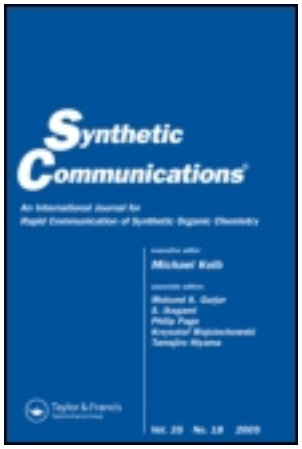

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HIGHLY CHEMOSELECTIVE CONDENSATION OF β-NAPHTHOL, ALDEHYDE, AND UREA CATALYZED BY THIAMINE HYDROCHLORIDE

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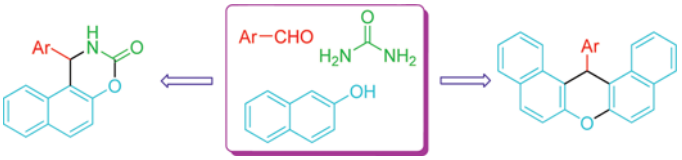
GRAPHICAL ABSTRACT



Abstract *A three-component condensation reaction involving β-naphthol, aldehyde, and urea in the presence of 10 mol% thiamine hydrochloride (VB_1) as a catalyst is described. Aromatic aldehydes bearing different functional groups exhibited different behavior than β-naphthol and urea under similar reaction conditions. A possible mechanism to account for the reaction is proposed.*

Keywords Catalysis; chemoselective; multicomponent reactions (MCRs); β-naphthol; thiamine hydrochloride (VB_1)

INTRODUCTION

Multicomponent reactions (MCRs) are of considerable importance in organic and medicinal chemistry because they have proved to be remarkably successful in generating molecular complexity in a single synthetic operation.[1] Bigenelli,[2] Ugi,[3] Mannich,[4] and Hantzsch[5] reactions are some examples of classical MCRs. However, great efforts have been and still are being made to find and develop new MCRs.

At the beginning of the new century, green chemistry has become a major driving force for organic chemists to develop environmentally benign routes to a myriad of materials.[6] Hence, organo-catalysts have received considerable attention in

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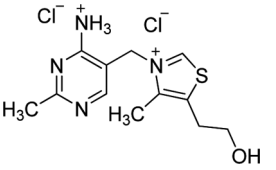
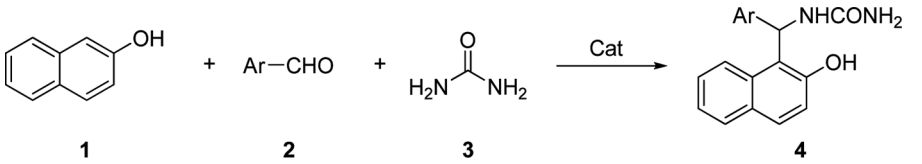


Figure 1. Thiamine hydrochloride.



Scheme 1. Three-component condensation of β-naphthol, aldehyde, and urea.

organic synthesis because they have greater efficiency and less toxicity, inexpensive, they are and metal ions are not retained in the product.

It is well known that thiamine hydrochloride (VB_1) is inexpensive, nontoxic, stable, and recoverable. The structure of VB_1 contains a pyrimidine ring and a thiazole ring linked by a methylene bridge (Fig. 1).

It is reported that the three-component condensation reaction of β-naphthol, aryl aldehydes, and urea in the presence of Lewis or Brøsted acid catalysts[7] synthesizes [(2-hydroxynaphthalen-1-yl)(aryl)methyl]urea (Scheme 1). As a part of our program aiming at developing selective and enviromentally friendly methodologies for MCRs, and in continuation of our interests in VB_1- catalyzed organic reactions, we highlight our findings about highly chemoselective three-component condensation of β-naphthol, aryl aldehydes, and urea. The aim of our work was to extend the scope of the three-component condensation using VB_1 as the catalyst.

RESULTS AND DISCUSSION

Very recently, we reported a simple, efficient, and practical procedure for the synthesis of amidoalkyl naphthols by a three-component condensation of β-naphthol, aromatic aldehydes, and amides or urea **3** by using VB_1 as a catalyst in alcohol.[8] The literature revealed that the three-component condensation reaction could take place under solvent-free conditions (Scheme 1).[7] Therefore, we began to explore the reaction of β-naphthol **1** (5 mmol), benzaldehyde **2a** (5 mmol), and urea **3** (7.5 mmol) under solvent-free conditions at 150 °C in the presence of 10 mol% VB_1 to determine the efficiency of the catalyst (Scheme 1). Curiously, the product 1,2-dihydro-1-phenylnaphth[1,2-*e*][1,3]oxazine-3-one **5a**, shown in Fig. 2 and confirmed by NMR measurements, was obtained in 92% yield, while in contrast the desired product [(2-hydroxynaphthalen-1-yl)(phenyl)methyl]urea **4a** was not obtained (Scheme 2).

To study the generality of this procedure, a series of aldehydes were selected to undergo the condensation reaction under solvent-free conditions at 150 °C in the

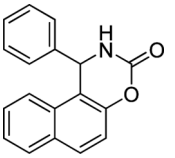
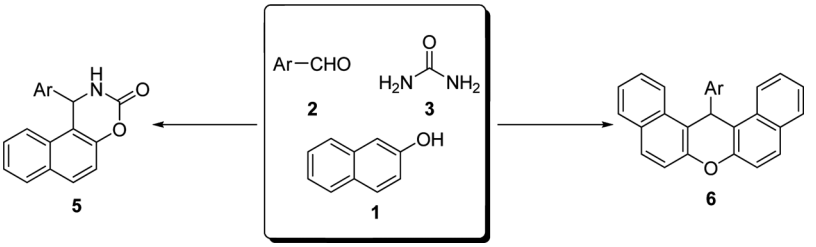


Figure 2. Structure of **5a**.



Scheme 2. The condensation of β-naphthol, aldehyde, and urea.

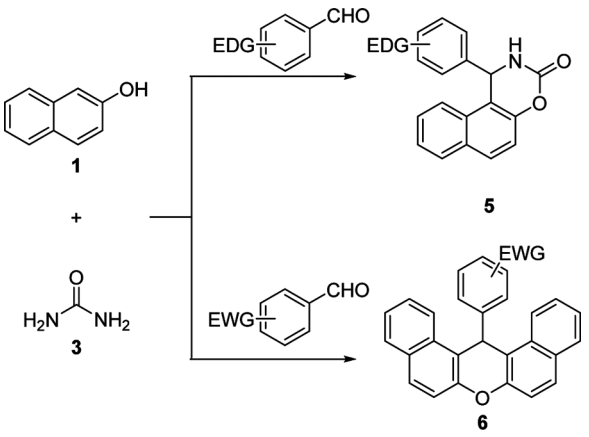
presence of 10 mol% VB_1 (Table 1). As shown in Table 1, in all of the studied examples, the aromatic aldehydes bearing functional groups, such as -H, $-CH_3$, $-OCH_3$, and -Cl, could react smoothly to give the corresponding products **5a–5d** in excellent yields (85–94%). However, we obtained the products **6e–6h** in good yields (83–92%) when using the aromatic aldehydes bearing strong electron-withdrawing substituents, such as $-NO_2$, -CN, and $-Cl_2$, as the starting materials (Scheme 3, Table 1).

The results in Table 1 clearly indicate that the functional groups of the aldehydes had significant effects on the reaction products. Based on these observations, the mixture of β-naphthol **1**, urea **3**, and 4-methylbenzaldehyde **2b** or 4-nitrobenzaldehyde **2f** was chosen as the model reaction to study the reaction behavior under different reaction conditions (Table 2). To determine the catalyst's effects, the three-component condensation was carried out with other commercially catalysts, such as TsOH, NH_2SO_3H, $FeCl_3$, $ZnCl_2$, and $MgCl_2$, which have been applied in

Table 1. Condensation of β-naphthol **1**, aryl aldehydes **2**, and urea **3**[a]

Entry	Aldehyde **2**	Product	Yield (%)[b]
1	C_6H_5CHO **2a**	**5a**	92
2	4-$CH_3C_6H_4CHO$ **2b**	**5b**	94
3	4-$CH_3OC_6H_4CHO$ **2c**	**5c**	88
4	4-ClC_6H_4CHO **2d**	**5d**	85
5	3-$NO_2C_6H_4CHO$ **2e**	**6e**	92
6	4-$NO_2C_6H_4CHO$ **2f**	**6f**	90
7	4-CNC_6H_4CHO **2g**	**6g**	91
8	2,4-$Cl_2C_6H_3CHO$ **2h**	**6h**	83

[a]Conditions: β-naphthol **1a** (5 mmol), aldehyde **2** (5 mmol), urea **3** (7.5 mmol), VB_1 (0.5 mmol), 150 °C for 30 min.
[b]Isolated yield.



Scheme 3. The condensation of β-naphthol, aldehyde, and urea.

related condensations.[7,9] The results summerized in Table 2 indicate that the reaction time was shortest and the yields were greatest when using VB_1 as the catalyst. Moreover, the results indicated that the reaction could afford the product **5b** with different catalysts when using 4-methylbenzaldehyde **2b** as the starting material, whereas only compound **6f** was obtained under similar reaction conditions when using 4-nitrobenzaldehyde **2f** as the starting material.

The results summarized in Tables 1 and 2 also revealed that VB_1 could catalyze the reaction of β-naphthol and aromatic aldehydes to synthesize of aryl-14-*H*-dibenzo[*a,j*]xanthenes **6**. Hence, several aromatic aldehydes were examined at 150 °C using 10 mol % VB_1 as the catalyst to synthesize compound **6** (Table 3).

In all cases studied, the condensation of β-naphthol **1** and aromatic aldehydes **2** proceeded smoothly to give the corresponding dibenzoxanthenes **6** in good yields. However, the condensation reaction could not take place as indicated by thin-layer

Table 2. Condensation of β-naphthol **1**, aldehydes **2b** or **2f**, and urea **3** under different conditions[a]

Entry	Aldehyde **2**	Cat. (mol %)	Temp. (°C)	Time	Product	Yield (%)[b]
1	4-$CH_3C_6H_4CHO$ **2b**	VB_1 (10)	150	30 min	**5b**	92
2	4-$CH_3C_6H_4CHO$ **2b**	TsOH (30)[10]	160	1.5 h	**5b**	60
3	4-$CH_3C_6H_4CHO$ **2b**	NH_2SO_3H (10)	150	1 h	**5b**	80
4	4-$CH_3C_6H_4CHO$ **2b**	$FeCl_3$ (20)	150	3 h	**5b**	45
5	4-$CH_3C_6H_4CHO$ **2b**	$ZnCl_2$ (50)	160	5 h	**5b**	35
6	4-$CH_3C_6H_4CHO$ **2b**	$MgCl_2$ (50)	160	5 h	**5b**	30
7	4-$NO_2C_6H_4CHO$ **2f**	VB_1 (10)	150	30 min	**6f**	88
8	4-$NO_2C_6H_4CHO$ **2f**	TsOH (30)	150	1.5 h	**6f**	76
9	4-$NO_2C_6H_4CHO$ **2f**	NH_2SO_3H (10)	150	1 h	**6f**	73
10	4-$NO_2C_6H_4CHO$ **2f**	$FeCl_3$ (20)	150	3 h	**6f**	50
11	4-$NO_2C_6H_4CHO$ **2f**	$ZnCl_2$ (50)	150	5 h	**6f**	30
12	4-$NO_2C_6H_4CHO$ **2f**	$MgCl_2$ (50)	150	5 h	**6f**	20

[a]Conditions: β-naphthol **1** (5 mmol), aldehyde **2b** or **2f** (5 mmol), and urea **3** (7.5 mmol).
[b]Isolated yields.

Table 3. Condensation of β-naphthol **1** and aryl aldehydes **2**[a]

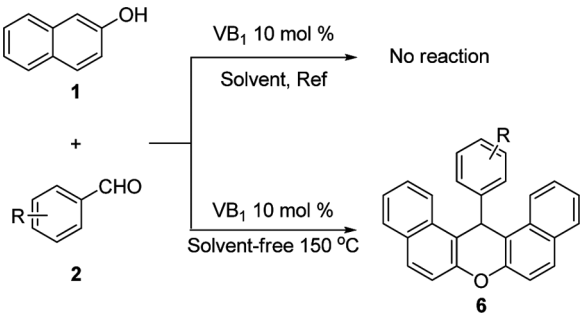
Entry	Aldehyde **2**	Product	Yield (%)[b]
1	C_6H_5CHO **2a**	**6a**	90
2	4-$CH_3C_6H_4CHO$ **2b**	**6b**	90
3	4-$CH_3OC_6H_4CHO$ **2c**	**6c**	84
4	4-ClC_6H_4CHO **2d**	**6d**	88
5	3-$NO_2C_6H_4CHO$ **2e**	**6e**	92
6	4-$NO_2C_6H_4CHO$ **2f**	**6f**	90
7	4-CNC_6H_4CHO **2g**	**6g**	91
8	2,4-$Cl_2C_6H_3CHO$ **2h**	**6h**	83

[a]Conditions: β-naphthol **1a** (10 mmol), aldehyde **2** (5 mmol), VB_1 (0.5 mmol), 150 °C for 30 min.
[b]Isolated yields.

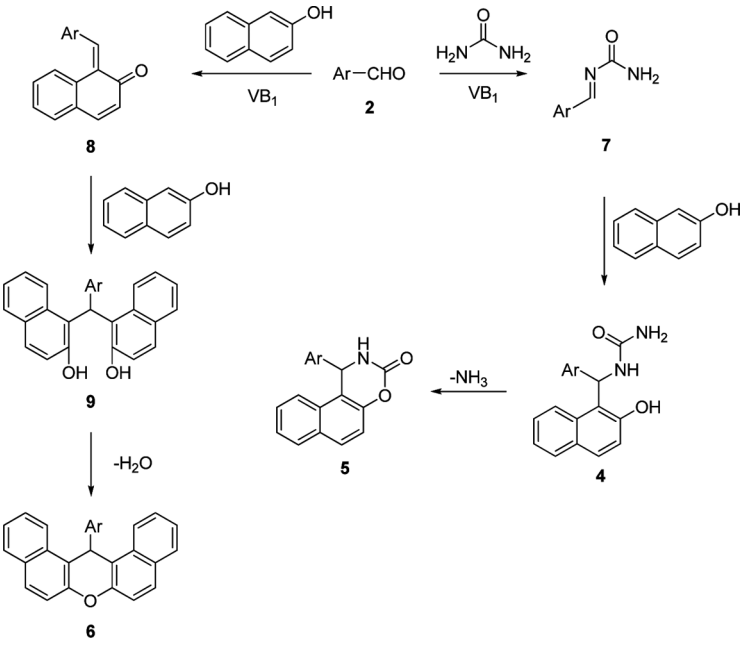
chromatography (TLC) in EtOH or other sovents, such as MeOH, tetrahydrofuran (THF), and 1,2-dichloroethane under reflux conditions (Scheme 4).

On the basis of all our experimental results, together with literature reports,[7,8,10] we have proposed the mechanistic pathway shown in Scheme 5 to account for the process. Initially, this condensation may proceed via intermediate **7**, formed by the reaction of aldehyde **2** and urea **3** at the action of the proton of VB_1. Then Michael addition of β-naphthol on intermediate **7** leads to the formation of **4**, which eliminates to form products **5**. A possible mechanism for the formation of dibenzoxanthenes **6** also has been proposed in Scheme 5. The reaction of β-naphthol **1** and aromatic aldehydes **2** were reacted in the presence of VB_1 to gave *ortho*-quinone methides **8**. Then conjugate addition between *ortho*-quinone methides **8** and β-naphthol **1** furnished the intermediate **9**, which upon intermolecular cyclization and dehydration gave products **6**.

In conclusion, we have demonstrated the multicomponent reaction of β-naphthol, aromatic aldehydes, and urea in the presence of VB_1 and have also studied the condensation of β-naphthol and aromatic aldehydes under similar conditions. Aromatic aldehydes bearing eletron-withdrawing groups exhibited different behavior than aromatic aldehydes bearing electron-donating groups. Undoubtedly, these reactions should be useful to design a simple workup procedure for the synthesis of [(2-hydroxynaphthalen-1-yl)(aryl)methyl]urea **4**, 1,2-dihydro-1-aryl-naphth[1,2-*e*][1,3]oxazine-3-ones **5**, as well as aryl-14-*H*-dibenzo[*a,j*]xanthenes **6**.



Scheme 4. The condensation of β-naphthol and aldehyde.



Scheme 5. A possible mechanism for the reaction catalyzed by VB_1.

EXPERIMENTAL

Reagents and all solvents were analytically pure and were used without further purification. ^1H and ^{13}C NMR spectra were recorded on a Varian 400-MHz spectrometer at 400 MHz and 100 MHz, respectively with tetramethylsilane (TMS) as internal standard. Chemical shifts (δ) are given in parts per million (ppm) relative to TMS, with coupling constants (*J*) in hertz (Hz). Melting points were determined with a an X-4 apparatus and are uncorrected. Mass spectra were measured with a Thermo Finnigan LCQ-Advantage instrument.

Compounds 5a–5d

A mixture of β-naphthol **1** (5 mmol), aromatic aldehyde **2a–2d** (5 mmol), urea **3** (7.5 mmol), and VB_1 (0.5 mmol) was heated to 150 °C under stirring for 30 min. After cooling, the reaction mixture was washed with cold water and then recrystallized from EtOAc–hexane (1:3) to afford the pure product **5a–5d**.

Compound 5a.[11] White solid, mp 214–216 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 8.92 (brs, 1H), 7.33–8.00 (m, 11H), 6.22 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 149.7, 147.8, 143.1, 130.5, 130.4, 129.1, 129.0, 128.8, 128.1, 127.4, 127.1, 125.4, 123.3, 117.1, 114.2, 54.2; MS (ESI) *m/z*: 298 ($[M + Na]^+$).

Compound 5b.[10] White solid, mp 163–165 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 8.82 (brs, 1H), 7.11–8.01 (m, 10H), 6.14 (s, 1H), 2.20 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 149.8, 147.8, 140.5, 137.8, 130.9, 130.6, 129.9,

129.4, 129.1, 127.8, 127.3, 125.5, 123.6, 117.3, 114.6, 54.0, 21.1; MS (ESI) m/z: 312 ($[M + Na]^+$).

Compound 5c.[10] White solid, mp 184–186 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77–7.85 (m, 2H), 7.49–7.56 (m, 1H), 7.35–7.41 (m, 2H), 7.30 (d, $J = 8.8$ Hz, 1H), 7.16 (d, $J = 8.4$ Hz, 2H), 6.78 (d, $J = 8.4$ Hz, 2H), 6.62 (brs, 1H), 6.01 (brs, 1H), 3.70 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.9, 145.6, 142.8, 129.3, 126.3, 125.7, 124.6, 124.0, 123.5, 122.6, 120.4, 118.1, 112.3, 109.9, 108.0, 50.8, 50.5; MS (ESI) m/z: 328 ($[M + Na]^+$).

Compound 5d.[11] White solid, mp 203–206 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.90 (brs, 1H), 7.35–8.05 (m, 10H), 6.24 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 149.7, 147.9, 142.1, 133.0, 130.6, 129.3, 129.2, 129.1, 129.0, 128.0, 127.7, 125.6, 123.3, 117.2, 114.0, 53.4; MS (ESI) m/z: 332, 334 ($[M + Na]^+$).

Compounds 6a–6h

A mixture of β-naphthol **1** (10 mmol), aromatic aldehyde **2a–2h** (5 mmol), and VB_1 (0.5 mmol) was heated to 150 °C under stirring for 30 min. After cooling, the reaction mixture was washed with cold water and then recrystallized from EtOH to afford the pure product **6a–6 h**.

Compound 6a.[12] White solid, mp 182–184 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, $J = 8.4$ Hz, 2H), 7.73–7.80 (m, 4H), 7.33–7.60 (m, 8H), 7.10 (t, $J = 7.2$ Hz, 2H), 6.94 (t, $J = 7.2$ Hz, 1H), 6.44 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.8, 145.1, 131.4, 131.1, 128.9, 128.8, 128.5, 128.3, 126.8, 126.4, 124.2, 123.0, 122.6, 118.1, 117.3, 38.1; MS (EI) m/z: 358 (M^+).

Compound 6b.[12] White solid, mp 227–229 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, $J = 8.4$ Hz, 2H), 7.45–7.80 (m, 4H), 7.25–7.35 (m, 8H), 6.94 (d, $J = 7.8$ Hz, 2H), 6.44 (s, 1H), 2.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.8, 141.2, 135.9, 131.6, 131.1, 129.3, 128.8, 128.2, 126.9, 124.3, 122.7, 118.0, 117.4, 109.5, 37.6, 21.0; MS (EI) m/z: 372 (M^+).

Compound 6c.[12] White solid, mp 202–204 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, $J = 8.4$ Hz, 2H), 7.70–7.80 (m, 4H), 7.31–7.55 (m, 8H), 6.62 (d, $J = 8.4$ Hz, 2H), 6.41 (s, 1H), 3.57 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.8, 148.7, 137.3, 131.4, 131.1, 129.2, 128.8, 128.7, 126.8, 124.2, 122.7, 117.9, 117.4, 113.8, 55.1, 37.0; MS (EI) m/z: 388 (M^+).

Compound 6d.[12] White solid, mp 286–289 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (d, $J = 8.4$ Hz, 2H), 7.75–7.85 (m, 4H), 7.42–7.61 (m, 8H), 7.14 (d, $J = 8.0$ Hz, 2H), 6.65 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.4, 144.9, 131.3, 131.2, 131.1, 130.1, 129.6, 129.1, 128.7, 127.4, 125.0, 123.7, 118.1, 117.3, 39.7; MS (EI) m/z: 392 (M^+).

Compound 6e.[12] Yellow solid, mp 207–211 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (s, 1H), 8.27 (d, $J = 8.4$ Hz, 2H), 7.76–7.83 (m, 6H), 7.57 (t, $J = 7.6$ Hz, Hz, 2H), 7.48 (d, $J = 8.4$ Hz, 2H), 7.41 (t, $J = 7.2$ Hz, 2H), 7.22 (t, $J = 7.6$ Hz, 1H), 6.55 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.0, 148.3, 147.2, 134.3, 131.3,

131.2, 129.8, 129.6, 129.2, 127.4, 124.8, 123.0, 122.1, 121.8, 118.3, 116.2, 37.7; MS (EI) m/z: 403 (M^+).

Compound 6f.[12] Yellow solid, mp > 300 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (s, 1H), 7.96–8.10 (m, 8H), 7.45–7.70 (m, 6H), 6.92 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.5, 148.0, 145.8, 130.7, 130.5, 129.5, 128.6, 128.7, 127.1, 124.5, 123.5, 123.0, 117.6, 116.1, 36.3; MS (EI) m/z: 403 (M^+).

Compound 6g.[13] White solid, mp > 300 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, $J = 8.8$ Hz, 2H), 7.40–7.80 (m, 14H), 6.53 (s, 1H);^{13}C NMR (100 MHz, $CDCl_3$) δ 150.1, 148.8, 132.5, 131.1, 129.6, 129.2, 123.0, 127.3, 124.6, 122.2, 122.1, 118.1, 116.0, 110.4, 38.1; MS (EI) m/z: 383 (M^+).

Compound 6h.[13] White solid, mp 248–250 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (d, $J = 8.4$ Hz, 2H), 7.80 (d, $J = 8.4$ Hz, 2H), 7.76 (d, $J = 8.8$ Hz, 2H), 7.60 (t, $J = 7.0$ Hz, 2H), 7.38–7.47 (m, 4H), 7.22–7.27 (m, 2H), 6.87 (d, $J = 8.4$ Hz, 1H), 6.74 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.9, 142.3, 132.8, 132.7, 131.6, 130.8, 130.5, 129.3, 129.1, 128.7, 128.3, 126.9, 124.4, 123.0, 118.0, 117.4, 34.2; MS (EI) m/z: 426 (M^+).

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