Selective Bromination of 4-Chloro-1-indanone and Synthesis of (4-Chloro-2, 3-Dihydro-1H-indene-2-yl)methanamine

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ABSTRACT
The synthesis of 4-chloro-1-indanone in four steps from 2-chlorobenzaldehyde was investigated. Bromination of this compound under various conditions occurred in the cyclopentanone ring, producing mono- and dibromo derivatives. Cyanation of 2-bromo-4-chloro-1-indanone followed by reduction gave (4-chloro-2, 3-dihydro-1H-indene-2-yl)methanamine in quantitative yield.

KEYWORDS
Indanone, bromination, cyanation, reduction, GABA_B receptors.

1. Introduction
The preparation of 4-chloro-1-indanone (5) as starting material for the synthesis of some potential anti-Parkinson’s disease drugs is of interest to the pharmaceutical industry, and has been prepared by a number of workers by the cyclization of 3-(2-chlorophenyl)propionic acid.1-6

Selective bromination of this compound on the cyclopentanone ring would give useful intermediates in C-C bond formation via metal-catalysed cross coupling reactions for the synthesis of pharmaceuticals and agrochemicals.7,8 A variety of bromination protocols have been developed and reported for the bromination of aromatic systems.9-19 Herein we report the synthesis and selective α-bromination of 4-chloro-1-indanone. We propose to use this molecule, and other indanones, as intermediates to synthesize potential binders for GABA_B receptors. GABA_B receptors are of considerable significance, being involved in a number of important physiological processes, such as autonomic function, memory and cognition, as well as motor and sensory control.20,21

In previous work,22,23 we outlined the working hypothesis (Fig. 1) for the structural requirements of possible GABA_B receptor modulators. The conformation mobility of the arylpropylamine moiety spacer group could be restrained if it were part of an indanylethylene group, as in structure 9. Hence, the synthesis of intermediate compounds of type 9 was an important requirement for further study.

2. Results and Discussion
3-(2-Chlorophenyl)propanoic acid (3) was cyclized to 4-chloro-1-indanone (5) by refluxing the corresponding acid chloride (4) in the presence of aluminum chloride in dichloromethane (Scheme 1).

This compound was then brominated in a number of solvents, with and without acid or base catalysts. The results are shown in Table 1. When compound 5 was reacted with Br2 in CH2Cl2 or CHCl3 at room temperature, 2,2-dibromo-4-chloro-1-indanone (6) was obtained as the major product in 40 % yield, along with recovered starting material. In the 1HNMR spectrum of 6 the two C3 proton signals were identified as a singlet at δ 4.26 ppm. The mass spectrum showed the required molecular ions for a dibrominated product. The reaction of 5 and Br2/K2CO3 in CH2Cl2 at room temperature for 1 h gave a mixture of compounds 6 and 7 in the ratio of 1:5, but at 0 °C only 7 was obtained in 45 % yield (Scheme 2).

Selective monobromination was quite difficult to control. Thus bromination in CHCl3 at 0 °C gave low yields of monobrominated product, but under the same conditions (1 eq Br2) at 25 °C only the 2,2-dibrominated indanone could be isolated. Relatively polar conditions were necessary to achieve high yields of monobrominated material in acetic acid at 25 °C. The presence of base (solid KOH or K2CO3) encouraged the formation of dibrominated product, presumably because the monobromocompound 7 was more readily enolized than the indanone (5).

2-Cyano-4-chloro-1-indanone (8) was synthesized from 7 by...
reaction with sodium cyanide. The optimal procedure was to react 7 with sodium cyanide in EtOH/H$_2$O. The FT-IR spectrum of this compound showed the peak for the CN group at 2213 cm$^{-1}$. The structure of 8 was confirmed by $^1$HNMR and $^{13}$CNMR spectroscopy. Hydrogenation with H$_2$/Pd-C in MeOH/HCl and neutralization with ammoniacal chloroform gave (4-chloro-2,3-dihydro-1H-indene-2-yl)methanamine (9) in 75 % yield (Scheme 3). The FT-IR spectrum of this product showed the NH$_2$ group at 3412 cm$^{-1}$ and lacked any signals attributable to carbonyl and nitrile groups. To what extent this compound, and similar analogues, are useful for the synthesis of compounds that mimic or antagonize the effects of baclofen (10) and fendiline (11) awaits further study.

Table 1 Bromination of 4-chloro1-indanone $^a$ (1 eq) (5).

<table>
<thead>
<tr>
<th>Reaction conditions</th>
<th>Major product</th>
<th>yield/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Br$_2$ (1 eq) / CCl$_4$ / rt / 2 h$^a$</td>
<td>6</td>
<td>40</td>
</tr>
<tr>
<td>Br$_2$ (1 eq) / CCl$_4$ / ice bath / 2 h$^a$</td>
<td>7</td>
<td>25</td>
</tr>
<tr>
<td>Br$_2$ (1 eq) / diethyl ether$^{14,15}$</td>
<td>7</td>
<td>90</td>
</tr>
<tr>
<td>Br$_2$ (1 eq) / AlCl$_3$ / CCl$_4$ / ice bath / 2 h$^a$</td>
<td>No reaction –</td>
<td>–</td>
</tr>
<tr>
<td>H$_2$O$_2$ (2 eq) / H$_2$O (1.3 mL) / HBr (48 % aqueous, 1 eq) / dark / rt / 24 h$^{10,11}$</td>
<td>7</td>
<td>42</td>
</tr>
<tr>
<td>NBS (1 eq) / H$_2$O (26 mL) / H$_2$SO$_4$ (40 % aqueous solution, 1 eq) / 60°C / 5 h$^{12}$</td>
<td>No reaction –</td>
<td>–</td>
</tr>
<tr>
<td>NBS (1 eq) / PTSA (0.1 eq) / 60°C / 10 min$^{13}$</td>
<td>No reaction –</td>
<td>–</td>
</tr>
<tr>
<td>NBS (1eq) / H$_2$O (1.3 mL) / 100W / 15 h$^a$</td>
<td>7</td>
<td>73</td>
</tr>
<tr>
<td>Br$_2$ (1 eq) / AcOH / rt / 2 h$^a$</td>
<td>Di:Mono (1:5)</td>
<td>60</td>
</tr>
<tr>
<td>Br$_2$ (2 eq) / K$_2$CO$_3$ (3 eq) / CH$_2$Cl$_2$ / rt / 1 h$^a$</td>
<td>7</td>
<td>45</td>
</tr>
<tr>
<td>Br$_2$ (2 eq) / K$_2$CO$_3$ (3 eq) / CH$_2$Cl$_2$ / ice bath / 1 h$^a$</td>
<td>No reaction –</td>
<td>–</td>
</tr>
<tr>
<td>Br$_2$ (2 eq) / KOH (3 eq) / CH$_2$Cl$_2$ / ice bath / 1 h$^a$</td>
<td>Several products –</td>
<td>–</td>
</tr>
<tr>
<td>Br$_2$ (2 eq) / KOH (3 eq) / CH$_2$Cl$_2$ / rt / 1 h$^a$</td>
<td>Several products –</td>
<td>–</td>
</tr>
</tbody>
</table>

$^a$ Yields refer to isolated products. The recovered starting materials and by-products are not listed.
3. Experimental

**General:** $^1$H NMR (300 MHz) and $^{13}$C NMR (75 MHz) spectra were recorded in CDCl$_3$, on a Bruker spectrometer. Chemical shifts (δ) are in parts per million (ppm) relative to tetramethylsilane, and coupling constants (J) are given in Hz. Infrared spectra were recorded on a Bruker FT-IR spectrometer using KBr disks. Mass spectra were recorded on an Agilent 6890-network-GC system. Melting points were determined on a Philips Harris C4954718 apparatus. Analytical thin-layer-chromatography (TLC) was carried out with Merck silica gel 60 F$_{254}$ aluminum sheets. Hydrogenation was carried out with stirring under hydrogen gas. The routine purification of aldehydes was achieved by recrystallization from n-hexane. All organic extracts were dried with anhydrous sodium sulphate. Recrystallization from water to give compound 3 was carried out using Merck silica gel 60 F$_{254}$ aluminum sheets. Hydrogenation was carried out with stirring under hydrogen gas. The routine purification of aldehydes was achieved by recrystallization from n-hexane.

3.1. Preparation of 4-Chloroindane-1-one

3.1.1. (E)-3-(2-Chlorophenyl) acrylic acid (2). 2-Chlorobenzaldehyde (28.10 g, 200.0 mmol), acetic anhydride (30.00 g, 294.0 mmol) and freshly fused finely powdered potassium acetate (12.00 g, 122.0 mmol) were heated in an oil bath at 160 °C for one hour and at 180 °C for a further 3 hours. While still hot, the mixture was poured into water (100 mL), and saturated aqueous sodium carbonate was added until the mixture was alkaline. The mixture was poured into water (100 mL), and saturated aqueous sodium carbonate was added until the mixture was alkaline. The solution was steam distilled to remove excess reagent, cooled and filtered. The filtrate was acidified with concentrated hydrochloric acid, cooled, and the 2-chloroacryloyl chloride (3.20 g, 21.0 mmol) was dissolved in anhydrous dichloromethane (35 mL) and refluxed for 8 hours. After cooling, the aluminium chloride complex was decomposed with crushed ice (10 g) and concentrated hydrochloric acid (2.5 mL). The mixture was extracted with dichloromethane, which was washed with 10 % sodium hydroxide (2 mL) and water (3 mL) and dried over anhydrous sodium sulphate. Removal of the solvent gave the desired product as pale yellow crystals (3.34 g, 93 %), m.p. 90–92 °C.

3.2. Bromination of 4-Chloroindane (5)

3.2.1. With bromine/CCl$_4$ at room temperature. Bromine (1.3 mL, 2.6 mmol) was added to a solution of 5 (0.43 g, 2.6 mmol) in CCl$_4$ (35 mL) at room temperature with the exclusion of light. After 2 hours, excess bromine and CCl$_4$ were removed, the residue was neutralized with 10 % NaOH and extracted with dichloromethane. The extract was then dried over anhydrous Na$_2$SO$_4$, filtered and concentrated. The residue was purified by recrystallization from n-hexane to give 2,2-dibromo-4-chloro-indanone (6) as pale yellow crystals (0.34 g, 40 %), m.p. 73–74 °C.

3.2.2. With Bromine/CCl$_4$ at 0 °C. The mixture was then hydrogenated at room temperature. After 15 hours, excess bromine and CCl$_4$ were removed, the residue was purified by recrystallization from n-hexane to give 2,2-dibromo-4-chloro-indanone (6) as pale yellow crystals (0.34 g, 40 %), m.p. 73–74 °C.
Increasing the reaction time to six hours gave a mixture of dibromo and monobromo indanones in a 3:1 ratios, respectively, with no sign of any starting material left.

3.2.3. With bromine/CHCl₃ at room temperature. The above procedure with CHCl₃ as solvent, at room temperature, gave 6 in 40 % yield (0.34 g). When this method was carried out with a 2:1 molar ratio of Br₂/5, the yield was increased to 0.57 g (68 %).

3.2.4. With bromine/CHCl₃ at 0 °C. Essentially unreacted starting materials were recovered under the conditions of 2.3 at 0 °C.

3.2.5. With bromine/diethyl ether. To a solution of 4-chloro-1-indanone (0.43 g, 2.6 mmol) in CCl₄ (35 mL) and acetic acid (40 mL). The 5 (1.43 mL, 2.86 mmol) was added dropwise to a solution of

3.2.6. With an aqueous H₂O₂-HBr system. Residue from light petroleum or benzene gave bicarbonate, and then evaporated. Recrystallization of the had formed, was completely dissolved. After pouring into ice temperature until the yellow, insoluble addition complex which before more was added. The mixture was then swirled at room temperature for a 1-minute period, allowing each drop of bromine to decolourize and the solution, which decolourized rapidly, was then cooled to 10 °C. The remaining bromine was added slowly over a ten-minute period, allowing each drop of bromine to decolourize before more was added. The mixture was then swirled at room temperature until the yellow, insoluble addition complex which had formed, was completely dissolved. After pouring into ice water, the ether layer was washed with water and dilute sodium bicarbonate, and then evaporated. Recrystallization of the residue from light petroleum or benzene gave 7 (2.60 g, 90 %).

3.2.7. With Bromine/AcOH at room temperature. Bromine (1.43 mL, 2.86 mmol) was added dropwise to a solution of 5 (0.43 g, 2.6 mmol) in CCl₄ (35 mL) and acetic acid (40 mL). The solution was stirred for 2 hours at room temperature, then poured into water and treated with 5 % sodium bisulphite solution. The product was filtered, washed with water and recrystallized from methanol to give 7 (0.464 g, 73 %).

3.2.8. With Bromine/K₂CO₃ at room temperature. Bromine (1.52 mL, 10 mmol) was added, with the exclusion of light, to mixture of 5 (0.99 g, 0.5 mmol) and K₂CO₃ (0.21 g, 1.6 mmol) in CH₂Cl₂ (20 mL) at room temperature. After 1 h the reaction was quenched with 1 M Na₂S₂O₇ and extracted with CH₂Cl₂ dried over anhydrous Na₂SO₄, and evaporated to give a mixture of mono- and dibromo products in the ratio of 5:1 (60 %).

3.2.9. With Bromine/K₂CO₃ at 0 °C. The procedure described in section 2.8 was followed, but with cooling in an ice-bath to give 7 (0.06 g, 45 %).

3.2.10. With Bromine/KOH at room temperature. The procedure described in section 2.8 was followed with KOH as base, but yielded a mixture of products, which was not further characterized.

3.3. Cyanation of 2-Bromo-4-chloro-1-indanone (7) A solution of 2-bromo-4-chloro-1-indanone (7) (2.40 g, 10.0 mmol) and sodium cyanide (4.9 g, 100.0 mmol) in ethanol (70 mL) and water (5 mL) was refluxed for 25 minutes. After cooling, the solution was diluted with water, extracted twice with ether, and the chilled aqueous phase acidified with cold HCl. The oily cyanoketone was extracted with chloroform, and the solution clarified with Norite and then extracted with small portions of 5 % KOH until a test portion no longer gave a precipitate on acidification. Acidification of the combined cold aqueous layers gave 2-cyano-4-chloro-1-indanone (8) as a white powder (1.36 g, 71 %), m.p. 112–114 °C. 1H NMR (CDCl₃) δ (ppm): 3.44 (dd, J₁ = 11.4 Hz, J₂ = 4.8 Hz, 1 H), 3.66 (dd, J₁ = 11.4 Hz, J₂ = 8.7 Hz, 1 H), 3.77 (dd, J₁ = 8.7 Hz, J₂ = 4.8 Hz, 1 H), 7.47 (dd, J₁ = 7.8 Hz, J₂ = 7.5 Hz, 1 H, ArH), 7.71 (d, J = 7.5 Hz, 1 H, ArH), 7.83 (d, J = 7.8 Hz, 1 H, ArH); 13CNMR (CDCl₃): δ (ppm) 30.23, 36.86, 116.21, 123.48, 130.25, 132.90, 135.83, 135.96, 149.07, 193.88; FT-IR(KBr) νmax (cm⁻¹) 3121, 2123, 1617, 1593, 1294, 788, 716 and m/z 193(M⁺+2), 191(M⁺), 164, 128, 119(100), 91, 43.

3.4. Hydrogenation of Indanone (8) A mixture of 8 (0.73 g, 3.8 mmol), methanol (38 mL), concentrated HCl (0.60 mL), and 10 % palladium on carbon (0.50 g) was stirred under an atmosphere of hydrogen at 25 °C and atmospheric pressure for 20 h. The mixture was filtered through Celite, and the solvent removed to give 0.85 g (96 %) of the hydrochloride salt of 9. This was suspended in chloroform, cooled to 0 °C, and treated with excess 1 % ammoniacal chloroform. The precipitated ammonium chloride was removed by filtration and the solvent removed to give 4-(chloro-2,3-dihydro-1H-indene-2-yl)methanamine (9) as a white powder (0.59 g, 86 %), m.p. 98–100 °C. 1H NMR (CDCl₃): δ (ppm) 1.31 (bs, 2 H, NH₂), 2.63 (dd, J₁ = 1.3 Hz, J₂ = 6.9 Hz, 2 H, C-1), 2.81 (d, J = 6.9 Hz, 2 H, CH₂-NH), 3.00 (dd, J₁ = 15.6 Hz, J₂ = 7.5 Hz, 2 H, C-3), 7.27–7.09 (m, 3 H, ArH); 13CNMR (CDCl₃): δ (ppm) 36.80, 40.81, 45.13, 46.55, 124.85, 125.15, 126.45, 143.02, 143.27, 158.23; FT-IR(KBr) νmax (cm⁻¹) 3393, 2925, 1577, 1288, 744 and m/z 183(M⁺+2), 181(M⁺), 164, 129(100), 115, 91, 44.

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*This solution was the lower phase obtained by shaking conc. NH₄OH (100 mL) and chloroform (900 mL).