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Synthetic Route to Enaminones via Metal-Free Four-Component Sequential Reactions of Aryl Olefins with $CHCl_3$, Et_3N, and TBHP

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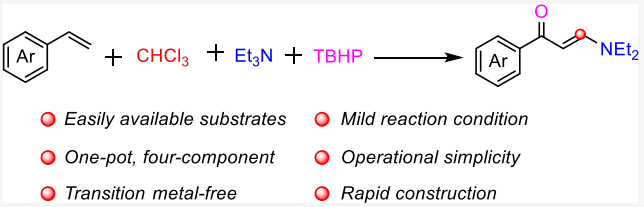
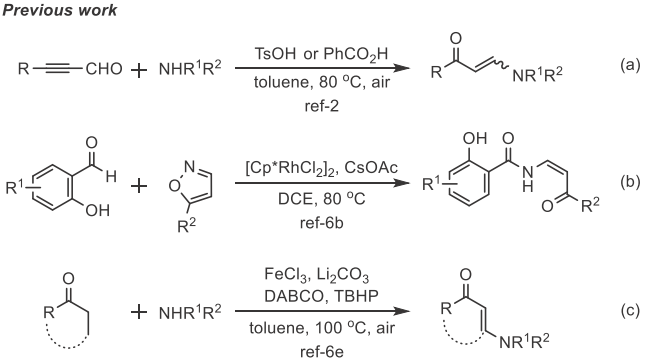
ABSTRACT: An efficient and modular strategy was used to obtain enaminones with a wide range of functional groups *via* a four-component sequential reaction. This reaction proceeded under mild conditions without a catalyst in one pot. Furthermore, the products could be transformed into thiadiazoles.



INTRODUCTION

Enaminones are important synthetic intermediates for the synthesis of various heterocyclic compounds.[1] Furthermore, the enaminone skeleton is present in drug molecules and natural products. Some new methods for enaminone synthesis have been developed in recent years.[2−6] For example, in 2016, Jang and co-workers reported the stereocontrolled Brønsted-acid-catalyzed rearrangement of hemiaminals to afford synthetically and biologically useful enaminones (Scheme 1a).[2] In 2019, the

Scheme 1. Synthetic Routes to Enaminones

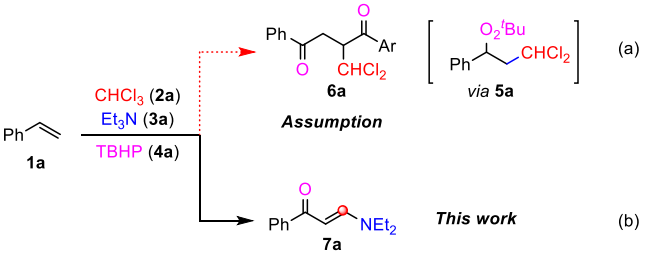


Maji group developed a phenol-directed Umpolung reactivity strategy for the Cp*Rh(III)-catalyzed C−H functionalization of aldehydes to obtain stereospecific acyclic *Z*-enaminones (Scheme 1b).[6b] An iron-catalyzed process for the synthesis of enaminones from ketones and amines was reported by the Chen group in the same year (Scheme 1c).[6e] Despite remarkable progress in this field, some drawbacks remain, such as the use of expensive transition-metal catalysts, superstoichiometric amounts of oxidant reagents, and harsh reaction conditions. Therefore, the development of concise and efficient methods for the synthesis of enaminones under metal-free, mild, and environmentally benign conditions remains highly desirable and challenging.

Multicomponent reactions have received much attention in molecular synthesis owing to their notable features regarding cost, atom and step economy, and synthetic divergence.[7] Furthermore, this powerful strategy can reliably construct highly functionalized compounds with structural complexity from simple and readily available starting materials in one pot.[8]

Additionally, the direct vicinal difunctionalization of alkenes, which installs two functional groups on a C═C bond in a single process, has emerged as a powerful tool for the generation of highly useful and complex skeletons.[9] Owing to renewed interest in radical chemistry, the radical difunctionalization of alkenes has attracted increasing research attention.[10] Continuing our research interest in alkene difunctionalization,[11−13] we envisaged that 1,4-diketones could be obtained by reacting olefins, tert-butyl hydroperoxide (TBHP), and $CHCl_3$ in a one-pot manner (Scheme 2a).

Scheme 2. Difunctionalization of Alkenes with TBHP



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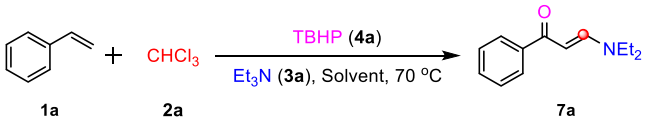
RESULTS AND DISCUSSION

To examine the feasibility of this hypothesis, we conducted initial trials using styrene (**1a**) and $CHCl_3$ as model substrates with TBHP (4.0 equiv) as the radical initiator and Et_3N as the solvent at 70 °C. Although expected product **6a** was not obtained, enaminone **7a** was isolated as the major product (Scheme 2b), suggesting that Et_3N acted as a substrate in the reaction. Encouraged by these results, the reaction was conducted using styrene (**1a**), $CHCl_3$ (**2a**), Et_3N (**3a**), and TBHP (**4a**) as benchmark substrates to screen for optimal reaction conditions (Table 1). To our delight, four-component

Table 1. Optimization of Reaction Conditions[a]



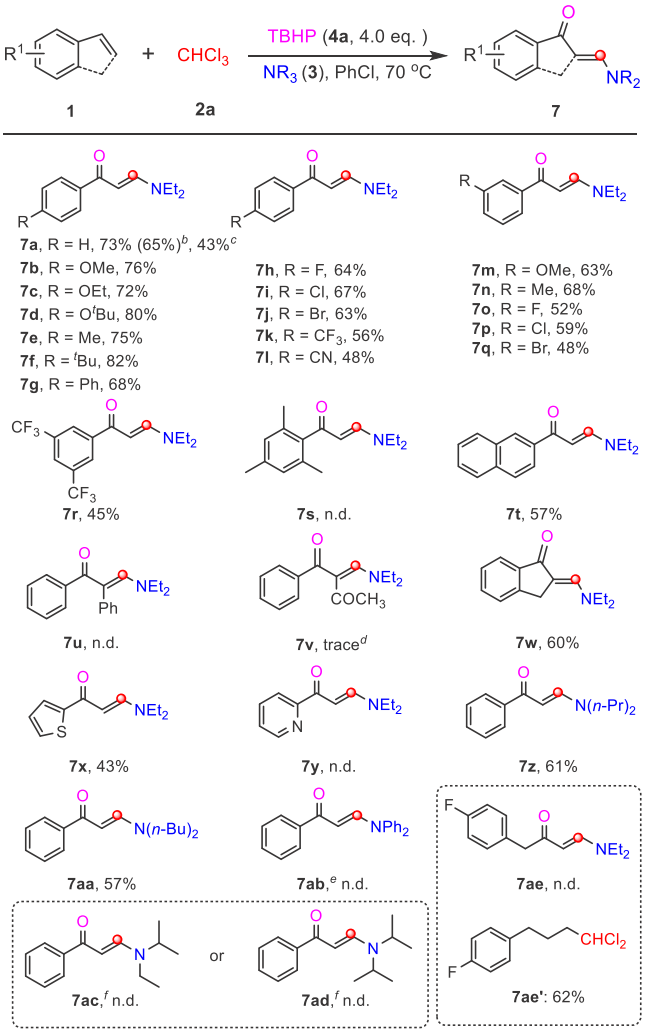
entry	solvent	2a/3a (equiv)	t/°C	TBHP (equiv)	7a/%
1[b]			70	4.0	56
2	DMSO	3.0/3.0	70	4.0	12
3	DMF	3.0/3.0	70	4.0	65
4	dioxane	3.0/3.0	70	4.0	59
5	**PhCl**	**3.0/3.0**	**70**	**4.0**	**73**
6	toluene	3.0/3.0	70	4.0	56
7	CH_3CN	3.0/3.0	70	4.0	69
8	PhCl	2.0/2.0	70	4.0	37
9	PhCl	4.0/4.0	70	4.0	67
10	PhCl	5.0/5.0	70	4.0	70
11	PhCl	3.0/3.0	70	2.0	42
12	PhCl	3.0/3.0	70	3.0	57
13	PhCl	3.0/3.0	70	5.0	69
14	PhCl	3.0/3.0	70	8.0	72
15[c]	PhCl	3.0/3.0	r.t.	4.0	49
16	PhCl	3.0/3.0	50	4.0	53
17	PhCl	3.0/3.0	60	4.0	62
18	PhCl	3.0/3.0	80	4.0	58

[a]Unless noted otherwise, the reaction was performed in air by using **1a** (0.5 mmol), **2a** (1.5 mmol), **3a** (1.5 mmol), and **4a** (2.0 mmol) in the solvent (1.0 mL) at 70 °C for 8 h. [b]**2a** (1.0 mL), **3a** (1.0 mL). [c]30 h.

product **7a** was delivered in 56% yield in a one-pot manner (Table 1, entry 1). To improve the efficiency, we examined the solvent effect by screening various reaction media [DMSO, DMF, dioxane, chlorobenzene (PhCl), toluene (PhMe), and CH_3CN] using **2a** (3.0 equiv) and **3a** (3.0 equiv), with PhCl (73% yield) performing better than the other solvents (entries 2−7). No improvement was obtained by increasing or decreasing the amounts of **2a** and **3a** (entries 8−10). As the next optimization step, we investigated using different amounts of TBHP, which resulted in lower yields of **7a** (entries 11−14). Unfortunately, the desired product **7a** was obtained in a lower yield (49%) when the reaction was conducted at room temperature (entry 15). The yield of **7a** clearly decreased at reaction temperatures above or below 70 °C (entries 16−18).

With optimized reaction conditions in hand (Table 1, entry 5), we examined the substrate scope of this four-component sequential reaction, with the results summarized in Table 2. Substituents with different electronic properties at the para-position of the aromatic ring were examined, with all tolerated well to give the desired products in moderate to good yields (**7b**−**l**). Electron-rich groups (**1b**−**g**) resulted in better yields

Table 2. Substrate Scope for the Synthesis of 7[a]



[a]Unless otherwise specified, all reactions were carried out by using **1** (0.5 mmol), **2a** (1.5 mmol), **3** (1.5 mmol), and **4a** (2.0 mmol) in PhCl (1.0 mL) at 70 °C for 8 h. [b]5 mmol of **1a** was used, 12 h. [c]1.5 mmol $CHBr_3$ was used instead of $CHCl_3$. [d]**7v** could be detected in the crude product. [e]*N*-methyl-*N*-phenylaniline was used instead of Et_3N. [f]Hunig's base (diisopropylethylamine) was used instead of Et_3N.

than electron-deficient groups (**1h**−**l**). Furthermore, all substrates with electron-donating or electron-withdrawing groups on the meta-position of the phenyl ring were smoothly transformed into the corresponding desired products in 48%−68% yields (**7m**−**q**). Additionally, 3,5-disubstituted substrate **1r** furnished the corresponding product **7r**. However, 2,4,6-trisubstituted styrene **1s** could not provide the desired product under the optimized conditions, which was attributed to the steric effect of the olefin. We also tried 2-substituted substrates (2-F, 2-Cl); it turned out that only a trace amount of the desired product was obtained and it could not be separated from the impurity substance (see the Supporting Information for details). Pleasingly, 2-naphthyl-substituted substrate **1t** participated in the reaction, affording **7t** in 57% yield. 1,2-Disubstituted olefins failed to react under the standard conditions (**7u** and **7v**). Indanone derivative **7w** was obtained in 60% yield from the reaction of indene **1w**. To our delight, replacing the phenyl group in **1a** with a heterocycle (thiophene) in **1x** caused only a

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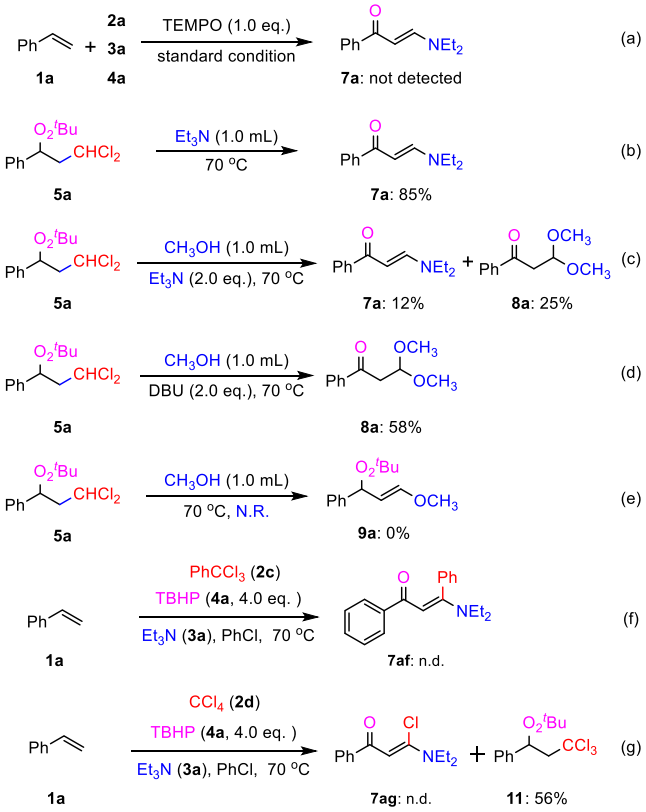
slight drop in yield (43%). In contrast, the desired product **7y** containing a pyridine ring was not formed, with the starting material mostly recovered. Tripropylamine and tributylamine were also compatible with this mild metal-free protocol, giving corresponding products **7z** and **7aa** in 61 and 57% yields, respectively. Unfortunately, *N*-methyl-*N*-phenylaniline was not a good candidate for this transformation (**7ab**). When the reaction was operated with diisopropylethylamine instead of Et_3N, however, neither **7ac** nor **7ad** was formed. No desired product **7ae** was detected when the alkyl olefin was used as the substrate, only the **7ae′** was obtained in 62% yield.[12]

Further experiments were conducted to better understand the mechanistic pathway (Scheme 3). First, adding radical trap agent 2,2,6,6-(tetramethylpiperidin-1-yl)oxyl (TEMPO) to the reaction under the optimized conditions led to no formation of product **7a** (Scheme 3a). Furthermore, enaminone **7a** was obtained when **5a**[11] was treated with Et_3N, suggesting that **5a** might be the intermediate product and that Et_3N acted as a nucleophilic reagent (Scheme 3b). Other than the expected product **7a** (12%), **8a** was also detected in 25% yield when the reaction was performed in CH_3OH using 2.0 equiv of Et_3N (Scheme 3c). Compound **8a**[14] was also generated in 58% yield when Et_3N was replaced by 1,5-diazabicyclo[5.4.0]undecene-5-ene (DBU) (Scheme 3d). Furthermore, no reaction occurred in the absence of Et_3N or DBU (Scheme 3e). In order to further explore the scope of the substrates, several other halogenated substrates were tested (**2c** and **2d**); all of the tested reactions did not work at all (Scheme 3f,g).

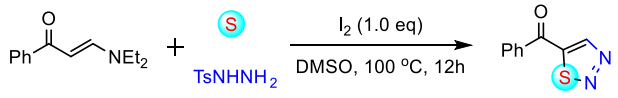
Based on the above results and related work,[11,12,15] we proposed a tentative mechanism for the formation of enaminone **7a** (Scheme 4). First, $^{\bullet}CHCl_2$ and $^{t}BuOO^{\bullet}$ radicals are generated by the reaction with TBHP, which then add to the styrene sequentially, forming the intermediate product **5a**.[11] Intermediate **5a** then undergoes a Kornblum−DeLaMare rearrangement[7,16] to give **G** in the presence of Et_3N. Subsequently, intermediate **G** goes through elimination by an amine to provide a *β*-chloro-*α*,*β*-unsaturated ketone **H**. Next, intermediate **I** is formed *via* conjugate addition of the amine to this *α*,*β*-unsaturated ketone, and then ethyl is removed by the aid of Cl^- to give **J**. Finally, **J** undergoes elimination to furnish the desired product **7a**, accompanied by HCl release.

To highlight the synthetic utility of these enaminone products, a further transformation of **7a** was performed (Scheme 5). When **7a** was treated with elemental sulfur, I_2, and *p*-toluenesulfonyl hydrazide in DMSO at 100 °C, thiadiazole **10** was obtained in 75% yield.[17]

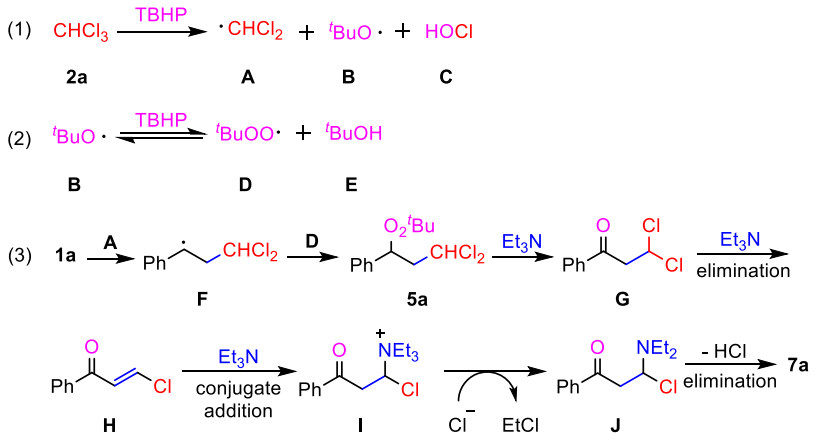
Scheme 3. Mechanistic Investigations



Scheme 5. Synthetic Transformation of 7a



Scheme 4. Possible Mechanism for the Synthesis of 7a



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CONCLUSIONS

In conclusion, we have developed a novel one-pot, catalyst-free, four-component sequential reaction for the construction of enaminones in moderate to good yields from aryl olefins using TBHP, chloroform, and triethylamine. Using this approach, multiple bonds were broken and formed under a single set of reaction conditions without any modification or adding other reagents. Mechanistically, the experimental results showed that the reaction proceeded *via* a radical addition/nucleophilic substitution/elimination process. In addition, the products could be further transformed into thiadiazoles. We anticipate that these transformations will be of high value in heterocycle and medicinal chemistry.

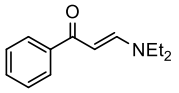
EXPERIMENTAL SECTION

General Information. Unless otherwise stated, compounds **1**−**4** and solvents were commercially available and used without purification, and styrene derivatives **1** are known compounds. All reactions (for the synthesis of **7**) were carried out at 70 °C for 8 h in a round-bottom flask equipped with a magnetic stir bar. ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded on a Bruker AVANCE NMR spectrometer (400 or 500 MHz for ^{1}H; 100 or 126 MHz for ^{13}C; and 376 MHz for ^{19}F) in $CDCl_3$ with tetramethylsilane as the internal standard. Chemical shifts (δ) are reported in ppm, and coupling constants (J) are in Hertz (Hz). Mass spectra were obtained from high-resolution ESI mass spectrometer. HR-MS were obtained on a quadrupole time-of-flight (Q-TOF) micro spectrometer.

General Procedures for the Preparation of 7. A mixture of styrene (**1**) (0.5 mmol), $CHCl_3$ (1.5 mmol, 179 mg), Et_3N (1.5 mmol, 151.8 mg), TBHP (2.0 mmol, 257.5 mg, 70% in water), and chlorobenzene (1.0 mL) was added successively in a round-bottom flask, and the resulting solution was stirred for 8 h at 70 °C. The mixture was purified by column chromatography on silica gel to afford the product.

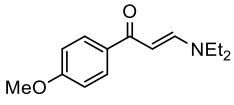
Larger Scale Reaction. A mixture of styrene (**1a**, 5 mmol, 0.52 g), $CHCl_3$ (**2a**, 15 mmol, 1.79 g), Et_3N (**3a**, 15 mmol, 1.518 g), TBHP (**4a**, 20 mmol, 2.575 g, 70% in water), and chlorobenzene (10 mL) was added successively in a round-bottom flask, and the resulting solution was stirred for 12 h at 70 °C. The mixture was purified by column chromatography on silica gel to afford product **7a** (65%, 0.659 g).

*(E)-3-(Diethylamino)-1-phenylprop-2-en-1-one (**7a**).*[3] Yield: 73% (74.1 mg), yellow liquid; R_f = 0.40 (EtOAc/petroleum ether = 1/2). ^{1}H



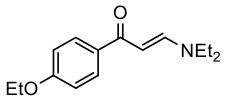
NMR (400 MHz, $CDCl_3$): δ 7.89 (dt, J = 6.6, 1.6 Hz, 2H), 7.82 (d, J = 12.5 Hz, 1H), 7.48−7.38 (m, 3H), 5.77 (d, J = 12.5 Hz, 1H), 3.38−3.27 (m, 4H), and 1.24 (t, J = 7.2 Hz, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 188.8, 152.4, 140.8, 130.8, 128.1, 127.5, 91.7, 50.6, 42.9, 14.8, and 11.6. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{13}H_{18}NO$, 204.1383; found, 204.1386.

*(E)-3-(Diethylamino)-1-(4-methoxyphenyl)prop-2-en-1-one (**7b**).* Yield: 76% (88.5 mg), yellow liquid; R_f = 0.37 (EtOAc/petroleum ether



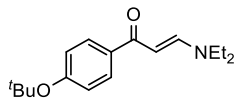
= 1/2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91−7.87 (m, 2H), 7.80 (d, J = 12.5 Hz, 1H), 6.93−6.89 (m, 2H), 5.76 (d, J = 12.5 Hz, 1H), 3.84 (s, 3H), 3.32 (q, J = 7.1 Hz, 4H), and 1.23 (t, J = 7.2 Hz, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 187.6, 161.9, 152.0, 133.3, 129.4, 113.3, 91.2, 55.3, 50.4, 42.9, 14.9, and 11.7. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{14}H_{20}NO_2$, 234.1489; found, 234.1481.

*(E)-3-(Diethylamino)-1-(4-ethoxyphenyl)prop-2-en-1-one (**7c**).* Yield: 72% (88.9 mg), yellow liquid; R_f = 0.37 (EtOAc/petroleum



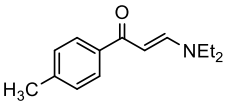
ether = 1/2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92−7.87 (m, 2H), 7.82 (d, J = 12.5 Hz, 1H), 6.94−6.89 (m, 2H), 5.78 (d, J = 12.5 Hz, 1H), 4.10 (q, J = 7.0 Hz, 2H), 3.34 (q, J = 7.1 Hz, 4H), 1.45 (t, J = 7.0 Hz, 3H), and 1.25 (t, J = 7.2 Hz, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 187.6, 161.3, 151.9, 133.2, 129.4, 113.8, 91.2, 63.5, and 14.8. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{15}H_{22}NO_2$, 248.1645; found, 248.1646.

*(E)-1-(4-(tert-Butoxy)phenyl)-3-(diethylamino)prop-2-en-1-one (**7d**).* Yield: 80% (110 mg), yellow liquid; R_f = 0.39 (EtOAc/petroleum



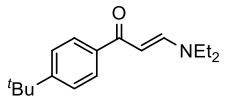
ether = 1/2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87−7.80 (m, 3H), 7.05−7.00 (m, 2H), 5.78 (d, J = 12.5 Hz, 1H), 3.38−3.31 (m, 4H), 1.40 (s, 9H), and 1.25 (d, J = 7.2 Hz, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 188.0, 158.2, 152.1, 135.6, 128.6, 122.9, 91.5, 79.1, 50.5, 42.9, 28.9, 14.7, and 11.5. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{17}H_{26}NO_2$, 276.1958; found, 276.1960.

*(E)-3-(Diethylamino)-1-(p-tolyl)prop-2-en-1-one (**7e**).* Yield: 75% (81.4 mg), yellow liquid; R_f = 0.41 (EtOAc/petroleum ether = 1/2). ^{1}H



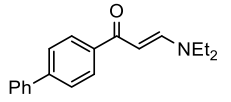
NMR (400 MHz, $CDCl_3$): δ 7.85−7.80 (m, 3H), 7.23 (d, J = 7.9 Hz, 2H), 5.78 (d, J = 12.5 Hz, 1H), 3.34 (q, J = 7.0 Hz, 4H), 2.40 (s, 3H), and 1.25 (t, J = 7.2 Hz, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 188.6, 152.2, 141.1, 138.0, 128.8, 127.6, 91.6, 50.6, 43.0, 14.7, and 11.6. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{14}H_{20}NO$, 218.1539; found, 218.1539.

*(E)-1-(4-(tert-Butyl)phenyl)-3-(diethylamino)prop-2-en-1-one (**7f**).* Yield: 82% (106.2 mg), yellow liquid; R_f = 0.43 (EtOAc/petroleum



ether = 1/2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87−7.81 (m, 3H), 7.45 (dd, J = 8.6, 2.0 Hz, 2H), 5.79 (d, J = 12.6 Hz, 1H), 3.34 (q, J = 7.0 Hz, 4H), 1.35 (s, 9H), and 1.25 (t, J = 7.2 Hz, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 188.6, 154.2, 152.1, 138.0, 127.3, 125.0, 91.7, 50.5, 42.8, 34.9, 31.2, 14.9, and 11.5. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{17}H_{26}NO$, 260.2009; found, 260.2002.

*(E)-1-([1,1′-Biphenyl]-4-yl)-3-(diethylamino)prop-2-en-1-one (**7g**).* Yield: 68% (94.9 mg), yellow liquid; R_f = 0.41 (EtOAc/petroleum



ether = 1/2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02−7.98 (m, 2H), 7.87 (d, J = 12.5 Hz, 1H), 7.68−7.62 (m, 4H), 7.46 (td, J = 6.8, 6.4, 1.6 Hz, 2H), 7.40−7.35 (m, 1H), 5.84 (d, J = 12.5 Hz, 1H), 3.34 (q, J = 7.0 Hz, 4H), and 1.25 (t, J = 7.2 Hz, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 188.2, 152.4, 143.5, 140.5, 139.5, 128.8, 128.0, 127.7, 127.2, 126.8, 91.7, 50.6, 42.9, 14.8, and 11.6. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{19}H_{22}NO$, 280.1696; found, 280.1693.

*(E)-3-(Diethylamino)-1-(4-fluorophenyl)prop-2-en-1-one (**7h**).* Yield: 64% (70.7 mg), yellow liquid; R_f = 0.40 (EtOAc/petroleum ether = 1/2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89 (td, J = 6.0, 2.8 Hz, 2H), 7.84−7.77 (m, 1H), 7.05 (td, J = 8.7, 2.7 Hz, 2H), 5.71 (d, J = 12.5 Hz, 1H), 3.31 (s, 4H), and 1.22 (s, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 187.1, 164.4 (d, J = 250.4 Hz), 152.5, 136.9 (d, J = 3.0 Hz),

https://doi.org/10.1021/acs.joc.1c00823
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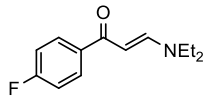
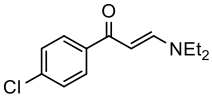


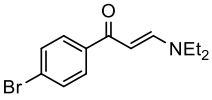
136.9, 129.7 (d, J = 8.8 Hz), 114.9 (d, J = 21.5 Hz). 91.1, 50.6, 42.8, 14.8, and 11.5. ^{19}F NMR (376 MHz, $CDCl_3$): δ −109.80. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{13}H_{17}FNO$, 222.1289; found, 222.1307.

*(E)-1-(4-Chlorophenyl)-3-(diethylamino)prop-2-en-1-one (**7i**).* Yield: 67% (79.4 mg), yellow liquid; R_f = 0.40 (EtOAc/petroleum



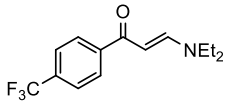
ether = 1/2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85−7.79 (m, 3H), 7.39−7.33 (m, 2H), 5.71 (d, J = 12.5 Hz, 1H), 3.33 (d, J = 7.3 Hz, 4H), and 1.23 (t, J = 7.0 Hz, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 187.2, 152.7, 139.1, 136.8, 128.9, 128.3, 91.2, 50.7, 42.9, 14.8, and 11.6. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{13}H_{17}ClNO$, 238.0993; found, 238.0995.

*(E)-1-(4-Bromophenyl)-3-(diethylamino)prop-2-en-1-one (**7j**).* Yield: 63% (88.5 mg), yellow liquid; R_f = 0.40 (EtOAc/petroleum



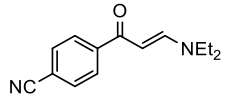
ether = 1/2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 (d, J = 12.5 Hz, 1H), 7.74 (d, J = 8.5 Hz, 2H), 7.51 (d, J = 8.5 Hz, 2H), 5.69 (d, J = 12.5 Hz, 1H), 3.32 (d, J = 16.9 Hz, 4H), and 1.21 (t, J = 6.6 Hz, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 187.2, 152.7, 139.5, 131.2, 129.1, 125.3, 91.1, 50.6, 42.9, 14.8, and 11.6. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{13}H_{17}BrNO$, 282.0488; found, 282.0484.

*(E)-3-(Diethylamino)-1-(4-(trifluoromethyl)phenyl)prop-2-en-1-one (**7k**).* Yield: 56% (75.9 mg), yellow liquid; R_f = 0.41 (EtOAc/



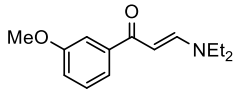
petroleum ether = 1/2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 (d, J = 8.1 Hz, 2H), 7.87 (d, J = 12.4 Hz, 1H), 7.68 (d, J = 8.1 Hz, 2H), 5.75 (d, J = 12.5 Hz, 1H), 3.42−3.33 (m, 4H), and 1.30−1.25 (m, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 187.3, 153.0, 144.0, 132.2 (q, J = 32.3 Hz), 127.7, 125.4, 125.1 (q, J = 3.8 Hz), 122.7, 120.0, 91.5, 50.8, 43.0, 14.7, and 11.6. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{14}H_{17}F_3NO$, 272.1257; found, 272.1256.

*(E)-4-(3-(Diethylamino)acryloyl)benzonitrile (**7l**).* Yield: 48% (54.7 mg), yellow liquid; R_f = 0.36 (EtOAc/petroleum ether = 1/2). ^{1}H NMR



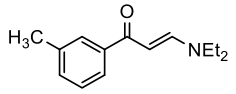
(400 MHz, $CDCl_3$): δ 7.96 (d, J = 8.4 Hz, 2H), 7.87 (d, J = 12.4 Hz, 1H), 7.73−7.69 (m, 2H), 5.72 (d, J = 12.4 Hz, 1H), 3.42−3.33 (m, 4H), and 1.26 (t, J = 6.9 Hz, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 186.5, 153.3, 144.6, 132.0, 127.9, 118.7, 113.9, 91.3, 50.9, 43.1, 14.7, and 11.6. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{14}H_{17}N_2O$, 229.1335; found, 229.1351.

*(E)-3-(Diethylamino)-1-(3-methoxyphenyl)prop-2-en-1-one (**7m**).* Yield: 63% (73.4 mg), yellow liquid; R_f = 0.37 (EtOAc/



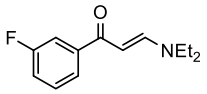
petroleum ether = 1/2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (d, J = 12.5 Hz, 1H), 7.51−7.44 (m, 2H), 7.33 (t, J = 8.0 Hz, 1H), 7.05−6.98 (m, 1H), 5.77 (d, J = 12.5 Hz, 1H), 3.88 (s, 3H), 3.41−3.29 (m, 4H), and 1.26 (t, J = 6.9 Hz, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 188.5, 159.6, 152.5, 142.4, 129.0, 119.9, 117.0, 112.4, 91.8, 55.4, 50.6, 42.9, 14.8, and 11.6. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{14}H_{20}NO_2$, 234.1489; found, 234.1512.

*(E)-3-(Diethylamino)-1-(m-tolyl)prop-2-en-1-one (**7n**).* Yield: 68% (73.8 mg), yellow liquid; R_f = 0.41 (EtOAc/petroleum ether = 1/2). ^{1}H



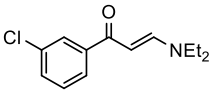
NMR (400 MHz, $CDCl_3$): δ 7.82 (d, J = 12.6 Hz, 1H), 7.71 (s, 1H), 7.67 (d, J = 7.3 Hz, 1H), 7.33−7.26 (m, 2H), 5.77 (d, J = 12.6 Hz, 1H), 3.34 (q, J = 6.9 Hz, 4H), 2.41 (s, 3H), and 1.25 (t, J = 7.2 Hz, 7H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 189.1, 152.4, 140.8, 137.8, 131.5, 128.1, 128.0, 124.6, 91.9, 50.5, 42.9, 21.4, 14.8, and 11.7. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{14}H_{20}NO$, 218.1539; found, 218.1540.

*(E)-3-(Diethylamino)-1-(3-fluorophenyl)prop-2-en-1-one (**7o**).* Yield: 52% (57.5 mg), yellow liquid; R_f = 0.40 (EtOAc/petroleum



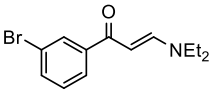
ether = 1/2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 (d, J = 12.5 Hz, 1H), 7.67 (d, J = 7.7 Hz, 1H), 7.59 (dt, J = 9.9, 1.9 Hz, 1H), 7.39 (td, J = 7.9, 5.7 Hz, 1H), 7.15 (td, J = 8.0, 2.6 Hz, 1H), 5.73 (d, J = 12.5 Hz, 1H), 3.56−3.28 (m, 4H), and 1.27 (s, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 187.1, 162.8 (d, J = 246.1 Hz), 152.8, 143.2 (d, J = 5.9 Hz), 129.6 (d, J = 7.7 Hz), 123.0 (d, J = 2.9 Hz), 117.6 (d, J = 21.5 Hz), 114.3 (d, J = 21.9 Hz), 91.3, 50.7, 42.9, 14.8, and 11.6. ^{19}F NMR (376 MHz, $CDCl_3$): δ −113.33. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{13}H_{17}FNO$, 222.1289; found, 222.1310.

*(E)-1-(3-Chlorophenyl)-3-(diethylamino)prop-2-en-1-one (**7p**).* Yield: 59% (69.9 mg), yellow liquid; R_f = 0.40 (EtOAc/petroleum



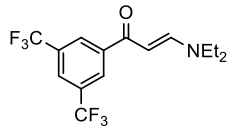
ether = 1/2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84−7.76 (m, 2H), 7.72 (d, J = 7.6 Hz, 1H), 7.37 (d, J = 8.0 Hz, 1H), 7.30 (t, J = 7.7 Hz, 1H), 5.67 (d, J = 12.5 Hz, 1H), 3.30 (s, 4H), and 1.20 (t, J = 6.6 Hz, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 186.9, 152.8, 142.5, 134.2, 130.6, 129.4, 127.6, 125.5, 91.2, 50.7, 42.9, 14.7, and 11.6. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{13}H_{17}ClNO$, 238.0993; found, 238.1015.

*(E)-1-(3-Bromophenyl)-3-(diethylamino)prop-2-en-1-one (**7q**).* Yield: 48% (67.4 mg), yellow liquid; R_f = 0.40 (EtOAc/petroleum



ether = 1/2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (s, 1H), 7.87−7.79 (m, 2H), 7.61−7.55 (m, 1H), 7.31−7.27 (m, 1H), 5.70 (d, J = 12.5 Hz, 1H), 3.36 (s, 4H), and 1.26 (t, J = 6.9 Hz, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 186.9, 152.9, 142.8, 133.6, 130.5, 129.7, 126.0, 122.4, 91.3, 50.7, 42.9, 14.8, and 11.6. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{13}H_{17}BrNO$, 282.0488; found, 282.0509.

*(E)-1-(3,5-Bis(trifluoromethyl)phenyl)-3-(diethylamino)prop-2-en-1-one (**7r**).* Yield: 45% (76.3 mg), yellow solid; R_f = 0.42 (EtOAc/



petroleum ether = 1/2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.31 (s, 2H), 7.93 (d, J = 11.8 Hz, 2H), 5.72 (d, J = 12.3 Hz, 1H), 3.41 (dt, J = 14.2,

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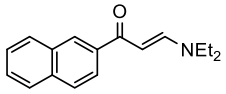
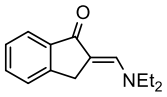
7.1 Hz, 4H), and 1.29 (q, J = 7.0 Hz, 6H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 184.7, 153.7, 142.6, 131.5 (q, J = 33.4 Hz), 127.50, 127.47, 127.4, 124.7, 124.0−123.9 (m), 122.0, 119.2, 90.4, 50.8, 43.1, 14.7, and 11.6. ^{19}F NMR (376 MHz, $CDCl_3$): δ −62.81. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{15}H_{16}F_6NO$, 340.1131; found, 340.1144.

*(E)-3-(Diethylamino)-1-(naphthalen-2-yl)prop-2-en-1-one (**7t**).* Yield: 57% (72.1 mg), yellow liquid; R_f = 0.41 (EtOAc/petroleum



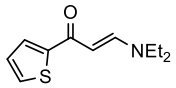
ether = 1/2). ^1H NMR (400 MHz, $CDCl_3$): δ 8.40 (s, 1H), 8.03 (dd, J = 8.6, 1.7 Hz, 1H), 7.97 (dd, J = 6.4, 2.7 Hz, 1H), 7.93−7.86 (m, 3H), 7.56−7.50 (m, 2H), 5.95 (d, J = 12.5 Hz, 1H), 3.39 (q, J = 7.2 Hz, 4H), and 1.29 (t, J = 7.2 Hz, 6H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 188.6, 152.5, 138.1, 134.7, 132.8, 129.1, 127.8, 127.71, 127.65, 127.1, 126.2, 124.7, 91.9, 50.6, 42.8, 14.8, and 11.6. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{17}H_{20}NO$, 254.1539; found, 254.1537.

*(E)-2-((Diethylamino)methylene)-2,3-dihydro-1H-inden-1-one (**7w**).* Yield: 60% (64.5 mg), yellow liquid; R_f = 0.41 (EtOAc/petroleum



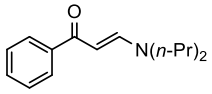
ether = 1/2). ^1H NMR (400 MHz, $CDCl_3$): δ 7.86 (d, J = 7.6 Hz, 1H), 7.62 (t, J = 1.1 Hz, 1H), 7.51−7.45 (m, 2H), 7.39 (td, J = 7.6, 1.8 Hz, 1H), 3.83 (s, 2H), 3.47 (q, J = 7.1 Hz, 4H), and 1.29 (t, J = 7.2 Hz, 6H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 192.4, 147.4, 145.5, 140.3, 131.6, 126.9, 125.1, 123.0, 103.3, 31.3, and 14.7. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{14}H_{18}NO$, 216.1383; found, 216.1384.

*(E)-3-(Diethylamino)-1-(thiophen-2-yl)prop-2-en-1-one (**7x**).* Yield: 43% (44.9 mg), yellow liquid; R_f = 0.39 (EtOAc/petroleum



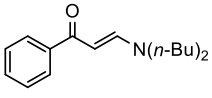
ether = 1/2). ^1H NMR (400 MHz, $CDCl_3$): δ 7.82 (d, J = 12.5 Hz, 1H), 7.64 (d, J = 3.7 Hz, 1H), 7.48 (d, J = 4.9 Hz, 1H), 7.12−7.07 (m, 1H), 5.70 (d, J = 12.5 Hz, 1H), 3.39−3.32 (m, 4H), and 1.26 (t, J = 7.1 Hz, 6H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 180.9, 151.8, 147.6, 130.1, 128.2, 127.5, 91.2, 50.5, 42.8, 14.8, and 11.6. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{11}H_{16}NOS$, 210.0947; found, 210.0963.

*(E)-3-(Dipropylamino)-1-phenylprop-2-en-1-one (**7z**).* Yield: 61% (70.5 mg), yellow liquid; R_f = 0.42 (EtOAc/petroleum ether = 1/2). ^1H



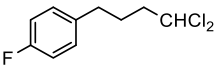
NMR (400 MHz, $CDCl_3$): δ 7.87 (d, J = 6.7 Hz, 2H), 7.81 (d, J = 12.5 Hz, 1H), 7.41 (q, J = 7.4, 6.4 Hz, 3H), 5.75 (d, J = 12.5 Hz, 1H), 3.26−3.16 (m, 4H), 1.65 (s, 4H), and 0.99−0.89 (m, 6H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 188.8, 153.5, 140.8, 130.7, 128.1, 127.4, 91.8, 58.2, 50.4, 22.5, 19.7, 11.5, and 11.0. HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{15}H_{21}NONa$, 254.1515; found, 254.1517.

*(E)-3-(Dibutylamino)-1-phenylprop-2-en-1-one (**7aa**).* Yield: 57% (73.8 mg), yellow liquid; R_f = 0.43 (EtOAc/petroleum ether = 1/2). ^1H



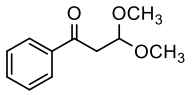
NMR (400 MHz, $CDCl_3$): δ 7.88 (dd, J = 7.9, 1.6 Hz, 2H), 7.81 (d, J = 12.5 Hz, 1H), 7.45−7.37 (m, 3H), 5.75 (d, J = 12.5 Hz, 1H), 3.29−3.20 (m, 4H), 1.60 (s, 4H), 1.39−1.29 (m, 4H), and 1.00−0.93 (m, 6H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 188.7, 153.3, 140.8, 130.7, 128.1, 127.4, 91.8, 56.3, 48.5, 47.2, 41.9, 31.3, 30.7, 29.4, 28.4, 20.3, 20.2, 19.8, 19.6, and 13.8. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{17}H_{26}NO$, 260.2009; found, 260.2009.

*1-(4,4-Dichlorobutyl)-4-fluorobenzene (**7ae'**).*[12]



Yield: 62% (68.2 mg), pale yellow liquid; R_f = 0.40 (EtOAc/petroleum ether = 1/20). ^1H NMR (400 MHz, $CDCl_3$): δ 7.17−7.09 (m, 2H), 7.02−6.92 (m, 2H), 5.74 (t, J = 6.0 Hz, 1H), 2.64 (t, J = 7.6 Hz, 2H), 2.27−2.09 (m, 2H), and 1.91−1.77 (m, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 161.4 (d, J = 243.8 Hz), 136.8 (m), 129.7 (d, J = 7.8 Hz), 115.3 (d, J = 21.1 Hz), 73.3, 42.9, 33.9, and 27.6.

*3,3-Dimethoxy-1-phenylpropan-1-one (**8a**).*[14]



General Procedure for the Synthesis of 8a. A mixture of **5a** (0.5 mmol, 138 mg), DBU (0.4 mmol, 152 mg), and CH_3OH (1.0 mL) was added successively in a round-bottom flask, and the resulting solution was stirred for 8 h at 70 °C. The mixture was purified by column chromatography on silica gel to afford the product. Yield: 58% (56.3 mg), colorless liquid; R_f = 0.40 (EtOAc/petroleum ether = 1/10). ^1H NMR (400 MHz, $CDCl_3$): δ 7.99−7.94 (m, 2H), 7.58 (m, 1H), 7.50−7.46 (m, 2H), 5.02 (t, J = 5.5 Hz, 1H), 3.43 (s, 6H), and 3.30 (d, J = 5.5 Hz, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 196.9, 137.1, 133.2, 128.6, 128.3, 102.2, 54.2, and 42.6.

General Procedure for the Synthesis of 1,2,3-Thiadiazole 10.[17] The mixture of enaminone **7a** (0.2 mmol, 40.6 mg), *p*-toluenesulfonyl hydrazide (0.24 mmol, 44.6 mg), S (0.4 mmol, 12.8 mg), I_2 (0.2 mmol, 25.4 mg), and DMSO (1.0 mL) was stirred at 100 °C for 12 h under air atmosphere in an oil bath. After the completion of the reaction, the reaction mixture was washed with water and extracted by ethyl acetate three times. The obtained top organic layer was dried with anhydrous Na_2SO_4. The mixture was concentrated in vacuo, and the residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 10:1) to afford the pure product **10** (75%, 28.5 mg). ^1H NMR (500 MHz, $CDCl_3$): δ 9.06 (s, 1H), 7.99−7.88 (m, 3H), 7.72 (t, J = 7.5 Hz, 1H), and 7.58 (t, J = 7.8 Hz, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 184.6, 153.2, 149.1, 136.7, 134.6, 129.4, and 129.2.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c00823.

^1H NMR and $^{13}C\{^1H\}$ NMR spectra of compounds (PDF)

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Notes

The authors declare no competing financial interest.

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