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Efficient synthesis of novel arylidene cyanoacetamide derivatives via Knoevenagel condensation

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Abstract: The widespread utility of unsaturated 2-cyanoacetamide derivatives in medicinal chemistry is fixed, as they serve as essential building blocks for synthesizing bioactive compounds, thereby facilitating the development of innovative pharmaceutical agents. This study presents an efficient and high-yielding synthetic approach to novel arylidene cyanoacetamide derivatives via Knoevenagel condensation. A series of *N*-substituted cyanoacetamides (2, 3, 4, and 5) were first prepared by reacting ethyl cyanoacetate (1) with cyclohexylamine, morpholine, piperidine, and piperazine. These intermediates were subsequently condensed with various aromatic aldehydes including cinnamaldehyde (6), 3-(4-dimethylamino) phenyl acrylaldehyde (7), and *4-(dimethylamino) benzaldehyde* (8) using trimethylamine as a base catalyst. The reaction afforded the target arylidene derivatives (I-VI) excellent yields (70.0-90.0%) under mild and straightforward conditions. All compounds were fully characterized by ^{1}H NMR, ^{13}C NMR, and mass spectrometry. This method provides a practical and scalable route to structurally diverse arylidene cyanoacetamides, which hold potential for applications in medicinal chemistry (e.g., as bioactive scaffolds) and materials science (e.g., as optoelectronic materials).

Introduction

Cyanoacetamides represent a highly versatile class of organic compounds that serve as key precursors in the synthesis of numerous pharmacologically active molecules and agrochemicals [1]. Their structural framework, characterized by the presence of reactive cyano and carbonyl functional groups, enables efficient transformations with bidentate reagents, facilitating the construction of diverse heterocyclic systems. Additionally, the active methylene group in these compounds participates in condensation and substitution reactions, further enhancing their utility as intermediates for the assembly of nitrogen-containing heterocycles [2-8]. Earlier reviews by Fadda et al. [1] and Litvinov [9] systematically documented the synthetic applications of cyanoacetamides. Building upon their foundational work, this review provides an updated and comprehensive survey of recent advancements in the utilization of cyanoacetamides for the synthesis of monocyclic five- and six-membered heterocycles, as well as, fused heterocyclic systems. Furthermore, it briefly outlines contemporary methodologies for the preparation of cyanoacetamides, including reactions of aryl or heteroaryl amines with alkyl cyanoacetates, cyanoacetic acid, or 3-oxopropanenitriles under varying conditions. Alternative synthetic routes, such as the treatment of amines with chloroacetyl chloride followed

by potassium cyanide, as well as condensations involving butylamine, potassium cyanate, cyanoacetic acid, and acetic anhydride, are also discussed [10].

The design and synthesis of novel cyanoacetamide-based derivatives continue to attract significant interest in both organic and medicinal chemistry. These compounds readily undergo Knoevenagel condensation with aldehydes, yielding arylidene derivatives that exhibit promising biological and physicochemical properties [11-12]. Such structural motifs hold considerable potential in pharmaceutical research, where they may serve as bioactive agents, as well as in materials science, owing to their tunable optical and electronic properties for advanced optoelectronic applications [13]. This study aims to highlight recent developments in this field, emphasizing the synthetic versatility and broad applicability of cyanoacetamides in heterocyclic chemistry.

Material and methods

All chemicals were purchased from Sigma Aldrich (St. Louis, MO, USA) and were used as received. Reactions were monitored on TLC using different rations from (methanol/hexane), (chloroform/hexane) and dichloromethane. All spectroscopic analysis of prepared compounds was conducted at the National Research Centre at Douqi. ^{1}H NMR spectra were carried out on a Bruker 500 MHz with chemical shift (δ) expressed in ppm downfield from tetramethyl silane as an internal standard (δ TMS=0) using $CDCl_3$ and DMSO-d_6 as solvents. The multiplicity of the signal is as follows: s (Singlet), d (Doublet), t (Triplet), q (Quartet), m (Multiplet). ^{13}C-NMR was measured on a Bruker 125 MHz with internal reference TMS δ=0. Mass spectroscopy was done using direct inlet in deuterochloroform ($CDCl_3$), unit (DI-50) of Shimadzu GC/MS-QP5050A, Ionization mode: EI, Ionization voltage: 70ev. Melting points (m.p.) of the synthesized compounds were measured in capillary tubes using a Stuart scientific apparatus and were uncorrected.

Synthetic procedure

Synthesis of cyanoacetamide: A mixture of ethyl cyanoacetate (0.01 mol) and a heterocyclic amine (primary or secondary, 0.01 mol) was placed in a 100 mL beaker and stirred at room temperature overnight without the addition of a catalyst. The resulting solid was collected by filtration, washed with diethyl ether, and dried under a vacuum to afford a white precipitate. The crude product was recrystallized from ethanol to yield the pure compounds (2, 3, 4, 5).

Synthesis of arylidienamide: Cyanoacetamide (0.01 mol) was dissolved in absolute ethanol, followed by the dropwise addition of trimethylamine. An aromatic aldehyde (0.01 mol) was then introduced into the reaction mixture with continuous stirring at room temperature. The reaction was completed within approximately 15 min, yielding a colored precipitate. The resulting product was isolated by filtration, washed with ethanol, and subsequently recrystallized from ethanol to afford compounds (I-VI).

Results

2-Cyano-N-cyclohexylacetamide (2): $C_9H_{14}N_2O$ (166.11 g/mol). 90.0% yield as a white solid m.p. 127-129°C. ^{1}H-NMR ($CDCl_3$): δ: 1.22 (m, 3H, H ^{4a}, H^{5a}, H^{6a}), 1.37 (m, 2H, H^{4e}, H^{6e}), 1.6 (m, 1H, H^{5e}), 1.7 (dt, 2H, H^{1a}, H^{3a}), 1.9 (dt, 2H, H^{1e}, H^{3e}), 3.3 (s, 2H, H^{10}), 3.7 (m, 1H, H^{2}), 6.2 (s, 1H, NH). ^{13}C-NMR ($CDCl_3$): δ: 24.8 (C^{4}, C^{6}), 25.4 (C ^{5}), 26.2 (C^{10}), 32.5 (C^{1}, C^{3}), 49.5 (C^{2}), 115.4 (C^{11}), 161.2 (C^{8}).

3-Morpholino-3-oxopropanenitrile (3): $C_7H_{10}N_2O_2$ (154.17 g/mol). 75.0% yield as a white solid m.p. 86-88°C. ^{1}H-NMR ($CDCl_3$): δ=3.45 (t, 2H, H^{1a}, H^{3a}), 3.49 (s, 2H, H^{9}), 3.62 (t, 2H, H^{1e}, H^{3e}), 3.68 (t, 2H, H^{4a}, H^{6a}), 3.71 (t, 2H, H^{4e}, H^{6e}). ^{13}C-NMR ($CDCl_3$): δ=24.9 (C^{9}), 42.7 (C^{1a}, C^{3a}), 46.6 (C^{1e}, C^{3e}), 66.3 (C^{4a}, C^{6a}), 66.5 (C^{4e}, C^{6e}), 114.4 (C^{10}), 160.8 (C^{7}).

3-Oxo-3-(piperidin-1-yl) propanenitrile (4): $C_8H_{12}N_2O$ (152.2 g/mol). 80.0% yield as a white solid m.p. 78-80°C. ^{1}H-NMR ($CDCl_3$): δ=1.5 (tt, 2H, H^{4a}, H^{6a}), 1.6 (tt, 4H, H^{5}, H^{4e}, H^{6e}), 3.3 (t, 2H, H^{1a}, H^{3a}), 3.5 (s, 2H, H^{9}), 3.6 (t, 2H, H^{1e}, H^{3e}). ^{13}C-NMR ($CDCl_3$): δ=24.0 (C^{9}), 25.1 (C^{5}), 26.0(C^{4}, C^{6}), 43.4 (C^{1}), 47.3 (C^{3}), 114.8 (C^{10}), 160.2 (C^{7}).

3-Oxo-3-(piperazin-1-yl) propanenitrile (5): $C_7H_{11}N_3O$ (153.19 g/mol). 70.0% yield as a white solid m.p. 248-250°C. ^{1}H-NMR (DMSO-d_6): δ=2.1 (s, 1H, NH), 3.29-3.50 (m, 8H, H^4, H^6, H^9, H^{1a}, H^{3a}), 4.2 (t, 2H, H^{1e}, H^{3e}). ^{13}C-NMR (DMSO-d_6): δ=25.4 (C^9), 41.7 (C^4, C^6), 45.6 (C^1, C^3), 116.6 (C^{10}), 162.3 (C^7).

2-Cyano-N-cyclohexyl-5-(4-(dimethylamino) phenyl) penta-2,4- dienamide (I): $C_{20}H_{25}N_3O$ (323.4 g/mol). 75.0% yield as a brown solid m.p. 196-198°C. ^{1}H-NMR ($CDCl_3$): δ=1.22 (tt, 3H, H^{4a}, H^{5a}, H^{6a}), 1.37 (tt, 2H, H^{4a}, H^{6a}), 1.6 (tt, 1H, H^{5e}), 1.7 (dt, 2H, H^{1a}, H^{3a}), 1.9 (dt, 2H, H^{1e}, H^{3e}) , 3.0 (s, 6H, H^{21}, H^{22}), 3.9 (m, 1H, H^2), 5.9 (s, H, NH), 6.7 (d, 2H, H^{16}, H^{18}), 7.0 (dd, 1H, H^{12}), 7.1 (d, 1H, H^{13}), 7.4 (d, 2H, H^{15}, H^{19}), 8.0 (d, 1H, H^{11}). ^{13}C-NMR ($CDCl_3$): δ=24.9 (C^4, C^6), 25.6 (C^5), 33.1 (C^1, C^3), 40.4 (C^{21}, C^{22}), 49.2 (C^2), 101.0 (C^{10}), 112 (C^{16}, C^{18}), 117 (C^{23}), 118.1 (C^{12}), 123 (C^{14}), 130 (C^{15}, C^{19}), 148 (C^{13}), 151 (C^{17}), 154 (C^{11}), 160 (C^8). MS (EI): m/z=323 (100%), 240 (10.0%), 224 (21.0%), 196 (35.0%).

5-(4-(dimethylamino) phenyl)-2-(morpholine-4-carbonyl) penta-2,4-dienenitrile (II): $C_{18}H_{21}N_3O_2$ (311.4 g/mol). 70.0% yield as a dark red solid m.p. 138-140°C. ^{1}H-NMR ($CDCl_3$): δ=3.1 (s, 6H, H^{21}, H^{22}), 3.6-3.72 (t, 8H, H^4, H^6, H^1, H^3), 6.70 (d, 2H, H^{15}, H^{17}), 7.0 (dd, d, 2H, H^{11}, H^{12}), 7.45 (d, 2H, H^{14}, H^{18}), 7.72 (d, 1H, H^{10}). ^{13}C-NMR ($CDCl_3$): δ=40.23 (C^{20}, C^{21}), 40.50 (C^1, C^3), 66 (C^4, C^6), 101.7 (C^9), 112.5 (C^{15}, C^{17}), 116 (C^{22}), 118 (C^{11}), 124 (C^{13}), 130 (C^{14}, C^{18}), 148 (C^{12}), 152 (C^{16}), 156 (C^{10}), 164 (C^7). MS (EI): m/z=311 (77.0%), 225 (79.0%), 196 (100%), 152 (24.0%), 114 (4.0%).

5-(4-(dimethylamino) phenyl)-2-(piperidine-1-carbonyl) penta-2,4-dienenitrile (III): $C_{19}H_{23}N_3O$ (309.41 g/mol). 74.0% yield as a purple solid m.p. 143-145°C. ^{1}H-NMR (CDC_{l3}): δ=1.62 (m, 6H, H^4, H^5, H^6), 3.02 (s, 6H, H^{20}, H^{21}), 3.57 (t, 4H, H^1, H^3), 6.7 (d, 2H, H^{15}, H^{17}), 7.03 (dd, d, 2H, H^{11}, H^{12}), 7.4 (d, 2H, H^{14}, H^{18}), 7.6 (d, 1H, H^{10}). ^{13}C-NMR ($CDCl_3$): δ=24.5 (C^4, C^6), 25.9 (C^5), 40 (C^{20}, C^{21}, C^1, C^3), 103 (C^9), 112 (C^{15}, C^{17}), 116 (C^{22}), 119 (C^{11}), 124 (C^{13}), 130 (C^{14}, C^{18}), 147 (C^{12}), 152 (C^{16}), 155 (C^{10}), 163 (C^7). MS (EI): m/z=309 (100%), 224.7 (395), 197 (29.0%), 147 (5.0%).

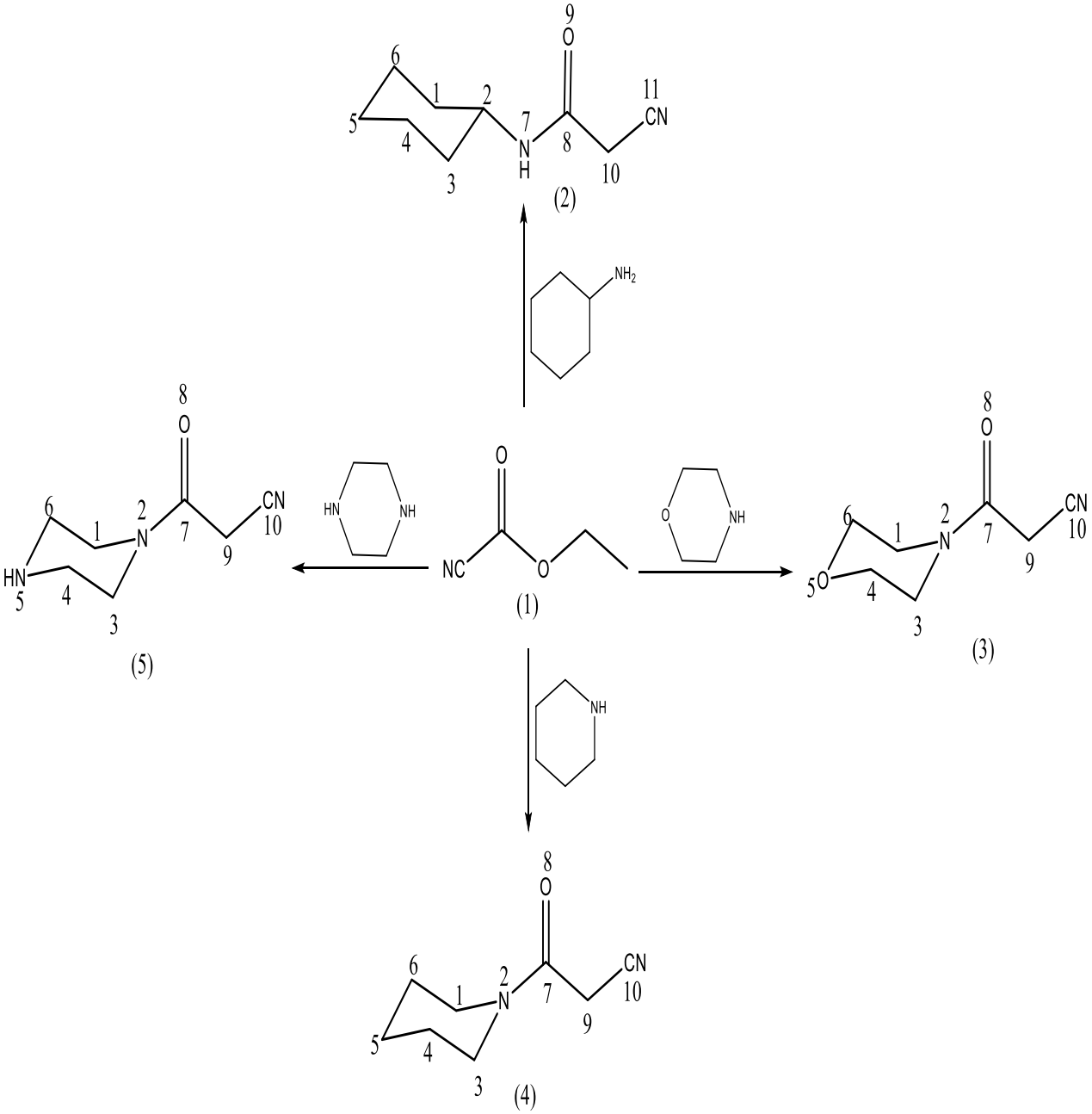
2-Cyano-N-cyclohexyl-5-phenylpenta-2,4-dienamide (IV): $C_{18}H_{20}N_2O$ (280.4 g/mol). 90.0% yield as a white solid m.p. 170-172°C. ^{1}H-NMR ($CDCl_3$): δ=1.24 (m, 3H, H^{4a}, H^{5a}, H^{6a}), 1.37 (m, 2H, H^{4e}, H^{6e}), 1.7 (m, 1H, H^{5e}), 1.75 (dt, 2H, H^{1a}, H^{3a}), 1.95 (dt, 2H, H^{1e}, H^{3e}), 3.8 (m, 1H, H^2), 6.02 (s, 1H, NH), 7.2 (d, 2H, H^{16}, H^{18}), 7.4 (m, 3H, H^{12}, H^{13}, H^{17}), 7.6 (d, 2H, H^{15}, H^{19}), 8.4 (d, 1H, H^{11}). ^{13}C-NMR ($CDCl_3$): δ=24.9 (C^4, C^6), 25.5 (C^5), 32.96 (C^1, C^3), 49.4 (C^2), 106 (C^{10}), 116 (C^{20}), 123 (C^{12}), 128 (C^{15}, C^{19}), 129 (C^{17}), 131 (C^{16}, C^{18}), 135 (C^{14}), 148 (C^{13}), 153 (C^{11}), 159 (C^8). MS (EI): m/z = 280 (100%), 196 (48.0%), 181 (53.0%).

2-Cyano-N-cyclohexyl-3-(4-(dimethylamino) phenyl) acrylamide (V): $C_{18}H_{23}N_3O$ (297.18 g/mol). 70.0% yield as a light yellow solid m.p. 184-186°C. ^{1}H-NMR ($CDCl_3$): δ=1.2 (m, 3H, H^{4a}, H^{5a}, H^{6a}), 1.4 (m, 2H, H^{4e}, H^{6e}), 1.72 (m, 1H, H^{5e}), 1.75 (q, 2H, H^{1a}, H^{3a}), 1.96 (q, 2H, H^{1e}, H^{3e}), 3.0 (s, 6H, H^{19}, H^{20}), 3.89 (m, 1H, H^2), 6.08 (s, 1H, NH), 6.7 (d, 2H, H^{14}, H^{16}), 7.8 (d, 2H, H^{13}, H^{17}), 8.13 (s, 1H, H^{11}). ^{13}C-NMR ($CDCl_3$): δ = 24.9 (C^4, C^6), 25.6 (C^5), 33 (C^1, C^3), 40 (C^{19}, C^{20}), 49.4 (C^2), 96 (C^{21}), 111 (C^{14}, C^{16}), 119 (C^{10}), 120 (C^{12}), 133 (C^{13}, C^{17}), 152 (C^{11}), 153 (C^{15}), 160.9 (C^8) MS (EI): m/z=297.2 (87%), 214 (100%), 198 (70.0%), 170 (50.0%), 133 (19.0%), 121 (12.0%).

3-(4-(dimethylamino) phenyl)-2-(piperidine-1-carbonyl) acrylonitrile (VI): $C_{17}H_{21}N_3O$ (283.4 g/mol). 70.0% yield as a dark yellow solid m.p. 158-160°C. ^{1}H-NMR ($CDCl_3$): δ=1.65 (m, 6H, H^4, H^5, H^6), 3.05 (s, 6H, H^{18}, H^{19}), 3.58 (t, 4H, H^1, H^3), 6.7 (d, 2H, H^{13}, H^{15}), 7.6 (s, 1H, H^{10}), 7.8 (d, 2H, H^{12}, H^{16}). ^{13}C-NMR ($CDCl_3$): δ=24.5 (C^4, C^6), 25.9 (C^5), 40,2 (C^1, C^3, C^{18}, C^{19}), 99 (C^{20}), 111 (C^{13}, C^{15}), 118 (C^9), 120 (C^{11}), 133 (C^{12}, C^{16}), 152 (C^{10}), 152.6 (C^{14}), 164.5 (C^7). MS (EI): m/z=283.4 (100%), 238 (9.0%), 198 (38.0%), 171 (54.0%), 133 (13.0%), 120 (4.0%).

Discussion

The synthesis of various heterocycles via an efficient and expedient pathway was achieved through the reaction of ethyl cyanoacetate with various amines, predominantly cyclic amines, under solvent-free conditions and without external heating. This approach afforded cyanoacetamide derivatives in high yields within a short reaction time, as illustrated in **Scheme 1**.



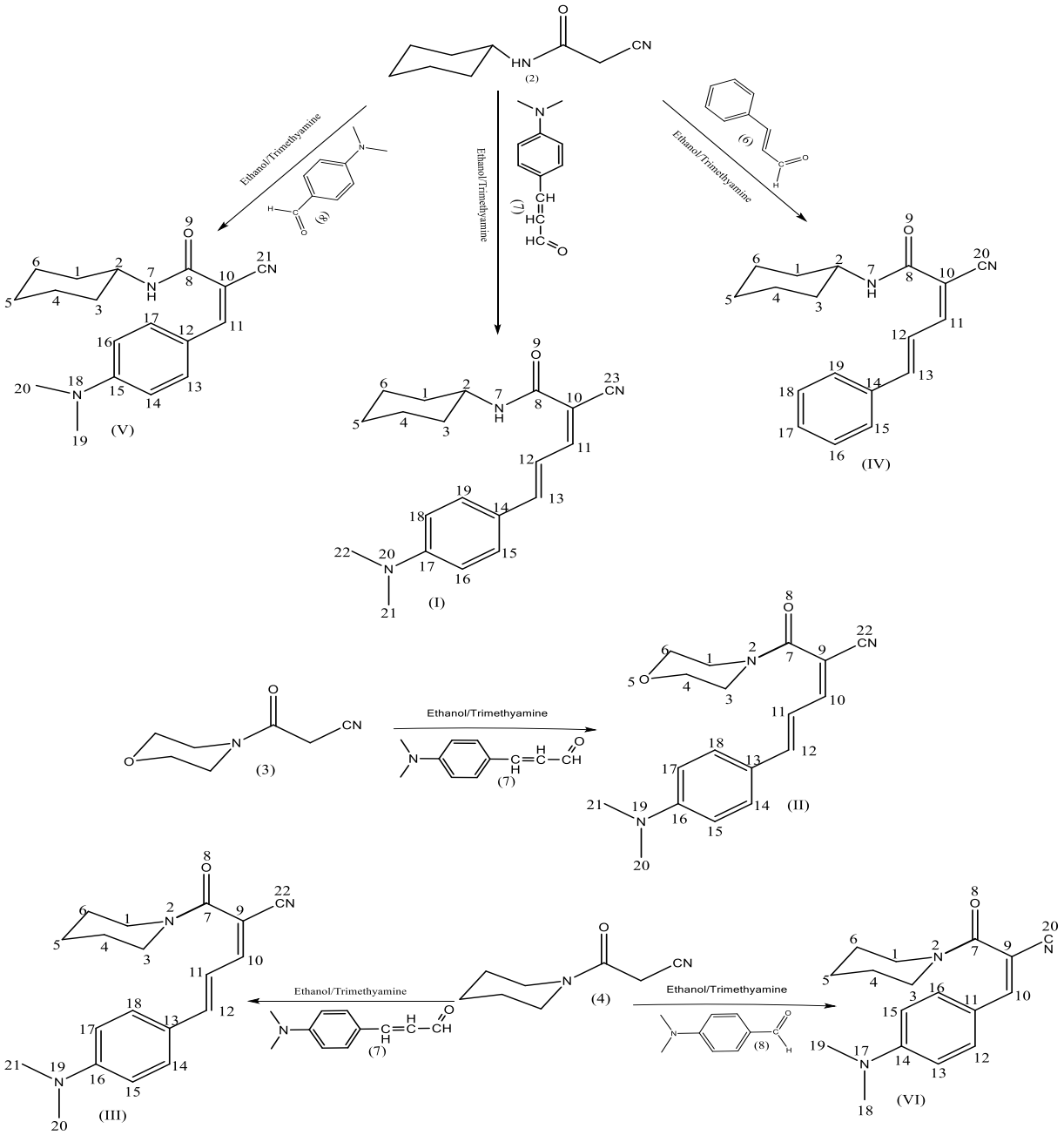
Scheme 1: Synthesis of *N*-substituted cyanoacetamides (2, 3, 4, and 5)

The subsequent condensation of these cyanoacetamides with various aldehydes in the presence of a base and solvent at room temperature yielded the corresponding arylidene cyanoacetamides rapidly and efficiently. The formation of cyanoacetamides at room temperature can be attributed to the nucleophilic attack of the amine's amino group on the carbonyl carbon of ethyl cyanoacetate, leading to the substitution of the ethoxy group and the formation of an amide bond. This mechanism proceeds via a nucleophilic acyl substitution pathway, wherein the amine acts as the nucleophile, displacing the ethoxide ion to generate the intermediate tetrahedral species, which subsequently collapses to release ethanol and form the cyanoacetamide product. The absence of solvent and external heating in the first step highlights the reaction's atom economy and energy efficiency, aligning with green chemistry principles. The high reactivity of cyclic amines, due to their constrained geometry and enhanced nucleophilicity, likely contributes to the rapid conversion and excellent yields observed. Furthermore, the mild conditions employed in the subsequent Knoevenagel condensation utilizing a base and room temperature reaction demonstrate the versatility and efficiency of this synthetic strategy, avoiding harsh conditions that could lead to side reactions or decomposition. This methodology offers a practical and scalable route to access structurally diverse heterocyclic frameworks, which are of significant interest in medicinal and materials chemistry.

The structural confirmation of the synthesized compounds (2-5) was unequivocally established through a comprehensive analysis of their ^{1}H and ^{13}C NMR spectra, which exhibited excellent agreement with the proposed architectures. The distinct splitting patterns, chemical shifts, and coupling constants observed for each compound provided compelling evidence for their respective molecular frameworks, while the absence of residual starting material signals underscored the purity of the products. For 2-cyano-N-cyclohexylacetamide (2), the ^{1}H NMR spectrum revealed characteristic signals consistent with the cyclohexyl ring's stereochemical heterogeneity. The axial and equatorial protons displayed predictable multiplicities (triplet of triplets or doublet of triplets) and chemical shifts, with deshielding effects observed for H^{2} (δ 3.7 ppm) due to its proximity to the amide nitrogen. The singlet at δ 3.3 ppm for the CH_2 group adjacent to the cyano moiety and the downfield NH resonance (δ 6.2 ppm) confirmed the amide formation, further supported by the absence of ester-related peaks. The ^{13}C NMR spectrum corroborated this assignment, with the carbonyl carbon (δ 161.2 ppm) and cyano group (δ 115.4 ppm) appearing at typical shifts for such functionalities. The cyclohexyl carbons resonated between δ 24-50 ppm, with C^{2} (δ 49.5 ppm) notably deshielded due to nitrogen's inductive effect.

In contrast, the morpholine derivative (3) exhibited simplified splitting patterns, with the methylene protons adjacent to the cyano group appearing as a sharp singlet (δ 3.49 ppm). The morpholine ring protons displayed distinct shifts influenced by oxygen's electronegativity (δ 3.45-3.71 ppm), while the ^{13}C NMR spectrum confirmed the expected seven-carbon framework, including the diagnostic carbonyl (δ 160.8 ppm) and cyano (δ 114.4 ppm) signals. For the piperidine-based analogue (4), the ^{1}H NMR spectrum highlighted the nitrogen's impact on proton shifts, with axial/equatorial distinctions (e.g., δ 3.3 ppm for H^{1a}/H^{3a} vs. δ 3.6 ppm for H^{1e}/H^{3e}). The ^{13}C NMR spectrum's seven signals, including the piperidine carbons (δ 24-47 ppm), aligned with the proposed structure. Finally, the piperazine-containing compound (5) showed more complex multiplicity due to its symmetrical yet conformationally flexible ring. The ^{13}C NMR spectrum's five signals, including the carbonyl (δ 162 ppm) and piperazine carbons (δ 41.7-45.6 ppm), further validated the structure. Collectively, the NMR data for 2-5 demonstrated remarkable consistency with their predicted structures, with key diagnostic signals (e.g., NH, cyano, and carbonyl groups) serving as definitive markers. The absence of extraneous peaks confirmed high synthetic efficiency, while the observed chemical shifts and coupling patterns reflected the anticipated electronic and steric environments. These findings not only validate the successful synthesis of the target compounds but also highlight the utility of NMR spectroscopy in elucidating subtle stereochemical and electronic features in heterocyclic systems.

The synthesis of arylidene cyanoacetamide derivatives via the Knoevenagel condensation reaction between cyanoacetamide and various aromatic aldehydes proved to be an efficient and straightforward method for carbon-carbon double bond formation. This reaction was successfully carried out under mild conditions (room temperature) in a remarkably short time, yielding the desired products with high purity and satisfactory yields (70.0%-90.0%). The Knoevenagel condensation mechanism involves the nucleophilic attack of the active methylene group in *N*-substituted cyanoacetamides (2, 3, 4, and 5) on the electrophilic carbonyl carbon of the aldehydes (6-8), followed by dehydration to form the corresponding arylidene derivatives (I-IV). The presence of electron-donating groups, such as the dimethylamino substituent in aldehydes (7) and (8), likely enhanced the electrophilicity of the carbonyl carbon, facilitating the condensation process. Additionally, the extended conjugation in cinnamaldehyde (6) contributed to the formation of the dienamide product (IV) with high efficiency as shown in scheme (2). The structural elucidation of the synthesized compounds was confirmed by ^{1}H NMR, ^{13}C NMR, and other spectroscopic techniques. The NMR spectra exhibited characteristic peaks corresponding to the vinylic protons and carbons of the newly formed double bonds, as well as the aromatic and amide functionalities, which aligned well with the proposed structures. The high yields and clean reaction profiles suggest that this method is both practical and scalable for the synthesis of structurally diverse arylidene cyanoacetamides. This work highlights the versatility of the Knoevenagel condensation in constructing α, β-unsaturated carbonyl systems, which are valuable intermediates in medicinal and materials chemistry. The mild reaction conditions, short reaction time, and excellent yields make this approach particularly advantageous for further applications in heterocyclic synthesis and drug development **(Scheme 2)**.



Scheme 2: Synthesis of arylidene cyanoacetamide derivatives

Conclusion: This study successfully demonstrated an efficient and rapid synthesis of arylidene cyanoacetamide derivatives via the Knoevenagel condensation of *N*-substituted cyanoacetamides (2, 3, 4, and 5) with various aromatic aldehydes (6-8) under mild conditions. The reaction proceeded smoothly, yielding the target compounds (I-VI) in high purity with excellent yields (70.0%-90.0%), confirming the robustness of this methodology. The structural characterization of the synthesized compounds was unequivocally established using ^{1}H NMR, ^{13}C NMR, and Mass spectroscopy, which confirmed the formation of the α, β-unsaturated carbonyl system through characteristic chemical shifts corresponding to the vinylic and aromatic protons. The presence of electron-donating groups on the aldehydes enhanced reactivity, facilitating the condensation process and leading to high product yields. This work underscores the significance of the Knoevenagel condensation as a powerful tool for C=C bond formation in organic synthesis. The mild reaction conditions, operational simplicity, and high efficiency make this approach highly attractive for the preparation of structurally diverse arylidene cyanoacetamides, which are valuable intermediates in pharmaceutical and materials chemistry. Future studies could explore the biological activity of these compounds or further optimize the reaction conditions for industrial-scale applications. Overall, this research provides a reliable, scalable, and environmentally friendly synthetic route to arylidene cyanoacetamides, contributing to the expanding toolbox of modern synthetic methodologies.

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Author contribution: AG conceived, and designed the study. YE collected data. NA, AG & YE contributed to data analysis and interpretation of data. NA & NE drafted and reviewed the manuscript for intellectual context. All authors approved the final version of the manuscript and agreed to be accountable for its contents.
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