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Iodine-Mediated Oxidative Rearrangement of α,β-Unsaturated Diaryl Ketones: A Facile Access to 1,2-Diaryl Diketones

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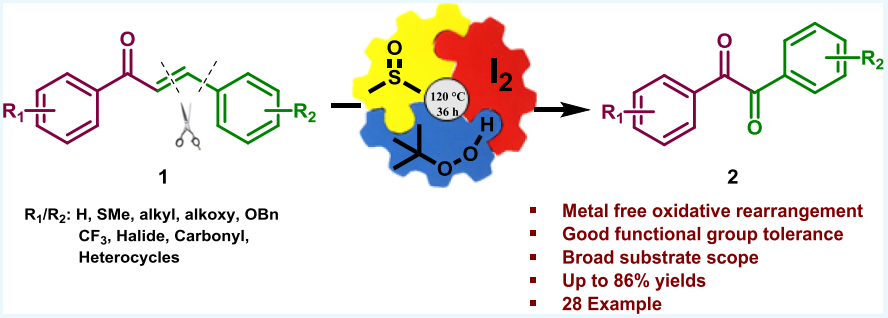
Supporting Information



ABSTRACT: A metal-free oxidative rearrangement was explored for the synthesis of 1,2-diaryl diketones by utilizing α,β-unsaturated diaryl ketones and I_2/TBHP in good to high yields. The reaction proceeds via oxidative aryl migration, followed by C−C bond cleavage. A simple and high-yielding protocol was developed for the synthesis of a wide range of 1,2-diaryl diketones, which are the backbone for a variety of medicinally important molecules.

INTRODUCTION

The transformations of alkenes are the most fundamental and synthetically important reactions in organic synthesis. In particular, oxidative rearrangement is one of those methods which plays a vital role in alkene transformations. Carbon−carbon double bond generation and cleavage are imperative for rapid and effective construction of a complex molecular framework from simple precursors.[1] These reactions follow a sequential C−C double bond cleavage and rearrangement on alkene to achieve new sets of scaffolds. Although effective and efficient methods have been studied extensively in the last few decades, oxidative rearrangement of an alkene remains a challenging task.

Though 1,2-diketones are not a direct part of natural products they serve as building blocks for the construction of natural products, precursors for pharmaceutical compounds, and biologically active compounds such as cholesteryl ester transfer protein inhibitor,[2a] U-protein tyrosine kinase inhibitor (SAG-1296),[2b] lepidiline B,[2c,d] trifenagrel,[2d,e] and antipancreatic cancer agent (PC-046) (Figure 1).[2f] 1,2-Diketones are widely used in organic chemistry as precursors for the synthesis of chiral alcohols,[3] diols,[4] carboxylic acids,[5] heterocyclic compounds,[6a,2d] as well as for the construction of compounds having electronic and photochemical properties in material chemistry.[6b,c] The importance of 1,2-diketones has gained attention in the last few decades; some metal and metal-free methods have been reported to synthesize them using phenyl ketone,[7] alkene oxidation,[8] alkyne oxidation,[9] oxidative

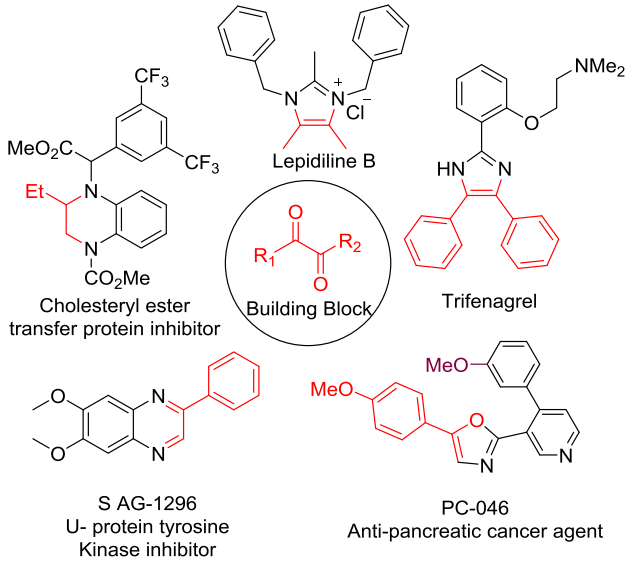


Figure 1. 1,2-Diketones as building blocks for natural products.

cleavage of 1,3-diketone,[10] and benzyl phenyl ketone oxidation using SeO_2.[11] Further, Mn(III) or Cu mediated oxidative

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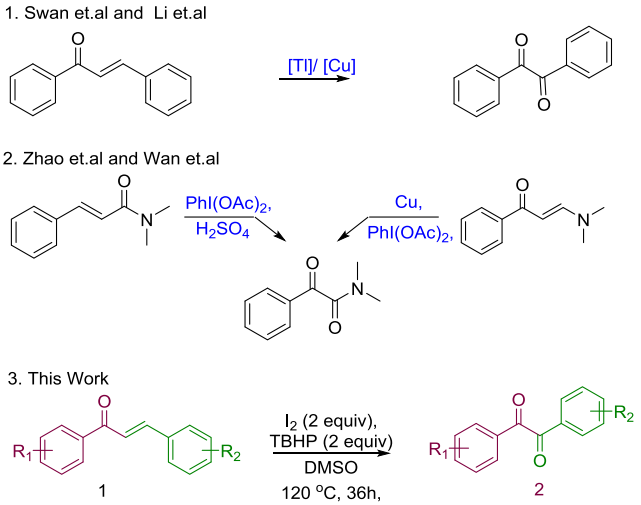
decarboxylative coupling of aryl boronic acids or aryl iodides with aryl propionic acids.[12] Palladium catalyzed the coupling of alkene-diazonium salts[13] and alkene-nitro compounds[14] to form 1,2-diketones. Additionally, I_2 mediated oxidation cleavage of 1,3-diketone, as an example of metal-free transformation to 1,2-diketones.[15] Recently, Das and co-workers synthesized 1,2-diketones from corresponding aldehydes by using the NHC catalyst and CO_2 as a soft promoter.[16] However, these recent methods for the synthesis of 1,2-diketones require mainly transition-metal catalysts and pre-functionalized starting material.

In recent years, the iodine/DMSO system in combination with TBHP has been extensively utilized for the oxidation reaction such as oxidation of acetophenones, 1,3-diketones, alkenes, and alkynes.[15,24e,27]

In recent decades, considerable efforts have been taken in the field of oxidative rearrangement on various substrates (Scheme 1). Swan and co-workers converted the α,β-unsaturated ketones into 1,2-diketones using thallium salts.[17]

Scheme 1. Oxidative Rearrangement for 1,2-Diketones and α-Ketoamides



Similarly, Li and co-workers have done transformation using a copper complex.[18] In 2014, Zhao and co-workers for the first time demonstrated the formation of an α-keto amide from enaminones using hypervalent iodine.[19] In continuation, Wan et al. used a copper salt catalyst to form α-keto amide from enaminones.[20] Although these methods have an efficient protocol for the oxidative rearrangement, they are associated with limitations such as the use of a metal catalyst and the need of an activated double bond. A critical review of the literature showed that there is no report for metal-free oxidative rearrangement of α,β-unsaturated ketones to form 1,2-diketones so far. Continuing with our efforts toward the metal-free organic transformations,[21] we herein report an iodine-mediated oxidative rearrangement of α,β-unsaturated ketones under the metal-free condition to obtain the desired 1,2-diketones in good to excellent yields.

RESULTS AND DISCUSSION

In this context, we started our investigation on the oxidative rearrangement of 4-methoxy chalcone (**1a**) as a model substrate with I_2, TBHP, and additive. At the very beginning, 2 equiv of I_2, 3 equiv of TBHP, and 1 equiv of NaI in DMSO at 120 °C gave 20% of the desired diketone within 12 h of reaction time (entry 1, Table 1). Additives NaI and LiI were used to check the improvement in yield of the reaction but failed to give the desired product in good yield. Different equivalents of iodine sources and oxidant were screened to increase the yield of the 1,2-diketone moiety but failed to obtain the desired product (entries 2−4, Table 1). Also, alternative sources of iodine and oxidants such as (diacetoxyiodo) benzene ($PhI(OAc)_2$) and TEMPO are incapable of giving 1,2-diketone (entry 5, Table 1). Further, 2 equiv of I_2 and 4 equiv of TBHP in DMSO at 150 °C for 12 and 24 h gave 30 and 47% yield of the desired diketone, respectively (entries 6 and 8, Table 1). In continuation, we kept 2 equiv of I_2 and 4 equiv of TBHP constant in DMSO and varied the temperature and additive as well, but it was inadequate to increase the yield of diketone beyond 50% (entries 9 and 14, Table 1). In combination with I_2 and TBHP, different additives such as H_2O and H_2SO_4 were used but were unable to give the desired product (entries 11 and 12, Table 1). The use of I_2 (2 equiv) and TBHP (2 equiv) in DMSO at 120 °C gave 63% yield of the desired diketone within 24 h (entry 15, Table 1). A slight increase in the time duration of the reaction from 24 to 36 h furnished the desired compound with 84% yield (entry 16, Table 1). It is noted that the reaction did not proceed without I_2 and TBHP (entries 18 and 19, Table 1) (see the Supporting Information).

With the optimized conditions in hand (entry 16, Table 1), a series of α,β-unsaturated ketones were prepared from substituted acetophenones and benzaldehydes by a known protocol[23] to investigate the scope and generality of the reaction (Scheme 2). The same substituted aromatic diketones synthesized including electron-donating groups such as methoxy (**2a**, **2g**), methyl (**2c**, **2m**), ethyl (**2d**), thiomethyl (**2b**), benzoyl (**2e**), and dimethoxy (**2i**, **2q**) were well tolerated and gave corresponding 1,2-diketones in 75−86% yields. Similarly, substitution of electron-withdrawing as well as halo groups on the α,β-unsaturated ketones such as fluoro-, chloro-, bromo-, and trifluoromethane was well tolerated and gave good yields of 1,2-diketones (**2u**, **2h**, **2p**, **2x**, **2f**). Moreover, the reaction was carried out on naphthyl α,β-unsaturated ketones and the corresponding product **2w** obtained in 82% yield. Also, hetero-aromatic 1,2-diketones such as thiophene (**2z**, **2za**), furan (**2y**), and symmetric 1,2-diketones (**2j**, **2m**) were obtained in good to excellent yields. Furthermore, the acid-sensitive group substituted on α,β-unsaturated ketone (**1v**) also tolerated to optimized reaction condition and gave corresponding product 2v in 84% yield. Gratefully, the ester substituent α,β-unsaturated ketone was well tolerated under oxidative rearrangement conditions, giving the desired ester-substituted 1,2-diketone (**2zc**) in 80% yield. Aldehyde-substituted α,β-unsaturated ketone undergoes oxidative rearrangement with the conversion of aldehyde to acid (**2zd**) in 63% yield. It is noteworthy to mention that, substrates with the electron-donating group underwent oxidative rearrangement very smoothly to diketones and gave higher yields as compared to the substrates with the electron-withdrawing group. It was observed that the reaction yield depends on the electronic factors of the substituent on α,β-unsaturated ketones. Unfortunately, the reaction failed to give the desired products when the reaction was performed with nitro-substituted α,β-unsaturated ketones (**1o**) as well as with aliphatic α,β-unsaturated ketones (**1aa**).

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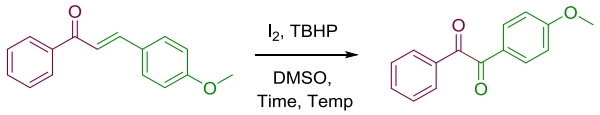
Table 1. Optimization of the Reaction Conditions[a]



1a 2a

entry	iodine source (equiv)	oxidant (equiv)	additive (equiv)	solvent	temp (°C)	time (h)	yield (%)
1	I_2 (2)	TBHP (3)	NaI (1)	DMSO	120	12	20
2	I_2 (2)	TBHP (3)	LiI (1)	DMSO	120	12	NR
3	I_2 (2)	H_2O_2 (2)	NaI (1)	DMSO	120	12	NR
4	I_2 (2)	H_2O_2 (2)	LiI (1)	DMSO	120	12	NR
5	$PhI(OAc)_2$ (1)	TEMPO (0.1)		DCM	25	12	NR
6	I_2 (2)	TBHP (4)		DMSO	150	12	30
7	I_2 (2)	TBHP (4)		MeOH	80	12	NR
8	I_2 (2)	TBHP (4)		DMSO	150	24	47
9	I_2 (2)	TBHP (4)		DMSO	130	24	50
10	I_2 (1)	TBHP (4)		DMSO	130	24	20
11	I_2 (2)	TBHP (4)	H_2O (2)	DMSO	130	24	NR
12	I_2 (2)	TBHP (4)	H_2SO_4 (2)	DMSO	130	24	NR
13		TBHP (4)	NaI (1)	DMSO	130	24	NR
14	I_2 (2)	TBHP (4)		DMSO	120	24	42
15	I_2 (2)	TBHP (2)		DMSO	120	24	63
16	**I_2 (2)**	**TBHP (2)**		**DMSO**	**120**	**36**	**84**
17	I_2 (2)	TBHP (2)		DMSO	120	48	86
18	I_2 (2)			DMSO	120	36	NR
19		TBHP (2)		DMSO	120	36	NR

[a]Reaction Condition: **1a** (1 equiv), I_2 (2 equiv), TBHP (2 equiv), DMSO (5 mL), 120 °C, 36 h.

Further, to show the synthetic utility of diketones, **2j** was converted into a variety of compounds (Scheme 3).[22] Benzil (**2j**) was converted into 2,3-diphenyl quinoxaline (**3a**) using benzene 1,2-diamine and acetic acid as a solvent at 60 °C in 2 h of reaction time, obtaining 95% yield.[22a] Spirocyclohexane isoimidazole (**3b**) was synthesized from benzil (**2j**), cyclohexanone, and ammonium acetate in acetic acid under reflux condition for 1.5 h, giving the desired product in 65% yield.[22a] 2,4,5-triphenyl-1-imidazole (**3c**) was formed from benzil (**2j**) using commercially available benzaldehyde, ammonium acetate in acetic acid for 2 h at 100 °C, obtaining the desired product in 82% yield.[22b] Desymmetrization reaction was carried out on benzil **2j** via reaction with 2-C Wittig salt, offering **3d** in 80% yield[22c] and with BaO/MeI, giving **3e** in 40% yield.[22d] Reduction reaction was carried out on compound **2j** by using $NaBH_4$ to achieve diol **3f** in 80% yield.[4]

To show the synthetic potential of our present methodology, we carried out the reaction on α,β-unsaturated ketones (**1q**)[23] with our optimized reaction conditions, which gives the desired product (**2q**) on a gram scale (2.3 gm, 80% yield). The synthesized diketone (**2q**) was further used to synthesize an anti-inflammatory imidazole-based natural product Fenflumizol in one step with 80% yield using ammonium acetate and 2,4-diflurobenzaldehyde in acetic acid at 100 °C within 3h (Scheme 4).[22b]

To gain an insight into the reaction mechanism, we carried out experiments (Scheme 5). We have synthesized alpha-substituted (**1ma**) and beta-substituted α,β-unsaturated ketones (**1zb**) as a starting material for control experiments. When we carried out the reaction with optimized reaction conditions on beta-substituted α,β-unsaturated ketones (**1zb**), we got our desired 1,2-diketone (**2m**) in 86% yield. However, with alpha-substituted α,β-unsaturated ketones (**1ma**), we did not observe the formation of the desired product **2zb**. From these two experiments, we can say that the alpha position of α,β-unsaturated ketones got oxidized, and the phenyl group at the beta group migrates to an alpha position. The reaction was carried out in the presence of 2 equiv of TEMPO to find out whether the reaction goes either a radical pathway or not and we did not observe the formation of 1,2-diketone. As a result, we can say that the reaction proceeds via a radical pathway.

From the above control experiments (Scheme 5) and literature reports,[24] a plausible reaction mechanism was proposed in Scheme 6. The reaction initiated with the generation of the tertiary butyl peroxide radical from 2 mol of tertiary butyl hydrogen peroxide, which undergoes 1,4-addition across α,β-unsaturated ketones in the presence of I_2, providing intermediate **A**. Under DMSO condition, intermediate **A** undergoes Kornblum oxidation to generate dicarbonyl intermediate **B** and released dimethyl sulfide. Subsequently, homolytic cleavage of the tertiary butyl peroxide part in intermediate **B** delivered the **C** intermediate under heating conditions. Finally, a radical rearrangement of intermediate **C** offered 1,2-diketone and gave out formyl radical, which was quenched by an in situ-generated hydroxyl radical from tertiary butyl hydrogen peroxide and formic acid formed as byproduct. This byproduct was confirmed by gas chromatography–mass spectrometry (GC–MS) analysis (see the Supporting Information).

CONCLUSIONS

We have developed a simple, efficient, and metal-free oxidative rearrangement protocol for the synthesis of 1,2-diketones in good to excellent yields from a simple starting material. Mechanistically, the reaction proceeds via oxidative aryl migration followed by C–C bond cleavage under I_2/TBHP/DMSO reaction condition. The simple starting material, inexpensive reagents, high yields, good functional group

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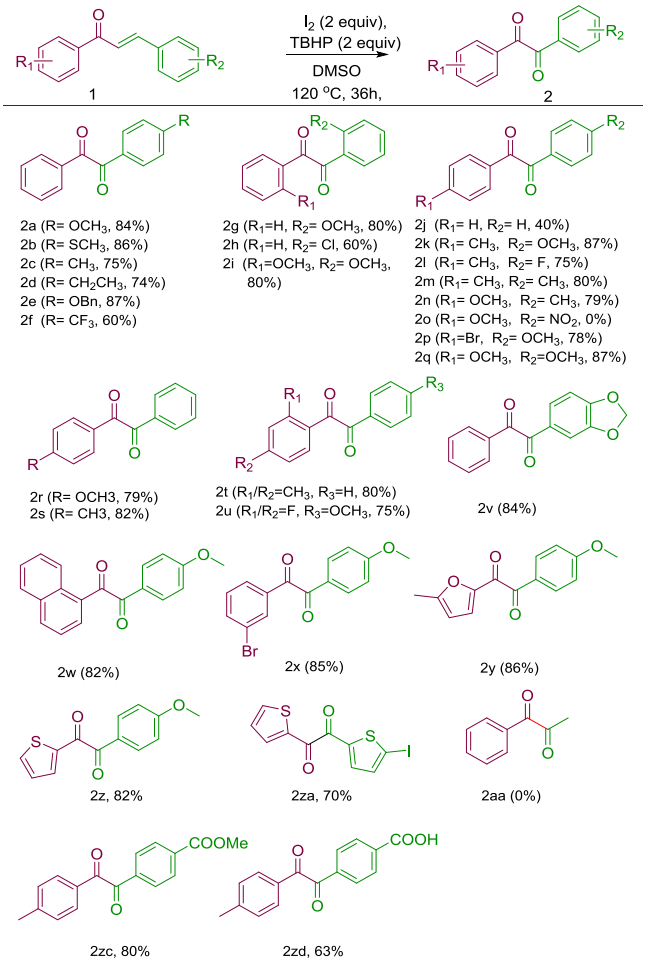
Scheme 2. Substrate Scope for 1,2-Diketones[a]



[a]Reaction condition: **1a** (1 equiv), I_2 (2 equiv), TBHP (2 equiv), DMSO (5 mL), 120 °C, 36 h. Yields mention are isolated yields.

tolerance, and the value of products make this protocol useful for organic synthesis and medicinal chemistry as well.

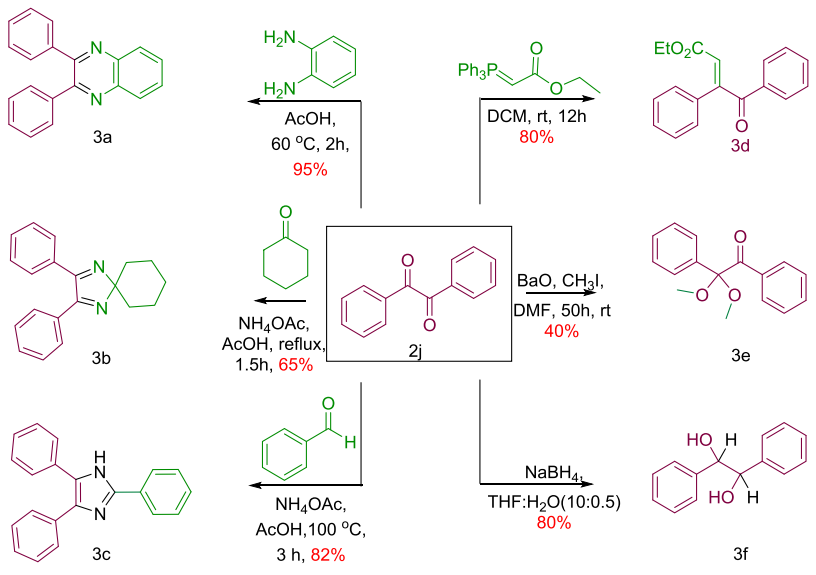
EXPERIMENTAL SECTION

General Procedure. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker ADVANCE 500 (^{1}H:500 MHz, ^{13}C:125 MHz) or a Bruker ADVANCE 400 (^{1}H:400 MHz, ^{13}C:100 MHz), or a Bruker ADVANCE 200 (^{1}H:200 MHz, ^{13}C:50 MHz) unless otherwise mentioned. Deuterated solvent $CDCl_3$ or $CDCl_3$ + CCl_4 (70:30) was used as the internal standard and the singlet at 96.1 ppm in ^{13}C NMR corresponds to carbon of CCl_4. A solvent signal was used as reference for ^{13}C NMR ($CDCl_3$, 77.0 ppm) or ^{13}C NMR (DMSO-d_6, 40.0 ppm). The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiple, br = broad. Chemical shifts are reported in ppm and referenced to residual solvent peak or TMS. Coupling constants are reported in Hertz. High-resolution mass spectra (HRMS) for all compounds were recorded on an ESI+ method and Orbitrap mass analyzer (Thermo Scientific Q-Exactive, Accela 1250 pump).

General Procedure for the α,β-Unsaturated Ketones (1).[23] The substituted acetophenone (1 mmol) and KOH (1 mmol) were dissolved in 5 mL of ethanol. In the above ethanolic solution, substituted benzaldehyde (1 mmol) was added slowly within 10 min and the reaction was stirred for 4 h. On completion [monitored by using thin-layer chromatography (TLC)], the reaction was quenched by ice cold water and extracted with ethyl acetate (5 mL × 3). The combined organic phases were washed with brine solution and dried over anhydrous Na_2SO_4. The crude product was purified by column chromatography using 100−200 mesh silica gel and 10% ethyl acetate in petroleum ether eluent, affording α,β-unsaturated ketones (**1**) in 90−95% yield.

General Procedure for the Oxidative Rearrangement of α,β-Unsaturated Ketones (1) for the Synthesis of 1,2-Diketones (2). To the solution of α,β-unsaturated ketones (**1**) (1 mmol) and iodine (2 mmol) in DMSO (5 mL) was added TBHP (5−6 M in decane, 2 mmol) at room temperature. Then, the reaction mixture was heated at 120 °C for 36 h with constant stirring. After completion of the reaction (monitored by TLC), the reaction mixture was poured into ice cold water and extracted with EtOAc (5 mL ×

Scheme 3. Transformation of 1,2-Diketone



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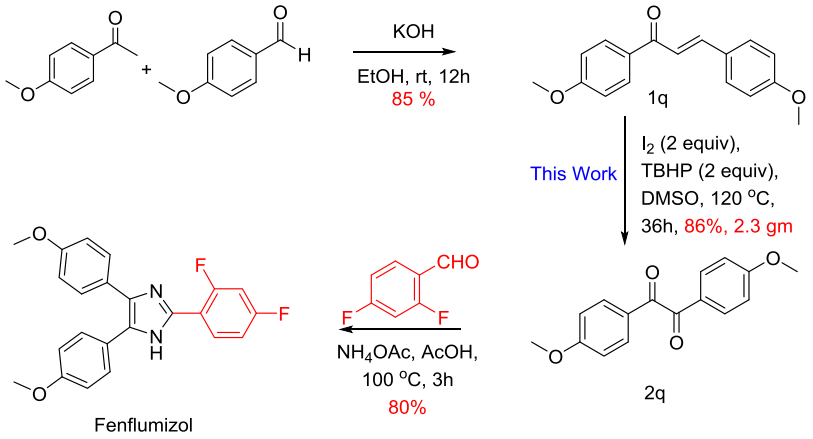
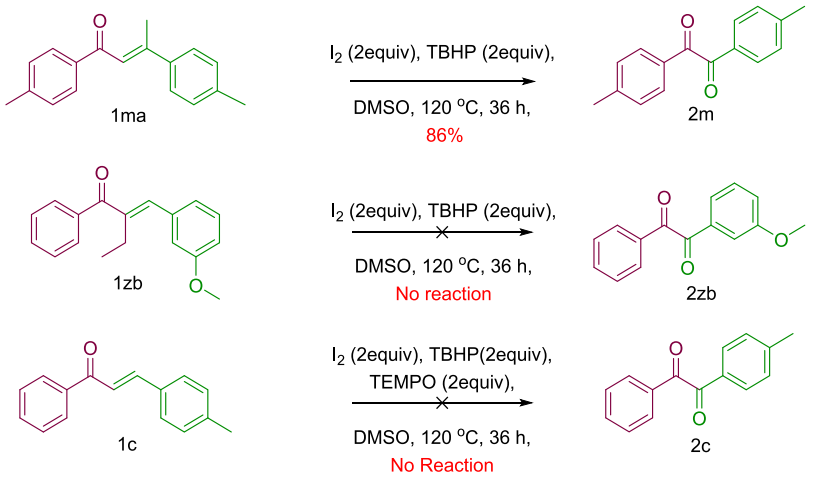
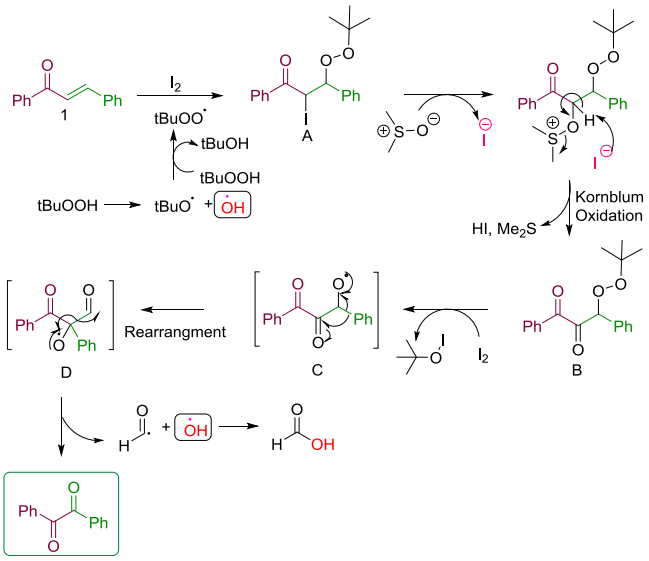
Scheme 4. Gram-Scale Synthesis of 2q, Synthesis of Fenflumizol



Scheme 5. Control Experiments



Scheme 6. Plausible Reaction Mechanism



3). The combined organic layer was washed with ice cold saturated solution of $Na_2S_2O_3$ (to remove iodine) and brine, and dried over anhydrous Na_2SO_4. The crude product was purified by column chromatography on silica gel (100−200 mesh) using ethyl acetate and petroleum ether (EtOAc/PE = 2:98) as an eluent to afford 1,2-diketones (**2**) with 40−86% yield.

Synthesis of Anti-Inflammatory Imidazole-Based Natural Product Fenflumizol from 1,2-Diketone (2q).[22c] To the mixture of 1,2-diketone (**2q**) (1 mmol) and 2,4-difluorobenzaldehyde (1.5 mmol) in AcOH (5.0 mL) and NH_4OAc (3.0 mmol) was added at room temperature. Then, the reaction mixture was heated at 100 °C for 3 h. After completion of the reaction (as monitored by TLC), the reaction mixture was added to ice cold water and extracted with ethyl acetate (5 mL × 3). A combined organic layer wash with brine was performed and it was dried over anhydrous Na_2SO_4. The crude product was purified by column chromatography on silica gel (100−200 mesh) using ethyl acetate and petroleum ether (EtOAc/PE = 2:8) as an eluent to afford 80% yield of Fenflumizol.

*1-(4-Methoxyphenyl)-2-phenylethane-1,2-dione (**2a**).*[9c] Yield: 110 mg, 84%; yellow solid; mp: 58−60 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.87 (s, 3 H), 6.94−6.98 (m, 2 H), 7.45−7.52 (m, 2 H), 7.60−7.66 (m, 1 H), 7.89−8.01 (m, 4 H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 55.7, 96.2, 114.4, 126.2, 129.0, 130.0, 132.5, 133.3, 134.8, 165.0, 193.2, 194.9; HRMS (ESI): calcd for $C_{15}H_{12}O_3Na$ $[M + Na]^+$, 263.0679; found, 263.0676.

*1-(4-(Methylthio)phenyl)-2-phenylethane-1,2-dione (**2b**).*[25a] Yield: 92 mg, 86%; yellow solid; mp: 63−65 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.52 (s, 3 H), 7.25−7.34 (m, 2

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H), 7.47−7.56 (m, 2 H), 7.63−7.69 (m, 1 H), 7.86−7.93 (m, 2 H), 7.94−8.03 (m, 2 H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 14.7, 125.1, 129.1, 129.2, 130.0, 130.2, 133.1, 134.9, 149.1, 193.6, 194.7; HRMS (ESI): calcd for $C_{15}H_{13}O_2S$ $[M + H]^+$, 257.0631; found, 257.0627.

1-Phenyl-2-(p-tolyl)ethane-1,2-dione (**2c**).[9c] Yield: 73 mg, 75%; yellow solid; mp: 94−96 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 2.44 (s, 3 H), 7.31 (d, *J* = 7.82 Hz, 2 H), 7.47−7.57 (m, 2 H), 7.61−7.68 (m, 1 H), 7.87 (d, *J* = 8.31 Hz, 2 H), 7.93−8.01 (m, 2 H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 22.0, 76.8, 77.1, 77.4, 129.1, 129.8, 130.0, 130.1, 130.7, 133.2, 134.9, 146.3, 194.4, 194.9; HRMS (ESI): calcd for $C_{15}H_{13}O_2$ $[M + H]^+$, 225.0910; found, 225.0907.

1-(4-Ethylphenyl)-2-phenylethane-1,2-dione (**2d**).[25b] Yield: 30 mg, 74%; yellow gummy oil; ^1H NMR (500 MHz, $CDCl_3$): δ 1.26 (t, *J* = 7.63 Hz, 3 H), 2.73 (d, *J* = 7.25 Hz, 2 H), 7.34 (m, *J* = 8.01 Hz, 2 H), 7.51 (t, *J* = 7.82 Hz, 2 H), 7.66 (s, 1 H), 7.90 (m, *J* = 8.01 Hz, 2 H), 7.94−8.04 (m, 2 H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 15.1, 29.2, 128.6, 129.0, 129.9, 130.2, 130.8, 133.1, 134.8, 152.4, 194.4, 194.9; HRMS (ESI): calcd for $C_{16}H_{14}O_2Na$ $[M + Na]^+$, 261.0886; found, 261.0885.

1-(4-(Benzyloxy)phenyl)-2-phenylethane-1,2-dione (**2e**).[25c] Yield: 25 mg, 87%; yellow solid; mp: 58−62 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 5.14 (s, 2 H), 7.00−7.06 (m, 2 H), 7.31−7.44 (m, 5 H), 7.46−7.52 (m, 2 H), 7.59−7.66 (m, 1 H), 7.90−7.99 (m, 4 H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 70.4, 115.3, 126.3, 127.6, 128.5, 128.8, 129.1, 130.0, 132.5, 133.3, 134.8, 135.9, 164.2, 193.2, 194.9; HRMS (ESI): calcd for $C_{21}H_{16}O_3Na$ $[M + Na]^+$, 399.0992; found, 399.0985.

1-Phenyl-2-(4-(trifluoromethyl)phenyl)ethane-1,2-dione (**2f**).[9c] Yield: 51 mg, 60%; yellow solid; mp: 44−45 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.51 (t, *J* = 7.79 Hz, 2 H), 7.66 (t, *J* = 7.33 Hz, 1 H), 7.76 (d, *J* = 8.24 Hz, 2 H), 7.96 (d, *J* = 7.79 Hz, 2 H), 8.09 (d, *J* = 8.24 Hz, 2 H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ (126.0, 126.1), 129.2, 130.0, 130.3, 132.7, 135.2, 135.7, 192.9, 193.3; HRMS (ESI): calcd for $C_{15}H_9O_2F_2Na$ $[M + Na]^+$, 301.0447; found, 301.1409.

1-(2-Methoxyphenyl)-2-phenylethane-1,2-dione (**2g**).[8b] Yield: 74 mg, 80%; yellow gummy oil; ^1H NMR (400 MHz, $CDCl_3$): δ 3.94 (s, 3 H), 6.91−7.10 (m, 2 H), 7.37−7.45 (m, 1 H), 7.51−7.70 (m, 4 H), 8.04−8.08 (m, 2 H), 8.17 (d, *J* = 15.89 Hz, 1 H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 55.57, 111.27, 120.78, 122.89, 123.94, 128.56, 129.26, 131.80, 132.58, 138.55, 140.43, 158.84, 191.15; HRMS (ESI): calcd for $C_{15}H_{13}O_3$ $[M + H]^+$, 241.0859; found, 241.0862.

1-(2-Chlorophenyl)-2-phenylethane-1,2-dione (**2h**).[9c] Yield: 34 mg, 60%; yellow solid; mp: 48−49 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.39−7.45 (m, 3 H), 7.49−7.55 (m, 4 H), 7.61−7.67 (m, 1 H), 7.87−7.91 (m, 1 H), 8.00−8.05 (m, 2 H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 127.47, 128.99, 130.32, 130.60, 132.21, 132.54, 134.09, 134.61, 192.09, 193.72; HRMS (ESI): calcd for $C_{14}H_9O_2ClNa$ $[M + Na]^+$, 267.0183; found, 267.0184.

1,2-Bis(2-methoxyphenyl)ethane-1,2-dione (**2i**).[25d] Yield: 57 mg, 80%; yellow solid; mp: 126−128 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 3.62 (s, 3 H), 6.97−6.99 (m, 2 H), 7.13−7.16 (m, 2 H), 7.58−7.61 (m, 2 H), 8.10−8.2 (m, 2 H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 55.88, 112.48, 121.36, 123.44, 130.47, 135.54, 160.37, 192.46; HRMS (ESI): calcd for $C_{14}H_{14}O_4$ $[M + Na]^+$, 293.0784; found, 293.0783.

1,2-Diphenylethane-1,2-dione (**2j**).[9c] Yield: 45 mg, 40%; yellow solid: 94−95 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.50−7.57 (m, 4 H), 7.68 (t, *J* = 7.02 Hz, 2 H), 8.00 (d, *J* = 7.93 Hz, 4 H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 129.06, 129.92, 132.99, 134.94, 194.62; HRMS (ESI): calcd for $C_{14}H_{11}O_2$ $[M + H]^+$, 211.0754; found, 211.0751.

1-(4-Methoxyphenyl)-2-(p-tolyl)ethane-1,2-dione (**2k**).[9c] Yield: 84 mg, 87%; yellow solid; mp: 95−96 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 2.46 (s, 3 H), 3.91 (s, 3 H), 7.00 (d, *J* = 8.80 Hz, 2 H), 7.33 (d, *J* = 7.82 Hz, 2 H), 7.90 (d, *J* = 8.07 Hz, 2 H), 7.97 (d, *J* = 9.05 Hz, 2 H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 22.0, 55.7, 114.4, 126.2, 129.7, 130.1, 130.9, 133.4, 146.1, 164.0, 193.4, 194.6. HRMS (ESI): calcd for $C_{16}H_{14}O_3Na$ $[M + Na]^+$, 277.0835; found, 277.0834.

1-(4-Fluorophenyl)-2-(p-tolyl)ethane-1,2-dione (**2l**).[9b] Yield: 50 mg, 75%; yellow solid; mp: 94−96 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 2.42 (s, 3 H), 7.16 (t, *J* = 8.47 Hz, 2 H), 7.30 (d, *J* = 7.79 Hz, 2 H), 7.85 (d, *J* = 8.24 Hz, 2 H), 7.99 (dd, *J* = 8.93, 5.27 Hz, 2 H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 22.0, 116.3, 116.5, 129.9, 130.0, 130.1, 132.8, 132.9, 146.5, 165.5, 168.1, 193.1, 193.9; HRMS (ESI): calcd for $C_{15}H_{11}O_2FNa$ $[M + Na]^+$, 265.0635; found, 265.0631.

1,2-Di-p-tolylethane-1,2-dione (**2m**).[12b] Yield: 47 mg, 80%; yellow solid; mp: 105−106 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 2.46 (s, 6 H), 7.32 (d, *J* = 7.32 Hz, 4 H), 7.88 (d, *J* = 7.93 Hz, 4 H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 21.9, 129.7, 130.0, 130.7, 146.1, 194.5; HRMS (ESI): calcd for $C_{16}H_{14}O_2Na$ $[M + Na]^+$, 261.0886; found, 261.0884.

1-(4-Methoxyphenyl)-2-(p-tolyl)ethane-1,2-dione (**2n**).[9c] Yield: 55 mg, 79%; yellow solid; mp: 95−96 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 2.46 (s, 3 H), 3.91 (s, 3 H), 7.00 (d, *J* = 8.80 Hz, 2 H), 7.33 (d, *J* = 7.82 Hz, 2 H), 7.90 (d, *J* = 8.07 Hz, 2 H), 7.98 (m, 2 H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 21.9, 55.7, 114.3, 126.2, 129.7, 130.0, 130.8, 132.4, 146.0, 164.9, 193.4, 194.6; HRMS (ESI): calcd for $C_{16}H_{14}O_3Na$ $[M + Na]^+$, 277.0835; found, 277.0834.

1-(4-Bromophenyl)-2-(4-methoxyphenyl)ethane-1,2-dione (**2p**).[25e] Yield: 74 mg, 78%; yellow solid; mp: 147−148 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 3.88 (s, 3 H), 6.97 (d, *J* = 8.70 Hz, 2 H), 7.64 (d, *J* = 8.70 Hz, 2 H), 7.82 (d, *J* = 8.70 Hz, 2 H), 7.92 (d, *J* = 8.70 Hz, 2 H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 55.8 (s), 114.5, 125.9, 130.4, 131.3, 132.0, 132.4, 132.5, 165.2, 192.5, 193.7; HRMS (ESI): calcd for $C_{15}H_{11}O_3BrNa$ $[M + Na]^+$, 340.9784; found, 340.9786.

1,2-Bis(4-methoxyphenyl)ethane-1,2-dione (**2q**).[9c] Yield: 120 mg, 87%; yellow solid; mp: 129−130 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 3.86 (s, 6 H), 6.95 (d, *J* = 9.16 Hz, 4 H), 7.93 (d, *J* = 8.70 Hz, 4 H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 55.7, 114.4, 126.4, 132.5, 164.9, 193.6; HRMS (ESI): calcd for $C_{16}H_{14}O_4Na$ $[M + Na]^+$, 293.0786; found, 293.0783.

1-(4-Methoxyphenyl)-2-phenylethane-1,2-dione (**2r**).[9c] Yield: 50 mg, 79%; yellow solid; mp: 60−61 °C; ^1H NMR (500 MHz, $CDCl_3$): δ 3.92 (s, 3 H), 7.01 (d, *J* = 8.77 Hz, 2 H), 7.53 (t, *J* = 7.82 Hz, 2 H), 7.68 (t, *J* = 7.44 Hz, 1 H), 7.92−8.05 (m, 5 H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 55.7, 114.4, 126.1, 128.5, 129.0, 129.9, 130.2, 132.4, 133.8, 134.8, 165.0, 193.2, 194.9; HRMS (ESI): calcd for $C_{15}H_{12}O_3Na$ $[M + Na]^+$, 263.0679; found, 263.0677.

1-Phenyl-2-(p-tolyl)ethane-1,2-dione (**2s**).[9c] Yield: 45 mg, 82%; yellow solid; mp: 94−96 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 2.43 (s, 3 H), 7.28 (m, *J* = 8.07 Hz, 2 H), 7.48 (t, *J* = 7.70 Hz, 2 H), 7.62 (t, *J* = 7.34 Hz, 1 H), 7.85 (m, *J* = 8.31 Hz, 2 H), 7.95 (d, *J* = 7.34 Hz, 2 H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 22.0, 128.9, 129.7, 129.9, 130.0, 130.7, 133.2,

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134.6, 145.9, 194.0, 194.4; HRMS (ESI): calcd for $C_{15}H_{12}O_2Na$ $[M + Na]^+$, 247.0730; found, 247.0728.

*1-(2,4-Dimethylphenyl)-2-phenylethane-1,2-dione (**2t**).*[9c] Yield: 34 mg, 80%; yellow oil; ^1H NMR (400 MHz, $CDCl_3$): δ 2.40 (s, 3 H), 2.71 (s, 3 H), 7.08−7.12 (m, 1 H), 7.18 (s, 1 H), 7.39−7.46 (m, 1 H), 7.46−7.52 (m, 1 H), 7.52−7.56 (m, 2 H), 7.57 (s, 1 H), 7.64−7.70 (m, 1 H), 7.97 (d, J = 1.22 Hz, 1 H), 7.99 (s, 1 H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 21.7, 22.0, 126.7, 128.4, 129.0, 129.9, 133.5, 134.6, 141.6, 145.0, 145.3, 195.1, 196.5; HRMS (ESI): calcd for $C_{16}H_{15}O_2$ $[M + H]^+$, 239.1067; found, 239.1066.

*1-(2,4-Difluorophenyl)-2-(4-methoxyphenyl)ethane-1,2-dione (**2u**).* Yield: 24 mg, 75%; gummy oil; ^1H NMR (400 MHz, $CDCl_3$): δ 3.88 (s, 3 H), 6.91−7.05 (m, 3 H), 7.24−7.32 (m, 1 H), 7.60 (d, J = 8.80 Hz, 1 H), 7.76 (dd, J = 15.65, 1.47 Hz, 1 H), 7.82−8.00 (m, 1 H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 55.4, 104.4, 104.7, 104.9, 112.0, 112.0, 112.2, 112.3, 114.5, 122.9, 122.9, 127.4, 130.9, 132.0, 132.8, 132.8, 132.9, 132.9, 145.0, 161.9, 187.4, 187.4, 190.8; HRMS (ESI): calcd for $C_{15}H_{11}F_2O_3$ $[M + H]^+$, 277.0664; found, 277.0656.

*1-(Benzo[d][1,3]dioxol-5-yl)-2-phenylethane-1,2-dione (**2v**).*[18] Yield: 80 mg, 84%; yellow solid; mp: 96−98 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 6.11 (s, 2 H), 6.89 (d, J = 8.56 Hz, 1 H), 7.48−7.58 (m, 4 H), 7.62−7.71 (m, 1 H), 7.99 (d, J = 7.34 Hz, 1 H), 8.15 (d, J = 7.34 Hz, 1 H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 102.3, 108.4, 108.4, 108.4, 127.9, 127.9, 128.5, 129.0, 129.9, 130.2, 133.1, 133.8, 134.8, 148.7, 153.5, 192.8, 194.6; HRMS (ESI): calcd for $C_{15}H_{11}O_4Na$ $[M + Na]^+$, 255.0652; found, 255.0646.

*1-(4-Methoxyphenyl)-2-(naphthalen-1-yl)ethane-1,2-dione (**2w**).*[25f] Yield: 65 mg, 82%; yellow solid; mp: 108−110 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 3.86 (s, 3 H), 6.95 (d, J = 9.16 Hz, 2 H), 7.45 (dd, J = 8.24, 7.33 Hz, 1 H), 7.56−7.62 (m, 1 H), 7.71 (ddd, J = 8.59, 6.98, 1.37 Hz, 1 H), 7.87−7.92 (m, 2 H), 7.98 (d, J = 9.16 Hz, 2 H), 8.07 (d, J = 8.24 Hz, 1 H), 9.26−9.30 (m, 1 H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 55.6, 96.2, 114.4, 124.5, 126.1, 126.6, 127.1, 128.8, 129.1, 129.4, 131.1, 132.5, 134.2, 134.9, 135.7, 164.8, 193.1, 197.3; HRMS (ESI): calcd for $C_{19}H_{14}O_3Na$ $[M + Na]^+$, 313.0835; found, 313.0833.

*1-(3-bromophenyl)-2-(4-methoxyphenyl)ethane-1,2-dione (**2x**).* Yield: 55 mg, 85%; yellow solid; mp: 84−85 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 3.91 (s, 3 H), 7.00 (d, J = 8.8 Hz, 2 H), 7.39 (t, J = 7.8 Hz, 1 H), 7.75−7.81 (m, 1 H), 7.89 (d, J = 7.8 Hz, 1 H), 7.95 (m, J = 8.8 Hz, 2 H), 8.13 (t, J = 1.6 Hz, 1 H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 55.7, 77.2, 114.5, 123.3, 125.8, 128.6, 130.5, 132.5, 132.5, 135.0, 137.5, 165.2, 192.1, 193.1; HRMS (ESI): calcd for $C_{15}H_{11}O_3BrNa$ $[M + Na]^+$, 340.9784; found, 340.9786.

*1-(4-Methoxyphenyl)-2-(5-methylfuran-2-yl)ethane-1,2-dione (**2y**).* Yield: 63 mg, 86%; yellow solid; mp: 66−68 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 2.48 (s, 3 H), 3.91 (s, 3 H), 6.27 (d, J = 4.1 Hz, 1 H), 6.97−7.01 (m, 2 H), 7.28−7.31 (m, 1 H), 8.01−8.06 (m, 2 H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 14.3, 55.7, 110.1, 114.3, 125.7, 125.9, 132.4, 132.8, 149.1, 161.2, 165.0, 190.5; HRMS (ESI): calcd for $C_{14}H_{13}O_4Na$ $[M + Na]^+$, 245.0808; found, 245.0811.

*1-(4-Methoxyphenyl)-2-(thiophen-2-yl)ethane-1,2-dione (**2z**).* Yield: 64 mg, 82%; yellow solid; mp: 62−65 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 3.90 (s, 3 H), 6.97 (d, J = 9.16 Hz, 2 H), 7.18 (d, J = 3.66 Hz, 1 H), 7.81 (d, J = 4.27 Hz, 2 H), 8.03 (d, J = 8.55 Hz, 2 H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 55.5, 96.2, 114.2, 125.7, 128.6, 132.7, 136.4, 140.2, 164.9, 185.6, 190.3; HRMS (ESI): calcd for $C_{13}H_{10}O_3NaS$ $[M + Na]^+$, 269.0243; found, 269.0243.

*1-(5-Iodothiophen-2-yl)-2-(thiophen-2-yl)ethane-1,2-dione (**2za**).* Yield: 26 mg, 70%; faint brown oil; ^1H NMR (400 MHz, $CDCl_3$): δ 7.20 (dd, J = 4.81, 3.89 Hz, 1 H), 7.35 (d, J = 4.12 Hz, 1 H), 7.69 (d, J = 4.12 Hz, 1 H), 7.84 (dd, J = 4.81, 1.14 Hz, 1 H), 8.09−8.12 (m, 1 H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 91.2, 128.8, 137.7, 138.0, 138.1, 138.5, 143.6, 180.1, 181.5; HRMS (ESI): calcd for $C_{10}H_5O_2IS_2Na$ $[M + Na]^+$, 370.8668; found, 370.8665.

*Methyl 4-(2-Oxo-2-(p-tolyl)acetyl)benzoate (**2zc**).* Yield: 36 mg, 80%; yellow solid; mp: 80−85 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 2.45 (s, 3 H), 3.96 (s, 3 H), 7.33 (d, J = 8.24 Hz, 2 H), 7.88 (d, J = 8.24 Hz, 2 H), 8.04 (m, J = 8.70 Hz, 2 H), 8.16 (m, J = 8.24 Hz, 2 H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 22.0, 52.6, 129.7, 129.8, 130.0, 130.1, 130.3, 135.2, 136.1, 146.6, 165.9, 193.5, 193.8; HRMS (ESI): calcd for $C_{17}H_{14}O_4Na$ $[M + Na]^+$, 305.0790; found, 305.0801.

*4-(2-Oxo-2-(p-tolyl)acetyl) Benzoic Acid (**2zd**).* Yield: 45 mg, 60%; yellow solid; mp: 95−97 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 2.43 (s, 3 H), 7.26 (d, J = 2.29 Hz, 2 H), 7.28 (s, 2 H), 7.97−8.01 (m, 2 H), 8.01−8.06 (m, 2 H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 21.9, 126.6, 129.3, 130.0, 130.0, 130.2, 130.3, 130.5, 144.7, 172.2, 191.5; HRMS (ESI): calcd for $C_{16}H_{12}O_4Na$ $[M + Na]^+$, 291.0635; found, 291.0652.

*2,3-Diphenylquinoxaline (**3a**).*[22a] Yield: 150 mg, 95%; white solid; mp: 128 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.28−7.39 (m, 6 H), 7.52 (dd, J = 8.01, 1.60 Hz, 4 H), 7.72−7.78 (m, 2 H), 8.16−8.20 (m, 2 H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 128.4, 128.9, 129.3, 129.9, 130.0, 139.2, 141.3, 153.6; HRMS (ESI): calcd for $C_{20}H_{15}N_2$ $[M + H]^+$, 283.1230; found, 283.1230.

*2,3-Diphenyl-1,4-diazaspiro [4.5] Deca-1,3-diene (**3b**).*[22a] Yield: yield: 154 mg, 65%; white solid; mp: 88−90 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 1.73 (d, J = 5.95 Hz, 2 H), 1.76−1.84 (m, 4 H), 1.89−2.00 (m, 4 H), 7.31−7.37 (m, 4 H), 7.39−7.44 (m, 2 H), 7.46−7.52 (m, 4 H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 24.2, 25.7, 34.8, 104.2, 128.4, 129.0, 130.0, 133.1, 164.1; HRMS (ESI): calcd for $C_{20}H_{21}N_2$ $[M + H]^+$, 289.1699; found, 289.1700.

*2,4,5-Triphenyl-1H-imidazole (**3c**).*[26a] Yield: 65 mg, 82%; white solid; mp: 276−278 °C; ^1H NMR (400 MHz, DMSO-d_6): δ 7.13−7.22 (m, 1 H), 7.22−7.30 (m, 2 H), 7.30−7.37 (m, 2 H), 7.37−7.49 (m, 6 H), 7.53 (d, J = 7.33 Hz, 2 H), 8.03−8.08 (m, 2 H); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6): δ 125.7, 127.0, 127.6, 128.3, 128.7, 128.8, 129.0, 129.2, 129.2, 130.9, 131.6, 135.7, 137.6, 146.0; HRMS (ESI): calcd for $C_{21}H_{17}N_2$ $[M + H]^+$, 297.1386; found, 297.1386.

*Ethyl 4-Oxo-3,4-diphenylbut-2-enoate (**3d**).*[26b] Yield: 54 mg, 80%; faint yellow solid; mp: 82−84 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 1.13 (t, J = 7.21 Hz, 3 H), 4.09 (q, J = 7.09 Hz, 2 H), 6.53 (s, 1 H), 7.32−7.62 (m, 9 H), 7.88−8.08 (m, 2 H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 13.9, 60.9, 117.9, 127.0, 128.8, 129.0, 129.0, 129.1, 130.5, 133.5, 134.3, 136, 155.5, 165.1, 196.4; HRMS (ESI): calcd for $C_{18}H_{16}O_3Na$ $[M + Na]^+$, 303.0992; found, 303.0988.

*2,2-Dimethoxy-1,2-diphenylethan-1-one (**3e**).*[26c] Yield: 45 mg, 40%; white solid; mp: 65−67 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 3.21 (s, 6 H), 7.25−7.42 (m, 6 H), 7.58−7.67 (m, 2 H), 8.06 (dd, J = 7.56, 1.14 Hz, 2 H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 50.1 (s), 103.7, 127.0, 128.2, 128.6, 129.0, 130.0, 133.0, 134.3, 136.9, 195.2; HRMS (ESI): calcd for $C_{16}H_{16}O_3Na$ $[M + Na]^+$, 279.0992; found, 279.0988.

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*1,2-Diphenylethane-1,2-diol (**3f**).*[4] Yield: 132 mg, 80%; white solid; mp: 140 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.33 (br s, 2 H), 4.80 (s, 2 H), 7.12−7.37 (m, 11 H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 78.15, 127.18, 128.17, 128.30, 139.84; HRMS (ESI): calcd for $C_{14}H_{14}O_2Na$ $[M + Na]^+$, 237.0886; found, 237.0885.

Fenflumizol. Yield: 44 mg, 80%; colorless liquid; ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.78−3.87 (m, 6 H), 6.85−7.08 (m, 6 H), 7.47 (d, J = 8.46 Hz, 4 H), 8.28−8.46 (m, 1 H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 55.0, 103.6, 103.9, 104.1, 112.1, 112.3, 113.8, 114.0, 128.7, 129.7, 129.7, 129.8, 132.1, 139.6, 158.0, 158.1, 158.8, 160.0, 160.1, 161.2, 161.3, 163.2, 163.3; HRMS (ESI): calcd for $C_{23}H_{19}O_2N_2F_2$ $[M + H]^+$, 393.1409; found, 393.1407.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsomega.9b00833.

^{1}H and ^{13}C spectra of all the compounds and GC−MS data for the byproduct formic acid (PDF)

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Notes

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