THE SYNTHESIS OF 2,2-DISUBSTITUTED 3-NITROCHROMENES FROM SALICYLALDEHYDE AND 2,2-DISUBSTITUTED 1-NITROALKENES

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Abstract- Reactions of salicylaldehyde (1) with β-nitrostyrenes (2), (4), and (6) in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO) without the use of solvent at 40 °C gave high yields of the corresponding 3-nitrochromenes, respectively. Other conjugated nitroalkenes were also used to react with salicylaldehyde under the similar conditions and the yields of substituted 3-nitrochromenes were moderate to high. 96% of cis-3-nitro-4-hydroxyflavane (11) was isolated as sole stereoisomer when 1 reacted with 2-nitromethyleneadamantane (10) under similar condition. When the reaction temperature was increased to 90 °C, 11 underwent dehydration to generate 74% of the corresponding 3-nitrochromene (12).

INTRODUCTION

The synthesis and biological activity of 3-nitrochromenes are important and have attracted significant attention in recent years because of their potential as precursor to a variety of medically important 2H-benzopyran derivatives such as flavonols, amines, etc. It also has been reported that 3-chromenes containing electron-withdrawing substituents at the 3-position possess radio-protecting properties and 3-nitrochromenes with appropriate substituents are potential candidates for nonlinear optical applications.

The synthesis of 2-aryl-3-nitrochromenes from salicylaldehyde (1) and β-nitrostyrenes by using triethylamine as base at room temperature always needs long reaction time (eq. 1). Similarly, additional procedures are also required to allow the reactants well-distributed on the solid surface because basic alumina and β-nitrostyrenes are solid (eq. 2). Herein, we report an improved, easy, and
efficient method to prepare 2-aryl-3-nitrochromenes and 2,2-disubstituted 3-nitrochromenes which are not well studied yet.

\[
\begin{align*}
\text{CHO} & \quad + \quad \text{NO}_2 \quad \text{cat. amount NEt}_3 \quad \text{rt, 18-20 h} \quad \text{Ar} \quad \text{NO}_2 \quad \text{Ar} \\
\text{CHO} & \quad + \quad \text{NO}_2 \quad \text{Al}_2\text{O}_3 \quad \text{supersonic, 2-4 h} \quad \text{Ar} \quad \text{NO}_2 \quad \text{Ar}
\end{align*}
\]

(1) 3 equiv. 1 equiv. 27-82%

(2) 2 equiv. 1 equiv. 36-85%

RESULTS AND DISCUSSION

Our recent study\(^7\) found that high yields of 3-nitrochromenes (3a-d) (a: Ar = Ph, 98%; b: Ar = p-MeOC\(_6\)H\(_4\), 75%; c: Ar = p-ClC\(_6\)H\(_4\), 99%; d: Ar = 2-thiophene, 79%) could be generated from the reaction mixture of salicylaldehyde (1) (4-10 equiv.), \(\Delta\)-nitrostyrenes (2a-d) (1 equiv., a: Ar = Ph, b: Ar = p-MeOC\(_6\)H\(_4\), c: Ar = p-ClC\(_6\)H\(_4\), d: Ar = 2-thiophene) and catalytic amount of 1,4-diazabicyclo[2.2.2]octane (DABCO) (0.5-1.0 equiv.) in the absence of solvent at 40 °C for 1.5 h (Table 1, entries 1-4). Under similar conditions, 99% of 5 could be isolated when compound (4) was used (Table 1, entry 5). When 6 or 8 were used, 98% of 7 or 99% of 9 could be separated (Table 1, entries 6 and 7). The structures of 3 and 5 could be assigned according to their \(^1\)H- and \(^13\)C-NMR spectra and all the spectral data are also consistent with literature reports.\(^1\) Compared to the reaction of entry 1 of Table 1, we found the reactions of entries 6 and 7 of Table 1 need longer time to complete the reaction and these results indicate that the bulkiness of the nitroalkenes plays an important role in the reaction.

On the basis of Table 1, we then focus our studies on the reactions of 1 with other more hindered substrates, 2,2-disubstituted 1-nitroalkenes, which were little studied in the literatures and only the derivatives of 2,2-dimethyl-3-nitrochromenes were mentioned in these papers.\(^6\) When 1 reacted with compounds (10) and (13), respectively, in the presence of DABCO under similar conditions, to our surprise, the isolated products were not 3-nitrochromenes (12) and (15), but high yields of 3-nitro-4-hydroxyflavans (11) (96%) and (14) (98%) were separated (eq. 3, 5). The structures of the nitro alcohols (11) and (14) were originally proposed to be \(\text{trans}\) form according to their \(^1\)H-NMR spectra; \(J_{3,4} = 6.0\) Hz for both compounds.\(^7\) However, the real structures of 11 (Figure 1) and 14 (Figure 2) are determined to be \(\text{cis}\) form by the X-Ray crystallographic method. The generation of the different products (7) and (9) or (11) and (14) probably can be explained by the steric effect of the groups in the 2-position of flavane and this effect plays an important role to the reaction conditions and to the product stability. To overcome the steric effect, the temperature was raised to 90 °C, and the expected 3-nitrochromenes (74% of 12 and 89% of 15) were produced from further dehydration of 11 or 14 (eq. 4, 6).
According to the above results, we can conclude that this method is easy for us to obtain either
3-nitro-4-hydroxyflavanes or 3-nitrochromenes just by controlling the reaction temperature when steric substrates (10) and (13) are used. Similar result was observed when substrate (16) was used (eq. 7, 8). When DABCO was replaced by triethylamine (1 equiv) in eq. 3, and 4, similar results were also observed and the yield of 11 was 99% at 40 °C for 20 h and the yields of 11 and 12 were 20% and 75% at 90 °C for 77 h. This result indicates that DABCO is actually superior to triethylamine at higher reaction temperature.
Nitroalkenes such as (16), (21), and (24) have two different faces, and the less hindered face is favored when nucleophiles approach. In eq. 7, 9, and 10, only 72% of 17 (the structure is assigned by X-Ray), 49% of 22 (the structure is assigned by X-Ray), and 94% of 25 were obtained from the attack of the less hindered face by the nucleophile. It is not surprised that the corresponding products (18), (23), and (26) were not observed due to the presence of the bulky steric hindrance. When 16 reacted with 1 at higher temperature (100 °C), neither the expected major 3-nitrochromene (19) nor the minor product (20) was observed and only 22% of 16 and trace of 17 were observed (eq. 8).

When 1 reacted with 2,2-disubstituted 1-nitroalkenes (27), (29), and (31) in the presence of DABCO under similar conditions, 31-99% of 2,2-disubstituted 3-nitrochromenes (28), (30), and (32) were obtained (eq. 11-13). It is believed that all the reactions (eq. 11-13) also proceed through the dehydration of the intermediates A-C to give 3-nitrochromenes only at 40 °C as described above.
Although this method is useful in the preparation of some 2,2-disubstituted 3-nitrochromenes, not all 2,2-disubstituted 1-nitroalkenes give the same results as eq. 3-13. For example, when nitromethylenecyclopentane (33) was used, the result was complicated. The reaction mixture was continuously checked by $^1$H-NMR and compound (49) was always found in the $^1$H-NMR spectra of the reaction mixture. This result indicates that compound (33) was equilibrium with 49 under these conditions. Because of the presence of the equilibrium between 33 and 49, both the spiro-compounds, (36-40) and the fused-ring-compounds, (41-45) were obtained not only from 33-35 but also from...
49-51 (eq. 14, 15). Possible reaction mechanism was proposed as Scheme 1. The special 2-isoxazoline derivatives (46), (47), and (48) were assumed to be produced from the reaction of 36, 37, or 38 with the nitrile oxides, which were believed to be generated from 49, 50, or 51 in the reaction. To prove this assumption, sodium nitrite was used to convert 33, which was proved to be equilibrium with 49, into nitrile oxide first and then reacted with 36 to generate 18% of 46 and other compounds (eq. 16).9

![Chemical reaction](image)

To prove the equilibrium between nitroalkenes (33-35) and allyl nitro compounds (49-51), 1-nitropropene (52) and 3-nitroprop-1-ene (54) were used to react with 1 under similar conditions and only the same product (53) was produced at room temperature (eq. 17, 19). At 40 °C, only 30% of 53 was obtained from the reaction of 1 and 52 for 20 min (eq. 18). The difference between eq. 17 and 18 indicates that the reaction at low temperature can improve the yield of 53. The low yields of eq. 12 and 13 could also be explained by the equilibrium between nitroalkenes and allyl nitro compounds.

**CONCLUSION**

This method is easy and useful not only in the synthesis of 3-nitro-2-aryl-2H-chromenes but also in the preparation of 2,2-disubstituted 3-nitrochromenes. Besides, this method also could be potential in the synthesis of 3-nitro-4-hydroxyflavanes by controlling the reaction temperature (eq. 3, 5, and 7). It is also
found that the diastereoselectivity is extremely high in eq. 7-10 during our research. However, this method is not suitable for the nitroalkenes that can convert into ally nitro compounds and all the reactions using these nitroalkenes give low yields of 3-nitrochromenes (eq. 12-14, and 17-18).
EXPERIMENTAL

General. All reactions were performed in oven-dried glassware. Analytical TLC was performed with E. Merck silica gel 60F glass plates and flash column chromatography by the use of E. Merck silica gel 60 (230-400 mesh). MS or HRMS spectrum were measured by JOEL JMS-D300 or JOEL JMS-HX110 spectrometer. $^1$H and $^{13}$C NMR spectra were recorded with Varian Gemini-200 instrument. All NMR data were obtained in CDCl$_3$ solution and chemical shifts ( $\delta$) were given in ppm relatives to TMS. Ethyl acetate and hexane were used in the recrystallization of all solid products.

Materials. Compounds (1), (2a-d), and DABCO were purchased from Acros, Lancaster, or Aldrich Chemical Co and compounds (2a-d) were purified by flash column chromatography before used. Other starting materials (8), (11), (14), (19), (22), (25), (27), (29), (31), (32), (33), (47), (48), and (49) were prepared according to or by modifying the literature procedures.

Typical experimental procedure for the synthesis of 3-nitrochromenes (eq 3): Salicylaldehyde (1) (0.488 g, 4 mmol) and $\alpha$-nitrostyrene (2a) (0.149 g, 1 mmol) were put together in a 10mL rounded bottle flask and stirred until the solution become homogeneous, then DABCO (0.056 g, 0.5 mmol) was added to the solution. The mixture was heated at 40 $^\circ$C for 1.5 h and then the solution was added to 5 % HCl aqueous solution, extracted with dichloromethane, and the extract was dried over with MgSO$_4$, and filtered. Dichloromethane was evaporated to obtained 98% (the yield was determined by NMR spectrometry) of 3a. Purification of the product was carried out by flash column chromatography (ethyl acetate : hexane = 1 : 50). Similar procedures were repeated as described above to obtain other products (eq. 3-19).

3a: Yellow solid. mp 88-89 $^\circ$. $^1$H NMR (200 MHz, CDCl$_3$) $\delta$ 8.06 (s, 1H), 7.28-7.40 (m, 7H), 6.96 (td, $J=7.3$, 0.6 Hz, 1H), 6.84 (d, $J=8.8$ Hz, 1H), 6.58 (s, 1H). $^{13}$C NMR (50 MHz, CDCl$_3$) $\delta$ 153.62, 141.24, 136.82, 134.35, 130.47, 129.51, 129.31, 128.39, 127.07, 122.56, 117.95, 117.31, 74.22. MS m/z (relative intensity) 253 (M$^+$, 60), 236 (40), 207 (100), 178 (41), 105 (20). HRMS calcd for C$_{15}$H$_{11}$NO$_3$ (M$^+$) 253.0739, found 253.0740.

3b: Yellow solid. mp 154-155 $^\circ$. $^1$H NMR (200 MHz, CDCl$_3$) $\delta$ 8.05 (s, 1H), 7.27-7.35 (m, 7H), 6.99 (td, $J=7.7$, 1.0 Hz, 1H), 6.79-6.87 (m, 3H), 6.52 (s, 1H). $^{13}$C NMR (50 MHz, CDCl$_3$) $\delta$ 160.52, 153.57, 141.38, 134.26, 130.36, 129.07, 128.95, 128.56, 122.44, 118.01, 117.36, 114.19, 73.94, 55.20. MS m/z (relative intensity) 283 (M$^+$, 24), 237 (100), 194 (17), 165 (19). HRMS calcd for C$_{16}$H$_{13}$NO$_4$ (M$^+$) 283.0845, found 283.0845.

3c: Yellow solid. mp 133-134 $^\circ$. $^1$H NMR (200 MHz, CDCl$_3$) $\delta$ 8.06 (s, 1H), 7.30-7.38 (m, 6H), 7.02 (td, $J=7.2$, 1.0 Hz, 1H), 6.87 (dd, $J=8.4$, 1.0 Hz, 1H), 6.55 (s, 1H). $^{13}$C NMR (50 MHz, CDCl$_3$) $\delta$ 153.35, 140.84, 135.49, 135.29, 134.53, 130.56, 129.54, 129.13, 128.46, 122.79, 117.80, 117.31, 73.45.
MS m/z (relative intensity) 287 (M⁺, 9), 204 (50), 176 (100), 148 (40). HRMS calcd for C₁₅H₁₀NO₃³⁵Cl (M⁺) 287.0349, found 287.0350; calcd for C₁₅H₁₀NO₃³⁷Cl (M⁺) 289.0320, found 289.0321.

3d: Yellow solid. mp 62-63 °. ¹H NMR (200 MHz, CDCl₃)  7.98 (s, 1H), 7.29-7.37 (m, 2H), 7.21 (dd, J=5.0, 1.0 Hz, 1H), 6.86-7.04 (m, 4H), 6.79 (s, 1H). ¹³C NMR (50 MHz, CDCl₃)  153.07, 141.22, 139.36, 134.32, 130.45, 128.95, 126.93, 126.90, 126.87, 122.88, 118.06, 117.60, 69.32. MS m/z (relative intensity) 259 (M+, 10), 213 (100), 184 (22), 156 (8). HRMS calcd for C₁₃H₈NO₃S (M⁺) 258.0225, found 258.0222.

5: Yellow solid. mp 202-204 °. ¹H NMR (200 MHz, CDCl₃)  8.00 (s, 2H), 7.28-7.36 (m, 8H), 6.99 (td, J=6.9, 1.0 Hz, 2H), 6.84 (dd, J=8.6, 1.0 Hz, 2H), 6.53 (s, 2H). ¹³C NMR (50 MHz, CDCl₃)  153.48, 140.86, 138.16, 134.50, 130.53, 129.37, 127.52, 122.70, 117.72, 117.30, 73.6. MS m/z (relative intensity) 428 (M⁺, 60), 411 (20), 382 (30), 336 (100), 205 (31), 176 (29). HRMS calcd for C₂₄H₁₆N₂O₆ (M⁺) 428.1008, found 428.1007.

7: Yellow solid. mp 116-118 °. ¹H NMR (200 MHz, CDCl₃)  8.02 (s, 1H), 7.24-7.28 (m, 12H), 6.90-7.02 (m, 2H). ¹³C NMR (50 MHz, CDCl₃)  153.41, 146.25, 140.15, 134.11, 130.29, 129.80, 128.71, 128.65, 127.95, 122.74, 118.95, 117.45, 85.74. MS m/z (relative intensity) 329 (M⁺, 16), 283 (100), 252 (40), 205 (21), 165 (24). HRMS calcd for C₂₁H₁₅NO₃ (M⁺) 329.1052, found 329.1060.

9: Yellow liquid. ¹H NMR (200 MHz, CDCl₃)  7.64 (s, 1H), 7.34 (td, J=7.6, 1.6 Hz, 1H), 7.22 (dd, J=7.6, 1.6 Hz, 1H), 6.98 (td, J=7.6, 1.6 Hz, 1H), 6.88 (d, J=7.6 Hz, 1H), 1.74 (s, 6H). ¹³C NMR (50 MHz, CDCl₃)  153.77, 147.81, 133.80, 129.69, 128.59, 122.20, 118.65, 117.12, 78.59, 25.81. MS m/z (relative intensity) 205 (M⁺, 21), 190 (100), 144 (39), 57 (84). HRMS calcd for C₁₁H₁₁NO₃ (M⁺) 205.0739, found 205.0740.

11: Colorless solid. mp 187-189 °. ¹H NMR (200 MHz, CDCl₃)  7.52 (d, J=7.4 Hz, 1H), 7.27 (td, J=7.4, 1.0 Hz, 1H), 7.04 (td, J=7.4, 1.0 Hz, 1H), 6.93 (dd, J=7.4, 1.0 Hz, 1H), 5.77 (d, J=6.2 Hz, 1H), 5.04 (d, J=6.2 Hz, 1H), 2.47 (d, J=13.0 Hz, 1H), 2.25 (d, J=13.0 Hz, 1H), 1.65-2.11 (m, 11H), 1.46 (dd, J=10.2, 2.4 Hz, 1H). ¹³C NMR (50 MHz, CDCl₃)  151.37, 129.77, 126.66, 122.55, 121.88, 117.05, 85.48, 81.16, 62.97, 37.43, 33.97, 33.41, 33.33, 32.52, 32.12, 32.08, 26.77, 26.45. MS m/z (relative intensity) 315 (M⁺, 100), 268 (42), 251 (67), 119 (41). HRMS calcd for C₁₈H₂₁NO₄ (M⁺) 315.1471, found 315.1471.

X-Ray Analysis of 11: A colorless single crystal of 11 was mounted on a glass fiber using 5-minute epoxy. Data collection was carried out at rt on a Nonius CAD4 equipped with graphite monocrated MoKα radiation (λ=0.71073 Å). Cell parameters were determined using 25 reflections. The structure was solved by direct methods followed by successive cycles of full-matrix least-squares refinement and difference Fourier analysis using NRCVAX 94’ Version software package. All non-hydrogen atoms
were refined anisotropically. The hydrogen atoms were not refined. Crystal data for compound 11: C\textsubscript{18}H\textsubscript{21}NO\textsubscript{4}, Monoclinic, space group P \textit{2}1/\textit{n} with \( a=10.869(3) \) Å, \( b=10.886(3) \) Å, \( c=13.808(4) \) Å, \( \beta=112.55(3) ^\circ \), \( V=1508.8(7) \) Å\(^3\), \( Z=4 \), \( D_c=1.388 \text{ g/cm}^3 \), \( \mu=(\text{MoK}^\alpha)=0.10 \text{ mm}^{-1} \), GOOF=1.8059, R1 [I>2\(\sigma(I)\)]=0.078, wR2=0.071 (all data).

**12:** Yellow solid. mp 96-98 \(^\circ\). \(^1\)H NMR (200 MHz, CDCl\textsubscript{3}) \( \delta \) 7.21-7.37 (m, 2H), 7.00-7.07 (m, 2H), 6.96 (s, 1H), 2.48 (s, 1H), 2.34 (d, \( J=12.6 \) Hz, 1H), 1.50-1.90 (m, 10H). \(^13\)C NMR (50 MHz, CDCl\textsubscript{3}) \( \delta \) 151.83, 149.20, 132.12, 128.62, 123.28, 122.21, 120.77, 117.21, 79.94, 37.07, 34.11, 33.82, 33.55, 33.03, 26.28, 25.90. MS m/z (relative intensity) 297 (M\(^+\), 34), 251 (100), 131 (22). HRMS calcd for C\textsubscript{18}H\textsubscript{19}NO\textsubscript{3} (M\(^+\)) 297.1365, found 297.1369.

**14:** Colorless solid. mp 142-144 \(^\circ\). \(^1\)H NMR (200 MHz, CDCl\textsubscript{3}) \( \delta \) 7.52 (d, \( J=8.0 \) Hz, 1H), 7.27 (t, \( J=8.0 \) Hz, 1H), 7.04 (t, \( J=8.0 \) Hz, 1H), 6.93 (d, \( J=5.8 \) Hz, 1H), 5.77 (d, \( J=5.8 \) Hz, 1H), 5.05 (d, \( J=5.8 \) Hz, 1H), 2.24-2.50 (m, 2H), 1.59-2.02 (m, 11H), 1.44 (d, \( J=7.0 \) Hz, 1H). \(^13\)C NMR (50 MHz, CDCl\textsubscript{3}) \( \delta \) 151.36, 129.77, 126.63, 122.93, 121.89, 117.18, 85.77, 80.37, 62.98, 33.84, 32.41, 27.96, 27.89, 26.60, 26.48, 20.33, 20.12. MS m/z (relative intensity) 303 (M\(^+\), 41), 256 (36), 213 (15), 134 (22), 122 (100). HRMS calcd for C\textsubscript{17}H\textsubscript{21}NO\textsubscript{4} (M\(^+\)) 303.1477, found 303.1474.

**X-Ray Analysis of 14:** A colorless single crystal of 14 was mounted on a glass fiber using 5-minute epoxy. Data collection was carried out at rt on a Nonius CAD4 equipped with graphite monocramed MoK\(^\alpha\) radiation (\( \theta=0.71073 \) Å). Cell parameters were determined using 25 reflections. The structure was solved by direct methods followed by successive cycles of full-matrix least-squares refinement and difference Fourier analysis using NRCVAX 94' Version software package. All non-hydrogen atoms were refined anisotropically. The hydrogen atoms were not refined. Crystal data for 14: C\textsubscript{17}H\textsubscript{21}NO\textsubscript{4}, Triclinic, space group P -1 with \( a=8.735(4) \) Å, \( b=13.643(2) \) Å, \( c=13.719(3) \) Å, \( \alpha=86.367(15) ^\circ \), \( \beta=73.87(3) ^\circ \), \( \gamma=76.749(19) ^\circ \), \( V=1528.7(8) \) Å\(^3\), \( Z=4 \), \( D_c=1.318 \text{ g/cm}^3 \), \( \mu=(\text{MoK}^\alpha)=0.09 \text{ mm}^{-1} \), GOOF=0.9466, R1 [I>2\(\sigma(I)\)]=0.0446, wR2=0.043 (all data).

**15:** Yellow solid. mp 94-96 \(^\circ\). \(^1\)H NMR (200 MHz, CDCl\textsubscript{3}) \( \delta \) 7.22-7.37 (m, 2H), 6.97-7.06 (m, 2H), 6.93 (s, 1H), 2.44 (s, 2H), 2.16-2.35 (m, 2H), 1.41-2.04 (m,10H). \(^13\)C NMR (50 MHz, CDCl\textsubscript{3}) \( \delta \) 151.83, 149.48, 132.03, 128.51, 122.90, 122.20, 120.88, 117.27, 79.46, 33.73, 28.12, 27.39, 19.85, 19.73. MS m/z (relative intensity) 285 (M\(^+\), 52), 268 (100), 251 (20), 181 (24), 157 (40), 131 (78), 115 (79), 91 (62). HRMS calcd for C\textsubscript{17}H\textsubscript{19}NO\textsubscript{3} (M\(^+\)) 285.1359, found 285.1362.

**17:** Colorless solid. mp 187-189 \(^\circ\). \(^1\)H NMR (200 MHz, CDCl\textsubscript{3}) \( \delta \) 7.52 (d, \( J=7.6 \) Hz, 1H), 7.29 (t, \( J=7.6 \) Hz, 1H), 7.04 (td, \( J=7.6, 1.0 \) Hz, 1H), 6.94 (dd, \( J=7.6, 1.0 \) Hz, 1H), 5.54-5.82 (m, 2H), 5.57 (d, \( J=5.6 \) Hz, 1H), 5.13 (d, \( J=5.6 \) Hz, 1H), 3.02 (d, \( J=18.6 \) Hz, 1H), 1.80-2.56 (m, 9H), 1.36-1.58 (m, 2H). \(^13\)C NMR (50 MHz, CDCl\textsubscript{3}) \( \delta \) 151.56, 129.85, 129.75, 126.77, 126.46, 122.30, 121.71, 117.02, 87.80,
22: Yellow solid. mp 108-110 º. ¹H NMR (200 MHz, CDCl₃) □ 7.92 (s, 1H), 7.28-7.41 (m, 2H), 7.02 (td, J=7.8, 1.2 Hz, 1H), 6.94 (d, J=7.8 Hz, 1H), 2.84 (dd, J=13.4, 2.6 Hz, 1H), 2.63 (d, J=3.8 Hz, 1H), 2.47 (s, 1H), 1.80-1.98 (m, 2H), 1.07-1.65 (m, 5H). ¹³C NMR (50 MHz, CDCl₃) □ 154.21, 144.38, 133.44, 131.21, 129.75, 122.37, 120.27, 117.27, 86.27, 45.05, 40.04, 36.38, 35.78, 27.19, 21.96. MS m/z (relative intensity) 257 (M⁺, trace), 207 (22), 121 (100). HRMS calcd for C₁₅H₁₅NO₃ (M⁺) 257.1052, found 257.1052.

25: Yellow liquid. ¹H NMR (200 MHz, CDCl₃) □ 7.50 (s, 1H), 7.29-7.39 (m, 2H), 7.06 (t, J=7.5 Hz, 1H), 3.40 (dd, J=7.5, 1.2 Hz, 1H), 3.07 (s, 3H), 3.00 (t, J=4.0 Hz, 1H), 2.44 (d, J=5.4 Hz, 1H), 2.37 (td, J=7.4, 3.6 Hz, 1H), 1.62-1.89 (m, 3H), 1.25-1.42 (m, 1H), 1.01-1.16 (m, 1H). ¹³C NMR (50 MHz, CDCl₃) □ 154.41, 144.93, 132.29, 129.34, 126.46, 122.56, 120.74, 116.22, 88.03, 81.46, 54.91, 45.55, 40.66, 37.39, 28.25, 22.21. MS m/z (relative intensity) 287 (M⁺, 7), 270 (6), 206 (100), 181 (27), 156 (45), 115 (36). HRMS calcd for C₁₇H₂₁NO₄ (M⁺) 303.1612, found 303.1581.

28: Yellow solid. mp 149-110 º. ¹H NMR (200 MHz, CDCl₃) □ 7.67 (s, 1H), 7.29-7.40 (m, 2H), 6.98-7.09 (m, 2H), 2.04-2.14 (m, 2H), 1.94 (t, J=5.2 Hz, 1H), 1.64 (t, J=5.2 Hz, 1H), 1.25-1.42 (m, 1H). ¹³C NMR (50 MHz, CDCl₃) □ 154.61, 144.15, 132.97, 129.81, 128.80, 128.46, 122.56, 120.74, 116.80, 88.32, 81.54, 31.35, 30.63, 18.50, 14.57, 15.80. MS m/z (relative intensity) 255 (M⁺, 20), 226 (78), 209 (100), 181 (68), 165 (36), 131 (39). HRMS calcd for C₁₅H₁₃NO₃ (M⁺) 255.0895, found 255.0907.

30: Yellow liquid. ¹H NMR (200 MHz, CDCl₃) □ 7.75 (s, 1H), 7.12-7.40 (m, 8H), 6.98 (d, J=8.0 Hz, 1H), 2.51-2.97 (m, 3H), 2.12-2.29 (m, 1H), 1.73 (s, 3H). ¹³C NMR (50 MHz, CDCl₃) □ 154.04, 146.40, 141.22, 133.96, 129.92, 129.85, 128.39, 128.34, 125.96, 122.08, 118.19, 116.80, 81.10, 40.53, 30.50, 24.81. MS m/z (relative intensity) 295 (M⁺, 8), 278 (6), 190 (100), 144 (46), 115 (20), 91 (31). HRMS calcd for C₁₈H₁₇NO₃ (M⁺) 295.1209, found 295.1200.

32: Yellow liquid. ¹H NMR (200 MHz, CDCl₃) □ 7.70 (s, 1H), 7.33 (td, J=7.6, 1.6 Hz, 1H), 7.20 (dd, J=7.6, 1.6 Hz, 1H), 6.95 (t, J=7.6 Hz, 1H), 6.86 (d, J=7.6 Hz, 1H), 2.23-2.40 (m, 1H), 1.78-1.97 (m, 1H), 1.68 (s, 3H), 1.10-1.61 (m, 4H), 0.87 (t, J=7.0 Hz, 3H). ¹³C NMR (50 MHz, CDCl₃) □ 154.17, 146.78, 133.79, 129.72, 129.60, 118.19, 116.74, 81.51, 38.42, 26.20, 24.88, 22.56, 13.78. MS m/z (relative intensity) 247 (M⁺, 39), 232 (18), 191 (82), 144 (100), 115 (81). HRMS calcd for C₁₄H₁₇NO₃ (M⁺) 247.1208, found 247.1209.

36: Yellow liquid. ¹H NMR (200 MHz, CDCl₃) □ 7.67 (s, 1H), 7.32 (td, J=7.6, 1.6 Hz, 1H), 7.22 (dd, J=7.6, 1.6 Hz, 1H), 6.96 (t, J=7.6 Hz, 1H), 6.84 (d, J=7.6 Hz, 1H), 2.08-2.36 (m, 4H), 1.78-2.02 (m, 4H). ¹³C NMR (50 MHz, CDCl₃) □ 153.63, 146.25, 133.62, 129.68, 129.54, 122.17, 119.13, 117.16, 88.67, 37.66, 24.67. MS m/z (relative intensity) 231 (M⁺, 10), 185 (100), 157 (21), 115 (34). HRMS calcd for
C_{13}H_{13}NO_{3} (M^+) 231.0895, found 231.0897.

37: Yellow liquid. $^1$H NMR (200 MHz, CDCl$_3$) δ 7.55 (s, 1H), 7.34 (td, $J$=7.4, 1.6 Hz, 1H), 7.20 (dd, $J$=7.4, 1.6 Hz, 1H), 6.91-7.02 (m, 2H), 2.00-2.30 (m, 4H), 1.54-1.94 (m, 4H), 1.25-1.48 (m, 2H). $^{13}$C NMR (50 MHz, CDCl$_3$) δ 153.38, 148.75, 133.49, 129.53, 128.60, 122.24, 119.38, 117.16, 79.72, 31.70, 24.58, 20.80. MS m/z (relative intensity) 245 (M^+, 14), 215 (31), 172 (42), 111 (48), 97 (62), 69 (78), 57 (100). HRMS calcd for C$_{14}$H$_{15}$NO$_3$ (M^+) 245.1052, found 245.1049.

39: Colorless solid. mp 112 $^\circ$. $^1$H NMR (200 MHz, CDCl$_3$) δ 7.48 (d, $J$=7.6 Hz, 1H), 7.25 (td, $J$=7.6, 1.6 Hz, 1H), 7.03 (td, $J$=7.6, 1.6 Hz, 1H), 6.84 (dd, $J$=7.6 Hz, 1H), 5.40 (d, $J$=8.8 Hz, 1H), 4.94 (d, $J$=8.8 Hz, 1H), 2.24 (br, 1H), 1.58-2.14 (m, 8H). $^{13}$C NMR (50 MHz, CDCl$_3$) δ 151.43, 129.92, 127.60, 122.55, 121.83, 117.36, 90.99, 86.88, 66.71, 35.72, 31.23, 23.37, 23.28. MS m/z (relative intensity) 249 (M^+, 82), 202 (71), 173 (100), 121 (93), 107 (45). HRMS calcd for C$_{13}$H$_{15}$NO$_4$ (M^+) 249.1001, found 249.1002.

40: Colorless solid. mp 136-138 $^\circ$. $^1$H NMR (200 MHz, CDCl$_3$) δ 7.50 (d, $J$=7.8 Hz, 1H), 7.27 (td, $J$=7.8, 1.6 Hz, 1H), 7.04 (td, $J$=7.8, 1.6 Hz, 1H), 6.92 (d, $J$=7.8 Hz, 1H), 5.46 (d, $J$=9.4 Hz, 1H), 4.73 (d, $J$=9.4 Hz, 1H), 2.45 (br, 1H), 1.46-2.08 (m, 8H), 1.08-1.30 (m, 2H). $^{13}$C NMR (50 MHz, CDCl$_3$) δ 150.99, 130.10, 127.45, 122.49, 121.88, 117.22, 94.66, 77.44, 66.02, 34.28, 27.11, 24.87, 20.73. MS m/z (relative intensity) 263 (M^+, 15), 245 (4), 216 (30), 173 (100), 121(95), 107 (26), 79 (35). HRMS calcd for C$_{14}$H$_{17}$NO$_4$ (M^+) 263.1158, found 263.1158.

41: Colorless solid. mp 121 $^\circ$. $^1$H NMR (200 MHz, CDCl$_3$) δ 7.24-7.34 (m, 2H), 6.93-7.06 (m, 2H), 5.7 (d, $J$=11.8 Hz, 1H), 4.70 (d, $J$=2.2 Hz, 1H), 4.51 (d, $J$=11.8 Hz, 1H), 2.32-2.44 (m, 1H), 1.74-2.06 (m, 4H), 1.24-1.47 (m, 1H). $^{13}$C NMR (50 MHz, CDCl$_3$) δ 150.93, 130.27, 130.03, 121.76, 121.36, 118.07, 82.52, 80.00, 65.15, 46.88, 36.87, 26.81, 20.53. MS m/z (relative intensity) 249 (M^+, 36), 231 (34), 219 (100), 185 (65), 173 (84), 131 (70), 121 (75), 69 (69). HRMS calcd for C$_{13}$H$_{15}$NO$_4$ (M^+) 249.1001, found 249.1001.

42: Colorless solid. mp 166-168 $^\circ$. $^1$H NMR (200 MHz, CDCl$_3$) δ 7.47 (d, $J$=7.4 Hz, 1H), 7.20 (td, $J$=7.4, 1.6 Hz, 1H), 7.00 (td, $J$=7.4, 1.6 Hz, 1H), 6.82 (dd, $J$=7.4, 1.6 Hz, 1H), 4.94 (d, $J$=6.2 Hz, 1H), 4.64 (d, $J$=11.2 Hz, 1H), 4.50 (d, $J$=11.2 Hz, 1H), 2.44-2.62 (m, 2H), 2.14 (t, $J$=7.5 Hz, 2H), 1.40-2.04 (m, 4H). $^{13}$C NMR (50 MHz, CDCl$_3$) δ 151.30, 129.13, 126.69, 123.53, 121.86, 117.25, 85.24, 79.67, 64.39, 45.64, 37.07, 24.40, 20.53. MS m/z (relative intensity) 249 (M^+, 20), 187 (80), 121 (100). HRMS calcd for C$_{13}$H$_{15}$NO$_4$ (M^+) 249.1001, found 249.1002.

43: Colorless solid. mp 160 $^\circ$. $^1$H NMR (200 MHz, CDCl$_3$) δ 7.24-7.34 (m, 2H), 6.93-7.06 (m, 2H), 5.7 (d, $J$=11.8 Hz, 1H), 4.70 (d, $J$=4.0 Hz, 1H), 4.59 (d, $J$=11.8 Hz, 1H), 1.34-2.30 (m, 11H). $^{13}$C NMR (50 MHz, CDCl$_3$) δ 151.74, 130.45, 129.47, 123.84, 121.65, 118.74, 79.50, 77.85, 67.93, 46.93, 36.55,
44: Colorless liquid. $^1$H NMR (200 MHz, CDCl$_3$) $\delta$ 7.22-7.34 (m, 2H), 6.88-7.04 (m, 2H), 5.04 (d, $J$=11.6 Hz, 1H), 4.80 (d, $J$=11.6 Hz, 1H), 4.62 (d, $J$=3.0 Hz, 1H), 1.34-2.32 (m, 11H). $^{13}$C NMR (50 MHz, CDCl$_3$) $\delta$ 151.51, 130.18, 129.45, 122.26, 121.71, 117.89, 80.34, 78.24, 70.34, 45.88, 36.52, 28.33, 27.27, 26.89, 20.80. MS m/z (relative intensity) 277 (M$,^+$, 40), HRMS calcd for C$_{15}$H$_{19}$NO$_4$ (M$^+$) 277.1314, found 277.1324.

45: Colorless solid. mp 138 $^\circ$. $^1$H NMR (200 MHz, CDCl$_3$) $\delta$ 7.49 (d, $J$=7.4 Hz, 1H), 7.25 (td, $J$=7.4, 1.2 Hz, 1H), 6.84-6.93 (m, 2H), 6.44 (s, 1H), 2.99 (br, 1H), 2.40-2.84 (m, 4H), 1.60-2.34 (m, 10H). $^{13}$C NMR (50 MHz, CDCl$_3$) $\delta$ 151.98, 130.04, 127.65, 124.60, 121.79, 118.00, 81.26, 76.36, 67.65, 50.02, 37.19, 29.50, 28.69, 25.58, 20.94. MS m/z (relative intensity) 277 (M$,^+$, 17), 187 (22), 173 (20), 121 (100), 107 (20). HRMS calcd for C$_{15}$H$_{19}$NO$_4$ (M$^+$) 277.1314, found 277.1321.

46: Colorless solid. mp 210 $^\circ$. $^1$H NMR (200 MHz, CDCl$_3$) $\delta$ 7.24 (d, $J$=7.0 Hz, 1H), 7.15 (t, $J$=7.0 Hz, 1H), 6.84-6.93 (m, 2H), 6.44 (s, 1H), 2.99 (br, 1H), 2.40-2.84 (m, 4H), 1.60-2.34 (m, 10H). $^{13}$C NMR (50 MHz, CDCl$_3$) $\delta$ 158.61, 152.10, 138.02, 134.70, 128.60, 128.56, 121.30, 120.56, 119.19, 107.88, 86.74, 52.83, 33.58, 33.40, 32.67, 32.32, 24.73, 24.67, 22.96. MS m/z (relative intensity) 311 (M$,^+$, 97), 293 (40), 185 (51), 173 (100), 144 (32), 131 (52). HRMS calcd for C$_{19}$H$_{21}$NO$_3$ (M$^+$) 311.1834, found 311.1835.

47: Colorless solid. mp 192 $^\circ$. $^1$H NMR (200 MHz, CDCl$_3$) $\delta$ 7.21 (d, $J$=7.6 Hz, 1H), 7.13 (dd, $J$=7.6, 1.6 Hz, 1H), 6.95 (dd, $J$=7.6, 1.6 Hz, 1H), 6.86 (td, $J$=7.6, 1.6 Hz, 1H), 6.46 (t, $J$=4.0 Hz, 1H), 4.32 (s, 1H), 2.75 (br, 1H), 1.20-2.60 (m, 18H). $^{13}$C NMR (50 MHz, CDCl$_3$) $\delta$ 162.43, 151.15, 135.25, 129.83, 128.51, 127.99, 121.05, 120.29, 118.75, 107.54, 76.39, 50.39, 28.40, 28.16, 25.93, 25.25, 25.20, 21.86, 21.74, 20.58. MS m/z (relative intensity) 339 (M$,^+$, 97), 323 (100), 278 (40), 107 (43), 81 (78). HRMS calcd for C$_{21}$H$_{25}$NO$_3$ (M$^+$) 339.1834, found 339.1835.

48: Colorless solid. mp 218 $^\circ$. $^1$H NMR (200 MHz, CDCl$_3$) $\delta$ 7.25 (d, $J$=7.4 Hz, 1H), 7.14 (td, $J$=7.4, 1.2 Hz, 1H), 6.92 (dd, $J$=7.4, 1.2 Hz, 1H), 6.85 (td, $J$=7.4, 1.2 Hz, 1H), 6.60 (t, $J$=6.8 Hz, 1H), 4.31 (s, 1H), 1.40-2.70 (m, 22H). $^{13}$C NMR (50 MHz, CDCl$_3$) $\delta$ 163.71, 151.47, 139.98, 136.85, 128.63, 127.93, 120.89, 120.18, 118.92, 109.20, 79.78, 77.02, 50.71, 33.38, 32.85, 32.15, 29.28, 29.21, 28.95, 26.31, 25.93, 22.78, 22.00. MS m/z (relative intensity) 367 (M$,^+$, 12), 349 (7), 280 (20), 212 (38), 173 (42), 134 (50), 95 (100). HRMS calcd for C$_{23}$H$_{29}$NO$_3$ (M$^+$) 367.2147, found 367.2146.

53: Yellow liquid. $^1$H NMR (200 MHz, CDCl$_3$) $\delta$ 7.78 (s, 1H), 7.24-7.42 (m, 2H), 6.92-7.05 (m, 2H), 5.67 (q, $J$=6.4 Hz, 1H), 1.47 (d, $J$=6.4 Hz, 3H). $^{13}$C NMR (50 MHz, CDCl$_3$) $\delta$ 151.66, 141.78,
132.37128.68, 126.38, 120.78, 116.36, 115.77, 67.87, 16.96. MS m/z (relative intensity) 191 (M⁺, 23),
176 (100), 147 (18), 130 (20), 121 (40), 115 (21). HRMS calcd for C₁₀H₉NO₃ (M⁺) 191.0582, found
191.0582.

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