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Article

Redefining Chalcone Synthesis: Aldol Adduct Elimination for the Rapid Access to Thienyl Chalcones

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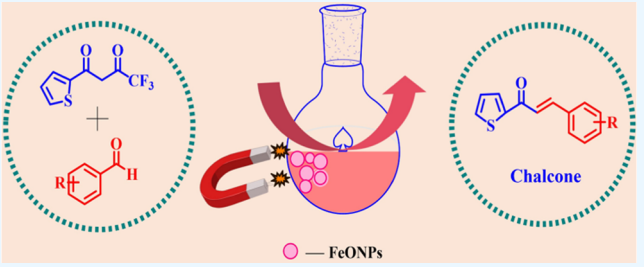
ABSTRACT: This paper introduces a unique and novel method for synthesizing thienyl chalcones using iron oxide nanoparticles (FeONPs) as a heterogeneous catalyst. It stands out as a rare example in the literature for the synthesis of these chalcones from 1,3-diketones and various aromatic aldehydes. The magnetic FeONPs employed as the catalyst bring several advantages, including their efficiency, affordability, and ecofriendly nature, making them an attractive choice for producing thiophene chalcones. One noteworthy aspect of this methodology is the utilization of mild reaction conditions, which greatly simplify the operational aspects of the reaction. Synthesized chalcones were confirmed through the application of various techniques, proton-NMR, ^{13}C NMR, mass spectrometry, and single-crystal X-ray diffraction analysis. These analyses provide valuable insights into the chemical compositions and structural characteristics of the synthesized compounds. Significantly, this methodology is reported for the first time in the literature, indicating its novelty and contribution to the field of chalcone synthesis.



1. INTRODUCTION

Today, there is a pressing need to develop efficient and environmentally friendly methods for synthesizing bioactive compounds such as chalcone.[1] Nanocatalysis involves the use of nanoparticles to facilitate chemical reactions, bridging the gap between traditional homo- and heterogeneous catalysis. During the last three decades, researchers have made significant progress in utilizing nanoparticles in synthetic organic chemistry. Nanocatalysts offer advantages such as a high surface area, which allows easy access to reactants at the nanoscale, resulting in enhanced catalytic activity. Furthermore, nanocatalysts exhibit superior stability and activity, and their recovery is efficient and cost-effective.[2] However, the practical implementation of nanoparticles as catalysts faces challenges related to their separation and recovery. A promising solution is the use of magnetic particles in catalysis, as nanoparticles can be easily recovered through magnetic decantation. Heterogeneous catalysts, particularly metal-based catalysts like Raney nickel, metal halides, platinum, and palladium, play a crucial role in chemical conversions.[3−5] Among these metal-based catalysts, iron oxide nanoparticles (FeONPs) have garnered significant attention due to their large surface area and high reactivity.[6,7] Chemists have extensively employed FeONPs in various transformations of organic functional groups.

Chalcone is a fascinating organic compound that has demonstrated a wide range of applications.[8] These molecules are biologically significant due to their diverse array of activities, including antibacterial,[9] anticancer,[10] antidiabetic,[11] antiulcer,[12] and anti-inflammatory[13] properties. Additionally, they serve as precursors for various organic compounds such as pyrazole, oxazole, flavonoids, and isoflavonoids.[14,15] Numerous research articles have been published on the medicinal importance of chalcone and its derivatives.[16] Thienyl chalcones have emerged as a prominent class of organic compounds with widespread applications in medicinal chemistry, materials science, and organic synthesis. These compounds are characterized by the fusion of a thienyl moiety with a chalcone framework that features an α,β-unsaturated ketone group. Thienyl chalcones possess a diverse array of biological activities, encompassing antimicrobial,[17] anti-inflammatory,[18] antioxidant,[19] and anticancer[20] properties. Consequently, they have garnered substantial attention in the field of drug discovery and development.

Several synthetic pathways have been suggested for the synthesis of chalcones, as depicted in Scheme 1[21,22] One method involves the preparation of chalcones from benzoyl

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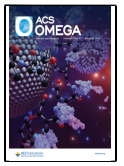
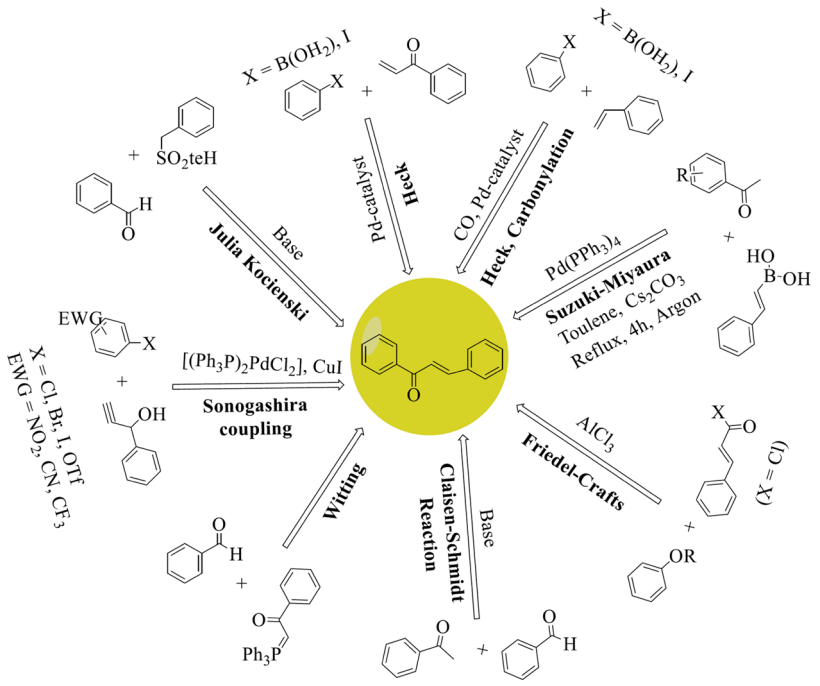


Scheme 1. Various Methods Employed to Prepare Chalcones



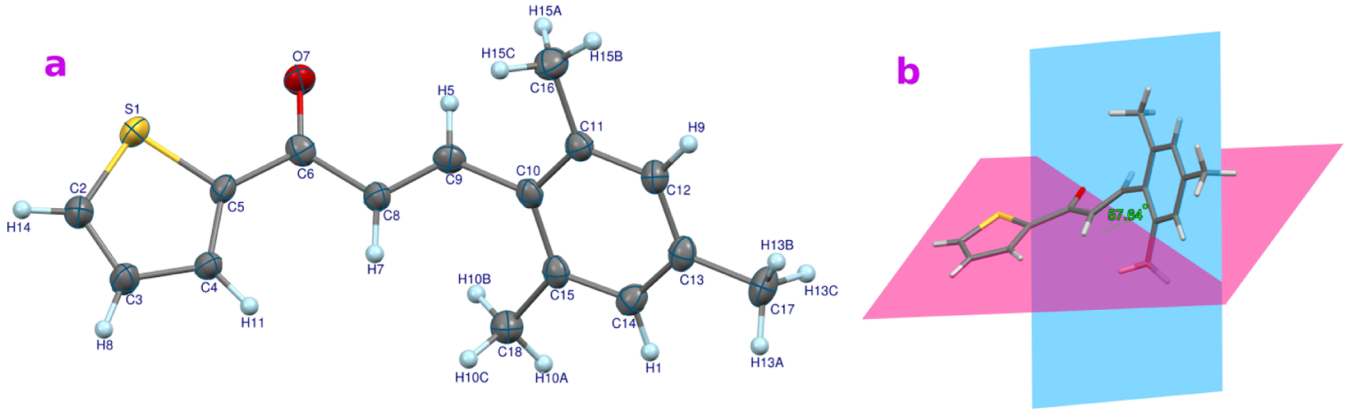


Figure 1. (a) ORTEP and (b) nonplanarity representation of 3-mesityl(1-thiophen)prop-2-en-1-one.

chlorides and phenylvinylboronic acid through a Suzuki coupling reaction.[23] However, in the classical approach, there is a higher likelihood of byproduct formation, which subsequently decreases the overall yield.

The novelty of this study lies in the development of novel methods and catalysts for synthesizing chalcones with a focus on enhancing the efficiency of the process. One notable aspect is the utilization of sonochemistry to synthesize iron oxide nanoparticles, which not only provides an approach for preparing nanoparticles but also allows for the investigation of their catalytic properties in chalcone synthesis. This integration of sonochemical synthesis with chalcone formation showcases the potential for more environmentally friendly and sustainable synthetic routes. Additionally, the article includes a comparative analysis between the classical method and the sonochemical method for chalcone synthesis, highlighting the advantages and benefits of the latter. Overall, this work makes a valuable contribution to the field by introducing innovative methods, catalysts, and techniques and underscoring their advantages in chalcone synthesis. This work reports a facile and efficient new method for the synthesis of chalcones using 1,3 diketones and aromatic aldehydes; this investigation constitutes a noteworthy addition to the field of organic synthesis and sustainable chemistry.

2. MATERIALS AND METHODS

The various reagents and chemicals were purchased from Sigma-Aldrich. PerkinElmer Spectrum Version 10.03.09 was used to record the infrared (IR) spectra. The ^{1}H and ^{13}C spectra (Agilent-NMR) were recorded by using $CDCl_3$. Chemical shift values were reported in parts per million relative to TMS as a standard; the mass spectra were determined using a water micro-TOF QII mass spectrophotometer. Sonication was performed in a Probe sonicator with a frequency of 25 kHz and a nominal power of 500 W (Figure 1). Field emission scanning electron microscopy (FE-SEM) was performed on a 4 FEI Quanta 200 SEM instrument operated at an accelerating voltage of 20 kV.

2.1. Synthesis of Chalcones by the Conventional Method. An equimolar ratio of ethanolic solution of 4,4,4-

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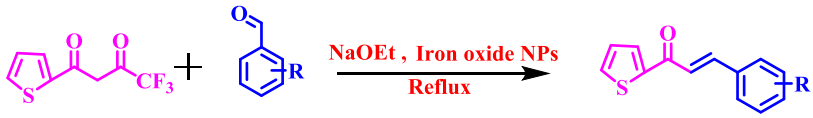
Scheme 2. Synthetic Route of Chalcone



trifluoro-1-(thiophen-2-yl)butane-1,3-dione and benzaldehyde was taken, and FeONPs are used as a catalyst. The above mixture was refluxed for 5 to 6 h. Progress and completion of the reaction were monitored by thin-layer chromatography (TLC).

2.2. Synthesis of Chalcones by the Sonochemical Method. An equimolar ratio of ethanolic solution of 4,4,4-trifluoro-1-(thiophen-2-yl)butane-1,3-dione and benzaldehyde as depicted in Scheme 2 was taken. FeONPs are used as a catalyst and sonicated at room temperature in the frequency of 25 kHz. The progress of the reaction was monitored by TLC using ethyl acetate and petroleum ether as the mobile phase (ratio of 20% and 80%), and the time taken for completion of the reaction was confirmed by triplicating the same reaction thrice.

*2.2.1. 3-Phenyl-1-(thiophen-2-yl)prop-2-en-1-one (**3a**).* ATR-IR (cm^{-1}): (−C═O)1654, (−C═C−)1588, (Ar−C = C−)1418, (−C−S−)720. ^{1}HNMR: (400 MHz) 7.86 (d, Ar−H, 1H), 7.74 (d, Ar−H, 1H), 7.70 (d, C═CH, 1H), 7.54 (d,Ar−H, 2H), 7.34 (t, Ar−H, 2H), 7.30 (t, Ar−H, 1H), 7.18 (t, Th−H, 1H), 6.99 (d, C═CH, 1H). ^{13}C: (400 Hz) 180.31, 145.12, 139.74, 135.22, 132.83, 130.12, 129.02,128.54, 121.31. HRMS *m*/*z*: 214.12. Elemental Analysis: Found: C: 72.53, H:4.48. Calculated:$C_{13}H_{10}SO$: C:72.87, H:4.70.

*2.2.2. 3-(4-Fluorophenyl)-1-(thiophen-2-yl)prop-2-en-1-one (**3b**).* ATR-IR (cm^{-1}): (−C═O)1648, (−C═C−)1585, (Ar−C═C−)1416, (C−F), 1217; (−C−S−)723. ^{1}HNMR: (400 MHz) 7.87 (d, Ar−H, 1H), 7.79 (d,Ar−H, 1H), 7.70 (d, C═CH, 1H), 7.60 (Ar−H, d, 2H), 7.42 (C═CH,d, 1H), 7.40 (d, Ar−H, 2H), 7.25 (t,Th−H, 1H). ^{13}C: (400 Hz) 180.31, 162.13. 145.12, 139.74, 132.83, 130.46, 129.02, 128.54, 121.32, 115.4. HRMS (ESI) *m*/*z*: 232.08. Elemental Analysis: Found: C: 67.08, H: 3.75. Calculated: $C_{13}H_9FOS$: C: 67.22, H: 3.91.

*2.2.3. 3-(4-Chlorophenyl)-1-(thiophen-2-yl)prop-2-en-1-one (**3c**).* ATR-IR (cm^{-1}): (−C═O−)1647, (−C═C−)1588, (Ar−C═C−)1419, (−C−Cl)727, (−C−S−)713. ^{1}HNMR: (400 MHz): 7.88 (d, Th−H, 1H), 7.80 (d, Th−H, 1H), 7.70 (d, C═CH, 1H), 7.58 (d, Ar−H, 2H), 7.42 (d, C═CH, 1H), 7.38 (d,Ar−H, 2H), 7.20 (t,Th−H, 1H), ^{13}C: (400 Hz) 180.31, 145.12, 139.74, 133.58, 132.83, 130.46, 129.02, 128.74, 121.32. HRMS *m*/*z*: 242.0062. Elemental Analysis: Found: C: 62.46, H: 3.42. Calculated: $C_{13}H_9ClOS$: C: 62.78, H: 3.65.

*2.2.4. 3-(4-Bromophenyl)-1-(thiophen-2-yl)prop-2-en-1-one (**3d**).* ATR-IR (cm^{-1}): (−C═O)1645, (−C═C−)1594, (Ar−C═C)1417, (−C−S−)713, (−C−Br)505. ^{1}HNMR: (400 MHz) 7.87 (d,Th−H, 1H), 7.78 (d, C═CH, 1H), 7.70 (d, Th−H, 1H), 7.54 (d,Ar−H, 2H), 7.52 (d,Ar−H, 2H), 7.41 (d,C═CH, 1H), 7.22 (t,Th−H, 1H). ^{13}C: (400 Hz) 180.31, 145.12, 139.74, 134.28, 132.83, 131.52, 130.16, 129.02, 128.64, 122.31, 121.32. HRMS *m*/*z*: 291.9558. Elemental Analysis: Found: C: 53.12, H: 2.96. Calculated: $C_{13}H_9BrOS$: C:53.26, H:3.09.

*2.2.5. 3-(4-Iodophenyl)-1-(thiophen-2-yl)prop-2-en-1-one (**3e**).* ATR-IR (cm^{-1}): (−C═O)1648, (−C═C−)1594, (Ar−C═C), 1419; (−C−S−)718, (−C−I)585. ^{1}HNMR: (400 MHz) 7.87 (d, Th−H, 1H), 7.80 (d, Th−H, 1H), 7.74 (d, Ar−H, 2H), 7.70 (d,C═CH, 1H), 7.40 (d, C═CH, 1H), 7.18 (t,Th−H, 1H), 7.11 (d,Ar−H, 2H). ^{13}C: (400 Hz) 180.31, 145.12, 139.74, 137.51, 134.68, 132.83, 130.16, 129.02, 121.32, 93.51. HRMS *m*/*z*: 339.9419. Elemental Analysis: Found: C: 45.62, H: 2.34.Calculated: For $C_{13}H_9IOS$: C: 45.90, H: 2.67.

*2.2.6. 3-(2-Nitrophenyl)-1-(thiophen-2-yl)prop-2-en-1-one (**3f**).* ATR-IR (cm^{-1}): (−C═O)1677, (−C═C−)1601, (Ar−C═C)1520, (Ar−NO_2)1343, and (C−S)720. ^{1}HNMR:(400 MHz) 8.22 (d,C═CH, 1H), 8.14 (d,Ar−H, 1H), 8.04 (d,Ar−H, 1H), 7.88 (d,Th−H, 1H), 7.81 (t,Ar−H, 1H), 7.76 (d,Th−H, 1H), 7.70 (t,Ar−H, 1H,), 7.20 (t,Th−H, 1H), 6.98 (d,C═CH, 1H). ^{13}C: (400 Hz) 180.31, 147.71, 145.12, 139.74, 134.68, 132.83, 130.16, 129.02, 127.34, 123.86, 121.32. HRMS (ESI) *m*/*z*: 259.0303. Elemental Analysis: Calculated:$C_{13}H_9SNO_3$: C:60.22. H: 3.50. N: 5.40.

*2.2.7. 3-(4-Nitrophenyl)-1-(thiophen-2-yl)prop-2-en-1-one (**3g**).* ATR-IR (cm^{-1}): (−C═O)677, (Ar−C═C)1618, (−C═C−)1567, (Ar−NO_2)1347, (C−S)722. ^{1}HNMR: (400 MHz) 8.32 (d, Ar−H, 2H), 8.03 (d,Ar−H, 2H), 7.89(d,Th−H, 1H), 7.84 (d,C═CH, 1H), 7.76 (d,Th−H, 1H), 7.20 (t,Th−H, 1H), 7.12 (d,C═CH, 1H). ^{13}C: (400 Hz) 180.31, 147.71, 145.12, 141.33, 139.74, 132.83, 130.16, 129.02, 123.86, 121.32. HRMS *m*/*z*: 259.0303. Elemental Analysis: Found: C: 60.08, H, 3.19, N: 5.24. Calculated:$C_{13}H_9SNO_3$: C: 60.22. H: 3.50. N: 5.40.

*2.2.8. 1-(Thiophen-2-yl)-3-(4-(trifluoromethyl)phenyl)-prop-2-en-1-one (**3h**).* ATR-IR (cm^{-1}): (−C═O)1677, (−C═C−)1591, (Ar−C═C−)1419, (−C−F)1122; (−C−S−)724. ^{1}HNMR: (400 MHz) 7.86 (d,Th−H, 1H), 7.80 (d,Th−H, 1H), 7.65 (d,C═CH, 1H), 7.57 (d,Ar−H, 2H), 7.48 (d,Ar−H, 2H), 7.18 (t,Th−H, 1H), 6.99 (d,C═CH, 1H). ^{13}C: (400 Hz) 180.31, 147.71, 145.12, 139.74, 138.51, 132.83, 130.16, 129.02, 125.06, 124.16, 121.32. HRMS *m*/*z*: 282.0326. Elemental Analysis: Found: C: 59.24, H: 3.06. Calculated: $C_{14}H_9F_3OS$: C: 59.57, H: 3.21.

*2.2.9. 3-(4-Methoxyphenyl)-1-(thiophen-2-yl)prop-2-en-1-one (**3i**).* ATR-IR (cm^{-1}): (−C═O)1648, (−C═C−)1594, (Ar−C═C)1419, (−C═O−)1136, and (−C−S−)720. ^{1}HNMR: (400 MHz) 7.85 (d,Th−H, 1H), 7.74 (d,Th−H, 1H), 7.70 (d,C═CH, 1H), 7.55(d,Ar−H, 2H), 7.20 (t,Th−H, 1H), 7.48 (d,Ar−H, 2H), 7.24 (d,C═CH, 1H), 3.75 (s,OCH_3, 3H). ^{13}C: (400 Hz) 180.31, 159.81, 145.12, 139.74, 132.83, 130.16, 129.02, 127.56, 121.32, 114.23, 55.84. HRMS *m*/*z*: 244.0554. Elemental Analysis: Found: C: 68.49, H: 4.58.Calculated: $C_{14}H_{12}SO_2$: C: 68.83, H: 4.95.

*2.2.10. 3-(3-Methoxyphenyl)-1-(thiophen-2-yl)prop-2-en-1-one (**3j**).* ATR-IR (cm^{-1}): (−C═O)648, (−C═C−)1594, (Ar−C═C)1419, (−C═O)1148, (−C−S−)722. ^{1}HNMR: (400 MHz) 7.88(d,Th−H, 1H), 7.80(d,Th−H, 1H), 7.68(d,C═CH, 1H), 7.52(t,Ar−H, 1H), 7.28(d, Ar−H,1H), 7.24(d,C═CH,1H), 7.18(t,Th−H,1H), 7.02(s,Ar−H, 1H), 6.82(d,Ar−H, 1H), 3.73(s, OCH_3, 3H). ^{13}C: (400 Hz) 180.31, 160.53, 145.12, 139.74, 135.06, 132.83, 130.16, 129.02, 121.36, 120.82, 113.33, 55.84. HRMS *m*/*z*: 244.0554. Elemental

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Analysis: Found: C: 68.42, H: 4.61. Calculated: $C_{14}H_{12}SO_2$: C: 68.83, H: 4.95.

*2.2.11. 3-(2-Hydroxyphenyl)-1-(thiophen-2-yl)prop-2-en-1-one (**3k**).* ATR-IR (cm^{-1}): (−C═O)1677, (−C═C−)1555, (Ar−C═C)1409, (−C−S)724. ^{1}HNMR: (400 MHz) 9.94(s,OH, 1H) 7.88(d,Th−H, 1H), 7.82(d,C═CH, 1H), 7.79(d, Th−H, 1H), 7.48(d,Ar−H, 1H), 7.32(d,C═CH, 1H), 7.19(t,Th−H, 1H), 7.06(t,Ar−H, 1H), 7.02(t,Ar−H, 1H), 6.72(d,Ar−H, 1H), ^{13}C: (400 Hz) 180.31, 141.02, 139.74, 132.83, 130.16, 129.02, 128.91, 122.62, 121.33, 117.61. HRMS *m*/*z*: 230.0408. Elemental Analysis: Found: C-67.56, H-4.11. Calculated: $C_{13}H_{10}O_2S$: C-67.81, H-4.38.

*2.2.12. 3-(4-Hydroxyphenyl)-1-(thiophen-2-yl)prop-2-en-1-one (**3l**).* ATR-IR (cm^{-1}): (Ar−O−H)3449, (−C═O)1677, (−C═C−)1555, (Ar−C═C−)1409, (−C−S−)732. ^{1}HNMR: (400 MHz) 9.58(s,OH, 1H) 7.88(d,Th−H, 1H), 7.80(d,Th−H, 1H), 7.69(d, C═CH, 1H), 7.55(d,Ar−H, 2H), 7.42(d,C═CH, 1H), 7.38(d,Ar−H, 2H), 7.18 (t,Th−H, 1H), ^{13}C: (400 Hz) 180.31, 157.72, 145.12, 139.74, 132.83, 130.16, 129.02, 127.81, 121.33, 115.83. HRMS *m*/*z*: 230.0408. Elemental Analysis: Found: C: 67.46, H: 4.03. Calculated: $C_{13}H_{10}O_2S$: C:67.81, H: 4.38.

*2.2.13. 3-Mesityl-1-(thiophen-2-yl)prop-2-en-1-one (**3m**).* ATR-IR (cm^{-1}): (−C = O)1648, (−C = C−)1590, (Ar−C = C−)1420, (−C−S−)720. ^{1}HNMR: (400 MHz) 7.88-(d,Th−H, 1H), 7.82(d,Th−H, 1H), 7.72(d,C═CH, 1H), 7.21(t, Th−H, 1H), 6.92(s,Ar−H, 2H), 6.73(d,C═CH, 1H), 2.44(s,CH_3, 3H), 2.32(s, CH_3, 3H), 2.14(s, CH_3, 3H). ^{13}C: (400 Hz) 180.31, 145.12, 139.74, 137.42, 134.66, 132.83, 130.16, 129.02, 127.86, 121.32, 21.93, 19.84. HRMS *m*/*z*: 256.0928. Elemental Analysis: Found: C: 74.53, H: 6.09. Calculated: $C_{16}H_{16}SO$: C: 74.96, H: 6.29.

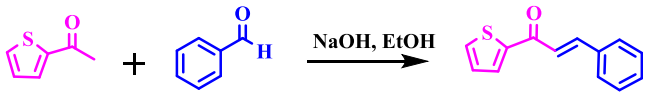
*2.2.14. 3-(4-(Methylthio)phenyl)-1-(thiophen-2-yl)prop-2-en-1-one (**3n**).* ATR-IR (cm^{-1}): (−C = O)1672, (−C = C−)1555, (Ar−C = C−)1489, (−C−S−)734. ^{1}HNMR: (400 MHz) 7.82(d,Th−H, 1H), 7.75(d,Th−H, 1H), 7.70(d,C═CH, 1H), 7.50 (d,Ar−H, 2H), 7.48(d, Ar−H, 2H), 7.21(t,Th−H, 1H,), 7.04(d,C═CH, 1H,), 2.40(s,SCH_3, 3H). ^{13}C:(400 Hz) 180.31, 145.12, 139.74, 138.63, 132.83, 131.61, 130.16, 129.02, 128.96, 126.72, 121.33, 14.84. HRMS *m*/*z*: 260.0338. Elemental Analysis: Found: C: 64.14, H: 4.52. Calculated:-$C_{14}H_{12}OS_2$: C: 64.58, H:4.65.

*2.2.15. 5-Phenyl-1-(thiophen-2-yl)penta-2,4-dien-1-one (**3o**).* ATR-IR (cm^{-1}): (−C═O)1677, (−C═C−)1636, (Ar−C═C−)1436, (−C−S−)723. ^{1}H NMR: (400 MHz) 7.88(d,Th−H, 1H), 7.76(d,Th−H, 1H), 7.46(d,Ar−H, 2H), 7.42(t,C═CH, 1H), 7.38(d,Ar−H, 2H), 7.31(t,Ar−H, 1H), 7.18(t,Th−H, 1H), 7.06(d,C═CH, 1H), 6.92(t,C═CH, 1H), 6.71(d,C═CH, 1H). ^{13}C:(400 Hz) 180.31, 144.42, 141.06, 139.74, 135.26, 132.83, 130.16, 129.02, 128.58, 127.92, 125.23, HRMS *m*/*z*: 240.0614. Elemental Analysis: Found: C: 74.57, H: 4.76. Calculated: $C_{15}H_{12}SO$: C:74.97, H:5.03.

3. RESULTS AND DISCUSSION

3.1. Synthesis of Chalcones. Several synthetic procedures have been reported for the synthesis of chalcones through the Claisen−Schmidt reaction (as shown in Scheme 3).[24] This reaction typically takes place under homogeneous conditions in either basic or acidic media. However, previously reported methodologies suffer from certain drawbacks, including prolonged reaction times, decreased yields, and the occurrence of parallel reactions. These limitations have necessitated the exploration of alternative approaches to improve the efficiency and selectivity of chalcone synthesis.

Scheme 3. Claisen−Schmidt Condensation Reaction



The condensation of active methylene compounds (such as β-diketones) with aromatic aldehydes typically proceeds via Knoevenagel condensation to form the desired products. However, in the present investigation (as shown in Scheme 3), this reaction did not occur. Instead, a set of thiophene chalcones were prepared by utilizing a β-diketone with a trifluoro substituent at the terminal carbon and various aromatic aldehydes bearing different electron-releasing or electron-withdrawing substituents.

To facilitate the synthesis, iron oxide nanoparticles (FeONPs) were employed as a heterogeneous catalyst, while sodium ethoxide served as the base in an ethanol solvent under reflux conditions. Subsequently, the method was modified to utilize the sonochemical approach, involving sonication, and the corresponding results were recorded and are discussed in Table S2. Based on the obtained results and observations, it was found that the reaction pathway favored the formation of aldol adduct elimination products rather than the expected Knoevenagel condensation products (Scheme 4). This unique behavior highlights the significance of the aldol adduct elimination process in this particular synthesis, deviating from the conventional Knoevenagel condensation. The utilization of FeONPs as a catalyst and the incorporation of sonochemical methodology contribute to the overall success and efficiency of the reaction, providing valuable insights into the reaction mechanisms and product selectivity.

In a model reaction, 1,3-dione (1 mmol), *p*-chlorobenzaldehyde, iron oxide nanoparticles, and sodium ethoxide (1 mmol) were added in ethanol (10 mL) medium and sonicated for 30 min, and the reaction progress was espied by TLC. The product was identified as 3-(4-chlorophenyl)-1-(thiophen-2-yl)prop-2-en-1-one via an aldol adduct; after the completion of the reaction, products were recrystallized from ethanol; the desired chalcones were achieved in good yields.

The compounds obtained were confirmed using IR, mass spectrometry, and proton-NMR techniques. Analogue structures are entered in Table S3. The elemental analyses yielded results that were in good reconciliation with experimental and theoretical values, deviating by only ±0.4%. FT-IR spectra of thiophene chalcones were obtained in the range of 4000−400 cm^{-1}. In the spectra, an absorption band was observed in the range of 1674−1677 cm^{-1}, indicating the presence of a carbonyl (−C═O) group. The −C═C− stretching vibrations were observed in the range of 1555−1636 cm^{-1}. A distinctive band range of 713−723 cm^{-1} is attributed to the −C−S stretching in chalcones.

The NMR analysis of their peak multiplicity and integration and expected resonances were assigned. Spectral integration displayed good alignment with the thiophene chalcones. The proton of aldehyde (−CH═O) peak in the range of δ10.0 ppm was absent in the spectra, which validates the formation of chalcones. The number of protons and their chemical shifts are in good agreement with the proposed structures. The doublet peaks observed at δ 7.78 and 7.41 with a coupling constant of 16 correspond to the protons of the −CH═CH− group. This

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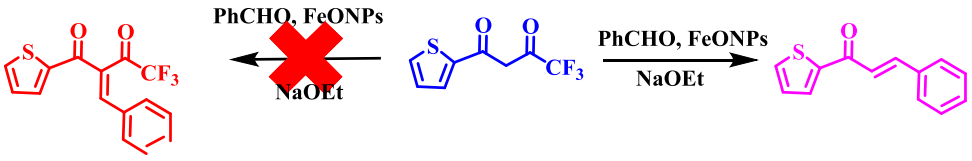
Scheme 4. Possible Reaction Pathway of the Active Methylene Compound (β-diketone) with an Aromatic Aldehyde



large coupling constant confirms the evidence for the transconfiguration in thienyl chalcones.[16] ^{1}H NMR spectra of chalcone **3d** are shown in Figure S21.

The confirmation of chalcones was further substantiated by the presence of a molecular ion peak in the mass spectra. The spectra of all newly synthesized chalcones exhibited M^+ fragmentation peaks that align well with their molecular formulas. The mass spectra of **3a** revealed a molecular ion peak at m/z 214.12, consistent with the molecular formula $C_{13}H_{10}OS$ shown in Figure S10.

To support the structure, a single crystal of chalcone 3m is obtained and the structure was deduced by an X-ray diffractometer. Structural analysis revealed that nonplanar 3-mesityl(1-thiophen)prop-2-en-1-one (**3m**) is crystallized in a monoclinic $P2_1/n$ space group with four molecules in its unit cell (Table S1). Figure 1a emphasizes the *ORTEP* of the crystal structure with thermal ellipsoids drawn at 30% probability. The thiophene-attached α,β-unsaturated carbonyl group is bent at about 120.86° at its β-position. The dihedral angle between the planes of the trimethylbenzene ring and thiophene-attached α,β-unsaturated carbonyl group is 57.64°, which clearly demonstrates the molecular nonplanar structure of 3-mesityl-(1-thiophen)prop-2-en-1-one (Figure 1b).

3.2. Characterization of FeONPs. A powder diffractometer is used to get the crystallographic information. Figure 2a emphasizes the XRD pattern of FeONPs. The Cu Kα radiation is used as a source and 2θ angular regions between 10 and 80° are explored at a scan rate of 2°/min. The designated peaks are seen in the region 20 to 70°. The peak positions and peak intensities obtained are comparable and are also in correlation with the reported patterns.[25] The FeONPs were well dispersive in nature in solution, and the DLS pattern showed an average particle size of 46 nm (Figure 2d). The zeta potential analysis showed good conductivity, found to be 14.0 mV. The surface morphology of FeONPs showed that the particles have spherical shape with are monodispersed in nature (Figure 2b). The EDS pattern demonstrates the reduction of iron ions into iron oxide nanoparticles (Figure 2c). The appearance of iron oxide nanoparticle peak in the region of ∼0.8, 6.5, and 7.1 keV and the weight percentage of 53.99% of Fe were observed. The signal of oxygen is obtained in the region of 0.5 keV with 40.90%. The BET surface area, total pore volume, and diameter were found to be 136.730 m^2/g, 3.1415 cm^2/g, and 5.8174 nm, respectively. The N_2 adsorption isotherms showed a type IV isotherm, which confirms the mesoporous structure of FeONPs (Figure 2e,f) According to IUPAC, If the pore size of nanoparticles was in the range of 2−50 nm, then, it is considered mesoporous. The pore sizes varying from 2 to 50 nm are referred to as mesoporous; it revealed that the pore volume is 0.173 cm^3/g and the BJH pore size is 2.44 nm.

3.3. Optimization of Reaction Conditions. To investigate the reaction conditions for the synthesis of chalcones, we utilized the model reaction involving 4,4,4-trifluoro-1-(thiophen-2-yl)butane-1,3-dione (1 mmol) and 4-chlorobenzaldehyde (1 mmol) to obtain product 3c. We examined the impact of the catalyst, base, and method, as summarized in Table 1. Initially, we observed that the reaction did not take place in the absence of a catalyst, indicating its necessity for the desired transformation. Furthermore, the use of a weak base did not produce better yields, emphasizing the importance of a strong base in promoting the reaction. Subsequently, we successfully synthesized a series of chalcones using conventional methods. To explore alternative synthetic approaches, we adopted the sonochemical method for the chalcone synthesis. Sonochemical reactions are preferred over conventional reactions due to their significantly enhanced reaction rates, making them highly suitable for the synthesis of various biologically active compounds. Additionally, sonochemical reactions typically occur at lower reaction times, resulting in energy savings. Hence, the sonochemical synthesis of chalcones offers a rapid, straightforward, energy-efficient, and environmentally friendly protocol. Initially, we conducted the sonochemical reaction using a weak base, which did not yield the desired product in a good yield. However, when a strong base was employed, the reaction proceeded smoothly, leading to satisfactory product yields. Furthermore, we varied the catalyst loading from 5 to 15 mg of iron oxide nanoparticles. Importantly, no parallel reactions were observed with any of the tested reactants and catalysts. Based on these selected conditions, we expanded our investigation to other compounds to verify the broader applicability of the initial protocol. By employing 4,4,4-trifluoro-1-(thiophen-2-yl)butane-1,3-dione and various aromatic aldehydes, we confirmed the successful formation of thiophene chalcones, as discussed in Table S2. These findings demonstrate the versatility and effectiveness of the developed methodology for synthesizing chalcones.

Sonication can enhance the rate of the reaction by promoting the mixing of reactants and improving the bulk transfer. Organic reactions require the dissolution of reactants. Sonication helps break down these materials into smaller particles and helps in dissolution.

3.4. Plausible Reaction Mechanism and Reusability of the Catalyst. The mechanism proposed for the formation of chalcones from the reaction between β-diketone and aromatic aldehydes, catalyzed by FeONPs in basic medium using sodium ethoxide, is illustrated in Figure 4a (Scheme 4) based on our experimental results and previous literature reports.[26] The reaction commences with the activation of β-diketone through the interaction with iron oxide, forming a complex. Subsequently, the enolized β-diketone iron complex reacts with the aromatic aldehyde, leading to the elimination of trifluoroacetic acid. This elimination step was confirmed by high-resolution mass spectrometry (HRMS), as shown in Figure S27. Under homogeneous reaction conditions, several challenges arise, including the recovery of the catalyst and proper disposal of waste materials. To address these issues, we employed a heterogeneous catalyst, which offers advantages such as ease of handling, simple workup, and reusability. Notably, the current method demonstrates the reusability of iron oxide nanoparticles as a catalyst. To assess the catalyst's

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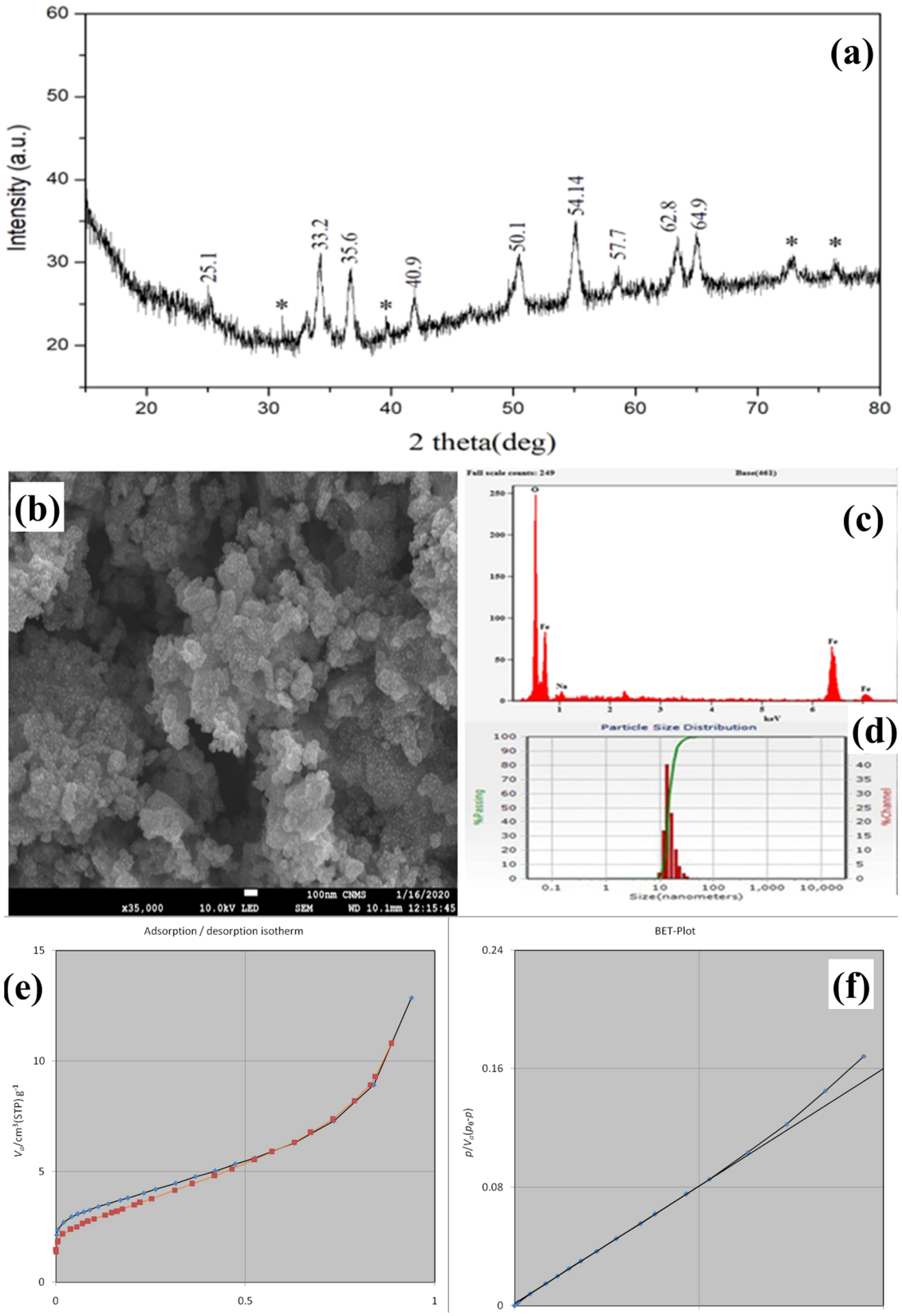

Figure 2. (a) P-XRD, (b) SEM, (c) DLS, (d) EDS of iron oxide nanoparticles, and Brunauer–Emmett–Teller (BET) analysis of FeONPs. (e) N_2 adsorption (Blue line) and desorption (Red Line) isotherms and (f) BET plot of FeONPs.

reusability, the reaction mixture was cooled, and the catalyst adhered to a magnetic bar, facilitating easy recovery (Figure 4b). The collected catalyst was subsequently reused for the reaction after washing with ethanol and drying at 120 °C in a hot air oven. Remarkably, no significant loss in the catalyst's activity was observed over three cycles of usage. Moreover, the

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Table 1. Optimization of Reaction Conditions

compound	entry	base	FeONPs in mg	time in hours in the conventional method	time in hours in the sonochemical method
3a	1.	TEA	5	24	0.5
	2.	NaOH	5	11	0.5
	3.	NaOH	10	11	0.5
	4.	NaOEt	5	6	0.5
	5.	NaOEt	10	6	0.5
	6.	NaOEt	15	6	0.5

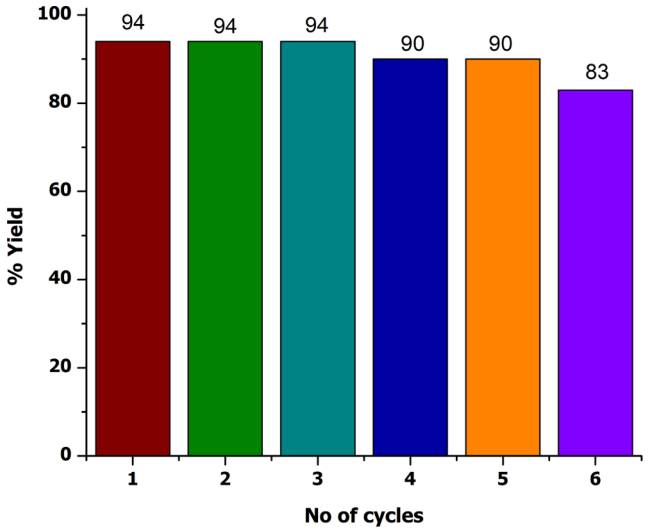

Figure 3. Reusability of FeONPs for the synthesis of chalcones.

conversion remained stable in subsequent cycles, indicating the stability and reusability of the catalyst (Figure 3). The magnetic nature of the catalyst and the X-ray diffraction (XRD) pattern of the catalyst after three and six cycles are depicted in Figure S26.

The experimental protocol we developed demonstrates outstanding performance in terms of both yield and reaction time. To further assess the effectiveness of our novel sonochemical method, we compared it with other Claisen–Schmidt methods described in the existing literature.[27−31] Upon careful examination of the data presented in Table S2, it can be inferred that the sonochemical method not only significantly reduces the reaction time but also delivers higher yields compared with the alternative methods. These results underscore the advantages and superiority of the sonochemical approach in the synthesis of chalcones.

4. CONCLUSIONS

In summary, we have successfully developed a new and efficient method using sonochemistry for synthesizing thienyl chalcones through an aldol adduct reaction. This method allows for the straightforward synthesis of thienyl chalcones with high yields of up to 94%. One of the major advantages of this method is its ability to operate under mild reaction conditions, simplifying the synthesis process, and reducing the formation of undesired byproducts. Additionally, the reduced reaction time associated with the sonochemical method enhances its practicality and efficiency. When compared to previous methods described in the literature, our novel protocol offers several distinct advantages. First, the use of sonochemistry as a synthetic tool provides a greener approach by eliminating the need for harsh reaction conditions and excessive reagents. The promising results obtained in this study suggest broad potential for this method in future research and industrial applications. By establishing an efficient and sustainable method for their synthesis, we opened up new avenues for exploring their diverse applications. In conclusion, this investigation represents a noteworthy contribution to the fields of chalcone synthesis and sustainable chemistry. Thienyl chalcones were prepared using 1,3-diketones catalyzed by iron oxide nanoparticles. The catalyst can be reusable up to six times without a decrease in the reactivity. Our innovative sonochemical method offers a practical and efficient approach for synthesizing thienyl chalcones with potential implications for future research and applications in various scientific disciplines.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.3c05897.

FT-IR spectra; mass spectra; and ^{1}H NMR spectra of the compounds and powder XRD pattern of nanoparticles after three cycles and six cycles; crystal data and

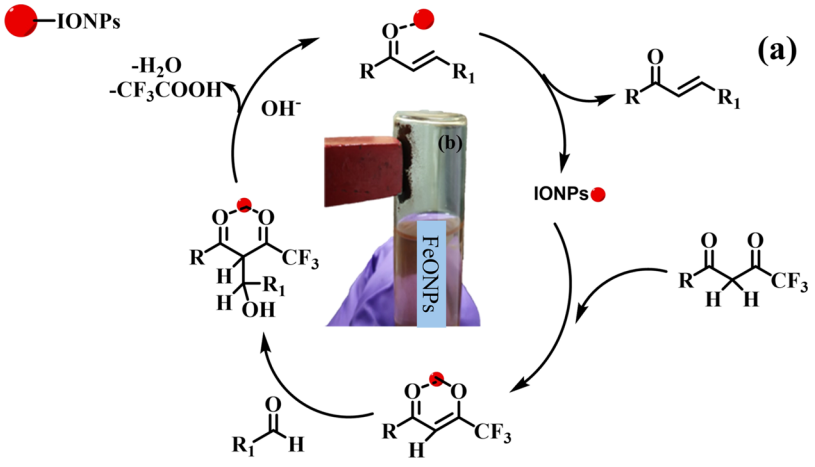

Figure 4. Possible proposed mechanism for the reaction (Scheme 4, (a)) and the catalyst attracted to the magnet and showing reusability (b).

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structure refinement details of compound **3m**; comparison of yield and time with the previous reported literature; and comparison of the solvothermal method and sonochemical method (PDF)

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Notes

The authors declare no competing financial interest.

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