H); $^{13}C\{H\}$ NMR (100 MHz, $CDCl_3$): δ 165.6, 161.1, 155.6, 149.1, 135.1, 131.6, 128.6, 120.2, 119.4, 116.6, 114.6, 104.9; HRMS (ESI) m/z: calcd for $C_{14}H_{11}N_2O_2$ $[M + H]^+$, 239.0821; found, 239.0795.

*5-(4-Chlorophenyl)-3-(thiophen-2-yl)isoxazole (**3h**).* Orange solid (215 mg, 78%); mp 103−105 °C; R_f 0.48 (1:9 EtOAc/hexane); IR (neat, cm^{-1}): 3111, 2952, 1557, 1081, 755; ^1H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, J = 8.4 Hz, 2H), 7.52 (dd, J = 3.6, 1.2 Hz, 1H), 7.46 (d, J = 8.4 Hz, 2H), 7.44 (d, J = 1.2 Hz, 1H), 7.14 (dd, J = 5.2, 3.6 Hz, 1H), 6.74 (s, 1H); $^{13}C\{H\}$ NMR (100 MHz, $CDCl_3$): δ 169.3, 158.3, 136.5, 130.6, 129.4, 127.74, 127.70, 127.5, 127.1, 125.7, 97.8; HRMS (ESI) m/z: calcd for $C_{13}H_9ClNOS$ $[M + H]^+$, and $[M + H + 2]^+$, 262.0093 and 264.0093; found, 262.0063.

*5-(Pyren-1-yl)-3-(thiophen-2-yl)isoxazole (**3i**).* Yellow solid (235 mg, 90%); mp 124−126 °C; R_f 0.52 (1:9 EtOAc/hexane); IR (neat, cm^{-1}): 3100, 2885, 1650, 1532, 956; ^1H NMR (400 MHz, $CDCl_3$): δ 8.61 (d, J = 9.2 Hz, 1H), 8.29 (d, J = 8.0 Hz, 1H), 8.24−8.15 (m, 4H), 8.13 (s, 1H), 8.08−8.05 (m, 2H), 7.62 (d, J = 2.4 Hz, 1H), 7.49 (d, J = 6.4 Hz, 1H), 7.19 (dd, J = 5.2, 3.6 Hz, 1H), 6.95 (s, 1H); $^{13}C\{H\}$ NMR (100 MHz, $CDCl_3$): δ 171.1, 158.1, 132.7, 131.2, 130.9, 130.6, 129.2, 128.9, 128.7, 127.74, 127.69, 127.5, 127.2, 126.65, 126.42, 126.13, 125.9, 124.9, 124.7, 124.4, 124.1, 121.5, 101.9; HRMS (ESI) m/z: calcd for $C_{23}H_{14}NOS$ $[M + H]^+$, 352.0796; found, 352.0737.

*5-(tert-Butyl)-3-(thiophen-2-yl)isoxazole (**3j**).* Yellow liquid (245 mg, 92%); R_f 0.48 (1:9 EtOAc/hexane); IR (neat, cm^{-1}): 3255, 3001, 1669, 1596, 1543, 755; ^1H NMR (400 MHz, $CDCl_3$): δ 7.43 (d, J = 3.6 Hz, 1H), 7.39 (d, J = 5.2 Hz, 1H), 7.09 (dd, J = 4.8, 3.6 Hz, 1H), 6.17 (s, 1H), 1.35 (s, 9H); $^{13}C\{H\}$ NMR (100 MHz, $CDCl_3$): δ 181.8, 157.3, 131.4, 127.5, 127.2, 126.9, 96.6, 32.8, 28.8; HRMS (ESI) m/z: calcd for $C_{11}H_{14}NOS$ $[M + H]^+$, 208.0796; found, 208.0825.

*5-(Furan-2-yl)-3-(thiophen-2-yl)isoxazole (**3k**).* White solid (210 mg, 85%); mp 134−136 °C; R_f 0.52 (1:9 EtOAc/hexane); IR (neat, cm^{-1}): 3255, 3001, 1669, 1596, 1543, 755; ^1H NMR (600 MHz, $CDCl_3$): δ 7.55 (s, 1H), 7.50 (d, J = 4.2 Hz, 1H), 7.43 (d, J = 5.4 Hz, 1H), 7.13 (d, J = 4.2 Hz, 1H), 6.94 (d, J = 3.6 Hz, 1H), 6.67 (s, 1H), 6.55 (d, J = 4.2 Hz, 1H); $^{13}C\{H\}$ NMR (150 MHz, $CDCl_3$): δ 157.9, 144.8, 144.3, 127.9, 127.8, 127.7, 112.1, 111.9, 110.9, 96.7; HRMS (ESI) m/z: calcd for $C_{11}H_8NO_2S$ $[M + H]^+$, 218.0276; found, 218.0233.

*3-(1-Methyl-1H-pyrrol-2-yl)-5-(4-(trifluoromethyl)phenyl)-isoxazole (**3l**).* Off-white solid (247 mg, 80%); mp 112−114 °C; R_f 0.48 (1:9 EtOAc/hexane); IR (neat, cm^{-1}): 3255, 3001, 1669, 1596, 1543, 755; ^1H NMR (400 MHz, $CDCl_3$): δ 7.93 (d, J = 8.0 Hz, 2H), 7.74 (d, J = 8.0 Hz, 2H), 6.79 (t, J = 2.4 Hz, 1H), 6.78 (s, 1H), 6.62 (dd, J = 4.0, 1.6 Hz, 1H), 6.23 (dd, J = 3.8, 2.6 Hz, 1H), 4.00 (s, 3H); $^{13}C\{H\}$ NMR (100 MHz, $CDCl_3$): δ 167.0, 157.2, 132.3, 131.9, 131.7, 131.3, 130.5, 127.8, 126.95, 126.09, 126.05, 126.01, 125.9, 125.1, 122.4, 121.9, 119.7, 112.7, 108.4, 99.9, 37.2; HRMS (ESI) m/z: calcd for $C_{15}H_{12}F_3N_2O$ $[M + H]^+$, 293.0902; found, 293.0872.

*3-(4-(Methylthio)phenyl)-5-(thiazol-2-yl)isoxazole (**3m**).* Yellow liquid; (230 mg, 80%); R_f 0.48 (1:9 EtOAc/hexane); IR (neat, cm^{-1}): 3255, 3001, 1669, 1596, 1543, 755; ^1H NMR (400 MHz, $CDCl_3$): δ 8.01 (d, J = 3.2 Hz, 1H), 7.79 (d, J = 8.4 Hz, 2H), 7.55 (d, J = 3.2 Hz, 1H), 7.34 (d, J = 8.4 Hz, 2H), 7.16 (s, 1H), 2.54 (s, 3H); $^{13}C\{H\}$ NMR (100 MHz, $CDCl_3$); 164.5, 162.8, 154.4, 144.5, 141.9, 127.2, 126.3, 124.8, 121.4, 99.7, 15.3; HRMS (ESI) m/z: calcd for $C_{13}H_{11}N_2OS_2$ $[M + H]^+$, 275.0313; found, 275.0287.

*5-(1-Methyl-1H-indol-2-yl)-3-phenylisoxazole (**3n**).* Yellow liquid (220 mg, 82%); R_f 0.51 (1:9 EtOAc/hexane); IR (neat, cm^{-1}): 3255, 3001, 1669, 1596, 1543, 755; ^1H NMR (400 MHz, $CDCl_3$): δ 8.24 (d, J = 7.2 Hz, 1H), 7.86 (dd, J = 8.2, 1.4 Hz, 2H), 7.52 (s, 1H), 7.51−7.44 (m, 3H), 7.39−7.27 (m, 3H), 6.79 (s, 1H), 3.85 (s, 3H); $^{13}C\{H\}$ NMR (100 MHz, $CDCl_3$): δ 168.9, 158.8, 137.4, 129.9, 128.9, 127.8, 125.8, 125.7, 122.7, 121.7, 120.9, 109.6, 104.9, 97.6, 33.1; HRMS (ESI) m/z: calcd for $C_{18}H_{15}N_2O$ $[M + H]^+$, 275.1184; found, 275.1187.

*5-(1-Methyl-1H-indol-3-yl)-5-(pyridin-3-yl)isoxazole (**3o**).* Yellow liquid (245 mg, 84%); R_f 0.48 (1:9 EtOAc/hexane); IR (neat, cm^{-1}): 3255, 3001, 1669, 1596, 1543, 755; ^1H NMR (400 MHz, $CDCl_3$): δ 9.08 (d, J = 2.0, 1H), 8.68 (d, J = 3.6 Hz, 1H), 8.22 (dd, J = 7.0, 1.4 Hz, 1H), 8.16 (dt, J = 7.6, 1.9 Hz, 1H), 7.55 (s, 1H), 7.46−7.28 (m, 4H), 6.89 (s, 1H), 3.87 (s, 3H); $^{13}C\{H\}$ NMR (100 MHz, $CDCl_3$): δ 166.1, 158.9, 150.7, 147.0, 137.5, 132.9, 129.2, 125.6, 124.0, 123.8, 122.9, 121.6, 121.1, 109.6, 104.5, 98.6, 33.2; HRMS (ESI) m/z: calcd for $C_{17}H_{14}N_3O$ $[M + H]^+$, 276.1136; found, 276.1138.

*N,N-Dimethyl-4-(5-(pyridin-3-yl)isoxazol-3-yl)aniline (**3p**).* Yellow solid (254 mg, 88%); mp 121−123 °C; R_f 0.46 (2:8 EtOAc/hexane); IR (neat, cm^{-1}): 3255, 3001, 1669, 1596, 1543, 755; ^1H NMR (600 MHz, $CDCl_3$): δ 9.06 (s, 1H), 8.69 (d, J = 3.6 Hz, 1H), 8.19 (d, J = 8.4 Hz, 1H), 7.71 (d, J = 9.0 Hz, 2H), 7.41 (dd, J = 7.8, 4.8 Hz, 1H), 6.76 (d, J = 9.0 Hz, 2H), 6.65 (s, 1H), 3.05 (s, 6H); $^{13}C\{H\}$ NMR (150 MHz, $CDCl_3$): δ 171.9, 160.4, 151.7, 150.9, 148.1, 134.1, 127.3, 125.9, 123.8, 114.9, 111.9, 94.3, 40.3; HRMS (ESI) m/z: calcd for $C_{16}H_{16}N_3O$ $[M + H]^+$, 266.1293; found, 266.1276.

*3,5-Di(pyridin-3-yl)isoxazole (**3q**).* Yellow liquid (260 mg, 79%); R_f 0.48 (1:9 EtOAc/hexane); IR (neat, cm^{-1}): 3255, 3001, 1669, 1596, 1543, 755; ^1H NMR (400 MHz, $CDCl_3$): δ 9.09 (d, J = 3.6 Hz, 2H), 8.72 (d, J = 4.8 Hz, 2H), 8.22 (dt, J = 8.0, 2.0 Hz, 1H), 8.16 (dt, J = 8.0, 2.0 Hz, 1H), 7.49−7.44 (m, 2H), 6.98 (s, 1H); $^{13}C\{H\}$ NMR (100 MHz, $CDCl_3$): δ 168.3, 160.7, 151.3, 147.9, 147.1, 144.9, 134.1, 133.0, 123.9, 123.5, 98.2; HRMS (ESI) m/z: calcd for $C_{13}H_{10}N_3O$ $[M + H]^+$, 224.0824; found, 224.0825.

*5-Methyl-3-phenylisoxazole (**3r**).*[4b] Yellow oil (215 mg, 86%); R_f 0.36 (1:9 EtOAc/hexane); ^1H NMR (400 MHz, $CDCl_3$): δ 7.72−7.69 (m, 2H), 7.37−7.35 (m, 3H), 6.21 (s, 1H), 2.47 (s, 3H); $^{13}C\{H\}$ NMR (100 MHz, $CDCl_3$): δ 168.9, 161.5, 128.8, 128.3, 127.8, 125.7,

https://dx.doi.org/10.1021/acs.joc.0c02216
J. Org. Chem. XXXX, XXX, XXX−XXX

98.7, 11.3; HRMS (ESI) m/z: calcd for $C_{10}H_{10}NO$ $[M + H]^+$, 160.0762; found, 160.0747.

*3-(4-Methoxyphenyl)-5-methylisoxazole (**3s**).*[4b] Pale yellow solid (200 mg, 92%); mp 84−87 °C; R_f 0.34 (1:9 EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69 (d, J = 8.8 Hz, 2H); 6.93 (d, J = 8.8 Hz, 2H), 6.19 (s, 1H), 3.82 (s, 3H), 2.45 (s, 3H); ^{13}C{H} NMR (100 MHz, $CDCl_3$): δ 169.6, 162.1, 160.4, 128.4, 121.5, 114.6, 101.6, 55.3, 12.2; HRMS (ESI) m/z: calcd for $C_{11}H_{12}NO_2$ $[M + H]^+$, 190.0868; found, 190.0854.

*5-Methyl-3-(thiophen-2-yl)isoxazole (**3t**).*[4b] Yellow oil (230 mg, 79%); R_f 0.35 (1:9 EtOAc/hexane); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.69 (dd, J = 5.2, 1.2 Hz, 1H), 7.63 (dd, J = 3.8, 1.4 Hz, 1H), 7.19 (dd, J = 5.2, 3.6 Hz, 1H), 6.71 (s, 1H), 2.45 (s, 3H); ^{13}C{H} NMR (100 MHz, DMSO-d_6): δ 170.2, 157.4, 130.2, 128.4, 128.3, 127.9, 99.9, 11.8; HRMS (ESI) m/z: calcd for C_8H_8NOS $[M + H]^+$, 166.0327; found, 166.0321.

General Procedure for the Synthesis of 3-(Het)aryl-5-styryl/aryldienyl Isoxazoles 8. To a stirred solution of β-(methylthio)-β-(het)aryl-3-styrl/aryldienyl-1-propen-3-ones 7 (1.0 mmol) in DMSO (5 mL), sodium azide (130 mg, 2.0 mmol) was added and the reaction mixture was heated at 100 °C in an oil bath for 10 h (monitored by TLC). The reaction mixture was then cooled at rt, quenched with saturated NH_4Cl solution (25 mL), and extracted with EtOAc (3 × 25 mL); the organic phase was washed with water (2 × 25 mL) and brine (1 × 25 mL), dried (Na_2SO_4), and evaporated under reduced pressure to give crude products **8**, which were purified by column chromatography on silica gel using hexane/ethyl acetate as eluent.

*(E)-3-(4-Methoxyphenyl)-5-styrylisoxazole (**8a**).* Yellow viscous liquid (234 mg, 80%); R_f 0.51 (1:9 EtOAc/hexane); IR (neat, cm^{-1}): 3255, 3001, 1669, 1596, 1543, 755; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.77 (d, J = 9.0 Hz, 2H), 7.54 (d, J = 7.2 Hz, 2H), 7.41−7.39 (m, 3H), 7.37−7.33 (m, 1H), 7.02−6.98 (m, 3H), 6.53 (s, 1H), 3.87 (s, 3H); ^{13}C{H} NMR (150 MHz, $CDCl_3$): δ 168.4, 162.1, 154.9, 135.6, 134.9, 130.1, 128.9, 128.3, 127.2, 114.9, 114.4, 109.6, 99.4, 55.5; HRMS (ESI) m/z: calcd for $C_{18}H_{16}NO_2$ $[M + H]^+$, 278.1181; found, 278.1161.

*(E)-5-(4-Bromostyryl)-3-(4-methoxyphenyl)isoxazole (**8b**).* White solid (200 mg, 75%); mp 105−106 °C; R_f 0.41 (1:9 EtOAc/hexane); IR (neat, cm^{-1}): 3255, 3001, 1669, 1596, 1543, 755; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.79 (d, J = 8.4 Hz, 2H), 7.63 (d, J = 8.4 Hz, 2H), 7.59 (d, J = 8.4 Hz, 2H), 7.38 (d, J = 16.2 Hz, 1H), 7.31 (d, J = 16.2 Hz, 1H), 7.09 (s, 1H), 7.04 (d, J = 8.4 Hz, 2H), 3.79 (s, 3H); ^{13}C{H} NMR (150 MHz, $CDCl_3$): δ 168.9, 162.5, 161.3, 135.2, 133.7, 132.4, 129.8, 128.6, 122.9, 121.4, 115.1, 114.8, 100.7, 55.9; HRMS (ESI) m/z: calcd for $C_{18}H_{15}BrNO_2$ $[M + H]^+$, 356.0286 and $[M + H + 2]^+$, 358.0286; found, 356.0321, 358.0312.

*(E)-3-(4-Methoxyphenyl)-5-(2-(thiophen-2-yl)vinyl)isoxazole (**8c**).* White solid (226 mg, 68%); mp 108−109 °C; R_f 0.41 (1:9 EtOAc/hexane); IR (neat, cm^{-1}): 3255, 3001, 1669, 1596, 1543, 755; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.76 (d, J = 7.8 Hz, 2H), 7.48 (d, J = 15.6 Hz, 1H), 7.32 (d, J = 4.8 Hz, 1H), 7.19 (d, J = 4.2 Hz, 1H), 7.06 (d, J = 7.8 Hz, 1H), 6.98 (d, J = 8.4 Hz, 2H), 6.79 (d, J = 15.6 Hz, 1H), 6.48 (s, 1H), 3.86 (s, 3H); ^{13}C{H} NMR (150 MHz, $CDCl_3$): δ 168.3, 162.5, 161.1, 141.1, 129.3, 128.3, 127.7, 126.7, 121.6, 114.5, 114.3, 112.4, 99.3, 56.3; HRMS (ESI) m/z: calcd for $C_{16}H_{14}NO_2S$ $[M + H]^+$, 284.0745; found, 284.0725.

*5-(1E,3E)-4-Phenylbuta-1,3-(dien-1-yl)-3-(thiophen-2-yl)-isoxazole (**8d**).* Yellow solid (212 mg, 67%); mp 107−108 °C; R_f 0.43 (1:9 EtOAc/hexane); IR (neat, cm^{-1}): 3255, 3001, 1669, 1596, 1543, 755; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47−7.41 (m, 3H), 7.38−7.34 (m, 2H), 7.29 (d, J = 6.4 Hz, 1H), 7.21−7.11 (m, 2H), 6.94 (d, J = 10 Hz, 1H), 6.90 (d, J = 5.12 Hz, 1H), 6.84 (d, J = 15.6 Hz, 1H), 6.54 (d, J = 15.2 Hz, 1H) 6.44 (s, 1H); ^{13}C{H} NMR (100 MHz, $CDCl_3$): δ 168.9, 157.9, 137.4, 136.5, 135.6, 130.9, 128.8, 128.6, 127.6, 127.5, 127.4, 127.3, 126.9, 116.0, 99.2; HRMS (ESI) m/z: calcd for $C_{17}H_{14}NOS$ $[M + H]^+$, 280.0796; found, 280.0803.

Methyl 3-(2-Methoxyphenyl)-3-oxopropanedithioate (9e). Yellow solid (220 mg, 78%); mp 95−97 °C; R_f 0.34 (1:9 EtOAc/hexane); IR (neat, cm^{-1}): 3255, 3001, 1669, 1596, 1543, 755; ^{1}H NMR (400 MHz, $CDCl_3$): δ 15.2 (br, 1H), 7.83 (dd, J = 7.6, 2.0 Hz, 1H), 7.36 (td, J = 7.2, 2.0 Hz, 1H), 7.28 (s, 1H), 6.97 (td, J = 7.6, 1.8 Hz, 1H), 6.89 (d, J = 8.0 Hz, 1H), 3.81 (s, 3H), 2.57 (s, 3H); ^{13}C{H} NMR (100 MHz, $CDCl_3$): δ 214.7, 167.6, 157.9, 132.8, 130.2, 123.1, 120.9, 113.0, 111.8, 55.5, 17.2; HRMS (ESI) m/z: calcd for $C_{11}H_{13}O_2S_2$ $[M + H]^+$, 241.0357; found, 241.0367.

General Procedure for the Reaction of β-Oxodithioesters 9 with Sodium Azide: Synthesis of β-Oxoacetonitriles 11. To a stirred suspension of NaN_3 (130 mg, 1.0 mmol) in DMF (3 mL), a solution of β-oxodithioester (1.0 mmol) in DMF (3 mL) was added dropwise at room temperature under an N_2 atmosphere, and the reaction mixture was heated 90 °C in an oil bath for 2 h (monitored by TLC) with continuous stirring. It was then quenched with saturated NH_4Cl solution (25 mL), extracted with EtOAc (3 × 25 mL), the combined organic layer was washed with water (3 × 25 mL) and brine (25 mL), dried (Na_2SO_4), and evaporated under vacuum to give products **11**, which were further purified by column chromatography using hexane/ethyl acetate as eluent.

*3-(4-Methoxyphenyl)-3-oxopropanenitrile (**11a**).* Pale yellow solid (220 mg, 80%); mp 132−137 °C (mp 132−137 °C);[17] R_f 0.32 (2:9 EtOAc/hexane); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.89 (d, J = 9.0 Hz, 2H), 6.98 (d, J = 9.0 Hz, 2H), 4.02 (s, 2H), 3.89 (s, 3H); ^{13}C{H} NMR (150 MHz, $CDCl_3$): δ 185.5, 164.8, 130.5, 124.9, 114.4, 114.2, 55.8, 26.3; HRMS (ESI) m/z: calcd for $C_{10}H_{10}NO_2$ $[M + H]^+$, 176.0706; found, 176.0701.

*3-Oxo-3-(4-(trifluoromethyl)phenyl)propanenitrile (**11b**).* Yellow solid (200 mg, 70%); mp 104−106 °C (mp 104−106 °C);[17] R_f 0.35 (2:9 EtOAc/hexane); ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.02 (d, J = 8.4 Hz, 2H), 7.79 (d, J = 7.8 Hz, 2H); ^{13}C{H} NMR (150 MHz, $CDCl_3$): δ 186.5, 136.9, 136.4, 136.1, 135.7, 135.4, 128.9, 127.8, 127.3, 126.3, 126.2, 124.6, 121.9, 113.3, 29.7; HRMS (ESI) m/z: calcd for $C_{10}H_6F_3NO$ $[M]^+$, 213.0401; found, 213.0429.

*3-(Naphthalen-2-yl)-3-oxopropanenitrile (**11c**).* White solid (210 mg, 76%); mp 100−101 °C (mp 100−101 °C);[17] R_f 0.31 (2:9 EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.39 (s, 1H), 7.98−7.89 (m, 4H), 7.66 (t, J = 7.6, Hz, 1H), 7.59 (t, J = 7.6, Hz, 1H), 4.21 (s, 2H); ^{13}C{H} NMR (100 MHz, $CDCl_3$): δ 185.6, 136.2, 132.3, 131.7, 130.7, 129.8, 129.5, 129.2, 127, 127.4, 123.4, 113.9, 29.9; HRMS (ESI) m/z: calcd for $C_{13}H_9NNaO$ $[M + Na]^+$, 218.0576; found, 218.0563.

*3-Oxo-3-(thiophen-2-yl)propanenitrile (**11d**).* Off-white solid (235 mg, 74%); mp 98−100 °C (mp 98−100 °C);[17] R_f 0.33 (2:9 EtOAc/hexane); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.79 (m, 2H), 7.19−7.18 (m, 1H), 3.99 (s, 2H); ^{13}C{H} NMR (150 MHz, $CDCl_3$): δ 179.5, 140.9, 136.2, 133.7, 128.7, 113.4, 29.5; HRMS (ESI) m/z: calcd for C_7H_6NOS $[M + H]^+$, 152.0170; found, 152.0182.

*3-(2-Methoxyphenyl)-3-oxopropanenitrile (**11e**).* White solid (250 mg, 72%); mp 102−104 °C (mp 102−104 °C); R_f 0.32 (2:9 EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 (dd, J = 7.6, 1.6 Hz, 1H), 7.57 (td, 7.9, 1.7 Hz, 1H), 7.07−7.01 (m, 2H), 4.08 (s, 2H), 3.97 (s, 3H); ^{13}C{H} NMR (100 MHz, $CDCl_3$): δ 188.1, 159.2, 135.7, 131.4, 124.5, 121.2, 114.6, 111.8, 55.8, 34.1; HRMS (ESI) m/z: calcd for $C_{10}H_{10}NO_2$ $[M + H]^+$, 176.0712; found, 176.0710.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c02216.

Copies of ^{1}H NMR, ^{13}C NMR, and spectra of compounds **2b−2t**, **6a−6b**, **7a−7d**, **3a−3t**, **8a−8d**, **9e**, and **11a−11e** (PDF)

Accession Codes

CCDC 1983738 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 Cam-

https://dx.doi.org/10.1021/acs.joc.0c02216
J. Org. Chem. XXXX, XXX, XXX−XXX

bridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

AUTHOR INFORMATION

Corresponding Author

Hiriyakkanavar Ila − *New Chemistry Unit, Jawaharlal Nehru Centre for Advanced Scientific Research, Bangalore 560064, India;* orcid.org/0000-0002-6971-8374; Email: hila@jncasr.ac.in

Authors

Mary Antony P − *New Chemistry Unit, Jawaharlal Nehru Centre for Advanced Scientific Research, Bangalore 560064, India*

Gantala L. Balaji − *New Chemistry Unit, Jawaharlal Nehru Centre for Advanced Scientific Research, Bangalore 560064, India*

Pethaperumal Iniyavan − *New Chemistry Unit, Jawaharlal Nehru Centre for Advanced Scientific Research, Bangalore 560064, India*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.joc.0c02216

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We acknowledge Professor C. N. R. Rao, FRS, for encouragement and support of our research. We thank University Grants Commission (UGC, New Delhi) for UGC-SRF (to M.A.P.), Science and Engineering Research Board (SERB, New Delhi) for National Post-doctoral fellowship (NPDF) (to P.I. and G.L.B.), and JNCASR for Hindustan Lever Research Professorship (to H.I.).

DEDICATION

This paper is dedicated to Prof. Paul Knochel on the occasion of his 65th Birthday.

REFERENCES

(1) Recent reviews: (a) Morita, T.; Yugandar, S.; Fuse, S.; Nakamura, H. Recent progresses in the synthesis of functionalized isoxazoles. *Tetrahedron Lett.* **2018**, *59*, 1159−1171. and references therein (b) Hu, F.; Szostak, M. Recent Developments in the Synthesis and Reactivity of Isoxazoles: Metal Catalysis and Beyond. *Adv. Synth. Catal.* **2015**, *357*, 2583−2614. (c) Pinho e Melo, T. Recent Advances on the Synthesis and Reactivity of Isoxazoles. *Curr. Org. Chem.* **2005**, *9*, 925−958. (d) Vitale, P.; Scilimati, A. Five-membered ring heterocycles by reacting enolates with dipoles. *Curr. Org. Chem.* **2013**, *17*, 1986−2000. (e) Cicchi, S.; Cordero, F. M.; Giomi, D. Five-Membered Ring Systems with O and N Atoms. In *Progress in Heterocyclic Chemistry*; Gribble, G., Joule, J., Eds.; Elsevier: Amsterdam, 2011; Vol. *23*, pp 303−320.

(2) (a) Giomi, D.; Cordero, F.; Machetti, F. In *Comprehensive Heterocyclic Chemistry III*; Katritzky, A. R., Ramsden, C. A., Scriven, E. F. V., Taylor, R. J. K., Joules, J., Eds.; Elsevier: Oxford, U.K., 2008; Vol. *4*, pp 365−378. (b) Sutharchanadevi, M.; Murgan, R. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Elsevier: Oxford, U.K., 1996; Vol. *3*, pp 221−2260. (c) See also: Wakefield, B. J. In *Science of Synthesis: Houben−Weyl Methods of Molecular Transformations*; Schaumann, E., Ed.; Georg Thieme Verlag: Stuttgart, 2001; Vol. *11*, pp 229−288.

(3) Reviews: (a) Sysak, A.; Obmińska-Mrukowicz, B. Isoxazole ring as a useful scaffold in search for new therapeutic agents. *Eur. J. Med. Chem.* **2017**, *137*, 292−309. (b) Zhu, J.; Mo, J.; Lin, H.-z.; Chen, Y.; Sun, H.-p. The recent progress of isoxazole in medicinal chemistry. *Bioorg. Med. Chem.* **2018**, *26*, 3065−3075. (c) Zhou, X.; Xu, X.; Shi, Z.; Liu, K.; Gao, H.; Li, W. Enolate-mediated 1,3-dipolar cycloaddition reaction of *β*-functionalized ketones with nitrile oxides: direct access to 3,4,5-trisubstituted isoxazoles. *Org. Biomol. Chem.* **2016**, *14*, 5246−5250. and references cited therein (d) Mohammed, S.; Vishwakarma, R. A.; Bharate, S. B. Metal-free DBU promoted regioselective synthesis of isoxazoles and isoxazolines. *RSC Adv.* **2015**, *5*, 3470−3473. and references cited therein (e) Raghava, B.; Parameshwarappa, G.; Acharya, A.; Swaroop, T. R.; Rangappa, K. S.; Ila, H. Cyclocondensation of Hydroxylamine with 1,3-Bis(het)-arylmonothio-1,3-Diketones and 1,3-Bis(het)aryl-3-(methylthio)-2-propenones:Synthesis of 3,5-Bis(het)arylisoxazoles with Complementary Regioselectivity. *Eur. J. Org. Chem.* **2014**, 1882−1892. and references cited therein (f) Morita, T.; Fuse, S.; Nakamura, H. Generation of an 4-Isoxazolyl Anion Species: Facile Access to MultifunctionalizedIsoxazoles. *Angew. Chem., Int. Ed.* **2016**, *55*, 13580−13584. and references cited therein

(4) (a) Kadam, K. S.; Gandhi, T.; Gupte, A.; Gangopadhyay, A. K.; Sharma, R. Alkyl Nitrites: Novel Reagents for One-Pot Synthesis of 3,5-Disubstituted Isoxazoles from Aldoximes and Alkynes. *Synthesis* **2016**, *48*, 3996−4008. and references cited therein (b) Dong, K.-Y.; Qin, H.-T.; Bao, X.-X.; Liu, F.; Zhu, C. Oxime-Mediated Facile Access to 5-Methylisoxazoles and applications in the Synthesis of Valdecoxib and Oxacillin. *Org. Lett.* **2014**, *16*, 5266−5268. and references cited therein

(5) Review: (a) Sahani, R. L.; Ye, L.-W.; Liu, R.-S. Synthesis of Nitrogen-Containing Molecules via Transition Metal-Catalyzed Reactions on Isoxazoles, Anthranils and Benzoisoxazoles. *Advances in Organometallic Chemistry*; Perez, P. J., Ed.; Elsevier Inc., 2019; Vol. *72*, pp 1−57. See also. (b) Lohrer, B.; Bracher, F. Novel access to 2-substituted quinolin-4-ones by nickel boride-mediated reductive ring transformation of 5-(2-nitrophenyl)isoxazoles. *Tetrahedron Lett.* **2019**, *60*, 151327−151330. (c) Galenko, E. E.; Linnik, S. A.; Khoroshilova, O. V.; Novikov, M. S.; Khlebnikov, A. F. Isoxazole Strategy for the Synthesis of *α*-Aminopyrrole Derivatives. *J. Org. Chem.* **2019**, *84*, 11275−11285. (d) Galenko, E. E.; Novikov, M. S.; Shakirova, F. M.; Shakirova, J. R.; Kornyakov, I. V.; Bodunov, V. A.; Khlebnikov, A. F. Isoxazole Strategy for the Synthesis of 2,2'-Bipyridine Ligands: Symmetrical and Unsymmetrical 6.6'-Binicotinates, 2,2'-Bipyridine-5-carboxylates, and Their Metal complexes. *J. Org. Chem.* **2019**, *84*, 3524−3536. (e) Charest, M. G.; Lerner, C. D.; Brubaker, J. D.; Siegel, D. R.; Myers, A. G. A Convergent Enantioselective Route to Structurally Diverse 6-Deoxytetracycline Antibiotics. *Science* **2005**, *308*, 395−398. (f) Manning, J. R.; Davies, H. M. L. One-Pot Synthesis of Highly Functionalized Pyridines via a Rhodium Carbenoid Induced Ring Expansion of Isozaxoles. *J. Am. Chem. Soc.* **2008**, *130*, 8602−8603.

(6) (a) Svejstrup, T. D.; Zawodny, W.; Douglas, J. J.; Bidgeli, D.; Sheikh, N. S.; Leonori, D. Visible-light-mediated generation of nitrile oxides for the photoredox synthesis of isoxazolines and isoxazoles. *Chem. Commun.* **2016**, *52*, 12302−12305. and references cited therein (b) Poh, J.-S.; García-Ruiz, C.; Zúñiga, A.; Meroni, F.; Blakemore, D. C.; Browne, D. L.; Ley, S. V. Synthesis of trifluoromethylated isoxazoles and their elaboration through inter- and intra-molecular C-H arylation. *Org. Biomol. Chem.* **2016**, *14*, 5983−5991. (c) Kesornpun, C.; Aree, T.; Mahidol, C.; Ruchirawat, S.; Kittakoop, P. Water-Assisted Nitrile Oxide Cycloadditions: Synthesis of Isoxazoles and Stereoselective Syntheses of Isoxazolines and 1,2,4-Oxadiazoles. *Angew. Chem., Int. Ed.* **2016**, *55*, 3997−4001. . See also: (d) Chalyk, B. A.; Hrebeniuk, K. V.; Gavrilenko, K. S.; Shablykin, O. V.; Yanshyna, O. O.; Bash, D.; Mykhailiuk, P. K.; Liashuk, O. S.; Grygorenko, O. O. Synthesis of Bi- and Polyfunctional Isoxazoles from Amino Acid Derived halogenoximes and Active Methylene Nitriles. *Eur. J. Org. Chem.* **2018**, 2753−2761. (e) Lai, Z.; Li, Z.; Liu, Y.; Yang, P.; Fang, X.; Zhang, W.; Liu, B.; Chang, H.; Xu, H.; Xu, Y. Iron-Mediated Synthesis of Isoxazoles from Alkynes: Using Iron (III) Nitrate as a Nitration and Cyclization Reagent. *J. Org. Chem.* **2018**, *83*, 145−153. (f) Chalyk, B. A.; Hrebeniuk, K. V.; Fil, Y.

V.; Gavrilenko, K. S.; Rozhenko, A. B.; Vashchenko, B. V.; Borysov, O. V.; Biitseva, A. V.; Lebed, P. S.; Bakanovych, I.; Moroz, Y. S.; Grygorenko, O. O. Synthesis of 5-(Fluoroalkyl)isoxazole Building Blocks by Regioselective Reactions of functionalized halogenoximes. *J. Org. Chem.* **2019**, *84*, 15877−15899. (g) Xu, H.; Fan, G.-P.; Liu, Z.; Wang, G.-W. Catalyst- and solvent-free mechanochemical synthesis of isoxazoles from N-hydroxybenzimidoylchlorides and enamino carbonyl compounds. *Tetrahedron* **2018**, *74*, 6607−6611. (h) Iwai, K.; Asahara, H.; Nishiwaki, N. Synthesis of Functionalized 3-Cyanoisoxazoles Using a Dianionic Reagent. *J. Org. Chem.* **2017**, *82*, 5409−5415. and references cited therein (i) Studer, A.; Hadida, S.; Ferritto, R.; Kim, S.-Y.; Jeger, P.; Wipf, P.; Curran, D. P. Fluorous Synthesis: A Fluorous- Phase Strategy for Improving Separation, Efficiency in Organic Synthesis. *Science* **1997**, *275*, 823−826.

(7) (a) Himo, F.; Lovell, T.; Hilgraf, R.; Rostovtsev, V. V.; Noodleman, L.; Sharpless, K. B.; Fokin, V. V. Copper(I)-CatalyzedSynthesis of Azoles. DFT Study Predicts Unprecedented Reactivity and Intermediates. *J. Am. Chem. Soc.* **2005**, *127*, 210−216. (b) Hansen, T. V.; Wu, P.; Fokin, V. V. One-Pot Copper(I)-CatalyzedSynthesis of 3,5-Disubstituted Isoxazoles. *J. Org. Chem.* **2005**, *70*, 7761−7764. (c) Kuribayashi, S.; Shida, N.; Inagi, S.; Fuchigami, T. Synthesis of fluorinated triazole and isoxazole derivatives by electrochemical fluorination. *Tetrahedron* **2016**, *72*, 5343−5349. (d) Grecian, S.; Fokin, V. V. Ruthenium-Catalyzed Cycloaddition of Nitrile Oxides and Alkynes: Practical Synthesis of Isoxazoles. *Angew. Chem., Int. Ed.* **2008**, *47*, 8285−8287.

(8) (a) Yoshimura, A.; Middleton, K. R.; Todora, A. D.; Kastern, B. J.; Koski, S. R.; Maskaev, A. V.; Zhdankin, V. V. Hypervalent Iodine Catalyzed Generation of Nitrile Oxides from Oximes and their Cycloaddition with Alkenes or Alkynes. *Org. Lett.* **2013**, *15*, 4010−4013. . See also: (b) Minakata, S.; Okumura, S.; Nagamachi, T.; Takeda, Y. Generation of Nitrile Oxides from Oximes Using t-BuOI and Their Cycloaddition. *Org. Lett.* **2011**, *13*, 2966−2969.

(9) (a) Nieto, C. I.; Cornago, M. P.; Cabildo, M. P.; Sanz, D.; Claramunt, R. M.; Torralba, M. C.; Elguero, J. Synthesis, structure and NMR study of fluorinated isoxazoles derived from hemicurcuminoids. *J. Fluorine Chem.* **2019**, *219*, 39−49. (b) Silva, R. G. M.; da Silva, M. J. V.; Jacomini, A. P.; Moura, S.; Back, D. F.; Basso, E. A.; Rosa, F. A. Development of methodologies for the regioselective synthesis of four series of regioisomer isoxazoles from β-enamino diketones. *RSC Adv.* **2018**, *8*, 4773−4778. (c) Harigae, R.; Moriyama, K.; Togo, H. Preparation of 3,5-Disubstituted Pyrazoles and Isoxazoles from Terminal Alkynes, Aldehydes, Hydrazines, and Hydroxylamine. *J. Org. Chem.* **2014**, *79*, 2049−2058. (d) Pei, Y.; Wickham, B. O. S. Regioselective synthesis of 3-aminomethyl-5-substituted isoxazoles: A facile and chemoselective reduction of azide to amine by sodium borohydride using 1,3-propanedithiol as catalyst. *Tetrahedron Lett.* **1993**, *34*, 7509−7512.

(10) (a) Gao, W.-C.; Cheng, Y.-F.; Chang, H.-H.; Li, X.; Wei, W.-L.; Yang, P. Synthesis of 4-Sulfenyl Isoxazoles through $AlCl_3$-Mediated Electrophilic Cyclization and Sulfenylation of 2-Alkyn-1-one O-Methyloximes. *J. Org. Chem.* **2019**, *84*, 4312−4317. and references cited therein (b) Waldo, J. P.; Larock, R. C. Synthesis of Isozaxoles via Electrophilic Cyclization. *Org. Lett.* **2005**, *7*, 5203−5205. (c) Waldo, J. P.; Larock, R. C. The Synthesis of Highly Substituted Isoxazoles by Electrophilic Cyclization: An Efficient Synthesis of Valdecoxib. *J. Org. Chem.* **2007**, *72*, 9643−9647. (d) Liu, X.; Hong, D.; She, Z.; Hersh, W. H.; Yoo, B.; Chen, Y. Complementary regioselective synthesis of 3,5-disubstituted isoxazoles from ynones. *Tetrahedron* **2018**, *74*, 6593−6606. (e) Sperança, A.; Godoi, B.; Zeni, G. Iron(III) Chloride/Diorganyl Diselenides: A Tool for Intramolecular Cyclization of Alkynone O-Methyloximes. *J. Org. Chem.* **2013**, *78*, 1630−1637.

(11) (a) Okitsu, T.; Sato, K.; Potewar, T. M.; Wada, A. Iodocyclization of Hydroxylamine Derivatives Based on the Control of Oxidative Aromatization Leading to 2,5-Dihyhydroisoxazoles and Isoxazoles. *J. Org. Chem.* **2011**, *76*, 3438−3449. (b) Gayon, E.; Quinonero, O.; Lemouzy, S.; Vrancken, E.; Campagne, J.-M. Transition-Metal-CatalyzedUninterruptedFour-Step Sequence to Access Trisubstituted Isoxazoles. *Org. Lett.* **2011**, *13*, 6418−6421. and ref cited therein. See also: (c) Tu, K. N.; Hirner, J. J.; Blum, S. A. Oxyboration with and without a Catalyst: Borylated Isoxazoles via B-O σ-Bond Addition. *Org. Lett.* **2016**, *18*, 480−483. . See also: (d) Sau, P.; Santra, S. K.; Rakshit, A.; Patel, B. K. tert-Butyl Nitrite-Mediated Domino Synthesis of Isoxazolines and Isoxazoles from Terminal Aryl Alkenes and Alkynes. *J. Org. Chem.* **2017**, *82*, 6358−6365.

(12) (a) Anand, D.; Patel, O. P. S.; Maurya, R. K.; Kant, R.; Yadav, P. P. Substrate Controlled Synthesis of Benzisoxazole and Benzisothiazole Derivatives via PhI(OAc)2-Mediated Oxidation Followed by Intramolecular Oxidative O-N/S-N Bond Formation. *J. Org. Chem.* **2015**, *80*, 12410−12419. and references cited therein (b) Prakash, O.; Saini, R. K.; Singh, S. P.; Varma, R. S. Hypervalent iodine oxidation of o-aminochalcones: A novel synthesis of 3-(β-styryl)-2,1-benzisoxazoles. *Tetrahedron Lett.* **1997**, *38*, 3147−3150. (c) Stokes, B. J.; Vogel, C. V.; Urnezis, L. K.; Pan, M.; Driver, T. G. Intramolecular Fe(II)-Catalyzed N-O or N-N Bond Formation from Aryl Azides. *Org. Lett.* **2010**, *12*, 2884−2887. (d) Smith, P. A. S.; Brown, B. B.; Putney, R. K.; Reinisch, R. F. TheSynthesis of Heterocyclic Compounds from Aryl Azides. III. Some Six membered Rings and Some Azidobiaryls. *J. Am. Chem. Soc.* **1953**, *75*, 6335−6337.

(13) (a) Zheng, Y.; Yang, C.; Zhang-Negrerie, D.; Du, Y.; Zhao, K. One-pot synthesis of isoxazoles from enaminones: an application of Fe(II) as the catalyst for ring expansion of 2H-azirine intermediates. *Tetrahedron Lett.* **2013**, *54*, 6157−6160. and references therein (b) Singh, B.; Zweig, A.; Gallivan, J. B. Wavelength-Dependent Photochemistry of 2-Aroyl-3-aryl-2H-azirines. Mechanistic Studies. *J. Am. Chem. Soc.* **1972**, *94*, 1199−1206. (c) Padwa, A.; Stengel, T. Transition metal-catalyzed ring opening reactions of 2-phenyl-3-vinyl substituted 2H-azirines. *Tetrahedron Lett.* **2004**, *45*, 5991−5993. (d) Brahma, S.; Ray, J. K. Synthesis of Azirines Containing Aldehyde Functionality and their Utilization as Synthetic Tools for Five Membered Oxazoles and Isoxazoles. *J. Heterocycl. Chem.* **2008**, *45*, 311−317.

(14) (a) Auricchio, S.; Bini, A.; Pastormerlo, E.; Truscello, A. M. Iron Dichloride Induced Isomerization or Reductive Cleavage of Isoxazoles: AFacileSynthesis of 2-Carboxy-azirines. *Tetrahedron* **1997**, *53*, 10911−10920. . See also: (b) Serebryannikova, A. V.; Galenko, E. E.; Novikov, M. S.; Khlebnikov, A. F. Synthesis of Isoxazole-and Oxazole-4-carboxylic Acids Derivatives by Controlled Isoxazole-Azirine-Isoxazole/Oxazole Isomerization. *J. Org. Chem.* **2019**, *84*, 15567−15577. (c) Li, C.; Yuan, J.; Zhang, Q.; Bhujanga Rao, C.; Zhang, R.; Zhao, Y.; Deng, B.; Dong, D. Oxidative Cyclization of β-AminoacrylamidesMediated by PhIO: ChemoselectiveSynthesis of Isoxazoles and 2H-Azirines. *J. Org. Chem.* **2018**, *83*, 14999−15008.

(15) (a) Kumar, G. R.; Kumar, Y. K.; Reddy, M. S. A direct access to isoxazoles from ynones using trimethylsilyl azide as amino surrogate under metal/catalyst free conditions. *Chem. Commun.* **2016**, *52*, 6589−6592. . See also: (b) Andreev, M. V.; Medvedeva, A. S.; Larina, L. I.; Demina, M. M. Synthesis of 5-aminoisoxazoles from 3-trimethylsilylprop-2-ynamides. *Mendeleev Commun.* **2017**, *27*, 175−177. (c) Ning, Y.; Otani, Y.; Ohwada, T. Contrasting C- and O-Atom Reactivities of Neutral Ketone and Enolate Forms of 3-Sulphonyloxyimino-2-methyl-1-phenyl-1-butanones. *J. Org. Chem.* **2018**, *83*, 203−219.

(16) (a) Kumar, S. V.; Yadav, S. K.; Raghava, B.; Saraiah, B.; Ila, H.; Rangappa, K. S.; Hazra, A. Cyclocondensation of Arylhydrazines with 1,3-Bis(het)arylmonothio-1,3-diketones and 1,3-Bis (het)aryl-3-(methylthio)-2-propenones: Synthesis of 1-Aryl-3,5-bis(het)-arylpyrazoles with complementary Regioselectivity. *J. Org. Chem.* **2013**, *78*, 4960−4973. (b) Acharya, A.; Parameshwarappa, G.; Saraiah, B.; Ila, H. Sequential One- Pot Synthesis of Tri-and Tetrasubstituted Thiophenes and Fluorescent Push- Pull Thiophene Acrylates involving (Het)aryl Dithioesters as thiocarbonyl Precursors. *J. Org. Chem.* **2015**, *80*, 414−427. (c) Yugandar, S.; Konda, S.; Parameshwarappa, G.; Ila, H. One-Pot Synthesis of 2,4,5-Trisubstituted Imidazoles via [2+2+1] Cycloannulation of 1,3-Bis(het)arylmonothio-1,3-diketones,α-Substituted Methylamines and Sodium

https://dx.doi.org/10.1021/acs.joc.0c02216
J. Org. Chem. XXXX, XXX, XXX−XXX

Nitrite through α-Nitrosation of Enaminones. *J. Org. Chem.* **2016**, *81*, 5606−5622. (d) Yugandar, S.; Konda, S.; Ila, H. Synthesis of Substituted Benzo[b]thiophenes via Sequential One-Pot, Copper-Catalyzed Intermolecular C-S Bond Formation and Palladium-Catalyzed Intramolecular Arene-Alkene Coupling of Bis(het)aryl/alkyl-1,3-monothiodiketones and o-Bromoiodoarenes. *Org. Lett.* **2017**, *19*, 1512−1515. . See also: (e) Acharya, A.; Gautam, V.; Ila, H. Synthesis of Thieno-Fused Five- and Six-Membered Nitrogen and Oxygen Heterocycles via Intramolecular Heteroannulation of 4,5-Substituted3-Amino or 3-Hydroxy 2-Functionalized Thiophenes. *J. Org. Chem.* **2017**, *82*, 7920−7938.

(17) Li, J.; Ma, W.; Ming, W.; Xu, C.; Wei, N.; Wang, M. Divergent Reactivity in the Reaction of β-Oxodithioesters and Hydroxylamine:Access to β-Ketonitriles and Isoxazoles. *J. Org. Chem.* **2015**, *80*, 11138−11142. and references cited therein

(18) Thotutumkara, A. P.; Bowsher, A. P.; Vinod, T. K. In Situ Generation of o-Iodoxybenzoic acid (IBX) and the Catalytic Use of it in Oxidation Reaction in the Presence of Oxone as a Co-oxidant. *Org. Lett.* **2005**, *7*, 2933−2936.

(19) Andrews, P. C.; Blair, V. L.; Ferrero, R. L.; Junk, P. C.; Kedzierski, L.; Peiris, R. M. Bismuth(III) β-thioxoketonates as antibiotics against Helicobacter pylori and as anti-leishmanial agents. *Dalton Trans.* **2014**, *43*, 1279−1291.

(20) (a) Mathew, P.; Asokan, C. V. Cyclization of functionalized ketene-N,S-acetals to substituted pyrroles: applications in the synthesis of marine pyrrole alkaloids. *Tetrahedron Lett.* **2005**, *46*, 475−478. (b) Singh, G.; Bhattacharjee, S. S.; Ila, H.; Junjappa, H. A Facile One-Step Synthesis of Methyl β-Oxodithiocarboxylates. *Synthesis* **1982**, 693−694.

https://dx.doi.org/10.1021/acs.joc.0c02216
J. Org. Chem. XXXX, XXX, XXX−XXX