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Facile synthesis of α,β-acetylenic ketones and 2,5-disubstituted furans: consecutive activation of triple and double bond with $ZnBr_2$ toward the synthesis of furan ring

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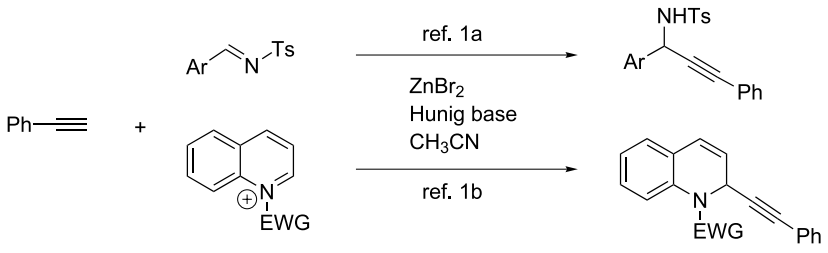
Abstract—α,β-Acetylenic ketones were synthesized from the reaction of acid chlorides and acetylenic compounds in the presence of $ZnBr_2$ and DIEA in acetonitrile. From the acetylenic ketones having nearby methylene unit, 2,5-disubstituted furan derivatives could be synthesized under the same reaction conditions.

1. Introduction

Recently, we reported the alkynylation of *N*-tosylimines[1a] and quinolinium salts[1b] with aryl acetylenes promoted by $ZnBr_2$ and *N*,*N*-diisopropylethylamine (DIEA, Hunig base) in acetonitrile. In the reactions, we obtained *N*-tosyl propargylamines[1a] and 1-acyl-1,2-dihydroquinolines[1b] in moderate to good yields by the addition of in situ generated zinc acetylide (Scheme 1). On the other hand, Carreira and co-workers have reported a mild procedure for the addition of acetylenic compounds to nitrones,[2a] *N*-acyliminium salts,[2b] and aldehydes[2c] involving the in situ generated zinc acetylide in the presence of zinc triflate and tertiary amine. The two procedures were similar conceptually, however, the latter procedure used hygroscopic and expensive zinc triflate instead of $ZnBr_2$.

α,β-Acetylenic ketones are very important synthetic intermediates[3] and numerous synthetic methods have been reported.[3,4] Among them the use of copper(I) salt in combination of a tertiary amine is widely used.[4] However, the method used carcinogenic triethylamine as the solvent and required long time (30 h) for the reaction.[4a,b] Very recently, the combination of palladium catalyst and CuI has been published.[4d,e] However, most of the reported methods have some problems such as low yields, use of toxic or expensive reagents, and long reaction time. Moreover, to the best of our knowledge, the use of zinc triflate and amine system of Carreira[2] has not been reported for the synthesis of α,β-acetylenic ketones. In searching for the usefulness of our reaction conditions,[1] we envisioned that the reaction of aryl acetylene **1** and acid chloride **2** under the conditions could afford valuable α,β-acetylenic ketones **3** (Scheme 2).

As expected the reaction of phenylacetylene (**1a**) and benzoyl chloride (**2a**) in acetonitrile in the presence of



Scheme 1.

Keywords: Acetylenic ketones; Phenylacetylene; Furans.
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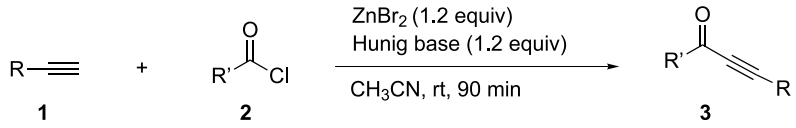
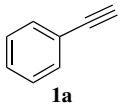
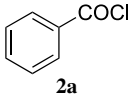
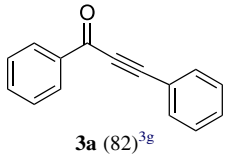
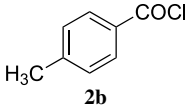
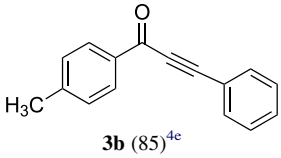
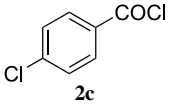
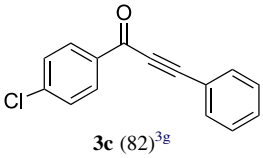
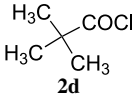
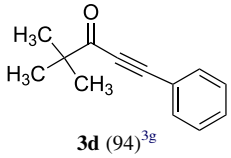
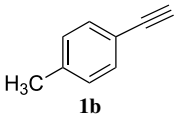
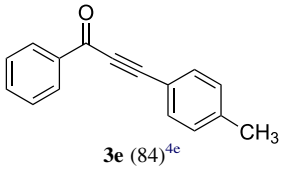
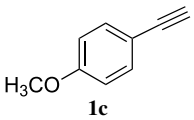
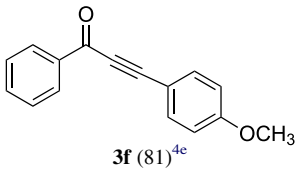
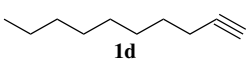
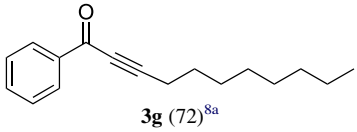
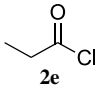
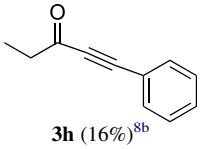
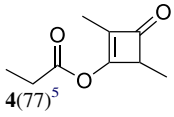


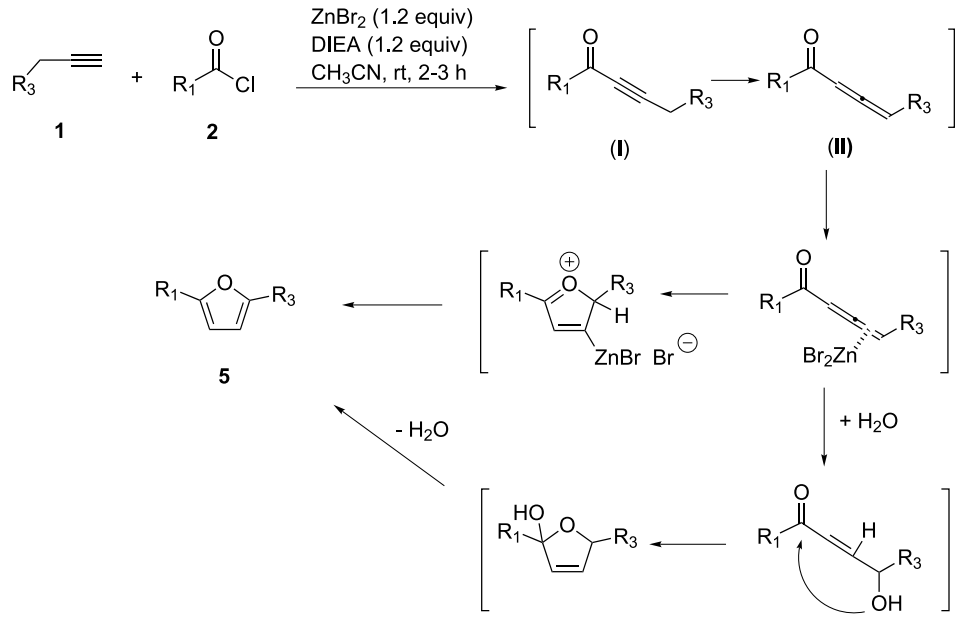
Scheme 2.

$ZnBr_2$ and DIEA gave the desired compound **3a** in high yield (82%). The yield was satisfactory and the reaction conditions were very convenient to carry out in a practical sense. Encouraged by the results we examined the reactions between **1a–d** and **2a–e** and the results are summarized in Table 1. As shown, substituted benzoyl chlorides (entries 2 and 3) and pivaloyl chloride (entry 4) could be used as the electrophilic components. The reaction with benzoic

Table 1. Synthesis of α,β-acetylenic ketones[a,b]

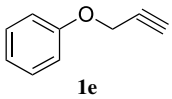
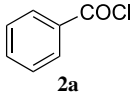
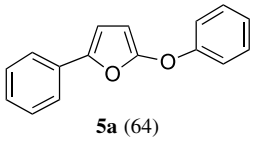
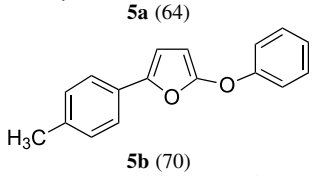
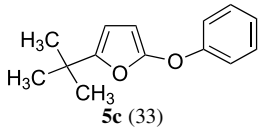
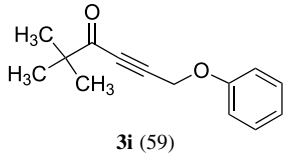
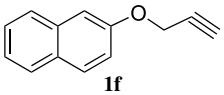
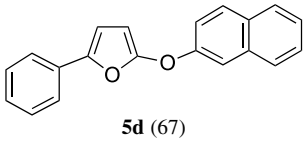
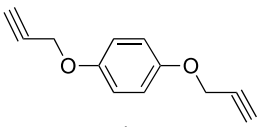
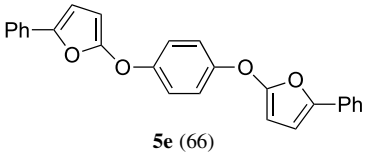
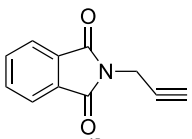
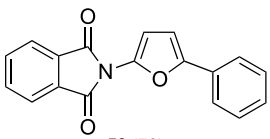
Entry	Acetylenes	Acid chlorides	Products (%)
1	 **1a**	 **2a**	 **3a** (82)[3g]
2	**1a**	 **2b**	 **3b** (85)[4e]
3	**1a**	 **2c**	 **3c** (82)[3g]
4	**1a**	 **2d**	 **3d** (94)[3g]
5	 **1b**	**2a**	 **3e** (84)[4e]
6	 **1c**	**2a**	 **3f** (81)[4e]
7	 **1d**	**2a**	 **3g** (72)[8a]
8	**1a**	 **2e**	 **3h** (16%)[8b]  **4**(77)[5]

[a] Conditions: acetylenic compound **1** (1 equiv), acid chloride **2** (1.2 equiv), $ZnBr_2$ (1.2 equiv), DIEA (1.2 equiv), rt, 90 min, CH_3CN.
[b] The reaction of **1a** and **2a** in the presence of $Zn(OTf)_2$ (1.2 equiv) and DIEA (rt, 90 min) gave **3a** in a similar yield (80%). The use of $ZnCl_2$, ZnI_2, or catalytic amounts of $ZnBr_2$ did not give **3a** in appreciable yield.



Scheme 3.

Table 2. Synthesis of 2,5-disubstituted furans[a]

Entry	Acetylenes	Acid chlorides	Time (h)	Products (%)
1	 **1e**	 **2a**	2	 **5a** (64)
2	**1e**	**2b**	3	 **5b** (70)
3	**1e**	**2d**	3	 **5c** (33)
				 **3i** (59)
4	 **1f**	**2a**	3	 **5d** (67)
5	 **1g**	**2a**	8	 **5e** (66)
6[b]	 **1h**	**2a**	20	 **5f** (70)

[a] Conditions: acetylenic compound **1** (1 equiv), acid chloride **2** (1.2 equiv), $ZnBr_2$ (1.2 equiv), DIEA (1.2 equiv), rt, times given in that table.
[b] Conditions: **2a** (2 equiv), $ZnBr_2$ (2 equiv). DIEA (2 equiv), rt, 20 h.

anhydride instead of benzoyl chloride failed. The acid chloride bearing α-proton showed different reactivity under the reaction conditions. As an example (entry 8), for the reaction of propionyl chloride (**2e**) and phenylacetylene we obtained the desired acetylenic ketone **3h** in low yield (16%) together with ketene dimer derivative **4** as the major product (77%).[5]

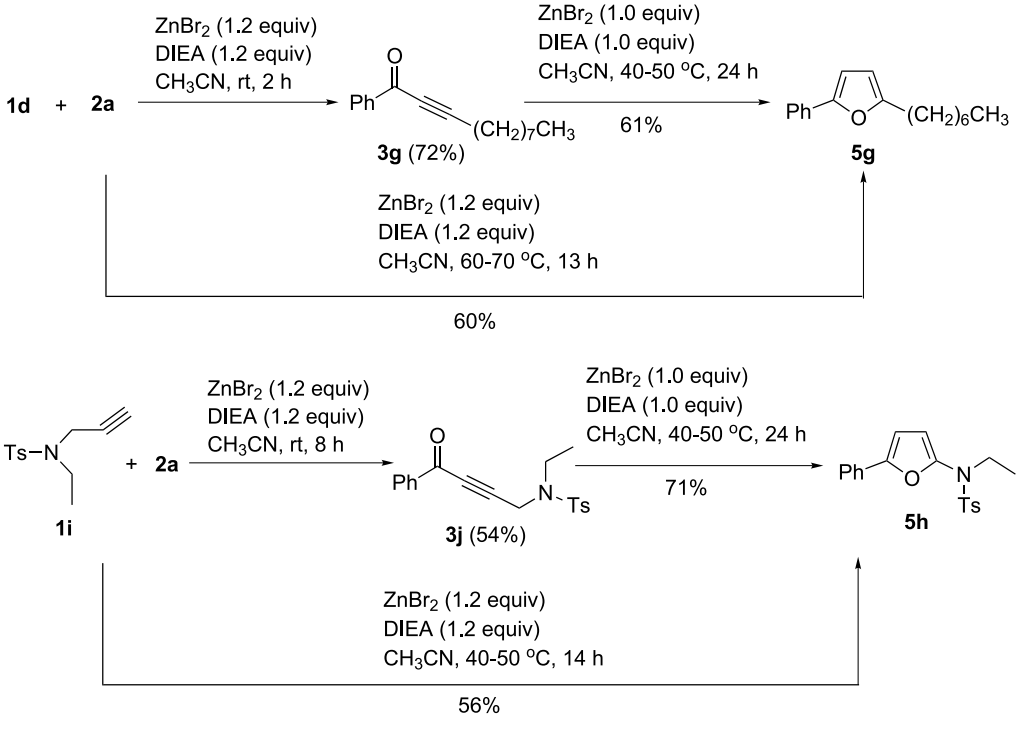
Aryl acetylenes **1a–c** gave the desired α,β-acetylenic ketones in good to excellent yields. However, the situations were different for the alkyl group-attached alkynes (vide infra). In our previous synthesis of *N*-tosylpropargylamines, alkyl group-substituted acetylenic compounds failed completely presumably due to the low acidity of the acetylenic hydrogen and the low electrophilicity of *N*-tosylimine.[1a] However, the reaction of benzoyl chloride and 1-decyne (**1d**) gave the desired α,β-acetylenic ketone **3g** in moderate yield.

Moreover, very interesting results were observed when we used aryl propargyl ethers **1e–g** or *N*-propargylphthalimide (**1h**) in the same reaction. 5-Phenyl-2-phenoxyfuran (**5a**) was obtained in 64% yield in a one-pot reaction from the reaction of **1e** and **2a**.[6,7] This compound was generated definitively from the corresponding α,β-acetylenic ketone intermediate with $ZnBr_2$ assistance. The plausible reaction mechanism is suggested in Scheme 3 (vide infra). The $ZnBr_2$-catalyzed and base-assisted propargyl-allenyl isomerization occurred to allene derivative (**II**), which immediately undergoes sequential transformation into furans as reported in a similar system.[6a,d,7] At this stage, we could not rule out the possibility of involvement of moisture in the reaction. Synthesis of furan derivatives from acetylenic ketones or allenic ketones has been accomplished with the aid of CuI/Et_3N or $AuCl_3$.[7] In our reaction, $ZnBr_2$ played the same role of CuI or $AuCl_3$ without any problems.

Although, the convertibility of acetylenic ketone into furan was known,[7] our findings suggest many important scientific issues: (1) furan could be synthesized in a one-pot from benzoyl chlorides and phenyl propargyl ethers in short time in high yield and (2) $ZnBr_2$ could act well for the acetylene–allene isomerization and concomitant activation of the allene moiety toward cyclization. In other words, triple bond of acetylenic compound was activated by $ZnBr_2$ to generate efficiently the corresponding zinc acetylide species.[1a] After the formation of α,β-acetylenic ketones $ZnBr_2$ played the role of activation of triple bond once more to be isomerized into the corresponding allenic ketone derivatives. Finally, during the formation of furan skeleton $ZnBr_2$ activates the double bond of allene moiety to facilitate the formation of furan ring. The results for the synthesis of furans are illustrated in Table 2. For the reaction of **1e** and **2d** (entry 3) the yield of **5c** was low. Instead acetylenic ketone **3i** was isolated as the major product. During the cyclization stage for furan the bulky *tert*-butyl group might affect. For the reaction of **1h** (entry 6), long reaction time was required in order to obtain moderate yield of **5f**.

The formation of furan derivatives occurs definitively from the corresponding α,β-acetylenic ketones (vide supra). When we carried out the reaction of **1d** and **2a** at rt we obtained only **3g**. The reaction of **3g** under the same conditions at elevated temperature afforded **5g** in 61% yield. The reaction of **1d** and **2a** at elevated temperature gave **5g** directly (Scheme 4) in 60% yield. We obtained same results from the reaction of **1i** and **2a**. From the experiments, we could conclude that the furan compounds **5a–h** were formed via the intermediacy α,β-acetylenic ketone compounds.

In conclusion, we found that zinc acetylide species can react with acyl chlorides to give α,β-acetylenic ketone derivatives in high yields in short time. The zinc acetylides can be



Scheme 4.

generated efficiently from the corresponding acetylenic compounds with the aid of $ZnBr_2$ and DIEA in acetonitrile. For the acetylenic ketones bearing nearby methylene unit, concomitant isomerization to allene and $ZnBr_2$-assisted cyclization occurred to afford 2,5-disubstituted furan derivatives.

2. Experimental

2.1. General procedure

^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded in $CDCl_3$. The signal positions are reported in ppm relative to TMS (δ scale) used as an internal standard. The separations were carried out by flash column chromatography over silica gel (230–400 mesh ASTM). Organic extracts were dried over anhydrous $MgSO_4$ and the solvents were evaporated on a rotary evaporator under water aspirator pressure. IR spectra are reported in cm^{-1}. Mass spectra were obtained from the Korea Basic Science Institute (Gwangju branch). Melting points are uncorrected. The combustion analyzes were carried out at Korea Research Institute of Chemical Technology, Taejon, Korea. The starting materials **1a–d** were obtained from commercial sources. Compounds **1e–h** were prepared from phenol, 2-naphthol, 1,4-dihydroxybenzene, and phthalimide with propargyl bromide in the presence of K_2CO_3 in DMF. Identification of starting materials **1e–h** was carried out with their ^{1}H and/or ^{13}C NMR spectra simply.

2.2. Typical procedure for the synthesis of 3a

To a stirred solution of benzoyl chloride (**2a**, 169 mg, 1.2 mmol) in CH_3CN (3 mL) was added phenylacetylene (**1a**, 102 mg, 1.0 mmol), $ZnBr_2$ (270 mg, 1.2 mmol), and *N*,*N*-diisopropylethylamine (DIEA, 155 mg, 1.2 mmol). The reaction mixture was stirred for 90 min at rt. After the usual aqueous workup and column chromatographic purification process (hexanes/ether, 10:1) we obtained **3a**, 169 mg (82%). Identification of prepared compounds **3a–h** and **4** was carried out with their melting points, ^{1}H and/or ^{13}C NMR spectra simply in comparison with the reported data (**3a**,[3g] **3b**,[4e] **3c**,[3g] **3d**,[3g] **3e**,[4e] **3f**,[4e] **3g**,[8a] **3h**,[8b] and **4**[5]). Spectroscopic data of compounds **3i** and **3j** are as follows.

2.2.1. Compound 3i. Oil (59%); IR (KBr) 2970, 2214, 1674, 1493 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.13 (s, 9H), 4.87 (s, 2H), 6.95–7.04 (m, 3H), 7.28–7.34 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.70, 44.69, 55.68, 83.97, 87.77, 115.05, 121.94, 129.53, 157.22, 193.36; ESIMS *m*/*z* 217 ($M^+ + H$). Anal. Calcd for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46. Found: C, 77.92; H, 7.59.

2.2.2. Compound 3j. Oil (54%); IR (KBr) 2229, 1647, 1346, 1265, 1161 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25 (t, J=7.2 Hz, 3H), 2.21 (s, 3H), 3.38 (q, J=7.2 Hz, 2H), 4.44 (s, 2H), 7.18–7.22 (m, 2H), 7.37–7.46 (m, 2H), 7.57–7.64 (m, 1H), 7.73–7.84 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.21, 21.29, 36.05, 41.79, 83.06, 86.99, 127.54, 128.49, 129.31, 129.69, 134.25, 135.41, 135.94, 143.90, 176.77; ESIMS *m*/*z* 342 ($M^+ + H$). Anal. Calcd for $C_{19}H_{19}NO_3S$: C, 66.84; H, 5.61; N, 4.10. Found: C, 66.95; H, 5.59, N, 4.00.

2.3. Typical procedure for the synthesis of 5a

To a stirred solution of benzoyl chloride (**2a**, 169 mg, 1.2 mmol) in CH_3CN (3 mL) was added phenyl propargyl ether (**1e**, 132 mg, 1.0 mmol), $ZnBr_2$ (270 mg, 1.2 mmol), and *N*,*N*-diisopropylethylamine (DIEA, 155 mg, 1.2 mmol). The reaction mixture was stirred for 2 h at rt. After the usual aqueous workup and column chromatographic purification process (hexanes/ether, 10:1) we obtained **5a**, 152 mg (64%). The spectroscopic data of the prepared furans **5a–h** are as follows.

2.3.1. Compound 5a. White solid (64%), mp 66–67 °C; IR (KBr) 1547, 1485, 1242 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.63 (d, J=3.3 Hz, 1H), 6.57 (d, J=3.3 Hz, 1H), 7.08–7.22 (m, 4H), 7.29–7.35 (m, 4H), 7.56–7.58 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 91.26, 106.09, 116.93, 122.97, 123.90, 126.89, 128.62, 129.69, 130.49, 146.28, 156.04, 156.85; ESIMS *m*/*z* 237 ($M^+ + H$). Anal. Calcd for $C_{16}H_{12}O_2$: C, 81.34; H, 5.12. Found: C, 81.28; H, 5.17.

2.3.2. Compound 5b. White solid (70%), mp 46–47 °C; IR (KBr) 1554, 1489, 1250 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.19 (s, 3H), 5.50 (d, J=3.3 Hz, 1H), 6.38 (d, J=3.3 Hz, 1H), 6.94–7.02 (m, 5H), 7.14–7.22 (m, 2H), 7.33–7.36 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.14, 91.23, 105.24, 116.82, 122.96, 123.78, 127.82, 129.28, 129.65, 136.66, 146.55, 155.64, 156.94. Anal. Calcd for $C_{17}H_{14}O_2$: C, 81.58; H, 5.64. Found: C, 81.50; H, 5.59.

2.3.3. Compound 5c. Oil (33%); IR (KBr) 2966, 1566, 1489, 1250 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26 (s, 9H), 5.44 (d, J=3.3 Hz, 1H), 5.89 (d, J=3.3 Hz, 1H), 6.98–7.11 (m, 3H), 7.28–7.35 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.83, 32.50, 89.32, 102.58, 116.46, 123.37, 129.57, 154.27, 156.62, 157.38. Anal. Calcd for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46. Found: C, 77.45; H, 7.38.

2.3.4. Compound 5d. White solid (67%), mp 109–110 °C; IR (KBr) 1547, 1250 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.72 (d, J=3.3 Hz, 1H), 6.64 (d, J=3.3 Hz, 1H), 7.19–7.24 (m, 1H), 7.31–7.49 (m, 6H), 7.58–7.62 (m, 2H), 7.72–7.85 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 91.49, 106.16, 112.42, 118.02, 123.02, 125.02, 126.73, 126.95, 127.29, 127.75, 128.66, 129.92, 130.48, 130.50, 134.02, 146.42, 154.60, 156.06. Anal. Calcd for $C_{20}H_{14}O_2$: C, 83.90; H, 4.93. Found: C, 83.95; H, 4.92.

2.3.5. Compound 5e. White solid (66%), mp 129–130 °C; IR (KBr) 1493, 1176 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.63 (d, J=3.3 Hz, 2H), 6.60 (d, J=3.3 Hz, 2H), 7.10 (s, 4H), 7.20–7.25 (m, 2H), 7.33–7.38 (m, 4H), 7.57–7.60 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 89.81, 105.10, 117.37, 121.97, 125.95, 127.65, 129.43, 145.26, 151.87, 155.35; ESIMS *m*/*z* 395 ($M^+ + H$). Anal. Calcd for $C_{26}H_{18}O_4$: C, 79.17; H, 4.60. Found: C, 79.34; H, 4.72.

2.3.6. Compound 5f. White solid (70%), mp 161–162 °C; IR (KBr) 1736, 1369 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.53 (d, J=3.3 Hz, 1H), 6.77 (d, J=3.3 Hz, 1H), 7.24–7.30

(m, 1H), 7.34–7.40 (m, 2H), 7.64–7.68 (m, 2H), 7.80–7.83 (m, 2H), 7.95–7.98 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 106.28, 108.74, 123.89, 124.11, 127.80, 128.62, 130.06, 131.57, 134.76, 137.03, 152.92, 166.09; ESIMS *m/z* 290 ($M^+ + H$). Anal. Calcd for $C_{18}H_{11}NO_3$: C, 74.73; H, 3.83; N, 4.84. Found: C, 74.75; H, 3.95; N, 4.89.

2.3.7. Compound 5g. Oil (60%); IR (KBr) 2927, 1546, 1461 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (t, J= 6.9 Hz, 3H), 1.25–1.40 (m, 8H), 1.64–1.74 (m, 2H), 2.68 (t, J=7.5 Hz, 2H), 6.06 (d, J=3.3 Hz, 1H), 6.55 (d, J= 3.3 Hz, 1H), 7.18–7.26 (m, 1H), 7.33–7.38 (m, 2H), 7.62–7.65 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.15, 22.70, 28.13, 28.22, 29.09, 29.21, 31.82, 105.64, 106.82, 123.31, 126.71, 128.60, 131.27, 152.07, 156.52. Anal. Calcd for $C_{17}H_{22}O$: C, 84.25; H, 9.15. Found: C, 83.99; H, 9.21.

2.3.8. Compound 5h. White solid (56%), mp 140–150 °C (dec); IR (KBr) 1681, 1354, 1169 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.56 (t, J=7.2 Hz, 3H), 2.44 (s, 3H), 3.59 (q, J=7.2 Hz, 2H), 6.30 (d, J=3.3 Hz, 1H), 6.62 (d, J=3.3 Hz, 1H), 7.26–7.38 (m, 5H), 7.46–7.50 (m, 2H), 7.67–7.71 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.94, 20.54, 44.28, 105.02, 108.57, 122.56, 126.60, 126.76, 127.62, 128.50, 129.27, 134.96, 142.77, 143.42, 150.54; ESIMS *m/z* 342 ($M^+ + H$). Anal. Calcd for $C_{19}H_{19}NO_3S$: C, 66.84; H, 5.61; N, 4.10. Found: C, 66.81; H, 5.85; N, 4.33.

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