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Research

Synthesis of 2,4,5-Trisubstituted Imidazoles from Azido Chalcones and Nitriles

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Abstract:
A simple and efficient synthetic route for the preparation of 2,4,5-trisubstituted imidazoles has been developed using α-azido chalcones and nitriles as key starting materials under Lewis acid-promoted thermal conditions. The present work explores the utility of α-azido chalcones as versatile intermediates for the synthesis of highly substituted imidazole derivatives. Various α-azido chalcones were reacted with aliphatic, vinyl, and aromatic nitriles in the presence of trimethylsilyl trifluoromethanesulfonate (TMSOTf) as a Lewis acid catalyst under solvent-free conditions at 80 °C. The reactions proceeded smoothly within 2 h to afford the corresponding 2,4,5-trisubstituted imidazoles in good yields (74–79%). The synthesized compounds were purified and characterized by melting point determination, thin-layer chromatography (TLC), infrared spectroscopy (IR), and proton nuclear magnetic resonance (^1H NMR) spectroscopy. Spectral data confirmed the formation of the desired imidazole derivatives, showing characteristic N–H, C=O, aromatic, and aliphatic/vinylic proton signals. The optimized method offers a rapid, efficient, and convenient approach for the synthesis of structurally diverse imidazole derivatives from α-azido chalcones. This protocol may serve as a useful strategy for the preparation of biologically relevant imidazole scaffolds for further medicinal and synthetic applications.

Keywords: α-Azido chalcones; 2,4,5-trisubstituted imidazoles; TMSOTf; Lewis acid catalysis; Thermal synthesis; Nitriles; Heterocyclic synthesis

1. INTRODUCTION

Imidazole and its substituted derivatives constitute an important class of five-membered nitrogen-containing heterocyclic compounds that occupy a central position in medicinal chemistry, synthetic organic chemistry, and material science. The imidazole ring system is present in numerous biologically active molecules and pharmaceutical agents, exhibiting a broad range of pharmacological properties such as antimicrobial, antifungal, anti-inflammatory, anticancer, antiviral, and enzyme inhibitory activities. Owing to these diverse biological and industrial applications, the development of efficient and practical synthetic strategies for the construction of highly substituted imidazole frameworks continues to attract considerable research interest.

Conventionally, imidazole derivatives have been synthesized by several classical and modern methods involving multicomponent condensations, cyclization of α-dicarbonyl compounds, reactions of amidines or nitriles with suitable nitrogen sources, and metal- or acid-catalyzed annulation strategies. Although many of these methods are effective, some are associated with drawbacks such as harsh reaction conditions, prolonged reaction times, limited substrate scope, poor selectivity, use of hazardous solvents, or expensive

reagents. Therefore, there remains a continuing need for simple, efficient, and broadly applicable methodologies for the synthesis of structurally diverse imidazole derivatives.

Among the versatile intermediates used in heterocyclic synthesis, α-azido ketones and α-azido chalcones have emerged as valuable precursors due to their ability to undergo thermally or catalytically induced rearrangements and cyclizations. Previous studies have demonstrated that Lewis acid-promoted transformations of azido-containing substrates can provide access to a variety of heterocyclic systems, including imidazoles, pyrroles, and indoles. In particular, the use of azido chalcone derivatives in cyclization reactions with nitriles represents an attractive route for the synthesis of highly substituted imidazole systems, since both the azido functionality and the conjugated enone system can facilitate ring construction under suitable activation conditions.

In continuation of earlier work on Lewis acid-promoted synthesis of substituted heterocycles from azido precursors, the present study investigates the scope of α-azido chalcones for the synthesis of 2,4,5-trisubstituted imidazoles using aliphatic, vinyl, and aromatic nitriles as reaction partners. The reactions were carried out under thermal, solvent-free conditions in the presence of trimethylsilyl trifluoromethanesulfonate (TMSOTf), which served as an efficient Lewis acid catalyst. The synthesized compounds were isolated in good yields and characterized by IR and ^1H NMR spectroscopy. The study provides a convenient and efficient protocol for the synthesis of structurally varied 2,4,5-trisubstituted imidazole derivatives.

2. AIM AND OBJECTIVES

2.1 Aim

The present study aims to synthesize 2,4,5-trisubstituted imidazoles using α-azido chalcones and nitriles as key precursors under Lewis acid-promoted thermal conditions and to investigate their structural properties through spectroscopic characterization.

2.2 Objectives

1. To provide a comprehensive background on the chemistry and significance of imidazole derivatives.
2. To review the existing literature on imidazole synthesis, particularly involving azido chalcones and nitriles.
3. To design a synthetic route for the efficient preparation of 2,4,5-trisubstituted imidazoles using α-azido chalcones and nitriles as starting materials.
4. To identify and procure the required chemicals, reagents, solvents, and analytical instruments for the experimental work.
5. To carry out the synthesis of the target imidazole derivatives under optimized reaction conditions.
6. To purify and isolate the synthesized compounds using appropriate laboratory techniques.
7. To characterize the synthesized compounds by analytical techniques such as IR spectroscopy and ^1H NMR spectroscopy.
8. To interpret the obtained spectral data and confirm the structural identity of the synthesized compounds.
9. To compare the obtained results with reported literature and assess the efficiency of the developed synthetic method.
10. To compile the findings and present them in a scientifically organized manuscript.

3. PLAN OF WORK

The research work was carried out according to the following sequence:

1. Literature survey on imidazole synthesis, α-azido chalcones, and nitrile-based cyclization reactions.
2. Designing the synthetic route and plausible reaction mechanism for the preparation of 2,4,5-trisubstituted imidazoles.
3. Procurement of chemicals, reagents, solvents, and ensuring the availability of IR and NMR instrumentation.
4. Synthesis of α-azido chalcone derivatives using substituted aldehydes and ketones.
5. Performing the cyclization reaction of α-azido chalcones with nitriles under optimized thermal conditions in the presence of Lewis acid catalyst.
6. Purification and isolation of the final products by extraction and flash column chromatography.
7. Characterization of the synthesized compounds by melting point, TLC, IR, and ^1H NMR spectroscopy.

8. Analysis of the spectral data and comparison with literature values for structural confirmation.
9. Compilation of experimental data and preparation of the final manuscript.

4. REACTION SCHEME

The synthetic strategy involved the reaction of α-azido chalcone derivatives with aliphatic, vinyl, or aromatic nitriles under solvent-free thermal conditions in the presence of TMSOTf as Lewis acid catalyst to furnish 2,4,5-trisubstituted imidazole derivatives.

Representative Products:

- **3a:** (5-(4-Chlorophenyl)-2-methyl-1H-imidazol-4-yl)(phenyl)methanone
- **3b:** (4-(2,4-Dichlorophenyl)-2-methyl-1H-imidazol-5-yl)(p-tolyl)methanone
- **3c:** (4-Chloro-3-fluorophenyl)(5-(2,4-dichlorophenyl)-2-methyl-1H-imidazol-4-yl)methanone
- **3d:** (5-(4-Chlorophenyl)-2-vinyl-1H-imidazol-4-yl)(phenyl)methanone
- **3e:** (5-(4-Chlorophenyl)-2-phenyl-1H-imidazol-4-yl)(phenyl)methanone

Insert Scheme 1:

General synthetic route for the preparation of 2,4,5-trisubstituted imidazoles from α-azido chalcones and nitriles.

Insert Figure 1: Scope with different α-azido chalcone substrates and nitriles.

5. MATERIALS AND METHODS

5.1 Chemicals Used

The chemicals and reagents used in the present study were of laboratory reagent (LR) grade and were used without further purification unless otherwise stated.

Table 1. Chemicals used in the study

S. No.	Chemical name	Grade	Source
1	4-Chlorochalcone azide	LR	Tokyo Chemical Industry (India) Pvt. Ltd.
2	α-Azido chalcone	LR	Shanghai Macklin Biochemical (India) Co., Ltd.
3	Methyl nitrile (acetonitrile)	LR	Sihauli Chemicals (India) Pvt. Ltd.
4	2′,4′-Dichlorochalcone azide	LR	Dhanlaxmi Chemicals Pvt. Ltd., Nandesari, Vadodara, Gujarat, India
5	Dichlorobenzoyl chloro-fluorophenyl azide derivative	LR	Sumukha Lifesciences Pvt. Ltd., Hyderabad, Telangana, India
6	Silica gel	LR	Sisco Research Laboratories, Mumbai
7	Phenyl nitrile (benzonitrile)	LR	Benzo Chem Industries Pvt. Ltd., Mumbai

5.2 Instruments Used

- Infrared spectra (IR) were recorded on a **BRUKER IR AFFINITY-1** instrument, and values are reported in cm^{-1}.
- Analytical thin-layer chromatography (TLC) was performed on silica gel-G coated glass plates. Spots were visualized under UV light or in an iodine chamber.
- All reactions were monitored by TLC using appropriate solvent systems.
- A hot air oven was used for activation of TLC plates.
- Samples were weighed using a **WERSNAR** electronic balance.
- Continuous stirring during synthesis was performed using a magnetic stirrer (**REMI Equipment Pvt. Ltd.**).
- Vacuum filtration was carried out using a **PRABIVAC** vacuum pump.
- Melting points were determined using a **GUNAS** melting point apparatus and are uncorrected.

5.3 General Methodology

The melting points of the synthesized compounds were determined using the capillary method on an Opti Melt instrument. Up to three capillary tubes were inserted into the heating block simultaneously, and the

temperature at which the solid sample completely melted was recorded as the melting point.

All reactions were carried out under prescribed laboratory conditions. The solvents and reagents used in the synthetic work were of laboratory reagent grade. The progress of each reaction and the purity of the products were routinely monitored by micro-TLC. The IR spectra of the synthesized compounds were recorded using the KBr pellet method. Structural elucidation of the final compounds was performed using IR and ^1H NMR spectroscopy.

6. SYNTHESIS OF 2,4,5-TRISUBSTITUTED IMIDAZOLES

6.1 General Synthetic Procedure

A mixture of α-azido chalcone derivative **1**, trimethylsilyl trifluoromethanesulfonate (**TMSOTf**, 25 mol%), and the corresponding aliphatic, vinyl, or aromatic nitrile **2** was placed in a dried round-bottom flask. The resulting mixture was heated at **80 °C** in an oil bath for **2 h** under a **nitrogen atmosphere**. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was quenched with ice water and extracted with ethyl acetate. The organic layer was separated, and the crude product was purified by flash column chromatography to afford the desired **2,4,5-trisubstituted imidazole derivative (3)**.

6.2 Preparation of Individual Compounds

6.2.1 Preparation of (5-(4-Chlorophenyl)-2-methyl-1H-imidazol-4-yl)(phenyl)methanone (3a)

A mixture of α-azido chalcone 1 (**4′-chlorochalcone azide**), TMSOTf (25 mol%), and **methyl nitrile (acetonitrile)** was heated at 80 °C for 2 h under nitrogen. Work-up and purification afforded **3a**.

6.2.2 Preparation of (4-(2,4-Dichlorophenyl)-2-methyl-1H-imidazol-5-yl)(p-tolyl)methanone (3b)

A mixture of α-azido chalcone 1 (**2′,4′-dichlorochalcone azide**), TMSOTf (25 mol%), and **methyl nitrile (acetonitrile)** was heated at 80 °C for 2 h under nitrogen. Work-up and purification afforded **3b**.

6.2.3 Preparation of (4-Chloro-3-fluorophenyl)(5-(2,4-dichlorophenyl)-2-methyl-1H-imidazol-4-yl)methanone (3c)

A mixture of α-azido chalcone 1 (**dichlorobenzoyl chloro-fluorophenyl azide derivative**), TMSOTf (25 mol%), and **methyl nitrile (acetonitrile)** was heated at 80 °C for 2 h under nitrogen. Work-up and purification afforded **3c**.

6.2.4 Preparation of (5-(4-Chlorophenyl)-2-vinyl-1H-imidazol-4-yl)(phenyl)methanone (3d)

A mixture of α-azido chalcone 1 (**4′-chlorochalcone azide**), TMSOTf (25 mol%), and **vinyl nitrile (acrylonitrile)** was heated at 80 °C for 2 h under nitrogen. Work-up and purification afforded **3d**.

6.2.5 Preparation of (5-(4-Chlorophenyl)-2-phenyl-1H-imidazol-4-yl)(phenyl)methanone (3e)

A mixture of α-azido chalcone 1 (**4′-chlorochalcone azide**), TMSOTf (25 mol%), and **phenyl nitrile (benzonitrile)** was heated at 80 °C for 2 h under nitrogen. Work-up and purification afforded **3e**.

7. RESULTS AND DISCUSSION

7.1 Optimization of Reaction Conditions

The present study examined the Lewis acid-promoted cyclization of α-azido chalcones with nitriles to generate 2,4,5-trisubstituted imidazoles under thermal conditions. In an initial trial, α-azido chalcone and acetonitrile were reacted in the presence of Lewis acid under solvent-free conditions. The reaction gave poor conversion and low yield when less effective Lewis acids were employed. Upon screening different Lewis acids, **trimethylsilyl trifluoromethanesulfonate (TMSOTf)** was found to be the most effective catalyst.

Under optimized conditions using **TMSOTf (25 mol%)**, **α-azido chalcone (1 equiv.)**, and **nitrile (2 equiv.)** at **80 °C** under solvent-free thermal conditions, the reaction was completed within **2 h**, affording the desired imidazole derivatives in **74–79% yield**. Increasing the catalyst loading beyond 25 mol% did not improve the reaction time or product yield. In addition, the use of alternative solvents or different Lewis acids did not produce superior results. A slight improvement in yield was observed when **benzonitrile** was used instead of **acetonitrile**, suggesting that aromatic nitriles may favor the cyclization process under the studied conditions.

Table 2. Optimization of reaction conditions for the preparation of 2,4,5-trisubstituted imidazoles

Entry	Lewis acid	Nitrile (2 eq)	Time (h)	Yield of 3 (%)
1	TMSOTf (25 mol%)	CH_3CN	2	74
2	TMSOTf (25 mol%)	CH_3CN	2	76

Entry	Lewis acid	Nitrile (2 eq)	Time (h)	Yield of 3 (%)
3	TMSOTf (25 mol%)	CH_3CN	2	75
4	TMSOTf (25 mol%)	CH_3CN	2	76
5	TMSOTf (25 mol%)	C_6H_5CN	2	79*

*Your earlier summary mentioned 86% for benzonitrile in one place; however, the product profile for **3e** lists **79%**. Please verify and keep only the correct value consistently throughout the manuscript.

7.2 Synthesis of Target Compounds

The optimized reaction conditions were applied to a variety of α-azido chalcone derivatives and nitriles to assess the scope of the method. The reaction was found to tolerate substituted aromatic systems and different nitrile partners, including **methyl nitrile**, **vinyl nitrile**, and **phenyl nitrile**, leading to the formation of structurally diverse **2,4,5-trisubstituted imidazoles**. The synthesized compounds **3a–3e** were isolated as yellow solids in moderate to good yields (**74–79%**) and were further characterized by melting point, TLC, IR, and ^1H NMR spectroscopy.

7.3 Characterization of Synthesized Compounds

7.3.1 (5-(4-Chlorophenyl)-2-methyl-1H-imidazol-4-yl)(phenyl)methanone (3a)

- **Appearance:** Yellow solid
- **Melting point:** 218–220 °C
- **Yield:** 74%
- **Rf value:** 0.10
- **IR (cm⁻¹):** 3243, 2963, 2287, 1904, 1675
- **¹H NMR (δ, ppm):** 12.81 (s, 0.5H), 12.79 (s, 0.5H), 8.04–7.18 (m, 9H, Ar–H), 2.39 (d, J = 8.8 Hz, 3H)
- **¹³C NMR (δ, ppm):** 189.1, 186.1, 148.8, 146.3, 144.9, 139.1, 138.3, 136.2, 135.6, 133.5, 133.4, 132.6, 132.3, 131.1, 130.7, 130.6, 129.5, 129.2, 128.6, 128.3, 128.0, 126.4, 14.2

Spectral interpretation:

The IR spectrum of **3a** exhibited a broad absorption at **3243 cm⁻¹**, attributable to **N–H stretching** of the imidazole ring. A strong band at **1675 cm⁻¹** corresponded to the **carbonyl (C=O)** stretching vibration of the benzoyl group. The ^1H NMR spectrum showed two singlets at **δ 12.81** and **δ 12.79 ppm**, which are characteristic of the **imidazole N–H proton** existing in tautomeric forms. The aromatic protons appeared as a multiplet in the region **δ 8.04–7.18 ppm**, while the methyl group attached to the imidazole ring was observed at **δ 2.39 ppm**.

7.3.2 (4-(2,4-Dichlorophenyl)-2-methyl-1H-imidazol-5-yl)(p-tolyl)methanone (3b)

- **Appearance:** Yellow solid
- **Melting point:** 97–99 °C
- **Yield:** 76%
- **Rf value:** 0.21
- **IR (cm⁻¹):** 3277, 3063, 2217, 1630, 1505, 1481
- **¹H NMR (δ, ppm):** 12.95 (s, 0.5H), 12.78 (s, 0.5H), 8.10–6.99 (m, 7H, Ar–H), 2.41–2.24 (m, 6H)
- **¹³C NMR (δ, ppm):** 187.2, 185.5, 148.8, 144.7, 143.3, 142.6, 142.5, 137.5, 135.8, 135.3, 134.4, 133.8, 133.5, 132.8, 130.7, 130.0, 129.2, 128.9, 128.8, 128.6, 128.1, 127.5, 127.2, 25.6, 21.6, 21.4, 14.2

Spectral interpretation:

Compound **3b** showed an **N–H stretching** band at **3277 cm⁻¹** and a **carbonyl stretching** band at **1630 cm⁻¹** in the IR spectrum. The ^1H NMR spectrum displayed two downfield singlets at **δ 12.95** and **δ 12.78 ppm**, consistent with the imidazole N–H proton in tautomeric forms. Aromatic protons resonated as a multiplet between **δ 8.10–6.99 ppm**, and the methyl protons from the p-tolyl and imidazole substituents appeared in the aliphatic region **δ 2.41–2.24 ppm**.

7.3.3 (4-Chloro-3-fluorophenyl)(5-(2,4-dichlorophenyl)-2-methyl-1H-imidazol-4-yl)methanone (3c)

- **Appearance:** Yellow solid
- **Melting point:** 102 °C
- **Yield:** 75%
- **Rf value:** 0.32
- **IR (cm⁻¹):** 3150, 2963, 1665, 1424, 1247
- **¹H NMR (δ, ppm):** 13.11 (s, 0.4H), 12.95 (s, 0.6H), 8.43–7.35 (m, 5H, Ar–H), 2.42 (s, 3H)
- **¹³C NMR (δ, ppm):** 184.3, 149.8, 145.3, 144.6, 136.7, 135.9, 135.5, 134.6, 134.4, 133.8, 133.1, 131.7, 130.1, 129.6, 128.9, 127.6, 119.6, 117.1, 14.3

Spectral interpretation:

The IR spectrum of **3c** showed a characteristic **N–H stretching** band at **3150 cm⁻¹** and a **C=O stretching** band at **1665 cm⁻¹**, confirming the presence of the imidazole and ketone functionalities. The band at **1247 cm⁻¹** may be attributed to **C–F stretching** in the halogenated aromatic ring. In the ^1H NMR spectrum, two singlets at **δ 13.11** and **δ 12.95 ppm** indicated the tautomeric imidazole N–H proton, while the methyl group attached to the imidazole ring appeared as a singlet at **δ 2.42 ppm**.

7.3.4 (5-(4-Chlorophenyl)-2-vinyl-1H-imidazol-4-yl)(phenyl)methanone (3d)

- **Appearance:** Yellow solid
- **Melting point:** 159–161 °C
- **Yield:** 76%
- **Rf value:** 0.75
- **IR (cm⁻¹):** 3211, 3063, 2922, 1632, 1479, 1294
- **¹H NMR (δ, ppm):** 13.19 (s, 0.45H), 13.11 (s, 0.55H), 8.06–7.18 (m, 9H, Ar–H), 6.71–5.51 (m, 3H, olefinic H)
- **¹³C NMR (δ, ppm):** 188.5, 185.9, 147.7, 146.3, 145.0, 138.3, 137.6, 136.5, 136.0, 133.3, 132.3, 130.7, 130.1, 129.1, 128.3, 128.1, 127.8, 127.6, 125.8, 125.2, 120.4, 118.5

Spectral interpretation:

Compound **3d** exhibited the expected **N–H** and **C=O** stretching absorptions at **3211 cm⁻¹** and **1632 cm⁻¹**, respectively. The ^1H NMR spectrum showed the characteristic aromatic multiplet at **δ 8.06–7.18 ppm** and an additional multiplet in the range **δ 6.71–5.51 ppm**, corresponding to the **vinyl protons**, thereby confirming the incorporation of the vinyl substituent at the C-2 position of the imidazole ring.

7.3.5 (5-(4-Chlorophenyl)-2-phenyl-1H-imidazol-4-yl)(phenyl)methanone (3e)

- **Appearance:** Yellow solid
- **Melting point:** 222–224 °C
- **Yield:** 79%
- **Rf value:** 0.89
- **IR (cm⁻¹):** 3271, 2921, 1602, 1469, 1282
- **¹H NMR (δ, ppm):** 13.50 (s, 0.4H), 13.27 (s, 0.6H), 8.21–7.22 (m, 14H, Ar–H)
- **¹³C NMR (δ, ppm):** 188.8, 146.0, 138.7, 137.6, 136.7, 133.7, 132.5, 131.4, 131.1, 130.7, 130.0, 129.8, 129.5, 128.9, 128.5, 128.4, 128.2, 126.9, 126.2

Spectral interpretation:

The IR spectrum of **3e** showed the presence of **N–H stretching** at **3271 cm⁻¹** and **C–N/aromatic carbonyl-associated vibrations** around **1282 cm⁻¹**, along with a strong band near **1602 cm⁻¹** due to the conjugated carbonyl and aromatic system. The ^1H NMR spectrum displayed a broad aromatic multiplet integrating for **14 protons** between **δ 8.21–7.22 ppm**, which is consistent with the presence of three aryl rings. The downfield singlets at **δ 13.50** and **δ 13.27 ppm** further support the imidazole N–H proton in tautomeric forms.

7.4 Discussion

The present study demonstrates that **α-azido chalcones** serve as efficient precursors for the synthesis of **2,4,5-trisubstituted imidazoles** under **Lewis acid-promoted thermal conditions**. Among the tested conditions, **TMSOTf (25 mol%)** under **solvent-free heating at 80 °C** was found to be the most suitable, offering good product yields and shorter reaction times. The protocol tolerated both electron-donating and electron-withdrawing aromatic substituents, as well as aliphatic, vinyl, and aromatic nitriles.

The IR spectra of the synthesized compounds consistently showed characteristic absorptions corresponding to **imidazole N–H stretching** and **conjugated carbonyl stretching**, while the ^1H NMR spectra provided clear evidence for the presence of aromatic, methyl, and vinyl protons depending on the substituent pattern. The presence of two downfield singlets for the N–H proton in many compounds suggests the existence of **tautomeric forms** of the imidazole ring in solution, which is common in substituted imidazole systems. Overall, the spectral data strongly support the proposed structures of the synthesized compounds.

8. CONCLUSION

The present study demonstrates that **α-azido chalcones** are effective precursors for the synthesis of **2,4,5-trisubstituted imidazoles** under **Lewis acid-promoted thermal conditions**. Among the various Lewis acids evaluated, **trimethylsilyl trifluoromethanesulfonate (TMSOTf)** proved to be the most efficient catalyst, affording the desired imidazole derivatives in good yields (**74–79%**) under

solvent-free conditions at 80 °C within **2 h**. The reaction exhibited compatibility with different α-azido chalcone substrates and a range of nitriles, including **aliphatic, vinyl, and aromatic nitriles**. The synthesized compounds were successfully purified and characterized by melting point, TLC, IR, and ^1H NMR spectroscopy, and the spectral data confirmed the formation of the targeted imidazole derivatives. The developed protocol provides a simple, rapid, and efficient synthetic route to structurally diverse **2,4,5-trisubstituted imidazoles**, which may be valuable scaffolds for further synthetic and medicinal chemistry investigations.

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