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A Novel Synthesis of [4-(3-methyl-1H-indol-2-yl) phenyl] (phenyl)methanone

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ABSTRACT

We have developed a simple route for the synthesis of [4-(3-methyl-1H-indol-2-yl)phenyl](phenyl)methanone from easily available starting materials. The (4-propylphenyl) phenylmethanone was prepared by Friedel Craft's benzoylation of n-propyl benzene with benzoyl chloride in dichloromethane using aluminium chloride as the Lewis acid catalyst. Side chain bromination with N-bromo succinimide in tetra chloro methane furnished the bromo derivative which on oxidation with bis-tetra butyl ammonium dichromate gave 1, 4–diacyl benzene. The target molecule was obtained through Fischer indole cyclisation of the diacyl benzene namely 1-(4-benzoylphenyl)propan-1-one via the formation of the hydrazone, followed by cyclization in presence of boron trifluoride ethyl etherate in acetic acid. The structure of the target molecule was elucidated by IR, H^1, C^{13} NMR, Mass spectroscopy and elemental analysis. This method proves to be an efficient route for the synthesis of [4-(3-methyl-1H-indol-2-yl)phenyl](phenyl)methanone in high yields, thereby facilitating the generation of potential biologically active compounds.

Keywords: Fischer indole synthesis, 1, 4-diacylbenzene, Friedel-Craft's benzoylation, Allylic bromination.

INTRODUCTION

Indole is one of the most important heterocyclic compounds found in nature. It consists of a six-membered benzene ring fused to five-membered nitrogen containing pyrrole ring[1]. The discovery of indomethacin, ethodolac and tenidap, as potent anti-inflammatory agents, has led to the exploration of the indole nucleus[2]. A significant number of derivatives were reported to possess potent wide spectrum of biological activity especially antibacterial[3-4], antifungal[5], anti inflammatory[6-10] and analgesic[11]. Due to high electron density at position 3, indole undergoes electrophilic substitutions at position 2 and 3, respectively. A variety of synthetic methods for the indole ring system have been developed for the past hundred years[12-15]. The palladium-catalyzed annulation of 2-haloanilines with alkynes, in particular, is of great importance due to the easy availability of substrates[16]. Indole integrated with diphenylmethanone at position 3 plays a significant role in control of larvicidal mosquitoes that cause malarial fever[17]. Similar compound with

diphenylmethanone substituent at position 2 was synthesized from o-ethynyl aniline and trifluoro sulfonyl benzophenone via two step reaction[18]. This reaction was catalyzed by palladium in variable oxidation state and high temperature had been used throughout the process. In this study, a novel 2-aryl indole has been synthesized with methyl substituent in position 3, using simple starting materials and novelty in the synthetic strategy.

EXPERIMENTAL

Material and Methods

All commercially available reagents and solvents were obtained from Sigma Aldrich Chemicals and SD Fine Chemicals. TLC was performed on pre-coated alumina sheets and visualized under UV light. Chromatographic separations were carried out on silica gel 60 Merck, & Co. Darmstadt, Germany). Melting points were obtained using open capillary tubes and uncorrected. Infra-red spectra were recorded on a Jasco Model 5300 FT-IR spectrometer in KBr over a range of 4000-200 cm^{-1}. The ^1H NMR and ^{13}C NMR data were recorded with a Bruker 500 MHz high resolution NMR Spectrophotometer and $CDCl_3$ was used as a solvent. Chemical shifts are reported in ppm and tetramethylsilane was taken as internal standard. Mass spectra were recorded on JEOL SX 102/DA-6000 mass spectrometer/data system. Elemental analysis results were found to be in good agreement (±0.4%) with the calculated values.

General procedure

Phényl(4-propylphényl)méthanone (2b)

This was prepared by the procedure[20] employed earlier by the Friedel-Crafts benzoylation of n-propyl benzene with benzoyl chloride. The product was obtained as an orange syrupy liquid. Yield: 75%

[4-(1-bromopropyl)phenyl](phenyl)methanone (3b)

This was prepared by the procedure[20] employed earlier using N-bromosuccinimide in tetrachloro methane. Yield: 85%

1-[4-(benzoyl)phenyl]propan-1-one(4b)

This was prepared by using bis tetrabutylammonium dichromate as the oxidizing agent by the method[20] employed earlier.

Yellow solid; Yield:99% m.p.86-88^0 C; IR (KBr): ν_{max} 1678, 1664 cm^{-1}; ^1H NMR ($CDCl_3$, ppm)**:** 1.2 (t,3H,CH_3), 3.1 (q, 2H,CH_2), 7.4-8.1 (m, 9H, Aromatic-H); ^{13}C NMR: 8.2, 32.3, 127.9, 128.5, 130.2, 133.1, 139.5, 141.2, 196.1, 200.4,Mass spectrum: *m/z* (%) = 238.281(M^+, 55.6) 209.2 (100), 181.2 (10.2), 105.1 (69.1), 77.1 (61.1) ; Anal Calcd. for ($C_{16}H_{14}O_2$): C 80.65 H 5.92; Found C 80.65 H 5.72; HRMS: ($C_{16}H_{14}O_2$) M^+ Calcd: 238.28116; Found: 238.28120

Synthesis of [4-(3-methyl-1H-indol-2-yl)phenyl](phenyl)methanone (5b)

To a solution of 1-[4-(benzoyl)phenyl] propan-1-one (4.76 g, 20 mmol) in ethanol (50 mL) phenyl hydrazine (2.2 mL, 20 mmol) was added. The solution was refluxed for 3 hours. The ethanol was distilled off and the resulting hydrazone was obtained as a dark brown solid. This was dissolved in acetic acid (50 mL) and BF_3-etherate (1 mL) was added drop wise. The solution was refluxed on a mantle for 3 hours. Finally the reaction mixture was cooled and poured over crushed ice. The precipitated bright yellow compound was filtered, washed with water and dried over anhydrous calcium chloride.

Yellow powder; Yield: (95%); m.p. :198-200^{o}C ; IR(KBr): ν_{max}1650 (C=O), 3343 (NH)cm^{-1},^1H NMR (500 MHz; DMSO-d_6): 2.46 (s, 3H, CH_3), 7.00-8.07 (m, 13H, Aromatic-H),11.34(s, 1H, indole-NH); ^{13}CNMR(125 MHz): 10.6,1 09.6, 111.8, 119.4, 119.4,122.9,127.6,129.1,129.9,130.1,130.8,132.9,133.1, 137.8,195.7.Mass m/z (%): 311.30 (M^+, 100%), 310.27 (37.2), 209.20(46.1), 130.17(25.8), 105.1(65.6) 77.14(64); Analysis Calcd. for $C_{22}H_{17}NO$: C 84.86,H 5.50, N 4.50 Found: C 84.51, H 5.51, N 4.62.

Phényl(4-ethylphényl)méthanone 2a

This was prepared by the earlier reported procedure by the Friedel-Craft's reaction of ethyl benzene with benzoyl chloride.Yield:78%

Synthesis of [4-(1-bromoethyl)phenyl](phenyl) methanone 3a

The compound was prepared by bromination of phényl(4-ethylphényl)méthanone 2a using N-bromosuccinimide in carbon tetra chloride using the procedure previously reported in our laboratory. The product was obtained as an orange syrupy liquid.Yield: 82%

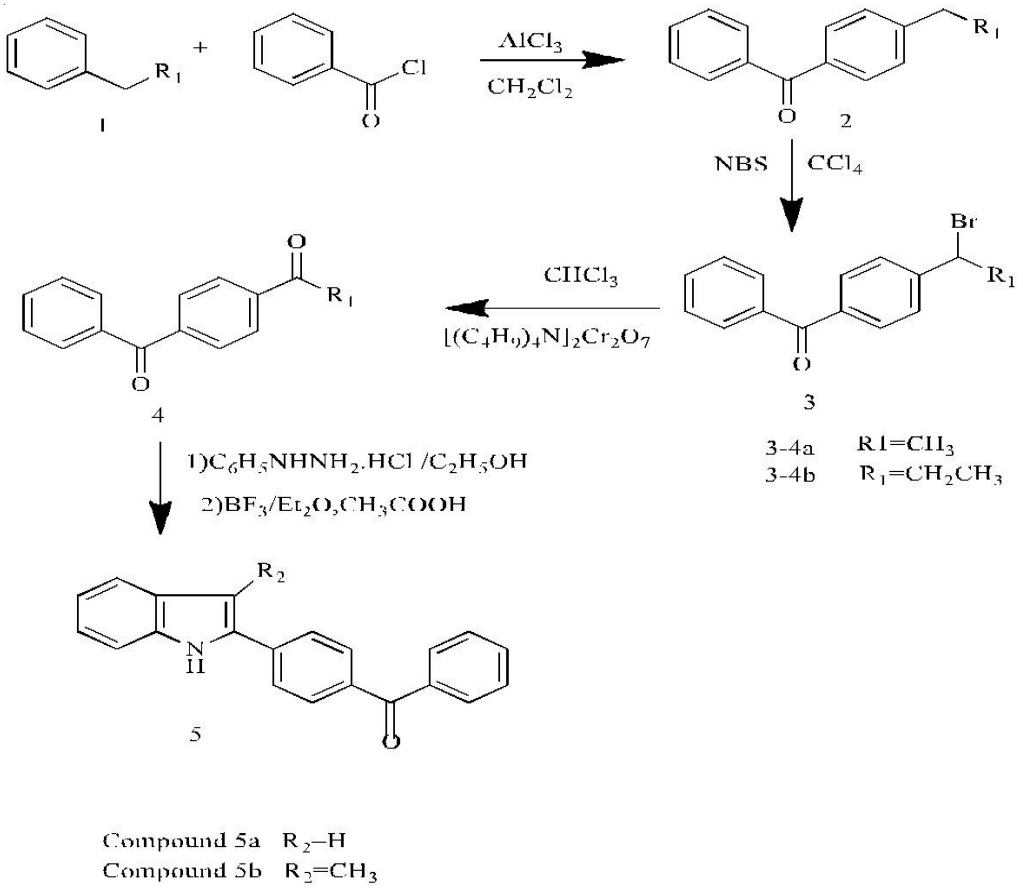
Preparation of (4-benzoylphenyl)ethanone (4a)

The (4-benzoylphenyl)ethanone was prepared from [4-(1-bromoethyl) phenyl] (phenyl) methanone 3a by the reported procedure[19] using bistetra butylammonium dichromate as the oxidizing agent. The melting point and spectral data were in close agreement with that reported earlier. Light yellow solid, Yield: 74%; m.p:80-84°C; IR(KBr):ν_{max}1689,1656cm^{-1},^{1}H NMR($CDCl_3$/TMS,ppm): 2.56(s, 3H, CH_3), 7.2-8(m, 9H, Ar)

Synthesis of [4-(1*H*-indol-2-yl)phenyl] (phenyl) methanone (5a)

To a solution of 1-(4-benzoylphenyl) ethanone (5.6 g, 25 mmol) in ethanol (50 mL) was added phenylhydrazine (3 mL, 25 mmol) and concentrated hydrochloric acid (0.5 mL). The reaction mixture was refluxed for 3 hours. Then ethanol was distilled off and the resulting hydrazone was obtained as a dark brown solid. This was dissolved in xylene (50mL) and anhydrous $ZnCl_2$ (6.8g, 50 mmol) was added. The reaction mixture was refluxed in an oil bath for 3 h and the progress of the reaction monitored by TLC. Then xylene was distilled off and the pot residue obtained was digested with water on a water bath for 0.5 h. A yellow glassy solid which separated out, was filtered and dried. It was purified by chromatography over silica gel using hexane / ethyl acetate (1:1) as the eluent .

Yield: 50%; m.p.: 110°C (decomposed); IR (KBr): 1669 (>C=O), 3313 (NH)) cm^{-1}; ^{1}H NMR($CDCl_3$/TMS): δ 6.4-7.7 (m, 13H, Aromatic), 10.9 (s, 1H, indole-NH); Mass *m/z* (%): 298.19 (100) 221.26 (29.5), 193.03 (43.7), 105.02 (41.9), 77.1 (90.3), 55.06 (43.7).



Scheme 1: Synthesis of diphenylmethanone integrated indoles

Preparation of bis-tetrabutyl ammonium dichromate

The above oxidizing agent was prepared by the method reported[19] in the literature, from tetra butyl ammonium bromide and potassium dichromate.

RESULTS AND DISCUSSION

In this research work, the target molecule containing a diphenyl methanone moiety and methyl group at positions 2 and 3 respectively was synthesized. The product was obtained in good yield whereas the yield of the 2-substituted product namely [4-(1H-indol-2-yl)phenyl](phenyl) methanone which was prepared[18] by the palladium catalysed coupling of diphenylmethanone triflate with 2-ethynyl aniline was only 39%. Moreover, the use of expensive and toxic starting materials was replaced with simple, inexpensive and less toxic starting materials.

To synthesise indoles with diphenylmethanone unit at the second position, 1-(4-benzoylphenyl)ethanone and 1-(4-benzoylphenyl) propan-1-one were required as starting materials. They were prepared by following the procedure[20] employed earlier. Initially Fischer indolization of 1-(4-benzoylphenyl)ethanone with phenylhydrazine in ethanol followed by refluxing the resulting hydrazone with anhydrous zinc chloride in xylene afforded [4-(1*H*-indol-2-yl)phenyl](phenyl) methanone 5a in 50% yield.

The product obtained was found to melt at 110^{0}C and the structure has been confirmed by IR and NMR spectra. The IR spectrum showed peaks at 3313 cm^{-1} due to indole NH and at 1669 cm^{-1} due to carbonyl group. The ^{1}H NMR spectrum showed a multiplet at 6.4-7.7 due to aromatic hydrogens and a broad singlet at • 10.9 due to indole NH. This compound has been reported[18] by the palladium catalyzed coupling of 4-benzophenone triflate with 2-ethynylaniline. The structure was confirmed by its IR and NMR data which was in agreement with that reported in the literature.

Further, it was decided to indolise the corresponding 1-[4-(benzoyl)phenyl]propan-1-one to the corresponding indole by the Fischer indolisation of the hydrazone. 1-[4-(benzoyl) phenyl] propan-1-one was treated with phenyl hydrazine in ethanol and the resulting hydrazone was subjected to Fischer indolization using BF_3- ethyl etherate in boiling acetic acid. The [4-(3-methyl-1*H*-indol-2-yl)phenyl](phenyl)methanone 5b was obtained in quantitative yield and the structure has been

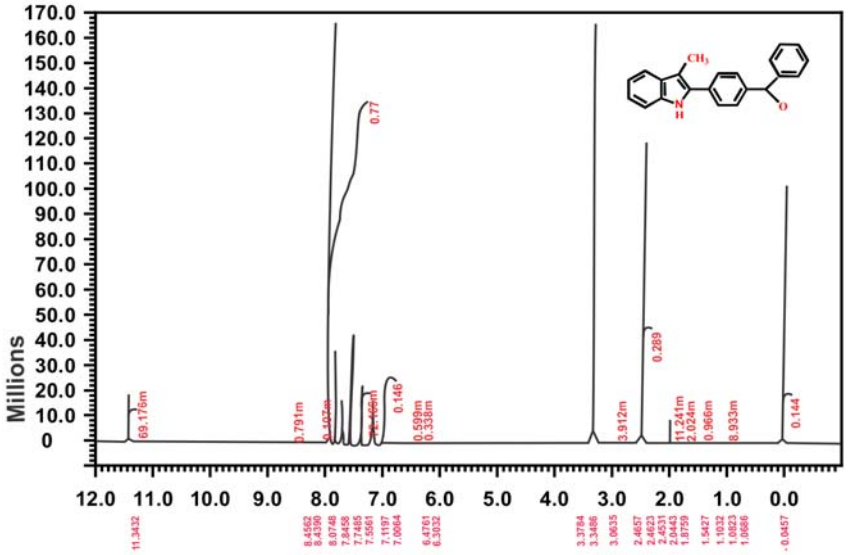


Fig.1. ^{1}H NMR spectrum of 4-(3-methylindol-2-yl) benzophenone

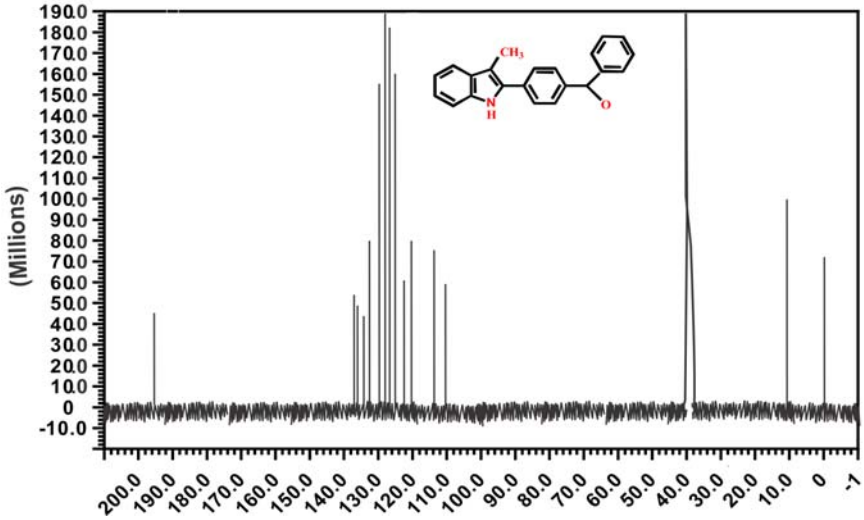


Fig. 2. ^{13}C NMR spectrum of 4-(3-methylindol-2-yl) benzophenone

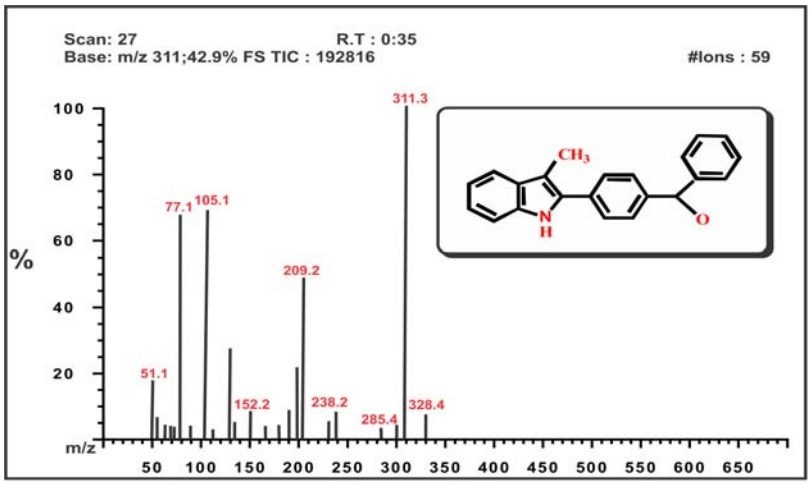


Fig. 3. Mass spectrum of 4-(3-methylindol-2-yl) benzophenone

Fig. 4. ^{1}H NMR spectrum of 4-propionyl benzophenone

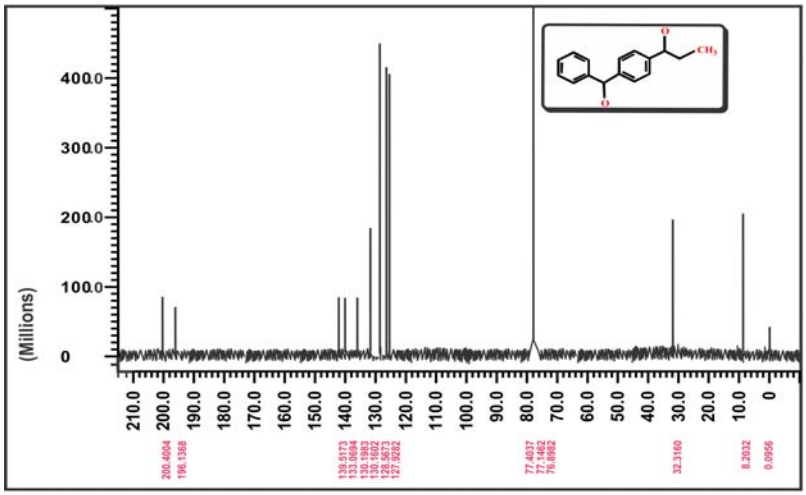


Fig. 5. ^{13}C NMR Spectrum of 4-propionyl benzophenone

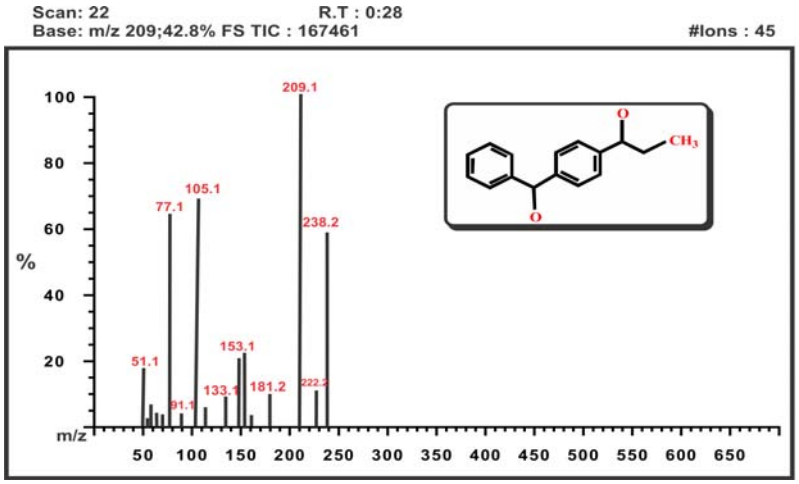


Fig. 6. Mass spectrum of 4-propionyl benzophenone

confirmed by IR, ^{1}H NMR and ^{13}C NMR spectra. The presence of a carbonyl group was confirmed from IR by the presence of a sharp peak at 1650 cm^{-1}. In the ^{1}H NMR spectrum, peak at δ 3.9 containing 3H singlet was due to indole methyl hydrogen, multiplet peak at δ 6.7-8.4 for aromatic hydrogens and a highly deshielded singlet peak at δ 8.5 was due to NH of indole. Fig. 1. The ^{13}C NMR spectrum showed 15 peaks (for twenty two carbons-18 signals) at 10.65, 109.63, 111.78, 119.38, 119.42, 122.94, 127.59, 129.13, 129.86, 130.08, 130.83, 132.93, 133.13, 137.77, and 195.72. Fig. 2. The mass spectrum showed a molecular ion peak at *m/z* = 311.30 Fig. 3. The scheme shown below represents the various steps involved in the synthesis.

CONCLUSION

In the present work, we have developed a simple but highly efficient method for the synthesis of a novel diphenylmethanone integrated indole, which is also supported by the IR and NMR spectral data. Further structural optimization of diphenylmethanone based indoles is well under way with the aim of evaluating their biological activity.

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