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Original article

Synthesis of Cyclopentanone and Cyclohexanone Derivatives

Naowara Alarafi*, Abdullah Gheath, Abdalhamid Alarafi

Department of Chemistry, Faculty of Science, Benghazi University, Benghazi, Libya
Corresponding Email. Nourapro@gmail.com

Abstract
A series of compounds (I–XIII) were synthesized by reacting ethyl 2-oxocyclopentane-1-carboxylate (1) or ethyl 2-oxocyclohexane-1-carboxylate (2) with various diamines, including ethane-1,2-diamine, benzene-1,4-diamine, hydrazine hydrate, benzidine, N^1, N^3-bis(2-aminoethyl) malonamide, 3-hydroxyaniline, malonohydrazide, and piperazine. Most derivatives (I, II, III, VI, VII, VIII, X, XIII) adopted enamine structures via a 2:1 reaction ratio, whereas compounds IX and XI exhibited distinct structural frameworks due to a 1:1 reaction pathway. Notably, the reaction of β-keto ester 1 with hydrazine hydrate yielded enamine III as a minor product and pyrazolone IV as the major derivative, while the analogous reaction with compound (2) exclusively produced pyrazolone V. Additionally, the reaction of compound (2) with malonohydrazide afforded an azine derivative (XII). All syntheses proceeded under mild conditions with moderate yields, and the structures were characterized using melting point, TLC, IR, MS, ^{1}H-NMR (with D_2O exchange), ^{13}C-NMR, and APT analyses. Preliminary screening revealed antimicrobial activity in selected derivatives.

Keywords. Diamines, Cyclopentanone Derivatives, Secondary Amines, Neat Synthesis.

Introduction

The structural analogs, enamines and enols, are produced when secondary amines react with carbonyl compounds. Pyrrolidine, piperidine, and morpholine are common secondary amines that are used to create enamines [1]. Enamines are substances with a lot of electrons and interesting redox characteristics. Here, several secondary enamines that were condensed from primary amine and β-keto carbonyls were created, and cyclic voltammetry was used to methodically examine their electrochemical oxidation characteristics [2], The first general synthesis of enamines was published by Mannich nine years before [3]. Wittig created the term "enamine" in 1927 to highlight the similarity between this family of chemicals and enols [4], although the first known instances of enamine chemistry were in 1884 [5-7]. It wasn't until 1954 that Stork's groundbreaking research revealed the synthetic potential of enamine-electrolyte interaction [8-11].

Enamine chemistry has been thoroughly examined [12]. Before the early 1970s, enamines held a special position as noncharged enolate equivalents; since then, they have shared this status with silylated enol ethers [13-20]. Their reactivity with acceptor-activated aryl halides [21], electron-deficient dienes π4 cycloaddition partners [22-24], and Michael acceptors [25-26]. Controllable and responsive systems may be created by constitutional exchange utilizing dynamic interactions and reactions of either a covalent or non-covalent nature [27-44]. Enamine compounds are widely recognized for their diverse biological activities, attributed to their unique structural motif—a nitrogen-containing group conjugated with a carbon-carbon double bond. This configuration enables enamines to serve as versatile intermediates in organic synthesis while facilitating strong interactions with biological targets. Extensive studies have demonstrated that enamine derivatives exhibit a broad spectrum of pharmacological properties, including antibacterial, antifungal, antiviral, anti-inflammatory, and anticancer activities [45]. Given their pharmacological relevance, this study focuses on the synthesis of new enamine derivatives using an innovative, facile, and high-yield preparation method. The approach aims to expand the library of bioactive enamines for further exploration of their therapeutic potential.

Materials and Methods

Materials

All chemicals were purchased from SigmaAldrich (St. Louis, MO, USA) and were used as received. Reactions were monitored on TLC (Chloroform /pet.methanol). All spectroscopic analysis of prepared compounds was conducted in the National Research Centre at Giza. 1H NMR spectra were carried out on a Bruker 400 MHz with chemical shift (δ) expressed in ppm downfield from tetramethyl silane as an internal standard (δ TMS = 0) using CDCl3 and DMSO-d6 as solvents. The multiplicity of the signal is as follows: s (Singlet), d (Doublet), t (Triplet), q (Quartet), m (Multiplet). 13C-NMR was measured on a Bruker 100 MHz with internal reference TMS δ = 0. Infrared spectra were recorded on a Perkin Elmer 2000 FT-IR system spectrometer, where the positions of absorptions have been expressed in wave number units (cm-1). Melting points (m.p) of the synthesized compounds were measured in capillary tubes using a Stuart scientific apparatus and are uncorrected.

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Synthetic procedure

Synthesis of enamines (I – VI)

Two equivalents of either ethyl 2-oxocyclopentane-1-carboxylate or ethyl 2-oxocyclohexane-1-carboxylate were added to one equivalent of the amine. the mixture was stirred at room temperature under solvent-free conditions. The resulting precipitate was collected by filtration, washed with ethanol, and recrystallized from ethanol.

Synthesis of enamines (VII-XIII)

Two equivalents of ethyl-2-oxocyclopentane-1-carboxylate or ethyl 2-oxocyclohexane-1-carboxylate were mixed with one equivalent of the amine, and the mixture was refluxed in ethanol until precipitation was observed. The formed precipitate was then filtered, washed with ethanol, and recrystallized from ethanol.

Diethyl 2,2'-(ethane-1,2-diylbis(azanediyl)) bis (cyclopent-1-ene-1-carboxylate) (I):36% yield as an off-white solid. m.p. 108-110 °C. IR (KBr) υmax: 1591.53 cm−1 (C=C), 1644.40 cm−1 (ester CO),), and 2945.33 cm−1(CH aliphatic), 3317.45 cm−1 (NH amine). 1H NMR (CDCl3): δ = 7.43 (2H, S, NH), 4.12 (4H, q, CH2CH3), 3.29 (4H, S, CH2-NH), 2.47 -2.41 (8H, dd, CH2), 1.79 – 1.74 (4H, m, CH2), 1.26 (6H, t, CH2CH3). 13C NMR (CDCl3): δ = 168.45 (CO), 164.16 (C=C-NH), 93.82, 58.49, 46 .00, 31.94, 29.07, 20.88, 14.68. MS EI m/z: M+.336, 168, 291, 245, 122, 94.

Diethyl 2,2'-(ethane-1,2-diylbis(azanediyl)) bis (cyclohexene-1-carboxylate) (II): 87% yield as a white solid. m.p. 70-72 °C. IR (KBr) υmax: 1582.55 cm−1 (C=C), 1637.54 cm−1 (ester CO), 2973.32 cm−1(CH aliphatic), 3252.81 cm−1 (NH amine). 1H NMR (CDCl3) δ = 8.99 (2H, S, NH), 4.12 (4H, q, CH2CH3), 3.29 (4H, dd, CH2-NH), 2.26 (8H, m, CH2), 1.62 (8H, m, CH2), 1.26(6H, t, CH3-CH2). 13C NMR (CDCl3): δ = 170.86 (CO), 159.03 (C=C-NH), 90.60, 58.66, 43 .09, 26.24, 23.81, 22.59, 22.26, 14.62. MS EI m/z: M+. 364, 320, 292, 264, 198, 183, 158, 155.

Ethyl(Z)-2-(2-(2-(ethoxycarbonyl) cyclopentylidene)hydrazineyl)cyclopent-1-ene-1-carboxylate (III): 14% yield as a yellow solid. m.p. 71-73°C. IR (KBr) υmax: 1604.55 cm−1 (C=C) , 1647.36 and 1732.91 cm−1 (ester CO), and 2996 cm−1(CH aliphatic), 3259.78 cm−1 (NH amine), 1H NMR (CDCl3): δ = 10 (1H, S, NH), 4.14-4.26 (4H, m, CH2CH3), 3.49 (1H, t, CH), 1.83-3.15 (12H, m, CH2), 1.26-1.30 (6H, m, CH2CH3) , 13C NMR (CDCl3): δ = 173.54 (CO), 169.42 (CO), 161..20 (C=N), 155.28 (N-C=C), 96 .15 (C=C), 61.97, 61.36, 38.06, 32.15, 27.38, 25.95, 25.91,23.22,21.44,14.67. MS m/z: 308.09. MS EI m/z: M+. 308, 263, 216, 188, 160, 108, 80.

1,4,5,6-tetrahydrocyclopenta[c]pyrazol-3(2H)-one (IV): 82% yield as a yellow solid. m.p. 243- 245°C. IR (KBr) υmax: 3400 – 2500 cm-1 (OH), 3000 cm-1 (CH aliphatic), 1590 cm-1 (C=N), and 1529 cm. (C=C). 1H NMR (DMSO-d6): δ = 10.51 (2H, S. br., NH), 2.46 (2H, m, CH2), 2.39-2.33(4H, m, CH2), 13C NMR (DMSO-d6): δ = 154.50 (CO), 153.50 (C=C-NH), 107.50 (C=C-CO), 30.47, 24.48, 22.62.

1,2,4,5,6,7-hexahydro-3H-indazol-3-one (V): 48% yield as a white solid. m.p. 268-270 °C. IR (KBr) υmax: 3400 – 2500 cm-1 (OH), 3000 cm-1 (CH aliphatic), 1611 cm-1 (NH),1560 cm-1 (C=N) and 1540 cm-1 (C=C). 1H NMR (DMSO-d6): δ = 10.26 (2H, S. br., NH), 2.5 (2H, t, CH2), 2.41(2H, t, CH2), 1.62 (4H, m, CH2), 13C NMR (DMSO-d6): δ = 158.95 (CO), 140.30 (C=C-NH), 98.94 (C=C-CO), 23.32, 22.75, 21.74, 19.35 MS EI m/z: M+. 138, 110, 81

Diethyl 2,2'-(piperazine-1,4-diyl) bis(cyclopent-1-ene-1-carboxylate) (VI): 85% yield, an off-white solid. m.p. 112-113 °C. IR (KBr) υmax: 1666.82 cm−1 (C=C), 1742.13 cm−1 (ester CO), and 2981.90 cm−1(CH aliphatic). 1H NMR (CDCl3): δ = 4.13 (4H, q, CH2CH3), 3.48 (6H, m, CH2), 2.64 (8H, m, CH2), 1.79 (4H, m, CH2) 1.26 (6H, t, CH3). 13C NMR (CDCl3): δ = 165.88 (CO), 161.79 (C=C-N), 103.09 (C=C-CO), 97.63 (C=C-CO), 61.31, 60.48, 49.88, 49.09, 35.25, 32.38, 20.93, 20.18, 14.64, 14.14. MS EI m/z: M+. 362, 333, 289, 243, 224, 194, 135, 122, 110.

Diethyl 2,2'-(1,4-phenylenebis(azanediyl)) bis(cyclopent-1-ene-1-carboxylate) (VII): 97% yield as a purple solid. m.p, 164-165°C. IR (KBr) υmax: 1601.08 cm−1 (C=C), 1653.82 cm−1 (ester CO), 2855.67 cm−1(CH aliphatic), 3055.82 (=CH), 3295.97cm−1 (NH amine), 1H NMR (CDCl3): δ 9.53 (2H, S, NH), 6.97 (4H, S, Ar-CH), 4.23 (4H, q, CH2CH3), 2.73 (4H, t, CH2), 2.55-2.76 (4H, t, CH2), 1.87 (4H, q, CH2), 1.31 (6H, t, CH2CH3) ,13C NMR (CDCl3): δ = 168.49. (CO), 160.57 (C=C-NH), 136.36, 121.90, 97.28, 58.94, 33.51, 28.79, 21.73, 14.68. MS EI m/z: M+. 384, 338, 292, 264, 237, 184, 156.

Diethyl 2,2'-(1,4-phenylenebis(azanediyl))bis(cyclohex-1-ene-1-carboxylate) (VIII): 36% yield as an off-gray color. m.p. 153- 154°C. IR (KBr) υmax: 1589.54 cm−1 (C=C), 1643.36 cm−1 (ester CO), 2978.18 cm−1(CH aliphatic), 3152.51cm−1 (=CH), 3207.53 cm−1 (NH amine). 1H NMR (CDCl3): δ = 10.70 (2H, S, NH), 6.98

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(4H, S, Ar-CH), 4.22 (4H, q, CH2CH3), 2.37 (8H, t, CH2), 1.62 (8H, m, CH2), 1.29 (6H, t, CH2CH3). 13C NMR (CDCl3): δ = 170.84 (CO), 156.58 (C=C-NH), 136.23, 125.38, 93.04, 57.22, 29.96, 27.09, 23.85, 22.32, 14.59. MS EI m/z: M+. 412, 364, 319, 136, 108, 79.

Ethyl 2-((4'-amino-[1,1'-biphenyl]-4-yl) amino) cyclopent-1-ene-1-carboxylate (IX): 12% yield as a yellow solid. m.p. 169-170°C. 1H NMR (CDCl3): δ = 9.70 (1H, S, NH) 7.53-7.48 (8H, m, Ar-CH), 4.25 (2H, q, CH2CH3), 3.60 (2H, S, NH2), 2.89 (2H, t, CH2), 2.06 (2H, t, CH2) 1.93(2H, quintet, CH2), 1.34 (3H, t, CH2CH3). 13C NMR (CDCl3): δ =168.53, 160.47, 139.80, 135.03, 127.58, 126.98, 120.79, 115.46, 98.09, 59.03, 33.77, 28.74, 21.84, 14.68. MS EI m/z: M+. 322, 276, 250, 184, 167, 138, 123, 77.

Diethyl 2,2'-([1,1'-biphenyl]-4,4'-diylbis(azanediyl)) bis(cyclopent-1-ene-1-carboxylate)

(X): 18% yield as a yellow solid. m.p. 154-160°C. 1H NMR (CDCl3): δ = 9.69 (1H, S, NH) 6.84-7.50 (8H, m, Ar-CH), 4.26 (4H, q, CH2CH3), 2.87 (4H, t, CH2), 2.60 (4H, t, CH2), 1.92 (4H, quintet, CH2), 1.34 (6H, t, CH2CH3) [enamine]. 13C NMR (CDCl3): δ =173.55, 165.40, 137.85, 129.96, 125.33, 118.83, 54.64, 37.48, 33.30, 29.49, 21.82, 19.82[imine].

Ethyl 2-((4'-amino-[1,1'-biphenyl]-4-yl) amino) cyclohex-1-ene-1-carboxylate (XI): 43% yield as a yellow solid. m.p. 162-164°C. IR (KBr) υmax: 1578.29 cm−1 (C=C), 1631.60 cm−1 (ester CO), 2980.96 cm−1(CH aliphatic), 3036.16 (=CH) 3223.09 cm−1 (NH amine), 3350.92,3453.78 (NH2). 1H NMR (CDCl3): δ = 10.87 (1H, d, NH) 6.75-7.52 (8H, m, Ar-CH), 4.24 (2H, q, CH2CH3), 3.70 (2H, S.br., NH2), 2.40 -1.62 (8H, m, CH2), 1.32 (3H, t, CH2CH3). MS EI m/z: M+. 336, 290, 234, 184, 167, 145, 91.

1,2,3,4,6,7,9,10,11,12,13,14-dodecahydrodibenzo [c, i][1,2,6,7]tetrazecine-5,8-dione (XII): 24% yield as an off-white solid. m.p. 280-282°C. 1H NMR (DMSO-d6): δ = 10.27 (4H, S.br., NH), 2.50-2.41 (4H, t, CH2), 2.24-2.21 (4H, t, CH2), 1.64-1.63 (8H, m, CH2). 13C NMR (DMSO-d6): δ = 159.04 (CO), 140.54 (C=C-NH), 99.03 (C=C-C=O), 23.30, 22.72, 21.74, 19.32.

Ethyl (Z)-2-((2-(3-((2-((2-(ethoxycarbonyl) cyclopentylidene) amino) ethyl) amino)-3-oxopropanamido) ethyl) amino) cyclopent-1-ene-1-carboxylate (XIII): 40% yield as a white solid m.p. 85-88°C. IR (KBr) υmax: 1585.80 cm−1 (C=C), 1642.43 cm−1 (ester CO), 2945.91 cm−1(CH aliphatic), 3316.82 cm−1 (NH amine). 1H NMR (DMSO-d6): δ = 8.161 (1H, S, NH), 7.452 (2H, S, NH) 4.031 (4H, q, CH2CH3), 3.02-3.65 (15H, m, CH2), 2.35 -2.54(8H, m, CH2), 1.18 (6H, t, CH2CH3) 13C NMR (DMSO-d6): δ = 179.25, 167.62, 167.50, 165.24, 91.83, 58.12, 45.15, 43.70, 40.54, 39.70, 39.29, 20.87, 15.18.

Results and Discussion

This paper reviews the chemistry of enamine and imine derivatives, with a focus on the synthesis of enamines via the reaction of cyclic β-ketoesters with primary or secondary amines. In these reactions, amines act as nucleophiles, while cyclic β-ketoesters function as electrophiles, undergoing nucleophilic attack to yield a novel series of enamine-containing compounds (I–XIII). In this study, ethyl 2-oxocyclopentane-1-carboxylate (1) and ethyl 2-oxocyclohexane-1-carboxylate (2) were reacted with various amines—including ethane-1,2-diamine, benzidine, benzene-1,4-diamine, piperazine, hydrazine hydrate, N^1,N^3-bis(2-aminoethyl)malonamide, and malonohydrazide—under neat conditions at room temperature and under reflux in ethanol.

Ethyl 2-oxocyclopentane-1-carboxylate (1) was reacted with a series of diamines, including ethane-1,2-diamine, hydrazine hydrate, piperazine, 1,4-phenylenediamine, benzidine, and N^1, N^3-bis(2-aminoethyl) malonamide, yielding compounds I, III, IV, VI, VII, IX, X, and XIII, respectively as shown in scheme (1).

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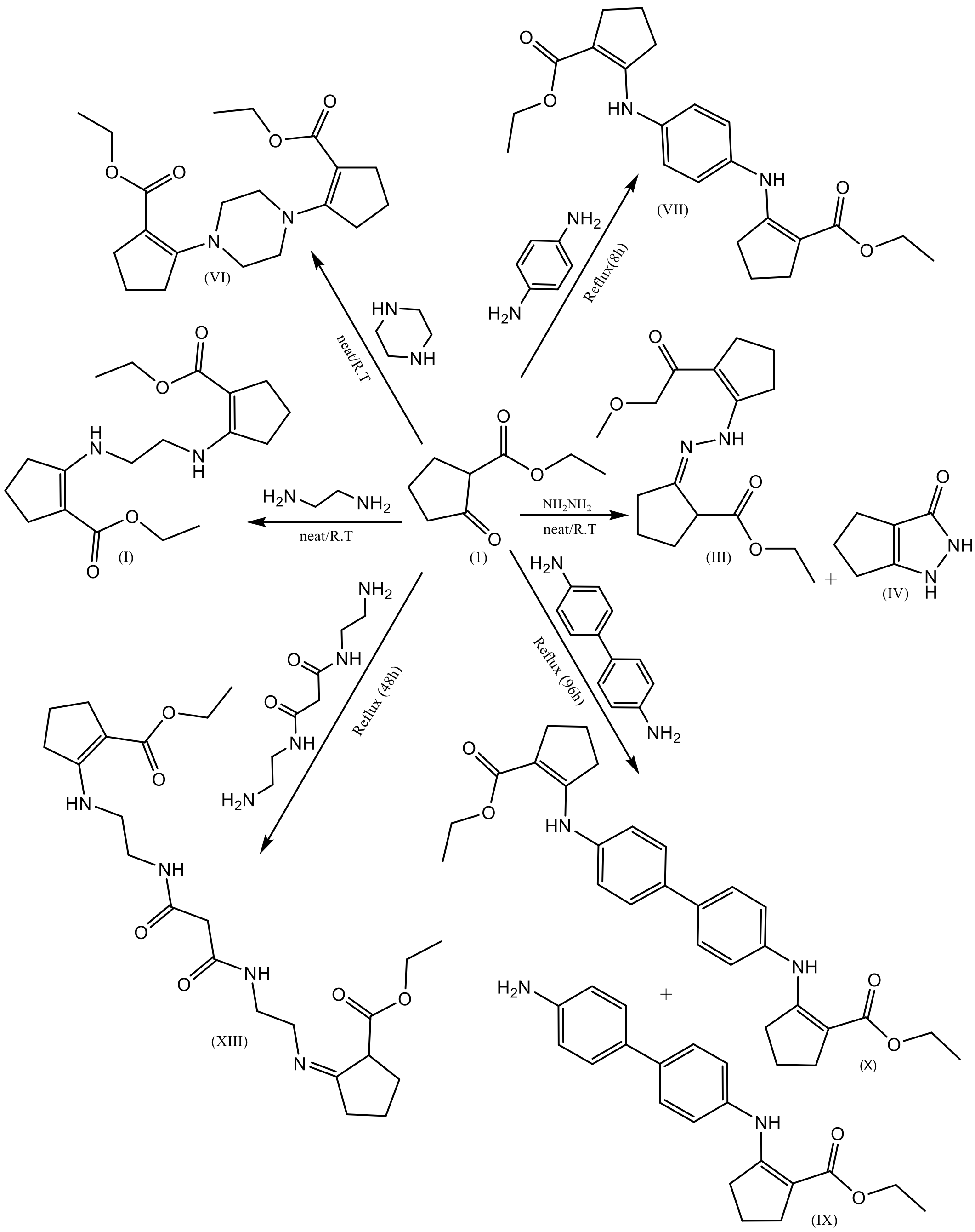
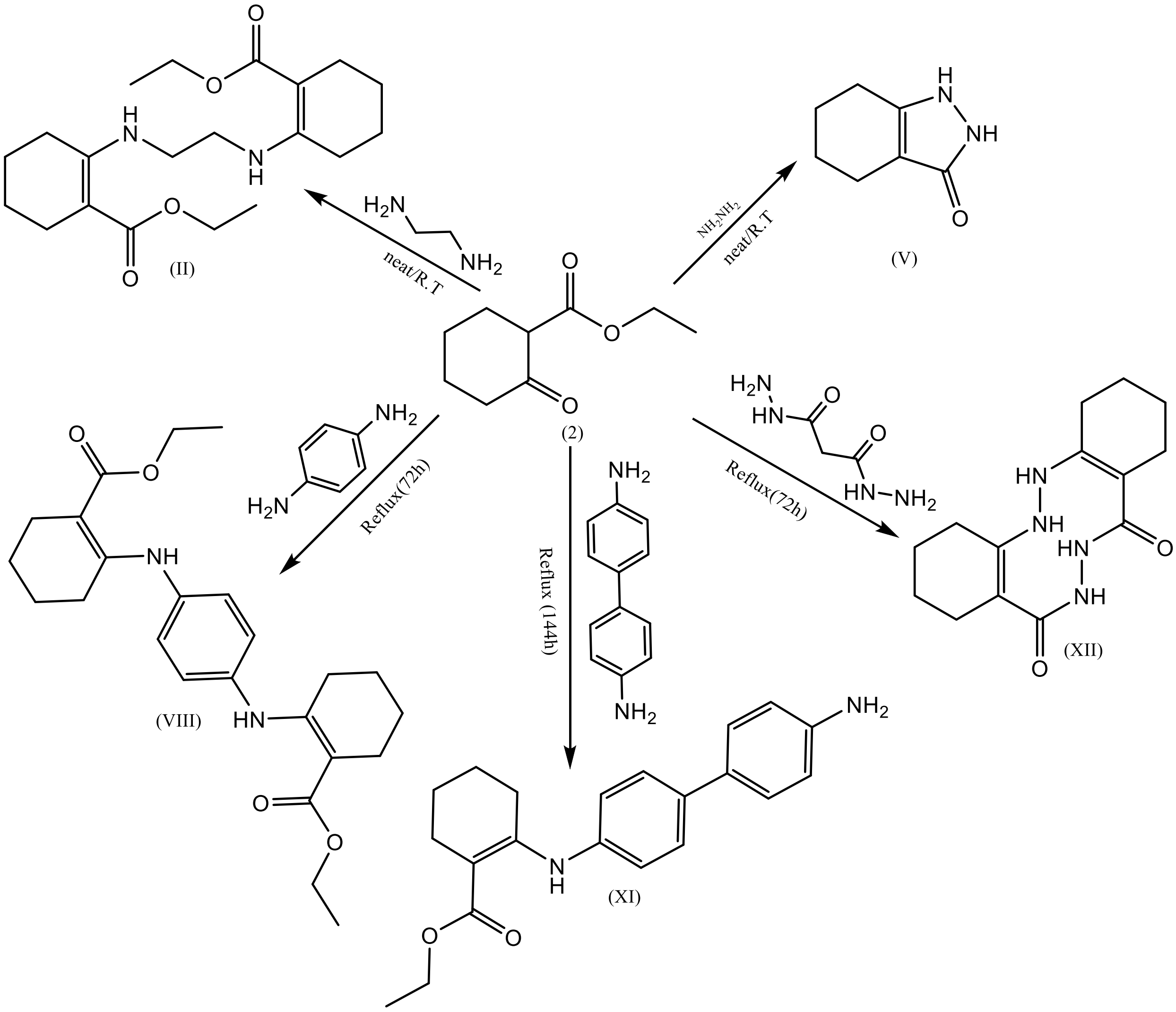


Scheme 1. Reaction of Ethyl 2-oxocyclopentane-1-carboxylate (1) with different diamines

In a parallel study, ethyl 2-oxocyclohexane-1-carboxylate (2) was treated with the same set of diamines namely ethane-1,2-diamine, hydrazine hydrate, 1,4-phenylenediamine, benzidine, and malonohydrazide resulting in the synthesis of compounds II, V, VIII, XI, and XII, as shown in scheme (2). These reactions demonstrate the versatility of β-keto esters in forming diverse heterocyclic and condensed structures upon condensation with different diamines.



Scheme 2. Reaction of Ethyl 2-oxocyclohexane-1-carboxylate (2) with different diamines

Compounds I, II, III, VI, VII, VIII, X, and XIII displayed nearly identical structural frameworks, with the reaction proceeding in a 2:1 stoichiometric ratio that is, two molecules of β-keto esters (1) or (2) reacted with one molecule of the diamine. In contrast, an analysis of the reaction schemes depicted in Figures 1 and 2 revealed that compounds IX and XI were formed via a 1:1 ratio reaction between β-keto esters (1) or (2) and benzidine. The proposed mechanism below scheme (3) outlines the reaction pathway of β-keto esters (1) or (2) with these diamines.

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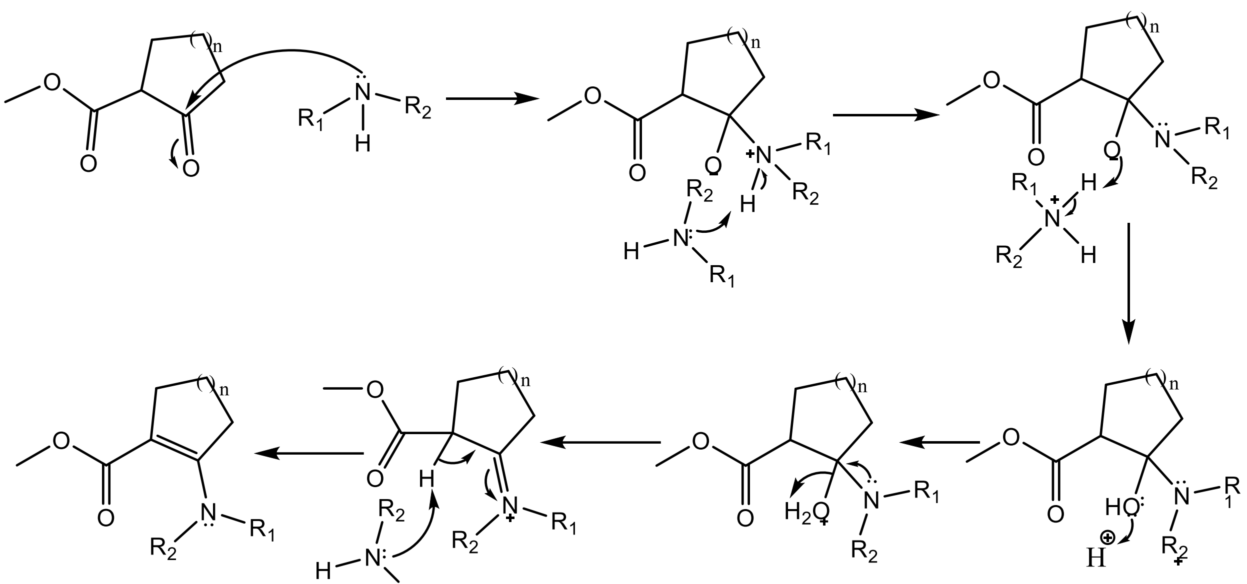
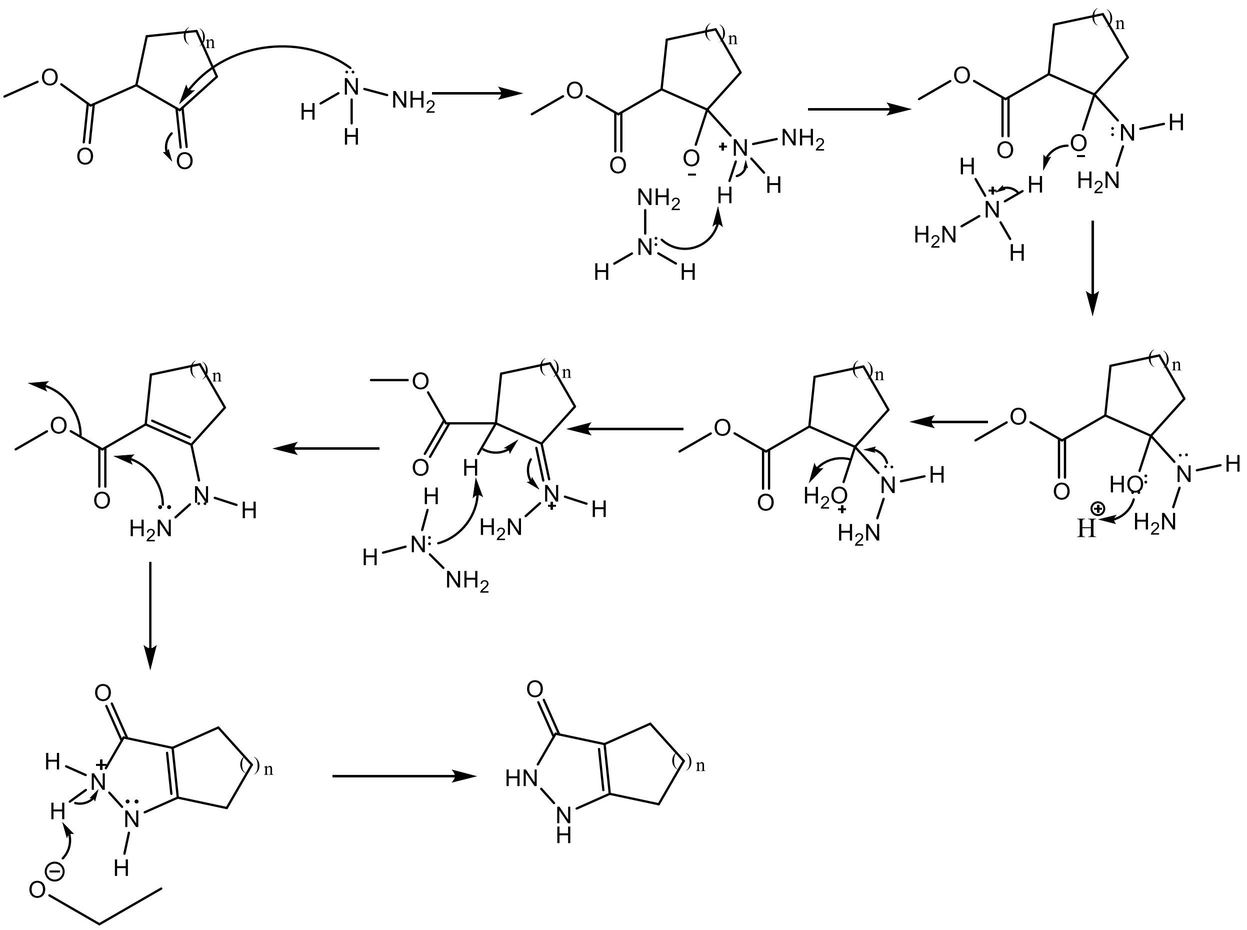


n= 1or 2

Scheme 3. The proposed mechanism of synthesis of compounds (I, II, III, VI, VII, VIII, X, XIII)

The reaction of ethyl 2-oxocyclopentanecarboxylate (1) with hydrazine hydrate proceeded via competing pathways, yielding two distinct products. A pyrazolone derivative (IV) was obtained as the major product (85% yield), while an enamine derivative (III) was isolated as the minor product (14% yield). In contrast, under identical conditions, ethyl 2-oxocyclohexane-1-carboxylate (2) reacted with hydrazine hydrate to exclusively form product V. A proposed mechanistic scheme (4) delineates the formation of IV and V, underscoring the divergent reactivity between the five- and six-membered ring systems.



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Scheme 4: The proposed mechanism of synthesis of compounds (IV and V)

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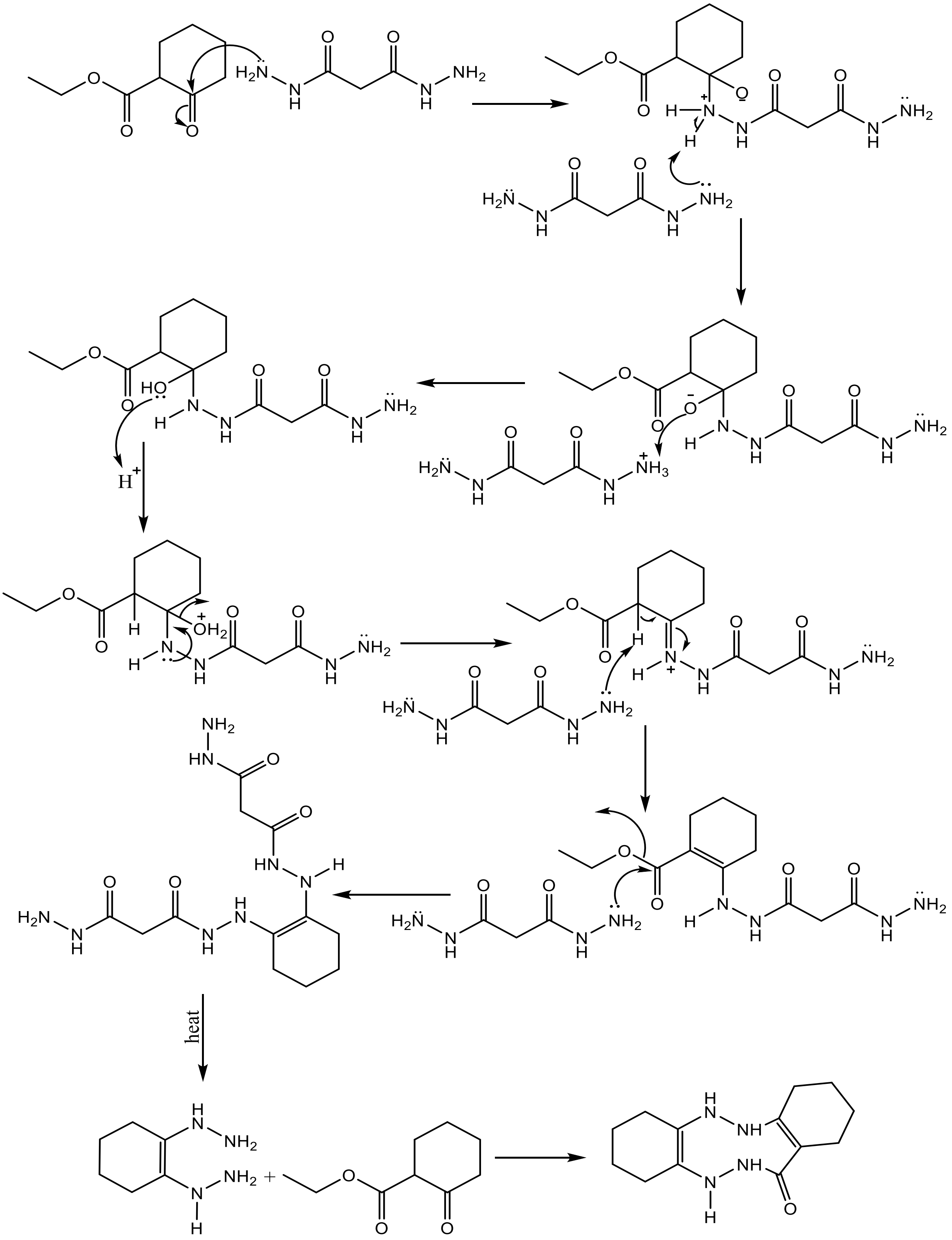
Additionally, the synthesis of a novel compound (XII) was achieved through the condensation of ethyl 2-oxocyclohexane-1-carboxylate (1) with malonohydrazide under reflux conditions. This transformation proceeded via the construction of a tetrazecine ring, as depicted in the mechanistic pathway (5). The observed product distribution suggests that the ring size significantly influences the reaction pathway, with the five-membered substrate favoring a competitive mechanism, while the six-membered analogue follows a more selective route. Further studies could explore the underlying steric and electronic factors governing these transformations.



Scheme 5. The proposed mechanism of synthesis of compound (XII)

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The successful preparation of these compounds was confirmed using various analytical techniques, including infrared (IR) spectroscopy and nuclear magnetic resonance (NMR) spectroscopy (^{1}H-NMR and ^{13}C-NMR). The IR spectra of these compounds exhibited characteristic absorption bands corresponding to the ester carbonyl group (C=O) and the secondary amine (N–H) functionality. Additionally, the ^{1}H-NMR spectra displayed signals consistent with the secondary amine proton and the ethyl group of the ester moiety. A notable distinction was observed in the ^{1}H-NMR spectra of compounds (IV) and (V). Specifically, the spectra of (IV) and (V) lacked signals attributable to the ethoxy group, indicating nucleophilic attack on the ester moiety and subsequent formation of the pyrazolone rings. In contrast, the ^{1}H-NMR spectra of (IX) and (XI) exhibited a triplet at 1.34, 1.32ppm and a quartet at 4.25, 4.24 ppm, respectively, confirming the retention of the ethoxy groups. Furthermore, a broad singlet at 3.60 ppm and 3.70 ppm, assigned to the amine protons (NH_2), suggested a 1:1 reaction stoichiometry with complete conversion. Meanwhile, the ^{1}H NMR spectrum of compound (XII) was also confirmed by the absence of the ethoxy group and the appearance of a broad signal representing four protons at 10.27 ppm, corresponding to the N–H protons in the azine ring. Furthermore, ^{13}C-NMR analysis verified the presence of the ester carbonyl carbon in selected compounds, while it was absent in others with a peak corresponding to the C=C-NH fragment. Additionally, the number of carbon signals in each compound's ^{13}C-NMR spectrum matched the expected number of carbons, further verifying the successful synthesis of these compounds. These combined spectroscopic analyses provided conclusive evidence for the successful preparation of the target compounds.

Conclusion

In this study, a series of novel enamine derivatives were successfully synthesized through the reaction of ethyl 2-oxocyclopentane-1-carboxylate (1) or ethyl 2-oxocyclohexane-1-carboxylate (2) with various diamines under mild conditions, yielding the target products with high efficiency. Structural elucidation via spectroscopic techniques (IR, ^{1}H NMR, ^{13}C NMR, and MS) confirmed the formation of the desired enamine derivatives.The reactivity of the substrates was found to be highly dependent on ring size and diamine structure. Compound (2), featuring a six-membered ring, predominantly formed single products with ethane-1,2-diamine, 1,4-phenylenediamine, and benzidine, adhering to 1:2 or 1:1 stoichiometries, respectively. In contrast, reactions with hydrazine hydrate and malonohydrazide afforded cyclic products. Compound (1), with its more strained five-membered ring, exhibited enhanced reactivity, leading to competitive pathways in some cases. For instance, reactions with benzidine yielded a mixture of 1:1 and 1:2 adducts, while hydrazine hydrate produced both pyrazolone and enamine derivatives. Other diamines, however, selectively afforded single products via 1:2 addition.The observed differences in reactivity and product distribution highlight the influence of ring strain and steric factors on the reaction pathways. The higher reactivity of the cyclopentane derivative (1) compared to the cyclohexane analogue (2) underscores the role of ring tension in governing mono- versus bis-addition and the preference for cyclic versus acyclic structures. These findings provide valuable insights into the design and synthesis of enamine-based derivatives with tailored structural and functional properties.

Conflict of interest. Nil

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