

Communication

Original Synthesis of Fluorenyl Alcohol Derivatives by Reductive Dehalogenation Initiated by TDAE

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Abstract: We report here a novel and easy-to-handle reductive dehalogenation of 9-bromofluorene in the presence of arylaldehydes and dicarbonyl derivatives to give the corresponding fluorenyl alcohol derivatives and Darzens epoxides as by-products in tetrakis(dimethylamino)ethylene (TDAE) reaction conditions. The reaction is believed to proceed via two successive single electron transfers to generate the fluorenyl anion which was able to react with different electrophiles. A mechanistic study was conducted to understand the formation of the epoxide derivatives.

Keywords: tetrakis(dimethylamino)ethylene; reductive dehalogenation; single electron transfer

1. Introduction

Fluorenyl derivatives have attracted interest from synthetic organic chemists due to their notable biological and pharmaceutical properties and applications. The literature reports that fluorenone Schiff base derivatives have a potential application and biological activity in therapeutic areas, such as antifungal agents [1,2]. The fluorene skeleton is found in numerous natural products. Dendroflorin and structurally-related nobiletin displayed higher antioxidant activity than vitamin C in the ORAC assay [3]. Gramniphensols were isolated from the whole plant of *Arundina grammifolia* by Yang and coworkers in 2012 and displayed anti-HIV-1 activity with therapeutic index values above 100:1 [4]. Many dermatological and photostable cosmetic compositions consist of lumefantrine, a 9-fluorenylidene derivative [5]. The fluorenyl core can be found in indecainide (Decabid[®]), which is a class Ic anti-arrhythmic agent [6].

In terms of non-steroidal anti-inflammatory agents (NSAIDs), this scaffold bearing an alkanolic acid moiety gives cycloprofen. Paranyline is used in dispersible formulations of anti-inflammatory agents [7]. However, although these drugs are very effective and abundantly prescribed, they have revealed some gastric or intestinal adverse effect [8]. The representatives containing the fluorenyl scaffold cited above are shown in Figure 1.

Since 2003, our laboratory has been developing original synthetic methods based on neutral, ground-state organic reducing agents [9–14], aimed at preparing new, potentially bioactive compounds [9]. Tetrakis(dimethylamino)ethylene (TDAE), as shown in Figure 1 [15–17], is a powerful tool in modern organic chemistry because it allows reduction under mild conditions. Reduction can occur without the use of organometallics or reactive metals. TDAE shows a single, two-electron oxidation peak at -0.62 V vs. SCE in dimethylformamide (DMF) which means it is about as reducing as zinc metal [18–20]. TDAE can react with activated alkyl halides, such as CF_3I , CF_2Br_2 , and activated benzyl halides, to produce the corresponding carbanions [21–30]. We report herein a valuable synthetic method to generate a 9-bromofluorenyl anion from fluorenyl bromide **1** and on its reaction with a series of carbonyl electrophiles affording the corresponding alcohol derivatives.

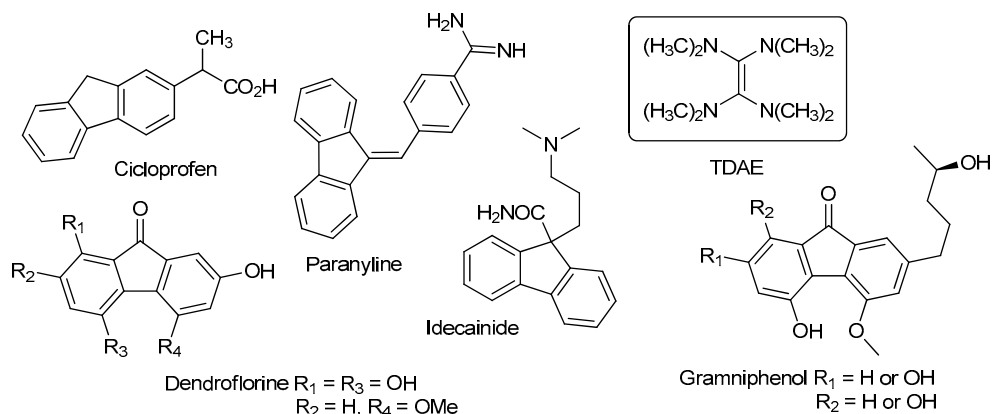
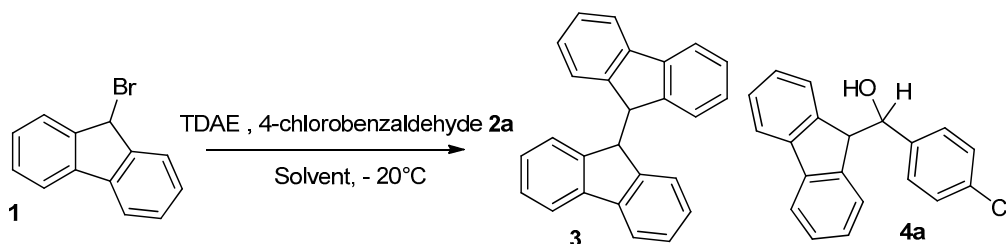


Figure 1. Structures of biological active molecules and TDAE.

2. Results and Discussion

It was anticipated that fluorenyl bromide **1** could be a good electron-acceptor, because of its large π -conjugated system. Initially, the reaction of 9-bromofluorene **1** and 4-chlorobenzaldehyde **2a** was investigated as the model system (Scheme 1).



Scheme 1. Optimization of the reaction of fluorenyl bromide **1** with 4-chlorobenzaldehyde **2a** using TDAE.

We performed the reactions using various aprotic polar solvents. The influence of the quantity of aldehyde **2a** and TDAE was also studied. The results are summarized in Table 1.

Table 1. Reactions of fluorenyl bromide **1** and aldehyde **2a** with TDAE under various conditions.

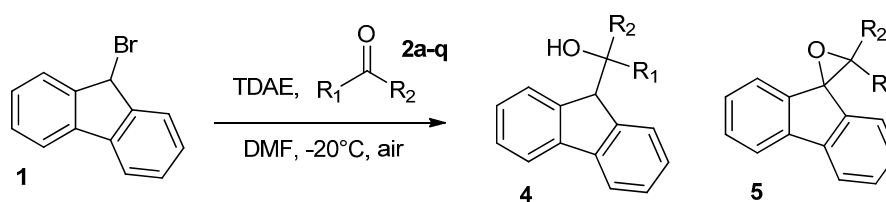
Entry	Aldehyde 2a (eq.)	TDAE (eq.)	Solvent	Yield ^{1,2} of Dimer 3	Yield ^{1,2} of 4a
1	2	1	DMF	44%	29%
2	3	1	DMF	8%	50%
3	3	2	DMF	10%	48%
4	4	1	DMF	8%	46%
5	3	1	THF	12%	48%
6	3	1	DMF ³	9%	56%
7	3	1	CH ₃ CN	16%	30%
8	3	1	DMSO	20%	12%
9	3	1	pyridine	11%	34%

¹ Isolated yields; ² Typical procedure: to a vigorously stirred solution of fluorenyl bromide **1** derivative in 4 mL anhydrous solvent, at -20°C , under N_2 ; ³ Moist DMF was used in the presence of a spatula of sodium sulfate in the reaction mixture and the reaction was run under air.

A first attempt (entry 1) was carried out with 2 equiv. of **2a** and 1 equiv. of RBr **1** to give 29% of the corresponding alcohol **4a**. TDAE was added at -20°C to maximize the charge transfer complex formation. Unfortunately, ¹H NMR spectra of the crude product showed a signal at δ 4.85 associated to the homo-coupling adduct of 9-bromofluorene (44%). To reduce the extent of dimer formation,

3 equiv. of **2a** was employed (entry 2), giving 50% of **4a** and the dimer was isolated with 8% yield (entry 2). The conversion to the 9,9'-bifluorenyl was not reduced by increasing the excess of aldehyde. The optimized protocol of 9-bromofluorene **1** was defined with 3 equiv. of aldehyde **2a**, 1 equiv. of TDAE in DMF, for 1 h at $-20\text{ }^{\circ}\text{C}$ followed by 2 h at room temperature. The reactions led to the corresponding alcohol **4a** with 56% yield (Table 1, entry 6). The 9-Bromofluorene was found to be a good substrate in such TDAE-mediated carbon-carbon coupling reactions. This methodology was then applied to other electrophiles. The TDAE-initiated reaction of **1** with various electrophiles was investigated according to the optimal procedure cited above and the results are summarized in Table 2. The expected corresponding alcohols **4a**, **4b**, **4e**, **4f**, **4i** were isolated in moderate to good yields, from 41% to 75% with aldehydes bearing an electron-withdrawing group.

Table 2. The scope of the reactivity of **1** in the presence of various electrophiles under TDAE reaction conditions.



Entry	Electrophiles		Yield ^{1,2} of 4	Yield ^{1,2} of 5
	R ₁	R ₂		
1	2a	4-ClC ₆ H ₄	56% (4a)	14% (5a)
2	2b	C ₆ H ₅	57% (4b)	17% (5b)
3	2c	4-BrC ₆ H ₄	75% (4c)	10% (5c)
4	2d	4-OMeC ₆ H ₄	34% (4d)	
5	2e	4-FC ₆ H ₄	54% (4e)	
6	2f	4-CNC ₆ H ₄	41% (4f)	30% (5f)
7	2g	4-MeC ₆ H ₄	24% (4g)	
8	2h	4-(NO ₂)C ₆ H ₄		17% (5h)
9	2i	4-CF ₃ C ₆ H ₄	49% (4i)	6% (5i)
10	2j	2-furyl	28% (4j)	19% (5j)
11	2k	4-pyridinyl	42% (4k)	11% (5k)
12	2l	3-pyridinyl	19% (4l)	
13	2m	Me	CO ₂ Et	47% (4m)
14	2n	CF ₃	CO ₂ Me	41% (4n)
15	2o	H	CO ₂ Et	25% (4o)
16	2p	CO ₂ Et	CO ₂ Et	70% (4p)
17	2q	C ₆ H ₅	Et	

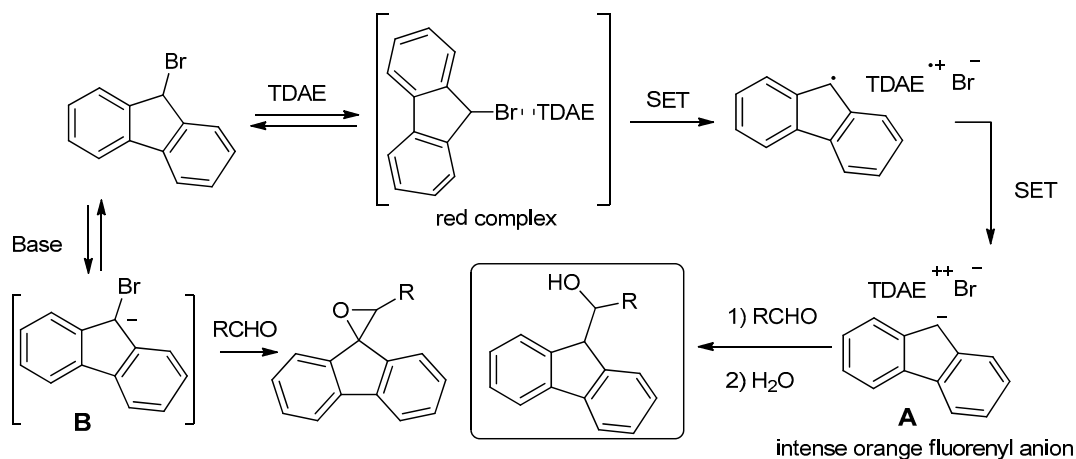
¹ Isolated yields; ² Typical procedure: to a vigorously-stirred solution of 9-bromofluorene **1** in 4 mL moist DMF with a spatula of sodium sulfate, under air, TDAE was slowly added at $-20\text{ }^{\circ}\text{C}$. The solution was then stirred 1 h at this temperature followed by 2 h at ambient temperature.

For 4-nitrobenzaldehyde **2h**, no alcohol product was isolated. Its strong electrophilic character, has already led to unexpected reactivity in these reaction conditions, as cited in our previous work [11]. With methylbenzaldehyde **2g** and 4-methoxybenzaldehyde **2d**, the conversions were lower with, respectively, 24% and 34% yields. This may be explained by their weak electrophilic character compared to the other aldehydes. Competitive epoxide formation was observed, which was obtained in low yield (from 6% to 30%, Table 2, entries 1–9). Subsequently, the methodology was generalized to heteroaromatic aldehydes (entries 10–12). When pyridine-4-carbaldehyde **2k** was employed, 42% of the corresponding alcohol **4k** was obtained. With pyridine-3-carbaldehyde **2l**, the yield reported was lower (19%). The scope of this original reactivity was extended to pyruvates, ethyl glyoxylate, methyl 3,3,3-trifluoropyruvate, and diethylketomalonate (entries 13–16). The best result was achieved with diethylketomalonate affording the corresponding fluorenyl alcohol **4p** in 70% yield (entry 16). This can, no doubt, be attributed to the stronger electrophilic character of its carbonyl function. It should be noted that we never observed the reaction of the fluorenyl anion with ester moiety. The poor yield

(19%) observed with ethyl glyoxylate **2o** could be due to a polymerization reaction of the aldehyde. With propiophenone **2q**, only starting materials were recovered (entry 17), which could be attributed to the acidity of the protons adjacent to the carbonyl function.

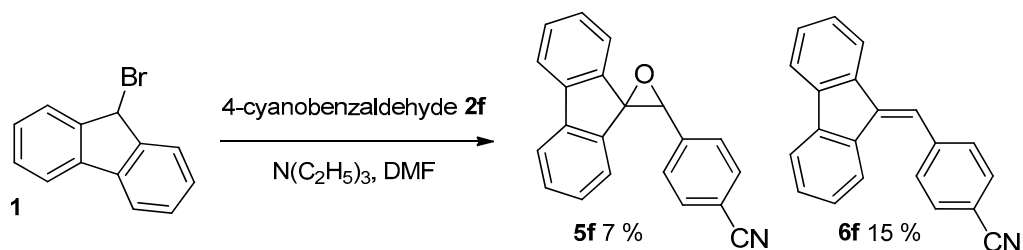
In order to extend the substrate scope of TDAE-initiated reactions, an attempt had been run with 1,1'-bromobiphenylmethane, but no alcohol adduct was formed. The corresponding dimer product was obtained with 74% yield. This difference in reactivity can be attributed to the better stabilization of the corresponding 9-fluorenyl aromatic anion.

The formation of the alcohol product can be conceived to proceed via two successive single electron transfers (Scheme 2). The first reduction leads to the cleavage of the C-Br bond to form the 9-fluorenyl radical and the bromide anion. A subsequent SET (single mono-electronic transfer) gave the fluorenyl anion **A**, which is aromatic and has an intense orange color, from the corresponding radical. An alcoholate was successively obtained by the nucleophilic addition of the fluorenyl anion **A** on the aldehyde which gave the corresponding alcohol after hydrolysis. As cited above, 9-bromofluorene **1** can react under our conditions with aromatic aldehydes, yielding epoxy products. Our hypothesis is that 9-bromofluorenyl anion **B** could be formed after deprotonation of **1** by the above alcoholate. The reaction of **B** with the aldehyde gave the epoxide derivatives via Darzens reaction. Our hypothesis is supported by literature data [31].



Scheme 2. Proposed mechanism.

When 9-bromofluorene **1** was treated with 3 equiv. of triethylamine in the presence of 4-cyanobenzaldehyde **2f** under classical TDAE conditions, the corresponding Darzens condensation product **5f** was afforded in low yields (7%) (Scheme 3).



Scheme 3. Reactivity of 9-bromofluorene and 4-cyanobenzaldehyde in the presence of trimethylamine.

Another compound had been observed by $^1\text{H-NMR}$ corresponding to 4-((9*H*-fluoren-9-ylidene)methyl)benzonitrile **6f** with 15% yield. However, another multistep pathway involving a carbene-like intermediate cannot be excluded. To verify this hypothesis, we examined the reaction of **1** in

the presence of cyclohexene [32]. The $^1\text{H-NMR}$ spectrum of the crude mixture showed no signal attributable to a cyclopropane adduct that could be formed by carbene insertion to the cyclohexene double bond: only peaks due to dimer **3** were found. These findings indicate that the epoxide derivative could be formed through the 9-bromofluorenyl anion sequence.

3. Materials and Methods

3.1. General Information

Melting points were determined on a Büchi melting point B-540 apparatus (BÜCHI Labortechnik AG, Flawil, Switzerland) and are uncorrected. Element analyses were performed on a Thermo Finnigan EA1112 (San Jose, CA, USA) at the spectropole of the Aix-Marseille University. Both $^1\text{H-}$ and $^{13}\text{C-NMR}$ spectra were determined on a Bruker Avance 250 spectrometer (Wissembourg, France) at the Service de RMN de la Faculté de Pharmacie de Marseille of the Aix-Marseille University and on a Bruker Avance III NanoBay 300 MHz spectrometer at the spectropole of Aix-Marseille University. The $^1\text{H-}$ and the $^{13}\text{C-}$ chemical shifts are reported from CDCl_3 peaks: ^1H (7.26 ppm) and ^{13}C (77 ppm) or $\text{Me}_2\text{SO-}d_6$ (39.6 ppm). Multiplicities are represented by the following notations: s, singlet; d, doublet; t, triplet; q, quartet; m, a more complex multiplet, or overlapping multiplets. The following adsorbents were used for column chromatography: silica gel 60 (Merck, particle size 0.063–0.200 mm, 70–230 mesh ASTM, (Merck, Darmstadt, Germany). Thin Layer Chromatography (TLC) was performed on 5 cm \times 10 cm aluminum plates coated with silica gel 60 F254 (Merck) in an appropriate solvent.

3.2. Typical Procedure

The TDAE (0.14 mL, 0.6 mmol) was slowly added, with a syringe, at $-20\text{ }^\circ\text{C}$ to a vigorously stirred solution of fluorenyl bromide **1** (150 mg, 0.6 mmol) with the appropriate aldehyde (1.8 mmol, 3 equivalents) and a spatula of sodium sulfate in 4 mL of DMF, under air. A red color was immediately developed with the formation of a fine white precipitate. The mixture was then stirred at $-20\text{ }^\circ\text{C}$ for 1 h and warmed to room temperature over a period of 2 h. Then 0.5 mL of water was added to quench the reaction. The solution was extracted with dichloromethane (3×30 mL), the combined organic layers were washed with brine (3×40 mL), and dried over MgSO_4 . The crude product was then obtained after evaporation of the solvent under reduced pressure. Purification by silica gel chromatographic column (dichloromethane: methanol) gave the corresponding fluorenyl derivatives.

3.3. Compound Characterizations

9H,9'H-9,9'-Bifluorene: 3 (9%); yellow powder; m.p. 216–217 $^\circ\text{C}$ (Lit.: 237–239 $^\circ\text{C}$). $^1\text{H-NMR}$ (200 MHz) (CDCl_3) 7.66 (d, $J = 7.51$ Hz, 4H); 7.33–7.26 (m, 4H); 7.15–7.07 (m, 4H); 6.97 (d, $J = 7.34$ Hz, 4H); 4.85 (s, 2H). $^{13}\text{C-NMR}$ (50 MHz) (CDCl_3) 144.6 (4CIV); 141.5 (4CIV); 127.3 (4CHar); 126.7 (4CHar); 124.0 (4CHar); 119.6 (4CHar); 49.8 (2CH). Physical and spectroscopic data agree with those reported in the literature [33,34].

(4-Chlorophenyl)(9H-fluorene-9-yl)methanol: 4a (56%); yellow powder; m.p. 142–143 $^\circ\text{C}$ (Lit.: 126.5 $^\circ\text{C}$). $^1\text{H-NMR}$ (200 MHz) (CDCl_3): 7.70 (d, $J = 7.5$ Hz, 2H); 7.40–7.17 (m, 10H); 5.15 (d, $J = 5.7$ Hz, 1H); 4.37 (d, $J = 5.7$ Hz, 1H); 1.90 (bs, OH). $^{13}\text{C-NMR}$ (50 MHz) (CDCl_3): 143.0 (CIV); 142.9 (2CIV); 141.7 (CIV); 140.2 (2CIV); 128.1 (2CHar); 127.7 (2CHar); 126.7 (2CHar); 125.9 (2CHar); 125.5 (2CHar); 119.8 (2CHar); 75.6 (CH); 56.4 (CH). HRMS (ESI $^+$): m/z $[\text{M} + \text{Na}]^+$ calculated for $\text{C}_{20}\text{H}_{15}\text{OCINa}^+$: 329.0704 Da; found: 329.0704 Da. Physical data agree with those reported in the literature [35].

3'-(4-Chlorophenyl)spiro(fluorene-9,2'-oxirane): 5a (14%) yellow powder; m.p. 63–64 $^\circ\text{C}$. $^1\text{H-NMR}$ (200 MHz) (CDCl_3) 7.76–7.68 (m, 2H); 7.51–7.29 (m, 8H); 7.02–6.94 (dd, $J = 1$ and 7.6 Hz, 1H); 6.50 (d, $J = 7.6$ Hz, 1H); 4.91 (s, 1H). $^{13}\text{C-NMR}$ (50 MHz) (CDCl_3) 141.6 (CIV); 141.4 (CIV); 140.6 (CIV); 138.4 (CIV); 134.0 (CIV); 133.7 (CIV); 129.4 (CHar); 129.3 (CHar); 128.6 (2CHar); 128.3 (2CHar); 127.6

(2CHar); 127.0 (CHar); 123.9 (CHar); 121.6 (CHar); 120.1 (CHar); 67.6 (CIV); 59.1 (CH). HRMS (ESI⁺): m/z [M + H]⁺ calculated for C₂₀H₁₄OCl⁺: 305.0728 Da; found: 305.0728 Da.

(9*H*-Fluoren-9-yl)(phenyl)methanol: **4b** (57%); yellow powder; m.p. 116–117 °C (Lit.: 120–121 °C). ¹H-NMR (200 MHz) (CDCl₃) 7.64–7.60 (m, 2H); 7.31–7.24 (m, 7H); 7.16–7.06 (m, 3H); 6.97 (d, J = 6.9 Hz, 1H); 5.09 (d, J = 6.1 Hz, 1H); 4.40 (d, J = 6.1 Hz, 1H); 1.68 (bs, OH). ¹³C-NMR (50 MHz) (CDCl₃) 143.6 (CIV); 143.3 (CIV); 142.1 (CIV); 141.8 (CIV); 141.7 (CIV); 128.1 (2CHar); 127.8 (CHar); 127.6 (CHar); 126.8 (2CHar); 126.7 (CHar); 126.6 (CHar); 126.6 (CHar); 126.2 (CHar); 125.5 (CHar); 119.8 (CHar); 119.7 (CHar); 76.3 (CH); 54.7 (CH). HRMS (ESI⁺): m/z [M + Na]⁺ calculated for C₂₀H₁₆ONa⁺: 295.1093 Da; found: 295.1093 Da. Physical and spectroscopic data agree with those reported in the literature [34,36].

3'-Phenylspiro(fluorene-9,2'-oxirane): **5b** (17%); yellow powder; m.p. 119–120 °C (Lit.: 130–131 °C). ¹H-NMR (200 MHz) (CDCl₃) 7.76–7.67 (m, 2H); 7.50–7.30 (m, 9H); 6.93 (dt, J = 7.6 and 0.9 Hz, 1H); 6.50 (d, J = 7.6 Hz, 1H); 4.97 (s, 1H). ¹³C-NMR (50 MHz) (CDCl₃) 141.7 (CIV); 141.5 (CIV); 140.6 (CIV); 138.7 (CIV); 135.2 (CIV); 129.3 (CHar); 129.1 (CHar); 128.3 (2CHar); 128.1 (CHar); 127.6 (CHar); 127.0 (CHar); 126.8 (2CHar); 124.1 (CIV); 121.6 (CHar); 120.2 (CHar); 120.1 (CHar); 67.6 (CIV); 65.7 (CH). HRMS (ESI⁺): m/z [M + Na]⁺ calculated for C₂₀H₁₄ONa⁺: 293.0937 Da; found: 293.0936 Da. Physical and spectroscopic data agree with those reported in the literature [37].

(4-Bromophenyl)(9*H*-fluoren-9-yl)methanol: **4c** (75%); yellow powder; m.p. 129–130 °C. ¹H-NMR (200 MHz) (CDCl₃) 7.70 (d, J = 7.4 Hz, 2H); 7.43–7.34 (m, 4H); 7.30–7.20 (m, 4H); 7.15 (d, J = 8.4 Hz, 2H); 5.15 (d, J = 5.5 Hz, 1H); 4.38 (d, J = 5.5 Hz, 1H). ¹³C-NMR (50 MHz) (CDCl₃) 143.0 (2CIV); 142.9 (CIV); 141.8 (CIV); 140.8 (2CIV); 131.1 (2CHar); 128.4 (2CHar); 127.7 (CHar); 126.8 (CHar); 126.7 (CHar); 125.9 (CHar); 125.5 (CHar); 121.5 (CHar); 119.9 (CHar); 119.8 (CHar); 75.7 (CH), 54.6 (CH). HRMS (ESI⁺): m/z [M + Na]⁺ calculated for C₂₀H₁₅OBrNa⁺: 373.0198 Da; found: 373.0198 Da.

3'-(4-Bromophenyl)spiro(fluorene-9,2'-oxirane) **5c** (10%) yellow powder; m.p. 122–123 °C. ¹H-NMR (200 MHz) (CDCl₃) 7.76–7.69 (m, 2H); 7.57–7.54 (m, 2H); 7.51–7.28 (m, 6H); 7.02–6.96 (m, 1H); 7.51 (d, J = 7.7 Hz, 1H); 4.86 (s, 1H). ¹³C-NMR (50 MHz) (CDCl₃) 141.6 (CIV); 141.3 (CIV); 140.6 (CIV); 138.2 (CIV); 134.2 (CIV); 131.6 (2CHar); 129.5 (CHar); 129.3 (CHar); 128.6 (2CHar); 127.7 (CHar); 127.1 (CHar); 123.9 (CHar); 122.2 (CIV); 121.6 (CHar); 120.2 (2CHar); 67.6 (CIV); 65.1 (CH). HRMS (ESI⁺): m/z [M + H]⁺ calculated for C₂₀H₁₄OBr⁺: 349.0223 Da; found: 349.0150 Da.

(9*H*-Fluoren-9-yl)(4-methoxyphenyl)methanol: **4d** (34%); white powder; m.p. = 115–116 °C (Lit.: 122–123 °C)³; ¹H-NMR (200 MHz) (CDCl₃) 7.74–7.70 (dd, J = 7.6 and 3.3 Hz, 2H); 7.46–7.32 (m, 3H); 7.27–7.15 (m, 4H); 7.03 (d, J = 7.6 Hz, 1H); 6.88 (d, J = 8.8 Hz, 2H); 4.97 (d, J = 6.5 Hz, 1H); 4.38 (d, J = 6.5 Hz, 1H); 3.83 (s, 3H) 1.96 (bs, OH). ¹³C-NMR (50 MHz) (CDCl₃) 159.1 (CIV); 143.9 (CIV); 143.3 (CIV); 141.8 (CIV); 141.6 (CIV); 134.4 (CIV); 128.0 (2CHar); 127.6 (CHar); 127.5 (CHar); 126.6 (CHar); 126.5 (CHar); 126.3 (CHar); 125.7 (CHar); 119.8 (CHar); 119.7 (CHar); 113.5 (2CHar); 76.1 (CH); 55.2 (CH); 54.7 (CH₃). HRMS (ESI⁺): m/z [M + Na]⁺ calculated for C₂₁H₁₈O₂Na⁺: 325.1199 Da; found: 325.1200 Da.

(9*H*-Fluoren-9-yl)(4-fluorophenyl)methanol: **4e** (54%); white powder; m.p. 120–121 °C; ¹H-NMR (200 MHz) (CDCl₃) 7.70 (d, J = 7.4 Hz, 2H); 7.41–7.33 (m, 3H); 7.26–7.14 (m, 5H); 7.01–6.95 (m, 2H); 5.11 (d, J = 5.6 Hz, 1H); 4.37 (d, J = 5.6 Hz, 1H); 2.01 (bs, OH). ¹³C-NMR (50 MHz) (CDCl₃) 160.5 (CIV); 143.5 (CIV); 143.2 (CIV); 142.0 (CIV); 141.9 (CIV); 134.8 (CIV); 128.5 (CHar); 128.4 (CHar); 127.7 (2CHar); 126.7 (2CHar); 126.0 (CHar); 125.7 (CHar); 119.9 (CHar); 119.8 (CHar); 115.0 (CHar); 114.7 (CHar); 75.9 (CIV); 54.9 (CH). HRMS (ESI⁺): m/z [M + Na]⁺ calculated for C₂₀H₁₅OFNa⁺: 313.0999 Da; found: 313.0999 Da.

4-((9*H*-Fluoren-9-yl)(hydroxy)methyl)benzotrile: **4f** (41%); white powder; m.p. 169–170 °C; ¹H-NMR (200 MHz) (CDCl₃) 7.68 (d, J = 7.7 Hz, 2H); 7.52 (d, J = 8.2 Hz, 2H); 7.41–7.18 (m, 8H); 5.36 (d, J = 4.7 Hz, 1H); 4.42 (d, J = 4.7 Hz, 1H); 2.07 (bs, 1H). ¹³C-NMR (50 MHz) (CDCl₃) 146.7 (CIV); 142.5 (CIV); 142.3 (CIV); 141.8 (2CIV); 131.6 (2CHar); 128.0 (2CHar); 127.3 (2CHar); 127.0 (CHar); 126.8 (CHar); 125.5

(CHar); 125.4 (CHar); 120.1 (CHar); 120.0 (CHar); 118.8 (CIV); 111.3 (CIV); 75.5 (CH), 54.5 (CH). HRMS (ESI⁺): m/z [M + H]⁺ calculated for C₂₁H₁₆NO⁺: 298.1154 Da; found: 298.1154 Da.

4-(Spiro(fluorene-9,2'-oxiran)-3'-yl)benzotrile: **5f** (30%) white powder; m.p. 139–140 °C; ¹H-NMR (200 MHz) (CDCl₃) 7.69–7.60 (m, 4H); 7.55–7.52 (m, 2H); 7.47–7.23 (m, 4H); 6.92–6.85 (m, 1H); 6.33 (d, $J = 7.7$ Hz, 1H); 4.86 (s, 1H). ¹³C-NMR (50 MHz) (CDCl₃) 141.1 (CIV); 141.0 (CIV); 140.7 (CIV); 140.6 (CIV); 132.2 (2CHar); 130.5 (CHar); 129.7 (CHar); 129.6 (CHar); 129.1 (CIV); 128.6 (CIV); 127.8 (2CHar); 127.1 (CHar); 123.7 (CHar); 121.6 (CHar); 120.8 (CIV); 120.4 (CHar); 120.3 (CHar); 65.0 (CIV); 60.3 (CH). HRMS (ESI⁺): m/z [M + Na]⁺ calculated for C₂₁H₁₃NONa⁺: 318.0889 Da; found: 318.0889 Da.

(9H-Fluoren-9-yl)(p-tolyl)methanol **4g** (24%); yellow powder; m.p. 86–87 °C; ¹H-NMR (200 MHz) (CDCl₃) 7.72 (d, $J = 7.7$ Hz, 1H); 7.41–7.04 (m, 11H); 5.02 (d, $J = 5.0$ Hz, 1H); 4.39 (d, $J = 5.0$ Hz, 1H); 2.38 (s, 3H). ¹³C-NMR (50 MHz) (CDCl₃) 143.7 (CIV); 143.4 (CIV); 141.8 (CIV); 141.7 (CIV); 139.2 (CIV); 137.5 (CIV); 128.9 (2CHar); 127.6 (CHar); 127.5 (CHar); 126.7 (2CHar); 126.6 (2CHar); 126.3 (CHar); 125.6 (CHar); 119.8 (CHar); 119.7 (CHar); 76.2 (CH); 54.7 (CH); 21.2 (CH₃). HRMS (ESI⁺): m/z [M + Na]⁺ calculated for C₂₁H₁₈ONa⁺: 309.1250 Da; found: 309.1249 Da.

3'-(4-Nitrophenyl)spiro(fluorene-9,2'-oxirane) **5h** (17%); yellow powder; m.p. 152–153 °C; ¹H-NMR (200 MHz) (CDCl₃) 8.30 (dd, $J = 8.6$ and 2.4 Hz, 2H); 7.77–7.66 (m, 4H); 7.52–7.31 (m, 4H); 6.97–6.94 (m, 1H); 6.45 (d, $J = 7.7$ Hz, 1H); 4.99 (s, 1H). ¹³C-NMR (50 MHz) (CDCl₃) 147.8 (CIV); 142.4 (CIV); 141.7 (CIV); 140.8 (CIV); 140.6 (CIV); 137.6 (CIV); 129.8 (CHar); 129.6 (CHar); 127.9 (2CHar); 127.8 (CHar); 127.1 (CHar); 123.7 (2CHar); 123.5 (CHar); 121.6 (CHar); 120.5 (CHar); 120.3 (CHar); 68.0 (CIV); 64.9 (CH). HRMS (ESI⁺): m/z [M + H]⁺ calculated for C₂₀H₁₄NO₃⁺: 315.0895 Da; found: 315.0895 Da.

(9H-Fluoren-9-yl)(4-(trifluoromethyl)phenyl)methanol **4i** (49%); white powder; m.p. 149–150 °C. ¹H-NMR (200 MHz) (CDCl₃) 7.72 (d, $J = 7.6$ Hz, 2H); 7.56 (d, $J = 8.3$ Hz, 2H); 7.42–7.21 (m, 8H); 5.31 (d, $J = 5.3$ Hz, 1H); 4.43 (d, $J = 5.3$ Hz, 1H). ¹³C-NMR (50 MHz) (CDCl₃) 145.7 (CIV); 142.8 (CIV); 141.6 (2CIV); 141.8 (2CIV); 127.8 (2CHar); 127.0 (2CHar); 126.9 (CHar); 126.7 (CHar); 125.8 (CHar); 125.3 (CHar); 125.0 (CHar); 124.9 (CHar); 124.8 (CIV); 120.0 (CHar); 119.9 (CHar); 75.6 (CH); 54.6 (CH). HRMS (ESI⁺): m/z [M + Na]⁺ calculated for C₂₁H₁₅OF₃Na⁺: 363.0967 Da; found: 363.0969 Da.

3'-(4-(Trifluoromethyl)phenyl)spiro[fluorene-9,2'-oxirane] **5i** (6%); yellow powder; m.p. 75–76 °C. ¹H-NMR (200 MHz) (CDCl₃) 7.67–7.16 (m, 10H); 6.90–6.63 (m, 1H); 6.39–6.35 (dd, $J = 6.4$ et 1.4 Hz, 1H); 4.87 (s, 1H). ¹³C-NMR (50 MHz) (CDCl₃) 145.3 (CIV); 144.2 (CIV); 141.3 (CIV); 140.2 (CIV); 140.0 (CIV); 129.7 (CHar); 129.4 (CHar); 127.6 (CIV); 127.5 (2CHar); 127.4 (2CHar); 125.5 (CHar); 124.1 (CHar); 123.7 (CHar); 123.6 (CHar); 120.1 (CHar); 120.0 (CIV); 84.7 (CIV); 78.9 (CH). HRMS (ESI⁻): m/z [M – H]⁻ calculated for C₂₁H₁₂OF₃⁻: 337.0846 Da; found: 337.0846 Da.

(9H-Fluoren-9-yl)(furan-2-yl)methanol **4j** (28%); brown powder; m.p. 91–92 °C. ¹H-NMR (200 MHz) (CDCl₃) 7.75 (d, $J = 7.7$ Hz, 2H); 7.50–7.20 (m, 6H); 7.05 (d, $J = 7.6$ Hz, 1H); 6.40–6.39 (m, 1H); 6.15–6.14 (m, 1H); 5.03 (d, $J = 6.2$ Hz, 1H); 4.56 (d, $J = 6.2$ Hz, 1H). ¹³C-NMR (50 MHz) (CDCl₃) 154.9 (CIV); 143.1 (CIV); 143.0 (CIV); 141.7 (2CIV); 127.7 (2CHar); 127.0 (2CHar); 126.0 (2CHar); 124.9 (CHar); 119.7 (2CHar); 110.5 (CHar); 107.4 (CHar); 70.3 (CH); 52.4 (CH). HRMS (ESI⁺): m/z [M + Na]⁺ calculated for C₁₈H₁₄O₂Na⁺: 285.0886 Da; found: 285.0884 Da.

3'-(Furan-2-yl)spiro(fluorene-9,2'-oxirane) **5j** (19%); brown crystals; m.p. 135–136 °C. ¹H-NMR (200 MHz) (CDCl₃) 8.70–8.63 (m, 2H); 8.45–8.41 (m, 1H); 7.83–7.50 (m, 7H); 6.78–6.70 (m, 2H). ¹³C-NMR (50 MHz) (CDCl₃) 148.7 (CIV); 148.3 (CIV); 143.4 (CHar); 131.6 (CIV); 131.4 (CIV); 128.0 (CHar); 127.1 (CHar); 126.7 (CHar); 126.4 (CIV); 124.9 (CHar); 124.8 (CHar); 124.3 (CHar); 123.5 (CHar); 122.7 (CHar); 122.5 (CHar); 111.8 (CHar); 111.4 (CHar); 106.5 (CIV).

(9H-Fluoren-9-yl)(pyridin-4-yl)methanol: **4k** (42%); orange powder; m.p. 235–236 °C; ¹H-NMR (200 MHz) (DMSO-*d*₆) 8.08 (d, $J = 6.0$ Hz, 2H); 7.96–7.92 (m, 2H); 7.87–7.83 (m, 2H); 7.44–7.36 (m, 4H); 6.74 (d, $J = 4.6$ Hz, 1H); 6.68 (d, $J = 6.0$ Hz, 2H); 5.50 (d, $J = 4.6$ Hz, 1H). ¹³C-NMR (50 MHz) (DMSO-*d*₆) 150.2 (CIV); 147.0 (2CHar); 143.2 (2CIV); 140.8 (2CIV); 127.2 (2CHar); 126.9 (2CHar); 125.8 (2CHar); 122.1

(2CHar); 118.9 (2CHar); 73.0 (CH); 63.73 (CH). HRMS (ESI⁺): m/z [M – H][–] calculated for C₁₉H₁₄NO[–]: 272.1081 Da; found: 272.1081 Da.

4-(Spiro(fluorene-9,2'-oxiran)-3'-yl)pyridine: **5k** (11%); Yellow powder; m.p. 197–198 °C ¹H-NMR (200 MHz) (DMSO-*d*₆) 8.13 (d, *J* = 8.0 Hz, 1H); 7.88 (d, *J* = 7.0 Hz, 2H); 7.36–7.18 (m, 4H); 6.50 (d, *J* = 7.0 Hz, 2H); 6.22 (d, *J* = 5.9 Hz, 1H); 5.83 (d, *J* = 5.9 Hz, 1H). ¹³C-NMR (50 MHz) (DMSO-*d*₆) 147.7 (2CHar); 144.4 (2CIV); 143.5 (2CIV); 139.0 (CIV); 129.3 (CHar); 129.2 (CHar); 127.5 (CHar); 127.3 (CHar); 126.7 (CHar); 125.1 (CHar); 122.4 (2CHar); 119.8 (CHar); 119.6 (CHar); 76.9 (CH); 75.6 (CH). HRMS (ESI⁺): m/z [M + Na]⁺ calculated for C₁₉H₁₃NONa⁺: 294.0889 Da; found: 294.0891 Da.

(9H-Fluoren-9-yl)(pyridin-3-yl)methanol **4l** (19%); white powder; m.p. 253–254 °C. ¹H-NMR (200 MHz) (DMSO-*d*₆) 8.16–8.14 (dd, *J* = 4.7 et 1.7 Hz, 1H); 7.88 (d, *J* = 1.9 Hz, 1H); 7.76–7.73 (m, 1H); 7.56–7.45 (m, 3H); 7.34–7.26 (m, 4H); 7.08–7.04 (dt, *J* = 7.9 et 1.9, 1H); 6.95–6.90 (dd, *J* = 7.7 ou 7.9 et 4.7 Hz, 1H); 6.03 (s, OH); 5.83 (d, *J* = 3.7 Hz, 1H); 5.17 (d, *J* = 3.7 Hz, 1H). ¹³C-NMR (50 MHz) (DMSO-*d*₆) 148.4 (CHar); 147.3 (CHar); 146.3 (2CIV); 139.8 (2CIV); 134.2 (CHar); 128.2 (CHar); 128.1 (CHar); 126.7 (2CHar); 126.6 (CIV); 125.6 (CHar); 124.5 (CHar); 121.4 (CHar); 119.2 (CHar); 119.0 (CHar); 83.71 (CH); 76.3 (CH). HRMS (ESI⁺): m/z [M + H]⁺ calculated for C₁₉H₁₆NO⁺: 274.1226 Da; found: 274.1226 Da.

Ethyl 2-(9H-fluoren-9-yl)-2-hydroxypropanoate **4m** (47%); orange oil. ¹H-NMR (200 MHz) (CDCl₃) 7.73 (d, *J* = 7.3 Hz, 2H); 7.63–7.54 (m, 2H); 7.39–7.35 (m, 4H); 4.31 (s, 1H); 4.05 (q, *J* = 7.1 Hz, 2H); 1.60 (s, 3H); 1.04 (t, *J* = 7.1 Hz, 3H). ¹³C-NMR (50 MHz) (CDCl₃) 175.3 (CIV); 143.0 (CIV); 142.6 (CIV); 142.2 (CIV); 141.8 (CIV); 127.9 (CHar); 127.7 (CHar); 126.7 (2CHar); 126.0 (CHar); 125.7 (CHar); 119.7 (CHar); 119.6 (CHar); 77.2 (CIV); 61.7 (CH₂); 56.0 (CH); 23.9 (CH₃); 13.7 (CH₃). HRMS (ESI⁺): m/z [M + NH₄]⁺ calculated for C₁₈H₂₂NO₃⁺: 300.1594 Da; found: 300.1592 Da.

Methyl 2-(9H-fluoren-9-yl)-3,3,3-trifluoro-2-hydroxypropanoate **4n** (41%); yellow powder; m.p. 94–95 °C. ¹H-NMR (200 MHz) (CDCl₃) 7.77–7.71 (m, 3H); 7.45–7.39 (m, 2H); 7.33–7.25 (m, 3H); 4.61 (s, 1H); 3.70 (s, 3H). ¹³C-NMR (50 MHz) (CDCl₃) 169.2 (CIV); 142.7 (CIV); 142.1 (CIV); 140.1 (CIV); 139.8 (CIV); 128.5 (CHar); 128.3 (CHar); 126.7 (CHar); 126.8 (2CHar); 125.5 (CHar); 119.8 (CHar); 119.6 (CHar); 80.0 (CIV); 79.5 (CIV); 53.8 (CH); 50.2 (CH₃). HRMS (ESI⁺): m/z [M + NH₄]⁺ calculated for C₁₇H₁₇NO₃F₃⁺: 340.1155 Da; found: 340.1157 Da.

Ethyl 2-(9H-fluoren-9-yl)-2-hydroxyacetate **4o** (25%); yellow powder; m.p. 135–136 °C. ¹H-NMR (200 MHz) (CDCl₃) 7.75 (d, *J* = 7.1 Hz, 2H); 7.65 (m, 1H); 7.43–7.26 (m; 5H); 4.94 (d, *J* = 2.7 Hz, 1H); 4.43 (d, *J* = 2.7 Hz, 1H); 4.08 (q, *J* = 7.1 Hz, 2H); 1.03 (t, *J* = 7.1 Hz, 3H). ¹³C-NMR (50 MHz) (CDCl₃) 173.2 (CIV); 143.3 (2CIV); 142.2 (2CIV); 127.8 (CHar); 127.7 (CHar); 127.2 (CHar); 127.0 (CHar); 124.7 (CHar); 124.5 (CHar); 119.9 (CIV); 119.8 (CHar); 72.6 (CH); 61.6 (CH); 48.31 (CH₂); 13.7 (CH₃). HRMS (ESI⁺): m/z [M + H]⁺ calculated for C₁₇H₁₇O₃⁺: 269.1172 Da; found: 269.1171 Da.

Diethyl 2-(9H-fluoren-9-yl)-2-hydroxymalonate **4p** (70%); white powder; m.p. 75–76 °C. ¹H-NMR (200 MHz) (CDCl₃) 7.74 (d, *J* = 7.4 Hz, 2H); 7.49 (d, *J* = 7.4 Hz, 2H); 7.43–7.36 (m, 2H); 7.30–7.22 (m, 2H); 4.93 (s, 1H); 4.25 (q, *J* = 7.2 Hz, 4H); 3.88 (bs, 1H); 1.19 (t, *J* = 7.2 Hz, 6H). ¹³C-NMR (50 MHz) (CDCl₃) 169.5 (2CIV); 142.1 (2CIV); 141.6 (2CIV); 128.0 (2CHar); 127.0 (2CHar); 125.3 (2CHar); 119.7 (2CHar); 81.3 (CIV); 62.6 (2CH₂); 54.6 (CH); 13.7 (2CH₃). HRMS (ESI[–]): m/z [M + H]⁺ calculated for C₂₀H₂₁O₅⁺: 341.1384 Da; found: 340.1311 Da.

3.4. Reactivity of 9-Bromofluorene and 4-Cyanobenzaldehyde in the Presence of Triethylamine

Triethylamine (150 mg, 1.2 mmol) was added to a stirred solution of fluorenyl bromide **1** (100 mg, 0.5 mmol) with the 4-cyanobenzaldehyde (160 mg, 1.2 mmol) and a spatula of sodium sulfate in 4 mL of DMF, under air. The mixture was then stirred at –20 °C for 1 h and warmed to room temperature over a period of 24 h. Then 0.5 mL of water was added to quench the reaction. The solution was extracted with dichloromethane (3 × 30 mL), the combined organic layers were washed with brine (3 × 40 mL), and dried over MgSO₄. The crude product was then obtained after evaporation of the

solvent under reduced pressure. Purification by silica gel chromatographic column (dichloromethane: methanol) gave the 20% of the unreacted 9-bromofluorene with 15% yield of the 4-((9H-fluoren-9-ylidene)methyl)benzo-nitrile **8c** and 7% yield of the 4-(spiro(fluorene-9,2'-oxiran)-3'-yl)benzonitrile **5f** gave the unreacted 9-bromofluorene (20%) with 4-((9H-fluoren-9-ylidene)methyl)benzonitrile **6f** (15%) and 4-(spiro(fluorene-9,2'-oxiran)-3'-yl)benzonitrile **5f** (7%).

4-((9H-Fluoren-9-ylidene)methyl)benzonitrile: **6f** (15%) yellow powder; m.p. 149–150 °C (Lit.: 150–151). ¹H-NMR (200 MHz) (CDCl₃) 7.97–7.94 (m, 1H); 7.75–7.73 (m, 1H); 7.41–7.30 (m, 6H); 7.12 (d, *J* = 8.3 Hz, 2H); 7.12 (d, *J* = 8.3 Hz, 2H); 6.80 (bs, 1H). Physical and spectroscopic data agree with those reported in the literature [38].

4. Conclusions

This strategy afforded a novel and convenient synthesis of various 9-fluorenylidene derivatives under mild reaction conditions. TDAE was used to generate the fluorenyl anion in situ and under practical conditions, which could be extended to electrophiles. In this study, TDAE, or another base present in the reaction mixture, was also able to promote the formation of epoxide derivatives. Moreover, because of their structural analogy with recently reported compounds, the anti-nociceptive properties of all intermediates are under active investigation.

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Sample Availability: Samples of the compounds **4a–4g**; **4i–4p** and **5a–5c**; **5f–5k**; **6f** are available from the authors.



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