Bromination of Benz[*f*]indene: Synthesis of New Benz[*f*]indane Derivatives

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(Received on 25th April 2012, accepted in revised form 26th July 2012)

Summary: The bromination reactions of benz[*f*]indene **1** were investigated with molecular bromine and photobromination. Dibromo- and tribromobenz[*f*]indane were synthesised by bromination of benz[*f*]indene **1**. Subsequent reactions of dibromobenz[*f*]indane **2** were accomplished with various silver salts (silver acetate, perchlorate, sulphate and nitrate). Treatment of *trans*-1-acetate-2-bromobenz[*f*]indane **6** with sodium methoxide resulted in the formation of corresponding 1,2-oxide-benz[*f*]indane **10**.

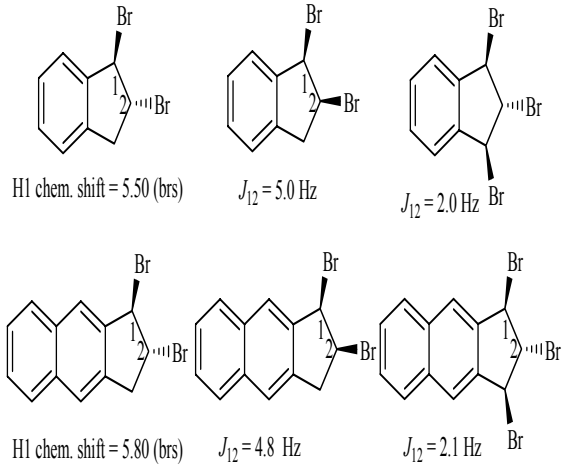
Introduction

Bromination of hydrocarbons is important processes in synthetic chemistry [1-5]. Brominated compounds are precursors in the preparation of organometallic reagents [6, 7] as well as the metal mediated coupling reactions [8–11]. Benz[*f*]indenes are potentially useful building blocks in organic and organometallic synthesis. Benz[*f*]indenes can satisfy the pharmacophore requirements of the critical hydrogen-bond donor and acceptor groups found in neuroactive steroids that modulate γ-aminobutyric acid receptor function. Thus, the benz[*f*]indene ring system provides an opportunity to extend the γ-aminobutyric acid receptor structure-activity relationships of neuroactive steroids to a different ring system [12]. Benz[*f*]indenes are also building blocks for electronic and optoelectronic materials [13].

Herein we developed a facile and efficient route for synthesising of bromo derivatives of benz[*f*]indene which could be starting materials for biologically, pharmaceutically and optically valuable compounds. Due to the good leaving group ability of bromine, we also accomplished the bromination reactions of *trans*-dibromobenz[*f*]indane with acetoxy, nitrate, hydroxy and methoxy. We also synthesised the epoxide from acetate derivative.

Result and Discussion

At first, the starting compound was synthesised according to the given literature [14]. The addition of bromine to the solution of benz[*f*]indene dropwise at rt for 2 h afforded the sole product of *trans*-1,2-dibromobenz[*f*]indane **2** in a quantitative yield. On the other hand, addition of benz[*f*]indene to the bromine solution yielded *trans*-1,2-dibromobenz[*f*]indane **2** and *cis*-1,2-dibromobenz[*f*]indane **3**. These phenomena were also observed in the bromination of indene carried out by Balci *et. al*.[15] The stereochemistry of the product could be either *trans* or *cis*. Comparison of the coupling constant of product **2** with the similar compounds [15, 16] indicated that bromines are in the *trans* configuration (Scheme-1).



Scheme-1: Comparison of coupling constant of synthesised compounds with known ones.

Due to the steric hindrance of the bromine atoms, the addition of bromine to the double bond as *trans* fashion is not surprising. The treatment of benz[*f*]indene **1** with 2.2 equivalents of bromine in photochemical reaction apparatus in non-polar solvent irradiating 50 watt projection lamp at rt for 12 h afforded the tribromobenz[*f*]indane **4** in quantitative yield. The stereochemistry of tribromobenz[*f*]indane **4** was elucidated by x-ray crystal structure [16] but spectroscopic data including ^{1}H- and ^{13}C-NMR weren't described. The reaction of benz[*f*]indene **1** with 2.2 equivalents of bromine in refluxing carbon tetrachloride while being irradiated with 150 W projector lamp for 12 h gave the tribromobenz[*f*]indane **4** in addition to tribromobenz[*f*]indene **5** in a yield of 4% and 19% respectively (Scheme-2).

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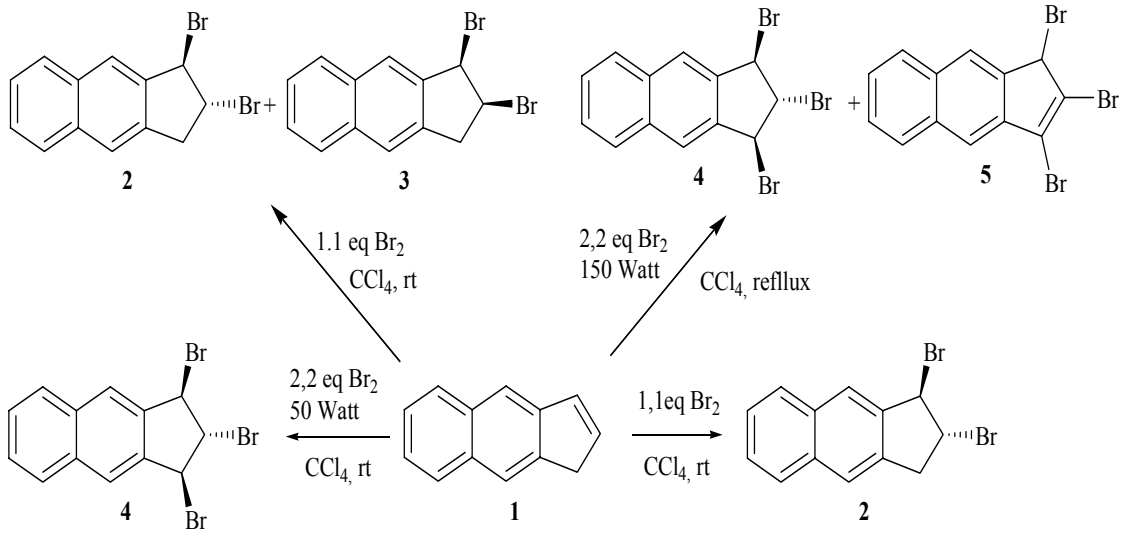


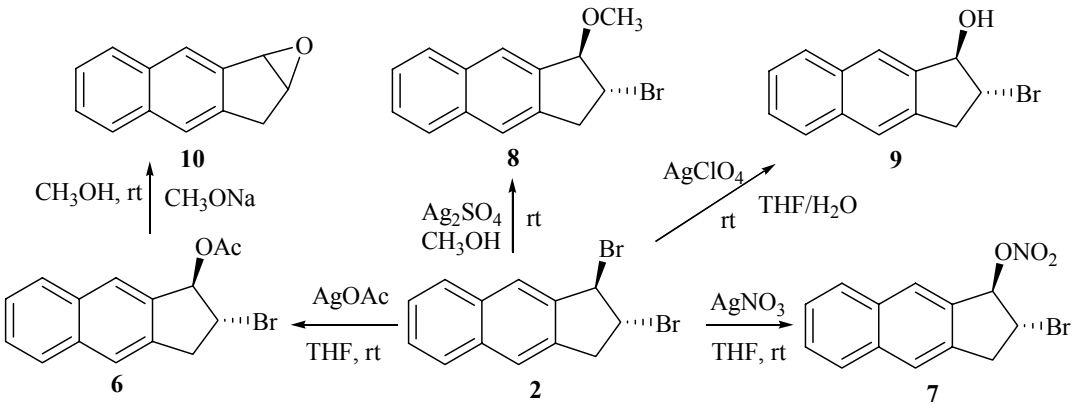
Scheme-2: Bromination reactions of benz[*f*]indene.

After successful synthesis of bromo derivatives of benz[*f*]indane we focused our attention to the synthesis of acetoxy, nitrato, methoxy, hydroxyl and epoxy derivatives of benz[*f*]indane. The treatment of dibromide **2** with 2.5 equivalents of silver acetate at rt in THF for 12 h. yielded the formation of *trans*-1-acetate-2-bromobenz[*f*]indane **6** purified by column chromatography (silica gel) eluted with hexane and EtOAc in the ratio of 9/1. Because of the configuration retention of bromine bounded to C-2-atom, there are two possible isomeric structures which are *cis* and *trans* forms. Reaction proceeds by an S_N1 mechanism and due to the bulky bromine, the acetate group attacks in *trans* fashion to form the corresponding product **6**. In addition, the ^{1}H-NMR spectrum of acetate **6** consists of five characteristic signals. The signal observed at 2.1 ppm as a singlet belongs to methyl of acetate. The aliphatic protons give rise to two AX spin systems, A part of the system which is H3 resonate at δ 3.42 as doublet of doublet and H3' gives doublet of doublet at δ 3.90. Other AX system belonging to H2 and H1 in which A part of the system appears at 4.62 belongs to H2. X part of the system exhibiting 6.44 as a doublet belongs to H1. Coupling constant of H1 which is J = 3.2 Hz indicates that the configuration of compound **6** is *trans* form. In the ^{13}C NMR spectrum, the observation of 10 aromatic peaks (4 quaternary and 6 methine carbons), one carbonyl, four aliphatic (one methyl, two methine, one methylene) is fully in agreement with the structure of *trans*-1-acetate-2-bromobenz[*f*]indane **6**. The reaction of dibromide **2** with 1.1 equivalents of silver nitrate in THF at rt for overnight afforded the *trans*-1-nitrate-2-bromobenz[*f*]indane **7** in 29% yield in which the configuration of the starting compound was retained. Reaction of dibromide **2** with silver sulphate in methanol at rt for 8 h resulted in the formation of *trans*-1-methoxy-2-bromobenz[*f*]indane **8** with retention of configuration. Treatment of dibromide **2** with 1.2 equivalents of silver perchloride in aqueous THF (5 ml THF/2 ml H_2O) at rt for 2 h. gave *trans*-1-hydroxy-2-bromobenz[*f*]indane **9**. *Trans*-1-acetate-2-bromobenz[*f*]indane **6** was treated with sodium methoxide in methanol for 4h at rt afforded 1,2-oxide-benz[*f*]indane **10** in a yield of 63%. To form the epoxide, bromine and acetate have to be *trans* to one another. So epoxide **10** synthesised from acetate **6** indicated that acetate **6** has *trans* configuration (Scheme-3).

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 Büchi B-540 apparatus and are uncorrected. ^{1}H- and ^{13}C NMR spectra were recorded with 400, 300 and 100, 75 MHz Bruker instrument. Chemical shifts are in ppm from Me_4Si, generated from the $CDCl_3$. IR spectra were taken with a Perkin-Elmer Paragon 1000 FT-IR spectrometer. Mass spectra were obtained with a FAB JMS-700 double focusing mass spectrometer.



Scheme-3: Derivatives of *trans*-1,2-dibromobenz[*f*]indane.

Trans-1,2-dibromobenz[f]indane 2

To a magnetically stirred solution of indene **1** (0.10 g, 0.60 mmol) in CCl_4 (3.0 ml) was added dropwise a solution of bromine (0.11 g, 0.66 mmol) in CCl_4 (3.0 ml). The reaction was completed for 2h. at rt. After removal of the solvent and excess bromine, the crude product was filtered through a short column (silica gel, 30 g), eluting with hexane/EtOAc (9/1) to give the product (0.19 g, 96%). υ_{max} IR (KBr)/cm^{-1} 754, 945, 958, 1073, 1145, 1208, 1288, 1414, 1450, 1502, 1606, 1633, 1732, 1939, 2925. δ_H (400 MHz, $CDCl_3$) 3.45 (d, *J* 17.6 Hz, 1H, H3), 4.0 (dd, *J* 5.0 Hz, *J* 17.6 Hz, 1H, H3'), 5.0 (d, *J* 5.0 Hz, 1H, H2), 5.80 (s, 1H, H1), 7.5 (m, 2H), 7.80 (m, 3H), 8.0 (s, 1H). δ_C (100 MHz, $CDCl_3$) 40.8, 54.9, 56.7, 124.2, 125.3, 125.9, 126.8, 127.8, 128.4, 133.2, 134.3, 137.9, 139.3.

Synthesising Trans-1,2-dibromobenz[f]indane **2** *and Cis-1,2-dibromobenz[f]indane*

To a magnetically stirred solution of bromine (50 mg, 0.31 mmol) in CCl_4 (3.0 ml) was added dropwise a solution of indene (50 mg, 0.30 mmol) in CCl_4 (3.0 ml). The reaction was completed for 1 h. at rt. H-NMR spectra indicated that the *trans*- and *cis*-dibromoindane formed as a ratio of 62% and 28% respectively.

Cis-1,2-dibromobenz[f]indane **3**

Spectroscopic data were extracted from a mixture consisting of *cis*- and *trans*-dibromides. δ_H (400 MHz, $CDCl_3$) 3.50 (dd, *J* 7.2 Hz, *J* 12.5 Hz, 2H, H3, H3'), 4.60 (dd, *J* 5.8 Hz, *J* 12.5 Hz, 1H, H2), 5.70 (d, *J* 4.8 Hz, 1H, H1), 7.50 (m, 2H), 7.85 (m, 3H), 8.0 (s, 1H, H8). δ_C (100 MHz, $CDCl_3$) 40.3, 50.9, 58.2, 123.1, 124.1, 126.1, 126.7, 127.7, 128.3, 129.0, 129.7, 131.6, 132.6.

Tribromobenz[f]indane **4**

To a magnetically stirred solution of benz[*f*]indene **1** (0.2 g, 1.2 mmol) in a photochemical reaction apparatus in CCl_4 (10 ml) was added dropwise a solution of bromine (0.42 g, 2.63 mmol) in CCl_4 (10 ml) while the reaction apparatus was irradiated by 50 watt projection lamp. The resulting reaction mixture was irradiated for 12 h at rt. After removal of the solvent and excess bromine, the crude product was filtered through a short column (silica gel) to give the product, crystallized from methylene chloride/hexane to give the white cubic crystal of tribromobenz[*f*]indane (0.44 g, 90%). Mp 223 °C. δ_H (400 MHz, $CDCl_3$) 5.09 (t, *J* 2.1 Hz, *J* 4.2 Hz, 1H, H2), 5.78 (d, *J* 2.1 Hz, 2H, H1, H3), 7.55 (m, 2H, H5, H6), 7.88 (m, 2H, H4, H7), 7.99 (s, 2H, H8, H9). δ_C (100 MHz, $CDCl_3$) 49.0, 52.0, 124.9, 126.2, 127.0, 131.7, 137.2.

High temperature bromination of benz[f]indene **1**

To a magnetically stirred solution of benz[*f*]indene **1** (0.2 g, 1.2 mmol) in a photochemical reaction apparatus in CCl_4 (10 ml) was added dropwise a solution of bromine (0.42 g, 2.63 mmol) in CCl_4 (10 ml) while the reaction apparatus was irradiated by 150 watt projection lamp. The resulting reaction mixture was irradiated for 12 h. at reflux. After removal of the solvent and excess bromine, the crude product was subjected to column chromatography (silica gel), eluted with hexane/EtOAc (9/1) to give the two products, tribromobenz[*f*]indane **4** (20 mg, 4%) and tribromobenz[*f*]indene **5** (91 mg, 19%).

Tribromobenz[f]indene **5**

δ_H (300 MHz, $CDCl_3$) 5.71 (s, 1H, H3), 7.54 (m, 2H, H5, H6), 7.72 (s, 1H, H9), 7.90 (m, 2H, H4, H7), 7.93 (s, 1H, H8). δ_C (75 MHz, $CDCl_3$) 48.0, 112.7, 120.8, 124.3, 125.3, 125.8, 127.1, 127.4, 127.6, 131.6, 132.3, 133.1, 136.8. Ms *m/z*, 405 (5), 404 (12), 403 (5) $[M]^+$, 340 (8), 325 (60), 323 (100), 243 (12), 164 (28), 163 (52), 162 (16).

Ag^+ assisted reaction of trans-1,2-dibromobenz[f]indane **2**

Trans-1-acetate-2-bromobenz[f]indane **6**

To a magnetically stirred solution of dibromide **2** (0.30 g, 0.92 mmol) in THF (5.0 ml) was added silver acetate (0.38g, 2.3 mmol). The reaction mixture was completed for 12 h. at rt. After filtration and evaporation, the crude product was purified by chromatography (silica gel) eluted with hexane/EtOAc (9/1) to give the product (0.140 g, 50%). υ_{max} IR (KBr)/cm^{-1} 754, 879, 960, 1016, 1220, 1369, 1425, 1502, 1735, 3016, 3060. δ_H (400 MHz, $CDCl_3$) 2.1 (s, 3H, Me), 3.42 (dd, *J* 3.6 Hz, *J* 17.2 Hz, 1H, H3), 3.90 (dd, *J* 6.0 Hz, *J* 17.2 Hz, 1H, H3'), 4.62 (ddd, *J* 3.6 Hz, *J* 6.8 Hz, 1H, H2), 6.44 (d, *J* 3.2 Hz, 1H, H1), 7.50 (m, ArH, 2H), 7.74 (s, ArH, 1H), 7.80-7.90 (m, ArH, 2H), 7.94 (s, ArH, 1H). δ_C (100 MHz, $CDCl_3$) 21.2, 40.9, 50.5, 82.9, 123.5, 125.7, 125.8, 126.6, 127.7, 128.5, 133.0, 134.4, 136.9, 138.7, 170.3. Ms *m/z*, 306 (8), 305 (2) $[M]^+$, 304 (8), 183 (9), 182 (24), 181 (9), 166 (28), 165 (100), 152 (12).

Trans-1-nitrate-2-bromobenz[f]indane **7**

To a magnetically stirred solution of dibromide **2** (0.36 g, 1.1 mmol) in THF (5.0 ml) was added silver nitrate (0.21 g, 1.2 mmol). The reaction mixture was completed for 12 h at rt. After filtration and evaporation, the crude material was purified by column chromatography (silica gel) eluted with hexane/EtOAc (9/1) to give the product (0.1 g, 29%). υ_{max} IR (KBr)/cm^{-1} 751, 965, 977, 1282, 1501, 1580, 1629, 1722, 2924, 2991, 3055 δ_H (400 MHz, $CDCl_3$) 3.52 (t, *J* 18.9 Hz, 1H, H3), 4.0 (dt, *J* 18.9 Hz, *J* 6.1 Hz, 1H, H3'), 4.75 (t, *J* 6.1 Hz, *J* 15.9 Hz, 1H, H2), 6.55 (d, *J* 22.8 Hz, 1H, H1), 7.36 (t, *J* 15.5 Hz, *J* 7.7 Hz, 1H, ArH), 7.60 (t, *J* 7.8 Hz, *J* 14.9 Hz, 1H, ArH), 7.68 (t, *J* 7.8 Hz, *J* 14.9 Hz, 1H, ArH), 7.88 (m, 1H, ArH), 8.02 (d, *J* 12.2 Hz, 1H, ArH), 8.27 (t, *J* 8.7 Hz, *J* 19.5 Hz, 1H, ArH); δ_C (100 MHz, $CDCl_3$) 43.4, 46.7, 91.8, 123.7, 126.5, 126.6, 126.8, 127.0, 127.6, 131.4, 133.3, 140.3, 140.9.

Trans-1-methoxy-2-bromobenz[f]indane **8**

To a magnetically stirred solution of dibromobenz[*f*]indane **2** (0.80 g, 1.98 mmol) in CH_3OH (5 ml) was added $AgSO_4$ (0.92 g, 2.96 mmol). After completion of the reaction for 8 h. at rt. water was added (10 ml), extracted with CH_2Cl_2 (3×10 ml), combined the organic part, dried over $MgSO_4$. After the removal of the solvent the crude product was subjected to column chromatography (silica gel) eluted with hexane/EtOAc (9/1) to afford the desired product, 1-methoxy-2-bromobenz[*f*]indane (0.25 g, 37%). υ_{max} IR (KBr)/cm^{-1} 752, 1115, 1439, 1502, 1580, 1629, 1721, 2829, 2853, 2924, 3056. δ_H (400 MHz, $CDCl_3$) 2.14 (s, 3H, Me), 3.42 (dd, *J* 4.1 Hz, *J* 16.9 Hz, 1H, H3), 3.63 (s, 3H, OCH_3), 3.87 (dd, *J* 6.3 Hz, *J* 16.7 Hz, 1H, H3'), 4.60 (dt, *J* 4.1 Hz, *J* 6.3 Hz, 1H, H2), 5.06 (d, *J* 3.2 Hz, 1H, H1), 7.45 (m, 2H, ArH), 7.71 (brs, 1H, ArH), 7.80-7.90 (m, 3H, ArH). δ_C (100 MHz, $CDCl_3$) 41.1, 51.5, 57.6, 90.6, 123.4, 124.7, 125.6, 126.3, 127.7, 128.3, 132.9, 134.3, 138.4, 138.6. Ms *m/z*, 279 (8), 278 (38), 277 (8) $[M]^+$, 276 (38), 247 (6), 246 (4), 245 (8), 198 (8), 197 (50), 196 (8), 167 (34), 166 (57), 165 (100), 154 (12), 153 (20).

Trans-1-hydroxy-2-bromobenz[f]indane **9**

To a magnetically stirred solution of dibromide **2** (0.75 g, 2.3 mmol) in THF (5.0 ml) was added silver perchloride (0.57 g, 2.67 mmol) in THF / H_2O (5/2 ml) dropwise. The reaction mixture was completed for 2 h. at rt. Water (10 ml) was added, extracted with dichloromethane (2×10 ml). The combined organic layer was dried ($MgSO_4$) and the solvent was removed. The residue was purified by column chromatography (silica gel), eluted with hexane/EtOAc (4/1) to yield the product (0.34 g, 56%). υ_{max} IR (KBr)/cm^{-1} 740, 779, 893, 1101, 1187, 1348, 1505, 1722, 3326. δ_H (400 MHz, $CDCl_3$) 2.50 (brs, 1H, OH), 3.35 (dd, *J* 7.6 Hz, *J* = 16.4 Hz, 1H, H3), 3.71 (dd, *J* 7.2 Hz, *J* 16.4 Hz, 1H, H3'), 4.34 (dd, *J* 7.2 Hz, *J* 13.6 Hz, 1H, H2), 5.41 (d, *J* 5.6 Hz, 1H, H1), 7.45-7.50 (m, 2H, ArH), 7.67 (s, 1H, ArH), 7.78-7.87 (m, 2H, ArH), 7.88 (s, 1H, ArH). δ_C (100 MHz, $CDCl_3$) 39.9, 54.6, 82.6, 123.1, 123.2, 125.8, 126.3, 127.7, 128.3, 133.1, 134.0, 137.5, 140.2. Ms *m/z*, 265 (8), 264 (52), 263 (8) $[M]^+$, 262 (60), 261 (10), 259 (8), 184 (8), 183 (86), 182 (16), 181 (26), 167 (6), 166 (36), 165 (100), 154 (20), 153 (32), 152 (56), 151 (20), 150 (10).

1, 2-oxide-benz[f]indane **10**

To a magnetically stirred solution of acetate **6** (0.23 g, 0.75 mmol) in MeOH (5.0 ml) was added

sodium methoxide (49 mg, 0.90 mmol) in methanol (3.0 ml). After the completion of the reaction for 4h. at rt., water (5.0 ml) was added, extracted with dichloromethane (3×5 ml). The combined organic layer was dried ($MgSO_4$) and solvent was removed. The crude material was chromatographed on silica gel, eluted with hexane/EtOAc (9/1) to give the product, 1, 2-oxide-benz[*f*]indane **10.** Yield, 86 mg, 63%. δ_H (400 MHz, $CDCl_3$) 3.35 (dd, *J* 7.6 Hz, *J* 16 Hz, 1H, H3), 3.72 (dd, *J* 6.8 Hz, *J* 16.4 Hz, 1H, H3'), 4.34 (dd, *J* 6.8 Hz, *J* 13.2 Hz, 1H, H2), 5.40 (d, *J* 6.0 Hz, 1H, H1), 7.45-7.51 (m, ArH, 2H), 7.65 (s, ArH, 1H), 7.80-7.86 (m, ArH, 3H). δ_C (100 MHz, $CDCl_3$) 39.9, 54.6, 82.5, 123.0, 123.1, 125.8, 126.3, 127.7, 128.3, 133.1, 134.0, 137.6, 140.2. Ms *m/z*, 184 (6), 183 (90), 182 (22) $[M]^+$, 181 (32), 167 (6), 166 (36), 165 (100), 163 (20), 154 (12), 153 (36).

Conclusions

Facile and efficient brominations of benz[*f*]indene were achieved with molecular bromine and fotobromination. Dibromo- and tribromobenz[*f*]indane were synthesised by bromination of benz[*f*]indene **1**. The optimum reaction conditions were depicted after many experiments. Many valuable materials could be synthesized by these brominated compounds *via* carbon-carbon bonds formation. Acetoxy, nitrate, methoxy, hydroxyl and epoxy derivatives of benz[*f*]indane were synthesised *via* substation reactions.

Acknowledgment

The authors thank to the Sakarya University Research Foundation and The Scientific and Technical Research Council of Turkey (TUBITAK, Grant 104T397) for financial support.

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