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Synthesis of 3-Hydroxy-9*H*-fluorene-2-carboxylates via Michael Reaction, Robinson Annulation, and Aromatization

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Abstract: A series of 3-hydroxy-fluorene-2-carboxylate compounds were prepared from Michael addition of acetoacetate to 2-benzylideneindan-l-one followed by Robinson annulation and aromatization. In this reaction, we were able to isolate two Robinson annulation products and characterize them. This sequential reaction could proceed without the isolation of intermediates to give the desired products directly in reasonable yields.

Keywords: fluorene; Michael reaction; Robinson annulation; oxidation

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1. Introduction

Fluorenes are important structural frameworks in natural products [1–3], pharmacophores [4–7], and carcinogens [8,9]. Figure 1 illustrates a few typical examples in this regard. Aelaginpulvilin B isolated from the Chinese medicine *Selaginella pulvinata* shows a potent activity against PDE4 [3]. Both **I** and **II** are fluorene derivatives for pharmaceutical uses, whereas *N*-(1-Methoxy-9*H*-fluoren-2-yl)acetamide **III** and 2-nitrofluorene **V** are known to be carcinogens [8,9]. Modification of fluorene cores with electron-donating or accepting groups makes the corresponding molecules useful materials for organic light-emitting devices such as compounds **V** and **VI** [10–12].

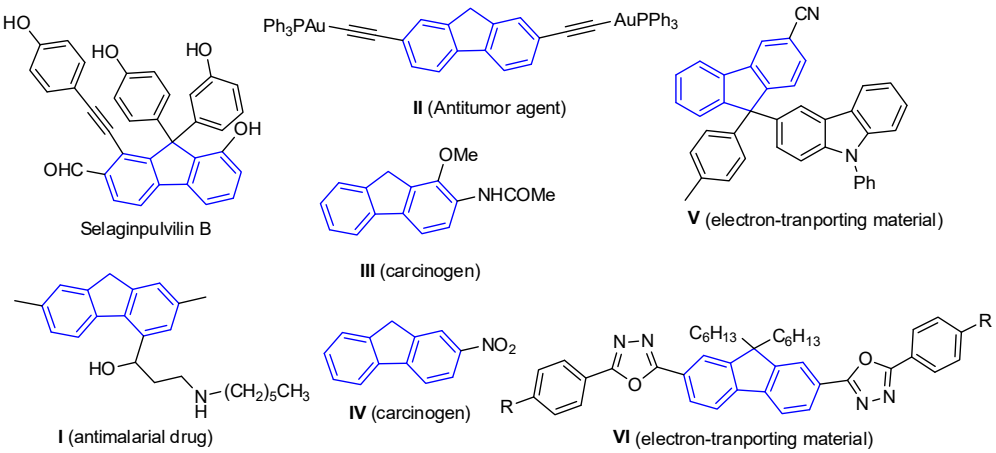
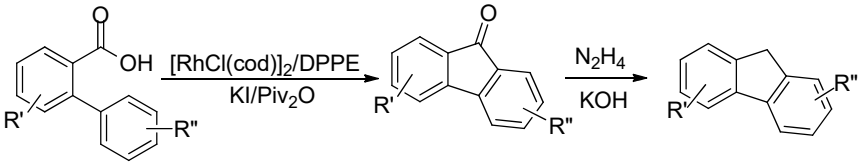


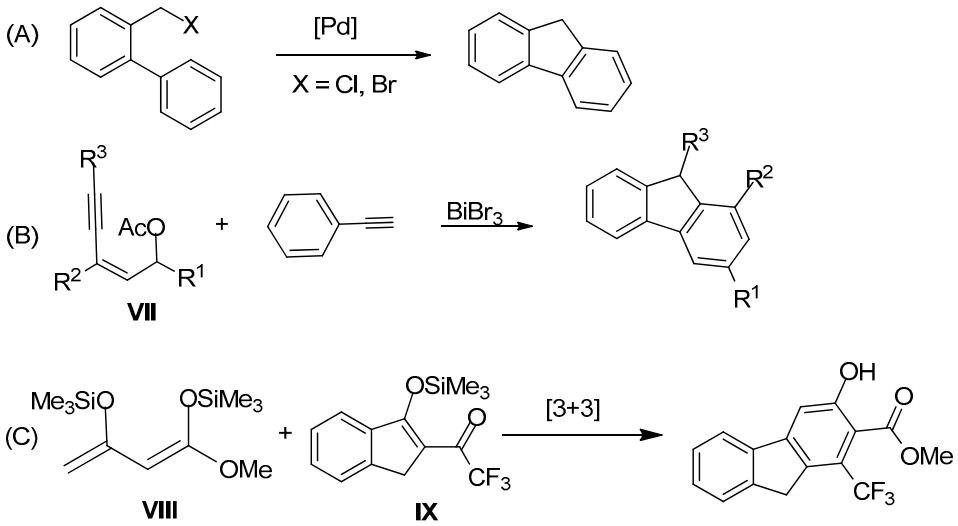
Figure 1. Selected fluorene molecules and their uses.

Substituted fluorenes are quite often obtained by reduction of the corresponding fluorenones, which could be prepared via the intramolecular Friedel–Crafts acylation or the related reaction followed by reduction (Scheme 1) [13,14]. Nevertheless, numerous approaches have been disclosed including metal-catalyzed reactions (Scheme 2A) [15,16]. Liang and coworkers reported a unique preparation of 9-substituted fluorene via a sequential cyclization of 2-en-4-yn-1-yl acetate (**VII**) and a terminal alkyne in the presence of $BiBr_3$ as the Lewis acid catalyst [17] (Scheme 2B). On the other hand, the construction

of aromatic ring fused to inden-1-one is another manner to yield the fluorene cores. A [3+3] cyclization of 1,3-bis(trimethylsilyloxy)-1,3-butadienes (**VIII**) with trimethylsilylated 2-trifluoroacetyl-3-indenol (**IX**) to provide a highly substituted fluorene derivatives was investigated by Langer's research group [18] (Scheme 2C).

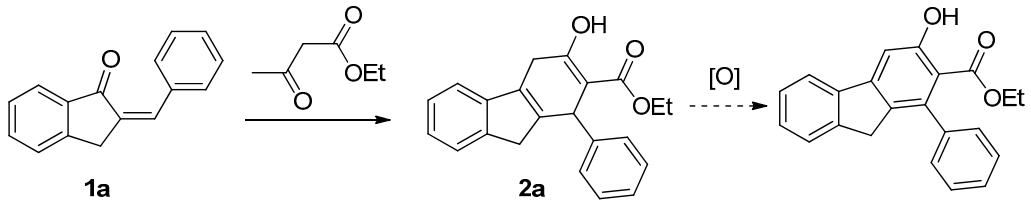


Scheme 1. Traditional approach for preparations of fluorenes.



Scheme 2. Typical synthetic preparations of fluorenes. (**A**) _Pd-catalyzed cyclization; (**B**) Lewis acid promoted cyclization; (**C**) [3+3] cyclization.

Back in the 1960s, Anderson and Leaver investigated that Michael reaction of acetoacetate with 2-benzylideneindan-l-one (**1a**) provided the annulation product **2a** as the sole product (Scheme 3) [19]. However, in this early work, no detailed NMR structural data or side products were reported. We envisioned that further oxidation of **2a** should give the corresponding fluorene. In addition, as well as **2a,** it will be also interesting to know any side product formed in this annulation. Thus, we decided to examine in more detail this reaction and to study the oxidation of **2a** leading to fluorenes with the substrate scope.



Scheme 3. Our approach to prepare fluorene compounds.

2. Materials and Methods

2.1. Materials and Instrumentation

All chemicals were purchased and used without any further purifications. Flash chromatography was performed using silica gel 230–400 mesh. Nuclear magnetic resonance spectra were recorded in $CDCl_3$ or acetone-d_6 on either a Bruker AM-300 or AVANCE 400 spectrometer. Chemical shifts are given in parts per million relative to Me_4Si for ^1H and $^{13}C\{^1H\}$ NMR. Infrared spectra were measured on a Nicolet Magna-IR 550 spectrometer

(Series-II) as KBr pallets. HRMS spectra were determined on a Bruker micrOTOF-QII spectrometer with electrospray ionization. Compound **1a** was prepared according to the reported procedure [20].

2.2. Reaction of **1a** *with Ethyl Acetoacetate*

A solution of 2-benzylidene-1-indanone **1a** (110.1 mg, 0.5 mmol) with ethyl acetoacetate (220.3 mg, 2.5 mmol) and *t*-BuOK (0.5 mmol) in 5 ml of dioxane was heated with stirring at 50 °C under nitrogen atmosphere for 24 h. After the reaction, mixture was quenched with 5 ml of saturated NH_4Cl aqueous solution then extract with 5 ml of ethyl acetate for three times. The crude product was then concentrated under reduced pressure. The residue was chromatographed on silica gel to afford the products **2a** and **3a**. Their spectral data are shown below.

Ethyl 3-hydroxy-1-phenyl-4,9-dihydro-1H-fluorene-2-carboxylate (**2a**) [19]. Light yellow solid. R_f = 0.40 (hexane/EA = 19:1); mp: 137–138 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ12.7 (s, 1H), 7.32–7.24 (m, 3H), 7.23–7.09 (m, 6H), 4.67 (t, *J* = 5.3 Hz, 1H), 4.13–4.00 (m, 2H), 3.59 (ddt, *J* = 22 Hz, *J* = 5.3 Hz, *J* = 2.8 Hz 1H), 3.48 (ddt, *J* = 22 Hz, *J* = 5.3 Hz, *J* = 2.5 Hz 1H), 3.21 (dt, *J* = 22 Hz, *J* = 2.5 Hz, 1H), 2.97 (dt, *J* = 22 Hz, *J* = 2.5 Hz, 1H), 1.06 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.0, 170.2, 144.9, 143.9, 143.2, 141.9, 130.0, 128.0, 127.8, 126.2, 126.1, 124.6, 123.5, 118.2, 100.9, 60.4, 43.3, 38.5, 28.2, 13.7. IR (KBr) $\upsilon_{C=O}$ 1663 cm^{-1}. ESI-HRMS (TOF) m/z $[M+Na]^+$ Calcd. for $C_{22}H_{20}O_3Na$: 355.1305. Found: 355.1298. The structure of this compound was confirmed by X-ray crystallography (see Supplementary Materials) and ORTEP plot of **2a** is illustrated in Figure 2.

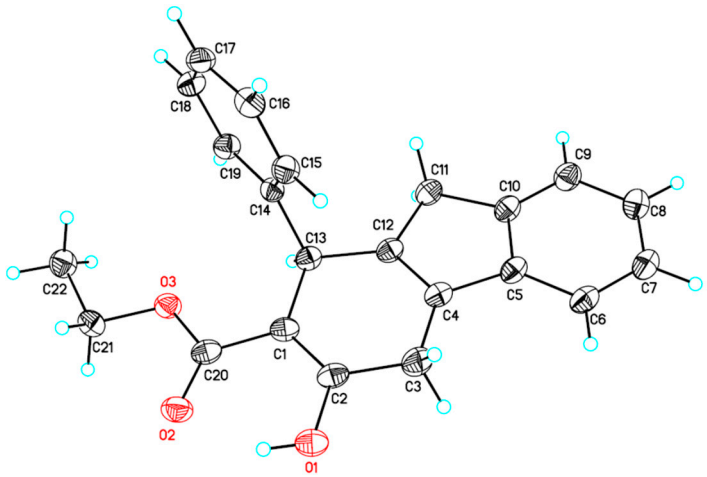


Figure 2. OPTEP plot of **2a**. Bond distances of C1-C2 1.355 (2) Å and C4-C12 1.343(2) Å.

Ethyl 3-oxo-1-phenyl-2,3,9,9a-tetrahydro-1H-fluorene-2-carboxylate (**3a**). Yellow orange oil. R_f = 0.26 (hexane/EA = 9:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 (d, *J* = 7.6 Hz, 1H), 7.38 (td, *J* = 11.2 Hz, 1.2 Hz, 1H), 7.36–7.24 (m, 7H), 6.43 (d, *J* = 2.6 Hz, 1H), 4.00 (q, *J* = 7.1 Hz, 2H), 3.74 (d, *J* = 12.3 Hz, 1H), 3.56 (t, *J* = 11.9 Hz, 1H), 3.51–3.42 (m, 1H), 2.91 (dd, *J* = 16.5 Hz, 7.7 Hz, 1H), 2.70 (dd, *J* = 16.5 Hz, 6.7 Hz, 1H), 0.99 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.0, 169.3, 164.6, 145.0, 136.8, 135.7, 132.6, 129.1, 128.5, 127.9, 126.1, 124.0, 117.1, 78.1, 60.9, 60.3, 55.7, 52.5, 45.2, 13.8; IR (KBr) $\upsilon_{C=O}$ 1738, 1655 cm^{-1}; ESI-HRMS (TOF) m/z $[M+H]^+$ Calcd. for $C_{22}H_{21}O_3$: 333.1485. Found: 333.1467.

2.3. Direct Preparation of Fluorenes without Isolation

A mixture of 2-benzylidene-1-indanone (0.5 mmol), ethyl acetoacetate, and t-BuOK (0.5 mmol) in toluene (5 mL) was heated at 80 °C for 24 h. After cooling, the reaction mixture was quenched with saturated NH_4Cl aqueous solution and extracted with ethyl acetate (5 mL × 3). Upon concentration, the residue was re-dissolved in dioxane (5 mL). DDQ (0.55 mmol) was added and the resulting mixture was heated at 100 °C under oxygen

atmosphere for another 24 h. The reaction mixture was filtered to remove insoluble solid and the filtrate was concentrated. The residue was chromatographed on silica gel with elution of hexane/ethyl acetate (19:1) to provide the desired product **4a** as a white yellow solid. (mg, %): R_f = 0.34 (hexane/EA = 19:1); mp 162–163 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.3 (s, 1H), 7.80 (d, J = 7.3 Hz, 1H), 7.42–7.28 (m, 7H), 7.22–7.18 (m, 2H), 3.94 (q, J = 7.2 Hz, 2H), 3.50 (s, 2H), 0.70 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.0, 170.2, 144.9, 143.9, 143.2, 141.9, 130.0, 128.0, 127.8, 126.2, 126.1, 124.6, 123.5, 118.2, 100.9, 60.4, 43.3, 38.5, 28.2, 13.7. IR (KBr) υ_{O-H} 3500–3200 (br), $\upsilon_{C=O}$ 1655 cm^{-1}. ESI-HRMS (TOF) m/z $[M+Na]^+$ Calcd. for $C_{22}H_{18}O_3Na$: 353.1148. Found: 353.1160.

Other fluorenes were prepared by a similar procedure and spectral data are listed below.

Ethyl 1-(4-fluorophenyl)-3-hydroxy-9H-fluorene-2-carboxylate (**4b**). White solid. R_f = 0.32 (*hexane/EA = 19:1*); mp 107–108 °C; (85 mg, 46%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ11.3 (s, 1H), 7.77 (d, *J* = 7.3 Hz, 1H), 7.42–7.28 (m, 4H), 7.20–7.06 (m, 4H), 3.99 (q, *J* = 7.2 Hz, 2H), 3.46 (s, 2H), 0.80 (t, *J* = 7.2 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ171.1, 163.1, 162.3, 160.6, 147.0, 145.1, 140.1, 139.6, 137.6, 134.0, 129.4, 129.3, 128.3, 126.9, 124.9, 121.2, 114.8, 114.6, 110.1, 107.9, 60.8, 36.4, 13.0. IR (KBr) υ_{O-H} 3400–3200 (br), $\upsilon_{C=O}$ 1655 cm^{-1}. ESI-HRMS (TOF) m/z $[M+H]^+$ Calcd. for $C_{22}H_{18}FO_3$: 349.1234. Found: 349.1224.

Ethyl 3-hydroxy-1-(4-(trifluoromethyl)phenyl)-9H-fluorene-2-carboxylate (**4c**). Pale yellow solid. R_f = 0.35 (hexane/EA = 19:1); mp 160–161 °C. (120.7 mg, 58%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 11.4 (s, 1H), 7.77 (d, *J* = 7.0 Hz, 1H), 7.69 (d, *J* = 8.0 Hz, 2H), 7.42–7.29 (m, 6H), 3.97 (q, *J* = 7.2 Hz, 2H), 3.43 (s, 2H), 0.70 (t, *J* = 7.2 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 170.8, 162.5, 147.3, 145.7, 145.0, 140.0, 139.1, 133.4, 129.5, 129.2, 128.8, 128.5, 128.3, 127.0, 125.7, 124.9, 124.8, 124.8, 122.9, 121.2, 109.5, 108.3, 60.9, 36.3, 12.6. IR (KBr) υ_{O-H} 3410–3200 (br), $\upsilon_{C=O}$ 1660 cm^{-1}. ESI-HRMS (TOF) m/z $[M+H]^+$ Calcd. for $C_{23}H_{18}F_3O_3$: 399.1203. Found: 399.1193.

Ethyl 3-hydroxy-1-(4-nitrophenyl)-9H-fluorene-2-carboxylate (**4d**). Light yellow solid. R_f = 0.20 (hexane/EA = 19:1); mp 209–210 °C. (111.5 mg, 59%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 11.4 (s, 1H), 8.29 (d, *J* = 8.8 Hz, 2H), 7.79 (d, *J* = 7.2 Hz, 1H), 7.45–7.27 (m, 6H), 3.98 (q, *J* = 7.2 Hz, 2H), 3.42 (s, 2H), 0.72 (t, *J* = 7.2 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 170.5, 162.6, 148.9, 147.6, 146.8, 144.8, 139.8, 138.2, 133.1, 128.9, 128.7, 127.1, 125.0, 123.2, 121.3, 109.1, 108.7, 61.1, 36.2, 13.0. IR (KBr) υ_{O-H} 3500–3200 (br), $\upsilon_{C=O}$ 1669 cm^{-1}. ESI-HRMS (TOF) m/z $[M+H]^+$ Calcd. for $C_{22}H_{18}NO_5$: 376.1179. Found: 376.1170.

Ethyl 3-hydroxy-1-(p-tolyl)-9H-fluorene-2-carboxylate (**4e**). Pale yellow solid. R_f = 0.32 (hexane/EA = 19:1); mp 104–105 °C. (89.7 mg, 51 %). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 11.3 (s, 1H), 7.79 (d, *J* = 7.3 Hz, 1H), 7.43–7.28 (m, 4H), 7.22 (d, *J* = 7.8 Hz, 2H), 7.10 (d, *J* = 8.0 Hz, 2H), 3.98 (q, *J* = 7.1 Hz, 2H), 3.51 (s, 2H), 2.44 (s, 3H), 0.75 (t, *J* = 7.1 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 171.4, 162.1, 146.8, 145.3, 140.9, 140.3, 138.7, 136.1, 134.0, 128.4, 128.2, 127.7, 126.8, 124.9, 121.1, 110.4, 107.5, 60.7, 36.5, 21.1, 12.9. IR (KBr) υ_{O-H} 3460–3200 (br), $\upsilon_{C=O}$ 1654 cm^{-1}. ESI-HRMS (TOF) m/z $[M+H]^+$ Calcd. for $C_{23}H_{21}O_3$: 345.1485. Found: 345.1474.

Ethyl 3-hydroxy-1-(o-tolyl)-9H-fluorene-2-carboxylate (**4f**). Pale yellow oil. R_f = 0.35 (hexane/EA = 19:1); (82.1 mg, 45%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 11.5 (s, 1H), 7.82 (d, *J* = 7.4 Hz, 1H), 7.49–7.18 (m, 7H), 7.04 (d, *J* = 7.4 Hz, 1H), 4.06–3.90 (m, 2H), 3.46 (d, *J* = 22.0 Hz, 1H), 3.31 (d, *J* = 22.0 Hz, 1H), 2.04 (s, 3H), 0.74 (t, *J* = 7.1 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 171.3, 162.6, 147.3, 145.2, 141.3, 140.4, 134.7, 133.6, 129.4, 128.3, 127.4, 126.9, 126.8, 125.4, 125.0, 121.2, 110.1, 107.7, 60.7, 36.3, 19.6, 12.9. IR (KBr) υ_{O-H} 3480–3200 (br), $\upsilon_{C=O}$ 1654 cm^{-1}. ESI-HRMS (TOF) m/z $[M+H]^+$ Calcd. for $C_{23}H_{21}O_3$: 345.1485. Found: 345.1479.

Ethyl 3-hydroxy-1-(4-methoxyphenyl)-9H-fluorene-2-carboxylate (**4g**). Light yellow solid. R_f = 0.20 (hexane/EA = 19:1); mp 120–121 °C. (89.3 mg, 45%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 11.3 (s, 1H), 7.77 (d, *J* = 7.3 Hz, 1H), 7.45–7.26 (m, 4H), 7.10 (d, *J* = 8.7 Hz, 2H), 6.94 (d, *J* = 8.7 Hz, 2H), 3.98 (q, *J* = 7.1 Hz, 2H), 3.86 (s, 3H), 3.50 (s, 2H), 0.79 (t, *J* = 7.2 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 171.4, 162.1, 158.5, 146.8, 145.2, 140.6, 140.3, 134.2, 134.1, 128.9, 128.2, 126.8, 124.9, 121.1, 113.3, 110.5, 107.5, 60.7, 55.3, 36.5, 13.1. IR (KBr) υ_{O-H}

3500–3200 (br), $\upsilon_{C=O}$ 1653 cm^{-1}. ESI-HRMS (TOF) m/z $[M+Na]^+$ Calcd. for $C_{23}H_{20}O_4Na$: 383.1254. Found: 383.1264.

Ethyl 3-hydroxy-1-(naphthalen-1-yl)-9H-fluorene-2-carboxylate (**4i**). Light yellow solid. R_f = 0.35 (hexane/EA = 19:1); mp 129–130 °C. (40.4 mg, 21%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 11.5 (s, 1H), 7.92–7.80 (m, 3H), 7.53–7.48 (m, 2H), 7.46–7.35 (m, 3H), 7.33–7.25 (m, 4H), 3.74–3.61 (m, 3H), 3.47 (d, *J* = 22.0 Hz, 1H), 3.21(d, *J* = 22.1 Hz, 1H), 0.17 (t, *J* = 7.1 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 171.1, 162.6, 147.2, 145.2, 140.3, 139.4, 138.9, 134.7, 133.4, 131.7, 128.3, 128.0, 126.9, 126.8, 125.9, 125.6, 125.3, 125.2, 124.9, 124.8, 121.2, 110.9, 108.0, 60.5, 36.2, 12.2. IR (KBr) υ_{O-H} 3420–3200 (br), $\upsilon_{C=O}$ 1653 cm^{-1}. ESI-HRMS (TOF) m/z $[M+Na]^+$ Calcd. for $C_{26}H_{20}O_3Na$: 403.1305. Found: 403.1303.

Ethyl 3-hydroxy-1-propyl-9H-fluorene-2-carboxylate (**4j**). Light yellow solid. R_f = 0.34 (hexane/EA = 19:1); mp 103–104 °C. (62.5 mg, 41%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 11.5 (s, 1H), 7.73 (d, *J* = 7.8 Hz, 1H), 7.51 (d, *J* = 6.4 Hz, 1H), 7.40–7.29 (m, 2H), 7.23 (s, 1H), 4.44 (q, *J* = 7.1 Hz, 2H), 3.77 (s, 2H), 3.07- 2.88 (m, 2H), 1.69–1.54 (m, 2H), 1.45 (t, *J* = 7.1 Hz, 3H), 1.04 (t, *J* = 7.3 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 171.9, 162.9, 146.9, 144.6, 141.4, 140.6, 133.6, 128.1, 126.8, 124.9, 121.0 110.1, 106.5, 61.4, 35.8, 35.1, 23.9, 14.6, 14.0. IR (KBr) υ_{O-H} 3400–3200 (br), $\upsilon_{C=O}$ 1646 cm^{-1}. ESI-HRMS (TOF) m/z $[M+Na]^+$ Calcd. for $C_{19}H_{20}O_3Na$: 319.1305. Found: 319.1308.

Ethyl 1-(3,4-dimethoxyphenyl)-3-hydroxy-9H-fluorene-2-carboxylate (**4k**). Light yellow oil. R_f = 0.09 (hexane/EA = 9:1); (82.3 mg, 42%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.3 (s, 1H), 7.81 (d, *J* = 7.4 Hz, 1H), 7.50–7.29 (m, 4H), 6.95 (d, *J* = 8.6 Hz, 1H), 6.84–6.71 (m, 2H), 4.03 (q, *J* = 7.1 Hz, 2H), 3.97 (s, 3H), 3.89 (s, 3H), 3.60 (s, 2H), 0.84 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.3, 162.0, 148.5, 147.8, 146.8, 145.2, 140.5, 140.2, 134.3, 134.1, 128.2, 126.8, 124.9, 121.1, 120.0, 111.5, 110.7, 110.4, 107.5, 60.7, 55.9, 55.8, 36.5, 13.2. IR (KBr) υ 3100–3440 (br), 1655 cm^{-1}. ESI-HRMS (TOF) m/z $[M+H]^+$ Calcd. for $C_{24}H_{23}O_5$: 391.1540. Found: 391.1527.

Isopropyl 3-hydroxy-1-phenyl-9H-fluorene-2-carboxylate (**4l**). Light yellow solid. R_f = 0.37 (hexane/EA = 19:1); mp 114–115 °C. (114.2 mg, 64%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.5 (s, 1H), 7.84 (d, *J* = 7.5 Hz, 1H), 7.50–7.32 (m, 7H), 7.24 (d, *J* = 7.8 Hz, 2H), 4.99 (sep, *J* = 6.2 Hz, 1H), 3.52 (s, 2H), 0.88 (d, *J* = 6.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.7, 162.2, 146.8, 145.2, 141.9, 140.8, 140.3, 133.9, 128.2, 127.9, 126.8, 126.5, 124.9, 121.2, 110.5, 107.6, 68.6, 36.5, 20.9. IR (KBr) υ 3200–3500 (br), 1654 cm^{-1}. ESI-HRMS (TOF) m/z $[M+H]^+$ Calcd. for $C_{23}H_{21}O_3$: 345.1485. Found: 345.1477.

2.4. Crystallogarphy

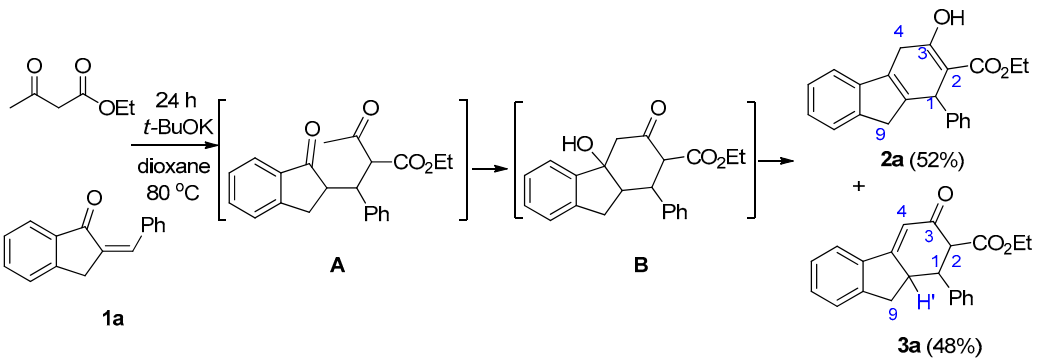
A crystal of **2a** suitable for X-ray determination was obtained from hexane/dichloromethane. The structure was solved using the SHELXS-97 program [21] and refined using the SHELXL-97 program [22] by full-matrix least-squares on F2 values. CCDC 2193935 contains the supplementary crystallographic data for **2a**. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, (accessed on 1 August 2022) or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Center, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44-1223-336033.

3. Results and Discussion

3.1. Preliminary study and Optimization

Substrate **1** for this investigation was prepared according to the reported method [20]. After several screenings of reaction conditions, we found that reaction of **1a** with excess of ethyl acetoacetate in the presence of one equivalent of potassium *t*-butoxide in dioxane reached a full conversion of **1a**, but giving two cyclized products **2a** and **3a** in a ratio of 1:1, which is quite different to that reported previously [19]. Scheme 4 illustrates the reaction and intermediates of Michael adduct (**A**) and annulation intermediate (**B**) leading to the products. Both **2a** and **3a** are isomers, which are resulted from the dehydration of **B** via two different β-hydrogens. Another finding is that both **2a** and **3a** did not interconvert to each other under the conditions of (i) *t*-BuOK (1 eq.) in dioxane at 80 °C for 24 h, and (ii) HBF_4

in dioxane at 80 °C for 24h, (iii) H_2SO_4 (1 eq) in dioxane at 80 °C for 24 h. Characterization of compounds **2a** and **3a** were performed by NMR and mass spectroscopy.



Scheme 4. Michael addition of **1a** with acetoacetate followed by cyclization and dehydration process leading to two isomeric products.

^{1}H NMR spectrum of **2a** shows two sets of AB splitting patterns, at δ 3.59 and 3.48 (J^2 = 22 Hz); δ 3.21 and 2.97 (J^2 = 22 Hz), for two distinct -CH_2- units at C(4) and C(9) due to the diastereotopic nature of these methylene protons. ^{13}C NMR spectral data and HRMS of **2a** are also consistent with the proposed structure. However, single crystal determination of **2a** confirms its structural details (Figure 2). As expected, bond lengths of both C1-C2 [1.355(2) Å] and C4-C12 [1.343(2) Å] are in the typical range for C=C. For **3a**, a characteristic shift for the vinylic proton of C(4)-H appears at δ 6.43 as a doublet due to the long range allylic coupling with C-H′. A signal at δ 3.74 as doublet for the C(2)-H indicates that **3a** does not enolize and retains the β-keto ester form, unlike **2a**. Other spectral data and HRMS of **3a** are all in agreement with the structure (see experimental section).

3.2. Reaction of **1a** *with Acetoacetate—Selectivity of Formation of* **2a** *Versus* **3a**

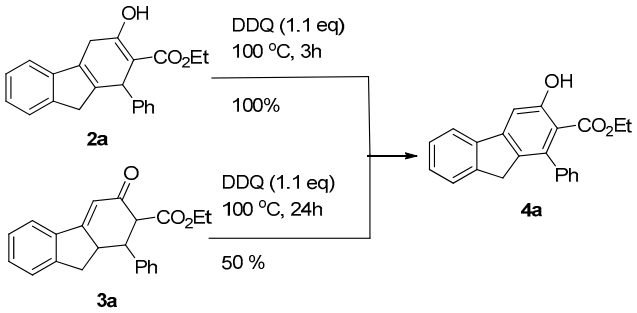
Next, we examined this reaction under various conditions to improve the selectivity of products. Table 1 summarizes the results. The use of DBU and DABCO as bases did not render good production of the desired products. The basicity of DABCO is too weak for the reaction to proceed with the reactant recovered, whereas the DBU causes the decomposition of the reactants (Entries 1 and 2). The lower reaction temperature gave a lower conversion (Entries 3–6). The formation of **3a** is preferred at 50 °C, but the reaction still provides 25% production of **2a** (Entry 5). For solvents, both dioxane and toluene are good choice to have full conversion (entries 3 and 8, respectively), however, the selectivity of **2a** versus **3a** remains as ca. 1:1. It seems unable to reach the selectivity for a single product.

Table 1. Optimization for reaction of **1a** with ethyl acetoacetate leading to **2a** and **3a** [1].

Entry	Base	Solvent	Temp	Time	2a [2]	3a [2]
1	DABCO	Dioxane	80 °C	24 h	0	0
2	DBU	Dioxane	80 °C	24 h	complex mixture	
3	*t*-BuOK	Dioxane	80 °C	24 h	52%	48%
4	*t*-BuOK	Dioxane	50 °C	24 h	7%	48%
5	*t*-BuOK	Dioxane	50 °C	48 h	24%	75%
6	*t*-BuOK	Dioxane	40 °C	48 h	6%	45%
7 [3]	*t*-BuOK	Dioxane	80 °C	24 h	Trace	Trace
8	*t*-BuOK	Toluene	80 °C	24 h	60%	40%
9	*t*-BuOK	THF	50 °C	48 h	20%	40%
10	*t*-BuOK	*t*-BuOH	50 °C	48 h	30%	55%

[1] Reaction conditions: **1a** (220.3 mg, 0.5 mmol), ethyl acetoacetate (220.3 mg, 2.5 mmol) and base in solvent (5 mL) under N_2 atmosphere. [2] NMR yields. [3] addition of LiCl (1 eq.).

With **2a** and **3a** in hand, oxidation of these compounds leading to the desired fluorene product **4a** was examined (Scheme 5). Air-oxidation of both compounds leading to **4a** proceeded very slowly. Hence, 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) was chosen as the reagent for this oxidation. It appeared that compound **2a** was completely converted into **4a** under the condition of the substrate in dioxane with DDQ (1.1 eq) at 100 °C for 3 h. By exposing a solution of **3a** in dioxane to DDQ, the desired oxidation compound **4a** was obtained, but not in full conversion. Other oxidants such as MnO_2 did not provide a better result. Table S2 summarizes the results of oxidations of **2a** and **3a** under various conditions (see supporting information).



Scheme 5. Oxidation of **2a** and **3a** leading to fluorene derivative **4a**.

3.3. Preparation of Fluorenes via a Two-Step Reaction without Isolation of **2** *and* **3**

Since oxidation of **2a** and **3a** yields the same product **4a**, we envisioned that we should investigate the direct preparation of fluorenes from reaction 2-benzylideneindan-l-one with acetoacetate without purification of **2a** and **3a**, i.e., carrying out the oxidation of a mixture **2a** and **3a** from the first step without a purification procedure. First, a reaction mixture obtained according the conditions shown in Table 1 entry 3 was acidified with 2 M $H_2SO_{4(aq)}$ and then treated with DDQ (1.1 eq.) at 100 °C. Upon workup, the desired product **4a** was obtained in 48% yield accompanied with **2a** and **3a**. Under the similar procedure, the use of 2 equivalent of DDQ did improve the yield up to 60%, but a larger amount of DDQ resulted in the formation of complicated reaction mixture. By switching to other oxidants such as MnO_2, production of **4a** did not get better. As shown in Table 1 entry 8, toluene is another good solvent for a full conversion, but the use of toluene as the solvent for this two-step treatment did not provide a better improvement. Apparently, the unreacted substrates or reagents caused the complication in having a better production of **4a**. Thus, we modified the procedure by a simple extraction of reaction mixture in the first step and then change the solvent for oxidation.

Typically, a solution of 2-benzylidene-1-indanone derivatives with ethyl acetoacetate and *t*-BuOK in dioxane was heated at 80 °C under inert atmosphere for 24 h. Then, the reaction mixture was quenched with saturated NH_4Cl aqueous solution and extracted with ethyl acetate. Upon concentration, the residue was re-dissolved in dioxane and treated with oxidant for another 24 h. After purification, **4a** was obtained in various amounts based on the oxidants as illustrated in Table 2. It showed that, in order to have a better yield of **4a**, reaction has to run in toluene as solvent in the first step and then oxidation in dioxane (Table 2, entry 6). Thus, this standard procedure was established for the further investigation.

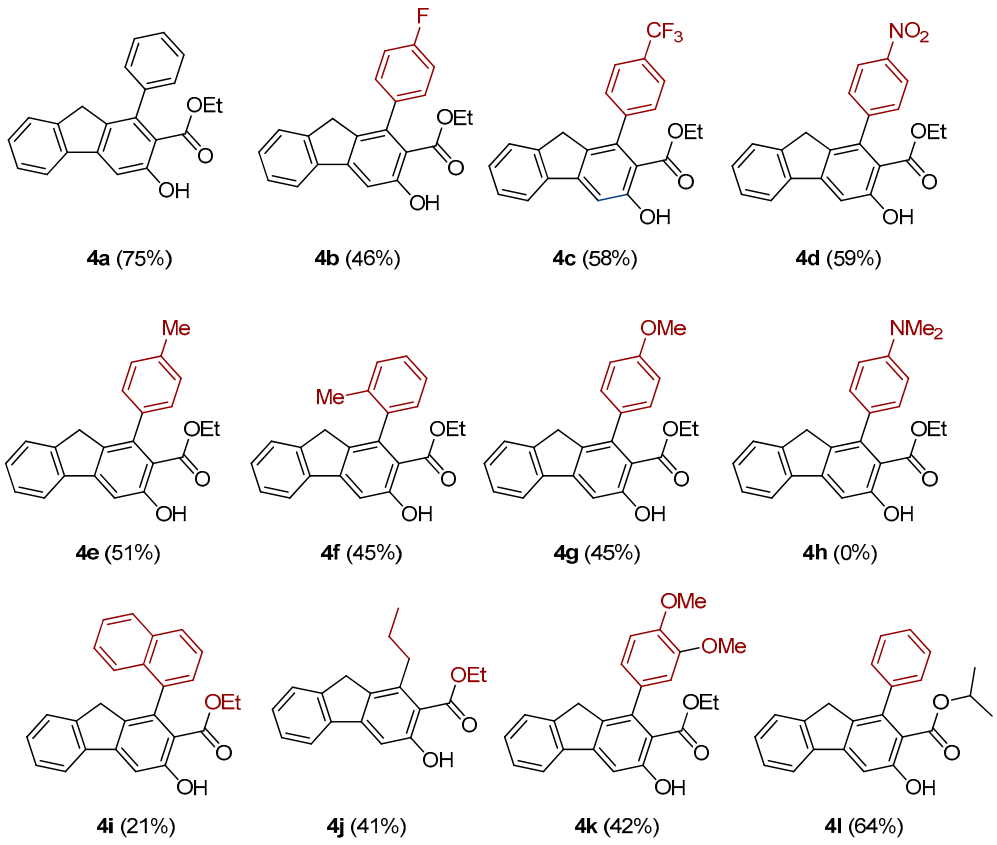
With the optimized protocol, we screened various substituted 2-benzylidene-1-indanones as substrates for the preparation of fluorenes (Scheme 6). All desired products were isolated in moderate to good yields. For the aryl ring with electron-withdrawing substituents at para position, the yields were slightly better than those with electron-donating groups (**4c** and **4d** vs. **4e** and **4g**). Compound **4i** was received in 21% yield presumably due to the steric hindrance of 1-naphthyl group. Alkylidene-1-indanone was also applicable to the reaction to give ethyl 3-hydroxy-1-propyl-9H-fluorene-2-carboxylate **4j** (41%). However, a tertiaryamino-substituted substrate did not deliver the expected product **4h**, which is

unexpected, presumably due to the basic nature of dimethylamino group. It was noticed that isopropyl acetoacetate is also a suitable reagent for this methodology, giving **4l** in 64% yield.

Table 2. Oxidation study of conversion of **2a** and **3a** into **4a** [1].

Entry	Oxidant	Temp	Yield
1	O_2/CF_3COOH	100 °C	trace
2	H_2O_2 (1.0 eq)	80 °C	trace
3	Cu(OTf)(10 mol%)/bipy/NHPI/KI (1.0 eq) [2]	80 °C	trace
4	CuBr(10 mol%)/LiBr(2.0 eq) [2]	80 °C	56%
5	DDQ (1.1 eq)	RT	41%
6 [3]	DDQ (1.1 eq)	100 °C	75%

[1] Reaction conditions: (i) **1a** (220.3 mg, 0.5 mmol), ethyl acetate (220.3 mg, 2.5 mmol) and *t*-BuOK (0.5 mmol) in dioxane (5 mL) was heated 80 °C for 24 h, (ii) Quench with saturated NH_4Cl and extraction with ethyl acetate, (iii) Concentration and re- dissolution in dioxane (5 mL), (iv) addition of oxidant and stirring for 24 h. in isolated yields. [2] Cu-catalyzed oxidation. [3] toluene used as the solvent in the first step.



Scheme 6. Reaction scope.

4. Conclusions

In summary, a two-step design for synthsis of 3-hydroxy-9H-fluorene-2-carboxylates was reported. In this work, the Robinson annulation from the intermediate **A** was studied, offering an understanding of the regiochemistry of dehydration. This method offers a simple and facile manipulation for the desired fluorene. These obtained compounds are expected to be valuable for pharmacophores and synthetic intermediates.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/org3040031/s1, Table S1. crystal data of **2a**; Table S2. Summary of Oxidation study of **2a** and **3a**; Figure S1. ^{1}H NMR and ^{13}C NMR spectra of **4a**; Figure S2. ^{1}H NMR and ^{13}C NMR spectra of **4b**; Figure S3. ^{1}H NMR and ^{13}C NMR spectra of **4c**; Figure S4. ^{1}H NMR and ^{13}C NMR spectra of **4d**; Figure S5. ^{1}H NMR and ^{13}C NMR spectra of **4e**; Figure S6. ^{1}H NMR and ^{13}C NMR spectra of **4f**; Figure S7. ^{1}H NMR and ^{13}C NMR spectra of **4g**; Figure S8. ^{1}H NMR and ^{13}C NMR spectra of **4i**; Figure S9. ^{1}H NMR and ^{13}C NMR spectra of **4j**; Figure S10. ^{1}H NMR and ^{13}C NMR spectra of **4k**; Figure S11. ^{1}H NMR and ^{13}C NMR spectra of **4l**.

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References

1. Yang, H.; Chou, G.-X.; Wang, Z.-T.; Guo, Y.-W.; Hu, Z.-B.; Xu, L.-S. Two New Compounds from *Dendrobium chrysotoxum*. *Helv. Chim. Acta* **2004**, *87*, 394–399. [CrossRef]
2. Ye, Q.-H.; Zhao, W.-M.; Qin, G.-W. New fluorenone and phenanthrene derivatives from *Dendrobium chrysanthum*. *Nat. Prod. Res.* **2003**, *17*, 201–205. [CrossRef] [PubMed]
3. Liu, X.; Luo, H.-B.; Huang, Y.-Y.; Bao, J.-M.; Tang, G.-H.; Chen, Y.-Y.; Wang, J.; Yin, S. Selaginpulvilins A–D, New Phosphodiesterase-4 Inhibitors with an Unprecedented Skeleton from *Selaginella pulvinate*. *Org. Lett.* **2014**, *16*, 282–285. [CrossRef] [PubMed]
4. Chui, C.-H.; Wong, R.S.-M.; Gambari, R.; Cheng, G.Y.-M.; Yuen, M.C.-W.; Chan, K.-W.; Tong, S.-W.; Lau, F.-Y.; Lai, P.B.-S.; Lam, K.-H.; et al. Antitumor activity of diethynylfluorene derivatives of gold(I). *Bioorg. Med. Chem.* **2009**, *17*, 7872–7877. [CrossRef] [PubMed]
5. Misaki, K.; Matsui, S.; Matsuda, T. Metabolic Enzyme Induction by HepG2 Cells Exposed to Oxygenated and Nonoxygenated Polycyclic Aromatic Hydrocarbons. *Chem. Res. Toxicol.* **2007**, *20*, 277. [CrossRef] [PubMed]
6. Sengupta, S.; Mehta, G. Natural products as modulators of the cyclic-AMP pathway: Evaluation and synthesis of lead compounds. *Org. Biomol. Chem.* **2018**, *16*, 6372–6390. [CrossRef] [PubMed]
7. Schneider, J.; Pradines, B.; Helle, F.; Dassonville-Klimpt, A.; Taudon, N.; Sonnet, P. Enantiopure aminoaryl-alcohols with fluorene core and their antimalarial activities. In *4th International Electronic Conference on Medicinal Chemistry*; MDPI: Basel, Switzerland, 2018. [CrossRef]
8. Beije, B.; Moeller, L. Correlation between induction of unscheduled DNA synthesis in the liver and excretion of mutagenic metabolites in the urine of rats exposed to the carcinogenic air pollutant 2-nitrofluorene. *Carcinogenesis* **1988**, *9*, 1465–1470. [CrossRef] [PubMed]
9. Gutmann, H.R.; Galitski, S.B.; Foley, W.A. Carcinogenicity of the o-methoxy derivatives of N-2-fluorenylacetamide and of related compounds in the rat. *Cancer Res.* **1968**, *28*, 234–244. [PubMed]
10. Mondal, E.; Hung, W.-Y.; Dai, H.-C.; Wong, K.-T. Fluorene-based asymmetric biopolar universial hosts for white organic light emitting devices. *Adv. Funct. Mater.* **2013**, *23*, 3096–3105. [CrossRef]
11. Oyston, S.; Wang, C.; Hughes, G.; Batsanov, A.S.; Perepichka, I.F.; Bryce, M.R.; Ahn, J.H.; Pearson, C.; Petty, M.C. New 2,5-diaryl-1,3,4-oxadiazolefluorene hybrids as electron transporting materials for blended-layer organic light emitting diodes. *J. Mater. Chem.* **2005**, *15*, 194–203. [CrossRef]
12. Wong, W.-Y. Metallated molecular materials of fluorene derivatives and their analogues. *Coord. Chem. Rev.* **2005**, *249*, 971–997. [CrossRef]
13. Fukuyama, T.; Maetani, S.; Miyagawa, K.; Ryu, I. Synthesis of Fluorenones through Rhodium-Catalyzed Intramolecular Acylation of Biarylcarboxylic Acids. *Org. Lett.* **2014**, *16*, 3216–3219. [CrossRef] [PubMed]

14. Kashulin, I.A.; Nifant'ev, I.E. Efficient Method for the Synthesis of Hetarenoindanones Based on 3-Arylhetarenes and Their Conversion into Hetarenoindenes. *J. Org. Chem.* **2004**, *69*, 5476–5479. [CrossRef] [PubMed]
15. Kaiser, R.P.; Caivano, I.; Kotora, M. Transition-metal-catalyzed methods for synthesis of fluorenes. *Tetrahedron* **2019**, *75*, 2981–2992. [CrossRef]
16. Hwang, S.J.; Kim, H.J.; Chang, S. Highly efficient and versatile synthesis of poly aryl fluorenes via Pd-catalyzed C-H bond activation. *Org. Lett.* **2009**, *11*, 4588–4591. [CrossRef] [PubMed]
17. Wang, X.C.; Yan, R.L.; Zhong, M.J.; Liang, Y.M. Bi(III)-Catalyzed Intermolecular Reactions of (*Z*)-Pent-2-en-4-yl Acetates with Ethynylarenes for the Construction of Multisubstituted Fluorene Skeletons through a Cascade Electrophilic Addition/Cycloisomerization Sequence. *J. Org. Chem.* **2012**, *77*, 2064–2068. [CrossRef] [PubMed]
18. Buettner, S.; Kelzhanova, N.K.; Abilov, Z.A.; Villinger, A.; Langer, P. [3+3] Cyclizations of 1,3-bis(trimethylsilyloxy)-1,3-butadienes-a new approach to diverse CF_3-substituted fluorenes, dibenzofurans, 9,10-dihydrophenanthrenes and 6H-benzo[c]chromenes. *Tetrahedron* **2012**, *68*, 3654–3668. [CrossRef]
19. Anderson, D.M.W.; Leaver, D. Stereochemistry and isomerization of some hydrofluorene and hydrophenanthrene β-oxo esters. *J. Chem. Soc.* **1962**, 450–456. [CrossRef]
20. Lantano, B.; Aguirre, J.M.; Drago, E.V.; Bollini, M.; de la Faba, D.J.; Mufato, J.D. Synthesis of benzylidenecycloalkan-1-ones and 1,5-diketones under Claisen-Schmidt reaction: Influence of the temperature and electronic nature of arylaldehydes. *Synth. Commun.* **2017**, *47*, 2202–2214. [CrossRef]
21. Sheldrick, G.M. SHELXS-97 Phase annealing in *SHELX*-90: Direct methods for larger structures, *Acta Crystallogr. Sect. A Found. Crystallogr.* **1990**, *46*, 467–473. [CrossRef]
22. Sheldrick, G.M. *SHELXL-97*; University of Göttingen: Göttingen, Germany, 1997.