S. Afr. J. Chem., 2010, **63**, 83–87,
<http://journals.sabinet.co.za/sajchem/>.

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

S. Jasouri[1,2], J. Khalafy[1,*], M. Badali[2] and M. Piltan[1]

[1]*Department of Chemistry, Urmia University, Urmia 57154, Iran.*
[2]*Daana Pharmaceutical Co., P.O. Box 5181-51575, Tabriz, Iran.*

Received 23 June 2010, Revised 10 July 2010, Accepted 12 July 2010.

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-1*H*-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 indanylethylamine 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 Br_2 in CCl_4 or $CHCl_3$ 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 ^{1}HNMR spectrum of **6** the two C_3 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 desired selective monobromination at C-2 was achieved using bromine in diethyl ether or in acetic acid at room temperature. Oxidative bromination of **5** in an aqueous H_2O_2-HBr system also gave monobrominated product **7**, but in only 42 % yield. The reaction of **5** and Br_2/K_2CO_3 in CH_2Cl_2 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).

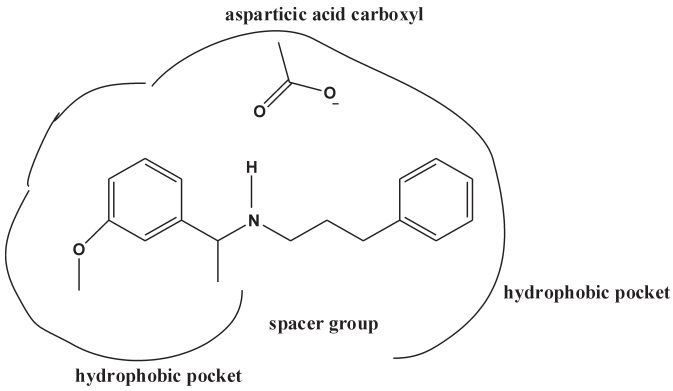
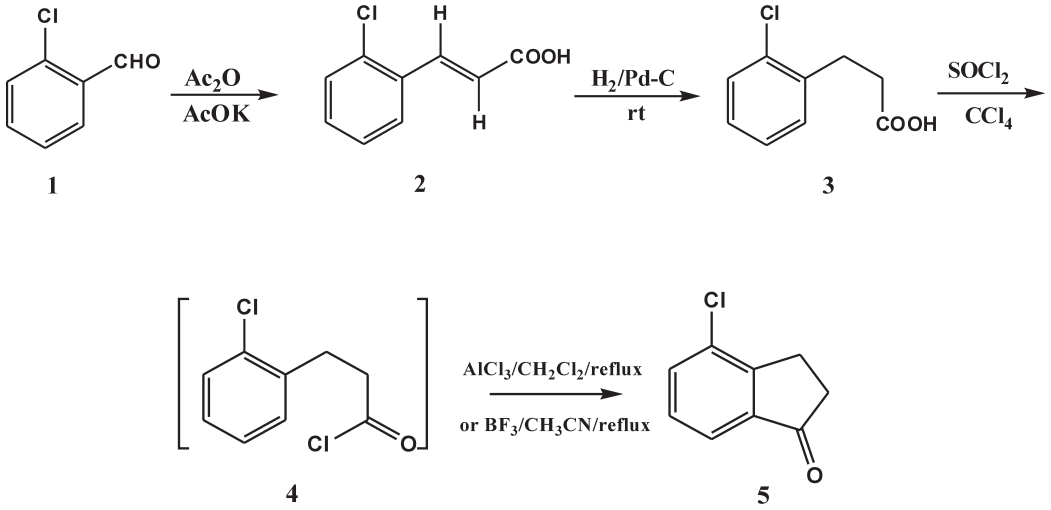


Figure 1 Proposed active site for 3-arylpropyl-α-methylbenzylamines.

Selective monobromination was quite difficult to control. Thus bromination in CCl_4 at 0 °C gave low yields of mono brominated product, but under the same conditions (1 eq Br_2) at 25 °C only the 2,2-dibrominated indanone could be isolated. Relatively polar conditions to were necessary to achieve high yields of monobrominated material in acetic acid at 25 °C. The presence of base (solid KOH or K_2CO_3) encouraged the formation of dibrominated product, presumably because the monobromo compound **7** was more readily enolized than the indanone (**5**).

2-Cyano-4-chloro-1-indanone (**8**) was synthesized from **7** by

* To whom correspondence should be addressed.
E-mail: j.khalafi@mail.urmia.ac.ir ; jkhalafi@yahoo.com

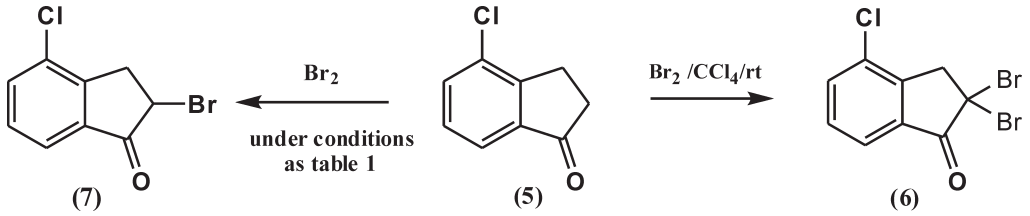


Scheme 1

Table 1 Bromination of 4-chloro1-indanone [a] (1 eq) (**5**).

Reaction conditions	Major product	yield/%
Br_2 (1 eq) / CCl_4 / rt / 2 h[9]	**6**	40
Br_2 (1 eq) / CCl_4 / ice bath / 2 h[9]	**7**	25
Br_2 (1 eq) / diethyl ether[14,15]	**7**	90
Br_2 (1 eq) / $AlCl_3$ / CH_2Cl_2 / ice bath / 2 h[9]	No reaction	–
H_2O_2 (2 eq) / H_2O (1.3 mL) / HBr (48 % aqueous, 1 eq) / dark / rt / 24 h[10,11]	**7**	42
NBS (1 eq) / H_2O (26 mL) / H_2SO_4 (40 % aqueous solution, 1 eq) / 60 °C / 5 h[12]	No reaction	–
NBS (1 eq) / PTSA (0.1 eq) / 60 °C / 10 min[12]	No reaction	–
NBS (1eq) / H_2O (1.3 mL) / 100W / 15 h[9]	No reaction	–
Br_2 (1 eq) / AcOH / rt / 2 h[9]	**7**	73
Br_2 (2 eq) / K_2CO_3 (3 eq) / CH_2Cl_2 / rt / 1 h[9]	Di:Mono (1:5)	60
Br_2 (2 eq) / K_2CO_3 (3 eq) / CH_2Cl_2 / ice bath / 1 h[9]	**7**	45
Br_2 (2 eq) / KOH (3 eq) / CH_2Cl_2 / ice bath / 1 h[9]	No reaction	–
Br_2 (2 eq) / KOH (3 eq) / CH_2Cl_2 / rt / 1 h[9]	Several products	–

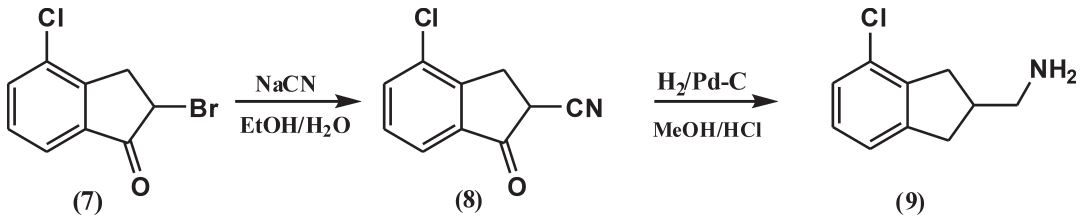
[a] Yields refer to isolated products. The recovered starting materials and by-products are not listed.



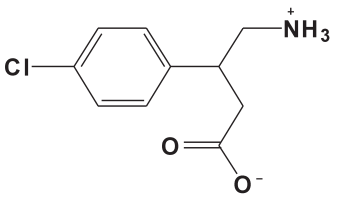
Scheme 2

reaction with sodium cyanide. The optimal procedure was to react **7** with sodium cyanide in EtOH/H_2O.[15] 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-1*H*-indene-2-yl)methanamine (**9**) in 75 % yield (Scheme 3).[24] 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.

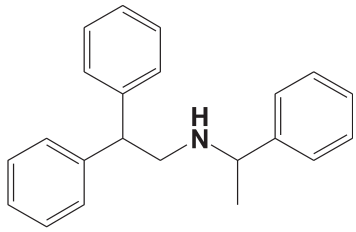
To what extent this compound, and similar analogues, are useful for the synthesis of compounds that mimic or antagonize the effects of baclofen[25] (**10**) and fendiline[26] (**11**) awaits further study.



Scheme 3



(10)



(11)

3. Experimental

General: ^{1}HNMR (300 MHz) and ^{13}CNMR (75 MHz) spectra were recorded in $CDCl_3$ on a Bruker spectrometer. Chemical shifts (δ) are in parts per million (ppm) relative to tetramethyl silane, and coupling constants (J) are given in Hertz. 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 by using Varian Aerograph - 9225, hydrogen generator. The routine purification of reagents and solutions was carried out by standard laboratory procedures. All organic extracts were dried with anhydrous sodium sulphate.

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 solution was steam distilled to remove excess reagent, cooled and filtered. The filtrate was acidified with concentrated hydrochloric acid, cooled, and the 2-chlorocinnamic acid collected and recrystallized from water to give compound **2** as white crystals (26.3 g, 72 %), m.p. 205–207 °C.

^{1}HNMR($CDCl_3$): δ (ppm) 6.50 (d, J = 16 Hz, 1 H), 7.36 (t, J = 7.5 Hz, 1 H, ArH), 7.38 (t, J = 7.5 Hz, 1 H, ArH), 7.49 (d, J = 7.8 Hz, 1 H, ArH), 7.71 (d, J = 7.5 Hz, 1 H, ArH), 8.26 (d, J = 16 Hz, 1 H), 10.4 (bs, 1 H, CO_2H); ^{13}CNMR ($CDCl_3$): δ (ppm) 39.9, 63.8, 121.7, 127.1, 127.6, 130.0, 130.9, 140.0, 168.1; FT-IR ν_{max} (cm^{-1}) 2836, 1686, 1622, 1470, 1441, 1337, 1286, 1038, 984, 756, 735, 598 and m/z 184(M^+), 182, 147, 103, 101, 91.

3.1.2. 3-(2-Chlorophenyl) Propanoic Acid (3). (*E*)-3(2-chlorophenyl) acrylic acid (1.00 g, 5.5 mmol) was dissolved in dried and preheated ethyl acetate (100 mL), 10 % Pd-C (0.05 g) was added, and the mixture was then hydrogenated at room temperature. Hydrogenation was carried out with stirring under hydrogen for 15 hours at atmospheric pressure. The suspension was filtered and the solvent removed to yield 3-(2-chlorophenyl) propanoic acid (**3**) as colourless needles (0.93 g, 92 %), m.p. 80–82 °C.

^{1}HNMR($CDCl_3$): δ (ppm) 2.71 (t, J = 7.8 Hz, 2 H), 3.08 (t, J = 7.8 Hz, 2 H), 7.18–7.33 (m, 4 H, ArH), 10.5 (1 H, bs, CO_2H); ^{13}CNMR ($CDCl_3$): δ (ppm) 28.1, 33.2, 126.4, 127.4, 129.1, 129.9, 133.4, 137.1, 178.8 ; FT-IR(KBr) ν_{max} (cm^{-1}) 2921, 1698, 1475, 1443, 1322, 1271, 1061, 1033, 933, 786, 751, 710, 665, 581 and m/z 186(M^+), 184, 167, 149, 138, 125, 103, 89, 77.

3.1.3. 4-Chloro-1-indanone (5). A mixture of thionylchloride (3.60 g, 30.0 mmol), carbon tetrachloride (20 mL) and 3-(2-chlorophenyl) propanoic acid (**3**) (4.60 g, 25.0 mmol) was refluxed for three hours. Removal of the solvent gave 3-(2-chlorophenyl) propanoyl chloride (**4**) as a colourless oil (4.3 g, 85 %).

The acid chloride (**4**) (4.30 g, 21.0 mmol) was dissolved in dichloromethane (20 mL) and freshly sublimed aluminum chloride (3.10 g, 23.0 mmol) added. The reaction mixture was refluxed for 8 hours. After cooling, the aluminum 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.

^{1}HNMR ($CDCl_3$): δ (ppm) 2.74 (t, J = 6.1 Hz, 2 H), 3.15 (t, J = 6.1 Hz, 2 H), 7.35 (dd, J_1 = 7.7 Hz, J_2 = 7.6 Hz, 1 H, ArH), 7.60 (d, J = 7.7 Hz, 1 H, ArH), 7.68 (d, J = 7.6 Hz, 1 H, ArH); ^{13}CNMR ($CDCl_3$): δ (ppm) 25.27, 36.40, 122.41, 129.29, 133.27, 134.52, 139.38, 152.97, 206.19; FT-IR ν_{max} (cm^{-1}) 3066, 2925, 1707, 1598, 1428, 1325, 1261, 1133, 1037, 788, 610 and m/z 168(M^++2), 166(M^+), 149(100), 138,125, 103, 77, 63, 51.

Using boron trifluride in acetonitrile instead of aluminium trichloride in dichloromethane under the above conditions gave the cyclized product in 95 % yield.

3.2. Bromination of 4-Chloro-1-indanone (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_2SO_4, filtered and concentrated. The residue was purified by recrystallization from n-hexane to give 2,2-dibromo-4-chloro-1-indanone (**6**) as pale yellow crystals (0.34 g, 40 %), m.p. 73–74 °C.

^{1}HNMR ($CDCl_3$): δ (ppm) 4.26 (s, 2 H, CH_2), 7.49 (dd, J_1 = 7.8 Hz, J_2 = 7.5 Hz, 1 H, ArH), 7.72 (d, J = 7.5 Hz, 1 H, ArH), 7.85 (d, J = 7.8 Hz, 1 H, ArH); ^{13}CNMR ($CDCl_3$): δ (ppm) 51.19, 55.30, 124.78, 130.47, 131.01, 132.20, 136.39, 144.86, 185.16; FT-IR(KBr) ν_{max} (cm^{-1}) 1740, 1598, 1461, 1259, 1133, 956, 813, 705, 596 and m/z 328(M^++6), 326(M^++4), 324(M^++2), 322(M^+), 247, 245(100), 243, 164, 136, 102, 99, 75.

3.2.2. With Bromine/CCl_4 at 0 °C. The above procedure at 0 °C yielded 2-bromo-4-chloro-1-indanone (**7**) as the main product (0.16 g, 25 %), m.p. 64–65 °C.

^{1}HNMR ($CDCl_3$): δ (ppm) 3.43 (dd, J_1 = 18.6 Hz, J_2 = 7.5 Hz, 1 H, CH_2), 3.84 (dd, J_1 = 18.6 Hz, J_2 = 3 Hz, 1 H, CH_2), 4.68 (dd , J_1 = 7.5 Hz, J_2 = 3 Hz, 1 H, CH), 7.43 (dd, J_1 = 7.8 Hz, J_2 = 7.5 Hz, 1 H, ArH), 7.68 (d, J = 7.8 Hz, 1 H, ArH),7.77 (d, J = 7.5 Hz, 1 H, ArH); ^{13}CNMR ($CDCl_3$): δ (ppm) 51.17, 55.37, 124.77, 130.51, 130.98, 132.19, 136.41, 144.82, 191.92; FT-IR(KBr) ν_{max} (cm^{-1}) 1724, 1597, 1460, 1337, 1262, 864, 753, 688 and m/z 248, 246, 244, 165(100), 137, 102, 75.

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/$CHCl_3$ at room temperature. The above procedure with $CHCl_3$ 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 Br_2: **5**, the yield was increased to 0.57 g (68 %).

3.2.4. With bromine/$CHCl_3$ 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 (**5**) (2.00 g, 12.0 mmol) in 200 mL anhydrous diethyl ether was added one drop of bromine from 0.6 mL, (12.0 mmol) 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 %).

3.2.6. With an aqueous H_2O_2-HBr system. 4-Chloro-1-indanone (**5**) (0.43 g, 2.6 mmol) was added to a mixture of water (1.30 mL), 48 % aqueous HBr (0.30 mL, 2.6 mmol) and 30 % H_2O_2 (0.53 mL, 5.2 mmol). The reaction mixture was stirred at room temperature in the dark. After 24 h, the reaction mixture was dissolved in hexane/ethyl acetate (20:1,13 mL) and solid $NaHSO_3$ added to neutralize any unreacted HBr or H_2O_2. The solution was then dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to give **7** (0.27 g, 42 %).

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 CCl_4 (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/K_2CO_3 at room temperature. Bromine (1.52 mL, 1.0 mmol) was added, with the exclusion of light, to mixture of **5** (0.09 g, 0.5 mmol) and K_2CO_3 (0.21 g, 1.6 mmol) in CH_2Cl_2 (20 mL) at room temperature. After 1 h the reaction was quenched with 1 M $Na_2S_2O_3$ and extracted with CH_2Cl_2, dried over anhydrous Na_2SO_4 and evaporated to give a mixture of mono- and dibromo products in the ratio of 5:1 (60 %).

3.2.9. With Bromine/K_2CO_3 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.

^{1}HNMR ($CDCl_3$) δ (ppm): 3.44 (dd, J_1 = 11.4 Hz, J_2 = 4.8 Hz, 1 H), 3.66 (dd, J_1 = 11.4 Hz, J_2 = 8.7 Hz, 1 H), 3.77 (dd, J_1 = 8.7 Hz, J_2 = 4.8 Hz, 1 H), 7.47 (dd, J_1 = 7.8 Hz, J_2 = 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); ^{13}CNMR ($CDCl_3$): 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) ν_{max} (cm^{-1}) 3112, 2213, 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-1*H*-indene-2-yl)methanamine (**9**) as a white powder (0.59 g, 86 %), m.p. 98–100 °C.

^{1}HNMR ($CDCl_3$): δ (ppm) 1.61 (bs, 2 H, NH_2), 2.50–2.59 (m, 1 H, CH), 2.68 (dd, J_1 = 15.6 Hz, J_2 = 6.9 Hz, 2 H, C-1), 2.81 (d, J = 6.9 Hz, 2 H, *CH_2-NH_2), 3.10 (dd, J_1 = 15.6 Hz, J_2 = 7.5 Hz, 2 H, C-3),7.27–7.09 (m, 3 H, ArH); ^{13}CNMR ($CDCl_3$): 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) ν_{max} (cm^{-1}) 3393, 2925, 1577, 1288, 744 and m/z 183(M^++2), 181(M^+), 164, 129(100), 115, 91, 44.

Acknowledgements

We are grateful for financial support from Urmia University and Daana Pharmaceutical Co. and S.J. is grateful to Daana Pharmaceutical Co. for a Ph.D. scholarship.

References

1 L.F. Fieser and E.B. Hershberg, *J. Am. Chem. Soc.*, 1937, **59,** 394–398.
2 C. Berrier, J.C. Jacquesy and M.P. Jouannetaaud, *Tetrahedron*, 1984, **40**, 4973–4979.
3 R.Takeuchi and H.Yasue, *J. Org. Chem.*, 1993, **58**, 5386–5392.
4 K. Lan and Z. Shan, *Synth. Comm.*, 2007, **37**, 2171–2177.
5 D.M. Cui, C. Zhang, M. Kawamura and S. Shimada, *Tetrahedron Letters*, 2004, **45**, 1741–1745.
6 S. Nan'ya, T. Kitahara, K. Fujii, A.C.Bajji and Y. Butsugan, *J. Heterocyclic Chem.*, 1992, **29**, 1525–1528.
7 *Ullmanns Encyclopedia of Industrial Chemistry*, Wiley-VCH, Weinheim, 2002.
8 D. La, P.B.D. Mare and R. Bolton, *Electrophilic Additions to Unsaturated Systems*, Elsevier, Amsterdam, the Netherlands, 1982.
9 T. Choi and E. Ma, *Molecules.*, 2007, **12**, 74–85.
10 A. Podgorsek, S. Stavber, M. Zupan and J. Iskra, *Tetrahedron Lett.*, 2006, **47**, 7245–7247.
11 A. Podgorsek, S. Stavber, M. Zupan and J. Iskra, *Tetrahedron*, 2009, **65**, 4429–4439.
12 I. Pravst, M. Zupan and S. Stavber, *Tetrahedron Lett.* 2006, **47**, 4707–4710.

*This solution was the lower phase obtained by shaking conc. NH_4OH (100 mL) and chloroform (900 mL).

13 J. Sam and T.C. Snapp, *J. Pharm. Sci.*, 1965, **54**, 756–760.
14 A.L. Wilds, *J. Am. Chem. Soc.*, 1942, **64**, 1421–1429.
15 W.S. Johnson, J.M. Anderson and W.E. Shelberg, *J. Am. Chem. Soc.*, 1944, **66**, 218–222.
16 H.O. House and V. Paragamian, *J. Am. Chem. Soc.*, 1959, **82**, 1452–1457.
17 N.S. Kus, *Turk. J. Chem*. 2009, **33,** 479–486.
18 Y. Kojima and S. Kawaguchi, *Bull. Chem. Soc. Japan*, 1972, **45**, 1293–1299.
19 A. Jordao, P. Afonso, V. Ferreira, M.D. Souza, M. Almeida and A. Cunha, *Eur. J. Med. Chem*., 2009, **44**, 3777–3781.
20 D.I.B. Kerr and J. Ong, *Pharmacol. Therap.*, 1995, **67,** 187–246.
21 D.I.B. Kerr, and J.Ong, *Current Med .Chem. CNS Agents.*, 2001, **1**, 27–42.
22 J. Khalafy, R.H. Prager and N.M. Puspawati, *Turk J. Chem.*, 2008, **32**, 755–763.
23 D.I.B. Kerr, J. Ong, M. Perkins, R.H. Prager and N.M. Puspawati, *Aust. J. Chem.*, 2006, **59**, 445–456.
24 D.W. James and M.Y. Kraig, *J. Am. Chem. Soc.* 1994, **116**, 1831–1838.
25 J. Ong, D.A.S. Parker, V. Marino, D.I.B. Kerr, N.M. Puspawati and R.H. Prager, *Eur. J. Pharmacology*, 2005, **507**, 35–42.
26 N.G. Bowery, *Trends Pharmacol. Sci.*, 1989, **10**, 401–407.