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From Expected Cyclization to Observed Solvolysis: The Case of a Conjugated Oxazolone

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ABSTRACT

This investigation delineates the solvent- and temperature-mediated divergent reactivity of 2-phenyl-4-(3-phenylallylidene)oxazol-5(4H)-one (1) with a series of amines. The mechanistic pathway is directed toward cyclization under specific conditions, as evidenced by the reaction with o-phenylenediamine, para-aminohippuric acid, 4-amino-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one, and 2-chloroaniline in glacial acetic acid at 110 °C, affording imidazolone and bis-amide derivatives (I, II, IV, Va, Vb, VI). A bis-amide product (III) was similarly obtained from 2-aminobenzothiazole in toluene at 230 °C. Conversely, a ring-opening mechanism predominated with p-chloroaniline, 2,4-dichloroaniline, or 2-aminobenzothiazole in glacial acetic acid at 110 °C, yielding the amide-acid (VII), and with o-chloroaniline, 2-aminobenzothiazole, or para-aminohippuric acid in absolute ethanol at 230 °C, producing the amide-ester (VIII). This work conclusively establishes solvent and temperature as critical parameters for steering the reaction mechanism, enabling the targeted synthesis of distinct molecular architectures via straightforward procedures. All novel compounds were isolated in satisfactory yields and unequivocally characterized by comprehensive spectroscopic analysis (^{1}H NMR, ^{13}C NMR, IR, and LC-MS).

KEYWORDS: Oxazol-5(4H)-one, Imidazole Derivatives, Solvent-Controlled Reactivity, Ring-Opening Reaction, Amine Addition, Reaction Mechanism, Bis-amide derivatives.

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1. INTRODUCTION

The utilization of simple, multifunctional molecules for the synthesis of heterocyclic compounds represents a significant and efficient strategy in modern organic chemistry. Among these, heterocycles containing nitrogen, oxygen, or sulfur are of profound interest due to their diverse physicochemical properties, which render them crucial for the development of novel pharmaceuticals, materials, and molecular conductors [1]. In particular, five-membered heterocycles are privileged scaffolds found in a multitude of biologically active molecules and drug-like compounds [2].

Imidazole, or 1,3-diazole, is a fundamental five-membered heterocyclic system containing two nitrogen atoms. Its structural analogs, such as oxazole (containing oxygen) and thiazole (containing sulfur), are equally significant. The imidazole ring is notably versatile, capable of forming various drug-ligand interactions through hydrophobic, van der Waals, and hydrogen bonding forces, thereby enhancing its biological relevance [3]. A specific subclass, imidazolones—hydroxyimidazoles that exist as tautomeric systems—further expands the chemical space and utility of this core structure. While the reactivity of oxazol-5(4H)-ones with nucleophiles is well-known, the precise control over their reaction pathways with amines remains a complex challenge. The initial findings indicated that a single precursor, 2-phenyl-4-(3-phenylallylidene)oxazol-5(4H)-one, could yield either cyclized imidazole derivatives or ring-opened products when reacted with different amines. This divergence suggested that factors beyond the amine's nature, such as solvent and temperature, play a critical but poorly defined role in steering the reaction mechanism, leading to an unpredictable mixture of products. In the present investigation, we aimed to systematically explore and control the reactivity of 2-phenyl-4-(3-phenylallylidene)oxazol-5(4H)-one with a series of amines. The primary objective was to elucidate the critical influence of reaction conditions specifically, the solvent medium and temperature on the product distribution. This study seeks to establish a methodological framework for the selective synthesis of new imidazolone derivatives versus ring-opened bis-amide or ester-amide structures, thereby transforming the reaction from an unpredictable process into a tunable and divergent synthetic tool.

2. MATERIAL AND METHOD

All chemicals were purchased from Sigma Aldrich (St. Louis, Mo, USA) and were used as received. Reactions were monitored on TLC with different ratios of (Chloroform /methanol) and (Hexane /ethyl acetate). ^{1}H NMR spectra were carried out in the Centre for drug discovery research & development at ain shams university on Bruker 400 MHz with chemical shift (δ) expressed in ppm downfield from tetramethylsilane as an internal stander (δ TMS = 0) using DMSO-d_6 as a solvent. The multiplicity of the signal is as following: s (Singlet), d (Doublet), t (Triplet), q (Quartet), m (Multiplet). D_2O is also used to determine the presence of acidic protons.^{13}C-NMR were measured in the Centre for drug discovery research & development at ain shams university on Bruker 100 MHz with internal reference TMS δ = 0. Infrared spectra were recorded in the National Research Centre (NRC) at Misrata University using 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 Stuart scientific apparatus and are uncorrected. Liquid Chromatography-Mass spectrometry (LC-MS) was also carried out in the Centre for Drug Discovery Research & Development at Ain Shams University.

A) Synthesis of 2-phenyl-4-(3-phenylallylidene)oxazol-5(4H)-one) (1)

The title compound (1) was synthesized following a modified Erlenmeyer Plöchl protocol [4]. A mixture of hippuric acid (0.05 mol, 8.95gr), acetic anhydride, and a catalytic amount of anhydrous sodium acetate was heated on a hot plate with stirring until a homogeneous solution was obtained. To this mixture, cinnamaldehyde (0.05 mol, 6.6 gr) was added portion-wise. The reaction vessel was then transferred to a pre-heated water bath, and the progress of the reaction was monitored by thin-layer chromatography (TLC). Upon completion, the reaction mixture was allowed to cool to ambient temperature and then carefully poured onto crushed ice with vigorous stirring. The resulting solid was precipitated by storing the mixture in a refrigerator

5(4H)-one (1) (0.8 g, 0.03 mol) in glacial acetic acid (20 mL), containing anhydrous sodium acetate

(0.2 g) as a catalyst, was heated in a round-bottom flask. Upon completion, the mixture was poured into crushed ice, yielding a precipitate that turned from yellow to brown. The crude product was collected and recrystallized from methanol/water to afford compound IV as a white solid. Following an analogous procedure, compounds Va, Vb, and VI were synthesized from their respective amine precursors (Scheme 1) and purified by recrystallization from ethyl acetate/hexane (Va, Vb) and ethanol/water (VI). Compound VII was similarly prepared but at an elevated temperature of 230 °C and recrystallized from ethanol.

Synthesis of ethyl-2-benzamido-5-phenylpenta-2,4-dienoate (VIII)

To a solution of the respective amine para-aminohippuric acid (0.39 g, 0.002 mol), 2-aminobenzothiazole (0.30 g, 0.002 mol), or 2-chloroaniline (0.38 g, 0.003 mol) and 2-phenyl-4-(3-phenylallylidene)oxazol-5(4H)-one (1 equiv.) in absolute ethanol (20 mL), anhydrous sodium acetate (0.2 g) was added. The reaction mixture was stirred and monitored by TLC. After approximately 6 hours, the oxazolone was fully consumed, as evidenced by the formation of a new product spot and the persistence of the amine starting material. The corresponding product was isolated via extraction with chloroform.

3. RESULTS AND DISCUSSION

N-1-((2-aminophenyl)amino)-1-oxo-5-phenylpenta-2,4-dien-2-yl)benzamide ($C_{24}H_{19}N_3O$, M.W=365g/mol) (I) and N-1-((2-aminophenyl)amino)-1-oxo-5-phenylpenta-2,4-dien-2-yl)benzamide ($C_{24}H_{21}N_3O_2$, M.W=383g/mol) (II): 70% yield as a pale brown solid, m.p.=192-197°C. IR (KBR): ν max (cm^{-1}): 3436-3463 (NH_2), 3359 and 3240 (2NH-C=O), 1638 (C=O). ^{1}H NMR (DMSO): δ= 4.9 (s, 2H, NH_2) 6.6-8 (m, 15H, aromatic protons and diene protons) 9.4 (s, 1H, NH), 10.3 (s, 1H, NH). ^{13}C NMR (DMSO): δ = 160 and 170 (2C=O), 115-145 (aromatic carbons, and 2 C=C). LC-MS: 366 (14.54%), 384 (37.37%).

N-1-(2-mercapto-1H-benzo[d]imidazol-1-yl)-1 oxo-5-phenylpenta-2,4-dien-2-yl)benzamide ($C_{25}H_{19}N_3O_2S$, M.W= 425.51 g/mol)(III): 75% yield as a white solid, m.p.= 226-228.5°C. ^{1}H NMR (DMSO): δ= 7.1-8.1(m,17H, aromatic protons and diene protons), 10.3 (s,1H, NH), 12.7(s,1H, SH). ^{13}C NMR (DMSO): δ=165 and 166.7 (2C=O), 16(C-SH), 120-149 (aromatic carbons, and 2 C=C). LC-MS: 426 (41.57%).

(4-(2-benzamido-5-phenylpenta-2,4-dienamido)benzoyl)glycine ($C_{27}H_{23}N_3O_5$, M.W= 469.50 g/mol) (IV): 35% yield as a brown solid, m.p. =175-177°C. ν max (cm^{-1}): ν = 3231 (NH), 1637(HO-C=O), 1601 (NH-C=O). ^{1}H NMR (DMSO): δ = 3.9 (s, 3H, CH_2+NH), 6.8-8.6 (m, 18H, NH, aromatic protons and diene protons), 10.2 (s, 1H, NH), 10.3 (s, 1H, OH). ^{13}C NMR (DMSO): δ = 164.5-166.6 (4C=O), 120-145 (aromatic carbons and 2C=C), 41 (CH_2). LC-MS: 470 (74.30%).

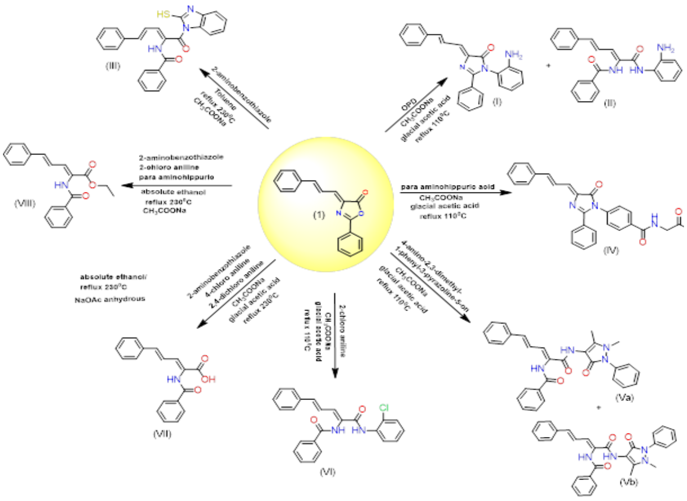
N-1-((1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)amino)-1-oxo-5-phenylpenta-2,4-dien-2-yl)benzamide ($C_{29}H_{26}N_4O_3$, M.W= 478.55g/mol Va and Vb): 45% yield as a yellow solid, m.p. = 199-204°C. ^{1}H NMR (DMSO): δ= 2.3 (s, 3H, CH_3), 3.1(s, 3H, CH_3), 6.5-8 (m, 19H, aromatic protons, tautomerism proton and diene protons), 9.3 (s, 1H, NH), 10.1(s, 1H, NH). ^{13}C-NMR (DMSO): δ= 157-170 for (C=O) and C4 (carbon atom of the pyrazalone ring attached to the amide group), 120-140 (aromatic carbons, and 2 C=C). LC-MS: 479 (43.49%), 479 (32.94%).

N-1-((2-chlorophenyl)amino)-1-oxo-phenylpenta-2,4-dien-2-yl)benzamide ($C_{24}H_{19}ClN_2O_2$, M.W= 402.88 g/mol) (VI): 30% yield as a yellow solid, m.p. = 229-230°C. ^{1}H NMR (DMSO): δ= 7.1-8.1 (m, 17H, aromatic protons and diene protons), 9.3 (s, 1H, NH), 10.2(s, 1H, NH). ^{13}C-NMR (DMSO): δ=165 and170 (2C=O), 120-140 (aromatic carbons and 2 C=C). LC-MS: 403.4 (16.30%).

2-benzamido-5-phenylpenta-2,4-dienoic acid ($C_{18}H_{15}NO_3$, M.W= 293.32g/mol) (VII): 30% as a white solid, m.p.= 238-240°C.^{1}H-NMR (DMSO): δ= 7.0-8.0 (m, 13H, aromatic protons and diene protons), 9.9 (s, 1H, NH), 12.5 (br, 1H, OH). ^{13}C-NMR: (DMSO): δ= 166.34 and 166.51 (2C=O), 123.7-136.8 (aromatic carbons and 2 C=C). LC-MS: 294.4 (90.35%).

ethyl -2-benzamido-5-phenylpenta-2,4-dienoate ($C_{20}H_{19}NO_3$, M. W= 321.38 g/mol) (VIII): 75% as a white solid, m.p.= 109-114°C. ^{1}H-NMR (DMSO): δ = 1.3 (t, 3H, CH_3), 4.3 (q, 2H, CH_2), 7.1-8.1 (m, 13H, aromatic protons and diene protons), 10 (s, 1H, NH). ^{13}C-NMR (DMSO): δ = 164.96 and 166.70 (2C=O), 123.3-139.4 (aromatic carbons and 2C=C), 61.2 (CH_2), and 14.54 (CH_3). LC-MS: 322.5(46.89%).

The initial objective of this study was to synthesize imidazolone derivatives via the cyclocondensation of 2-phenyl-4-(3-phenylallylidene)oxazol-5(4H)-one (1) with various nucleophilic amines as shoen in schem 1.



Scheme 1: Reaction of 2-phenyl-4-(3-phenylallylidene)oxazol-5(4H)-one (1) with various amines

This approach is predicated on the well-established reactivity of oxazolones as versatile synthons, particularly their ability to undergo ring-opening followed by recyclization to form diverse heterocyclic systems, including imidazolones. However, our experimental results deviated significantly from this anticipated pathway, consistently yielding open-chain bis-amide, acid-amide, and ester-amide derivatives instead of the target heterocycles. Initially, the reaction of oxazolone (1) with amines such as o-phenylenediamine, para-aminohippuric acid, 4-amino-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one, and 2-chloroaniline in glacial acetic acid at 110°C uniformly produced the open-chain bis-amide structures (II, IV, Va, Vb). This outcome indicates that the initial nucleophilic attack by the amine on the electrophilic carbonyl carbon of the oxazolone ring proceeds efficiently, leading to ring opening and the formation of an intermediate N-acyl-α,β-unsaturated ketone. In contrast, the critical step that fails under these conditions is the subsequent intramolecular cyclization. For imidazolon formation, the nucleophilic nitrogen of the amine must attack the carbonyl carbon of the amide group, eliminating a water molecule. At 110°C in acetic acid, it appears that this cyclization is either kinetically disfavored or that the open-chain bis-amide is the thermodynamically more stable product. Furthermore, acetic acid, while a good solvent for facilitating the initial ring-opening, may promote protonation of potential nucleophilic sites or create an equilibrium that favors the stable, crystalline bis-amide adducts, thereby trapping the reaction pathway in the open-chain form.Subsequently, in an attempt to drive the reaction towards cyclization by providing the necessary activation energy, the temperature was significantly increased to 230°C. This high-temperature regime was tested with amines like o-chloroaniline, 2-aminobenzothiazole, and 2,4-dichloroaniline. When using glacial acetic acid, the product remained the open-chain form, but with a distinct structural variation identified as (VII), characterized as a carboxylic acid-amide. This suggests that at 230°C, acetic acid may act not only as a solvent but also as a participant. Specifically, it is plausible that under these harsh conditions, the enol-keto tautomerism is enhanced, or a transient O-acetylation occurs, followed by hydrolysis upon work-up to yield the free carboxylic acid. Moreover, when the solvent was changed to absolute ethanol while maintaining the temperature at 230°C, the result was the formation of compound (VIII), an ester-amide derivative. This is a clear demonstration of solvolysis, whereby the high temperature facilitates the alcoholysis of the oxazolone ring or an intermediate, leading to the ethyl ester functionality. This reaction effectively competes with and completely overshadows any potential cyclization pathway, permanently locking the system into an open-chain architecture. Most importantly, using toluene as a solvent at 230°C yielded the open-chain compound (III). This is a critical observation because toluene is a non-polar, aprotic solvent with no catalytic properties. Therefore, the failure to cyclize even in this inert solvent at 230°C provides compelling evidence that the barrier to cyclization is not a lack of catalysis, but is instead rooted in a fundamental thermodynamic preference. In other words, the reaction simply converges on the most stable product, which is the open-chain form. The consistent failure to achieve cyclization at 230°C, a temperature typically sufficient to drive such dehydrative ring closures, is highly significant. This indicates that the barrier to cyclization is not merely kinetic but is rooted in the intrinsic structural propertiesof the system. The most compelling explanation for our observations lies in the structure of the starting oxazolone (1), specifically the 3-phenylallylidene (cinnamylidene) substituent at the 4-position. This group introduces a conjugated π-system that extends from the exocyclic carbon into the oxazolone ring. We postulate that this extended conjugation imparts significant stability to the open-chain forms (II-VIII). Indeed, the planar, conjugated system of the bis-amide and related derivatives is likely a global energy minimum, making the cyclized imidazolone product less stable by comparison. This is because the proposed cyclization would disrupt this favorable conjugation, creating a higher-energy, non-planar intermediate or product. Thus, thermodynamics overwhelmingly favor the open-chain adducts.

This rationale is strongly supported by the contrast with previous literature [7-9]. Studies employing oxazolones derived from other aldehydes (e.g., aliphatic or simpler aromatic aldehydes) successfully obtained imidazolones. In those cases, the substituent at the 4-position lacks the extended conjugation present in the cinnamylidene group. Without this stabilizing feature, the driving force for ring closure outweighs the stability of the open-chain form.

In conclusion, the failure to synthesize imidazolones from 2-phenyl-4-(3-phenylallylidene)oxazol-5(4H)-one (1) is not an operational artifact but a direct consequence of its molecular architecture. To summarize, the cinnamylidene side chain creates a highly stabilized, conjugated open-chain system. This thermodynamic sink effectively traps any reaction intermediate, rendering it inert to intramolecular cyclization. Ultimately, all attempts to force ring closure—through increased temperature or solvent variation—only resulted in alternative open-chain derivatives via solvolysis, unequivocally demonstrating that the stability of the conjugated open-chain form is the dominant factor governing the reactivity in this system. Finally, this study underscores the critical influence of substituent effects on the divergent reactivity of oxazolones and provides a cautionary note for applying generalized synthetic strategies without considering the unique electronic properties of the substrates involved.

4. CONCLUSION

Based on the study, the failure to synthesize imidazolones from oxazolone (1) was due to the thermodynamic stability of the open-chain intermediates, not kinetic limitations. The cinnamylidene group's extended conjugation made the open-chain forms the global energy minimum, preventing cyclization even at high temperatures (230°C) in various solvents. This highlights how substituent effects can override expected reactivity, cautioning against applying generalized strategies without considering specific molecular electronic properties.

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