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Synthesis And Characterization Of Fluorinated Chalcones and Its Derivatives From Trifluoromethylacetophenone

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Abstract:

This study presents the synthesis and characterization of fluorinated chalcone derivatives using trifluoromethylacetophenone as the primary starting material. Employing the Claisen-Schmidt condensation method, various fluorinated chalcones were synthesized by reacting trifluoromethylacetophenone with different aromatic aldehydes under basic conditions. The introduction of trifluoromethyl groups into the chalcone framework significantly enhances chemical stability, lipophilicity, and potential biological activity. The synthesized compounds were characterized using Fourier Transform Infrared Spectroscopy (FTIR), Nuclear Magnetic Resonance (^1H and ^{13}C NMR), Mass Spectrometry (MS), and melting point analysis to confirm their structures and purity. The study highlights the influence of different substituents on reaction efficiency, product yield, and structural properties.

Keywords: Trifluoromethylacetophenone, substituted aldehydes, Claisen-Schmidt condensation, Chalcone, Characterization

Introduction:

Chalcones, defined by their α,β-unsaturated carbonyl framework, form a crucial class of organic compounds known for their diverse biological and pharmacological activities, including antimicrobial, anti-inflammatory, antioxidant, and anticancer properties.[1]

The literature survey reveals that Chalcones are structural derivatives of 1,3-diphenylprop-2-en-1-one. They are ubiquitous in natural products and belong to the family of flavonoids examples licochalcone A, licochalcone D and morachalcone A[2,3]They have been reportedly used as anticancer[4-5], antidiabetics[6], antioxidants[7], antimalarial[8-9], antitubercular[10-11], antiviral[12], anti-inflammatory[13-14],antibacterial[15-16] agents etc. Furthermore, chalcones are industrially used as light stabilizing agent[17], sweetening agent[18], analytical reagent in amperometry[19], spectrometric reagent[20] and synthetic reagent for the synthesis of pharmacologically active heterocyclic compounds[21-23].Their structural flexibility and ease of synthesis make them valuable intermediates in the development of various bioactive molecules and functional materials[24] Among structural modifications, the incorporation of fluorine atoms, particularly trifluoromethyl (-CF_3) groups, has emerged as an effective strategy to enhance the chemical and biological properties of organic molecules.[25]

Fluorinated compounds exhibit unique characteristics, such as increased

lipophilicity, metabolic stability, and improved binding affinity to biological targets, which significantly influence their pharmacokinetic and pharmacodynamics profiles.[26]in medicinal chemistry, trifluoromethyl-substituted chalcones have gained attention due to their enhanced bioavailability and potent biological activities, including anticancer, antiviral, and anti-inflammatory effects.[27]The Claisen-Schmidt condensation, a base-catalyzed aldol condensation between acetophenones and aromatic aldehydes, remains the most widely used method for synthesizing chalcones due to its simplicity, high yields, and mild reaction conditions.[28]

When trifluoromethylacetophenone is employed as the key reactant, the resulting chalcones exhibit improved chemical stability and potential for further functionalization.This study focuses on the synthesis of fluorinated chalcone derivatives using trifluoromethylacetophenone and a range of aromatic aldehydes. The synthesized compounds were characterized using Fourier Transform Infrared Spectroscopy (FTIR), Nuclear Magnetic Resonance (^{1}H and ^{13}C NMR) spectroscopy, Mass Spectrometry (MS), and melting point analysis to confirm their structures and evaluate their purity. The influence of various substituents on reaction yield, structural features, and potential bioactivity was also explored, contributing to the growing field of fluorinated bioactive compounds.

Experimental Materials and Methods:

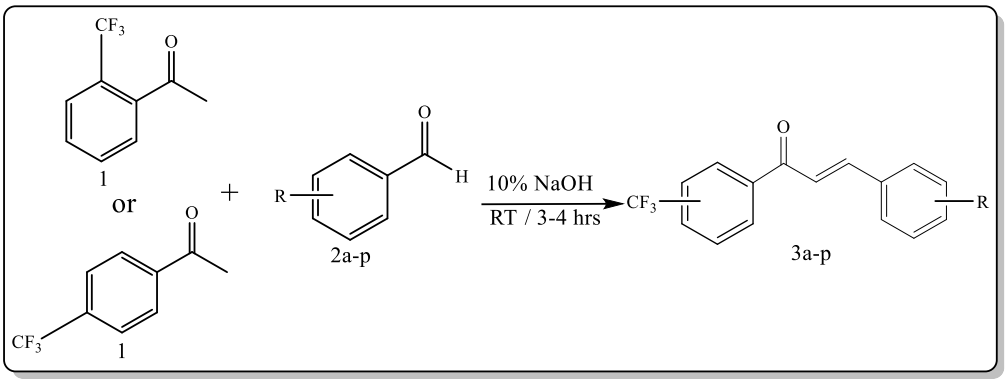
General:

Allthechemicalsandsyntheticgradere agentwereproducedfromSigmaAldrichIndia andMerckchemicals.

Trifluoromethylacetophenone, substituted aldehydes used in this work were used withoutfurther purification, melting points were taken in open capillary and are un-corrected. ^{1}H-NMR spectrawere recorded on a Bucker DRX-400 instrument and IR was recorded in KBr on a Nicolet impact 410 and^{13}C NMR spectra recorded on Shimanzu GCMS and on JEOL–Accu TOF DARTMS-T 100 Lc. Theprogressofreactionsandthepurityofthepr oductswereobserved by TLCon silicagel.

Procedure for the Synthesis of Chalcones:

In a 100 mL round-bottom flask, dissolve 0.01 mol of trifluoromethylacetophenone (1) and 0.01 mol of an aromatic aldehyde (2) in 20 mL of ethanol.Stirr the solution magnetically at room temperature. Add 5 mL of 10% NaOH solution drop wise to the reaction mixture under continuous stirring at room temperature for the completion of the reaction. Monitor the reaction by thin-layer chromatography (TLC) using a solvent system of ethyl acetate: hexane (3:7).Once the reaction is complete (as indicated by TLC), neutralize the mixture with dilute HCl until a neutral pH is achieved. The chalcone precipitates out as a solid. Filter the solid product under vacuum and wash it with cold deionized water to remove residual salts. Recrystallize the crude product from ethanol to obtain pure fluorinated chalcone derivatives. (Scheme-1)



Scheme: 1

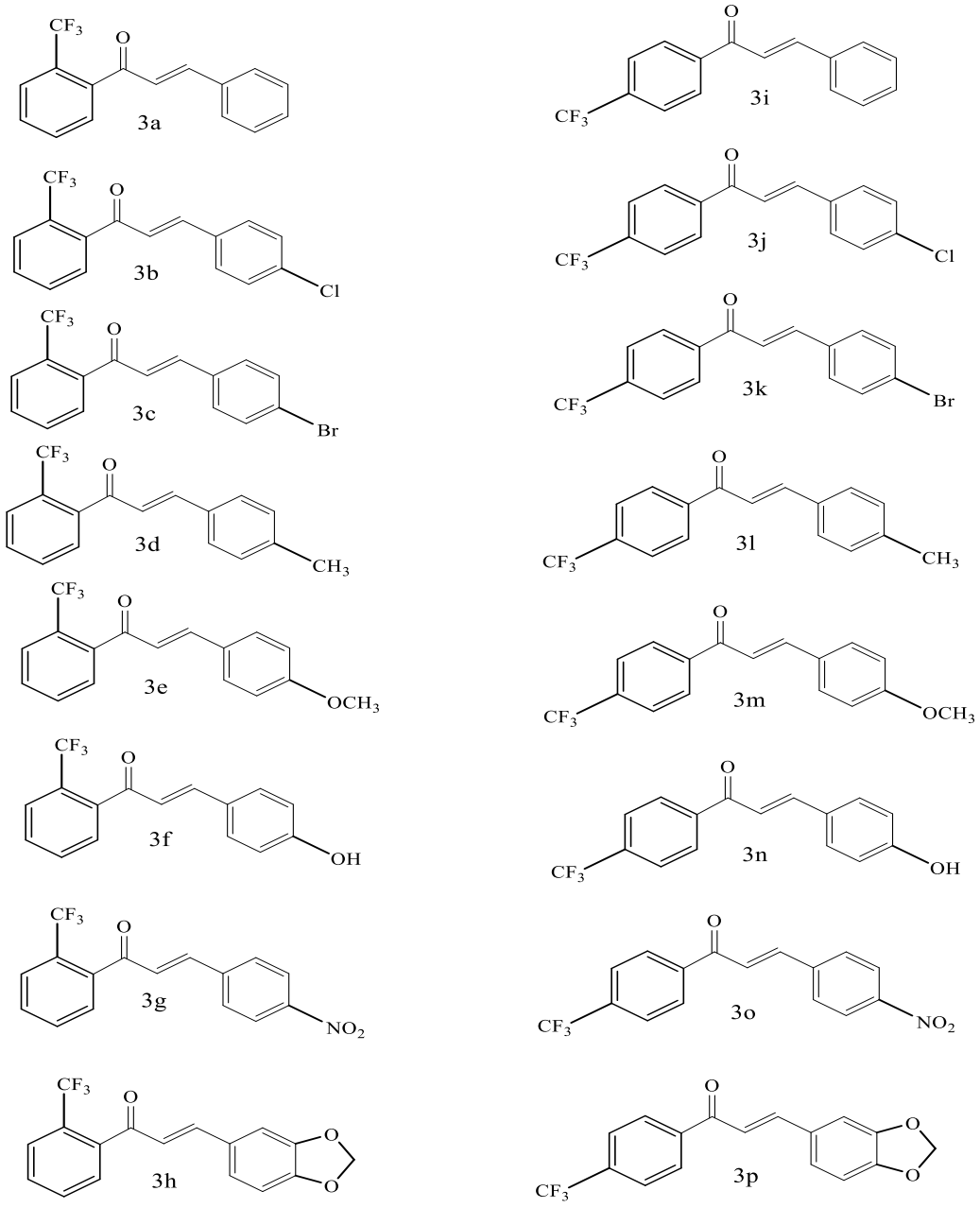
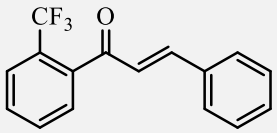
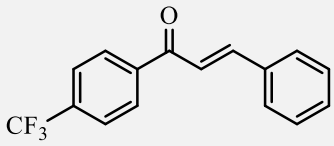


Fig. 1. Synthesized Chalconesand its Derivatives structures.

Table 1: Synthesis of fluorinated chalcones and its derivatives.

Entry	R	Time in hrs	% yield	Melting Point in ^{o}C
				
3a	H	4.00	82	123 ^{o}C
3b	4-Cl	3.20	91	143 ^{o}C
3c	4-Br	3.10	90	160 ^{o}C
3d	4-CH_3	4.00	83	120 ^{o}C
3e	4-OCH_3	3.50	80	130 ^{o}C
3f	4-OH	4.00	81	150 ^{o}C
3g	4-NO_2	2.90	91	166 ^{o}C
3h	benzo[d][1,3]dioxole-5-carbaldehyde	3.00	88	75 ^{o}C
				
3i	H	4.00	84	132 ^{o}C
3j	4-Cl	3.00	92	155 ^{o}C
3k	4-Br	2.70	89	165 ^{o}C
3l	4-CH_3	4.10	82	125 ^{o}C
3m	4-OCH_3	3.40	83	138 ^{o}C
3n	4-OH	4.20	82	162 ^{o}C
3o	4NO_2	2.80	93	172 ^{o}C
3p	benzo[d][1,3]dioxole-5-carbaldehyde	3.40	85	120 ^{o}C

Result and Discussion:

Fluorinated chalcones were successfully synthesized through the Claisen–Schmidt condensation of trifluoromethylacetophenone with various aromatic aldehydes under basic conditions. The reaction was carried out using sodium hydroxide as a catalyst in ethanol at room temperature. The presence of the electron-withdrawing trifluoromethyl (-CF_3) group in the acetophenone significantly influenced the reactivity, leading to high yields (80–90%) of the desired chalcones. The reaction mechanism followed the classical aldol condensation pathway, where deprotonation of the acetophenone generated an enolate ion that attacked the carbonyl carbon of the aldehyde. The intermediate β-hydroxy ketone underwent dehydration to afford α,β-unsaturated chalcone framework. The -CF_3 group, due to its strong inductive effect, enhanced the acidity of the α-hydrogen, promoting enolate formation and improving reaction efficiency.

The incorporation of the trifluoromethyl group into the chalcone framework enhanced the chemical stability and lipophilicity of the synthesized compounds, properties often desirable in drug design. The electron-withdrawing nature of -CF_3 increased the acidity of α-hydrogens in acetophenone, facilitating enolate formation and improving reaction rates and yields.Substituent effects from various aromatic aldehydes also influenced the reaction outcomes. Electron-donating

groups (e.g., -OCH_3, -CH_3, -OH in **Table 1**) on the aldehyde ring slightly decreased yields due to reduced electrophilicity of the carbonyl carbon, while electron-withdrawing groups (e.g., -NO_2, -Cl, Brin **Table 1**) enhanced reactivity, leading to higher product yields.The spectroscopic analyses confirmed the successful synthesis of fluorinated chalcones. The introduction of fluorine into organic frameworks is known to modulate biological activity, making these fluorinated chalcones potential candidates for further pharmacological evaluation.

Characterization of Fluorinated: Chalcones:

The synthesized fluorinated chalcones were characterized using spectroscopic techniques such as Fourier-transform infrared spectroscopy (FT-IR), nuclear magnetic resonance (^{1}H-NMR, and ^{13}C NMR), and Mass spectrometry (MS).

FT-IR Analysis: The IR spectra displayed characteristic absorption bands for the chalcone framework. The C=O stretching vibration appeared around 1650–1675 cm^{-1}, while the C=C stretching of the,β-unsaturated system was observed near 1580–1600 cm^{-1}. A distinct band around 1120–1150 cm^{-1} corresponded to the C–F stretching of the trifluoromethyl group, confirming its presence.[1]

H NMR Analysis: The ^{1}H NMR spectra exhibited the typical chalcone proton signals. The olefinic protons (α,β-unsaturated system) appeared as doublets in the range of δ 7.5–7.9 ppm with coupling constants (J ≈ 15–16 Hz), indicating trans-configuration. Aromatic protons resonated between δ 7.0–8.0 ppm, while the influence of the -CF_3 group caused slight downfield shifts in neighboring proton signals. **^{13}C NMR Analysis:** The ^{13}C NMR spectra confirmed the presence of carbonyl carbon signals at δ 190–195 ppm and olefinic carbons at δ 120–140 ppm. The –CF_3 carbon resonated around δ 125 ppm.

Mass Spectrometry: The mass spectra confirmed the molecular weights of the synthesized chalcones, with molecular ion peaks ($[M]^+$) corresponding to the expected m/z values.

3a (E)-3-phenyl-1-(2-(trifluoromethyl)phenyl)prop-2-en-1-one
IR (KBr, $\gamma_{max,}$ cm^{-1}) 2985 (Ar-H str.), 2939 (C-H str.), 1725 (C=O str.), 1609 (C=C str.), 1455 (C-H bend), 1310 (C-CF_3 str.), ^{1}H NMRspectrum,δ, ppm:6.98-7.05 d (1H, C=C-H, *J* = 8.0 Hz), 7.33–7.36 d (1H, Ar-H, *J* = 8.0 Hz), 7.72-7.86d (2H, Ar-H, CF_3 benzene), 7.92-7.95d (2H, Ar-H, *J* = 8.0 Hz), 8.32–8.35d(2H, Ar-H, *J* = 8.0 Hz), ,^{13}CNMR: 192, 145, 135,134,132, 129,127 128, 121. Mass spectrum (m/z) 276.5 $(M)^+$

3h (2*E*)-3-(1,3-benzodioxol-5-yl)-1-[2-(trifluoromethyl)phenyl]prop-2-en-1-one
IR (KBr, $\gamma_{max,}$ cm^{-1}) 2923 (Ar-H str.), 2851 (C-H str.), 1726 (C=O str.), 1628 (C=C str.), 1484 (C-H bend), 1314 (C-CF_3 str.),1132 (C-O str.), ^{1}H NMR spectrum,δ, ppm: 6.01 s (2H, O-CH_2-O piperonal); 6.79–6.81 d (1H, Ar-H, *J* = 8.0 Hz); 6.84–6.88 d (1H, Ar-H, *J* = 14.0 Hz); 6.95–6.98 d (1H, Ar-H, *J* = 9.7 Hz); 7.05–7.06 (1H, Ar-H); 7.18–7.22 d (1H, Ar-H, *J* = 16.4 Hz); 7.44–7.45 d (1H, Ar-H), 7.56–7.64 m (2H, Ar-H), 7.74–7.76 d (1H,Ar-H, *J* = 7.2 Hz),^{13}CNMR: 193, 146, 135,134,131, 129,127 128, 121Mass spectrum (m/z) 320.45 $(M)^+$

3p (2*E*)-3-(1,3-benzodioxol-5-yl)-1-[4-(trifluoromethyl)phenyl]prop-2-en-1-one
IR (KBr, $\gamma_{max,}$ cm^{-1}) 2981 (Ar-H str.), 2937 (C-H str.), 1723 (C=O str.), 1608 (C=C str.), 1456 (C-H bend), 1309 (C-CF_3 str.),1106 (C-O str.), ^{1}H NMRspectrum,δ, ppm: 6.09 – 6.11 s (2H, O-CH2-O Piperonal), 6.99–7.01 d (1H, C=C-H, *J* = 8.0 Hz), 7.35–7.37 d (1H, Ar-H, *J* = 8.0 Hz), 7.67 s (1H, Ar-H Piperonal), 7.71–7.84 d (2H, Ar-H, CF_3 benzene), 7.91-7.93 d (2H, Ar-H, *J* = 8.0 Hz), 8.31–8.33 d(2H, Ar-H, *J* = 8.0 Hz.

^{13}CNMR: 191, 144, 134,133,132, 129,127 128, 121Mass spectrum (m/z) 322.55 $(M)^+$

Conclusion:

In this study, fluorinated chalcones were successfully synthesized through the Claisen–Schmidt condensation of trifluoromethylacetophenone with various aromatic aldehydes under basic conditions. The presence of the trifluoromethyl ($-CF_3$) group played a crucial role in enhancing the reactivity of the acetophenone derivative, leading to efficient enolate formation and resulting in high yields of the desired chalcones. The reaction conditions proved to be mild, cost-effective, and adaptable to a range of aldehyde derivatives, highlighting the versatility of this synthetic approach. Comprehensive characterization using FT-IR, ^{1}H-NMR, ^{13}C-NMR, and Mass spectrometry confirmed the successful formation of the fluorinated chalcone framework. The spectroscopic data clearly indicated the presence of key functional groups, including the,β-unsaturated carbonyl system.The introduction of the $-CF_3$ group not only enhanced the chemical stability and electron-withdrawing nature of the chalcones but also potentially improved their pharmacokinetic properties, making them promising candidates for further biological evaluations. This work contributes to the growing interest in fluorinated organic compounds, particularly in the field of medicinal chemistry, where fluorine-containing molecules often exhibit improved bioactivity and metabolic stability.

Future studies could explore the biological activities of these fluorinated chalcones and further investigate structure-activity relationships (SAR) to optimize their potential as therapeutic agents.

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