

An improved synthesis of substituted indan-1-carboxylic acid

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Substituted indan-1-carboxylic acid compounds have been prepared by cyclisation of the phenyl succinic acid and reduction of the indanon-1-carboxylic acid with triethylsilane in trifluoroacetic acid.

Keyword: indan-1-carboxylic acid, anti-inflammatory, analgesic, triethylsilane

Compounds containing indan or 2,3-dihydro-1H-inden-1-one ring systems have been studied recently in the context of the synthesis of compounds with anti-inflammatory and analgesic properties. Juby *et al.*¹ had reported that a series of indan-1-carboxylic acid derivatives, especially the compound TAI-284 (Brand name, Clidanac), exhibited potent anti-inflammatory, analgesic and antipyretic activity. It was introduced as an anti-inflammatory and analgesic drug in 1981. Das² observed that the writhing of Swiss albino mice induced by acetic acid was significantly reduced by 6-fluoro-3-oxoindan-1-carboxylic acid and 6-fluoroindan-1-carboxylic acid, in a dose dependent manner. In addition, halogen substituted 5-(indan-1'-yl)-tetrazoles prepared from substituted indan-1-carboxylic acid by Bachar³ were also found to possess analgesic activity. The preparation of substituted indan-1-carboxylic acids has become increasingly important and we wished to develop a convenient synthetic route to indan derivatives.

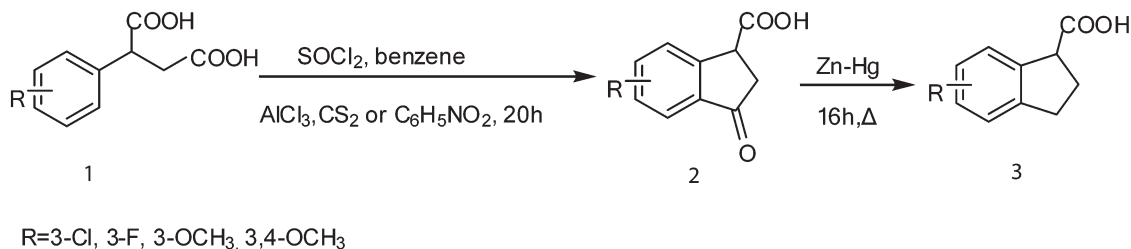
The synthesis of substituted indan-1-carboxylic acids reported by several workers^{2,4-6} was mainly focused on a procedure starting from substituted phenylsuccinic acids (Scheme 1). This route had several weak points involving time-consuming procedures and inconvenient operations. Moreover, some

toxic and environment-unfriendly reagents such as benzene, nitrobenzene and zinc amalgam were employed in this route.

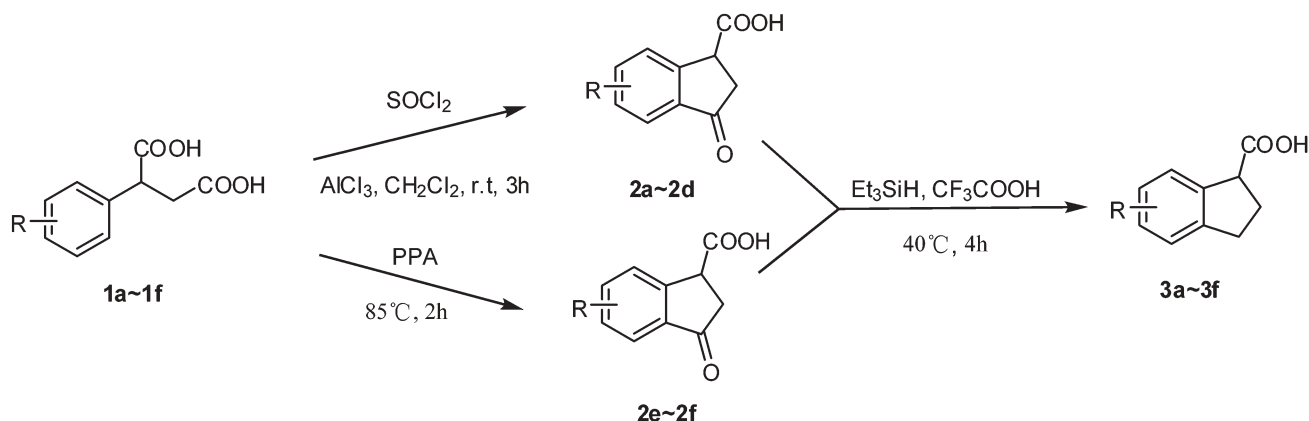
Therefore, we report an alternative synthesis of substituted indan-1-carboxylic acid in which the target compounds were obtained more efficiently in high yield and good quality (Scheme 2).

Results and discussions

According to the literature², substituted 3-oxoindan-1-carboxylic acid (**2**) was prepared from substituted phenylsuccinic acid (**1**) by reaction with thionyl chloride in benzene to form an acylchloride intermediate, which was then cyclised with AlCl_3 catalysis in nitrobenzene or carbon disulfide at ambient temperature. Twenty hours were necessary to complete the cyclisation reaction. Obviously, the above method was time-consuming and environment-harmful. In fact, (**1**) can be converted into an acylchloride intermediate using thionyl chloride both as a chlorinating agent and as a solvent. Furthermore, we found that methylene dichloride was a better solvent than nitrobenzene or CS_2 in the cyclisation reaction, not only because it was a low-toxicity solvent, but also the reaction time could be reduced to 3h after modification. It was also observed



Scheme 1 Synthesis of substituted indan-1-carboxylic acid from the appropriate phenylsuccinic acid.



Scheme 2 An improved and convenient synthesis of substituted indan-1-carboxylic acids.

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that when the substituent on the benzene ring was an electron-donating group such as 3-OCH₃, 3,4-OCH₃, polyphosphoric acid (PPA) was the preferred cyclising agent compared to SOCl₂/AlCl₃, and a high yield (>70%) was obtainable.

Substituted 3-oxo-indan-1-carboxylic acid (**2**) have been converted to the corresponding indan-1-carboxylic acid (**3**) by Clemmensen reaction employing zinc amalgam, a hazardous reagent, as the reducing reagent^{2,6,7}. Olah⁸ had reported trifluoromethanesulfonic acid/triethylsilane as a hydrogenation reagent for the reduction of diaryl and alkyl, aryl ketones to hydrocarbons. Based on this report, we used Et₃SiH-CF₃COOH instead of zinc amalgam as the reducing agent in the reduction of 3-oxo-indan-1-carboxylic acid derivatives, and a satisfactory yield was readily achieved.

In addition, the HMBC (¹H-detected heteronuclear multiple-bond correlation) of **2b** have indicated that H-4 (δ: 7.66–7.69) was coupled with C-3 (carbonyl carbon δ: 202.7), which means the cyclisation of 3-chlorophenylsuccinic acid **1b** was occurred at the C-4 position in benzene, not the C-2 position to afford 6-chloro-3-oxo-indan-1-carboxylic acid.

In conclusion, we have described a convenient method for the synthesis of the indan derivatives **3a–f**, which has the advantages of simplicity, mild reaction conditions, and avoids the use of toxic reagents such as nitrobenzene and amalgamated zinc. This route would be more acceptable in industry.

It should be noted that the target compounds **3c–f** have not been reported before. In addition, we found that the melting points of **2a** and **3a** were not in accord with that reported by literature,² so their IR, MS, ¹H NMR and HRMS data were recorded in detail.

Experimental

Chemicals and solvents were either purchased or purified by standard techniques and used without any further purification. Substituted phenylsuccinic acids (**1a–f**) were prepared from corresponding phenylamine according to the literature method⁹. Melting points were recorded on a RY-1 melting point apparatus and were uncorrected. The IR spectra (in KBr pellets) were recorded on a Nicolet Impact 410 spectrometer. MS spectra were acquired on a Agilent 1100 series LC/MSD Trap(SL). The NMR spectra were recorded on a BRUKER AV-300 NMR spectrometer using TMS as the internal standard. The HRMS spectra were acquired on a Waters Micros Q-TOF apparatus.

Synthetic procedure for **2a–f**, exemplified by 6-fluoro-3-oxo-indan-1-carboxylic acid (**2a**)

1a (5g, 0.023 mol) and thionyl chloride (20 mL) were refluxed together for 30 min, then the excess of thionyl chloride was removed under vacuum. After the mixture was cooled, a suspension of the anhydrous aluminium chloride (15.81 g, 0.11 mol) in 50 mL CH₂Cl₂ was added into the solution. Stirring was continued for 3 h at ambient temperature. When the reaction was complete, the mixture was poured onto ice-water, and extracted with EtOAc (3 × 60 mL). Then the combined extracts were treated with saturated aqueous Na₂CO₃ (3 × 60 mL), the combined aqueous layers were acidified by conc. HCl to pH = 1–2 and extracted with EtOAc (3 × 60 mL), which were washed successively with water and brine, dried over anhydrous Na₂SO₄, filtered and evaporated to dryness. The residue was recrystallised from petroleum–EtOAc to afford pure **2a** as a white powder. (2.82g, yield 50%), m.p. 96–98 °C. lit.² m.p. 162–164 °C; IR (KBr cm⁻¹): 3475 (OH), 2929, 2703, 1723, 1694 (C=O), 1610, 1590, 1483, 1435, 1213 (C-F), 945, 885, 843. ¹H NMR(300MHz, CDCl₃), δ (ppm): 2.82–2.93 (1H, dd, *J* = 3.5 Hz, 19.1 Hz, H₃), 3.07–3.15 (1H, dd, *J* = 8.1 Hz, 19.2 Hz, H₂), 4.23–4.26 (1H, m, H₁), 7.02–7.12 (1H, m, ArH₅), 7.36–7.39 (1H, m, ArH₄), 7.69–7.74 (1H, m, ArH₇), 9.82 (1H, bs, COOH). MS (ESI (-)70V, *m/z*): 192.8 [(M-H)]⁻. HRMS Calcd for C₁₀H₆O₃F (M-H) 193.0301. Found 193.0305.

6-Chloro-3-oxo-indan-1-carboxylic acid (2b): White powder, yield 59%, m.p. 146–148 °C. (lit.⁷ 148–151 °C); ¹H NMR(300 MHz, DMSO-d₆), δ (ppm): 2.88–2.90 (2H, m, H₂), 4.31–4.34 (1H, m, H₁), 7.54–7.57 (1H, d, *J* = 8.1 Hz, ArH₅), 7.64–7.67 (1H, d, *J* = 8.1 Hz, ArH₄), 7.76(1H, s, ArH₇), 13.06(1H, bs, COOH). MS (ESI(-)70V, *m/z*): 208.7 [(M-H)]⁻.

5-Methyl-3-oxo-indan-1-carboxylic acid (2c): Yellow powder, yield 54%, m.p. 134–136 °C; IR (KBr⁻¹): 3441, 2966, 1729(C=O), 1491, 1404, 1202, 885, 864, 833. ¹H NMR (300 MHz, CDCl₃), δ (ppm): 2.42 (3H, s, CH₃), 2.85–2.94 (1H, m, H₂), 3.10–3.17 (1H, m, H₁), 4.28–4.30 (1H, t, *J* = 2.4 Hz, H₁), 7.46–7.48 (1H, d, *J* = 7.8 Hz, ArH₆), 7.57 (1H, s, ArH₄), 7.62–7.65 (1H, d, *J* = 7.8 Hz, ArH₇), 11.26 (1H, bs, COOH).

5,6-Dichloro-3-oxo-indan-1-carboxylic acid (2d): Off-white powder, yield 48%, m.p. 202–204 °C; IR (KBr⁻¹): 3232, 1743 (C=O), 1718, 1591, 1377, 1168, 884, 846, 824. ¹H NMR (300 MHz, CDCl₃), δ (ppm): 2.94–3.08 (2H, m, H₂), 4.30–4.39 (1H, t, *J* = 7.0 Hz, H₁), 7.80–7.87 (1H, s, ArH₇), 7.92–7.99 (1H, s, ArH₄). MS(ESI(-)70V, *m/z*): 242.8 [(M-H)]⁻.

Synthetic procedure for **2e–2f**, exemplified by 6-methoxy-3-oxo-indan-1-carboxylic acid (**2e**)

A suspension of 3-methoxyphenylsuccinic acid (**1e**) (2 g, 0.0089 mol) in 30 g PPA was heated at 85 °C (bath temperature) for 2 h. Then crushed ice was added into the mixture. The aqueous layer was extracted with EtOAc (3 × 50 mL). The combined extracts were then treated with saturated aqueous Na₂CO₃, the separated aqueous layer was acidified by conc. HCl to pH = 1–2 and extracted with EtOAc (3 × 60 mL), which were washed successively with water, and brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residual was recrystallised from ethanol-water to afford **2e** as an off-white powder (1.36 g, yield 75%), m.p. 185–187 °C, lit.⁵ 186–186.5 °C.

5,6-dimethoxy-3-oxo-indan-1-carboxylic acid (2f). Off-white powder, yield 70%, m.p. 188–191 °C, lit.⁶ 190–191 °C.

Synthetic procedure for **3a–f**, exemplified by 6-fluoroindan-1-carboxylic acid (**3a**)

Et₃SiH (6.4 mL, 0.4 mol) was added to a solution of **2a** (0.97 g, 0.05 mol) in anhyd. CF₃COOH (15 mL) at 40 °C and stirred for 4 h. The solution was concentrated and the pH was adjusted to 11–13 by 2M NaOH. After another 15 min stirring at ambient temperature, the mixture was then acidified to pH 2–3 by addition of conc. HCl. The precipitated solid was collected by filtration and washed with water to give crude product which was recrystallised from petroleum ether–EtOAc to yield **3a**, as a colourless needles (0.69 g, yield 76%), m.p. 82–84 °C. (lit.² 128–130 °C); IR (KBr⁻¹): 2986, 2947, 1705 (C=O), 1596, 1487, 1446, 1417, 1217 (C-F), 921, 860, 818. ¹H NMR (300 MHz, CDCl₃), δ (ppm): 2.35–2.56 (2H, m, H₃), 2.85–2.95, 3.02–3.12 (2H, m, H₂), 4.06–4.11 (1H, t, *J* = 7.2 Hz, H₁), 6.91–6.97 (1H, m, ArH₇), 7.14–7.27 (2H, m, ArH_{4,5}), 11.74 (1H, bs, COOH). MS(ESI (-)70V, *m/z*): 178.9 [(M-H)]⁻. HRMS Calcd for C₁₀H₈O₂F (M-H) 179.0508. Found 179.0513.

6-Chloroindan-1-carboxylic acid (3b): Colourless needles (from petroleum ether–EtOAc), yield 72%, m.p. 126–128 °C; (lit.⁷ 128–130 °C). IR (KBr⁻¹): 3419, 2961, 2917, 1716 (C=O), 1507, 1437, 1247 (C-F), 930, 817. ¹H NMR (300 MHz, CDCl₃), δ (ppm): 2.32–2.52 (2H, m, H₃), 2.83–3.09, 3.11–3.18(2H, m, H₂), 4.04–4.09 (1H, t, *J* = 7.5 Hz, H₁), 7.14–7.21 (2H, m, ArH_{4,5}), 7.42 (1H, s, ArH₇). MS(ESI(-)70V, *m/z*): 194.9 [(M-H)]⁻.

5-Methylindan-1-carboxylic acid (3c): Colourless needles (from petroleum ether–EtOAc), yield 54%, m.p. 74–76 °C; IR (KBr⁻¹): 3415, 2947, 1703 (C=O), 1596, 1486, 1414, 1228, 920, 830, 807. ¹H NMR (300 MHz, CDCl₃), δ (ppm): 2.32 (3H, s, CH₃), 2.29–2.43 (2H, m, H₃), 2.82–2.89, 2.92–3.11 (2H, m, H₂), 3.99–4.04 (1H, t, *J* = 7.5 Hz, H₁), 6.99–7.01 (1H, d, *J* = 7.5 Hz, ArH₇), 7.06 (1H, s, ArH₄), 7.27–7.30 (1H, d, *J* = 7.5 Hz, ArH₆). MS(ESI(-)70V, *m/z*): 174.9 [(M-H)]⁻. HRMS Calcd for C₁₀H₁₁O₂ (M-H) 175.0759. Found 175.0763.

5,6-Dichloroindan-1-carboxylic acid (3d): White powder (from petroleum ether–EtOAc), yield 64%, m.p. 145–147 °C; IR (KBr⁻¹): 3420, 2929, 1743 (C=O), 1718, 1591, 1168, 884, 846, 824. ¹H NMR (300 MHz, DMSO-d₆), δ (ppm): 2.22–2.34 (2H, m, H₃), 2.79–3.00 (2H, m, H₂), 4.00–4.05 (1H, t, *J* = 7.3 Hz, H₁), 7.53 (2H, s, ArH₇, ArH₄). MS(ESI(-)70V, *m/z*): 228.9 [(M-H)]⁻. HRMS Calcd for C₁₀H₇O₂Cl₂ (M-H) 228.9823. Found 228.9829.

6-Methoxyindan-1-carboxylic acid (3e): Colourless crystalline solid (from petroleum ether–EtOAc), yield 70%, m.p. 104–106 °C; IR (KBr⁻¹): 3414, 2947, 1706 (C=O), 1608, 1497, 1446, 1416, 1229, 915, 820. ¹H NMR (300 MHz, CDCl₃), δ (ppm): 2.30–2.50 (2H, m, H₃), 2.79–2.89, 2.98–3.08 (2H, m, H₂), 3.78 (3H, s, OCH₃), 4.01–4.05 (1H, t, *J* = 6.7 Hz, H₁), 6.76–6.79 (1H, dd, *J* = 2.3 Hz, 8.1 Hz, ArH₃), 6.96–6.97 (1H, d, *J* = 1.8 Hz, ArH₇), 7.11–7.14 (1H, d, *J* = 8.2 Hz, ArH₄). 10.95 (1H, bs, COOH). MS(ESI(-)70V, *m/z*): 190.9 [(M-H)]⁻. HRMS Calcd for C₁₁H₁₁O₃ (M-H) 191.0708. Found 191.0712.

5,6-Dimethoxyindan-1-carboxylic acid (3f). Colourless needles (from petroleum ether–EtOAc), yield 61%, m.p. 98–100°C; ¹H NMR (300 MHz, DMSO-*d*₆), δ (ppm): 2.20–2.25 (2H, m, H₃), 2.72–2.82, 2.86–2.96 (2H, m, H₂), 3.70–3.71 (6H, s, OCH₃), 3.87–3.94 (1H, t, *J* = 11.6 Hz, H₁), 6.85 (1H, s, ArH₄), 6.88 (1H, s, ArH₇). MS(ESI (-)70V, *m/z*): 220.9 [M-H]⁻. HRMS Calcd for C₁₂H₁₃O₄ (M-H) 221.0814. Found 221.0819.

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