Intramolecular Friedel–Crafts Alkylation of Chalcone Epoxides Using Indium(III) Chloride as an Efficient Catalyst

Naseem Ahmed,* B. Venkata Babu, Harendra Kumar

Department of Chemistry, Indian Institute of Technology, Roorkee 247 667, Uttarakhand, India
Fax +91(1332)285745; E-mail: nasemfcy@iitr.ernet.in

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Abstract: Indium(III) chloride catalyzes the ring opening of chalcone epoxides followed by intramolecular Friedel–Crafts alkylation under mild conditions at room temperature to afford highly functionalized 3-aryl-2-hydroxy-2,3-dihydro-1*H*-inden-1-ones in excellent yields (81–95%).

Key words: indium(III) chloride, intramolecular Friedel–Crafts alkylation, chalcones epoxides, epoxide ring opening, 2,3-dihydro-1*H*-inden-1-ones

Indan-1-one and indan-2-one derivatives constitute the core structures of many natural products, agrochemicals, and medicines[1] including indacrinone,[1a–c] indanoyl isoleucine conjugates,[1d] and indanocines.[1e] 2-(Alkoxycarbonyl)- and 2-acetylindan-1-ones are present in the cytotoxic natural compounds pterosines,[1,2] the potent and selective COX-2 inhibitor flosulide[2,3] and the acetylcholinesterase inhibitor donepezil hydrochloride,[4] used for the treatment of Alzheimer's disease.[3] They are also used as intermediates in the synthesis of norditerpene taiwaniaquinol B,[5] sulindac,[5a] a nonsteroidal anti-inflammatory drug (NSAID),[4a–c] and have shown ligand properties for important receptors, such as NMDA receptor antagonists,[4d] benzodiazepines,[4e] melatonin precursor,[4f] and glutamate subtype-2 receptor (Figure 1).[4g] Enantiomerically pure derivative, 1-aminoindan-2-ol is a key precursor of the chiral ligand and the chiral auxiliary in the asymmetric synthesis of Indinavir, a potent inhibitor of the protease of human immunodeficiency virus (HIV).[6] Baeyer–Villiger oxidation of indan1-ones gives biologically active coumarins, for example, 3,4-dihydro-4-arylcoumarins (neoflavonoids) present in natural product calomelanols.[7] Diacetoxydihydrocoumarin and natural dihydrocoumarins (DHC) are of great interest in the flavor industry[8] and precursors for the synthesis of important bioactive compounds Detrol LA (tolterodine tartrate), a muscarine receptor antagonist used for the treatment of urinary bladder disorder.[9]

A number of synthetic approaches have been reported for the synthesis of indan-1-ones, for example, intramolecular Friedel–Crafts alkylation,[10] Nazarov cyclization[11] annulation methodology,[12] tandem Knoevenagel condensation–cycloalkylation,[13] photochemical process,[14] palladium-catalyzed Heck and Negishi cyclization,[14a,b] and ring-closing metathesis.[15] Different Lewis acids catalyze this reaction, for example, TFA, SbF_5,[16a] $AlCl_3$,[16b] $TiCl_4$,[17] PPA,[18] MsOH,[19] HF,[20] P_2O_5,[21] TFAA,[22] and perfluorinated sulfonic acid resin (Nafion-H).[23] The Friedel–Crafts reaction calls for high temperatures or highly acidic conditions and catalytic enantioselective Negishi reaction of indanones requires multistep synthesis of 3-substituted indanones and suffers from high catalyst loading.[5]

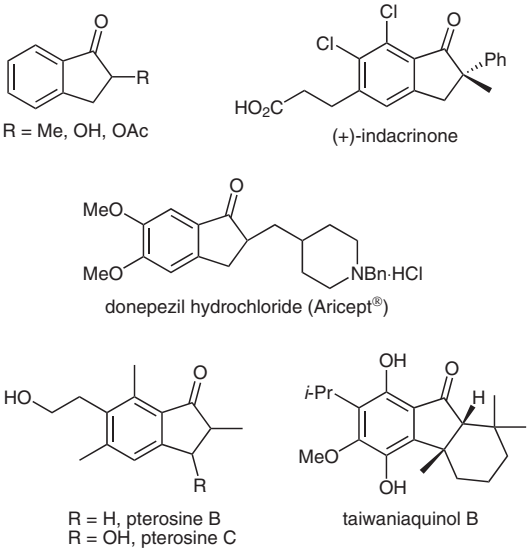
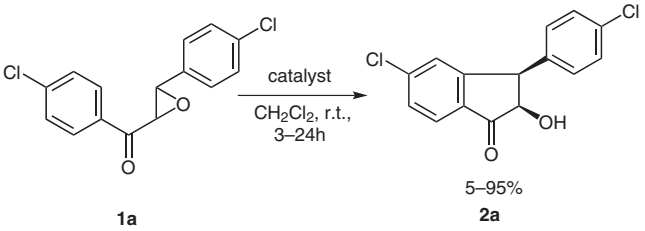


Figure 1 Bioactive indan-1-one derivatives

In continuation of our interest in Lewis acid catalysis [24] and the importance of metal halides as inexpensive, easily available, and stable catalysts in epoxide ring opening.[25] Herein, we report the catalytic properties of metal halides in the synthesis of highly functionalized 2-hydroxyindan-1-one derivatives at room temperature (Scheme 1,



Scheme 1

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Table 1). In comparison with other methods, our method gave high yields in a shorter reaction time (4–5 h), and with easy product workup.

The catalytic efficiency of metal halides is given in Table 1. Zirconium, aluminum, and bismuth salts (entries 2–4) showed poor to moderate catalytic activity in the formation of **2a** (Scheme 1). Other metal halides (e.g., with 10 mol% of ZnO, $TaCl_5$, $ZnCl_2$, $CuBr_2$, $SnCl_2$, $LaCl_3$, LiBr, $TiCl_4$, $FeCl_3$, or $FeCl_3 \cdot 6\ H_2O$) failed to give the product even after reaction for a prolonged time. Indium(III) chloride (entry 1) was found to be the most efficient catalyst at 10 mol% catalyst loading, which gave the optimal yield (95%). To optimize the catalyst loading, the reactions were carried out with 2, 5, 10, and 20 mol% catalyst (entries 1, 5–7) in dichloromethane and the efficiency of the catalyst loading was determined from the time needed for the complete conversion of the epoxide **1a**. Using 2 and 5 mol% indium(III) chloride gave the product **2a** in lower yield and the reaction slowly, whereas using 20 mol% indium(III) chloride the product **2a** was formed in 82% yield together with 2,5-dichloro-3-(4-chlorophenyl)-2,3-dihydro-1*H*-inden-1-one (7%), which was isolated and characterized by GCMS/HRMS, without improvement in the yield or reaction time.

Table 1 Screening of Metal Salts and Optimization for Intramolecular Friedel–Crafts Alkylation of Chalcone Epoxide **1a** (Scheme 1)

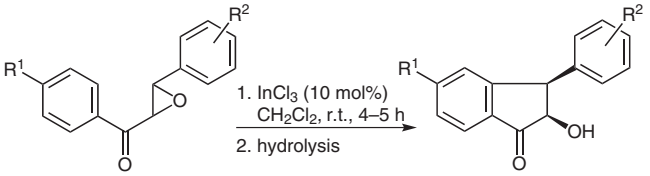
Entry	Catalyst	Loading (mol%)	Time (h)	Yield[a] (%)
1	$InCl_3$	10	4–5	90
2	$ZrOCl_2$	10	20	<5
3	anhyd $AlCl_3$	10	5	35
4	$BiCl_3$	10	6	10
5	$InCl_3$	2	16	50
6	$InCl_3$	5	15	65
7	$InCl_3$	20	4–5	82[b]

[a] Yields refer to isolated product **2a**.
[b] Together with 2,5-dichloro-3-(4-chlorophenyl)- 2,3-dihydro-1*H*-inden-1-one (7%).

Various chalcones were prepared by the condensation of acetophenones and aromatic aldehydes following a reported procedure.[26] Epoxidation of the chalcones was carried out using sodium hydroxide and hydrogen peroxide in aqueous tetrahydrofuran to give the corresponding epoxides **1a–p** in high yields (80–90%). Following a simple experimental procedure, chalcone epoxides **1a–p** were dissolved in dichloromethane by stirring, indium(III) chloride was added in one portion and the mixture was stirred at room temperature for four to five hours. After the usual workup, the 3-aryl-2-hydroxyindan-1-ones **2a–p** were obtained in 81–95% yields (Table 2).

The assigned structures of chalcone epoxides **1a–p** and products **2a–p** were confirmed on the basis of their spectral analysis (IR, ^1H and ^{13}C NMR, and GC–MS/EI MS) and also compared with reported data in the literature.[7b] The *trans*-stereochemistry of epoxides **1a–p** was confirmed by the coupling constants of the protons α and β to the carbonyl group. For example, for **1c** the ^1H NMR contained peaks at δ = 4.07 ppm [d, *J* = 2.0 Hz, 1 H, Ar-C*H*(-O-)CH] and 4.21 ppm [d, *J* = 2.0 Hz, 1 H, C(O)CH], in which the coupling constant (2 Hz) indicates a *trans*-substituted epoxide. Similarly, the *cis*-configuration of 2-hydroxyindan-1-ones **2a–p** was confirmed by the coupling constants of the protons at positions 2 and 3. For example, for **2c** the ^1H NMR contained peaks at δ = 5.18 ppm (d, *J* = 3.5 Hz, 1 H, H3) and 5.33 ppm (d, *J* = 3.5 Hz, 1 H, H2), in which the coupling constant (3.5 Hz) indicates a *cis*-configuration. The stereoselectivity and high yields for indan-1-ones under acidic condition might be due to the carbon β to the carbonyl group possessing considerable cationic character as it is also at the benzylic position and therefore resonance stabilized. The *cis*-configuration in 3-aryl-2-hydroxyindan-1-ones **2a–p**, fur-

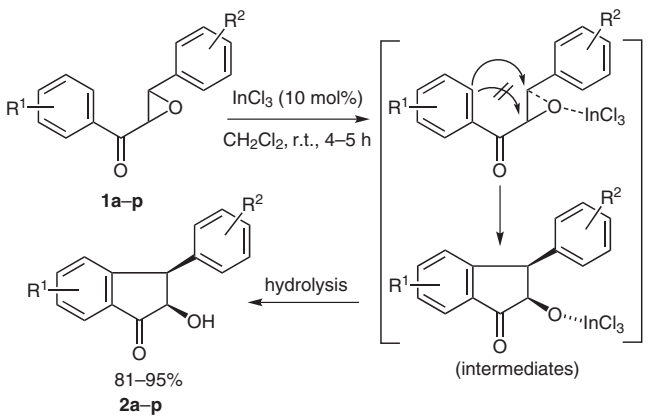
Table 2 Indium(III) Chloride Catalyzed Intramolecular Friedel–Crafts Alkylation Synthesis of 2-Hydroxyindan-1-ones



1a–p **2a–p**

Chalcone epoxide	R^1	R^2	Product	Yield[a] (%)
1a	Cl	4-Cl	**2a**	90
1b	Cl	4-Me	**2b**	92
1c	Cl	4-Br	**2c**	94
1d	Cl	3,4,5-$(MeO)_3$	**2d**	81
1e	Cl	3-O_2N	**2e**	91
1f	Cl	H	**2f**	95
1g	Br	4-Me	**2g**	92
1h	Br	4-Cl	**2h**	93
1i	Br	4-Br	**2i**	95
1j	Br	3,4,5-$(MeO)_3$	**2j**	83
1k	Br	3-O_2N	**2k**	92
1l	Br	H	**2l**	94
1m	H	H	**2m**	95
1n	H	4-Cl	**2n**	95
1o	H	3-O_2N	**2o**	94
1p	H	4-Br	**2p**	92

[a] Yields refer to isolated products.



Scheme 2

ther support benzylic resonance stabilization, which results in an S_N1-like mechanism. Hence, the epoxide ring regioselectively opened via the carbon β to the carbonyl group (Scheme 2).

In conclusion, we have explored the properties of different metal halides for as mild and efficient catalysts for chalcone epoxide ring opening and intramolecular Friedel–Crafts alkylation in the regioselective synthesis of 3-aryl-2-hydroxyindan-1-ones. To the best of our knowledge, indium(III) chloride has not been studied in this capacity before and therefore represents a novel subject for investigation.

Organic solvents were dried by standard methods when necessary. Commercially available reagents were used without further purification unless mentioned. All reactions were monitored by TLC using precoated silica gel aluminum plates. Visualization of TLC plates was accomplished with UV lamp or in an I_2 chamber. Column chromatography was performed using silica gel 100–200 mesh size (SD Fine-Chem Limited) with EtOAc–hexanes as eluent; petroleum ether = PE. Melting points were recorded on perfit apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded at 500 and 125 MHz, respectively; ^{1}H NMR spectra were recorded in $CDCl_3$ using TMS as an internal standard. Mass spectra were recorded by GC-MS and EI-MS.

Chalcone Epoxides 1; General Procedure

A 5 M aq NaOH soln (10 mL) was added dropwise to a stirred soln of chalcone (18 mmol) in H_2O–THF (1:2, 30 mL) and further stirred for 10 min. Then, H_2O_2 (15 mL, 30 wt%) was added dropwise and the mixture was stirred at r.t. for 6–7 h (TLC monitoring). The mixture was poured into H_2O and the resulting precipitate was filtered, washed with H_2O, and dried under reduced pressure. The product was recrystallized (EtOH) or subjected to column chromatography (silica gel, PE–CH_2Cl_2, 8:2). Spectral data are given below for new compounds. Epoxides **1a**,**b**,**f**–**h**,**l**–**n**,**p** are known.[27]

[3-(4-Bromophenyl)oxiran-2-yl](4-chlorophenyl)methanone (1c)

White solid; yield: 5383 mg (89%); mp 127–129 °C.

IR (KBr): 3039 (arom C–H str), 1675 (C=O str), 1587 (arom C=C str), 1430, 1400, 1236, 1177, 1092, 1011, 735 cm^{-1} (C–Cl str).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.99 (dd, *J* = 7.0, 2.0 Hz, 2 H, H_{Ar}), 7.54 (m, 4 H, H_{Ar}), 7.27 (dd, *J* = 7.0, 2.0 Hz, 2 H, H_{Ar}), 4.21 [d, *J* = 2.0 Hz, 1 H, C(O)CH], 4.07 [d, *J* = 2.0 Hz, 1 H, Ar-C*H*(-O-)CH].

^{13}C NMR (125 MHz, $CDCl_3$): δ = 191.69 (C=O), 60.96 [C(O)-*C*H], 58.71 (Ar-*C*H-O), 140.76, 134.37, 133.62, 132.04, 129.82, 129.31, 127.40, 123.21.

MS (EI, 70 eV): *m*/*z* (%) = 336 (21) [M$^{+\cdot}$], 139 (100).

(4-Chlorophenyl)[3-(3, 4, 5-trimethoxyphenyl)oxiran-2-yl]methanone (1d)

White crystalline solid; yield: 5638 mg (90%); mp 128–130 °C.

IR (KBr): 2928 (arom C–H str), 1692 (C=O str), 1590 (arom C=C str), 1462, 1399, 1233, 1130 (C–O–C str), 1007, 824 cm^{-1} (C–Cl str).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.99 (d, *J* = 8.5 Hz, 2 H, H_{Ar}), 7.47 (d, *J* = 8.5 Hz, 2 H, H_{Ar}), 6.60 (s, 2 H, H_{Ar}), 4.20 [d, *J* = 1.5 Hz, 1 H, C(O)C*H*], 4.04 [d, *J* = 1.5 Hz, 1 H, Ar-C*H*(-O-)CH], 3.89 (s, 9 H, OMe).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 191.89 (C=O), 153.79, 140.65, 138.74, 133.72, 130.84, 129.83, 129.26, 102.57, 60.97 [C(O)-*C*H], 59.54 (Ar-*C*H-O), 56.22 (OMe).

MS (EI, 70 eV): *m*/*z* (%) = 348 (16) [M$^{+\cdot}$], 219 (53), 181 (100).

(4-Chlorophenyl)[3-(3-nitrophenyl)oxiran-2-yl]methanone (1e)

White crystalline solid; yield: 4745 mg (87%); mp 126–128 °C.

IR (KBr): 3091, 2971 (arom C–H str), 1687 (C=O str), 1582 (arom C=C str), 1523 (N–O, str), 1353 (N–O bending), 1237, 1003, 732 cm^{-1} (C–Cl str).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.27 (d, *J* = 8.5 Hz, 2 H, H_{Ar}), 8.01 (dd, *J* = 7.0, 1.5 Hz, 2 H, H_{Ar}), 7.74 (d, *J* = 7.5 Hz, 1 H, H_{Ar}), 7.63 (m, 1 H, H_{Ar}), 7.52 (m, 2 H, H_{Ar}), 4.27 [d, *J* = 1.5 Hz, 1 H, C(O)C*H*], 4.24 [d, *J* = 1.5 Hz, 1 H, Ar-C*H*(-O-)CH].

^{13}C NMR (125 MHz, $CDCl_3$): δ = 191.18 (C=O), 148.74, 141.02, 137.70, 133.49, 131.75, 129.98, 129.89, 129.40, 124.00, 120.80, 60.76 [C(O)-*C*H], 57.96 (Ar-*C*H-O).

MS (EI, 70 eV): *m*/*z* (%) = 303 (34) [M$^{+\cdot}$], 139 (100).

(4-Bromophenyl)[3-(4-bromophenyl)oxiran-2-yl]methanone (1i)

White crystalline solid; yield: 5883 mg (86%); mp 124–126 °C.

IR (KBr): 3091, 2924 (arom C–H str), 1674 (C=O str), 1579 (arom C=C str), 1398, 1234, 1006, 880, 812 cm^{-1} (C–Br str).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.90 (d, *J* = 8.5 Hz, 2 H, H_{Ar}), 7.67 (d, *J* = 8.0 Hz, 2 H, H_{Ar}), 7.56 (d, *J* = 7.0 Hz, 2 H, H_{Ar}), 7.27 (m, 2 H, H_{Ar}), 4.19 [d, *J* = 1.5 Hz, 1 H, C(O)C*H*], 4.07 [d, *J* = 1.5 Hz, 1 H, Ar-C*H*(-O-)CH].

^{13}C NMR (125 MHz, $CDCl_3$): δ = 191.91 (C=O), 134.36, 134.01, 132.31, 132.04, 129.87, 129.54, 127.40, 123.22, 60.94 [C(O)-*C*H], 58.72 (Ar-*C*H-O).

MS (EI, 70 eV): *m*/*z* (%) = 380 (16) [M$^{+\cdot}$], 183 (83), 89 (100).

(4-Bromophenyl)[3-(3,4,5-trimethoxyphenyl)oxiran-2-yl]methanone (1j)

White crystalline solid; yield: 5998 mg (85%); mp 130–132 °C.

IR (KBr): 2940 (arom C–H str), 1692 (C=O str), 1590 (arom C=C str), 1232, 1129 (C–O–C str), 1005, 826, 735, 686 cm^{-1} (C–Br str).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.92 (d, *J* = 9.0 Hz, 2 H, H_{Ar}), 7.68 (d, *J* = 9.0 Hz, 2 H, H_{Ar}) 6.60 (s, 2 H, H_{Ar}), 4.20 [d, *J* = 1.5 Hz, 1 H, C(O)C*H*], 4.05 [d, *J* = 1.5 Hz, 1 H, Ar-C*H*(-O-)CH], 3.90 (s, 9 H, OMe).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 192.11 (C=O), 153.79, 138.75, 134.11, 130.82, 129.88, 129.42, 102.57, 60.97 [C(O)-*C*H], 59.55 (Ar-*C*H-O), 56.23 (OMe).

MS (EI, 70 eV): *m*/*z* (%) = 392 (15) [$M^{+\cdot}$], 181 (92), 105 (100).

(4-Bromophenyl)[3-(3-nitrophenyl)oxiran-2-yl]methanone (1k)
White crystalline solid; yield: 5309 mg (85%); mp 132–134 °C.

IR (KBr): 3087, 3041 (arom C–H str), 1687 (C=O str), 1581 (arom C=C str), 1522 (N–O str), 1353 (N–O bending), 1236, 1072, 675 cm^{-1} (C–Br str).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.26 (dd, *J* = 4.0, 1.0 Hz, 2 H, H_{Ar}), 7.92 (dd, *J* = 9.0, 2.0 Hz, 2 H, H_{Ar}), 7.70 (m, 4 H, H_{Ar}) 4.26 [d, *J* = 2.0 Hz, 1 H, C(O)C*H*], 4.24 [d, *J* = 2.0 Hz, 1 H, Ar-C*H*(-O-)CH].

^{13}C NMR (125 MHz, $CDCl_3$): δ = 191.41 (C=O), 137.66, 133.85, 132.41, 131.78, 130.01, 129.93, 129.83, 124.04, 120.81, 60.73 [C(O)-*C*H], 58.00 (Ar-*C*H-O).

MS (EI, 70 eV): *m*/*z* (%) = 347 (19) [$M^{+\cdot}$], 185 (82), 183 (100).

[3-(3′-Nitrophenyl)oxiran-2-yl](phenyl)methanone (1o)
Yellow solid; yield: 4164 mg (86%); mp 125–129 °C.

IR (KBr): 1689 (C=O str), 1589 (arom C=C str), 1525 (N–O str), 1405, 1344 (N–O bending), 1232, 1081, 1009, 891, 812, 691, 601 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.25–8.24 (m, 2 H, H_{Ar}), 8.03–8.01 (m, 2 H, H_{Ar}), 7.73 (d, *J* = 6.5 Hz, 1 H, H_{Ar}), 7.67–7.59 (m, 2 H, H_{Ar}), 7.53–7.50 (dd, *J* = 8.0, 1.5 Hz, 2 H, H_{Ar}), 4.31 (d, *J* = 2.0 Hz, 1 H, C(O)C*H*], 4.22 (d, *J* = 1.5 Hz, 1 H, Ar-C*H*(-O-)CH].

^{13}C NMR (125 MHz, $CDCl_3$): δ = 192.22 (C=O), 148.63, 137.91, 135.22, 134.69, 133.42, 131.89, 129.97, 129.44, 128.71, 128.42, 123.90, 120.79, 60.91 [C(O)-*C*H], 58.77 (Ar-*C*H-O).

MS (EI, 70 eV): *m*/*z* (%) = 269 (24) [$M^{+\cdot}$], 253 (23), 105 (100), 91 (68).

3-Aryl-2-hydroxy-2,3-dihydro-1*H*-inden-1-ones 2a–p; General Procedure
Chalcone epoxide **1** (2.5 mmol) was dissolved in CH_2Cl_2 (15 mL) with stirring, $InCl_3$ (0.25 mmol, 10 mol%) was added in one portion and the mixture was stirred at r.t. for 4–5 h. H_2O was added and the mixture was extracted with CH_2Cl_2. The organic layer was dried (anhyd Na_2SO_4), filtered, and evaporated under reduced pressure to obtain the pure product or purified by flash column chromatography (silica gel, hexane–CH_2Cl_2, 8:2) to afford the products in 81–95% yields.

5-Chloro-3-(4-chlorophenyl)-2-hydroxy-2,3-dihydro-1*H*-inden-1-one (2a)
Light yellow solid; yield: 657 mg (90%); mp 202–204 °C.

IR (KBr): 3438 (OH str), 2922 (arom C–H str), 1674 (C=O str), 1591 (arom C=C str), 1396, 1282, 1173, 1091, 756 cm^{-1} (C–Cl str).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.06 (d, *J* = 8.5 Hz, 1 H, H_{Ar}), 7.89 (m, 1 H, H_{Ar}), 7.53 (d, *J* = 8.5 Hz, 1 H, H_{Ar}), 7.47 (d, *J* = 8.5 Hz, 1 H, H_{Ar}), 7.28 (m, 2 H, H_{Ar}), 7.16 (d, *J* = 8.5 Hz, 1 H), 5.48 (d, *J* = 3.5 Hz, 1 H, H2), 5.21 (d, *J* = 3.5 Hz, 1 H, H3), 3.72 (br s, 1 H, D_2O exchangeable).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 196.48 (C=O), 62.22 (C2), 29.71 (C3), 141.85, 141.29, 135.02, 134.10, 132.54, 131.41, 130.12, 129.50, 128.70.

MS (EI, 70 eV): *m*/*z* (%) = 292 (10) [$M^{+\cdot}$], 245 (25), 139 (100).

5-Chloro-2-hydroxy-3-(4-tolyl)-2,3-dihydro-1*H*-inden-1-one (2b)
Light yellow solid; yield: 626 mg (92%); mp 182–184 °C.

IR (KBr): 3439 (OH str), 2922 (arom C–H str), 1670 (C=O str), 1594 (arom C=C str), 1491, 1399, 1296, 1095, 760 cm^{-1} (C–Cl str).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.01 (dd, *J* = 8.0, 2.0 Hz, 2 H, H_{Ar}), 7.74 (m, 1 H, H_{Ar}), 7.54 (m, 2 H, H_{Ar}), 7.21 (m, 2 H, H_{Ar}), 5.02 (d, *J* = 4.0 Hz, 1 H, H2), 4.95 (d, *J* = 4.0 Hz, 1 H, H3), 3.68 (br s, 1 H, D_2O exchangeable), 2.49 (s, 3 H, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 193.48 (C=O), 63.91 (C2), 31.95 (C3), 146.50, 141.51, 131.46, 131.24, 130.38, 130.09, 129.83, 129.42, 128.89, 22.30.

MS (EI, 70 eV): *m*/*z* (%) = 272 (25) [$M^{+\cdot}$], 160 (55), 141 (72), 139 (100), 111 (62), 105 (73).

3-(4-Bromophenyl)-5-chloro-2-hydroxy-2,3-dihydro-1*H*-inden-1-one (2c)
Light yellow solid; yield: 790 mg (94%); mp 210–212 °C.

IR (KBr): 3426 (OH str), 2923 (arom C–H str), 1678 (C=O str), 1591 (arom C=C str), 1417, 1395, 1282, 1170, 1092, 757 cm^{-1} (C–Cl str).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.94 (d, *J* = 8.5 Hz, 1 H, H_{Ar}), 7.88 (m, 2 H, H_{Ar}), 7.47 (m, 3 H, H_{Ar}), 6.99 (d, *J* = 8.5 Hz, 1 H, H_{Ar}), 5.33 (d, *J* = 3.5 Hz, 1 H, H2), 5.18 (d, *J* = 3.5 Hz, 1 H, H3), 4.09 (br s, 1 H, D_2O exchangeable).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 192.38 (C=O), 60.52 (C2), 31.86 (C3), 134.13, 134.08, 132.57, 132.41, 131.96, 131.57, 131.23, 130.81, 129.18, 128.70.

MS (EI, 70 eV): *m*/*z* (%) = 336 (18) [$M^{+\cdot}$], 139 (100), 111 (53).

5-Chloro-2-hydroxy-3-(3,4,5-trimethoxyphenyl)-2,3-dihydro-1*H*-inden-1-one (2d)
Light yellow solid; yield: 705 mg (81%); mp 220–222 °C.

IR (KBr): 3440 (OH str), 2920 (arom C–H str), 1666 (C=O str), 1592 (arom C=C str), 1406, 1336, 1233, 1125 (C–O–C str), 1091, 771 cm^{-1} (C–Cl str).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.63 (d, *J* = 8.0 Hz, 1 H, H_{Ar}), 7.57 (d, *J* = 8.0 Hz, 1 H, H_{Ar}), 7.39 (m, 1 H, H_{Ar}), 6.25 (s, 1 H, H_{Ar}), 6.19 (s, 1 H, H_{Ar}), 5.03 (d, *J* = 4.0 Hz, 1 H, H2), 4.92 (d, *J* = 4.0 Hz, 1 H, H3), 4.49 (br s, 1 H, D_2O exchangeable), 3.61 (s, 9 H, OMe).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 192.89 (C=O), 61.10 (C2), 30.96 (C3), 153.67, 134.06, 132.51, 131.73, 131.31, 129.91, 129.46, 128.95, 128.56, 107.26, 56.38 (OMe).

MS (EI, 70 eV): *m*/*z* (%) = 348 (29) [$M^{+\cdot}$], 181 (69), 139 (100), 111 (59).

5-Chloro-2-hydroxy-3-(3-nitrophenyl)-2,3-dihydro-1*H*-inden-1-one (2e)
Light yellow solid; yield: 690 mg (91%); mp 215–217 °C.

IR (KBr): 3358 (OH str), 3075, 2924 (arom C–H str), 1686 (C=O str), 1591 (arom C=C str), 1527 (N–O str), 1317 (N–O bending), 758 cm^{-1} (C–Cl str).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.17 (d, *J* = 1.5 Hz, 1 H, H_{Ar}), 8.04 (d, *J* = 8.5 Hz, 2 H, H_{Ar}), 7.55 (m, 2 H, H_{Ar}), 7.46 (d, *J* = 8.5 Hz, 2 H, H_{Ar}), 5.50 (d, *J* = 4.0 Hz, 1 H, H2), 5.25 (d, *J* = 4.0 Hz, 1 H, H3), 4.49 (br s, 1 H, D_2O exchangeable).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 192.57 (C=O), 98.81 (C2), 31.95 (C3), 132.53, 131.92, 131.69, 131.30, 130.79, 129.19, 123.22.

MS (EI, 70 eV): *m*/*z* (%) = 303 (15) [$M^{+\cdot}$], 219 (45), 139 (90), 69 (100).

5-Chloro-2-hydroxy-3-phenyl-2,3-dihydro-1*H*-inden-1-one (2f)
Light yellow solid; yield: 613 mg (95%); mp 180–182 °C.

IR (KBr): 3449 (OH str), 2950 (arom C–H str), 1682 (C=O str), 1582 (arom C=C str), 1389, 1275, 1059, 854, 723 cm^{-1} (C–Cl str).

^1H NMR (500 MHz, $CDCl_3$): δ = 7.95 (d, *J* = 8.5 Hz, 1 H, H_{Ar}), 7.78 (d, *J* = 8.5 Hz, 2 H, H_{Ar}), 7.48 (m, 3 H, H_{Ar}), 7.21 (m, 2 H, H_{Ar}), 5.49 (d, *J* = 4.5 Hz, 1 H, H2), 5.23 (d, *J* = 4.0 Hz, 1 H, H3), 3.61 (br s, 1 H, D_2O exchangeable).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 195.86 (C=O), 63.53 (C2), 34.12 (C3), 137.55, 132.41, 132.32, 131.40, 130.92, 130.47, 127.95, 127.05, 126.87.

MS (EI, 70 eV): *m*/*z* (%) = 258 (35) [$M^{+\cdot}$], 139 (100).

5-Bromo-2-hydroxy-3-(4-tolyl)-2,3-dihydro-1*H*-inden-1-one (2g)

Light yellow solid; yield: 727 mg (92%); mp 181–183 °C.

IR (KBr): 3464 (OH str), 2917, 2849 (arom C–H str), 1685 (C=O str), 1586 (arom C=C str), 1279, 1071, 815, 757 cm^{-1} (C–Br str).

^1H NMR (500 MHz, $CDCl_3$): δ = 7.82 (m, 2 H, H_{Ar}), 7.67 (m, 3 H, H_{Ar}), 7.32 (d, *J* = 8.0 Hz, 1 H, H_{Ar}), 7.18 (d, *J* = 8.0 Hz, 1 H, H_{Ar}), 5.33 (d, *J* = 3.5 Hz, 1 H, H2), 5.18 (d, *J* = 3.5 Hz, 1 H, H3), 3.98 (br s, 1 H, D_2O exchangeable), 2.35 (s, 3 H, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 197.03 (C=O), 63.71 (C2), 29.57 (C3), 138.93, 134.85, 132.55, 132.49, 131.91, 131.69, 130.05, 129.56, 129.31, 127.84, 21.18.

MS (EI, 70 eV): *m*/*z* (%) = 316 (14) [$M^{+\cdot}$], 219 (59), 185 (100), 183 (82).

5-Bromo-3-(4-chlorophenyl)-2-hydroxy-2,3-dihydro-1*H*-inden-1-one (2h)

Light yellow solid; yield: 782 mg (93%); mp 205–207 °C.

IR (KBr): 3422 (OH str), 3087 (arom C–H str), 1678 (C=O str), 1583 (arom C=C str), 1404, 1278, 1169, 1091, 830, 752 cm^{-1} (C–Br str).

^1H NMR (500 MHz, $CDCl_3$): δ = 7.84 (d, *J* = 8.5 Hz, 1 H, H_{Ar}), 7.77 (d, *J* = 8.5 Hz, 1 H, H_{Ar}), 7.69 (m, 1 H, H_{Ar}), 7.49 (m, 2 H, H_{Ar}), 7.35 (d, *J* = 8.5 Hz, 1 H, H_{Ar}), 7.13 (d, 1 H, H_{Ar}), 5.34 (d, *J* = 4.0 Hz, 1 H, H2), 5.17 (d, *J* = 4.0 Hz, 1 H, H3), 3.62 (br s, 1 H, D_2O exchangeable).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 196.69 (C=O), 100.00 (C2), 31.95 (C3), 132.63, 132.57, 132.53, 131.91, 130.13, 129.99, 129.54, 129.41, 128.82.

MS (EI, 70 eV): *m*/*z* (%) = 336 (30) [$M^{+\cdot}$], 185 (79), 183 (100), 125 (49), 89 (36).

5-Bromo-3-(4-bromophenyl)-2-hydroxy-2,3-dihydro-1*H*-inden-1-one (2i)

Light yellow solid; yield: 903 mg (95%); mp 198–200 °C.

IR (KBr): 3441 (OH str), 2921, 2853 (arom C–H str), 1676 (C=O str), 1588 (arom C=C str), 1276, 1066, 820, 746 cm^{-1} (C–Br str).

^1H NMR (500 MHz, $CDCl_3$): δ = 7.94 (d, *J* = 8.5 Hz, 1 H, H_{Ar}), 7.83 (d, *J* = 8.5 Hz, 1 H, H_{Ar}), 7.76 (m, 1 H, H_{Ar}), 7.56 (m, 3 H, H_{Ar}), 7.14 (m, 1 H, H_{Ar}), 5.30 (d, *J* = 3.5 Hz, 1 H, H2), 5.15 (d, *J* = 3.5 Hz, 1 H, H3), 4.05 (br s, 1 H, D_2O exchangeable).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 192.58 (C=O), 60.94 (C2), 31.59 (C3), 134.31, 134.05, 132.75, 132.53, 131.92, 131.69, 131.30, 130.79, 129.10, 128.90.

MS (EI, 70 eV): *m*/*z* (%) = 380 (32) [$M^{+\cdot}$], 185 (75), 183 (100).

5-Bromo-2-hydroxy-3-(3,4,5-trimethoxyphenyl)-2,3-dihydro-1*H*-inden-1-one (2j)

Light yellow solid; yield: 814 mg (83%); mp 218–220 °C.

IR (KBr): 3413 (OH str), 2924 (arom C–H str), 1675 (C=O str), 1592 (arom C=C str), 1397, 1330, 1117 (C–O–C str), 823, 628 cm^{-1} (C–Br str).

^1H NMR (500 MHz, $CDCl_3$): δ = 7.80 (d, *J* = 8.5 Hz, 1 H, H_{Ar}), 7.65 (d, *J* = 8.5 Hz, 1 H, H_{Ar}), 7.58 (m, 1 H, H_{Ar}), 6.48 (s, 1 H, H_{Ar}), 6.34 (s, 1 H, H_{Ar}), 5.27 (d, *J* = 4.5 Hz, 1 H, H2), 5.15 (d, *J* = 4.0 Hz, 1 H, H3), 4.71 (br s, 1 H, D_2O exchangeable), 3.82 (s, 9 H, OMe).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 192.71 (C=O), 61.21 (C2), 30.87 (C3), 152.98, 134.11, 132.45, 131.67, 131.29, 129.78, 129.31, 128.83, 128.44, 107.13, 57.01 (OMe).

MS (EI, 70 eV): *m*/*z* (%) = 392 (26) [$M^{+\cdot}$], 181 (100).

5-Bromo-2-hydroxy-3-(3-nitrophenyl)-2,3-dihydro-1*H*-inden-1-one (2k)

Light yellow solid; yield: 798 mg (92%); mp 223–225 °C.

IR (KBr): 3355 (OH str), 3075, 2924 (arom C–H str), 1683 (C=O str), 1596 (arom C=C str), 1526 (N–O str), 1319 (N–O bending), 670 cm^{-1} (C–Br str).

^1H NMR (500 MHz, $CDCl_3$): δ = 8.19 (dd, *J* = 8.0, 2.0 Hz, 1 H, H_{Ar}), 7.95 (dd, *J* = 8.5, 2.0 Hz, 1 H, H_{Ar}), 7.71 (m, 4 H, H_{Ar}), 7.52 (d, *J* = 8.0 Hz, 1 H, H_{Ar}), 5.52 (d, *J* = 4.0 Hz, 1 H, H2), 5.28 (d, *J* = 4.0 Hz, 1 H, H3), 4.10 (br s, 1 H, D_2O exchangeable).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 192.54 (C=O), 95.2 (C2), 32.0 (C3), 132.74, 131.87, 131.64, 130.40, 130.14, 129.39, 123.18.

MS (EI, 70 eV): *m*/*z* (%) = 347 (10) [$M^{+\cdot}$], 185 (100), 183 (80), 157 (52), 155 (28).

5-Bromo-2-hydroxy-3-phenyl-2,3-dihydro-1*H*-inden-1-one (2l)

Light yellow solid; yield: 710 mg (94%); mp 192–194 °C.

IR (KBr): 3466 (OH str), 2920 (arom C–H str), 1678 (C=O str), 1593 (arom C=C str), 1398, 1281, 1095, 843, 713 cm^{-1} (C–Br str).

^1H NMR (500 MHz, $CDCl_3$): δ = 7.99 (dd, *J* = 8.5, 1.5 Hz, 1 H, H_{Ar}), 7.87 (dd, *J* = 8.5, 1.5 Hz, 2 H, H_{Ar}), 7.69 (m, 3 H, H_{Ar}), 7.54 (m, 2 H, H_{Ar}), 5.48 (d, *J* = 4.5 Hz, 1 H, H2), 5.15 (d, *J* = 4.5 Hz, 1 H, H3), 3.51 (br s, 1 H, D_2O exchangeable).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 196.95 (C=O), 63.45 (C2), 35.15 (C3), 137.95, 132.54, 132.45, 131.95, 131.45, 130.04, 128.96, 128.66, 127.94.

MS (EI, 70 eV): *m*/*z* (%) = 302 (18) [$M^{+\cdot}$], 185 (69), 183 (53), 91 (100).

2-Hydroxy-3-phenyl-2,3-dihydro-1*H*-inden-1-one (2m)

Light yellow solid; yield: 532 mg (95%); mp 178–180 °C.

IR (KBr): 3452 (OH str), 2963 (arom C–H str), 1686 (C=O str), 1599 (arom C=C str), 1451, 1419, 1262, 1021, 933, 868, 799, 704 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 4.10 (br s, 1 H, D_2O exchangeable), 5.21 (d, *J* = 3.0 Hz, 1 H, H3), 5.23 (d, *J* = 6 Hz, 1 H, H2), 7.19–7.80 (m, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 196.06, 136.48, 134.31, 131.80, 130.32, 129.92, 123.81, 120.82, 117.37, 116.22, 115.98, 75.81, 64.29.

MS (EI, 70 eV): *m*/*z* (%) = 224 (35) [$M^{+\cdot}$], 207 (25), 195 (29), 178 (37), 165 (40), 152 (33), 121 (64), 105 (100), 91 (62), 77 (74), 51 (69).

3-(4-Chlorophenyl)-2-hydroxy-2,3-dihydro-1*H*-inden-1-one (2n)

Light yellow solid; yield: 613 mg (95%); mp 188–190 °C.

IR (KBr): 3408 (OH str), 2917 (arom C–H str), 1689 (C=O str), 1589 (arom C=C str), 1489, 1415, 1288, 1177, 1091, 1014, 929, 701 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.19–781 (m, 8 H, H_{Ar}), 4.12 (br s, 1 H, D_2O exchangeable), 5.17 (d, *J* = 3.0 Hz, 1 H, H3), 5.47 (d, *J* = 3.0 Hz, 1 H, H2).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 197.89, 160.11, 147.09, 135.75, 134.79, 133.88, 132.30, 131.60, 130.25, 129.07, 128.83, 128.53, 118.19, 76.54, 59.89.

MS (EI, 70 eV): *m*/*z* (%) = 258 (17) [$M^{+\cdot}$], 242 (28), 207 (36), 179 (43), 165 (32), 135 (57), 130 (61), 105 (100), 89 (49), 77 (61), 75 (55), 51 (62).

2-Hydroxy-3-(3-nitrophenyl)-2,3-dihydro-1*H*-inden-1-one (2o)
Light yellow solid; yield: 633 mg (94%); mp 196–198 °C.

IR (KBr): 3369 (OH str), 2923 (arom C–H str), 1680 (C=O str), 1613 (arom C=C str), 1528 (N–O str), 1393, 1348 (N–O bending), 1259, 1094, 986, 911, 840, 728, 687 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 3.96 (br s, D_2O exchangeable), 5.34 (d, *J* = 3.5 Hz, 1 H, H3), 5.55 (d, *J* = 3.0 Hz, 1 H, H2), 7.49–8.12 (m, 8 H, H_{Ar}).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 197.92, 161.68, 148.39, 136.25, 135.77, 135.00, 132.69, 130.39, 129.69, 128.96, 128.63, 124.90, 122.90, 122.50, 116.01, 75.12, 58.86.

MS (EI, 70 eV): *m*/*z* (%) = 269 (13) [$M^{+\cdot}$], 241 (21), 196 (61), 176 (32), 165 (48), 136 (43), 105 (100), 89 (64), 77 (44), 63 (39), 51 (60).

3-(4-Bromophenyl)-2-hydroxy-2,3-dihydro-1*H*-inden-1-one (2p)
Light yellow solid; yield: 695 mg (92%); mp 183–185 °C.

IR (KBr): 3434 (OH str), 2924 (arom C–H str), 1670 (C=O str), 1588 (arom C=C str), 1485, 1413, 1288, 1177, 1071, 930, 703, 545 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.11–7.80 (m, 8 H, H_{Ar}), 4.11 (br s, D_2O exchangeable), 5.19 (d, *J* = 3.0 Hz, 1 H, H3), 5.47 (d, *J* = 3.0 Hz, 1 H, H2).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 198.11, 159.87, 136.28, 133.86, 131.92, 130.24, 129.28, 128.52, 126.67, 125.81, 124.81, 123.14, 76.56, 60.12.

MS (EI, 70 eV): *m*/*z* (%) = 302 (16) [$M^{+\cdot}$], 196 (55), 169 (45), 139 (73), 105 (100), 89 (47), 77 (54), 63 (49), 51 (66).

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