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Original Article

SYNTHESIS OF PYRAZOLE AND 1,3,4-OXADIAZOLE DERIVATIVES OF PHARMACEUTICAL POTENTIAL

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ABSTRACT

Heterocyclic compounds are important molecules that serve as scaffolds or linkers for the core structure of numerous drug substances. In particular, pyrazole and 1,3,4-oxadiazole are compounds of great interest due to their comprehensive biological activities and interesting structural features. Here, we described an efficient and economical synthetic route leading to *N*-phenyl substituted pyrazole and 1,3,4-oxadiazole derivatives. Retrosynthetic disconnective analysis showed that the *N*-phenyl substituted pyrazole can be obtained from chalcone, accessible from the respective aldehyde, and acetophenone. The disubstituted 1,3,4-oxadiazole can be constructed from the respective aldehyde, which originates from pyrrole-containing compound, and formyl chloride. Based on our retrosynthetic analysis, *N*-phenyl substituted pyrazole was obtained by cyclization of the respective chalcone with phenylhydrazine to give pyrazoline which was in turn converted into pyrazole by oxidative aromatization. Potassium carbonate and a catalytic amount of molecular iodine were used to oxidatively cyclize semicarbazones into 1,3,4-oxadiazoles in a transition metal-free process. Novel pyrazole and 1,3,4-oxadiazoles with potential biological activity are investigated as antituberculosis, anticonvulsant, antidiabetic, anticancer, and tyrosinase inhibitory agents.

KEYWORDS: pyrazoline, pyrazole, oxidative aromatization, 1,3,4-oxadiazole, oxidative intramolecular cyclization.

1. Introduction

Heterocyclic compounds are widely spread in nature and vital in physiological processes. They exist as nucleic acids, plant alkaloids, anthocyanins, flavones, haem, chlorophyll, and other natural compounds. Additionally, vitamins, proteins, and hormones contain aromatic heterocyclic systems. Synthetically obtained heterocycles are used as agrochemicals and pharmaceuticals and play an important role in human life. Heterocycles have enormous potential as the most promising molecules for lead structures of new drug substances [1].

Numerous heterocyclic compounds exhibit diverse biological activities [2-5]. Most heterocyclic compounds have a five or six-membered ring containing nitrogen, oxygen, or sulfur. Pyrazole and 1,3,4-oxadiazole are significant heterocyclic scaffolds [2-5], demonstrating a broad range of biological activities, including anti-inflammatory, antifungal, antiviral, antihypertensive, anticonvulsant, antidiabetic, anticancer, and alkaline phosphatase-inhibiting properties [6-9].

Five-membered ring nitrogen heterocycles, pyrazoles (Fig. 1) and pyrazolines, represent molecules that are particularly useful in synthesis of other organic compounds. These are among the most investigated classes of the azole family of chemicals. Indeed, over the years, several synthetic analogs and techniques have been reported. The pyrazole nucleus exists in various structures of compounds used in medicine and agriculture [10-21]. The *N*-phenyl pyrazoline derivatives were synthesized from a chalcone derivative through cyclo-condensation [17]. Substituted pyrazolines can be converted into aromatic pyrazoles by oxidative aromatization.

Chalcones can be useful starting point for synthesizing various heterocycles of biological importance. Chalcone, the flavonoid family member, has a remarkable range of biological actions, including cytotoxic [22], chemoprotective [22], anti-inflammatory [23-24], anti-invasive [22], antimalarial [23-24], anticancer [23-24], anti-diabetic, and antibacterial properties [22-24].

N-Phenyl pyrazoline derivatives are important compounds in organic chemistry because of their

application in heterocyclic synthesis and have been subjects of preclinical investigations [10]. Both pyrazolines and pyrazoles have been reported to show a wide spectrum of biological activities, including anti-inflammatory [19], antibacterial [20-21], antifungal [20], antimicrobial [22], antiamoebic [12], antidepressant [12-14] and anticonvulsant properties [12-15].

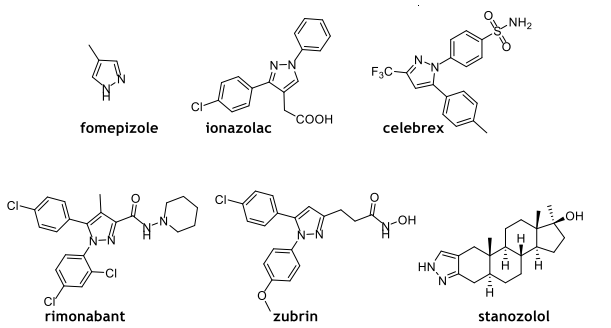


Fig.1. Drug substances containing pyrazole core

Oxadiazoles are significant nitrogen-containing five-membered ring heterocycles used as substrates or intermediates in chemical synthesis, material science, and pharmaceutical chemistry [1]. The oxadiazole ring contains two nitrogen and one oxygen atom (Fig. 2). Oxadiazole exists in four isomeric forms, depending on the position of nitrogen atoms in the ring (Fig. 2).

1,2,3-Oxadiazole (**1**), 1,2,4-oxadiazole (**2**), 1,2,5-oxadiazole (**3**), and 1,3,4-oxadiazole (**4**) are known, but the 1,2,3-isomer (**1**) is unstable and by ring-opening, forms the respective diazo keto tautomer [25-31].

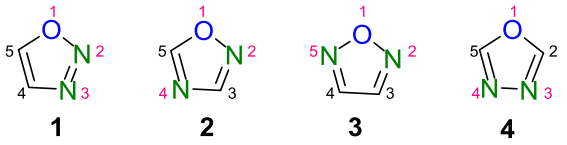


Fig.2. Isomeric oxadiazoles: 1,2,3-oxadiazole (**1**), 1,2,4-oxadiazole (**2**), 1,2,5-oxadiazole (**3**), and 1,3,4-oxadiazole (**4**)

Out of four isomers, 1,3,4-oxadiazole (Fig. 2), especially bearing a 2-amino substituent, has become an important construction motif and a valuable building block in drug design [27, 29]. Such compounds show improved thermal and metabolic stability, aqueous solubility, and lower lipophilicity [29]. Derivatives of 1,3,4-oxadiazole exhibit a wide range of biological activities, including antibacterial, antifungal, anti-inflammatory, antiviral, anticancer, antihypertensive, anticonvulsant, and antidiabetic properties [6-9, 12-14]. The 1,3,4-oxadiazoles (Fig. 3) showed particularly strong antimicrobial activity against several microorganisms like fungi, Gram +ve, and Gram -ve bacteria [29-31].

Recently, oxadiazoles have been demonstrated as highly proficient tyrosinase inhibitors [25, 32-34].

Pyrazoles are typically synthesized from various substituted hydrazones [35-40]. In this paper, we report the construction of the novel pyrazole from chalcone [41-45], and pyrazoline [46]. Intermediate pyrazolines were converted into aromatic pyrazoles by oxidative aromatization [46-47].

The substituted 1,3,4-oxadiazoles were obtained by replacing certain substituents in previously reported 1,3,4-oxadiazoles [48-52]. 1,3,4-Oxadiazoles are synthesized from the respective acyl hydrazone *via* oxidative cyclization [52]. However, the synthesis of 2-amino-substituted 1,3,4-oxadiazole is rarely reported. The substrate contains an amino group that competes with the oxygen atom during the cyclization [52-54].

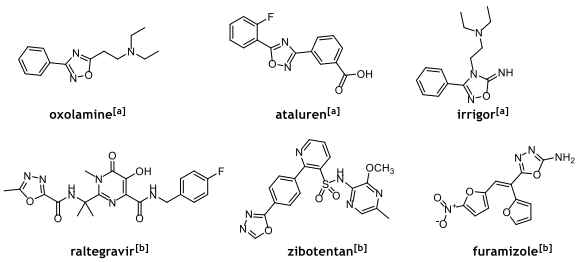


Fig.3. Drug substances containing 1,2,4- oxadiazole moieties[a] and 1,3,4-oxadiazole moieties.[b]

Here, we report a simple, efficient and economical procedure for the total synthesis of 1,3,4-oxadiazole derivatives. We describe the iodine-mediated oxidative cyclization that creates the 2-amino-1,3,4-oxadiazole framework [52]. Moreover, using this transition metal-free procedure, the 2-amino-1,3,4-oxadiazole derivative was synthesized from the respective semicarbazone C-O bond. Molecular iodine has been extensively used in organic synthesis. In this paper, we have described the oxidative intramolecular C-O bond-forming processes, mediated by iodine and used for the synthesis of 1,3,4-oxadiazoles.

2. Materials and methods

2.1. Syntheses

All reactions were carried out by standard syringe and septa technique under a nitrogen atmosphere. The solvents were purified, and dried before use by conventional methods. Column chromatography was performed on 60-120 or 230-400 mesh silica gel withethyl acetate (EtOAc) and hexane as eluents. The progress of all reactions was monitored by TLC on alumina sheets precoated with silica gel 60 F_{254} to a thickness of 0.5 mm. Spots were located using UV light or iodine vapors as the visualizing agent. Melting points were obtained by an open capillary method and are uncorrected.

2.2. Analytical data

The ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on 200 and 500 MHz spectrometers (Bruker Avance DPX200) and (Bruker Avance DRX500) at ambient temperature. Chemical shifts are reported in part per million (ppm) using tetramethylsilane (TMS) as an internal standard. The splitting pattern abbreviations are designated as singlet (s), doublet (d), double doublet (dd), triplet (t), quartet (q), and multiplet (m).

2.3. General synthetic procedure for the key intermediates 25, 26, 28a-f, 38a-c, and 39a-c

The intermediates **25** and **38a-c** [61], **26** and **39a-c** [62-63], as well as the intermediates **28a-f** were prepared by the previously reported methods [10, 17].

2.4. General procedure for the synthesis of the key intermediates 30a-f (exemplified by 30a)

A mixture of chalcone **28a** (2.00 g, 5.95 mmol) and phenyl hydrazine hydrate (2.58 g, 17.86 mmol) in pyridine (20 mL) was refluxed for 15 hrs. Then the reaction mixture was cooled down, acidified with 1:1 HCl:H_2O solution (20 mL), and stirred for 1 hr at 25 ºC. The solid product was separated, filtered, and washed with a 10% $NaHCO_3$ solution and water, filtered, dried, and the residue was purified by silica gel column chromatography using a mixture of ethyl acetate:petroleum ether (30:70) as eluent to afford pure compound **30a**.

2.5. General procedure for the synthesis of the target compounds 31a-f (exemplified by 31a)

To a stirred solution of **30a** (1.00 g, 2.35 mmol) in CH_2Cl_2 (5 mL) was added DDQ (0.80 mg, 3.52 mmol) at 0 ºC. The mixture was stirred at 0ºC for 2 hrs and concentrated *in vacuo*. The crude product was purified by column chromatography over silica gel using a mixture of ethyl acetate:petroleum ether (20:80) to afford compound **31a.**

2.5.1. Characterization of pyrazole 31a

Sample: 0.57 g, 50% yield; brownish solid, m.p.148-150 ºC.

^{1}H NMR (200 MHz, $CDCl_3$) δ 7.75 - 7.84 (m, 4H), 7.11 - 7.32 (m, 10H), 6.54 (s, 1H), 5.56 - 5.67 (s, 1H), 2.02 (s, 3H), 1.82 (s, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 137.1, 134.1, 132.7, 129.5, 128.8, 128.7, 128.1, 127.6, 127.2, 126.0, 124.9, 109.9, 104.0, 22.7, 12.8; IR ($CHCl_3$, cm^{-1}): ν 3020 (C-CH-H), 2927 (aromatic sp^2 C-H), 1595 (aromatic C=C bending), 1217 (sp^2 C-N, bending), 1038 (sp^2 C-Cl, bending), and 845 (C-C).

2.6. General procedure for the synthesis of 1,3,4-oxadiazoles 42a-c

To a stirred solution of semicarbazide hydrochloride (0.238 g, 2.13 mmol) and sodium acetate (0.175 g, 2.13 mmol) in H_2O (1 mL), was added a solution of aldehyde **39a-c** (0.500 g, 2.13 mmol) in MeOH (1 mL). After stirring at room temperature for 10 min, the solvent was evaporated under reduced pressure, and the resulting residue was dissolved in 1,4-dioxane (5 mL), followed by the addition of potassium carbonate (0.888 g, 6.417 mmol) and iodine (0.597 g, 2.35 mmol) in sequence. The reaction mixture was stirred at 80 ºC until the conversion was complete (1-4.5 hrs). After cooling to room temperature, it was treated with 5% $Na_2S_2O_3$ (20 mL) and extracted with MeOH:CH_2Cl_2 (5:95) (3 x 20 ml). The combined organic layer was dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography using a mixture of ethyl acetate: petroleum ether (75:25) as eluent to afford the corresponding product.

2.6.1. Characterization of oxadiazole 42a

Sample: 0.310 g, 62% yield; dark brown solid, m.p. 204-206 ºC.

^{1}H NMR (200 MHz, $CDCl_3$) δ 7.43 - 7.62 (m, 2H), 7.09 - 7.32 (m, 2H), 6.22 (br s, 1H), 5.42 (br s, 2H), 2.28 (d, J = 9.73 Hz, 3H), 1.96 - 2.11 (m, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 157.8, 136.3, 134.5, 130.6, 129.7, 129.5, 105.4, 105.1, 12.7, 12.4; IR ($CHCl_3$, cm^{-1}): at ν 3326 (C-NH_2), 3022 (C-CH-H), 2924 (aromatic sp^2C-H), 1595 (aromatic C=C bending), 1217 (sp^2 C-O, bending), 1038 (sp^2 C-Cl, bending), and 845 (C-C).

2.6.2. Characterization of oxadiazole 42b

Sample: 1.1 g, 60% yield; brownish yellow solid, m.p 172-174 ºC.

^{1}H NMR (200 MHz, DMSO-d6) δ 7.16 - 7.38 (m, 2H), 6.98 - 7.14 (m, 2H), 6.85 (s, 1H), 6.07- 6.30 (s, 2H), 3.82 (s, 3H), 1.85 -2.26 (m, 6H); IR ($CHCl_3$, cm^{-1}): at ν 3326 (C-NH_2), 3022 (C-CH-H), 2924 (aromatic sp^2 C-H), 1595 (aromatic C=C bending), 1217 (sp^2 C-O, bending), 1040 (C-O-CH_3), and 845 (C-C).

2.6.3. Characterization of oxadiazole 42c

Sample: 1.2 g, 60 % yield; brownish solid, m.p. 140-142 ºC.

^{1}H NMR (200 MHz, $CDCl_3$) δ 7.39 - 7.75 (m, 2H), 7.31 (m, 2H), 6.27 (s, 1H), 6.03 (brs, 2H), 2.19 (s, 3H), 1.91 (s, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 157.0, 140.3, 134.0, 134.6, 131.1, 130.6, 130.1, 129.9, 115.9, 113.7, 106.7, 106.4, 12.8, 12.5; IR ($CHCl_3$, cm^{-1}): at ν 1040 (sp^2 C-CN, bending), 3326 (C-NH_2), 3022 (C-CH-H), 2924 (aromatic sp^2 C-H), 2403 (C-CN), 1595 (aromatic C=C bending), 1217 (sp^2 C-O, bending) and 845 (C-C).

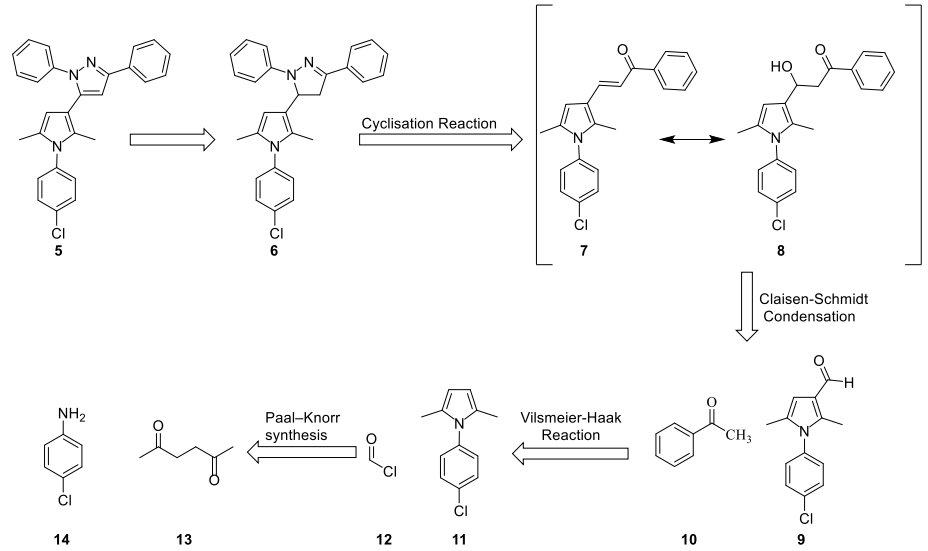
3. Retrosynthetic analysis

3.1. Substances containing disubstituted pyrazole moiety

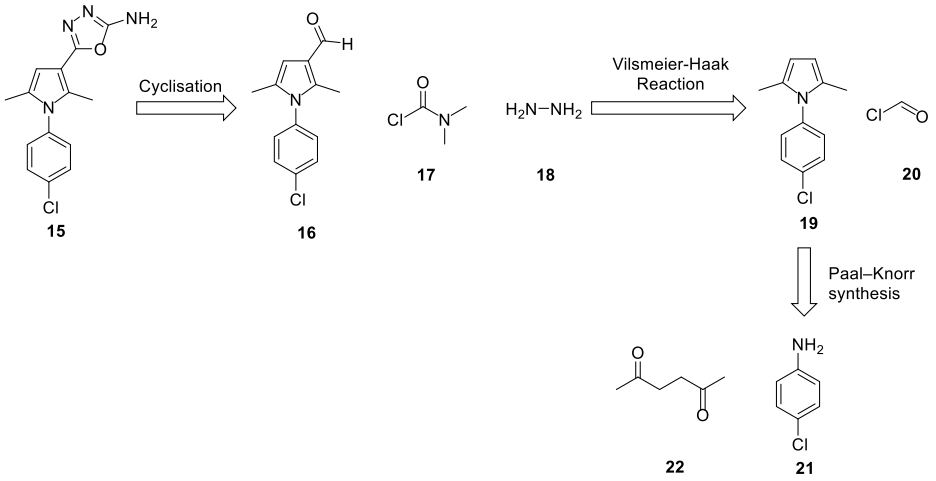
The target molecule **5** (Scheme 1), containing a pyrazole ring, can be obtained by reducing a pyrazoline derivative **6**. This derivative can be disconnected to chalcone **7**. Such a moiety has no suitable functional group for disconnection. Then, functional group interconversion is applied to obtain alcohol **8**. Further disconnection leads to aldehyde **9** and acetophenone **10**. Aldehyde **9** is disconnected to a pyrrole-containing compound **11** and formyl chloride **12**. Finally, **11** is disconnected to hexane-2,5-dione (**13**) and p-chloroaniline (**14**).

3.2. Substances containing disubstituted 1,3,4-oxadiazole moiety

The target molecule **15** (Scheme 2), containing a 2-amino 5-substituted 1,3,4-oxadiazole, can be disconnected to aldehyde **16**, and dimethylcarbamoyl chloride (**17**), and hydrazine (**18**). Then aldehyde **16** is disconnected to a pyrrole-containing compound **19** and formyl chloride (**20**). Finally, **19** is disconnected to p-chloroaniline (**21**) and hexane-2,5-dione (**22**).



Scheme 1. Retrosynthetic analysis of *N*-phenyl substituted pyrazole **5**



Scheme 2. Retrosynthetic analysis of 2-amino 5-substituted 1,3,4-oxadiazole **15**

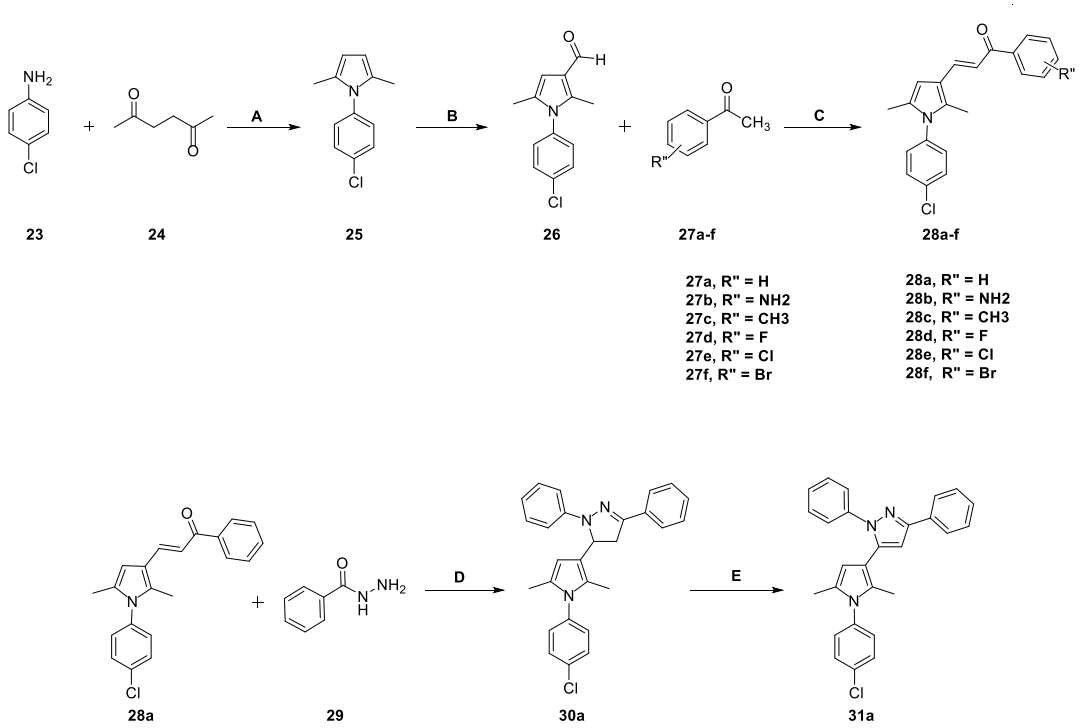
4. Results

4.1. Synthesis and characterization of substituted pyrazoles

Based on our retrosynthetic analysis, we have synthesized novel *N*-phenyl pyrazole **31a** (Scheme 3) *via* pyrazoline **30a** obtained from the respective chalcones **28a** [41-45]. It is known that an oxidative aromatization of pyrazolines gave aromatic pyrazoles [46-47].

Firstly, the Paal-Knorr synthesis converted the 4-chloroaniline (**23**) into its corresponding *N*-substituted pyrrole **25**. In this step, the **23** was refluxed with 2,5-hexandione (**24**) in dry acetic acid, to afford *N*-substituted pyrrole **25** in a 91% yield. Secondly, **25** was converted into the substituted aldehyde **26** by the Vilsmeier-Haack reaction. In this process, refluxing of **25** with DMF and $POCl_3$ afforded aldehyde **26** in 80% yield. Then Claisen-Schmidt condensation of aldehyde **26** with substituted acetophenones **27a-f** with 40% KOH in EtOH at room temperature yielded the respective chalcones **28a-f** in 81–97% yield.The usefulness of chalcones **28a-f** for the preparation of the final *N*-substituted pyrazoles was demonstrated by cyclization of chalcone **28a** with phenyl hydrazine **29** in refluxing pyridine to pyrazoline **30a** in 60% yield. Finally, pyrazoline **30a** was transformed into pyrazole **31a** through oxidative aromatization with DDQ in DCM at 0 °C in 50% yield.

^1H, ^{13}C NMR, and IR spectra confirmed the structure of the target compound **31a**. Several proton signals have been evaluated using the ^1H NMR spectroscopy. The deshielded aromatic protons present in compound **31a** were indicated by their different signals at δ 7.75–7.84 (m, 4H), 7.11–7.32 (m, 10H), 6.54 (s, 1H), and 5.56–5.67 (s, 1H), apart from the aromatic region. The spectrum of compound **31a** showed also two signals of methyl groups in the aliphatic region at δ 2.02 (s, 3H) and 1.82 (s, 3H), respectively. Also, the carbon skeleton of compound **31a** was systematically identified using the ^{13}C NMR spectrum. The formation of the *N*-substituted pyrrole framework has been confirmed by two quaternary carbons observed at δ 137.1, and 134.1, respectively. Similarly, the spectrum



Scheme 3. Synthesis of substituted N-phenyl pyrazole (**31a)**

Reagents and conditions: **A**) HOAc, reflux; 1 h, 91% yield of **25**, **B**) DMF, $POCl_3$, reflux; 3 h, 80% yield of **26**, **C**) 40% KOH, EtOH, rt; 2 h, 81-97% yield of **28a-f**, **D**) pyridine, reflux; 16 h, 60% yield of **30a**, **E**) DDQ, DCM, 0 °C; 2 h, 50% yield of **31a.**

of this compound involves two aromatic regions with carbon signals at δ 132.72, 129.5, 128.8, 128.7, 128.1, 127.6, 127.2, 126.0, 124.9, 109.9, and 107.51. Moreover, two aliphatic signals of the methyl groups present in compound **31a** appeared at δ 22.7 and 12.8. To validate different functional characteristics, vibrational studies of the molecule were analyzed by IR spectroscopy. The significant bands appeared in the IR spectrum ($CHCl_3$, cm^{-1}) at ν 3020 (C-CH-H), 2927 (aromatic sp^2 C-H), 1595 (aromatic C=C bending), 1217 (sp^2 C-N, bending), 1038 (sp^2 C-Cl, bending), and 845 (C-C).

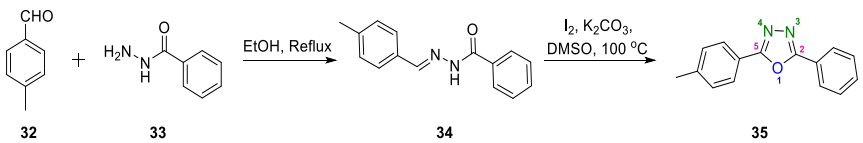
4.2. Synthesis and characterization of 5-substituted 2-amino-1,3,4-oxadiazoles

We have systematically synthesized novel 5-substituted 2-amino-1,3,4-oxadiazoles **42a-c** by modifying several structural aspects of the previously described compounds of various biological activities [28, 52-53]. Molecular iodine plays an important role in organic synthesis owing to its commercial availability, low cost, and low toxicity [52-53]. Recently, it has been successfully employed in preparation of indoles [55-57], and oxazoles [58-60]. Yu and co-workers successfully obtained numerous 1,3,4-oxadiazoles by cyclization of benzoyl hydrazone to the corresponding 1,3,4-oxadiazole [52]. The substrate, benzoyl hydrazone **34** (Scheme 4), was readily prepared *via* the condensation of 4-methylbenzaldehyde (**32**) and benzohydrazide (**33**) in ethanol at reflux in 90% yield.

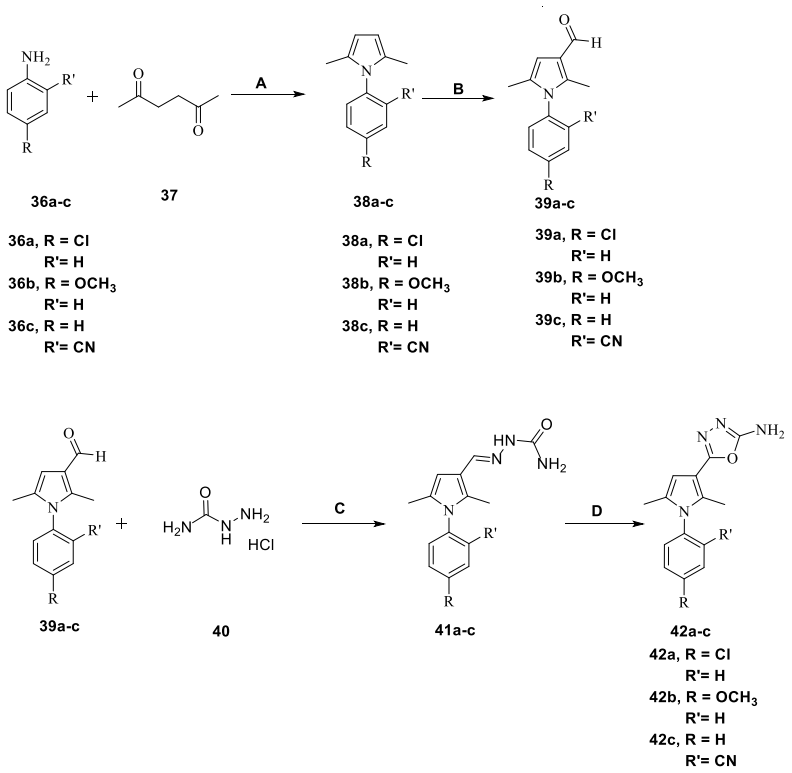
The oxidative cyclization of **34** to give 1,3,4-oxadiazole **35** was achieved by utilizing molecular iodine in the presence of potassium carbonate [52].

We have replaced the phenyl at the 2-position of **35** (Scheme 4) with the amine by using semicarbazide hydrochloride **40** (Scheme 5) to form a corresponding 1,3,4 oxadiazole framework **42a-c**.

Firstly, substituted anilines **36a-c** were converted into their corresponding *N*-substituted pyrroles **38a-c** by the Paal-Knorr synthesis. In this process, the amines **36a-c** were refluxed with 2,5-hexanodione (**37**) in the presence of dry acetic acid to afford the *N*-substituted pyrroles **38a-c** in 90-92% yield. Secondly, these pyrroles were converted into substituted aldehydes **39a-c** by the Vilsmeier-Haack reaction. In this process, pyrroles **38a-c** were refluxed with $POCl_3$ in DMF to give substituted aldehydes **39a-c** in 80–86% yield. Next, the corresponding semicarbazones **41a-c** (not isolated) were synthesized *via* the condensation of **39a-c** and semicarbazide hydrochloride (**40**) in the presence of HOAc, MeOH, and H_2O at room temperature. Finally, the oxidative cyclization of the formed semicarbazones **41a-c** in the presence of iodine and potassium carbonate, as a weak base, in 1,4-dioxane gave the corresponding 5-substituted 2-amino-1,3,4-oxadiazoles **42a-c** in a 60–62% yield.



Scheme 4. Synthesis [52] of 1,3,4-oxadiazole **35** from benzoyl hydrazone **34**



Scheme 5. Synthesis of 2-amino 5-substituted 1,3,4 oxadiazole (**42a-c)**
Reagents and conditions: **A**) HOAc, reflux; 1 h, 90-92% yield of **38a-c**, **B**) DMF, $POCl_3$, reflux; 3 h, 80-86% yield of **39a-c**, **C**) HOAc, MeOH/H_2O, **D**) I_2, K_2CO_3, 1,4-Dioxane, reflux; 4 h, 60-62% yield of **42a-c** from **39a-c**.

The structures of target oxadiazoles **42a-c** were confirmed by ^1H and ^{13}C NMR, and IR. The structural elucidation of oxadiazole **42a** is discussed in detail. Oxadiazole **42a** was acquired as a dark brown solid in 62% yield. The number and type of protons have been evaluated using the ^1H NMR. The signals of the deshielded aromatic protons present in **42a** appeared at δ 7.43–7.22 (m, 2H), 7.09–7.32 (m, 2H), and 6.22 (brs, 1H). Also, the amine protons were observed at δ 5.42 (br s, 2H). The spectrum of **42a** showed also two methyl signals in the aliphatic region which appeared at δ 2.28 (s, 3H) and 1.96 (s, 3H), respectively. Also, the carbon skeleton of **42a** was systematically validated using the ^{13}C NMR. In **42a**, the formation of the 5-substituted 2-amino-1,3,4-oxadiazole framework has been confirmed by signals of two quaternary carbons observed at δ 165.3 and 157.8, respectively. Similarly, **42a** showed two aromatic regions containing carbon signals at δ 136.3, 134.5, 130.6, 129.7, 129.5, 105.4, and 105.1, respectively. Moreover, two aliphatic signals of the methyl groups appeared at δ 12.7, and 12.4. To validate different functional characteristics, vibrational studies of the molecule were analyzed through IR. The significant bands appeared in the IR spectrum ($CHCl_3$, cm^{-1}) at ν 3326 (C-NH_2), 3022 (C-CH-H), 2924 (aromatic sp^2 C-H), 1595 (aromatic C=C bending), 1217 (sp^2 C-O, bending), 1038 (sp^2 C-Cl, bending), and 845 (C-C).

5. Discussion

Our retrosynthetic disconnective analysis showed that the *N*-phenyl substituted pyrazole **5** can be obtained from chalcone **7**, accessible from the respective aldehyde **9**. 1,3,4-Oxadiazoles can be synthesized from the respective aldehyde **16**, which originates from pyrrole-containing compound **19** and formyl chloride **20**. Based on our retrosynthetic analysis, we used the existing methodologies to obtain novel *N*-substituted pyrazole **31a** *via* pyrazoline **30a**. Oxidative aromatization of pyrazoline derivative **30a** treated with DDQ gave aromatic *N*-substituted pyrazole **31a**. We have synthesized a series of chalcones **28a**-**f** as advanced intermediates for *N*-substituted pyrazoles **31a-f**. To prove the usefulness of the new intermediates, we transformed chalcone **28a** into *N*-substituted pyrazole **31a**.

Cyclization of benzoyl hydrazone **34** and its derivatives was reported in the synthesis of numerous 1,3,4-oxadiazoles [52] In our work, we have applied a scalable iodine-mediated process and noted that the oxidative C-O bond formation of the 5-substituted 2-amino-1,3,4-oxadiazoles **42a-c** may be achieved by using a convenient inorganic base. Semicarbazones **41a**-**c** derived from the related aldehydes **39a**-**c** were easily transformed into the corresponding diazoles under sequential synthetic conditions without purification of the condensation intermediates. This adaptable and transition metal-free procedure enables the scalable and effective synthesis of a wide range of substituted diazole derivatives with a 2-amino group. In this cyclization, we have replaced the phenyl at the 2-position of **35** (Scheme 4) with the amine by using semicarbazide hydrochloride **40** (Scheme 5) to form a corresponding 1,3,4-oxadiazole framework **42a-c**.

Evaluation of biological activity of our novel pyrazoles and 1,3,4-oxadiazoles as potential antituberculosis, anticonvulsant, antidiabetic, and anticancer agents, and tyrosinase inhibitors is underway in this laboratory.

Author Contributions:
Conceptualization: M.A.K., N.L.J. and J.M.G.; methodology: M.A.K. and N.L.J.; validation: M.A.K. and N.L.J.; investigation: M.A.K. and N.L.J.; resources: M.A.K., N.L.J. and J.M.G.; data curation: M.A.K.; writing-original draft preparation: M.A.K.; writing-review and editing: M.A.K., N.L.J. and J.M.G.; visualization: M.A.K.; supervision: J.M.G.; project administration: M.A.K.; funding acquisition: J.M.G. All authors have read and agreed to the published version of the manuscript.

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