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Selenium Dioxide-Mediated Bromination of α,β-Unsaturated Ketones Using *N*-Bromosuccinimide in the Presence of *p*-Toluenesulfonic Acid: A Versatile Route for the Synthesis of α′-Bromo-4-arylbut-3-en-2-one and α′,α′-Dibromo-4-arylbut-3-en-2-one

Tyrchain Mitre Lipon, Ibakyntiew D. Marpna, Kmendashisha Wanniang, O. Risuklang Shangpliang, Badaker M. Laloo, Rishanlang Nongkhlaw, and Bekington Myrboh*

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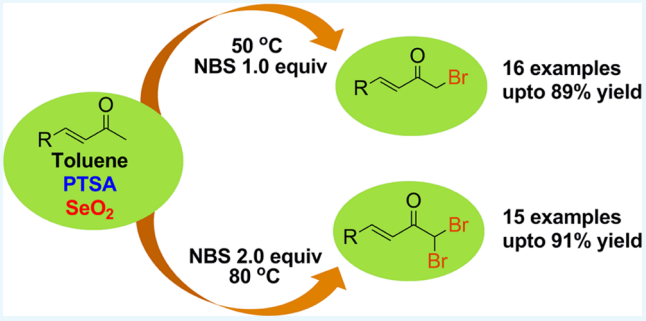
ABSTRACT: An efficient method for the synthesis of α,β-unsaturated α′-bromoketones and α,β-unsaturated α′,α′-dibromoketones is described using *N*-bromosuccinimide (NBS) as the brominating agent mediated by selenium dioxide (SeO_2) in the presence of *p*-toluenesulfonic acid (PTSA) monohydrate in toluene. The method is simple, employing easily available shelf reagents to afford a wide range of products in good yields. The method highlighted that simple fine-tuning of the reaction conditions and molar equivalents of the reactants easily affords either mono- or dibrominated products in excellent yields. A number of these products have not been reported in the literature. All of the reactions were carried out in gram-scale quantities.



INTRODUCTION

α-Haloketones are important intermediates in organic synthesis because of their high reactivity shown toward nucleophiles by both the electrophilic methylene and the carbonyl carbon atoms.[1] They are key building blocks, valuable for the synthesis of a wide variety of biologically active heterocyclic compounds,[2,3] natural products,[1a] pesticides, diagnostic aids, and surfactants.[1a,2c,4] They serve as an important precursor for various transformations utilized in pharmaceutical synthesis.[5] In particular, α-brominated carbonyl compounds are one of the most sought-after intermediates for further transformations both in industrial chemistry as well as in organic synthesis due to the wide range of utility of this bifunctional moiety.[2c,6,7] Synthesis of α-bromoketones has been accomplished over the past decades by direct bromination of ketones[8a−d] and using various available brominating agents.[8e−k] α-Haloketones have also been achieved by hydration of haloalkynes employing expensive catalysts.[9] However, literature survey revealed that not many procedures are available for the synthesis of α,β-unsaturated α′-bromoketones and α,β-unsaturated α′,α′-dibromoketones despite the fact that these moieties are commonly employed as an important intermediate in the synthesis of various pharmaceutical analogues.[7] The few known synthetic routes of α,β-unsaturated α′-bromoketones and α,β-unsaturated α′,α′-dibromoketones are shown in Scheme 1. Earlier, Calo' and co-workers reported the synthesis of α,β-unsaturated α′-bromoketones using 2,4,4,6-tetrabromocyclohexa-2,5-dienone (Scheme 1a),[10] while Cristau et al. reported that a mixture of α,β-unsaturated α′-bromoketones and α,β-unsaturated α′,α′-dibromoketones were obtained when α,β-unsaturated ketones were treated with tribromo triphenylmethylphosphonium (Scheme 1b).[11] In 1991, Mitami et al. reported a regioselective α′-bromination of α,β-unsaturated ketones by an electrochemical procedure (Scheme 1c).[12] Recently, Pace et al. reported the synthesis of some α,β-unsaturated α′-haloketones through the chemoselective addition of halomethylithiums to Weinreb amides (Scheme 1d).[13] Ngo and co-workers in their paper on the synthesis and antiproliferative activity study of new vinca alkaloids containing α,β-unsaturated aromatic side chains have reported the selective monobromination of the α′-methylketone of three α,β-unsaturated aryl ketones using *N*-bromosuccinimide (NBS) in the presence of PTSA (Scheme

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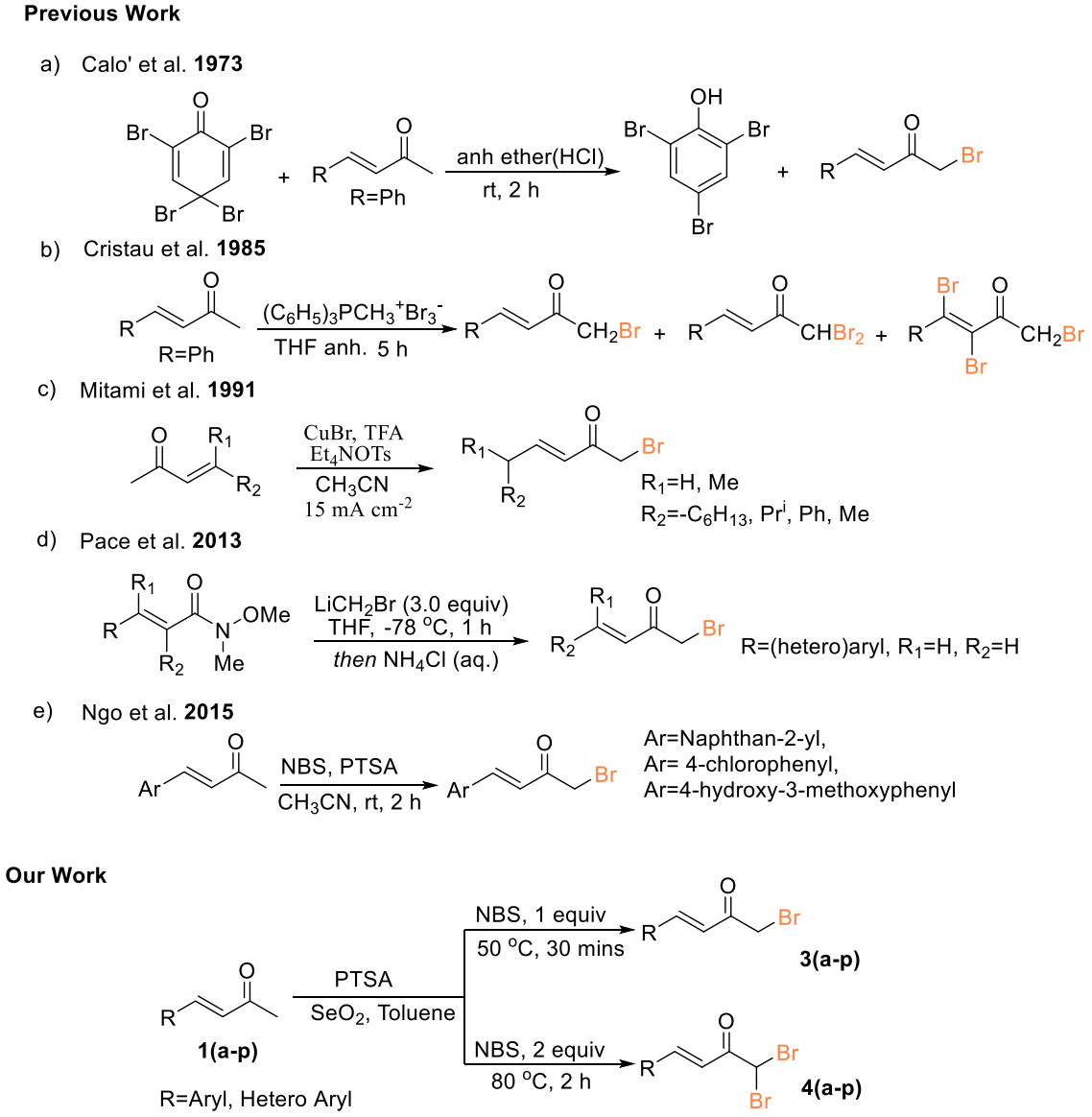
Scheme 1. Synthesis of α,β-Unsaturated α′-Bromoketones and α,β-Unsaturated α′,α′-Dibromoketones



1e).[7] However, when we repeated the experiments under the same reaction conditions as described in the paper, except for naphtha-2-yl analogue, the other substituted benzylideneacetones yielded mixtures of mono- and disubstituted bromoketones. Unfortunately, these reported methodologies suffer from a series of drawbacks ranging from chemo- and regioselective issues to low proficiency and lack of generality.

Recently, we have shown the effective utilization of SeO_2 as a proficient inorganic reagent, which, in the presence of a Lewis acid, facilitated the reaction between aromatic ketones and aromatic hydrocarbons to influence C−C coupling at the α-carbon atom;[14a] however, the same reaction catalyzed by an organic acid PTSA yielded unsymmetrical benzils.[14b] Also, aryl methyl ketones reacted efficiently with secondary amines in dimethyl sulfoxide (DMSO) in the presence of SeO_2 to affect α-selenoamidation of aryl methyl ketones.[14c] Thus, in continuation of our study on the synthetic utility of SeO_2 in organic synthesis, we wish to report herein an efficient protocol for the synthesis of α,β-unsaturated α′-bromoketones and α,β-unsaturated α′,α′-dibromoketones from α,β-unsaturated ketones with NBS in the presence of PTSA mediated by SeO_2. Bromination of variously functionalized α,β-unsaturated α-ketones is highly emphasized here. We are employing NBS as the brominating agent, which has been widely used as an efficient and successful brominating agent[15] in organic synthesis as it is user-friendly, easy to handle being solid at room temperature, inexpensive, and easily available.[16]

RESULTS AND DISCUSSION

We began our investigation using benzylidene acetone (**1a**) and NBS (**2**) as the model substrates to determine the optimal reaction conditions (Table 1). Initially, a mixture of benzylidene acetone (**1a**, 1 equiv), NBS (**2**, 1 equiv), and SeO_2 (0.5 equiv) was stirred with PTSA (0.5 equiv) in toluene (3 mL) at room temperature for 3 h when thin-layer chromatography (TLC) showed the selective formation of the monobrominated product **3a** in 50% yield along with the unreacted starting ketone **1a** (Table 1, entry 1). When the reaction was allowed to stir for a longer time (6 h), it was observed that 65% of the desired product **3a** and a trace amount of the dibrominated product **4a** were obtained (Table 1, entry 2). On further allowing the reaction to stir for a longer

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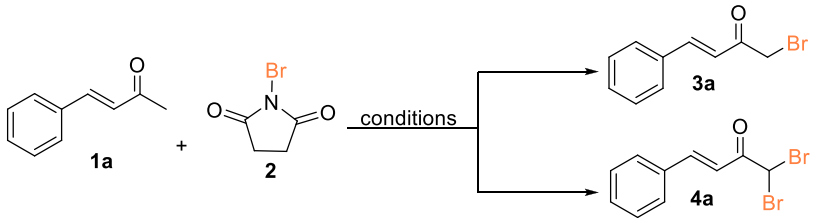
Table 1. Optimization of the Reaction Conditions[a]



							yield (%)	
entry	NBS (2) (equiv)	SeO_2 (equiv)	acid (equiv)	solvent	temp (°C)	time	3a	4a
1	1	0.5	PTSA (0.5)	toluene	rt	3 h	50	
2	1	0.5	PTSA (0.5)	toluene	rt	6 h	65	trace
3	1	0.5	PTSA (0.5)	toluene	rt	12 h	80	10
4	**1**	**0.5**	**PTSA (0.5)**	**toluene**	**50**	**30 min**	**84**	**5**
5	1	0.5	PTSA (0.5)	toluene	50	3 h	70	20
6	1		PTSA (0.5)	toluene	50	30 min	50	trace
7	1	0.5		toluene	50	30 min		
8	1	0.5	BF_3Et_2O (0.5)	toluene	50	30 min	50	30
9	1	0.5	TFA (0.5)	toluene	50	30 min	65	25
10	1	0.5	AcOH (0.5)	toluene	50	30 min	30	trace
11	1	0.5	$AlCl_3$ (0.5)	toluene	50	30 min		
12	1	0.5	PTSA (0.5)	CH3CN	50	30 min	75	5
13	1	0.5	PTSA (0.5)	DMSO	50	30 min	55	20
14	1	0.5	PTSA (0.5)	H_2O	50	30 min		
15	1	0.5	PTSA (0.5)	DCM	50	30 min	75	5
16	1	0.5	PTSA (0.5)	THF	50	30 min	70	5
17	1	0.5	PTSA(1)	toluene	50	30 min	70	25
18	2	0.5	PTSA (0.5)	toluene	50	30 min	50	40
19	2	0.5	PTSA (0.5)	toluene	50	2 h	25	60
20	2	0.5	PTSA (0.5)	toluene	50	6 h		83
21	2	0.5	PTSA (1)	toluene	50	2 h	20	70
22	2	1	PTSA (0.5)	toluene	50	2 h	15	78
23	2	1	PTSA (1)	toluene	50	2 h	10	80
24	**2**	**1**	**PTSA (1)**	**toluene**	**80**	**2 h**		**87**
25	2		PTSA (1)	toluene	80	2 h	25	45
26	2	1	PTSA (1)	toluene	90	2 h		87
27	2	1	PTSA (1)	toluene	100	2 h	5	75

[a]Reaction conditions: α,β-unsaturated ketones (**1a**) (1.0 mmol, 1.0 equiv), solvent (3 mL).

time (12 h), the starting material was completely consumed, affording 10% of compound **4a**, while product **3a** increased to 80% yields (Table 1, entry 3). When the reaction temperature of the reaction mixture was increased to 50 °C, surprisingly, we were able to obtain up to 84% of product **3a** and only less than 10% of product **4a** in just 30 min (Table 1, entry 4). On allowing the reaction to stir for a longer time (3 h), it was observed that 70% of the desired product **3a** and 20% of the dibrominated product **4a** was obtained (Table 1, entry 5). In the absence of selenium dioxide, when the reaction was heated at 50 °C for 30 min, 50% of product **3a** and a trace amount of product **4a** were obtained (Table 1, entry 6). In the absence of an acid, the formation of the desired product does not take place (Table 1, entry 7). Attempts to improve the efficiency of the reaction using different acids and solvents provided only mixtures of the two products in varying yields (Table 1, entries 8−11, 12−16). When the amount of PTSA was increased to 1 equiv, there was a marked decrease in the yield of product **3a** (70%) with a corresponding increase of product **4a** (25%; Table 1, entry 17). Interestingly, increasing the amount of NBS to 2 equiv showed a steady decrease in the formation of product **3a** with increased reaction time and a corresponding increase in the formation of product **4a** (Table 1, entries 18, 19). When the reaction was allowed to stir for 6 h, only product **4a** was observed and was isolated in 83% yield (Table 1, entry 20). Increasing the amount of PTSA to 1 equiv increases the yield of product **4a** to 70% with a corresponding decrease in the yield of product **3a** to 20% (Table 1, entry 21). Similarly, increasing the amount of SeO_2 to 1 equiv resulted in a marked decrease in the yield of product **3a** (15%) with a corresponding increase of product **4a** (78%; Table 1, entry 22). When the amount of SeO_2 and PTSA was increased to 1 equiv, each resulted in 80% yield of product **4a** and 10% of product **3a** (Table 1, entry 23). Finally, when the reaction amount of SeO_2 and PTSA was 1 equiv each and the temperature was increased to 80 °C, only product **4a** (87%) was obtained, where the reaction time was appreciatively reduced to 2 h (Table 1, entry 24). In the absence of selenium dioxide under the same reaction condition, 25% of product **3a** and 45% of product **4a** were obtained (Table 1, entry 25). It was noted that there was no improvement in the yield of the products when the amount of SeO_2 and PTSA was further increased, nor when the temperature was increased above 80

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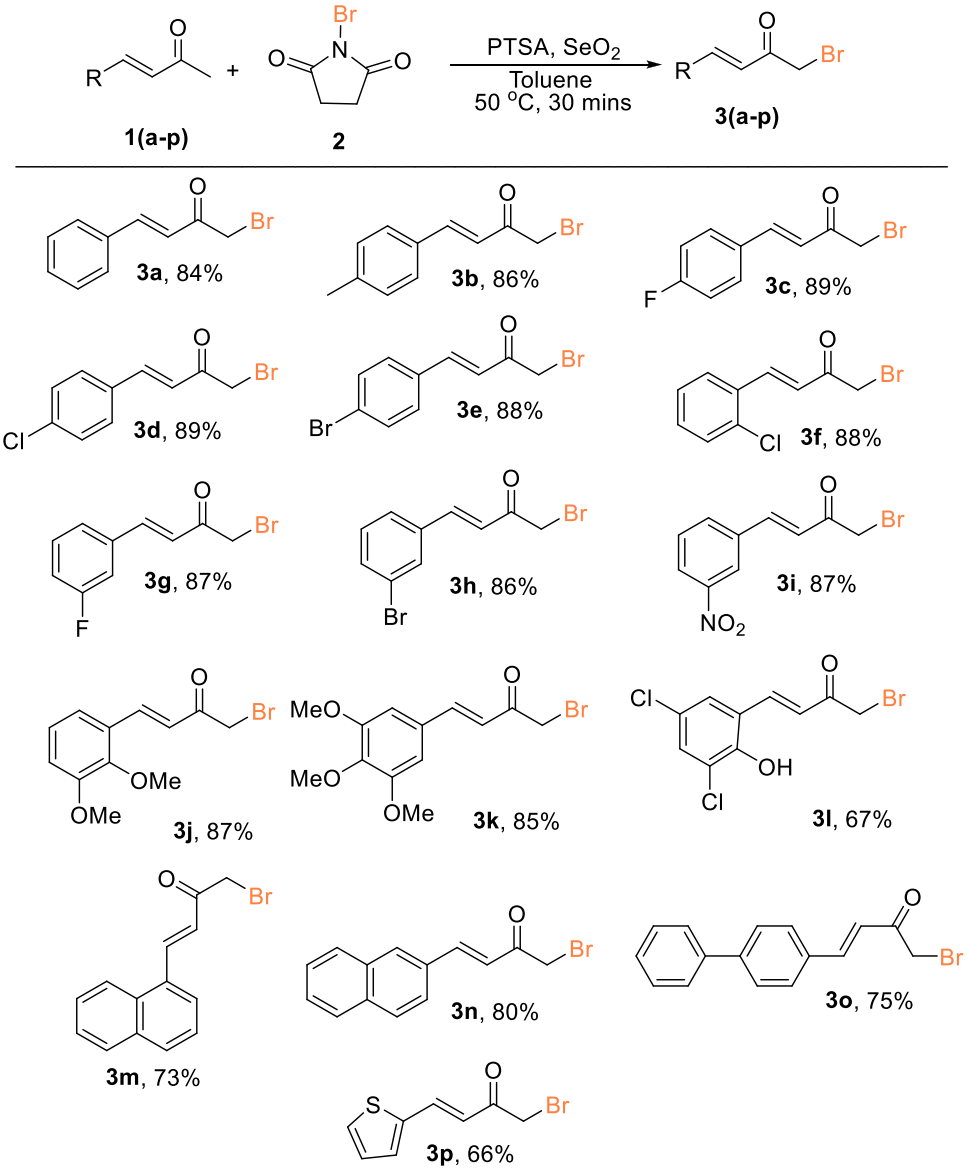
Scheme 2. Substrate Scope of α,β-Unsaturated Ketones[a,b]



[a]Reaction conditions: α,β-unsaturated ketones (**1a**) (6.84 mmol, 1.0 equiv), NBS (**2**) (6.84 mmol, 1.0 equiv), SeO_2 (3.42 mmol, 0.5 equiv), PTSA (3.42 mmol, 0.5 equiv) toluene (3.0 mL), at 50 °C for 30 min. [b]Isolated yields after column chromatography.

°C, which at 100 °C, causes the product to decompose (Table 1, entries 26−27).

Having optimized the conditions for the monobromination of the α,β-unsaturated ketone (Table 1, entry 3), we proceeded to investigate the scope of the reactions to establish the generality of the methodology for the synthesis of α,β-unsaturated α′-bromoketones (Scheme 2). Various substituted α,β-unsaturated ketones, viz, 4-methylbenzylideneacetone (**1b**), 4-fluorobenzylideneacetone (**1c**), 4-chlorobenzylideneacetone (**1d**), 4-bromobenzylideneacetone (**1e**), and 2-chlorobenzylideneacetone (**1f**), readily reacted with NBS (**2**) in the presence of SeO_2 and PTSA in toluene, affording the corresponding products **3b**, **3c**, **3d**, **3e**, and **3f** in excellent yields (86, 89, 89, 88, and 88%, respectively). Other α,β-unsaturated ketones bearing electron-withdrawing groups substituted at the meta position, *viz*, 3-fluorobenzylideneacetone (**1g**), 3-bromorobenzylideneacetone (**1h**), and 3-nitrobenzylideneacetone (**1i**), similarly afforded the corresponding desired products **3g**, **3h**, and **3i** in excellent yields (87, 86, and 87%, respectively). The scope of the reaction was further extended to di- and trisubstituted benzylideneacetones having an electron-donating group (−OMe) as the substituent. Thus, 2,3-dimethoxybenzylideneacetone (**1j**) and 3,4,5-trimethoxybenzylideneacetone (**1k**) were easily converted to the corresponding products **3j** (87%) and **3k** (85%) in satisfactory yields. It is worth mentioning that the reaction also proceeded smoothly with 3,5-dichloro(2-hydroxyphenyl)but-3-en-2-one (**1l**) to afford the desired product **3l** in 67%. The generality of the method was further strengthened when α,β-unsaturated naphthylidene acetones (**1m, 1n**) reacted effortlessly to afford **3m** and **3n** in 73 and 80% yields, respectively. The reactions were also performed with α,β-unsaturated ketones containing biphenyl moiety (**1o**) and thiophene moiety (**1p**), which, to our delight readily afforded the desired products **3o** and **3p** in satisfactory yields (75 and 66%, respectively). Compound **3i**

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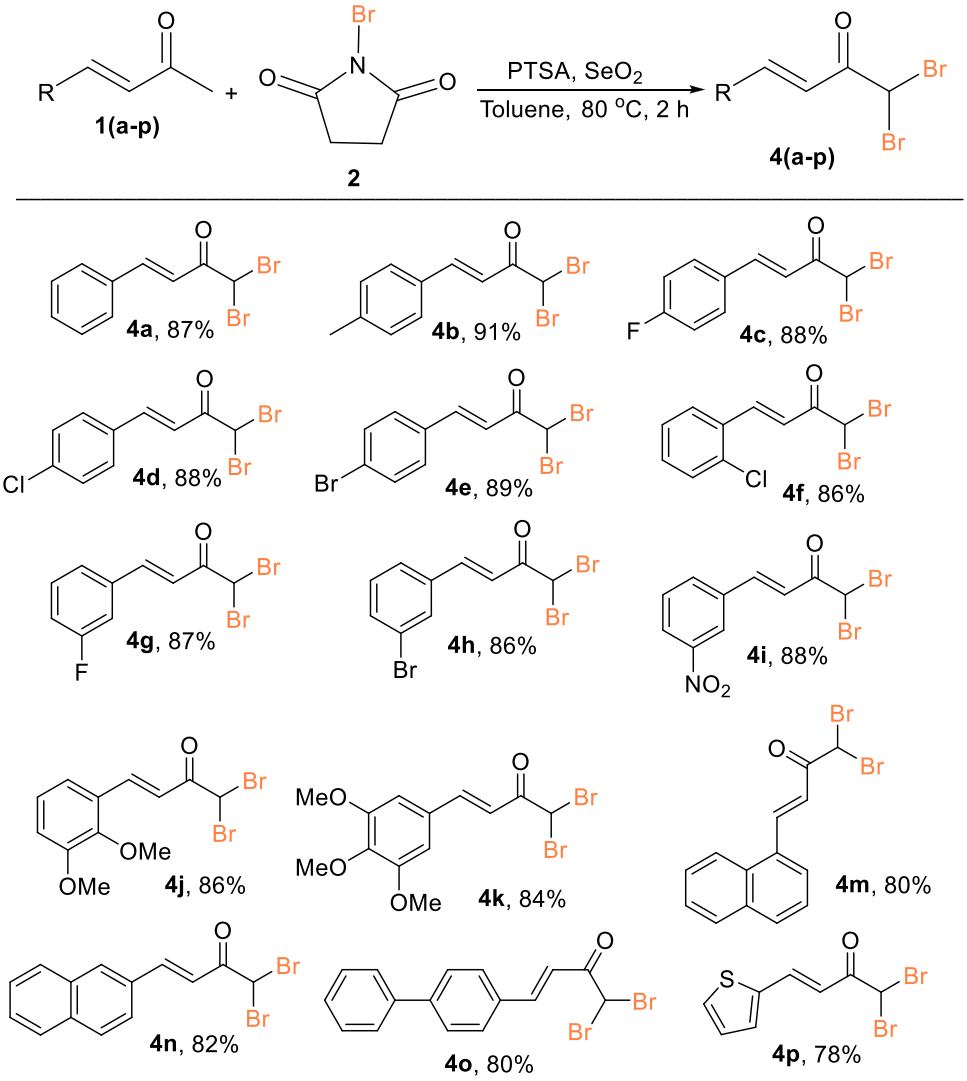
Scheme 3. Substrate Scope of α,β-Unsaturated Ketones[a,b]



[b]Isolated yields after column chromatography. [a]Reaction conditions: α,β-unsaturated ketones (**1a**) (6.84 mmol, 1.0 equiv), NBS (**2**) (13.68 mmol, 2.0 equiv), SeO_2 (6.84 mmol, 1.0 equiv), PTSA (6.84 mmol, 1.0 equiv), toluene (3.0 mL), at 80 °C for 2 h.

was obtained as crystal, and the structure was confirmed by X-ray analysis (included in the Supporting Information).

Second, with the conditions optimized for the synthesis of α,β-unsaturated ketone by dibromination (Table 1, entry 9), we next examined the scope of the reaction to establish the generality of the method for the synthesis of α,β-unsaturated α′,α′-dibromoketones (Scheme 3). Differently substituted α,β-unsaturated ketones, such as 4-methylbenzylideneacetone (**1b**), 4-fluorobenzylideneacetone (**1c**), 4-chlorobenzylideneacetone (**1d**), 4-bromobenzylideneacetone (**1e**), and 2-chlorobenzylideneacetone (**1f**), were selected and allowed to react as per the standardized procedure. All of the reactions afforded the corresponding dibrominated products **4b**, **4c**, **4d**, **4e**, and **4f** in excellent yields (91, 88, 88, 89, and 86%, respectively). Here, the substrates exhibited a similar tolerance to the electron-withdrawing group and the electron-donating group. The substituted α,β-unsaturated ketones, at the meta position bearing electron-withdrawing substituents, viz, 3-fluorobenzylideneacetone (**1g**), 3-bromorobenzylideneacetone (**1h**), and 3-nitrobenzylideneacetone (**1i**), were successfully converted to the corresponding desired products **4g** (87%), **4h** (86%), and **4i** (88%). The reaction worked equally well with the di- and trisubstituted benzylideneacetones having an electron-donating group (-OMe), *viz*, 2,3-dimethoxybenzylideneacetone (**1j**) and 3,4,5-trimethoxybenzylideneacetone (**1k**), to afford the corresponding products **4j** and **4k** in 89% and 84% overall yields, respectively. It may be noted that (3,5-dichloro 2-hydroxyphenyl)but-3-en-2-one did not react satisfactorily since only trace quantities of the required product were formed. The presence of the 2-OH group on the phenyl ring evidently hindered the attack of the next bromine atom on the α-carbon. The protocol was also found to be compatible with the extended aromatic ring system, such as α,β-unsaturated naphthylidene acetones (**1m, 1n**), which afforded products **4m** and **4n** in 85 and 88% overall yields, respectively. To further strengthen the generality of the method, reactions were also performed with α,β-unsaturated ketones containing the biphenyl moiety (**1o**) and thiophene moiety (**1p**), which furnished the desired products **4o** and **4p** in 83 and 81% overall yields. The structure of compound **4f** was confirmed by X-ray analysis (included in the Supporting Information).

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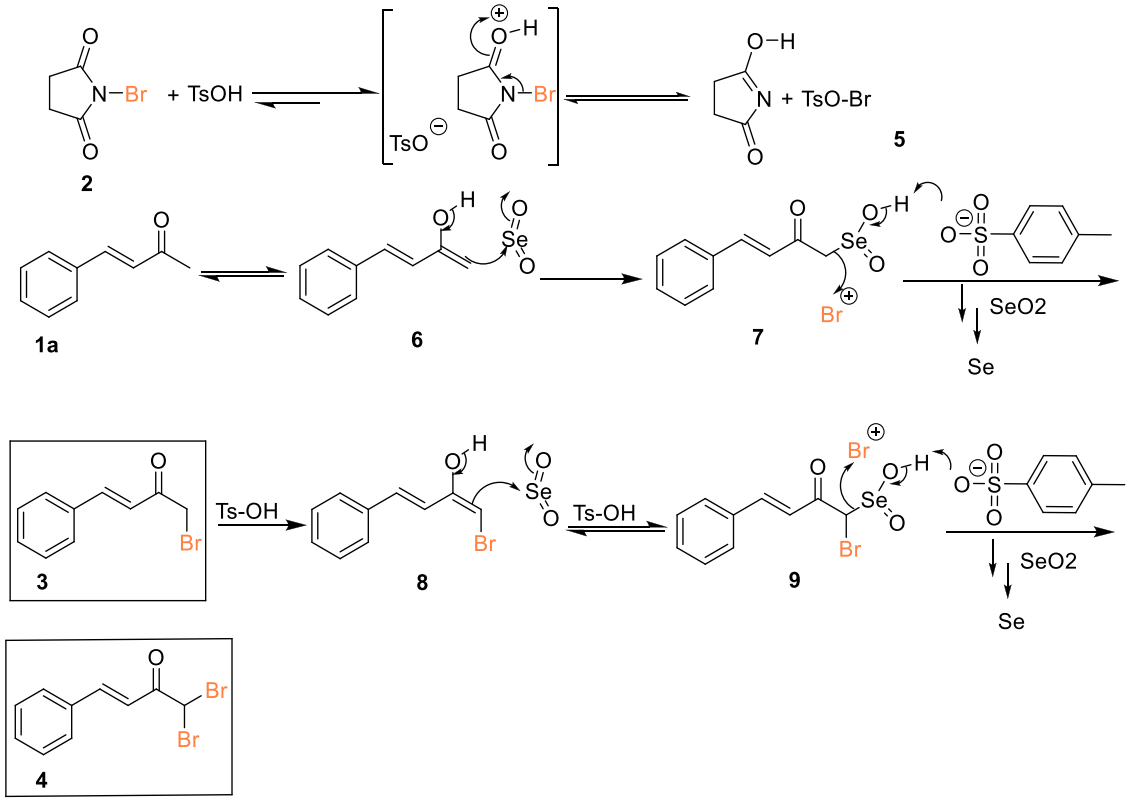
Scheme 4. Plausible Mechanism



The plausible mechanism involved in the reaction of the α,β-unsaturated ketone **1** with NBS (**2**) in the presence of SeO_2 and PTSA is depicted in Scheme 4. The initial reaction of the enol form **6** with SeO_2 resulted in the formation of the organoselenium intermediate **7**, which evidently underwent a PTSA-assisted electrophilic attack to the bromonium ion **5** generated from NBS[17] to afford the α,β-unsaturated α′-bromoketone **3**. In a similar fashion, in the presence of excess NBS, the enolate **8** presumably underwent a second electrophilic attack with the bromonium ion **5** to afford the α′,α′-dibromoketone **4**. Although the role of SeO_2 appears to be that of a catalyst, a little excess of it is always required since it is highly susceptible to reduction to elemental selenium as observed by red deposits at the end of each reaction.

CONCLUSIONS

In summary, this work reports an efficient protocol for the direct and quick access to α,β-unsaturated α′-bromoketones and α′,α′-dibromoketones from easily available α,β-unsaturated ketones. The method is general and allows a broad range of substrates with good product yields. It may be noted that most of the α′,α′-dibromoketones synthesized have not been reported so far except for compound **4a**.[11] The advantage of this method lies in the fact that the bromination methods have been improved and enhanced through the mediation of selenium dioxide.

EXPERIMENTAL SECTION

General Information. The arylidene methyl ketones were all prepared in the laboratory as per the standard procedure.[18] Other reagents were purchased directly from commercial suppliers and used as such without any further purification unless otherwise mentioned. The reactions were monitored by thin-layer chromatography (TLC) using precoated aluminum sheets (silica gel 60 F_{254} 0.2 mm thickness). The spots were visualized under UV (λ = 254 nm). Purification of the products was done by flash chromatography using silica gel (230−400 mesh). Characterization of compounds was done for ^1H and ^{13}C NMR spectra, which were recorded on a Bruker Avance II-400 spectrometer in $CDCl_3$ using tetramethylsilane (TMS) as an internal standard; chemical shifts were reported in delta (δ) units, in parts per million (ppm), and coupling constants (*J*) in hertz (Hz). IR spectra were recorded on a PerkinElmer Spectrum 400 Fourier transform infrared (FTIR) instrument, and the frequencies are expressed in cm^{-1}. Mass spectral data were obtained with a Waters ultraperformance liquid chromatography-TQD (UPLC-TQD) equipped with an electrospray ionization-mass spectrometer (ESI-MS). High-resolution mass spectra (ESI-HRMS) data were obtained using the accurate-mass Q-TOF LC/ME system (Agilent Technologies, Santa Clara, CS) equipped with an Agilent 1290 UPLC system and an ESI source. Melting points were recorded by the open capillary tube method and were uncorrected.

*General Procedure A for the Synthesis of 1-Bromo-4-arylbut-3-en-2-one (**3**).* To a stirring mixture of α,β-unsaturated ketones (**1**) (6.84 mmol, 1 equiv), NBS (**2**) (6.84 mmol, 1 equiv), and SeO_2 (3.42 mmol, 0.5 equiv) in toluene (3.0 mL) at 50 °C, PTSA (3.42 mmol, 0.5 equiv) was added portionwise for a period of 1 min. The reaction was allowed to stir for 30 min in an oil bath. On completion of the reaction, which was monitored by TLC, the reaction mixture was allowed to cool down to room temperature. The precipitate elemental selenium settled at the bottom of the flask, which was then filtered off and washed with ethyl acetate (2 × 10 mL), and the combined filtrate was transferred to a

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separating funnel and washed with conc. sodium bicarbonate solution (2 × 10 mL), followed by a wash with brine (2 × 10 mL). The organic layer was separated followed by the removal of water residual by filtering the organic layer over anhydrous Na_2SO_4, and the organic layer was concentrated in vacuum. The crude mass was purified by flash chromatography on silica gel (230−400 mesh) and using ethyl acetate/hexane as the eluent to obtain the corresponding products **3a−3p**.

*General Procedure B for the Synthesis of 1,1-Dibromo-4-arylbut-3-en-2-one (**4**).* To a stirring mixture of α,β-unsaturated ketones (**1**) (6.84 mmol, 1 equiv), NBS (**2**) (13.69 mmol, 2 equiv), and SeO_2 (6.84 mmol, 1 equiv) in toluene (3.0 mL) at 80 °C, PTSA (6.84 mmol, 1 equiv) was added little by little for a short period of time. The reaction was allowed to stir for 2 h in an oil bath. On completion of the reaction, which was monitored by TLC, the precipitate elemental selenium settled at the bottom of the flask, which was then filtered off and washed with ethyl acetate (2 × 10 mL), and the combined filtrate was transferred to a separating funnel and washed with conc. sodium bicarbonate solution (2 × 10 mL), followed by a wash with brine (2 × 10 mL). The organic layer was separated, dried over anhydrous Na_2SO_4, and concentrated in vacuum. The crude mass was purified by flash chromatography on silica gel (230−400 mesh) and using ethyl acetate/hexane as the eluent to obtain the corresponding products **4a−4p**.

*1-Bromo-4-phenylbut-3-en-2-one (**3a**).*[5e,10−13,19] The title compound was prepared via the general procedure A starting from 4-phenylbut-3-en-2-one (1.000 g, 6.84 mmol, 1 equiv), SeO_2 (0.379 g, 3.420 mmol, 0.5 equiv), NBS (**2**) (1.217 g, 6.84 mmol, 1 equiv), and PTSA (0.650 g, 3.420 mmol, 0.5 equiv) in toluene (3.0 mL) at 50 °C. The product was isolated by flash chromatography using hexane/ethyl acetate as an eluent (9:1): brown solid (1.293 g, 84% yield); mp 45 °C; IR (KBr film) 3058, 3017, 2934, 2376, 2254, 1945, 1876, 1811, 1687, 1618, 1560, 1471, 1420, 131, 1199, 1155, 1060, 975, 881, 857, 782, 739, 676, 651, 566 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, with 1% v/v TMS) δ 7.70 (d, *J* = 16.4 Hz, 1H), 7.59−7.57 (m, 2H), 7.43 (d, *J* = 1.6 Hz, 2H), 7.41 (d, *J* = 2 Hz, 1H), 6.96 (d, *J* = 16 Hz, 1H), 4.09 (s, 1H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 191.0, 145.4, 133.9, 131.1, 129.0, 128.6, 122.2, 33.1 ppm; HRMS (ESI) calcd for $C_{10}H_{10}BrO$ $[M + H]^+$ 224.9915; found 225.0000.

*1-Bromo-4-(p-tolyl)but-3-en-2-one (**3b**).*[5e] The title compound was prepared via the general procedure A starting from 4-phenylbut-3-en-2-one (1.095 g, 6.84 mmol, 1 equiv), SeO_2 (0.379 g, 3.420 mmol, 0.5 equiv), NBS (**2**) (1.217 g, 6.84 mmol, 1 equiv), and PTSA (0.650 g, 3.420 mmol, 0.5 equiv) in toluene (3.0 mL) at 50 °C. The product was isolated by flash chromatography using hexane/ethyl acetate as an eluent (9:1): white solid (1.406 g, 86% yield); mp 88 °C; IR (KBr film) 3027, 2983, 2934, 2381, 2354, 2306, 1922, 1689, 1667, 1614, 1598, 1564, 1510, 1449, 1411, 1386, 1327, 1308, 1285, 1184, 1154, 1114, 1069, 980, 891, 841, 798, 712, 642, 590, 542, 516 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, with 1% v/v TMS) δ 7.61 (d, *J* = 16 Hz, 1H), 7.41 (d, *J* = 8 Hz, 2H), 7.15 (d, *J* = 8 Hz, 2H), 6.83 (d, *J* = 16.4 Hz, 1H), 4.02 (s, 2H), 2.32 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 191.1, 145.5, 141.8, 131.2, 129.8, 129.8, 128.7, 128.7, 121.2, 33.2, 21.6 ppm; MS (ES^+) calcd for $C_{11}H_{14}BrO$ $[M + H]^+$ 239.00; found 239.00.

*1-Bromo-4-(4-fluorophenyl)but-3-en-2-one (**3c**).*[5e] The title compound was prepared via the general procedure A starting from 4-phenylbut-3-en-2-one (1.123 g, 6.84 mmol), SeO_2 (0.379 g, 3.420 mmol), NBS (**2**) (1.217 g, 6.84 mmol), and PTSA (0.650 g, 3.420 mmol) in toluene (3.0 mL) at 50 °C. The product was isolated by flash chromatography using hexane/ethyl acetate as an eluent (9:1): brown solid (1.479 g, 89% yield); mp 100 °C; IR (KBr film) 3105, 3068, 2984, 2937, 1698, 1674, 1618, 1592, 1506, 1382, 1227, 1158, 1066, 986, 848, 810, 646 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, with 1% v/v TMS) δ 7.60 (d, *J* = 16 Hz, 1H), 7.53 (q, *J* = 3.2 Hz, 2H), 7.04 (t, *J* = 8.4 Hz, 2H), 6.82 (d, *J* = 16 Hz, 1H), 4.01 (s, 2H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 189.8, 163.3 (*J* = 251.3 Hz), 143.0, 129.6 (*J* = 8.7 Hz), 129.2 (*J* = 3.4 Hz), 120.8 (*J* = 2.4 Hz), 115.3 (*J* = 21.9 Hz), 33.1 ppm; HRMS (ESI) calcd for $C_{10}H_9BrFO$ $[M + H]^+$ 242.9821; found 242.9824.

*1-Bromo-4-(4-chlorophenyl)but-3-en-2-one (**3d**).*[5e,7] The title compound was prepared via the general procedure A starting from 4-phenylbut-3-en-2-one (1.235 g, 6.84 mmol), SeO_2 (0.379 g, 3.420 mmol), NBS (**2**) (1.217 g, 6.84 mmol), and PTSA (0.650 g, 3.420 mmol) in toluene (3.0 mL) at 50 °C. The product was isolated by flash chromatography using hexane/ethyl acetate as an eluent (9:1): brown solid (1.579 g, 89% yield); mp 115 °C; IR (KBr film) 3096, 3033, 2994, 2852, 1695, 1581, 1483, 1400, 1260, 1129, 1073, 1047, 745 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, with 1% v/v TMS) δ 7.59 (d, *J* = 15.6 Hz, 1H), 7.45 (d, *J* = 8.4 Hz, 2H), 7.32 (d, *J* = 8 Hz, 2H), 6.86 (d, *J* = 16 Hz, 2H), 4.01 (s, 2H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 187.3, 140.0, 136.9, 131.6, 128.9, 118.6, 32.5 ppm; HRMS (ESI) calcd for $C_{10}H_9BrClO$ $[M + H]^+$ 258.9525; found 258.9615.

*1-Bromo-4-(4-bromophenyl)but-3-en-2-one (**3e**).*[5e] The title compound was prepared via the general procedure A starting from 4-phenylbut-3-en-2-one (1.539 g, 6.84 mmol), SeO_2 (0.379 g, 3.420 mmol), NBS (**2**) (1.217 g, 6.84 mmol), and PTSA (0.650 g, 3.420 mmol) in toluene (3.0 mL) at 50 °C. The product was isolated by flash chromatography using hexane/ethyl acetate as an eluent (9:1): brown solid (1.829 g, 88% yield); mp 120 °C; IR (KBr film) 3014, 1672, 1600, 1327, 1142, 1067, 585 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, with 1% v/v TMS) δ 7.57 (d, *J* = 16.4 Hz, 1H), 7.48 (d, *J* = 8 Hz, 2H), 7.38 (d, *J* = 8 Hz, 2H), 6.80 (d, *J* = 16 Hz, 1H), 4.01 (s, 2H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 189.8, 142.9, 131.7, 131.3, 128.9, 124.5, 121.5, 32.1 ppm; MS (ES^+) calcd for $C_{10}H_9Br_2O$ $[M + H]^+$ 304.90; found 304.90.

*1-Bromo-4-(2-chlorophenyl)but-3-en-2-one (**3f**).* The title compound was prepared via the general procedure A starting from 4-phenylbut-3-en-2-one (1.235 g, 6.84 mmol), SeO_2 (0.379 g, 3.420 mmol), NBS (**2**) (1.217 g, 6.84 mmol), and PTSA (0.650 g, 3.420 mmol) in toluene (3.0 mL) at 50 °C. The product was isolated by flash chromatography using hexane/ethyl acetate as an eluent (9:1): brown solid (1.562 g, 88% yield); mp 62 °C; IR (KBr film) 3061, 2854, 1695, 1607, 1388, 1129, 1073, 1047, 745 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, with 1% v/v TMS) δ 8.05 (d, *J* = 16 Hz, 1H), 7.61 (dd, *J* = 6 Hz, 1H), 7.37 (dt, *J* = 1.6 Hz, 1H), 7.29−7.22 (m, *J* = 2H), 6.85 (d, *J* = 16.4 Hz, 1H), 4.06 (s, 2H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 190.8, 141.1, 135.6, 132.2, 131.8, 130.3, 127.7, 127.2, 124.7, 32.8 ppm; HRMS (ESI) calcd for $C_{10}H_9BrClO$ $[M + H]^+$ 258.9525; found 258.9615.

*1-Bromo-4-(3-fluorophenyl)but-3-en-2-one (**3g**).* The title compound was prepared via the general procedure A starting from 4-phenylbut-3-en-2-one (1.123 g, 6.84 mmol), SeO_2 (0.379 g, 3.420 mmol), NBS (**2**) (1.217 g, 6.84 mmol), and PTSA (0.650 g, 3.420 mmol) in toluene (3.0 mL) at 50 °C. The product was isolated by flash chromatography using

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hexane/ethyl acetate as an eluent (9:1): yellow solid (1.446 g, 87% yield); mp 78 °C; IR (KBr film) 3059, 2985, 1698, 1616, 1582, 1485, 1386, 1327, 1270, 1145, 991, 971, 913, 866, 713 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, with 1% v/v TMS) δ 7.59 (d, J = 16 Hz, 1H), 7.30 (q, J = 6.8 Hz, 2H), 7.23 (s, 1H), 7.06 (t, J = 8.4 Hz, 1H), 6.88 (d, J = 15.6 Hz, 1H), 4.01 (s, 2H), ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 190.7, 162.9 (J = 246.9 Hz), 143.8 (J = 3.2 Hz), 136.2 (J = 7.9 Hz), 130.6 (J = 7.6 Hz), 124.7 (J = 3.4 Hz), 123.3, 117.9 (J = 21 Hz), 114.7 (J = 21.7 Hz), 33.1 ppm; HRMS (ESI) calcd for $C_{10}H_9BrFO$ $[M + H]^+$ 242.9821; found 242.9824.

*1-Bromo-4-(3-bromophenyl)but-3-en-2-one (**3h**).*[5e] The title compound was prepared via the general procedure A starting from 4-phenylbut-3-en-2-one (1.539 g, 6.84 mmol), SeO_2 (0.379 g, 3.420 mmol), NBS (**2**) (1.217 g, 6.84 mmol), and PTSA (0.650 g, 3.420 mmol) in toluene (3.0 mL) at 50 °C. The product was isolated by flash chromatography using hexane/ethyl acetate as an eluent (9:1): brownish white solid (1.788 g, 86% yield); mp 60 °C; IR (KBr film) 3059, 3025, 2981, 2934, 1695, 1615, 1492, 1446, 1385, 1332, 1182, 1069, 991, 890, 746, 687, 554 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, with 1% v/v TMS) δ 7.64 (d, J = 16 Hz, 1H), 7.52 (t, J = 5.2 Hz, 2H), 7.36 (d, J = 1.2 Hz, 1H), 7.35 (s, 1H), 6.89 (d, J = 16.4 Hz, 1H), 4.03 (s, 2H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 191.1, 145.4, 133.9, 131.2, 129.1, 128.6, 122.2, 33.1 ppm; MS (ES^+) calcd for $C_{10}H_9Br_2O$ $[M + H]^+$ 304.90; found 305.00.

*1-Bromo-4-(3-nitrophenyl)but-3-en-2-one (**3i**).* The title compound was prepared via the general procedure A starting from 4-phenylbut-3-en-2-one (1.307 g, 6.84 mmol), SeO_2 (0.379 g, 3.420 mmol), NBS (**2**) (1.217 g, 6.84 mmol), and PTSA (0.650 g, 3.420 mmol) in toluene (3.0 mL) at 50 °C. The product was isolated by flash chromatography using hexane/ethyl acetate as an eluent (9:1): brown solid (1.607 g, 87% yield); mp 130 °C; IR (KBr film) 3043, 2927, 2393, 1688, 1614, 1351, 1139, 994, 727, 680 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, with 1% v/v TMS) δ 8.38 (s, 1H), 8.21 (dd, J = 7.2 Hz, 1H), 7.82 (d, J = 7.6 Hz, 1H), 7.68 (d, J = 15.6, 1H), 7.56 (t, J = 8, 1H), 7.02 (d, J = 16 Hz, 1H), 4.04 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 190.4, 148.7, 142.2, 135.7, 134.3, 130.2, 125.2, 124.6, 122.7, 33.1 ppm; HRMS (ESI) calcd for $C_{10}H_9BrNO_3$ $[M + H]^+$ 269. 9766; found 269.9772.

*1-Bromo-4-(2,3-dimethoxyphenyl)but-3-en-2-one (**3j**).* The title compound was prepared via the general procedure A starting from 4-phenylbut-3-en-2-one (1.410 g, 6.84 mmol), SeO_2 (0.379 g, 3.420 mmol), NBS (**2**) (1.217 g, 6.84 mmol), and PTSA (0.650 g, 3.420 mmol) in toluene (3.0 mL) at 50 °C. The product was isolated by flash chromatography using hexane/ethyl acetate as an eluent (9:1): green solid (1.696 g, 87% yield); mp 78 °C; IR (KBr film) 3065, 2999, 2937, 2830, 1696, 1606, 1496, 1386, 1218, 1047, 991, 801, 717 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, with 1% v/v TMS) δ 8.01 (d, J = 16 Hz, 1H), 7.09 (d, J = 3.2 Hz, 1H), 6.98−6.94 (m, 2H), 6.87 (d, J = 9.2 Hz, 1H), 4.14 (s, 2H), 3.87 (s, 3H), 3.81 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 191.5, 153.5, 153.3, 140.5, 123.3, 123.1, 118.2, 113.2, 112.5, 56.1, 55.8, 33.1 ppm; HRMS (ESI) calcd for $C_{12}H_{14}BrO_3$ $[M + H]^+$ 285.0126; found 285.0000.

*1-Bromo-4-(3,4,5-trimethoxyphenyl)but-3-en-2-one (**3k**).* The title compound was prepared via the general procedure A starting from 4-phenylbut-3-en-2-one (1.616 g, 6.84 mmol), SeO_2 (0.379 g, 3.420 mmol), NBS (**2**) (1.217 g, 6.84 mmol), and PTSA (0.650 g, 3.420 mmol) in toluene (3.0 mL) at 50 °C. The product was isolated by flash chromatography using hexane/ethyl acetate as an eluent (9:1): yellow solid (1.832 g, 85% yield); mp 86 °C; IR (KBr film) 3043, 2998, 2971, 2834, 1680, 1594, 1481, 1424, 1247, 1201, 1109, 1000, 854 $cm^{-1;}$ ^1H NMR (400 MHz, $CDCl_3$, with 1% v/v TMS) δ 8.01 (d, J = 16 Hz, 1H), 7.20 (s, 1H), 6.91 (s, 1H), 6.68 (d, J = 16 Hz, 1H), 4.08 (s, 1H), 3.87 (s, 3H), 3.85 (s, 3H), 3.83 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 190.8, 152.9, 151.3, 145.6, 143.9, 129.2, 124.26, 113.9, 106.0, 61.3, 61.1, 56.3, 32.5 ppm; HRMS (ESI) calcd for $C_{13}H_{16}BrO_4$ $[M + H]^+$ 315.0232; found 315.0227.

*1-Bromo-4-(3,5-dichloro-2-hydroxyphenyl)but-3-en-2-one (**3l**).* The title compound was prepared via the general procedure A starting from 4-phenylbut-3-en-2-one (1.580 g, 6.84 mmol), SeO_2 (0.379 g, 3.420 mmol), NBS (**2**) (1.217 g, 6.84 mmol), and PTSA (0.650 g, 3.420 mmol) in toluene (3.0 mL) at 50 °C. The product was isolated by flash chromatography using hexane/ethyl acetate as an eluent (9:1): dark orange solid (1.420 g, 67% yield); mp 102 °C; IR (KBr film) 3073, 2982, 2930, 1687, 1606, 1250, 1165, 1077, 861, 753, 559 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, with 1% v/v TMS) δ 7.81 (d, J = 16 Hz, 1H), 7.37 (d, J = 2.4 Hz, 1H), 7.33 (d, J = 2 Hz, 1H), 7.07 (d, J = 16 Hz, 1H), 4.78 (s, 1H), 4.03 (s, 2H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 191.1, 149.5, 138.2, 130.3, 127.6, 125.8, 124.3, 123.4, 121.6, 33.1 ppm; HRMS (ESI) calcd for $C_{10}H_7BrCl_2O_2$ $[M + H]^+$ 308.9085; found 308.9101.

*1-Bromo-4-(naphthalen-1-yl)but-3-en-2-one (**3m**).*[5g] The title compound was prepared via the general procedure A starting from 4-phenylbut-3-en-2-one (1.342 g, 6.84 mmol), SeO_2 (0.379 g, 3.420 mmol), NBS (**2**) (1.217 g, 6.84 mmol), and PTSA (0.650 g, 3.420 mmol) in toluene (3.0 mL) at 50 °C. The product was isolated by flash chromatography using hexane/ethyl acetate as an eluent (9:1): dark solid (1.373 g, 73% yield); mp 110 °C; IR (KBr film) 3049, 2937, 1689, 1600, 1381, 1346, 1098, 1063, 977, 789, 770, 585, 550 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, with 1% v/v TMS) δ 8.52 (d, J = 15.6 Hz, 1H), 8.13 (d, J = 8.4Hz, 1H), 7.87 (d, J = 8 Hz, 1H), 7.87 (d, J = 8 Hz, 1H), 7.82 (d, J = 7.6 Hz, 1H), 7.77 (d, J = 7.2 Hz, 1H), 7.55−7.42 (m, 3H), 6.99 (d, J = 15.6 Hz, 1H), 4.07 (s, 2H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 190.9, 142.2, 133.7, 131.7, 131.4, 131.2, 128.9, 127.2, 126.4, 125.5, 124.5, 123.2, 33.3 ppm; MS (ES^+) calcd for $C_{14}H_{12}BrO$ $[M + H]^+$ 275.00; found 275.23.

*1-Bromo-4-(naphthalen-2-yl)but-3-en-2-one (**3n**).*[5g,7] The title compound was prepared via the general procedure A starting from 4-phenylbut-3-en-2-one (1.342 g, 6.84 mmol), SeO_2 (0.379 g, 3.420 mmol), NBS (**2**) (1.217 g, 6.84 mmol), and PTSA (0.650 g, 3.420 mmol) in toluene (3.0 mL) at 50 °C. The product was isolated by flash chromatography using hexane/ethyl acetate as an eluent (9:1): brown solid (1.505 g, 80% yield); mp 78 °C; IR (KBr film) 3054, 2982, 2932, 1687, 1606, 1360, 1072, 978, 814, 745, 648 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, with 1% v/v TMS) δ 7.93 (s, 1H), 7.82−7.77 (m, 4H), 7.64 (dd, J = 8.8 Hz, 1H), 7.47 (t, J = 7.6 Hz, 2H), 6.99 (d, J = 16 Hz, 1H), 4.06 (s, 2H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 190.0, 144.5, 133.6, 133.2, 130.4, 130.2, 127.9, 126.8, 126.7, 125.9, 122.4, 121.2, 32.2 ppm; MS (ES^+) calcd for $C_{14}H_{12}BrO$ $[M + H]^+$ 275.00; found 275.23.

*4-([1,1′-Biphenyl]-4-yl)-1-bromobut-3-en-2-one (**3o**).*[5f,g] The title compound was prepared via the general procedure A starting from 4-phenylbut-3-en-2-one (1.520 g, 6.84 mmol),

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SeO_2 (0.379 g, 3.420 mmol), NBS (**2**) (1.217 g, 6.84 mmol), and PTSA (0.650 g, 3.420 mmol) in toluene (3.0 mL) at 50 °C. The product was isolated by flash chromatography using hexane/ethyl acetate as an eluent (9:1): brown solid (1.545 g, 75% yield); mp 120 °C; IR (KBr film) 3085, 3029, 2985, 2963, 1695, 1606, 1381, 1483, 1385, 1068, 983, 761, 654 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, with 1% v/v TMS) δ 7.74 (d, J = 16 Hz, 1H), 7.62 (d, J = 17.2 Hz, 5H), 7.45 (d, J = 6 Hz, 2H), 7.39 (d, J = 6.8 Hz, 2H), 6.91 (d, J = 15.6 Hz, 1H), 4.09 (s, 2H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 190.9, 144.9, 143.9, 139.9, 132.9, 129.2, 128.9, 128.1, 127.7, 127.1, 122.0, 33.1 ppm; MS (ES^+) calcd for $C_{16}H_{14}BrO$ $[M + H]^+$ 301.02; found 301.02.

*1-Bromo-4-(thiophen-2-yl)but-3-en-2-one (**3p**).* The title compound was prepared via the general procedure A starting from 4-phenylbut-3-en-2-one (1.041 g, 6.84 mmol), SeO_2 (0.379 g, 3.420 mmol), NBS (**2**) (1.217 g, 6.84 mmol), and PTSA (0.650 g, 3.420 mmol) in toluene (3.0 mL) at 50 °C. The product was isolated by flash chromatography using hexane/ethyl acetate as an eluent (9:1): dark brown solid (1.043 g, 66% yield); mp 60−70 °C; IR (KBr film) 3005, 2946, 2856, 1674, 1590, 1416, 1154, 1002, 714 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, with 1% v/v TMS) δ 7.76 (d, J = 15.6 Hz, 1H), 7.39 (d, J = 5.2 Hz, 1H), 7.29 (d, J = 3.6 Hz, 1H), 7.03 (t, J = 4.8 Hz, 1H), 6.68 (d, J = 15.6 Hz, 1H), 3.98 (s, 2H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 190.1, 137.2, 132.4, 129.4, 128.0, 126.9, 120.3, 32.7 ppm; HRMS (ESI) calcd for C_8H_1BrOS $[M + H]^+$ 230.9479; found 230.9488.

*1,1-Dibromo-4-phenylbut-3-en-2-one (**4a**).*[11] The title compound was prepared via the general procedure B starting from 4-phenylbut-3-en-2-one (1.000 g, 6.840 mmol), SeO_2 (0.759 g, 6.840 mmol), NBS (**2**) (2.435 g, 13.680 mmol), and PTSA (1.301 g, 6.840 mmol) in toluene (2.5 mL) at 80 °C. The desired product obtained was isolated by flash chromatography using hexane/ethyl acetate as an eluent (9:1): reddish brown semisolid, (1.808 g, 87% yield); IR (KBr film) 3058, 3022, 1686, 2922, 2852, 1686, 1608, 1494, 1448, 1331, 1135, 1062, 980, 728 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, with 1% v/v TMS) δ 7.80 (d, J = 15.6 Hz, 1H), 7.58 (q, J = 1.2 Hz, 3H), 7.37 (q, J = 2.8 Hz, 1H), 7.22 (d, J = 16 Hz, 1H), 5.86 (s, 1H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 185.5, 147.6, 133.8, 131.4, 139.0, 128.8, 117.7, 42.6 ppm; HRMS (ESI) calcd for $C_{10}H_9Br_2O$ $[M + H]^+$ 304.9000; found 304.8990.

*1,1-Dibromo-4-(p-tolyl)but-3-en-2-one (**4b**).* The title compound was prepared via the general procedure B starting from 4-phenylbut-3-en-2-one (1.095 g, 6.840 mmol), SeO_2 (0.759 g, 6.840 mmol), NBS (**2**) (2.435 g, 13.680 mmol), and PTSA (1.301 g, 6.840 mmol) in toluene (2.5 mL) at 80 °C. The desired product obtained was isolated by flash chromatography using hexane/ethyl acetate as an eluent (9:1): brown solid (1.979 g, 91% yield); mp 80 °C; IR (KBr film) 3027, 2964, 2918, 1671, 1591, 1564, 1329, 1138, 809, 750, 586 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, with 1% v/v TMS) δ 7.85 (d, J = 15.6 Hz, 1H), 7.54 (d, J = 8 Hz, 2H), 7.24 (d, J = 8 Hz, 1H), 7.24 (d, J = 15.6 Hz, 1H), 5.93 (s, 1H), 2.41 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 185.7, 147.8, 142.2, 131.1, 129.8, 128.9, 116.7, 42.7, 21.6 ppm; HRMS (ESI) calcd for $C_{11}H_{11}Br_2O$ $[M + H]^+$ 318.9156; found 318.9155.

*1,1-Dibromo-4-(4-fluorophenyl)but-3-en-2-one (**4c**).* The title compound was prepared via the general procedure B starting from 4-phenylbut-3-en-2-one (1.123 g, 6.840 mmol), SeO_2 (0.759 g, 6.840 mmol), NBS (**2**) (2.435 g, 13.680 mmol), and PTSA (1.301 g, 6.840 mmol) in toluene (2.5 mL) at 80 °C. The desired product obtained was isolated by flash chromatography using hexane/ethyl acetate as an eluent (9:1): brown solid, (1.938 g, 88% yield); mp 85−90 °C; IR (KBr film) 3336, 3252, 3172, 3103, 3075, 3024, 1831, 1842, 1765, 1725, 1673, 1600, 1499, 1408, 1353, 1227, 940, 919, 775, 752, 399, 635, 586, 514 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, with 1% v/v TMS) δ 7.84 (d, J = 16 Hz, 1H), 7.65 (q, J = 2.8 Hz, 2H), 7.26 (d, J = 6 Hz, 2H), 7.14 (s, 1H), 7.14 (d, J = 16.8 Hz, 1H), 5.92 (s, 1H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 185.4, 164.5, (J = 251.9 Hz), 146.3, 130.9 (d, J = 8.7 Hz), 130.1 (d, J = 2.3 Hz), 117.4 (d, J = 2.5 Hz), 116.3 (d, J = 21.9 Hz), 42.5 ppm; HRMS (ESI) calcd for $C_{10}H_7Br_2FO$ $[M + H]^+$ 322.8905; found 322.8878.

*1,1-Dibromo-4-(4-chlorophenyl)but-3-en-2-one (**4d**).* The title compound was prepared via the general procedure B starting from 4-phenylbut-3-en-2-one (1.235 g, 6.840 mmol), SeO_2 (0.759 g, 6.840 mmol), NBS (**2**) (2.435 g, 13.680 mmol), and PTSA (1.301 g, 6.840 mmol) in toluene (2.5 mL) at 80 °C. The desired product obtained was isolated by flash chromatography using hexane/ethyl acetate as an eluent (9:1): brown solid (2.037 g, 88% yield); mp 110 °C; IR (KBr film) 3093, 3019, 1672, 1597, 1561, 1401, 1351, 1109, 1087 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, with 1% v/v TMS) δ 7.82 (d, J = 15.6 Hz, 1H), 7.57 (d, J = 8.4 Hz, 2H), 7.41 (d, J = 8.4 Hz, 2H), 7.27 (d, J = 15.6. Hz, 2H), 5.92 (s, 1H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 185.3, 146.1, 137.4, 132.2, 130.0, 129.3, 118.1, 42.5 ppm; HRMS (ESI) calcd for $C_{10}H_8Br_2ClO$ $[M + H]^+$ 338.8610; found 338.8575.

*1,1-Dibromo-4-(4-bromophenyl)but-3-en-2-one (**4e**).* The title compound was prepared via the general procedure B starting from 4-phenylbut-3-en-2-one (1.539 g, 6.840 mmol), SeO_2 (0.759 g, 6.840 mmol), NBS (**2**) (2.435 g, 13.680 mmol), and PTSA (1.301 g, 6.840 mmol) in toluene (2.5 mL) at 80 °C. The desired product obtained was isolated by flash chromatography using hexane/ethyl acetate as an eluent (9:1): yellow solid (2.330 g, 89% yield); mp 138 °C; IR (KBr film) 3093, 3054, 3015, 1672, 1600, 1581, 1558, 1481, 1326, 1109, 1065, 944, 711, 563 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, with 1% v/v TMS) δ 7.73 (d, J = 15.6 Hz, 1H), 7.51 (d, J = 8.8 Hz, 2H), 7.43 (d, J = 8.4 Hz, 2H), 7.22 (d, J = 16 Hz, 1H), 5.85 (s, 1H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 185.3, 146.2, 132.7, 132.3, 130.2, 125.9, 118.3, 42.5 ppm; HRMS (ESI) calcd for $C_{10}H_8Br_3O$ $[M + H]^+$ 382.8105; found 382.8098.

*1,1-Dibromo-4-(2-chlorophenyl)but-3-en-2-one (**4f**).* The title compound was prepared via the general procedure B starting from 4-phenylbut-3-en-2-one (1.235 g, 6.840 mmol), SeO_2 (0.759 g, 6.840 mmol), NBS (**2**) (2.435 g, 13.680 mmol), and PTSA (1.301 g, 6.840 mmol) in toluene (2.5 mL) at 80 °C. The desired obtained product was isolated by flash chromatography using hexane/ethyl acetate as an eluent (9:1): light yellow crystalline solid (1.990 g, 86% yield); mp 100−105 °C; IR (KBr film) 3018, 1760, 1674, 1466, 1437, 1324, 1266, 1199, 1142, 1043, 973, 921, 741, 681, 616, 586, 565 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, with 1% v/v TMS) δ 8.23 (d, J = 16 Hz, 1H), 7.70 (q, J = 5.6 Hz, 1H), 7.40 (dd, J = 8 Hz, 1H), 7.30−7.27 (m, 2H), 7.23 (d, J = 16 Hz, 1H), 5.88 (s, 1H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 185.2, 143.2, 135.9, 132.1, 130.4, 128.1, 127.2, 120.123, 42.4 ppm; HRMS (ESI) calcd for $C_{10}H_8Br_2ClO$ $[M + H]^+$ 338.8610; found 338.3410.

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1,1-Dibromo-4-(3-fluorophenyl)but-3-en-2-one (**4g**). The title compound was prepared via the general procedure B starting from 4-phenylbut-3-en-2-one (1.123 g, 6.840 mmol), SeO_2 (0.759 g, 6.840 mmol), NBS (**2**) (2.435 g, 13.680 mmol), and PTSA (1.301 g, 6.840 mmol) in toluene (2.5 mL) at 80 °C. The desired obtained product was isolated by flash chromatography using hexane/ethyl acetate as an eluent (9:1): brown solid, (1.915 g, 87% yield); mp 70 °C; IR (KBr film) 3060, 3027, 2964, 1685, 1612, 1577, 1486, 1444, 1323, 1238, 1163, 943, 790, 749, 699, 566, 561 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, with 1% v/v TMS) δ 7.82 (d, J = 15.6 Hz, 1H), 7.41 (t, J = 4 Hz, 2H), 7.34 (d, J = 9.6 Hz, 1H), 7.30 (d, J = 16 Hz, 1H), 7.18−7.13 (m, 1H), 5.93 (s, 1H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 185.3, 162.9 (J = 246.1 Hz), 146.1 (d, J = 2.9 Hz), 136.0 (d, J = 7.7 Hz), 130.6 (d, J = 8.1 Hz), 124.9 (d, J = 2.9 Hz), 119.0, 118.3 (d, J = 21.3 Hz), 114.9 (d, J = 21.8 Hz), 42.4 ppm; HRMS (ESI) calcd for $C_{10}H_7Br_2FO$ $[M + H]^+$ 322.8905; found 322.8878.

1,1-Dibromo-4-(3-bromophenyl)but-3-en-2-one (**4h**). The title compound was prepared via the general procedure B starting from 4-phenylbut-3-en-2-one (1.539 g, 6.840 mmol), SeO_2 (0.759 g, 6.840 mmol), NBS (**2**) (2.435 g, 13.680 mmol), and PTSA (1.301 g, 6.840 mmol) in toluene (2.5 mL) at 80 °C. The desired product obtained was isolated by flash chromatography using hexane/ethyl acetate as an eluent (9:1): yellow solid (2.252 g, 86% yield); mp 56−60 °C; IR (KBr film) 3018, 2922, 1689, 1611, 1562, 1471, 1315, 1135, 786 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, with 1% v/v TMS) δ 7.72 (d, J = 16 Hz, 1H), 7.71 (s, 1H), 7.49 (t, J = 9.2 Hz, 2H), 7.26 (d, J = 8 Hz, 1H), 7.23 (d, J = 2.8 Hz, 1H), 5.85 (s, 1H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 185.2, 145.8, 135.9, 134.1, 131.3, 130.6, 127.6, 123.2, 119.1, 42.4 ppm; HRMS (ESI) calcd for $C_{10}H_8Br_3O$ $[M + H]^+$ 382.8105; found 382.8098.

1,1-Dibromo-4-(3-nitrophenyl)but-3-en-2-one (**4i**). The title compound was prepared via the general procedure B starting from 4-phenylbut-3-en-2-one (1.307 g, 6.840 mmol), SeO_2 (0.759 g, 6.840 mmol), NBS (**2**) (2.435 g, 13.680 mmol), and PTSA (1.301 g, 6.840 mmol) in toluene (2.5 mL) at 80 °C. The desired product obtained was isolated by flash chromatography using hexane/ethyl acetate as an eluent (9:1): brown solid (2.100 g, 88% yield); mp 140 °C; IR (KBr film) 3093, 3044, 1686, 1614, 1524, 1351, 1140, 992, 814, 725 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, with 1% v/v TMS) δ 8.430 (s, 1H), 8.24 (d, J = 1.2 Hz, 1H), 8.23 (d, J = 1.2 Hz, 1H), 7.86 (q, J = 3.2 Hz, 1H), 7.59 (t, J = 8 Hz, 1H), 7.36 (d, J = 15.6 Hz, 1H), 5.87 (s, 1H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 183.8, 147.7, 143.4, 133.5, 129.2, 124.4, 121.9, 119.6, 41.2 ppm; HRMS (ESI) calcd for $C_{10}H_8Br_2NO_3$ $[M + H]^+$ 349.8850; found 349.8838.

1,1-Dibromo-4-(2,3-dimethoxyphenyl)but-3-en-2-one (**4j**). The title compound was prepared via the general procedure B starting from 4-phenylbut-3-en-2-one (1.410 g, 6.840 mmol), SeO_2 (0.759 g, 6.840 mmol), NBS (**2**) (2.435 g, 13.680 mmol), and PTSA (1.301 g, 6.840 mmol) in toluene (2.5 mL) at 80 °C. The desired product obtained was isolated by flash chromatography using hexane/ethyl acetate as an eluent (9:1): green solid (2.141 g, 86% yield); mp 78 °C; IR (KBr film) 3005, 2964, 2936, 2835, 1687, 1605, 1576, 1476, 1267, 1000, 802, 749 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, with 1% v/v TMS) δ 8.11 (d, J = 16 Hz, 1H), 7.29 (d, J = 16 Hz, 1H), 7.20 (d, J = 6.8 Hz, 1H), 7.04 (t, J = 8 Hz, 1H), 6.93 (d, J = 8.4 Hz, 1H), 5.88 (s, 1H), 3.83 (s, 6H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 184.8, 152.2, 148.3, 141.4, 126.9, 123.3, 118.8, 118.1, 113.9, 60.5, 54.9, 41.7 ppm; HRMS (ESI) calcd for $C_{12}H_{13}B_2O_3$ $[M + H]^+$ 364.9211; found 364.9223.

1,1-Dibromo-4-(3,4,5-trimethoxyphenyl)but-3-en-2-one (**4k**). The title compound was prepared via the general procedure B starting from 4-phenylbut-3-en-2-one (1.616 g, 6.840 mmol), SeO_2 (0.759 g, 6.840 mmol), NBS (**2**) (2.435 g, 13.680 mmol), and PTSA (1.301 g, 6.840 mmol) in toluene (2.5 mL) at 80 °C. The desired obtained product was isolated by flash chromatography using hexane/ethyl acetate as an eluent (9:1): light yellow solid, (2.264 g, 84% yield); mp 100−105 °C; IR (KBr film) 3000, 2935, 1690, 1599, 1553, 1479, 1420, 1390, 1349, 1290, 1252, 1200, 1162, 1105, 1072, 1043, 1004, 975, 923, 856, 813, 745, 724, 679, 649, 608, 586, 565 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, with 1% v/v TMS) δ 8.3 (d, J = 15.6 Hz, 1H), 7.41 (s, 1H), 7.15 (d, J = 15.6 Hz, 1H), 7.04 (s, 1H), 5.98 (s, 1H), 3.95 (s, 6H), 3.91 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 185.1, 152.9, 146.0, 129.1, 119.3, 106.4, 61.3, 61.0, 56.4, 42.3 ppm; HRMS (ESI) calcd for $C_{13}H_{15}Br_2O_4$ $[M + H]^+$ 394.9317; found 394.9281

1,1-Dibromo-4-(naphthalen-1-yl)but-3-en-2-one (**4m**). The title compound was prepared via the general procedure B starting from 4-phenylbut-3-en-2-one (1.342 g, 6.840 mmol), SeO_2 (0.759 g, 6.840 mmol), NBS (**2**) (2.435 g, 13.680 mmol), and PTSA (1.301 g, 6.840 mmol) in toluene (2.5 mL) at 80 °C. The desired obtained product was isolated by flash chromatography using hexane/ethyl acetate as an eluent (9:1): yellow solid, (1.937 g, 80% yield); mp 30−35 °C; IR (KBr film) 3047, 2924, 2853, 1667, 1595, 1574, 1246, 1198, 1144, 108, 1030, 848, 743, 699, 581 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, with 1% v/v TMS) δ 8.75 (d, J = 15.2 Hz, 1H), 8.24 (d, J = 8.4 Hz, 1H), 7.97−7.89 (m, 3H), 7.64−7.52 (m, 3H), 7.41 (d, J = 15.2 Hz, 1H), 5.98 (s,1H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 185.6, 144.4, 133.7, 131.8, 131.7, 131.1, 128.9, 127.3, 126.5, 125.8, 125.4, 123.2, 120.1, 42.7 ppm; HRMS (ESI) calcd for $C_{14}H_{11}Br_2O$ $[M + H]^+$ 354.9156; found 354.9200.

1,1-Dibromo-4-(naphthalen-2-yl)but-3-en-2-one (**4n**). The title compound was prepared via the general procedure B starting from 4-phenylbut-3-en-2-one (1.342 g, 6.840 mmol), SeO_2 (0.759 g, 6.840 mmol), NBS (**2**) (2.435 g, 13.680 mmol), and PTSA (1.301 g, 6.840 mmol) in toluene (2.5 mL) at 80 °C. The desired product obtained was isolated by flash chromatography using hexane/ethyl acetate as an eluent (9:1): yellow solid, (1.985 g, 82% yield); mp 75 °C; IR (KBr film) 3052, 3010, 2962, 2926, 1679, 1598, 1359, 1129, 960, 812, 750, 578 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, with 1% v/v TMS) δ 8.04−8.00 (m, 2H), 7.87 (d, J = 8 Hz, 3H), 7.76 (d, J = 8 Hz, 2H), 7.57 (d, J = 3.2 Hz, 2H), 7.39 (d, J = 15.6 Hz, 1H), 5.97 (s, 1H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 185.6, 147.8, 134.8, 133.2, 131.5 (d, J = 9.3 Hz), 128.9 (d, J = 6.0 Hz), 127.9 (d, J = 2.4 Hz), 126.9, 123.7, 117.9, 42.7 ppm; HRMS (ESI) calcd for $C_{14}H_{11}Br_2O$ $[M + H]^+$ 354.9156; found 354.9200.

4-([1,1′-Biphenyl]-4-yl)-1,1-dibromobut-3-en-2-one (**4o**). The title compound was prepared via the general procedure B starting from 4-phenylbut-3-en-2-one (1.520 g, 6.840 mmol), SeO_2 (0.759 g, 6.840 mmol), NBS (**2**) (2.435 g, 13.680 mmol), and PTSA (1.301 g, 6.840 mmol) in toluene (2.5 mL) at 80 °C. The desired product obtained was isolated by flash chromatography using hexane/ethyl acetate as an eluent (9:1): yellow solid, (2.079 g, 80% yield); mp 76 °C; IR (KBr film) 3081, 3014, 2962, 2854, 1680, 1604, 1325, 1141,

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951, 804, 747, 689, 561 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, with 1% v/v TMS) δ 7.91 (d, J = 15.6 Hz, 1H), 7.72−7.61 (m, J = 9.6 Hz, 5H), 7.47 (t, J = 7.2 Hz, 2H), 7.40 (d, J = 6.8 Hz, 2H), 7.32 (d, J = 15.6 Hz, 1H), 5.95 (s, 1H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 185.5, 147.2, 144.247, 139.9, 132.8, 129.4, 128.9, 128.1, 127.7, 127.1, 117.6, 42.6 ppm; HRMS (ESI) calcd for $C_{16}H_{13}Br_2O$ $[M + H]^+$ 380.9313; found 380.9327.

*1,1-Dibromo-4-(thiophen-2-yl)but-3-en-2-one (**4p**).* The title compound was prepared via the general procedure B starting from 4-phenylbut-3-en-2-one (1.041 g, 6.840 mmol), SeO_2 (0.759 g, 6.840 mmol), NBS (**2**) (2.435 g, 13.680 mmol), and PTSA (1.301 g, 6.840 mmol) in toluene (2.5 mL) at 80 °C. The desired product obtained was isolated by flash chromatography using hexane/ethyl acetate as an eluent (9:1): brown solid, (1.653 g, 78% yield); mp 58 °C; IR (KBr film) 3009, 2948, 1674, 1592, 1155, 713 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, with 1% v/v TMS) δ 7.96 (d, J = 15.2 Hz, 1H), 7.48 (d, J = 5.2 Hz 1H), 7.39 (d, J = 3.6 Hz, 1H), 7.10 (t, J = 4.2 Hz, 1H), 7.00 (d, J = 15.2 Hz, 1H), 5.89 (s, 1H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 185.4, 139.9, 139.3, 133.2, 130.4, 128.5, 116.4, 42.4 ppm; HRMS (ESI) calcd for $C_8H_7Br_2OS$ $[M + H]^+$ 310.8564; found 310.8557.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.1c04352.

CIF file for compound 3i .cif (CIF)

CIF file for compound 4f .cif (CIF)

Single-crystal XRD data of **3i** and **4f** and copies of ^1H and ^{13}C NMR spectra of all synthesized compounds **3a**−**3p** and **4a**−**4p** (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Bekington Myrboh − *Department of Chemistry, North-Eastern Hill University, Shillong, Meghalaya 793022, India;* orcid.org/0000-0001-9349-2216; Email: bmyrboh@nehu.ac.in

Authors

Tyrchain Mitre Lipon − *Department of Chemistry, North-Eastern Hill University, Shillong, Meghalaya 793022, India*

Ibakyntiew D. Marpna − *Department of Chemistry, North-Eastern Hill University, Shillong, Meghalaya 793022, India*

Kmendashisha Wanniang − *Department of Chemistry, North-Eastern Hill University, Shillong, Meghalaya 793022, India*

O. Risuklang Shangpliang − *Department of Chemistry, North-Eastern Hill University, Shillong, Meghalaya 793022, India*

Badaker M. Laloo − *Department of Chemistry, North-Eastern Hill University, Shillong, Meghalaya 793022, India*

Rishanlang Nongkhlaw − *Department of Chemistry, North-Eastern Hill University, Shillong, Meghalaya 793022, India;* orcid.org/0000-0001-8193-5833

Complete contact information is available at: https://pubs.acs.org/10.1021/acsomega.1c04352

Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) De Kimpe, N.; Verhe, R. In Chemistry of α-Haloketones, α-Haloaldehydes and α-Haloimines. Patai, S., Ed, Wiley, Chichester, 1988, pp 1−119. (b) Hoyle, J. *Patai's Chemistry of Functional Groups*, Some Synthetic Uses of halides, Willey, 2009, pp 1−77.

(2) (a) Erian, A.; Sherif, S.; Gaber, H. The Chemistry of α-Haloketones and Their Utility in Heterocyclic Synthesis. *Molecules* **2003**, *8*, 793−865. (b) Jiang, J.; Zou, H.; Dong, Q.; Wang, R.; Lu, L.; Zhu, Y.; He, W. Synthesis of 2-Keto(hetero)aryl Benzox(thio)azoles through Base Promoted Cyclization of 2-Amino(thio)phenols with α,α-Dihaloketones. *J. Org. Chem.* **2016**, *81*, 51−56. (c) Talegaonkar, J.; Mukhija, S.; Boparai, K. S. Determination of thiosemicarbazones by reaction with omega-bromoacetophenone. *Talanta* **1982**, *29*, 327−328. (d) Marek, A.; Kulhanek, J.; Ludwig, M.; Bures, F. Facile Synthesis of Optically Active Imidazole Derivatives. *Molecules* **2007**, *12*, 1183−1190. (e) Loughlin, W. A. A Heterocyclic Chemist's Perspective. *Aust. J. Chem.* **1998**, *51*, 875−894. (f) Cho, J.; Kim, K. Reaction of Tetrasulfur Tetranitride with Bromomethyl Ketones. *J. Heterocycl. Chem.* **1992**, *29*, 1433−1439. (g) Fülöpovaá, V.; Soural, M. Solid-Phase Synthesis of Heterocycles with α-Haloketones as the Key Building Blocks. *Synthesis* **2016**, *48*, 3684−3695. (h) Alajarín, M.; Cabrera, J.; Pastor, A.; Sánchez-Andrada, P.; Bautista, D. Diels-Alder Reactions of 4-Alkenylthiazoles: A New Approach to Thiazole Functionalization. *J. Org. Chem.* **2007**, *72*, 2097−2105.

(3) Li, X.-C.; Ferreira, D.; Jacob, M. R.; Zhang, Q.; Khan, S. I.; ElSohly, H. N.; Nagle, D. G.; Smillie, T. J.; Khan, I. A.; Walker, L. A.; Clark, A. M. Antifungal Cyclopentenediones from Piper coruscans. *J. Am. Chem. Soc.* **2004**, *126*, 6872−6873.

(4) (a) Conde, S.; Pérez, D. I.; Martínez, A.; Perez, C.; Moreno, F. J. Thienyl and Phenyl α-Halomethyl Ketones: New Inhibitors of Glycogen Synthase Kinase (GSK-3â) from a Library of Compound Searching. *J. Med. Chem.* **2003**, *46*, 4631−4633. (b) Arabaci, G.; Guo, X.-C.; Beebe, K. D.; Coggeshall, K. M.; Pei, D. α-Haloacetophenone Derivatives As Photoreversible Covalent Inhibitors of Protein Tyrosine Phosphatases. *J. Am. Chem. Soc.* **1999**, *121*, 5085−5086.

(5) (a) Larock, R. C. A Guide to Functional Group Preparations. In *Comprehensive Organic Transformations*, 2nd ed., VCH-New York, Wiley, 1999, pp 715−719. (b) Yunus, U.; Winterfeldt, E. Studies on α-Bromination of Ketone in Hydrindane Ring System. *J. Chin. Chem. Soc.* **2007**, *54*, 1087−1092. (c) Dagani, M. J.; Barda, H. J.; Benya, T. J.; Sanders, D. C. Ullmann's Encyclopedia of Industrial Chemistry, In *Bromine Compounds*, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, 2002, Vol *6*, pp 331−358. (d) Qin, N.; Li, C.-B.; Jin, M.-N.; Shi, L.-H.; Duan, H.-Q.; Niu, W.-Y. Synthesis and biological activity of novel tiliroside derivants. *Eur. J. Med. Chem.* **2011**, *46*, 5189−5195. (e) Musso, L.; Cincinelli, R.; Zuco, V.; Zunino, F.; Nurisso, A.; Cuendet, M.; Giannini, G.; Vesci, L.; Pisano, C.; Dallavalle, S. Investigation on the ZBG-functionality of phenyl-4-yl-acrylohydroxamic acid derivatives as histone deacetylase inhibitors. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 4457−4460. (f) Revuelto, A.; Ruiz-Santaquiteria, M.; de Lucio, H.; Gamo, A.; Carriles, A. A.; Gutiérrez, K. J.; Sanchez-Murcia, P. A.; Hermoso, J. A.; Gago, F.; Camarasa, M.-J.; Jiménez-Ruiz, A.; Velazquez, S. Pyrrolopyrimidine vs Imidazole-Phenyl-Thiazole Scaffolds in Nonpeptidic Dimerization Inhibitors ofLeishmania infantum Trypanothione Reductase. *ACS Infect. Dis.* **2019**, *5*, 873−891. (g) Sadhukan, S.; Santhi, J.; Baire, B. The *a,a*-Dihalocarbonyl Building Blocks: An Avenue for New Reaction Development in Organic Synthesis. *Chem. - Eur. J.* **2020**, *26*, 7145−7175. (h) Imperiali, B.; Abeles, R. H. Inhibition of Serine Proteases by Peptidyl Fluoromethyl Ketones. *Biochemistry* **1986**, *25*, 3760−3767.

(i) Fäh, C.; Hardegger, L. A.; Baitsch, L.; Schweizer, W. B.; Meyer, S.; Bur, D.; Diederich, F. New organofluorine building blocks: inhibition of the malarial aspartic proteases plasmepsin II and IV by alicyclic α,α-difluoroketone hydrates. *Org. Biomol. Chem.* **2009**, *7*, 3947−3957. (j) Babu, K. S.; Li, X.-C.; Jacob, M. R.; Zhang, Q.; Khan, S. I.; Ferreira, D.; Clark, A. M. Synthesis, Antifungal Activity, and Structure-Activity Relationships of Coruscanone A Analogues. *J. Med. Chem.* **2006**, *49*, 7877−7886.

(6) (a) Zhang, W.; Curran, D. P.; Chen, C. H.-T. Use of fluorous silica gel to separate fluorous thiol quenching derivatives in solutions-phase parallel synthesis. *Tetrahedron* **2002**, *58*, 3871−3875. (b) Harwood, H. Reactions of the Hydrocarbon chain of fatty acids. *Chem. Rev.* **1962**, *62*, 99−154.

(7) Ngo, Q. A.; Nguyen, L. A.; Vo, N. B.; Nguyen, T. H.; Roussi, F.; Nguyen, T. H.; Nguyen, V. T. Synthesis and antiproliferative activity of new vinca alkaloids containing an *a,ß*-unsaturated aromatic side chain. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 5597−5600.

(8) (a) Curran, D. P.; Chang, C.-T. Atom Transfer Cyclization Reactions of α-Iodo Esters, Ketones, and Malonates: Examples of selectives 5-Exo, 6-Endo, 6-Exo, and 7-Endo Ring Closures. *J. Org. Chem.* **1989**, *54*, 3140−3157. (b) Karimi, S.; Grohmann, K. G. Intramolecular Ring-Opening of Cyclopopranone by Enolate Anions. *J. Org. Chem.* **1995**, *60*, 554−559. (c) Kumar, R. S.; Kulangiappar, K.; Kulandainathan, M. A. Convenient Electrochemical Method for the Synthesis of α-Bromo Alkyl Aryl Ketones. *Synth. Commun.* **2010**, *40*, 1736−1742. (d) Sultan, A.; Abbas, M.; Raza, A. R.; Tahir, M. N. Optimization of Conditions for the Facile, Efficient & Selective α-Bromination of Methyl And Methylene Ketones. *Sci. Int.* **2017**, *29*, 875−882. (e) Tanemura, K.; Suzuki, T.; Nishida, Y.; Satsumabayashi, K.; Horaguchi, T. A mild and efficient procedure for *a*-bromination of ketones using N-bromosuccinimide catalysed by ammonium acetate. *Chem. Commun* **2004**, *4*, 470−471. (f) Vražič, D.; Jereb, M.; Laali, K. K.; Stavber, S. Brønsted Acidic Ionic Liquid Accelerated Halogenation of Organic Compounds with N-Halosuccinimides (NXS). *Molecules* **2013**, *18*, 74−96. (g) Terent'ev, A. O.; Khodykin, S. V.; Krylov, I. B.; Ogibin, Y. N.; Nikishin, G. I. A Convenient Synthesis of 2,2-Dibromo-1-arylethanones by Bromination of 1-Arylethanones with the H_2O_2−HBr System. *Synthesis* **2006**, 1087−1092. (h) Jagatheesan, R.; Raj, K. J. S.; Lawrence, S.; Christopher, C. Electroselective α-bromination of acetophenone using in situ bromonium ions from ammonium bromide. *RSC Adv.* **2016**, *6*, 35602−35608. (i) Nobuta, T.; Hirashima, S.; Tada, N.; Miura, T.; Itoh, A. Facile aerobic photo-oxidative synthesis of α,α-dibromoacetophenones from alkynes with 48% aq HBr. *Tetrahedron Lett.* **2010**, *51*, 4576−4578. (j) Madabhushi, S.; Jillella, R.; Mallu, K. K. R.; Godala, K. R.; Vangipuram, V. S. A new and efficient method for the synthesis of α,α-dihaloketones by oxyhalogenation of alkynes using oxone-KX. *Tetrahedron Lett.* **2013**, *54*, 3993−3996. (k) Chawla, R.; Singh, A. K.; Yadav, L. D. S. Catalyst- and Metal-Free Rapid Functionalizations of Alkynes Using TsNBr2. *Synlett* **2013**, *24*, 1558−1562.

(9) (a) Xie, L.; Wu, Y.; Yi, W.; Zhu, L.; Xiang, J.; He, W. Gold-Catalyzed Hydration of Haloalkynes to α-Halomethyl Ketones. *J. Org. Chem.* **2013**, *78*, 9190−9195. (b) Chen, Z.-W.; Ye, D.-N.; Ye, M.; Zhou, Z.-G.; Li, S.-H.; Liu, L.-X. AgF/TFA-promoted highly efficient synthesis of α-haloketones from haloalkynes. *Tetrahedron Lett.* **2014**, *55*, 1373−1375.

(10) Calo', V.; Lopez, L.; Pesce, G.; Todesco, P. E. Contribution to the Bromination of Conjugate Unsaturated Ketones Synthesis of a,ß-Unsaturated Bromo Ketones. *Tetrahedron* **1973**, *29*, 1625−1628.

(11) Cristau, H.-J.; Toreiles, E.; Morand, P.; Christol, H. Tribromures De Phosphoniums. Agents De Bromation De Substrats Organiques. *Phosphorus Sulfur Relat. Elem.* **1985**, *25*, 357−367.

(12) Mitani, M.; Kobayashi, T.; Koyama, K. α′-Bromination of α,β-Unsaturated Ketones by an Electrochemical Procedure. *J. Chem. Soc., Chem. Commun.* **1991**, *20*, 1418−1419.

(13) Pace, V.; Castoldi, L.; Holzer, W. Synthesis of α,β-Unsaturated α′-Haloketones through the Chemoselective Addition of Halomethyllithiums to Weinreb Amides. *J. Org. Chem.* **2013**, *78*, 7764−7770.

(14) (a) Laloo, B. M.; Mecadon, H.; Rohman, M. R.; Kharbangar, I.; Kharkongor, I.; Rajbangshi, M.; Nongkhlaw, R.; Myrboh, B. Reaction of Selenium Dioxide with Aromatic Ketones in the presence of Boron Trifluoride Etherate: A Protocol for the Synthesis of Triarylethanones. *J. Org. Chem.* **2012**, *77*, 707−712. (b) Rohman, M. R.; Kharkongor, I.; Rajbangshi, M.; Mecadon, H.; Laloo, B. M.; Sahu, P. R.; Kharbangar, I.; Myrboh, B. One-Pot Synthesis of Unsymmetrical Benzils by Oxidative Coupling Using Selenium Dioxide and *p*-Toluenesulfonic Acid Monohydrate. *Eur. J. Org. Chem.* **2012**, *2012*, 320−328. (c) Shangpliang, O. R.; Kshiar, B.; Wanniang, K.; Marpna, I. D.; Lipon, T. M.; Laloo, B. M.; Myrboh, B. Selenium Dioxide As an Alternative Reagent for the Direct α-Selenoamidation of Aryl Methyl Ketones. *J. Org. Chem.* **2018**, *83*, 5829−5835.

(15) (a) Wohl, A. Bromination of Unsaturated Compounds with *N*-Bromoacetamide. A Contribution to the Study of the Course of Chemical Processes. *Ber. Dtsch. Chem. Ges. A/B* **1919**, *52*, 51−63. (b) Koval, I. V. N-Halo Reagents. N-Halosuccinimides in Organic Synthesis and in Chemistry of Natural Compounds. *Russ. J. Org. Chem.* **2002**, *38*, 301−337.

(16) (a) Lee, J. C.; Bae, Y. H.; Chang, S.-K. Efficient α-Halogenation of Carbonyl Compounds by N-Bromosuccinimide and N-Chlorosuccinimde. *Bull. Korean Chem. Soc.* **2003**, *24*, 407−408. (b) Das, B.; Venkateswarlu, K.; Mahender, G.; Mahender, I. A simple and efficient method for α-bromination of carbonyl compounds using N-bromosuccinimide in the presence of silica-supported sodium hydrogen sulfate as a heterogeneous catalyst. *Tetrahedron Lett.* **2005**, *46*, 3041−3044.

(17) Adhikari, M. V.; Samant, S. D. Sonochemical bromination of Acetophenones usings *p*-toluenesulfonic acid-N-bromosuccinimide. *Ultrason. Sonochem.* **2002**, *9*, 107−111.

(18) Furniss, B. S.; Hannaford, A. J.; Rogers, V.; Smith, P. W. G.; Tatchell, A. R. *Vogel's Textbook of Practical Organic Chemistry*, 4th ed., Longman, London, 1979, p 796.

(19) Awang, D. V. C.; Wolfe, S. Pyrrolidone hydrotribrornide: a brominating agent with selectivity for ketones. *Can. J. Chem.* **1969**, *47*, 706−709.

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