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Synthesis and Characterization of Benzophenone Based Phenyl Ether Derivatives

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Abstract:

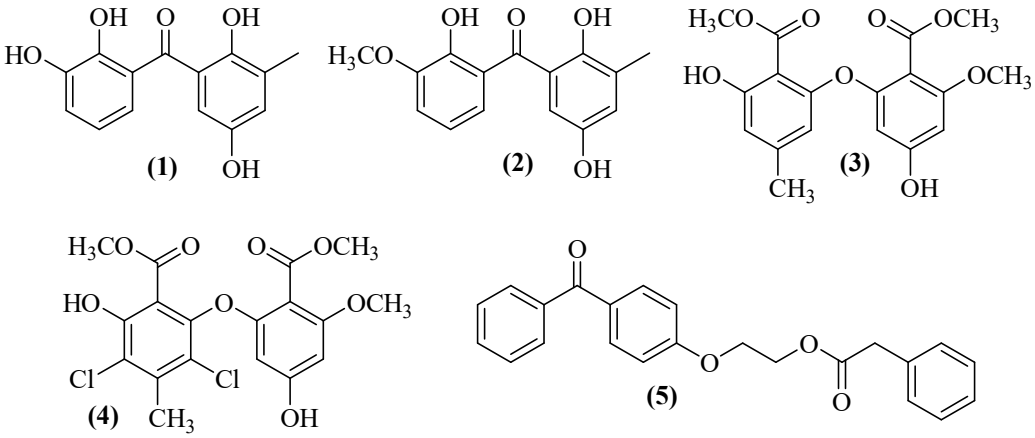
*Benzophenone and diphenyl ether derivatives are important compounds because of their biological activities and materialistic applications. Such compounds have also been isolated from a number of natural products. Individually, both these categories of compounds have found numerous applications in medicinal and material world. Therefore, the work presented here describes synthesis of benzophenone derivatives of diphenyl ethers. Three compounds **D, E** and **F** were synthesized using same benzophenone precursor, (2-hydroxy-4-methoxyphenyl)(phenyl) methanone and 2-bromo-5-nitrobenzaldehyde to get 2-(2-benzoyl-5-methoxyphenoxy)-5-nitrobenzaldehyde. Using different concentration of the same reducing agent ($NaBH_4$) two different products were obtained. In one case only aldehyde was reduced while in other case both aldehyde and ketone present in the molecule were reduced. Characterization was done using ^{1}H and ^{13}C spectroscopic methods.*

Keywords: *Benzophenone, diphenyl ether, reducing agent.*

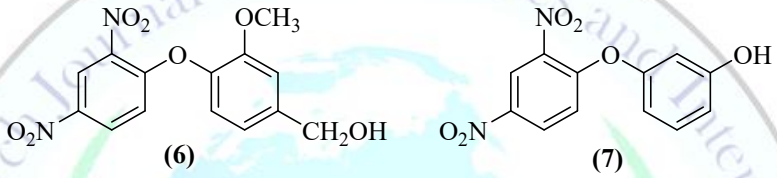
Introduction:

Benzophenone and diphenyl ether derivatives are a series biologically active compounds obtained from nature. Most of these classes of compounds are extracted from marine sources like sponges, algae and various marine fungal species. Compounds **(1)**and **(2)**shown below**,** for example, have been isolated from endophytic fungus of marine red alga *Laurenciaokamurai*. Both these compounds have shown antibacterial activity against human pathogens (*Escherichia coli*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus*), and aquatic bacteria (*Vibrio alginolyticus*, *V. harveyi*, and *V. parahaemolyticus*) with minimum inhibitory concentration (MIC) ranging from 4 to

32 µg/m and antioxidant activity with IC50 value ranging from 1.23 to 6.92 µg/mL[1].



Similarly compounds **(3)**and (**4**)isolated from the cultures of *Aspergillus sp.* have shown antinematodal activity using *Caenorhabditiselegans*as the nematode model. The LD90 of the above two compounds was found to be 75ppm within 24 hours [2].



Literature shows that synthetic benzophenone and diphenyl ether derivatives have application in material science as well. The compound **(5)** is a well-known agent in the textile industry that is applicable to polyester materials for the improvement of light fastness with dye providing substantial resistance to its sublimation [3]. Some of the diphenyl ethers synthesized recently have shown selectivity for various ions. For example, compound (**6**)is selective for Fe^{3+} and compound**(7)**is selective for F-[4][17]. The work hypothesized here is to synthesize benzophenone-ether hybrids to make a new class of molecules that may show enhanced and variable properties. Present thesis describes the synthesis and characterization of few of these molecules.

Benzophenone and diphenyl ether derivatives have shown various biological activities like anti-inflammatory [5], antibacterial [1], anti-malarial [6] and anti-androgenic [7] activities. These benzophenone and biphenyl ether derivatives have been found in various marine species. Due to their potential biological activities there are a number of reports for their synthesis using organic chemistry as tool[5][8][9].

Materials and Methods:

All chemicals and solvents were LR grade. Purification of organic compounds was done by column chromatography using silica gel (60-120 mesh) and specified solvents. TLC monitoring was done using silica coated aluminium sheets (60 F254; 0.2mm thickness, Merck, India). Characterization of all the organic compounds was done using ^{1}H (400 MHz) and ^{13}C (100 MHZ) NMR spectrometer.

Synthesis of 2-bromo-5-nitrobenzaldehyde (B):

2-Bromobenzaldehyde (0.400 g, 2.16 mmol) was taken in 100ml round bottom flask. To this was added DCM (7ml) and H_2SO_4 (3ml) in the ratio of 7:3 and then added HNO_3 (0.3ml, 7.2 mmol) and H_2SO_4 (0.9ml, 17 mmol). Reaction mixture was stirred for 2 hours at temperature (10-15^oC) in waterbath.TLC was done to monitor the reaction progress and after the reaction is complete; the mixture was extracted by using DCM (2×25), washed with water (2×25), and dried over anhydrous sodium sulphate. The solvent was evaporated and the crude product purified by column chromatography using ethyl acetate and hexane as an eluent to obtain white colored solid (363mg). Yield = 72%; Melting Point= 92-95^oC. ^1H NMR (δ; 400 MHz; $CDCl_3$): 7.8 (d, J=8.72Hz, 1H), 8.2 (dd, J=2.72, 9.2Hz, 1H), 8.7 (d, J=2.72Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 124.7, 128.8, 133.1, 134.4, 135.2, 147.6, 189.4.

Synthesis 2-(2-benzoyl-5-methoxyphenoxy)-5-nitrobenzaldehyde (D):

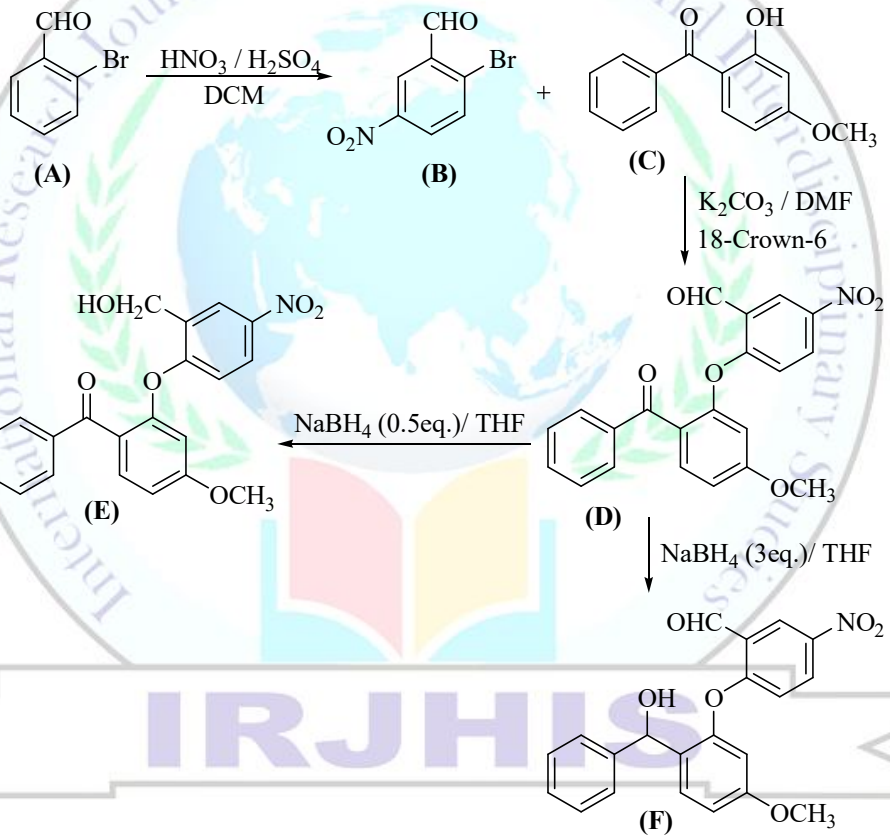
Method1: The compound **(C)** procured commercially (2-hydroxy-4-methoxyphenyl) (phenyl) methanone (0.360 g, 1.5 mmol) was taken in a 100mL round bottom flask to which was added DMF (10ml), K_2CO_3 (0.326 g, 2.3 mmol) and catalytic amount of 18-Crown-6. The contents were stirred in a round bottom flask for 10-15 minutes. To the stirred solution 2-bromo-5-nitrobenzaldehyde **(B)** (0.363g, 1.5 mmol), synthesized above, was added and further stirred for 12 hours at room temperature. TLC monitoring after 12 hour indicated formation of product that was extracted by using DCM (2×25), washed with water (2×25) and dried over anhydrous sodium sulphate. The solvent was evaporated and the crude product purified by column chromatography using ethyl acetate and hexane as eluent to give a light yellow colored solid (0.406 g). Yield = 55%; Melting Point =115-119^oC.

Synthesis of (2-(2-(hydroxymethyl)-4-nitrophenoxy)-4-methoxyphenyl)(phenyl)methanone(E):

Compound **(D)** obtained above, 2-(2-benzoyl-5-methoxyphenoxy)-5-nitrobenzaldehyde, (0.200 g, 0.53 mmol) was taken in 100ml round bottom flask to which THF (8mL), H_2O (0.1mL) and $NaBH_4$ (0.010g, 0.26mmol) were added. The resulting mixture was stirred magnetically for 5 minutes at room temperature. Reaction progress was monitored by TLC**.** After the completion of the reaction, distilled water (3mL) was added to the reaction mixture and solution stirred for another 5 minutes. The mixture was extracted with DCM and dried over anhydrous Na_2SO_4. Solvent evaporated gave crude product that was purified using column chromatography (hexane and ethylacetate) giving yellowish brown solid (.180g). Yield= 89%; Melting Point=109-112^oC. ^1H NMR (δ; 400MHz; $CDCl_3$): 3.9 (s, 3H), 4.5 (s, 2H), 6.6 (dd, J= 2.28Hz, 1H), 6.7 (d, J=9.20Hz, 1H), 6.8 (dd, J=2.72, 8.72Hz, 1H), 7.4 (m, 2H), 7.5 (m, 1H), 7.6 (d, J=8.68Hz, 1H), 7.6 (m, 2H), 8.0 (dd, J=2.72, 9.16Hz, 1H), 8.2 (d, 1H). ^{13}C NMR ($CDCl_3$): δ 55.8, 59.9, 107.5, 110.9, 114.6, 122.8, 124.6, 124.8, 128.3, 129.7, 131.6, 133.0, 133.8, 137.9, 142.8, 154.3, 159.7, 163.7, 193.9.

Synthesis of (2-(2-(hydroxymethyl)-4-nitrophenoxy)-4-methoxyphenyl)(phenyl)methanol(F):

Compound **(D)**, 2-(2-benzoyl-5-methoxyphenoxy)-5-nitrobenzaldehyde (0.150g, 0.39mmol) was taken in 100ml round bottom flask to which THF (8ml), H_2O (0.1ml) and $NaBH_4$ (0.045 g, 1.1 mmol) was added. The resulting mixture was stirred magnetically for 5 minutes at room temperature. Reaction progress was monitored by TLC, after the completion of the reaction; distilled water (3ml) was added and then stirred the reaction mixture for another 5 minutes. Then the mixture was extracted with DCM and dried over anhydrous Na_2SO_4. Solvent evaporated gave crude product that was purified using column chromatography (hexane and ethylacetate) giving light yellow colored solid (0.139g). Yield= 91%. ^{1}H NMR (δ; 400MHz;$CDCl_3$): 3.8 (s, 3H), 4.6 (d, J=5.96Hz, 2H), 5.8 (s, 1H), 6.4 (d, J=2.32Hz, 1H), 6.5 (d, J=9.16Hz,1H), 6.8 (dd, J=2.72, 8.68Hz, 1H), 7.2 (m, 5H), 7.4 (d, J=8.64, 1H), 7.9 (dd, J= 2.72, 9.2Hz, 1H),8.2 (d, J=2.76Hz, 1H). ^{13}C NMR ($CDCl_3$): 55.6, 60.3, 71.4, 106.5, 110.9, 115.0, 124.6, 124.7, 126.4, 127.5, 127.6, 128.4, 129.7, 135.0, 142.5, 142.5, 152.4, 159.9, 160.4.



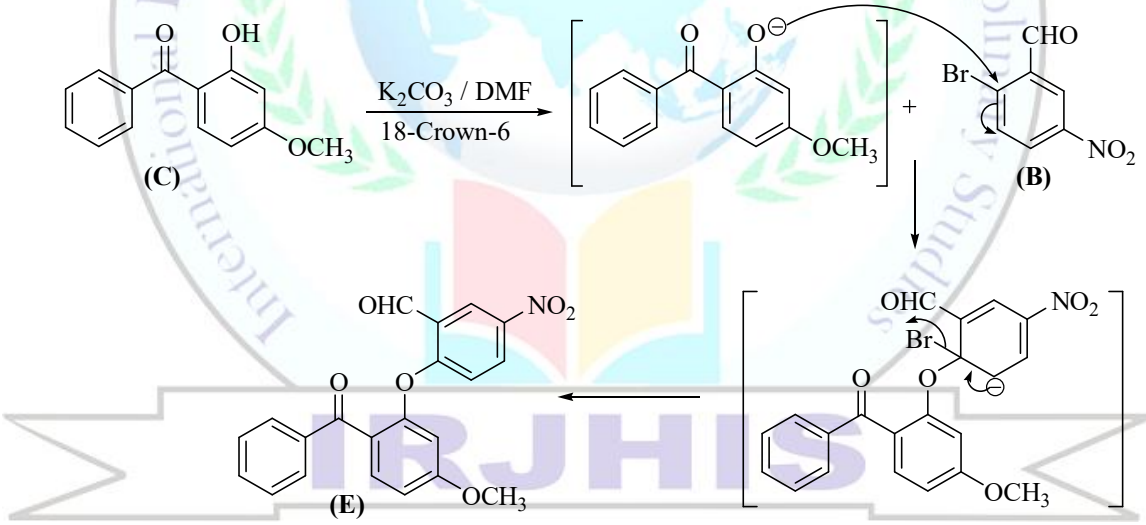
Scheme 1: Synthesis of benzophenone based phenyl ether

Result and Discussion:

Benzophenone based phenyl ether were synthesized (**scheme 1**). Nitration of 2-bromo benzaldehyde was carried out using concentrated nitric and sulphuric acid in dichloromethane using water bath. The product was obtained in the quantitative amount. Appearance of signals at 7.8 & 8.7ppm towards downfield δ value due to nitro group and decrease of one proton in the aromatic

region confirmed the nitration. This was further confirmed by a double doublet at 8.2ppm having J= 2.7Hz. Absence of double doublets at 7.8 & 7.6 ppm [22] confirmed that nitration has been achieved. Nitration product **(B)** obtained, was reacted with (2-hydroxy-4-methoxyphenyl) (phenyl) methanone **(C)** via nucleophilic aromatic substitution using mild base (K_2CO_3) in aprotic solvent and phase transfer catalyst (18-Crown-6) to obtain benzophenone based phenyl ether product **(D).** Presence of two carbonyl carbon at 193.5 and 186.4ppm due to ketone and aldehyde groups respectively and methoxy carbon at 55.9ppm confirmed the formation of product **(D)**. **Scheme2** briefly describes the mechanism of formation of ether bond by K_2CO_3. We envisaged to selectively reducing both the carbonyl groups one by one in the presence of other and total reduction of all the carbonyls. It was observed that 0.5 equivalents of $NaBH_4$ reduced only aldehyde group in the presence of ketone giving compound **(E)**.While excess of same reagent (3 equivalents) carries out reduction of both aldehyde and ketone to yield product **(F)**. Absence of proton in ^{1}H NMR at 9.9ppm and appearance of a new methylene proton at 4.5ppm confirmed the reduction of aldehyde to corresponding benzyl alcohol derivatives **(E)**. In ^{13}C NMR also the carbonyl at 186.4ppm due to aldehyde group disappeared with simultaneous appearance of methylene carbon at 59.9ppm. Other carbon at 193.9ppm due to ketone was intact. In aliphatic region of ^{13}C methoxy carbon of the benzophenone moiety appeared at 55.8ppm. Above observation confirmed the synthesis of compound **(E)**.

Mechanism:



Scheme 2: Mechanism of formation of ether bond with K_2CO_3

Compound **(F)** that was obtained by 3 equivalents of reducing agent as described above was also confirmed by ^{1}H and ^{13}C NMR. The disappearance of carbon due to carbonyl ketone from 193.5ppm and simultaneous appearance of alcoholic carbon at 71.3ppm along with methoxy and benzylic carbons at 55.5 and 60.3ppm respectively indicated the reduction of both carbonyl due to aldehyde and ketone together. In ^{1}H NMR also, besides methoxy protons (3.7ppm) the signals due to methyne proton (5.8ppm) corresponding to one hydrogen and benzylic proton corresponding to two

hydrogen's (4.6ppm) confirmed the reduction of both the carbonyl groups.

Earlier we attempted the synthesis of compound**(E)**using alternative route where aldehyde groups of compound B was 1st converted to corresponding alcohol in the presence of $NaBH_4$ and methanol **(Scheme 1).** The conversion compound **(B)**was confirmed by disappearance of aldehyde proton at 9.9ppm and simultaneous appearance of methylene proton of corresponding alcohol at 4.8ppm.

Conclusion:

The work described above successfully demonstrates the synthesis and characterization of three compounds **D, E** and **F**. use of same benzophenone precursor, (2-hydroxy-4-methoxyphenyl) (phenyl) methanone and 2-bromo-5-nitrobenzaldehyde to get 2-(2-benzoyl-5-methoxyphenoxy)-5-nitrobenzaldehyde. Using different concentration of the same reducing agent $NaBH_4$ two different products were obtained. Two of synthesis compounds **E** and **F** contain a chiral center also which needs to be resolved before its application in any field.

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