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Trifluoroacetic Acid-Mediated Oxidative Self-Condensation of Acetophenones in the Presence of SeO_2: A Serendipitous Approach for the Synthesis of Fused [1,3]Dioxolo[4,5-*d*][1,3]dioxoles

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

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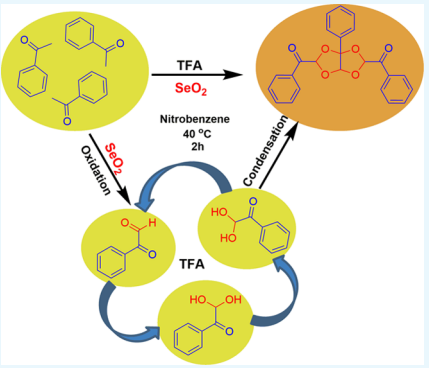
ABSTRACT: A method for the synthesis of fused 1,3-dioxolanes was developed by self-condensation of glyoxal generated *in situ* by oxidation of acetophenones with SeO_2 in the presence of trifluoroacetic acid. Three molecules of the glyoxal generated by oxidation of ketone with SeO_2 condensed to form architecturally novel oxygen-containing heterocycles (3a-aryldihydro-[1,3]dioxolo[4,5-*d*][1,3] dioxole-2,5-diyl)bis-(phenylmethanones). This reaction provides a unique methodology for the construction of four C−O bonds in a concerted fashion, generating highly embedded oxygen heterocycles from readily available ketones using affordable shelf reagents and simple reaction conditions.

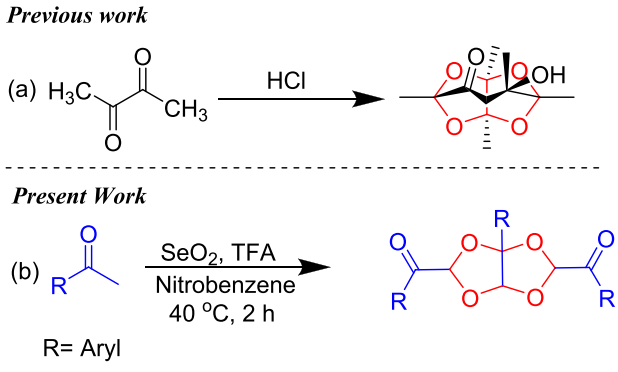


INTRODUCTION

Oxygen-containing heterocyclic molecules occur widely in nature and constitute an important class of compounds because of their diverse biological applications and utility as versatile intermediates in organic synthesis.[1] A recent report revealed that oxygen heterocycles are considered as the second most common type of heterocycle that form part of the structural components in many drugs.[2] Among them, 1,3-dioxolane is an important moiety frequently encountered as structural motifs in many oxygen-based drugs. Many such compounds have proven to be an effective 5-lipoxygenase inhibitor,[3] anti-obesity,[4] anti-HIV, anti-cancer,[5] and anti-Alzheimer's.[6] Over the past years, various synthetic protocols have been successfully developed for the synthesis of 1,3-dioxolane-based compounds.[7] The literature review revealed a wide range of heterocyclic compounds containing one or more 1,3-dioxolane moieties in their molecular framework.[8] To the best of our knowledge however, the only available method for the synthesis of fused 1,3-dioxalane was reported by Diels and Jost[9] in 1902 by the reaction of biacetyl with HCl to give a product, which was later deduced by Hudec and Turner[10] to be a fused dioxole biacetyl trimer (Scheme 1a). Therefore, development of a first method for the synthesis of such compounds having novel structural features will undoubtedly be of interest to synthetic organic chemists, particularly those working in the field of drug development and pharmaceuticals.

Earlier, we have successfully demonstrated that aryl/alkyl ketones react with arenes in the presence of SeO_2 and a Lewis acid ($BF_3{\cdot}Et_2O$) to give triaryl ethanones[11] via an Umpolung type of electrophilic addition at the α-carbon of the ketones. In the presence of an organic acid (PTSA) however, the aromatic ketones were converted to benzils[12] through the Riley oxidation pathway.[13] It was observed that the course of the

Scheme 1. (a, b) Synthesis of Compounds Containing a Fused 1,3-Dioxolane Moiety



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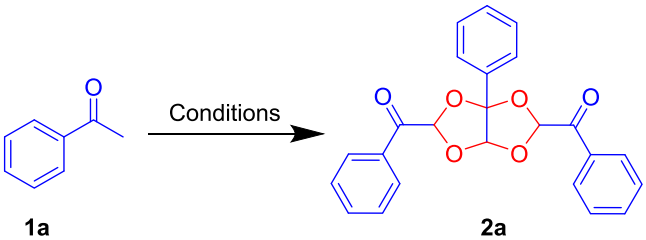
SeO_2-mediated reaction is dictated by the nature of the acid as well as the solvent used in a particular set of reactions. Thus, as part of our ongoing research on the synthetic utility of selenium dioxide in organic synthesis,[11,12,14] we wish to report here a direct and efficient one-step protocol for the synthesis of oxygen-based fused heterocyclic compounds (3a-aryldihydro-[1,3]dioxolo[4,5-*d*][1,3]dioxole-2,5-diyl)bis-(phenylmethanones) by self-condensation of arylglyoxals derived from arylketones in the presence of SeO_2 and trifluoroacetic acid (TFA) (Scheme 1b).

RESULTS AND DISCUSSION

For optimization of the reaction conditions, acetophenone was chosen as the model substrate. Initially, when 1 equiv of acetophenone **1a** was treated with 0.5 equiv of SeO_2 and 2 equiv of TFA in the presence of nitrobenzene at 40 °C, the condensed product **2a** was obtained at only 30% yield (Table 1, entry 1). When the amounts of SeO_2 and TFA were simultaneously increased to 1 and 4 equiv, respectively, the yield of product **2a** increased to 65% (Table 1, entry 3). An attempt to further increase the amount of either SeO_2 or the acid resulted in the formation of multiple spots while lowering the yield of the desired product (Table 1, entries 4 and 5). To further investigate the efficacy of the reaction, different solvents were screened and it was found that the reaction proceeded well with aromatic solvents like nitrobenzene, benzene, chlorobenzene, and toluene (Table 1, entries 3 and 6–8) but showed negative results with non-aromatic solvents like DMSO, acetonitrile, and DMF (Table 1, entries 9–11). Of all the aromatic solvents employed, it was found that the optimum yields were obtained when the reactions were carried out with nitrobenzene as the solvent (Table 1, entry 3). Next, the reactions were performed under the standard condition using the Lewis acid $BF_3{\cdot}Et_2O$ and protonic acids such as acetic acid and sulfuric acid to see if there was any improvement in the yields. The use of $BF_3{\cdot}Et_2O$ resulted in an intractable mass, while the two protonic acids did not give any product at all (Table 1, entries 12–14). It may be noted that product **2a** was not obtained in the absence of either TFA or SeO_2 even when the reaction temperature was increased up to 60 °C (Table 1, entries 15 and 16). Thus, the optimum condition for the reaction to give a satisfactory yield of 65% for compound **2a** requires 1 equiv of SeO_2, 4 equiv of TFA, employing nitrobenzene as the solvent at 40 °C, and a maximum reaction time of 2 h (Table 1, entry 3).

Table 1. Optimization of Reaction Conditions[a]



Sl no.	SeO_2 (equiv)	acid (equiv)	solvent	temperature (°C)	yield (%)[b]
1	0.5	TFA (2)	nitrobenzene	40	30
2	0.5	TFA (4)	nitrobenzene	40	45
3	1	TFA (4)	nitrobenzene	40	65
4	1.5	TFA (4)	nitrobenzene	40	40
5	1	TFA (5)	nitrobenzene	40	55
6	1	TFA (4)	benzene	40	50
7	1	TFA (4)	chlorobenzene	40	60
8	1	TFA (4)	toluene	40	50
9	1	TFA (4)	DMSO	60	
10	1	TFA (4)	acetonitrile	60	
11	1	TFA (4)	DMF	60	
12	1	$BF_3{\cdot}EtOH$	nitrobenzene	60	
13	1	acetic acid	nitrobenzene	60	
14	1	sulfuric acid	nitrobenzene	60	
15		TFA (4)	nitrobenzene	RT-60[c]	
16	1		nitrobenzene	RT-60[c]	

[a]Reaction was carried out with 1 equiv of **1a**. [b]Isolated yield. [c]Initially, the reaction was carried out at room temperature and then heated to 60 °C.

Equipped with the optimized reaction conditions, we proceeded to investigate the generality of the method by carrying out reactions with differently substituted aryl methyl ketones. It was observed that both electron-donating and electron-withdrawing substituents are equally compatible for the reaction to give products in moderate to good yields. Thus, irrespective of the nature of substitution on the benzene ring of the ketones, the *p*-substituted aryl methyl ketones (*p*-CH_3, *p*-OCH_3, *p*-Br, *p*-Cl, and *p*-F) reacted easily to give the corresponding products in satisfactory yields (**2b**, 70%; **2c**, 68%; **2d**, 70%; **2e**, 72%; **2f**, 75%) (Scheme 2). Similarly, *m*-substituted ketones (*m*-Cl, *m*-Br, and *m*-CH_3) displayed comparable reactivity, generating the desired products (**2g**, 60%; **2h**, 52%; **2i**, 62%) in moderate yields. It may be noted that *o*-substituted ketones (*o*-CH_3 and *o*-OCH_3) also reacted albeit with lesser product yields (**2j**, 50% and **2k**, 52%), presumably due to steric hindrance. The effect is more pronounced with trisubstituted ketone (**1n**) when the reaction failed to react altogether. Disubstituted ketone (**1l**) also reacted to give the product **2l** in 55% yield. The scope of the reaction was further extended to 2-acetylnaphthalene (**1m**), which successfully underwent self-condensation to give the product **2m** in reasonable yield. With heteroaryl methyl ketones (**1o** and **1p**) however, the reactions gave only trace amounts of the products (**2o** and **2p**). The structures of some of these new compounds (**2a**, **2b**, **2e**, **2j**, **2k**, and **2l**) were confirmed by X-ray diffraction analysis (included in the Supporting Information). The Oak Ridge Thermal-Ellipsoid Plot (ORTEP) diagram representation of compounds **2a** and **2e** is shown in Figure 1. From the above results, it is evident that the formation of the product is not defined by the nature of the substituents on the benzene ring of the ketones but rather depends on the position of the substituents where unsubstituted and *p*-substituted aryl methyl ketones (**1a–f**) gave the maximum yield of the condensed product, whereas substitution at the *o*-position (**1j–l**) resulted in lesser product yields. ^{1}H NMR and ORTEP diagrams of few products (**2b**, **2f**, **2h**, **2k**, and **2m**) indicated the presence of a mixture of symmetrical and unsymmetrical isomers. Heteronuclear Multiple Bond Coherence (HMBC) analysis of compound **2f** confirmed the presence of both the isomers. It was further observed from ^{1}H NMR that *o*-substituted ketones (**1j**, **1k**, and **1l**) afforded the symmetric products **2j**, **2k**, and **2l**, although **2k** gave a mixture of symmetrical and unsymmetrical forms. The *p*- and *m*-substituted ketones however yielded unsymmetrical isomers as the major product. Thus, it appears that *o*-

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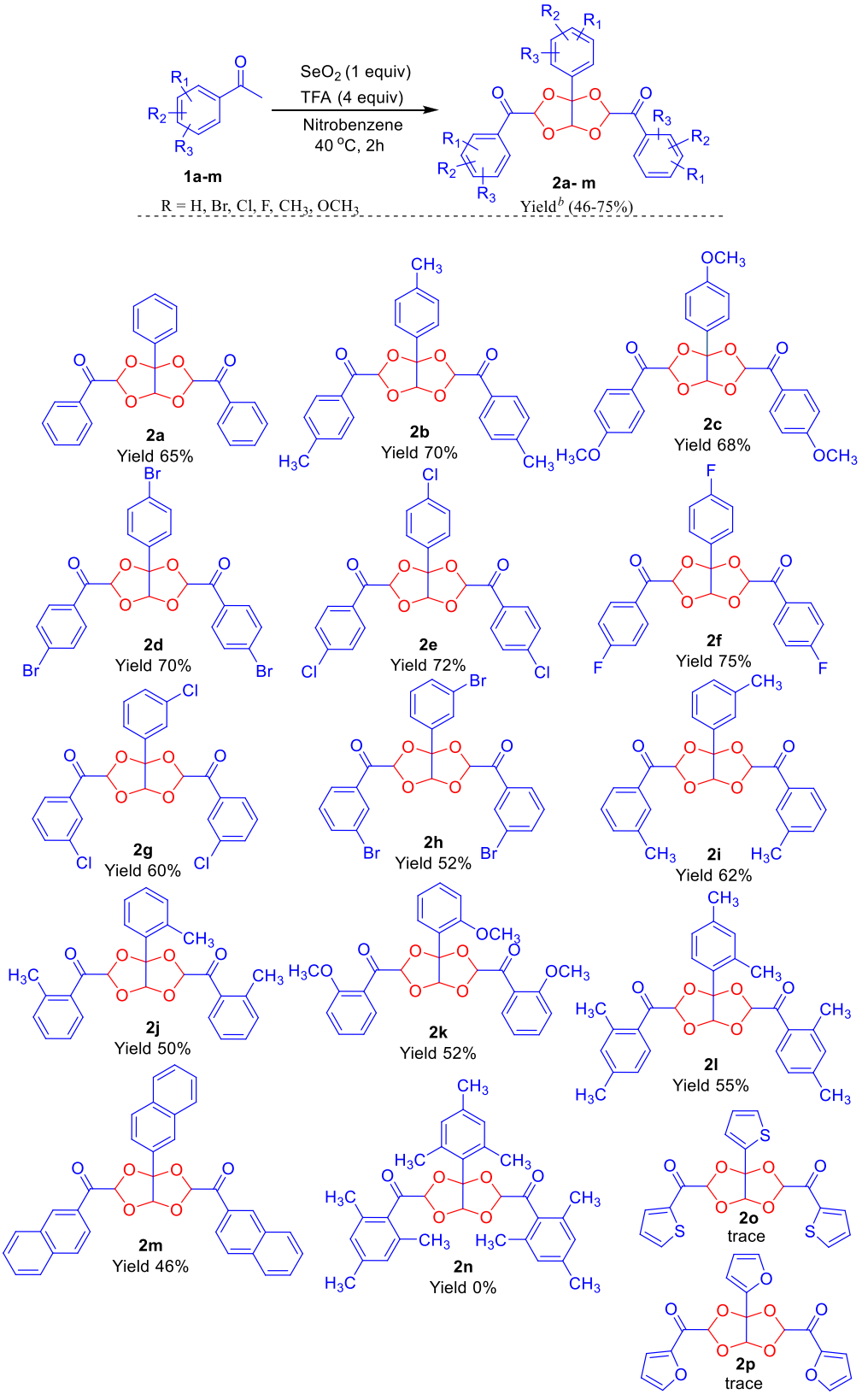
Scheme 2. Scope of Self-Condensation of Aryl Methyl Ketones[a] in the Presence of SeO_2 and TFA



[a]The reaction was carried out with **1a** (2.0 mmol, 1 equiv), SeO_2 (0.222 g, 2.0 mmol, 1 equiv), and TFA (0.6 mL, 4 equiv) in nitrobenzene at 40 °C. [b]Isolated yield.

substituents effect the formation of symmetric products may be due to the steric repulsion.

The plausible mechanistic pathway is depicted in Scheme 3. Evidently, the initial step of the reaction involves the well-

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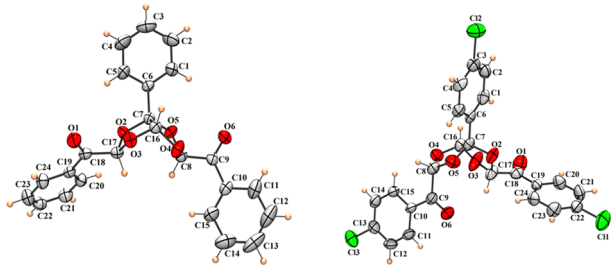
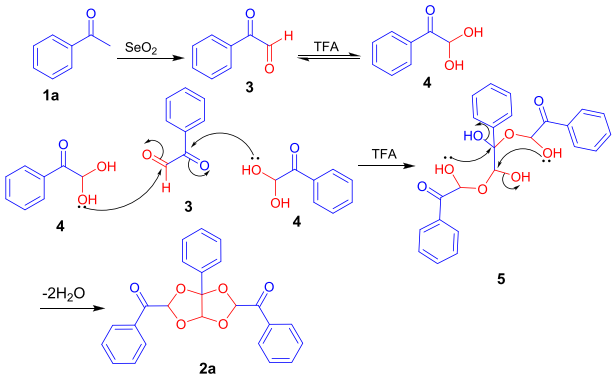


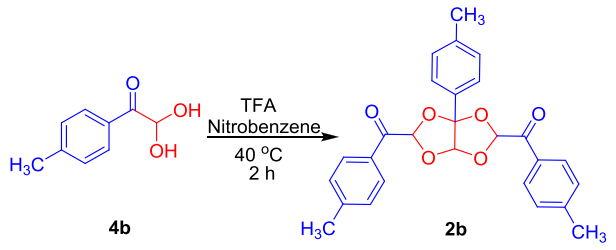
Figure 1. ORTEP of **2a** (CCDC 1991160) and **2e** (CCDC 1991162), with thermal ellipsoids at the 50% probability level.

Scheme 3. Plausible Mechanism



established Riley oxidation of the acetophenone **1a** by SeO_2 to gyloxal **3**, which, in the presence of TFA, existed in equilibrium with its monohydrated substrate **4**.[15] A concerted acid-catalyzed double acetalization of the glyoxal with two molecules of its monohydrate resulted in the formation of the condensed product **2a** with elimination of water. The above proposed mechanism was further strengthened by the condensation of 2,2-dihydroxy-1-(*p*-tolyl)ethan-1-one **4b** in the presence of acid TFA under the standard reaction condition to give the expected product **2b** in 76% yield (Scheme 4).

Scheme 4. Condensation of 2,2-Dihydroxy-1-(*p*-tolyl)ethan-1-one to 2b



CONCLUSIONS

In summary, this work highlights a new TFA-mediated intermolecular oxidative self-condensation reaction of three molecules of aromatic ketone via multiple C−O bond formations using a common shelf reagent, SeO_2, as the oxidant under mild reaction conditions to afford (3a-phenyldihydro-[1,3]dioxolo[4,5-*d*][1,3]dioxole-2,5-diyl)bis-(phenylmethanones), a structurally unique class of oxygen heterocycles.

EXPERIMENTAL SECTION

All chemicals and reagents were purchased from available commercial companies and were used without further purification. Reactions were monitored by thin-layer chromatography using pre-coated aluminum sheets (silica gel 60 F_{254}, 0.2 mm thickness). Formation of the desired product was confirmed by infrared (IR), ^{1}H NMR, ^{13}C NMR, and mass spectra (LC−MS/HRMS). IR spectra were recorded on a Perkin Elmer Spectrum 400 FTIR instrument, and the frequencies are expressed in cm^{-1}. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance II-400 spectrometer in $CDCl_3$, and chemical shifts were recorded in ppm with TMS as the internal standard. The HMBC spectrum was recorded on an ECZR series 600 MHz NMR spectrometer (Jeol, Japan). Melting points were recorded by an open capillary tube method. Mass spectral data were obtained with a Waters UPLC-TQD mass spectrometer (ESI-MS). High-resolution mass spectra (ESI-HRMS) were recorded on an Agilent 6545 Quadrupole Time-of-Flight. All reactions were purified by column chromatography over silica gel (100−200 mesh) using ethyl acetate and hexane as the eluent.

General Procedure for the Preparation of (3a-Aryldihydro-[1,3]dioxolo[4,5-*d*][1,3]dioxole-2,5-diyl)bis-(phenylmethanone). To a solution of nitrobenzene (5 mL) and aryl methyl ketone (**1a**−p) (2.0 mmol, 1 equiv) in a 25 mL dry round-bottom flask, SeO_2 (0.222 g, 2.0 mmol, 1 equiv) was added and the mixture was allowed to stir in an ice bath where TFA (0.6 mL) was added dropwise. The reaction was then allowed to stir at 40 °C for 2 h using a temperature-controlled magnetic stirrer in an oil bath. After the reaction is completed, ethyl acetate (20 mL) was added to dilute the reaction mixture, which was then washed with a saturated solution of sodium bicarbonate and thereafter with brine solution. The organic layer was then collected separately and dried over anhydrous sodium sulfate and reduced in a rotatory evaporator to a minimum amount. The compound was then purified by column chromatography over a silica gel 100−200 mesh using ethyl acetate:hexane as the eluent.

(3a-Phenyldihydro-[1,3]dioxolo[4,5-*d*][1,3]dioxole-2,5-diyl)bis(phenylmethanone) (2a). The product was prepared *via* the general procedure from acetophenone **1a** (0.240 g, 2.0 mmol, 1 equiv) in the presence of SeO_2 (0.222 g, 2.0 mmol, 1 equiv) and TFA (0.6 mL). The crude was purified by column chromatography using hexane:ethyl acetate (9:1) as the eluent; white solid (0.174 g, 65%); mp 120−122 °C; IR (KBr): 3065, 3032, 2923, 1701, 1596, 1451, 1113, 1071, 857, 689 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08 (d, J = 7.2 Hz, 4H), 7.59 (t, J = 7.2 Hz, J = 7.6 Hz, 2H), 7.51−7.45 (m, 6H), 7.29−7.27 (m, 3H), 6.53 (s, 2H), 5.95 (s, 1H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 188.50, 133.45, 133.09, 132.35, 128.68, 128.43, 127.87, 127.48, 125.47, 111.74, 105.89, 101.23 ppm. MS (ES^+) calcd for $C_{24}H_{18}O_6$, 402.1; found m/z, 425.1 $[M + Na]^+$.

(3a-(*p*-Tolyl)dihydro-[1,3]dioxolo[4,5-*d*][1,3]dioxole-2,5-diyl)bis(*p*-tolylmethanone) (2b). The product was prepared *via* the general procedure from 4-methylacetophenone **1b** (0.268 g, 2.0 mmol, 1 equiv) in the presence of SeO_2 (0.222 g, 2.0 mmol, 1 equiv) and TFA (0.6 mL). The crude was purified by column chromatography using hexane:ethyl acetate (9:1) as the eluent. The product was collected as a mixture of isomers; white solid (0.201 g, 70%); mp 130−131 °C; IR (KBr): 3076, 3010, 2947, 1689, 1596, 1289, 1163,

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1104, 1045, 759 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.98 (d, J = 8 Hz, 2H), 7.91 (d, J = 8.4 Hz, 2H), 7.43 (d, J = 8.4 Hz, 2H), 7.26−7.20 (m, 4H), 7.13 (d, J = 8 Hz, 2H), 6.47 (s, 1H), 6.30 (s, 1H), 5.84 (s, 1H), 2.37 (s, 3H), 2.34 (s, 3H), 2.28 (s, 3H), 6.49 (s, 2H), 5.91 (s, 1H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 191.83, 189.67, 145.43, 145.37, 139.65, 131.93, 131.08, 131.03, 129.58, 129.56, 129.50, 129.23, 126.20, 113.18, 107.04, 103.58, 101.39, 21.86, 21.24 ppm. MS (ES^+) calcd for $C_{27}H_{24}O_6$, 444.1; found m/z, 467.1 $[M + Na]^+$.

(3a-(4-Methoxyphenyl)dihydro-[1,3]dioxolo[4,5-*d*]-[1,3]dioxole-2,5-diyl)bis((4-methoxyphenyl)-methanone) (2c). The product was prepared *via* the general procedure from 4-methoxyacetophenone **1c** (0.300 g, 2.0 mmol, 1 equiv) in the presence of SeO_2 (0.222 g, 2.0 mmol, 1 equiv) and TFA (0.6 mL). The crude was purified by column chromatography using hexane:ethyl acetate (6:4) as the eluent; white solid (0.222 g, 68%); mp 120−122 °C; IR (KBr): 3071, 3005, 2961, 2840, 1689, 1598, 1250, 1114, 1027, 827, 601 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.07 (d, J = 8.8 Hz, 2H), 8.00 (d, J = 9.2 Hz, 2H), 7.48 (d, J = 8.8 Hz, 2H), 6.93−6.83 (m, 6H), 6.45 (s, 1H), 6.29 (s, 1H), 5.82 (s, 1H), 3.82 (s, 3H), 3.81 (s, 3H), 3.74 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 190.65, 188.50, 164.36, 160.54, 131.92, 131.88, 127.72, 126.94, 126.59, 126.47, 114.09, 114.04, 113.83, 113.06, 106.91, 103.48, 101.18, 55.59, 55.55, 55.33 ppm. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{27}H_{25}O_9$, 493.1499; found, 493.1491.

(3a-(4-Bromophenyl)dihydro-[1,3]dioxolo[4,5-*d*][1,3]-dioxole-2,5-diyl)bis((4-bromophenyl)methanone) (2d). The product was prepared *via* the general procedure from 4-bromoacetophenone **1d** (0.398 g, 2.0 mmol, 1 equiv) in the presence of SeO_2 (0.222 g, 2.0 mmol, 1 equiv) and TFA (0.6 mL). The crude was purified by column chromatography using hexane:ethyl acetate (8:2) as the eluent; white solid (0.298 g, 70%); mp 132−134 °C; IR (KBr): 3090, 2912, 2576, 1707, 1584, 1127, 1071, 869, 814 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.93 (d, J = 8.8 Hz, 2H), 7.86 (d, J = 8.4 Hz, 2H), 7.63−7.58 (m, 4H), 7.47 (d, J = 8.8 Hz, 2H), 7.41 (d, J = 8.4 Hz, 2H), 6.46 (s, 1H), 6.21 (s, 1H), 5.83 (s, 1H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 191.25, 188.99, 133.48, 132.32, 132.28, 131.94, 131.86, 131.84, 130.86, 130.78, 130.03, 130.00, 128.03, 124.33, 112.76, 106.90, 103.65, 101.47 ppm. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{24}H_{16}Br_3O_6$, 638.8477; found, 638.8469.

(3a-(4-Chlorophenyl)dihydro-[1,3]dioxolo[4,5-*d*][1,3]-dioxole-2,5-diyl)bis((4-chlorophenyl)methanone) (2e). The product was prepared *via* the general procedure from 4-chloroacetophenone **1e** (0.309 g, 2.0 mmol, 1 equiv) in the presence of SeO_2 (0.222 g, 2.0 mmol, 1 equiv) and TFA (0.6 mL). The crude was purified by column chromatography using hexane:ethyl acetate (8:2) as the eluent; white solid (0.245 g, 72%); mp 132−136 °C; IR (KBr): 3021, 2927, 2929, 1714, 1702, 1589, 1172, 1094, 830, 759 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.09 (d, J = 8.8 Hz, 2H), 8.01 (d, J = 9.2 Hz, 2H), 7.56−7.48 (m, 6H), 7.39 (d, J = 8.8 Hz, 2H), 6.53 (s, 1H), 6.30 (s, 1H), 5.91 (s, 1H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 191.04, 188.79, 141.17, 141.12, 136.07, 133.02, 131.61, 131.54, 130.84, 130.76, 129.34, 129.29, 128.88, 127.78, 112.75, 106.98, 103.67, 101.49 ppm. MS (ES^+) calcd for $C_{24}H_{15}Cl_3O_6$, 503.9; found m/z, 526.9 $[M + Na]^+$.

(3a-(4-Fluorophenyl)dihydro-[1,3]dioxolo[4,5-*d*][1,3]-dioxole-2,5-diyl)bis((4-fluorophenyl)methanone) (2f). The product was prepared *via* the general procedure from 4-fluoroacetophenone **1f** (0.276 g, 2.0 mmol, 1 equiv) in the presence of SeO_2 (0.222 g, 2.0 mmol, 1 equiv) and TFA (0.6 mL). The crude was purified by column chromatography using hexane:ethyl acetate (8:2) as the eluent. The product was collected as a mixture of isomers; white solid (0.228 g, 75%); mp 109−111 °C; IR (KBr): 3079, 2934, 1705, 1601, 1512, 1243, 1127, 836 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.14−8.10 (m, 4H), 7.56−7.53 (m, 2H), 7.17−7.10 (m, 6H), 6.48 (s, 2H), 5.84 (s, 1H), 8.07−8.04 (m, 4H), 7.51−7.48 (m, 2H), 7.05−6.97 (m, 6H), 6.48 (s, 1H), 6.26 (s,1H), 5.90 (s, 1H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 190.63, 188.38, 187.85, 166.53 (d, J_{C-F} = 257 Hz), 166.44 (d, J_{C-F} = 255 Hz), 163.60 (J_{C-F} = 248 Hz), 132.39−132.27 (m), 128.62 (d, J_{C-F} = 8.7 Hz), 128.40 (d, J_{C-F} = 8.6 Hz), 116.41−116.10 (m), 115.66 (d, J_{C-F} = 21 Hz), 115.60 (d, J_{C-F} = 22 Hz), 112.78, 112.48, 106.97, 106.74, 103.62, 102.07, 101.43 ppm. HMBC cross peak: δ 5.86/101.43, 5.86/103.62, 5.86/112.78, 6.55/188.38, 7.12−7.17/132.26, 7.12−7.17/115.77, 7.12−7.17/167.82, 7.53−7.56/112.78, 7.53−7.56/128.66, 7.53−7.56/112.78, 8.11−8.14/132.39, 8.11−8.14/167.82; δ 5.96/102.07, 5.96/112.48, 6.32/187.85, 6.50/190.63, 6.50/112.48, 6.50/106.74, 6.96−7.05/115.56, 6.96−7.05/132.26, 6.95−7.05/164.84, 7.48−7.51/112.48, 7.48−7.51/128.44, 7.48−7.51/164.84, 8.04−8.07/132.26, 8.04−8.07/167.72, 8.04−8.07/187.85. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{24}H_{16}F_3O_6$, 457.0899; found, 457.0891.

(3a-(3-Chlorophenyl)dihydro-[1,3]dioxolo[4,5-*d*][1,3]-dioxole-2,5-diyl)bis((3-chlorophenyl)methanone) (2g). The product was prepared *via* the general procedure from 3-chloroacetophenone **1g** (0.309 g, 2.0 mmol, 1 equiv) in the presence of SeO_2 (0.222 g, 2.0 mmol, 1 equiv) and TFA (0.6 mL). The crude was purified by column chromatography using hexane:ethyl acetate (8:2) as the eluent; yellow thick liquid (0.202 g, 60%); IR (KBr): 3069, 2923, 1708, 1571, 1427, 1235, 1171, 1032, 791 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.05 (s, 1H), 7.98−7.88 (m, 3H), 7.58−7.54 (m, 3H), 7.45−7.41 (m, 3H), 7.35−7.29 (m, 2H), 6.49 (s, 1H), 6.23 (s, 1H), 5.87 (1H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 191.31, 189.04, 136.60, 135.63, 135.58, 135.02, 134.99, 134.95, 134.72, 133.34, 130.59, 130.55, 130.41, 130.33, 129.65, 129.44, 127.89, 127.87, 126.89, 124.87, 112.78, 107.20, 103.97, 101.86 ppm. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{24}H_{16}Cl_3O_6$, 505.0012; found, 505.0013.

(3a-(3-Bromophenyl)dihydro-[1,3]dioxolo[4,5-*d*][1,3]-dioxole-2,5-diyl)bis((3-bromophenyl)methanone) (2h). The product was prepared *via* the general procedure from 3-bromoacetophenone **1h** (0.398 g, 2.0 mmol, 1 equiv) in the presence of SeO_2 (0.222 g, 2.0 mmol, 1 equiv) and TFA (0.6 mL). The crude was purified by column chromatography using hexane:ethyl acetate (8:2) as the eluent. The product was collected as a mixture of isomers; yellow thick liquid (0.221 g, 52%); IR (KBr): 3067, 2922, 2852, 1707, 1566, 1120, 1032, 788 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.20 (s, 1H), 8.11 (s, 1H), 8.01 (d, J = 8.4 Hz, 1H), 7.93 (d, J = 7.6 Hz, 1H), 7.73−7.69 (m, 3H), 7.48 (t, J = 8.8 Hz, J = 8.4 Hz, 2H), 7.39−7.32 (m, 2H), 7.24 (d, J = 8 Hz, 1H), 6.48 (s, 1H), 6.22 (s, 1H), 5.86 (s, 1H), 6.46 (s, 2H), 5.93 (s, 1H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 190.95, 188.69, 137.36, 136.51, 135.98, 134.88, 133.07, 132.29, 132.08, 130.54, 130.49, 130.30, 129.48, 128.06, 126.86, 125.08, 123.31, 123.31, 122.74, 112.40, 106.98, 103.66, 102.15, 101.54 ppm. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{24}H_{16}Br_3O_6$, 638.8477; found, 638.8471.

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(3a-(*m*-Tolyl)dihydro-[1,3]dioxolo[4,5-*d*][1,3]dioxole-2,5-diyl)bis(*m*-tolylmethanone) (2i). The product was prepared *via* the general procedure from 3-methylacetophenone **1i** (0.268 g, 2.0 mmol, 1 equiv) in the presence of SeO_2 (0.222 g, 2.0 mmol, 1 equiv) and TFA (0.6 mL). The crude was purified by column chromatography using hexane:ethyl acetate (9:1) as the eluent; yellow thick liquid (0.183 g, 62%); IR (KBr): 2922, 1702, 1605, 1262, 1115, 1035, 788 cm^{-1}; ^1H NMR (400 MHz, CDCl3): δ 7.90−7.81 (m, 4H), 7.39−7.32 (m, 6H), 7.22 (t, J = 7.6 Hz, 1H), 7.14 (d, J = 7.2 Hz, 1H), 6.50 (s, 1H), 6.32 (s, 1H), 5.87 (s, 1H), 2.37 (s, 3H), 2.35 (s, 3H), 2.30 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, CDCl3): δ 190.20, 189.76, 138.81, 138.78, 138.67, 138.39, 138.27, 135.31, 135.16, 134.63, 134.04, 130.47, 129.82, 129.72, 129.32, 128.75, 128.70, 128.50, 128.42, 128.07, 126.86, 126.81, 126.77, 107.06, 106.93, 103.64, 102.32, 101.46, 21.49, 21.42, 21.40 ppm. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{27}H_{25}O_6$, 445.1651; found, 445.1646.

(3a-(*o*-Tolyl)dihydro-[1,3]dioxolo[4,5-*d*][1,3]dioxole-2,5-diyl)bis(*o*-tolylmethanone) (2j). The product was prepared *via* the general procedure from 2-methylacetophenone **1j** (0.268 g, 2.0 mmol, 1 equiv) in the presence of SeO_2 (0.222 g, 2.0 mmol, 1 equiv) and TFA (0.6 mL). The crude was purified by column chromatography using hexane:ethyl acetate (9:1) as the eluent; white solid (0.147 g, 50%); mp 128−130 °C ; IR (KBr): 3065, 2972, 2928, 2873, 1702, 1599, 1111, 864, 741 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.85 (d, J = 7.2 Hz, 2H), 7.60 (d, J = 8 Hz, 1H), 7.39 (t, J = 6.4 Hz, J = 7.6 Hz, 2H), 7.26−7.23 (m, 4H), 7.16 (d, J = 6.4 Hz, 1H), 7.07−7.05 (m, 2H), 6.39 (s, 2H), 6.17 (s, 1H), 2.47 (s, 6H), 2.23 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 191.87, 191.67, 139.96, 139.83, 136.17, 132.80, 132.72, 132.30, 132.17, 131.80, 131.78, 131.66, 131.60, 131.39, 131.34, 129.95, 129.55, 129.42, 129.40, 129.26, 127.06, 126.63, 125.48, 125.35, 125.31, 125.29, 113.10, 112.67, 105.13, 104.80, 102.42, 102.06 ppm. MS (ES^+): calcd for $C_{27}H_{24}O_6$, 444.1; found m/z, 467.2 $[M + Na]^+$.

(3a-(2-Methoxyphenyl)dihydro-[1,3]dioxolo[4,5-*d*]-[1,3]dioxole-2,5-diyl)bis((2-methoxyphenyl)-methanone) (2k). The product was prepared *via* the general procedure from 2-methoxyacetophenone **1k** (0.300 g, 2.0 mmol, 1 equiv) in the presence of SeO_2 (0.222 g, 2.0 mmol, 1 equiv) and TFA (0.6 mL). The crude was purified by column chromatography using hexane:ethyl acetate (6:4) as the eluent. The product was collected as mixture of isomers; white solid (0.170 g, 52%); mp 128−130 °C; IR (KBr): 3076, 3010, 2843, 1689, 1596, 1487, 1289, 1247, 1104, 1045, 870, 759 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.72−7.69 (m, 3H), 7.55−7.49 (m, 3H), 7.07−6.98 (m, 6H), 6.47 (s, 1H), 6.41 (s, 1H), 6.12 (s, 1H), 3.98 (s, 3H), 3.93 (s, 3H), 3.82 (s, 3H), 7.81−7.73 (m, 3H), 7.36−7.31 (m, 3H) ppm; 6.95−6.87 (m, 6H), 6.58 (s, 2H), 6.19 (s, 1H), 3.96 (s, 6H), 3.70 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 195.66, 193.26, 193.21, 159.43, 159.13, 158.95, 156.87, 156.79, 134.55, 134.47, 130.82, 130.80, 128.44, 128.37, 125.66, 125.38, 125.30, 123.48, 121.04, 120.94, 120.68, 120.28, 120.05, 112.17, 112.09, 111.95, 111.023, 110.89, 105.60, 105.53, 104.67, 103.83, 103.23, 56.12, 55.98, 55.90, 55.37, 55.10 ppm. MS (ES^+) calcd for $C_{27}H_{24}O_9$, 492.1; found m/z, 493.2 $[M + H]^+$.

(3a-(2,4-Dimethylphenyl)dihydro-[1,3]dioxolo[4,5-*d*]-[1,3]dioxole-2,5-diyl)bis((2,4-dimethylphenyl)-methanone) (2l). The product was prepared *via* the general procedure from 2,4-Dimethylacetophenone **1l** (0.296 g, 2.0 mmol, 1 equiv) in the presence of SeO_2 (0.222 g, 2.0 mmol, 1 equiv) and TFA (0.6 mL). The crude was purified by column chromatography using hexane:ethyl acetate (8:2) as the eluent; white solid (0.178 g, 55%); mp 134−135 °C; IR (KBr): 3032, 2967, 2922, 1712, 1614, 1107,845, 656 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.79 (d, J = 8.8 Hz, 2H), 7.51 (d, J = 8 Hz, 1H), 7.04 (d, J = 6.4 Hz, 4H), 6.88−6.85 (m, 2H), 6.39 (s, 2H), 6.13 (s, 1H), 2.46 (s, 6H), 2.30 (s, 6H), 2.19 (s, 6H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 191.40, 143.76, 140.96, 139.57, 136.44, 133.20, 132.67, 130.56, 130.39, 128.79, 127.64, 126.45, 126.37, 113.17, 105.30, 102.41, 21.69, 21.59, 20.93, 20.31 ppm. MS (ES^+) calcd for $C_{30}H_{30}O_6$, 486.2; found m/z, 509.1 $[M + Na]$.

(3a-(Naphthalen-2-yl)dihydro-[1,3]dioxolo[4,5-*d*]-[1,3]dioxole-2,5-diyl)bis(naphthalen-2-ylmethanone) (2m). The product was prepared *via* the general procedure from 1-(naphthalen-2-yl)ethan-1-one **1m** (0.340 g, 2.0 mmol, 1 equiv) in the presence of SeO_2 (0.222 g, 2.0 mmol, 1 equiv) and TFA (0.6 mL). The crude was purified by column chromatography using hexane:ethyl acetate (5:5) as the eluent. The product was collected as a mixture of isomers; white solid (0.169 g, 46%); mp 179−180 °C; IR (KBr): 3056, 2929, 2854, 1706, 1625, 1271, 1191, 1108, 821, 752 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$: DMSO-d_6): δ 8.75 (s, 1H), 8.55 (s, 1H), 8.15−8.14 (m, 2H), 8.02−7.94 (m, 3H), 7.89−7.80 (m, 7H), 7.63−7.50 (m, 5H), 7.48−7.45 (m, 2H), 6.93 (s, 1H), 6.55 (s, 1H), 6.05 (s, 1H); 7.02 (s, 2H), 6.08 (s, 1H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6: acetone-d_6): δ 193.03, 190,37, 135.93, 133.74, 132.88, 132.72, 132.47, 132.30, 132.13, 131.60, 131.57, 131.27, 130.20, 130.10, 129.72, 129.64, 129.11, 128.98, 128.81, 128.70, 128.21, 128.01, 127.67, 127.61, 127.48, 127.133, 126.13, 124.55, 124.19, 123.94, 113.08, 106.65, 103.99, 101.63 ppm. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{36}H_{25}O_6$, 553.1651; found, 553.1648.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.1c01466.

Crystallographic data of compounds **2a**, **2b**, **2e**, **2j**, **2k**, and **2l** (CIF)

Single-crystal XRD data of **2a**, **2b**, **2e**, **2j**, **2k**, and **2l**; ^1H and ^{13}C NMR spectra of synthesized compounds; and HMBC spectrum of **2f** (PDF)

■ AUTHOR INFORMATION

Corresponding Author

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

Authors

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

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

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

Baskhemlang Kshiar − *Department of Chemistry, North-Eastern Hill University, Shillong 793022, India*

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

Complete contact information is available at: https://pubs.acs.org/10.1021/acsomega.1c01466

Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Liao, M.; Dong, S.; Deng, G.; Wang, J. Synthesis of oxygen-containing heterocyclic compounds based on the intramolecular O−H insertion and Wolff rearrangement of α-diazocarbonyl compounds. *Tetrahedron Lett.* **2006**, *47*, 4537−4540. (b) Li, C. H.; Yuan, G. Q.; Zheng, J. H.; He, Z. J.; Qi, C. R.; Jiang, H. F. Effective synthesis of symmetrical oxygen and nitrogen-heterocycles from electron-deficient alkynes via the catalysis of electrogenerated base and $Fe3^{+}$ ions. *Tetrahedron* **2011**, *67*, 4202−4205.

(2) Delost, M. D.; Smith, D. T.; Anderson, B. J.; Njardarson, J. T. From Oxiranes to Oligomers: Architectures of U.S. FDA Approved Pharmaceuticals Containing Oxygen Heterocycles. *J. Med. Chem.* **2018**, *61*, 10996−11020.

(3) Zhou, Y.; Liu, J.; Zheng, M.; Zheng, S.; Jiang, C.; Zhou, X.; Zhang, D.; Zhao, J.; Ye, D.; Zheng, M.; Jiang, H.; Liu, D.; Cheng, J.; Liu, H. Structural optimization and biological evaluation of 1,5-disubstituted pyrazole-3-carboxamines as potent inhibitors of human 5-lipoxygenase. *Acta Pharm. Sin.* **2016**, *6*, 32−45.

(4) (a) El Hadri, A.; Nicolle, E.; Leclerc, G.; Pietri-Rouxel, F.; Strosberg, A. D.; Archimbault, P. New series of *N*-substituted phenyl ketone oxime ethers: synthesis and bovine β_3-adrenergic agonistic activities. *Pharmazie* **2003**, *58*, 13−17. (b) Meriga, B.; Parim, B.; Chunduri, V. R.; Naik, R. R.; Nemani, H.; Suresh, P.; Ganapathy, S.; Sathibabu Uddandrao, V. V. Antiobesity potential of Piperonal: promising modulation of body composition, lipid profiles and obesogenic marker expression in HFD-induced obese rats. *Nutr. Metab.* **2017**, *14*, 1−14.

(5) Carter, N. J.; Keam, S. J. Trabectedin: A Review of its Use in the Management of Soft Tissue Sarcoma and Ovarian Cancer. *Drugs* **2007**, *67*, 2257−2276.

(6) Qi, C.; Zhou, Q.; Gao, W.; Liu, M.; Chen, C.; Li, X.-N.; Lai, Y.; Zhou, Y.; Li, D.; Hu, Z.; Zhu, H.; Zhang, Y. Anti-BACE1 and anti-AchE activities of undescribed spiro-dioxolane-containing meroterpenoids from the endophytic fungus *Aspergillus terreus* Thom. *Phytochemistry* **2019**, *165*, 112041−112048.

(7) (a) Adams, R. D.; Barnard, T. S.; Brosius, K. Synthesis of 1,3-dioxolanes by the addition of ketones to epoxides by using $[Cp^{*}Ir(NCMe)_3]^{2+}$ as catalyst. *J. Organomet. Chem.* **1999**, *582*, 358−361. (b) Nagpal, Y.; Kumar, R.; Bhasin, K. K. Synthesis and characterization of novel benzo[*d*][1,3]dioxole substituted organo selenium compounds: X-ray structure of 1-((benzo[*d*][1,3]dioxol-5-yl)methyl)-2-((benzo[*d*] [1,3]dioxol-6-yl)methyl)diselane. *J. Chem. Sci. Vol.* **2015**, *8*, 1339−1346. (c) Komori, S.; Yamaguchi, Y.; Kataoka, Y.; Ura, Y. Palladium-Catalyzed Aerobic Anti-Markovnikov Oxidation of Aliphatic Alkenes to Terminal Acetals. *J. Org. Chem.* **2019**, *84*, 3093−3099.

(8) (a) Soto, M.; Soengas, R. G.; Silva, A. M. S.; Gotor-Fernández, V.; Rodríguez-Solla, H. Synthesis of carbohydrate-derived (*Z*)-vinyl halides and silanes: Samarium-promoted stereoselective 1,2-elimination on sugar-derived α-halomethylcarbinol acetates. *Tetrahedron* **2018**, *74*, 5475−5480. (b) Sasano, Y.; Kogure, N.; Nagasawa, S.; Kasabata, K.; Iwabuchi, Y. 2-Azaadamantane N-oxyl (AZADO)/Cu Catalysis Enables Chemoselective Aerobic Oxidation of Alcohols Containing Electron-Rich Divalent Sulfur Functionalities. *Org. Lett.* **2018**, *20*, 6104−6107. (c) Wessig, P.; John, L.; Mertens, M. Extending the Class of [1,3]-Dioxolo[4.5-*f*]benzodioxole (DBD) Fluorescent Dyes. *Eur. J. Org. Chem.* **2018**, 1674−1681.

(9) Diels, O.; Jost, H. Ueber die Darstellung des Diacetyls und ein Polymerisationsproduct desselben. *Ber. Dtsch. Chem. Ges.* **1902**, *35*, 3290−3299.

(10) Hudec, J.; Turner, D. L. Determination of the Structure of a Trimer of Biacetyl by Carbon-13 Autocorrelation Nuclear Magnetic Resonance Spectroscopy. *J. Chem. Soc., Perkin Trans. 2* **1982**, 951−955.

(11) 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 Triflouride Etherate: A Protocol for the Synthesis of Triarylethanones. *J. Org. Chem.* **2012**, *77*, 707−712.

(12) 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**, 320−328.

(13) Riley, H. L.; Morley, J. F.; Friend, N. A. C. Selenium dioxide, a new oxidising agent. Part I. Its reaction with aldehydes and ketones. *J. Chem. Soc.* **1932**, 1875−1883.

(14) (a) 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. (b) Shangpliang, O. R.; Wanniang, K.; Kshiar, B.; Marpna, I. D.; Lipon, T. M.; Mizar, P.; Myrboh, B. PTSA-Catalyzed Reaction of Alkyl/Aryl Methyl Ketones with Aliphatic Alcohols in the Presence of Selenium Dioxide: A Protocol for the Generation of an α-Ketoacetals Library. *ACS Omega* **2019**, *4*, 6035−6043. (c) Wanniang, K.; Shangpliang, O. R.; Marpna, I. D.; Lipon, T. M.; Laloo, B. M.; Myrboh, B. Metal-Free Three-Component Coupling Reaction of Ketones with Electron-rich Arenes and Selenium Dioxide for the Synthesis of α-Arylselanyl Ketones. *J. Org. Chem.* **2020**, *85*, 15652−15659. ((d)) Marpna, I. D.; Wanniang, K.; Lipon, T. M.; Shangpliang, O. R.; Myrboh, B. Selenocyanation of Aryl and Styryl Methyl Ketones in the Presence of Selenium Dioxide and Malononitrile: An Approach for the Synthesis of α-Carbonyl Selenocyanates. 2021, *86*, 1980−1986, DOI: 10.1021/acs.joc.0c02630.

(15) Young, R. M.; Davies-Coleman, M. T. Microwave-assisted selenium dioxide oxidation of aryl methyl ketones to aryl glyoxals. *Tetrahedron Lett.* **2011**, *52*, 4036−4038.