Bromination of 4-Bromoindanone and 5-Bromoindanone, Facile Synthetic Access to 3,5,10-tribromo-7H-benzo[*c*]fluoren-7-one

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Summary: Bromination reactions of 4-bromoindanone and 5-bromoindanone were presented and optimum reaction conditions were introduced. 2,2,4-Tribromoindanone was synthesized by treatment of 4-bromoindanone with molecular bromine at room temperature in a high yield. Bromination of 4-bromoindanone with NBS, SiO_2 and $LiClO_4$ in PEG yielded the corresponding 2,4-dibromoindanone which was reduced to 1-hydroxy-2,4-dibromoindane. Acetylation of hydroxydibromoindane in pyridine gave the 1-acetoxy-2,4-dibromoindane in excellent yield. The radical bromination of 5-bromoindanone with NBS at 77 °C in CCl_4 yielded the corresponding 3,5-dibromoindene-1-one which was converted to 3,5,10-tribromo-7H-benzo[*c*]fluoren-7-one by thermolysis.

Keywords: Bromination reactions, 4-bromoindanone, 5-bromoindanone, Diels-Alder reaction, 3,5,10-tribromo-7H-benzo[*c*]fluoren-7-one

Introduction

Brominated arylhydrocarbons are known as a significant class of molecules in synthetic organic chemistry. They are key intermediates for the synthesis of organometallic compounds and play crucial function for coupling reactions [1-7]. Many compounds consisting of halogen have been used for plastic, fire retardant, pesticides, herbicides, insecticides and pharmaceutical materials [8, 9].

Indanone derivatives are significant class of active molecules in pharmaceutical industries. They have a great variety of biological activities such as antimicrobial, antibacterial, antifungal [10, 11], antiproliferative [12, 13], antiviral activity against the hepatitis C virus (HCV) [14], anti-trypanosoma cruzi[15, 16], anticonvulsant [17], inhibitors against Alzheimer's disease[18-20] and inhibitors for breast cancer therapy[21]. Many significant compounds were synthesized from bromoindanes suh as antimicrobial agents, triazolo and thiadiazines which were synthesized efficiently from α-bromo and α,α-dibromoindanones [22].

In previous papers, we presented the facile and efficient bromination of benz[*f*]indane [23] and benz[*f*]indan-1-one [24]. We also demonstrated synthesis of bromoaminoindane and bromoaminoindanone derivatives [25]. Herein, we described optimum reaction conditions for bromination of 4-bromoindanone and 5-bromoindanone and displayed the synthesis of benzo[*c*]fluoren frame from 3,5-dibromoindene-1-one by Diels-Alder reaction.

Experimental

General Procedures

Column chromatography was carried out on Silica Gel 60 (230-400 mesh, E. Merck). TLC was performed on pre-coated glass plates of Silica Gel 60 F_{254} (0.25 mm, E. Merck). Melting points were determined with a Thomas-Hoover apparatus and are uncorrected. NMR spectra were recorded with 400, 300 MHz for ^{1}H-NMR and 100, 75 MHz for ^{13}C-NMR in Bruker instruments. Chemical shifts are in ppm from Me_4Si, generated from the $CDCl_3$. IR spectra were taken with a Jasco FT-IR 430 spectrometer. The elemental analysis was carried out with a CHNS-932 (LECO) analyzer. LC-MS/MS/MS measurements were performed on AB Sciex (3200 QTrap).

*Synthesis of tribromide **2a-2b.** General Procedure*

To a solution of bromoindanone (4-bromoindanone and 5-bromoindanone) in CH_2Cl_2 (25 ml) was added a solution of bromine (2.2 equiv per substrate) in CH_2Cl_2 (25 ml) dropwise during 30 minutes at ambient temperature while stirring. **CAUTION:** Due to the carcinogenity and toxicity of bromides and the HBr which is produced from the reaction, all bromination reactions should be

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performed in an efficient fume hood and chemicals handled with appropriate precautions! The HBr outlet from the reaction vessel should be connected to a HBr gas trap (bubbler containing 1.0 M NaOH solution. The resulting solution was stirred at rt for additional 1.5 h in the dark, solvent and excess bromine were removed in *vacuo,* solid material was crystalised (hexane/dichloromethane) to yield the tribromide **2a** and **2b**.

Synthesis of 2,2,4-tribromoindanone (**2a**)

4-bromoindanone **1a** (0.16 g, 0.76 mmol), bromine (0.27 g, 1.67 mmol) yielded tribromide (0.27 g, 96%). Mp: 88 °C. IR (KBr, cm^{-1}): 3444, 1743, 1593, 1454, 1415, 1257, 1118, 1010, 860, 814, 698. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.92 (d, *J* = 8.0 Hz, 1H, H-7), 7.86 (d, *J* = 8.0 Hz, 1H, H-5), 7.41 (t, *J* = 8.0 Hz, 1H, H-6), 4.20 (s, 2H, H-3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 192.4, 147.2, 139.8, 131.4, 130.9, 125.6, 121.4, 55.6, 53.3. Anal. Calcd for $C_9H_5Br_3O$ (368.8): C, 29.31, H, 1.37%. Found: C, 29.12, H, 1.45.

Synthesis of 2,2,5-tribromoindanone (**2b**)

5-bromoindanone **1b** (0.24 g, 1.13 mmol), bromine (0.4 g, 2.5 mmol), yielded the yellow crystal of tribromide (0.38 g, 95%). Mp: 93 °C (Lit. 94 °C) [26], (Lit. 9 3 °C) [27]. IR (KBr, cm^{-1}): 3433, 3055, 2360, 1921, 1731, 1589, 1415, 1257, 1207, 1169, 1057, 953, 868, 841, 779, 702. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.80 (d, *J* = 8.4 Hz, 1H, H-7), 7.64 (s, 1H, H-4), 7.60 (d, *J* = 8.4 Hz, 1H, H-6), 4.20 (s, 2H, H-3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 191.9, 148.8, 133.0, 132.7, 129.5, 128.1, 127.9, 56.0, 52.1. Anal. Calcd for $C_9H_5Br_3O$ (368.8): C, 29.31, H, 1.37%. Found: C, 29.17, H, 1.45.

Synthesis of dibromoindanone **3a, 3b.** *General Procedure*

A mixture of bromoindanone (4-bromoindanone and 5-bromoindanone), NBS, $LiClO_4$, SiO_2 in PEG-400 was stirred magnetically for 2 days at rt. The reaction mixture was diluted with water (30 ml), extracted with diethyl ether (3×30 ml), dried (Na_2SO_4). After removal of the solvent, the residue was passed through silica gel column to yield the product.

Synthesis of 2,4-dibromoindanone (**3a**)

4-bromoindanone **1a** (0.50 g, 2.37 mmol), NBS (0.46 g, 2.61 mmol), $LiClO_4$ (0.076 g), SiO_2 (0.2 g) in PEG-400 (2.0 g), a product in a yield of 91% (0.63 g). Mp: 77 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.70 (d, *J* = 8.5 Hz, 1H, H-7), 7.61 (d, *J* = 8.5 Hz, 1H, H-5), 7.50 (t, *J* = 8.5 Hz, 1H, H-6), 4.60 (X part of the ABX system), 3.80-3.40 (AB part of the ABX system). ^{13}C NMR (75 MHz, $CDCl_3$): δ 199.3, 151.2, 138.9, 132.8, 130.3, 124.1, 122.0, 43.3, 39.1. Anal. Calcd for $C_9H_6Br_2O$ (290.0): C, 37.28, H, 2.09%. Found: C, 37.14, H, 2.25. LC-MS/MS: 293.1, 291.1, 290.3, 289.0 [28].

Synthesis of 2,5-dibromoindanone (**3b**)

5-bromoindanone **1** (0.20 g, 0.95 mmol), NBS (0.19 g, 1.04 mmol), $LiClO_4$ (0.030 g, 0.29 mmol), SiO_2 (0.1 g) in PEG-400 (2.0 g), yielded the product (0.24 g, 89%). Mp: 101 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.70 (d, *J* = 8.4 Hz, 1H, H-7), 7.59 (s, 1H, H-4), 7.50 (d, *J* = 8.4 Hz, 1H, H-6), 4.60 (X part of the ABX system), 3.80-3.40 (AB part of the ABX system). ^{13}C NMR (75 MHz, $CDCl_3$): δ 198.7, 152.8, 132.6, 132.3, 131.8, 130.0, 126.5, 43.7, 37.9. Anal. Calcd for $C_9H_6Br_2O$ (290.0): C, 37.28, H, 2.09%. Found: C, 37.19, H, 2.21.

Synthesis of 1-hydroxy-dibromoindane **4a, 4b.** *General Procedure*

To a magnetically stirred solution of dibromoindanone (2,4-dibromoindanone and 2,5-dibromoindanone) in THF/MeOH (8 ml/5 ml) was added a solution of $NaBH_4$ (1.1. equv per dibromoindanone) in THF (5.0 ml) at 0 °C. The reaction mixture was stirred for 30 min at 0 °C then the stirring was carried out additional 1 h at room temperature. HCl was added (15 ml, 5%) to reaction mixture, extracted with diethyl ether (3 × 30 ml), dried ($NaSO_4$), filtered and concentrated in *vacuo* to yield the white solid.

Synthesis of 1-hydroxy-2,4-dibromoindane (**4a**)

2,4-dibromoindanone **3** (0.87 g, 2.99 mmol), $NaBH_4$ (0.12 g, 3.3 mmol), yielded the white solid (0.85 g, 97%). Mp: 150 ºC. ^{1}H NMR (400 MHz,$CDCl_3$): δ 7.48 (d, *J* = 8.0 Hz, 1H, H-5), 7.41 (d, *J* = 8 Hz, 7-H), 7.23 (t, *J* = 8 Hz, H-6), 5.05 (d, *J* = 8 Hz, 1H, H-1), 4.96 (m, 1H, H-2), 3.45 (d, 2H, H-3, H-3' overlap), 2.60 (brs, OH). ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 143.8, 139.5, 131.8, 129.4, 123.5, 120.2, 76.9, 59.4, 41.2. Anal. Calcd for $C_9H_8Br_2O$: C, 37.02, H, 2.76. Found: C, 37.13, H, 2.64%. LC-MS/MS: 294.2, 293.4, 292.8, 291.9, 291.1.

Synthesis of 1-hydroxy-2,5-dibromoindane (**4b**)

2,5-dibromoindanone **3** (0.60 g, 2.1 mmol), $NaBH_4$ (0.087 g, 2.3 mmol), yielded the white solid as an excellent yield (0.59 g, 98%). Mp: 144 ºC. ^{1}H NMR (400 MHz,$CDCl_3$): *δ* 7.46 (d, *J* = 8 Hz, 1H, H-7), 7.43 (s, 1H, H-4), 7.34 (d, *J* = 8 Hz, 1H, H-6), 4.93 (brs, 2H, overlap H-1 and H-2), 3.35-3.51 (m,

2H, H-3, H-3'), 2.48 (brs, C1-OH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.6, 140.9, 130.9, 128.5, 126.4, 122.6, 76.0, 60.8, 40.1. LC-MS/MS: 295.0, 293.8, 293.0, 292.1, 291.2.

Synthesis of 1-acetoxy-dibromoindane **5a, 5b.** *General Procedure*

To a stirred solution of 1-hydroxy-2,4-dibromoindane (1-hydroxy-2,4-dibromoindane (**4a)** and 1-hydroxy-2,5-dibromoindane (**4b**)) in Ac_2O (6 ml) was added pyridine (5 ml) at 0 °C. After the reaction mixture was stirred for 5 h at rt, water was added, then extracted with CH_2Cl_2 (3 x 10 ml). The organic layer was dried ($MgSO_4$) and the solvent was removed. The residue was purified by chromatography (silica, hexane/EtOAc, 9/1) affording the product.

Synthesis of 1-acetoxy-2,4-dibromoindane (**5a**)

1-Hydroxy-2,4-dibromoindane **4a** (0.2 g, 0.68 mmol), Ac_2O (6 ml), pyridine (5 ml), afforded the product (0.22 g, 96%). Mp: 87 ºC. ^{1}H NMR (400 MHz,$CDCl_3$): *δ* 7.50 (d, *J* = 8 Hz, 1H, H7), 7.36 (d, *J* = 8 Hz, 1H, H5), 7.19 (t, *J* = 8 Hz, 1H, H6), 6.06 (d, *J* = 8 Hz, 1H, H-1), 4.87-4.90 (m, 1H, H-2), 3.52 (dd, *J* = 4 Hz, 16 Hz, 1H, H-3), 3.43 (dd, *J* = 8 Hz, 16 Hz, 1H, H-3'), 2.20 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.4, 140.8, 140.2, 132.5, 129.3, 124.0, 119.9, 77.3, 50.1, 42.1, 20.9. LC-MS/MS: 337.3, 336.3, 336.0, 335.6, 335.1, 334.5, 334.1, 333.9, 333.1.

Synthesis of 1-acetoxy-2,5-dibromoindane (**5b**)

1-hydroxy-2,5-dibromoindane **4b** (0.4 g, 1.37 mmol), Ac_2O (7 ml), pyridine (6 ml), product (0.45 g, 98%). Mp: 144 ºC. ^{1}H NMR (400 MHz,$CDCl_3$): *δ* 7.45 (s, 1H, H-4), 7.43 (d, *J* = 8 Hz, 1H, H-6), 7.30 (d, *J* = 8 Hz, 1H, H-7), 5.95 (d, *J* = 8 Hz, 1H, H-1), 4.85-4.89 (m, 1H, H-2), 3.49 (dd, *J* = 4 Hz, 16 Hz, 1H, H-3), 3.44 (dd, *J* = 4 Hz, 16 Hz, 1H, H-3'), 2.20 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.5, 142.5, 137.4, 130.7, 128.1, 126.7, 123.4, 76.3, 51.1, 40.6, 20.2. LC-MS/MS: 337.1, 336.1, 335.1, 334.4, 333.9, 333.1, 332.8, 332.6.

Synthesis of 3,5-dibromoindene-1-one (**6**)

To a solution of 5-bromoindanone (0.25 g, 1.18 mmol)) in CCl_4 (20 ml) in a photochemical reaction apparatus (100 ml) equipped with a reflux condenser was added NBS (0.46 g, 2.6 mmol) and catalytic amount of benzoyl peroxide while irradiating with a 50-W projector lamp. HBr was exactly removed during the reaction. After completion of the reaction (2 h), the excess bromine and solvent were removed under reduced pressure. The crude product was subjected to column chromatography (silica gel, 15 g, 70-230 mesh), eluted with hexane and ethyl acetate (9/1) to yield the 3,5-dibromoindene-1-one **6** (0.22 g, 65%). Mp 135 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7,43 (dd, *J*=7.5 Hz, *J* = 1.8 Hz, 1H, H-7), 7.30 (d, *J* = 1.8 Hz, 1H, H-4), 7.07 (d, *J* = 7.5 Hz, 1H, H-6), 6.22 (s, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$): *δ* 192.9, 147.4, 145.0, 133.5, 129.4, 128.9, 128.7, 125.6, 123.5. IR: υ/cm^{-1} (KBr): 3095, 2850, 1703, 1591, 1535, 1334, 1253. Anal. Calcd for $C_9H_4Br_2O$: C, 37.54, H, 1.40%. Found: C, 37.46, H, 1.35%.

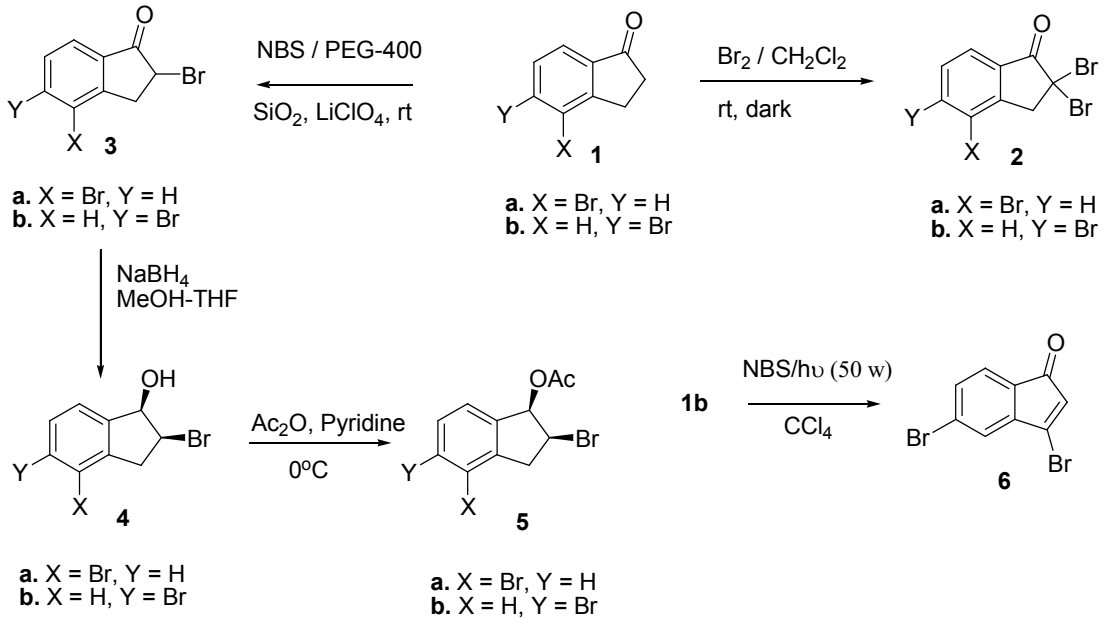
Thermolise of 3,5-dibromoindenone 5b, synthesis of 3,5,10-tribromo-7H-benzo[c]fluoren-7-one (**8**)

3,5 Dibromoinden-1-one (0,15g, 0,32mmol) was heated in a sealed glass tube at 120 ºC for 3 h. The black solid was washed with methylene chloride to achieve the brown product **7** (0.12 g, 63%). Mp 310-311 °C. ^{1}H NMR (400 MHz, *d*-DMSO): δ 8.69 (s, 1H), 8.23 (s, 1H), 8.20 (d, *J* = 8.0 Hz, 1H), 8.01 (s, 1H), 7.98 (s, 1H), 7.83 (d, *J* = 8.0 Hz, 1H), 7.75 (s, 1H). ^{13}C NMR (100 MHz, *d*-DMSO): δ 193.1, 145.5, 142.3, 136.7, 133.2, 132.1, 131.6, 131.4, 131.2, 129.9, 128.9, 128.4, 126.7, 126.2, 125.6, 123.4, 120.7. IR (KBr)ν_{max} =3451, 1713, 1380, 870, Anal. Calcd for $C_{17}H_7Br_3O$: C, 43.73, H, 1.51. Found: C, 43.95, H, 1.53%. LC-MS/MS: 470.1, 469.2, 468.0, 467.2, 466.2, 465.8.

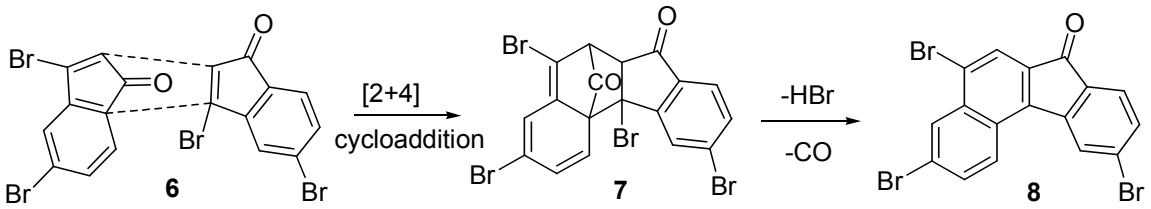
Results and Discussion

The treatment of 4-bromoindanone (**1a)** with bromine in dichloromethane at rt afforded the corresponding 2,2,4-tribromoindanone **(2a)** in excellent yield. In ^{1}H-NMR spectrum, H-3 proton gave the signal at δ 4.20 as a singlet and the signals of aromatic protons were observed at δ 7.92 (d, *J* = 8.0 Hz, 1-H, H-7), 7.86 (d, *J* = 8.0 Hz, 1-H, H-5), 7.41 (t, *J* = 8.0 Hz, 1-H, H6). In ^{13}C-NMR spectrum, the observation of six aromatic peaks (3 quaternary and 3 methine carbons), one sp^3 carbon and one carbonyl carbon is fully agreement with the compound (**2a**). 2,4-Dibromoindanone (**3a**) was generated by the treatment of 4-bromoindanone (**1a**) with NBS, $LiClO_4$, SiO_2, in PEG-400 at rt for 2 days in a good yield. This reaction method is significant due to the hindrance of further bromination, thus only one bromine was bonded to benzylic position. 2,5-Dibromoindanone (**3b**)[29] was synthesized by the same method using the 5-bromoindanone (**1b**) as a starting compound. PEG-400 was preferred as a green solvent in this work. Due to the low cost, easy degradation, recyclability, miscibility with a wide variety of organic solvents makes PEG-400 as an alternative solvent in organic synthesis [25]. The reduction of 2,4-dibromoindanone (**3a**) with sodium

borohydride in methanol and tedrahydrofuran mixture at 0 ºC led to the formation of 1-hydroxy-2,4-dibromoindane (**4a**) in an excellent yield. In ^{1}H-NMR spectra the signal sets were observed in aromatic and aliphatic regions in **4a**. The signal observed at 7.48 ppm as a doublet with 8 Hz coupling constant belonged to downfield H-5 proton due to the electron withdrawing effect of adjacent bromine. The H-7 proton appeared as a doublet at 7.41 ppm and the triplet signal at 7.23 ppm suited with the H-6 proton. In aliphatic region, three signal sets were appeared. The signal detected at 5.05 ppm with 8 Hz coupling constant matched with H-1. The signal that appeared at δ 4.96 as multiplet could be attributed to H-2. The resonance peak of H-3 and H-3' arisen at the same frequency so the peaks overlapped. The hydroxyl proton resonated at 2.60 ppm as broad singlet as usual. The stereochemistry of the hydroxyl and bromine at C-1 and C-2 respectively was recognized by the coupling constant of H-1 and H-2 protons. The coupling constant (J_{12} = 8 Hz) indicated the *cis*-orientation of the hydroxyl and bromine atom in **4a.** However the low coupling constant (J_{12} = 5.4 Hz) revealed that the configuration was in *trans* fashion [30]. In the ^{13}C NMR spectra, observation of nine peaks at aliphatic and aromatic region accorded with the proposed structure (**4a**). The exact molecular mass was determined by the LC-MS/MS. The same reaction procedure was applied for the synthesis of 1-hydroxyl-2,5-dibromoindane (**4b**)[31] and the exact molecule geometry and *cis*-configuration of the hydroxyl and bromine atoms was precisely determined by X-ray crystallographic analysis [32]. The acetylation of **4a** with acetic anhydride in pyridine at 0 °C yielded the 1-acetoxy-2,4-dibromoindane (**5a**) in an excellent yield. In the ^{1}H-NMR spectra, three resonances signal seemed at the aromatic region. The ABX spin system appeared in the aliphatic region. The resonance at 6.06 ppm as a doublet with an 8 Hz coupling constant could be attributed to H-1. The signal observed at 4.90 ppm as multiplet belonged to H-2. The resonance signal at 3.52 ppm as doublet of doublet with 4 Hz and 16 Hz coupling constant suited with H-3. Whereas the signal appeared at 3.43 ppm as doublet of doublet with vicinal and germinal coupling were assigned to H-3' which resonated at more upfield than H-3 due to the γ-gauche effect of H-3' with bromine caused by a *cis* orientation of H-3' and the bromine. The methyl protons signal seemed at 2.20 ppm as a singlet. In the ^{13}C-NMR spectra, the appearance of 6 aromatic peaks (3 quaternary and 3 methine carbons), one carbonyl, four aliphatic (one methyl, two methine, one methylene) is fully in agreement with the structure of 1-acetoxy-2,4-dibromoindane (**5a**). The exact configuration of 1-acetoxy-2,4-dibromoindane (**5a**) was elucidated by X-ray crystallographic analysis [33]. 1-Acetoxy-2,5-dibromoindane (**5b**) was synthesized and the structure was identified by the same methods. 3,5-Dibromoindene-1-one (**6**) was generated by radical bromination of 5-bromoindanone (**1b**) using 2.2 equivalents of N-bromosuccinimid (NBS) in a photochemical reaction apparatus equipped with a reflux condenser in CCl_4 at 77 ºC (Scheme 1).



Scheme-1: Bromination of 4-bromoindanone and 5-bromoindanone.



Scheme-2: Proposed reaction mechanism of compound **8.**

In the ^{1}H-NMR spectra, four methine signals and in the ^{13}C-NMR spectra, nine lines of which four methine, four quaternary, one carbonyl carbons verified the structure of 3,5-dibromoindene-1-one (**6**). 3,5-Dibromoindene-1-one (**6**) was heated in a sealed tube at 120 ºC for 3 h in neat condition yielded the 3,5,10-tribromo-7H-benzo[c]fluoren-7-one (**8**). 3,5-Dibromoindene-1-one (**6**) underwent an intramolecular [2+4] cycloaddition reaction in which cyclopentadienone structure acted as both diene and dienophile. After the hydrogen bromide elimination and carbon monoxide expulsion from the intermediate molecule (**7**), the desired product **8** was formed (Scheme 2).

In the ^{1}H-NMR spectra, seven protons resonances with 8 Hz coupling with the adjacent proton were observed. In ^{13}C-NMR spectra, observation of seven methine carbons, nine quaternary carbons and one carbonyl carbon is fully in agreement with the proposed structure **8**. This method was firstly presented by Tutar et al [34, 35] and then the reaction conditions were extended by Zheng et al [36] who used various indenone derivatives to further explore the scope and limitations of the reaction.

Conclusion

Bromination reactions of 4-bromoindanone and 5-bromoindanone were carried out. 2,2,4-tribromoindanone, 2,4-dibromoindanone, 1-hydroxy-2,4-dibromoindane, 1-acetoxy-2,4-dibromoindane, 3,5-dibromoindene-1-one, 3,5,10-tribromo-7H-benzo[*c*]fluoren-7-one were synthesized and efficient reaction conditions were presented.

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