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REVIEW

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Aryl glyoxal: a prime synthetic equivalent for multicomponent reactions in the designing of oxygen heterocycles

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The category of bifunctional building blocks overrides many others because of their fascinating wide applicability in synthetic chemistry. Aryl glyoxal is one of the key molecules that has been extensively used in heterocyclic chemistry to afford nearly all types of five- and six-membered heterocycles, which are the structural constituents of many natural products. The multicomponent reaction is a practical strategy to utilize this wonderful moiety with different types of starting materials to obtain numerous diverse oxygen heterocycles. This review covers the advancement of aryl glyoxal as a prime synthetic equivalent in recent years for the synthesis of oxygen heterocycles.

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1. Introduction

Organic synthesis has served as an all-time interesting topic for researchers from the very beginning. There have been many changes in synthesis paradigms since the first synthesis of an organic compound by Wöhler.¹ The quest for easy and efficient methodologies brought about the concept of the one-pot multicomponent reaction approach. Multicomponent reactions (MCRs) are a type of reaction where at least three different starting materials are made to react in a single reaction vessel.^{2–5} The availability of various reacting sites in the reaction mixture increases the chances of probable novelty in the desired product. Therefore, MCRs have expedited organic synthesis by a significant level in novel compound formation. The pronounced benefits of multicomponent reactions, like efficient atom economy, minimization of extra time consumption, and reduced environmental waste, over traditional methods have revolutionized the work of synthetic chemists to produce

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a chemical library of novel moieties.⁶ MCRs are the only way to meet the intermittent demands of advanced technology-driven research, such as medicines, drugs, agrochemicals, polymers, and cosmetic industries. Many important building blocks and manifolds are the results of rationally designed multicomponent named reactions. Owing to their significance, recently reagent- and substrate-based multicomponent reactions are being reported in increasingly high numbers.^{7,8}

Heterocycles occupy a key functional position in many living processes, and consequently provide an in-line sustained research area to be worked upon. Among the heterocycles, hydrocarbons with oxygen as their constituent element in the ring exhibit a special place in the category owing to their several benefits to the life. In addition to their occurrence in natural products and living systems, including the human body, scaffolds belonging to each class are known to show distinctive biological and pharmacological properties. Pyran derivatives are often screened for antianaphylatic, diuretic, spasmolytic, anticoagulant, and anticancer properties, etc.9-11 Alkaloids possessing pyranoquinoline as the structural unit feature antimicrobial characteristics.12 Also, a number of them act as photoactive enhancers in the treatment of neurodegenerative diseases.13,14 Another oxygen heterocycle, namely the furan skeleton, is available in combranolides,15 kailolides,16 in fragrances, and in dye-like commercial products. The furan derivative furoquinolinone blocks the potassium channel Kv1.3,



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which is the target for immunosuppressive therapy in the treatment of auto-immune diseases and transplantations.¹⁷ Likewise, the pyrazoline derivative containing a furan moiety shows anti-malarial activity against Plasmodium falciparum.18 Isoxazoles, as oxygen-nitrogen heterocycles, add to the synthetic utility of oxygen heterocycles as they offer anti-tubercular,¹⁹ anti-inflammatory,20 and COX-2 inhibitor properties,21 and are thus a constituent of many therapeutic drugs. The newly synthesized 2H-chromene-2-one derivative was tested and found to show the potential anti-convulsant²² activity. One of the benzopyranone derivatives, Enasculin, is a pharmacologically tested neuronal activator KA 672-HCl, which works as an antagonist by simultaneously activating several neurotransmitters that are deactivated in dementia. Further, the structural presence of benzo[g]chromene in many natural products with reported anticancer activity and the synergistic effect of β lapachone with Taxol against tumour growth²³⁻²⁵ are driving the search for newer strategies to synthesize oxygen heterocyclic moieties in economical and environmentally friendly conditions. The therapeutic functions of some O-heterocycles are illustrated in Fig. 1.

The revolutionary advancements in the physiological studies of living beings for the sake of mankind and the environment seek acknowledgment from organic biomimetic pathways adopted by synthetic chemists to produce optimum results. So, the challenging process of synthesizing heterocyclic moieties can be facilitated by employing bifunctional building blocks in the reaction design, in which the multiple reactive centres lead to product diversity. Aryl glyoxal is one of the Aldo-ketone bifunctional building block molecule used by synthetic chemists to produce a diverse library of molecules.26 The presence of a reactive aldehyde group adjacent to the carbonyl group is the peculiar structural feature that makes aryl glyoxal distinctive for the synthesis of heterocyclic as well as carbocyclic compounds. The electron-withdrawing ketone group makes any glyoxal more reactive than benzaldehyde and allows the site to be open to nucleophilic attack followed by cyclization in various ways. Further, the non-enolizability of the ketone group under acidic or basic conditions is responsible for its sufficient stability and for making aryl glyoxal monohydrate commercially available. Interestingly, besides the numerous applications of all types of oxygen heterocycles as drugs and therapeutic agents, there are some biologically potent molecules with a phenyl glyoxal unit embedded in their structure (as shown in Fig. 2), such as 4-aroyl chromene derived from phenyl glyoxal hydrate and naphthyl glyoxal, which have shown antibacterial properties by inhibiting Escherichia coli growth with a minimum inhibitory concentration (MIC) of 32 µg cm⁻³.²⁷ Also, a furan-substituted guaiazulene moiety synthesized through a simple route by utilizing phenyl glyoxal exhibited significant in vitro anti-oxidant activity against lipid peroxidation with a minimum IC_{50} value of 3.9 μ g mL⁻¹.²⁸ Guaiazulene, a derivative of azulene, acts therapeutically against skin and asthma-like diseases due to allergy or inflammation reactions.²⁹ Coumarin targets the α-glucosidase enzyme, which is responsible for the hydrolysis of starch and higher carbohydrates into simple sugars.³⁰ Dihydrochromeno [4,3-b]pyrrol-3-yl obtained by using phenyl glyoxal as one of the



Fig. 1 Some biologically active O-heterocycles.

starting materials exhibits α-glucosidase inhibitory activity, thus aiding the drug-development process for hyperglycaemia and Type 2 diabetes mellitus (T2DM).³¹ This in vitro evaluation was further extended by in silico docking studies with reference to the standard drug acarbose.32 Also, attempts are being made to synthesize the C-4 aroyl group-substituted pyrano[3,2-c] chromene and benzo[g]chromene by employing phenyl glyoxal due to their divergent properties.33,34 A new HIV integrase inhibitor, namely a pyrano[2,3-d:6,5-d']dipyrimidine (V-165)-like framework of pyrano[2,3-d:6,5-d']dipyrimidines, constructed through phenyl glyoxal showed increased chances for extensive use in drug precursors development.35 Phenyl glyoxal was further used in the synthesis of a furo(2,3-b)furan moiety³⁶ mimicking drug candidates like Brecanavir (GW640385), an HIV inhibitor³⁷ and Darunavir (TMC-114),^{38,39}, another HIV-1 protease inhibitor. A coumarin-glyoxal hybrid, namely the tartrate salt of a Mannich base bearing coumarin derivatives,40 was found to be an efficient contraceptive as it shows activity as both a spermicide and microbicide. The compound was tested for spermicidal activity against nonoxynol (N-9),41 a contraceptive. The two compounds of the series showed activity better than N-9. For anti-microbial activity, again the two compounds showed activity better than the metronidazole42 chosen as the standard for the study. For this reason, from many years in the past up to recent years, aryl glyoxal has been extensively used and studied as a key building block in multicomponent singlepot reactions.43

In this review article, we intend to highlight the extensive use of the bifunctional building block aryl glyoxal monohydrate as a key starting material in the construction of many novel and mimics of naturally found heterocyclic moieties. Here, is a brief account of the reactivity pattern of aryl glyoxal with different substrates leading to the synthesis of various derivatives and fused oxygen heterocycles.

2. Use of aryl glyoxal in designing *O*heterocycles using multicomponent reactions

Aryl glyoxal is unique in having two adjacent carbonyl groups, but it mostly exists in the hydrated form. It forms different types of five-membered and six-membered heterocyclic rings depending on the type of other substrates, attacking nucleophiles, and cyclization pattern in the reaction. The application of aryl glyoxal in the synthesis of five- and six-membered *O*heterocycles is discussed in the following sections.

2.1. Synthesis of five-membered furan derivatives

Jian's group efficiently utilized aryl glyoxal **1** in the goldcatalyzed three-component reaction with amine **2** and a terminal alkyne **3** to obtain substituted furans **4** through cyclization in a nitrogen atmosphere with methanol as a solvent. This reaction provides an effective protocol for the preparation of synthetic and pharmacological derivatives of



Fig. 2 Biologically active O-heterocycles obtained from phenyl glyoxal



 $\begin{array}{l} R_1 = C_6H_5, 4 + FC_6H_4, 4 - MeC_6H_4, 4 - pentylC_6H_4, \\ R_2 = C_6H_5, 4 + FC_6H_4, 3 - CIC_6H_4, 4 - CIC_6H_4, 4 - NO_2C_6H_4, 4 - CF_3C_6H_4, 4 - BrC_6H_4, \\ R_3, R_4 = Sec.amine \end{array}$



furan (Scheme 1).⁴⁴ The plausible mechanism of the protocol started from the coupling of aryl glyoxal 1, amine 2, and alkyne 3 in a Mannich–Grignard pattern to give a propargyl intermediate **aa**, which was followed by the attack of the oxygen lone pair to the electrophilic triple bond, forming a cation **ab** and then leading to the final product indolizines 4 through deprotonation and demetallation, respectively (Scheme 2).

For the synthesis of isoxazolyl amino furo[3,2-*c*]quinolinone scaffolds 7, Nagi and co-workers developed an efficient one-pot, three-component reaction of aryl glyoxal monohydrate, 4-hydroxy-1-methyl-2-quinilinone **6**, and 4-amino-3-methyl-5-

styrylisoxazoles **5** under reflux conditions in aqueous medium with a 5 mol% of *p*-TSA. The scheme was tested with different Lewis acids and organic acids, but *p*-TSA in water was found to give the best results in terms of the time, yield, and environmentally friendly protocol (Scheme 3).⁴⁵ The reaction mechanism (as shown in Scheme 4) starts from the *p*-TSA-catalyzed condensation of compound **5** and **1** yielding the iminium ion intermediate **ba**, which serves as an electrophilic site for the nucleophile **6**. The nucleophilic addition reaction between **ba** and **6** produces the **bb** intermediate, which is in tautomeric isomerization with **bc**. The intermediate **bd** undergoes intramolecular cyclization initiated by the acid to give the final product 7 through the dehydration of **be** (Scheme 4).

For the synthesis of the furan-2(5*H*)-one derivative **10** with indole as a structural fragment, Andrey's group established a facile and one-pot novel methodology, which was completed in two steps starting with the interaction of aryl glyoxal **1**, indole **9**, and Meldrum's acid **8** in acetonitrile with triethylamine at reflux, followed by a further acidic reflux using acetic acid (Scheme 5).⁴⁶ The formation of the new oxygen heterocycle was considered to go through the aryl glyoxal **1** condensation with Meldrum's acid (intermediate) **ca** followed by the Michael





 $\label{eq:rescaled} \begin{array}{l} \mathsf{Are} = \mathsf{C}_{6}\mathsf{H}_{5}\mathsf{.4}\mathsf{-}\mathsf{CH}_{3}\mathsf{C}_{6}\mathsf{H}_{4}.\mathsf{2}\mathsf{-}\mathsf{CH}_{3}\mathsf{C}_{6}\mathsf{H}_{4}.\mathsf{4}\mathsf{-}\mathsf{BrC}_{6}\mathsf{H}_{4}.\mathsf{4}\mathsf{-}\mathsf{BrC}_{6}\mathsf{H}_{4}.\mathsf{4}\mathsf{-}\mathsf{NO}_{2}\mathsf{C}_{6}\mathsf{H}_{4}\\ \mathsf{R} = \mathsf{C}_{6}\mathsf{H}_{5}\mathsf{.4}\mathsf{-}\mathsf{CH}_{3}\mathsf{C}_{6}\mathsf{H}_{4}.\mathsf{2}\mathsf{-}\mathsf{CH}_{3}\mathsf{C}_{6}\mathsf{H}_{4}.\mathsf{4}\mathsf{-}\mathsf{OC}_{3}\mathsf{C}_{6}\mathsf{H}_{4}.\mathsf{4}\mathsf{-}\mathsf{CIC}_{6}\mathsf{H}_{4}.\mathsf{2}\mathsf{-}\mathsf{CIC}_{6}\mathsf{H}_{4}.\mathsf{4}\mathsf{BrC}_{6}\mathsf{H}_{4}.\mathsf{2}\mathsf{-}\mathsf{BrC}_{6}\mathsf{H}_{4}.\mathsf{2}\mathsf{-}\mathsf{BrC}_{6}\mathsf{H}_{4}.\mathsf{2}\mathsf{-}\mathsf{Hild}_{3}\mathsf{C}_{6}\mathsf{H}_{4}.\mathsf{4}\mathsf{-}\mathsf{CIC}_{6}\mathsf{H}_{4}.\mathsf{4}\mathsf{-}\mathsf{CIC}_{6}\mathsf{H}_{4}.\mathsf{4}\mathsf{-}\mathsf{BrC}_{6}\mathsf{H}_{4}.\mathsf{2}\mathsf{-}\mathsf{BrC}_{6}\mathsf{H}_{4}.\mathsf{2}\mathsf{-}\mathsf{BrC}_{6}\mathsf{H}_{4}.\mathsf{2}\mathsf{-}\mathsf{Hild}_{3}\mathsf{C}_{6}\mathsf{H}_{4}.\mathsf{4}\mathsf{-}\mathsf{CIC}_{6}\mathsf{H}_{4}.\mathsf{4}\mathsf{-}\mathsf{CIC}_{6}\mathsf{H}_{4}.\mathsf{4}\mathsf{-}\mathsf{BrC}_{6}\mathsf{H}_{4}.\mathsf{4}\mathsf{-}\mathsf{BrC}_{6}\mathsf{H}_{4}.\mathsf{4}\mathsf{-}\mathsf{Hild}_{3}\mathsf{C}_{6}\mathsf{H}_{4}.\mathsf{4}\mathsf{-}\mathsf{Hild}_{4}\mathsf{-}\mathsf{CIC}_{6}\mathsf{H}_{4}.\mathsf{4}\mathsf{-}\mathsf{BrC}_{6}\mathsf{H}_{4}.\mathsf{4}\mathsf{-}\mathsf{BrC}_{6}\mathsf{H}_{4}.\mathsf{4}\mathsf{-}\mathsf{BrC}_{6}\mathsf{H}_{6}\mathsf{H}_{6}\mathsf{-}\mathsf{Hild}_{4}\mathsf{-}\mathsf{Hild}_{6}\mathsf{-}\mathsf{Hild}_{6}\mathsf{Hild}_{6}\mathsf{-}\mathsf{H$

Scheme 3 Synthesis of isoxazolyl amino furo[3,2-c]quinolinone scaffolds 7 using *P*-TSA.⁴⁵

addition to indole **cb** and finally cyclization with the elimination of CO_2 to give **10** (Scheme 6).

Shahbazi-Alavi and co-workers demonstrated an environmentally friendly nanocatalyzed synthesis of substituted furans. The target molecule 13 was afforded through the heterogeneous catalysis of the aryl glyoxal 1, dimethyl acetylenedicarboxylate 11, and primary amine 12 reaction at room temperature by using the HPA-ZSM-5 nanocatalyst in dichloromethane (Scheme 7).47 The mechanistic pathway of the reaction is initiated by the nucleophilic attack of the amine lone pair 12 on the electrophilic site of dimethyl acetylenedicarboxylate 11 forming an enaminone, namely aminobutenedioate da. This aminobutenedioate acts as a C-nucleophile and attacks the electrondeficient carbon of phenyl glyoxal 1, thereby generating the second intermediate iminium-oxoanion db, which tautomerizes to the intermediate dc. Intermediate dc then undergoes γ -lactonization to give 5-oxo-2,5-dihydro-3-furancarboxylate 13 as the final product (Scheme 8). The low loading and reusability of the green catalyst for up to 6 cycles were particularly interesting aspects of this strategy.

In 2021, Ebrahimi and co-workers synthesised 5-oxo-2,5dihydro-3-furancarboxylate derivatives **13** by assembling aryl glyoxal 1, dimethyl acetylenedicarboxylate 11, and primary amines 12 in one-pot using nano-CuO at room temperature with dichloromethane as a reaction promoter. This work gained popularity due to its ease of operation, facile and quick extraction of the product, quick response time, high yield, and low loading and re-utilization of the catalyst (Scheme 9).⁴⁸ The reaction design mimics the mechanism of HPA-ZSM-5 catalysis (Scheme 10).

Aldo-X reagents 1 and α -oxoketene dithioacetals 14 with indoles 15 as the precursors were utilized by Changhui's group to create six-multicomponent reactions, which were used to synthesize a variety of heterocycles, including quinolines, dihydrocoumarins, furans 16, and pyrroles 17. The discovery of these multicomponent reactions was made feasible by the coupling of two bifunctional aldo-X reagents and α -oxoketene dithioacetals, because these reagents contain a minimum of two reactive sites, which allows diverse substrates to be put together in different ways (Scheme 11).⁴⁹

Fatemah and co-workers applied aryl glyoxal **1** for the fabrication of 5-(furan-yl)barbiturate and 5-(furan-3-yl) thiobarbiturate **20** *via* a one-pot assembly of **1** with acetylace-tone **18** and barbituric acid and thiobarbituric acid **19**, respectively, in water at 60 °C (Scheme 12).⁵⁰ The plausible mechanism starts with the Knoevenagel reaction between **1** and **18** to give the intermediate **fa**, which undergoes a 1,4-conjugated addition with barbiturate **19** yielding 1,4-diketone **fb**, followed by a Paal–Knorr cyclization **fc** to finally give 5-(furan-3-yl)barbiturate/thiobarbiturate **20** (Scheme 13).

2.2. Synthesis of benzofuran derivatives

In 2019, Ahmed and co-workers used aryl glyoxal for synthesizing functionalized benzofuran through an ionic liquid catalysis. The desired product **23** was obtained by the assembly

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Scheme 5 Three-component synthesis of furan-2(5H)-one derivative 10 using Meldrum's acid 8.46

of aryl glyoxal hydrate **1**, sesamol **22**, and indole **21** in an imidazolium-based Brønsted acid ionic liquid/butyl acetate green system. The above catalyst was recovered and used for further reactions (Scheme 14).⁵¹

Further synthesis was done by Mahnaz Saraei's group using aryl glyoxal 1 as a building block for obtaining novel 4*H*-indeno [1,2-b]furan-4-ones 28 through a one-pot condensation with 2aminopyridines 25 and 1,3-indandione 27 in water in the absence of any catalyst. In addition, by employing aryl glyoxal 1, 25, and barbituric acid 19 under the same green conditions, Khoeiniha *et al.* obtained furo[2,3-d]pyrimidine 29 derivatives in high yield (Scheme 15).⁵² The reaction was believed to start from the aldol condensation of 1 and 1,3-indanedione 27 generating the intermediate **ga**. Amine 25 was added to this intermediate through a Michael addition **gb** followed by intramolecular cyclization **gc** with subsequent dehydration to produce the final



Scheme 6 Mechanism to explain the synthesis of furan-2(5H)-one 10 using indole 9, Meldrum's acid 8, and aryl glyoxal 1 as starting materials.



Scheme 7 Nanocatalyzed protocol for the synthesis of substituted furans 13.4^{47}

product **28**. When 1,3-indandione was replaced with barbituric acid following the same methodology, a furo-pyrimidine derivative was obtained as the product (Scheme 16).

In 2020, Palanivel explored the combination of **1** and benzimidazole acetonitrile **30** with malononitrile **31** at room temperature in a trifilic acid/acetonitrile system to afford tricyclic aza-cyclopenta(**cd**)diindene **32**. The above combination was also executed with benzoyl acetonitrile **35** at room temperature in ethanol/water to access the furo(2,3-*b*)furan derivative **36** in the presence of the organic base DABCO. Further, he obtained the pyrrolo-pyridine carboxamide **34** and furo-pyrrolo imidazole carboxamide **33** when the aryl glyoxal **1** was made to react with two equivalents of benzimidazole acetonitrile **30** in a pseudothree-component reaction employing DABCO and NaO'Bu as additives, respectively, in ethanol/water at room temperature (Scheme **17**).³⁶

In 2020, Boris and co-workers effectively used aryl glyoxal for the preparation of terarylenes **39**, a starting material for the synthesis of naphtho(1,2-*b*)benzofuran-7(8*H*)-ones **40** *via* a green photochemical rearrangement reaction of 4*H*-chromen-4-one derivatives. Aryl glyoxal **1** underwent a three-component tandem reaction with 3-(dimethylamino)-1-(2 hydroxyaryl) prop-2-en-1-one **37** and cyclic 1,3-diketone **38** in the presence of an inert solvent and base at room temperature followed by the subsequent addition of a hydrochloric and acetic acid mixture in the last. The model reaction was optimized by using



 $\label{eq:R12} R_1 = 2 - methoxybenzylamine, 4 - methoxybenzylamine, 4 - methylbezylamine, benzlamine, 4 - fluorobenzylamine, propylamine, 3, 4 - dichlorobenzylamine, (furan-2-yl)methanamine.$

Scheme 9 Three-component Cu nanoparticles-catalyzed synthesis of 5-oxo-2,5-dihydro-3-furancarboxylate derivatives 13.48

different solvents and varying the system temperature. Terarylenes were best obtained in a good yield at room temperature with acetonitrile and triethylamine as the solvent/base system. The limitation of the novel multicomponent methodology to cyclic diketones was also confirmed by the unsuccessful test reaction of 2,4-pentanedione (Scheme 18).⁵³ The plausible mechanism for this reaction includes the expected basecatalyzed condensation reaction of 1,3-diketone **38** with **1** followed by the subsequent addition of enaminone **37** to the generated Michael acceptor, forming the adduct **hb**. Intramolecular cyclization through nucleophilic attack of the hydroxyl group to the iminium ion generates an intermediate **hc**, which finally undergoes acid-catalyzed dehydration to form the desired product **39** with a new furan moiety in the structure (Scheme 19).

Recently, P. *et al.* successfully demonstrated a threecomponent calcium-catalyzed approach for obtaining 3-aminofurans **43** in good yield *via* annulation of the *in situ* intermediate C, *N*-diacyliminium generated as a result of a threecomponent reaction between a variety of aryl glyoxal **1** and lactams **41** with 2-naphthols **42** under solvent-free conditions at 100 °C (Scheme 20).⁵⁴ The proposed mechanism includes formation of the Ca²⁺-catalyzed imine **ia** in the initial step followed by ligand metathesis between Ca²⁺ and the hydroxyl group of β -naphthol to form a C–C bond **ic**, and then an intermediate **id** with a new C–O bond. Finally, **id** undergoes



Scheme 8 Mechanistic pathway to explain the nanocatalyzed synthesis of furan derivatives 13.



Scheme 10 Mechanism that explains the synthesis of 5-oxo-2,5-dihydro-3-furancarboxylate 13 via Cu NPs



Scheme 11 Syntheses of furan 16 and pyrrole 17 derivatives *via* threecomponent reactions.⁴⁹



Scheme 12 Three-component synthesis of 5-(furan-yl)barbiturate and 5-(furan-3-yl)thiobarbiturate 20 from acetylacetone 18 and barbituric acid 19.50

aromatization yielding the naphthofuran **43** (Scheme 21). The reaction was also tested against different solvents and Lewis acid catalysts, but none of them gave a yield of more than 50%. The ligand metathesis between $Ca(OTf)_2$ and Bu_4NPF_6 increases the acidity of the catalyst by making it more efficient to provide an excellent yield. Interestingly, they also repeated the same protocol by changing the nucleophile source to mequinol (substituted phenol) **44** to access the corresponding benzofuran

45 and later glyoxal with the 9*H*-fluoren-3-ol derivative **46** and lactam-furnished fluorenofuran **47** in a good yield of 84%. Further, the annulation reaction of glyoxal and lactam with 4-hydroxycoumarin as a nucleophile did not prove efficient under solvent-free conditions. The products were studied for their photophysical properties and a broad substrate scope was established for all of these protocols.

The utility of aryl glyoxal as a synthetic building block was explored by Lichitsky *et al.* through the triethylamine-promoted reaction of the 4-methoxy derivative of **1** with Meldrum's acid **8** and 8-hydroxyquinoline **48** in acetonitrile followed by cyclization in refluxing acetic acid to afford furylacetic acid **49**. The protocol is marked by a simple work-up route and high atom economy (Scheme 22).⁵⁵

In 2021, Komogortsev and co-workers performed a reaction involving **1**, Meldrum's acid **8**, and colchiceine **50**, which led to a practical one-pot method to synthesize colchicine derivatives **51** with different substitutions. One of the distinctive aspects of the method was the production of the 6,7-dihydrobenzo[9,10] heptaleno[3,2-*b*]furan-9(5*H*)-one **51** molecule. Some of the key features of this method include the use of easily available precursors, facile execution of the protocol, and the ease with which the target products could be separated. The twodimensional (2D) NMR spectrum verified the structure of one of the furotropolone products (Scheme 23).⁵⁶

A multicomponent reaction protocol was developed by Yang's group for the formation of 2-aryl-3-aminobenzofuran **53** derivatives by reacting aryl glyoxal monohydrates **1**, phenols **44**, and *para*-toluenesulfonamide **52**, catalyzed by 10mol% of indium trichloride in the presence of dichloromethane as the solvent to obtain excellent yield (Scheme 24).⁵⁷

Mosslemin's group in 2009 reported the isocyanide-based formation of furo[3,2-*c*]chromen-ones **56** through a condensation–cycloaddition of the easily available 4-hydroxy coumarin **54** with the extensively used aryl glyoxal and alkyl isocyanides **55** in



Scheme 13 Mechanism proposed to explain the formation of 5-(furan-3-yl)thiobarbiturate 20.





Scheme 15 Three-component synthesis of 4H-indeno[1,2-b]furan-4-ones 28 via an aldol condensation.⁵²

neutral acetonitrile medium. The scheme also gave the same result when 4-hydroxycoumarin was substituted with dimethyl cyclohexandione (Scheme 25).⁵⁸ The underlying mechanism for the synthesis begins with the generation of the Knoevenagel adduct **ja** of 4-hydoxycoumarin **54** and **1** with a subsequent [4 + 1] cycloaddition reaction between the resulting hetero-diene and isocyanide to form iminolactone **jb** as an intermediate. Lastly, a [1,3]-H shift in this iminolactone leads to furo[3,2-*c*] coumarin **56** (Scheme 26).

The application of aryl glyoxal was demonstrated by Khodabakhshi and Hashemi in the construction of 2-aryl-3benzamido-benzofurans **58** *via* a solvent-free three-component

Scheme 16 Plausible mechanism for the synthesis of 4*H*-indeno[1,2*b*]furan-4-ones 28.

condensation reaction of **1**, benzamide **57**, and the phenolic substrate **44** with a catalytic amount of tungstate sulfuric acid (TSA) at 120 °C (Scheme 27).⁵⁹ The plausible mechanism for the formation of benzofuran consisted of three steps, starting with the generation of the intermediate **ka** through an *in situ* condensation of amide **57** and **1**, followed by the regio-specific formation of the oxygen-containing five-membered ring **kc** *via* the intramolecular cyclization of **kb**, and finally dehydration leading to the final product **58** (Scheme 28).

The use of aryl glyoxal **1** by Salari and co-workers set an efficient protocol for the synthesis of functionalized *trans*-tetrahydrobenzofuran-4-ones **60** *via* the condensation reaction of aryl glyoxal, *N*-(4-halophenacyl)-pyridinium bromide **59**, and cyclic **1**,3- diketone **8** utilizing DABCO in a catalytic amount with the evergreen solvent water under reflux. Further optimization of the protocol was accomplished by using different derivatives of aryl glyoxal, showing that *p*-nitroaryl glyoxal and *o*-bromoaryl glyoxal gave the highest yields under the same conditions (Scheme 29).⁶⁰

A pentacyclic product named as *trans*-(4-chloroAryl)-7-aryl-6,7dihydro(1,3)dioxolo(4,5-*f*)(1)benzofuran-6-yl)methanones **60** was



Scheme 17 DABCO-catalyzed three-component reactions to yield various furo-furan derivatives 36, 32, and 33.36



Scheme 18 Syntheses of naphtho(1,2-*b*)benzofuran-7(8*H*)-ones and terarylene **39/40** *via* photochemical rearrangement reactions of 4*H*-chromen-4-one derivative.⁵³

afforded by Selari *et al.*, *via* a one-pot 1,4-diaza-bicyclo[2.2.2] octane (DABCO)-catalyzed condensation of three components, namely 2-(2-(4-chloroAryl)-2-oxoethyl))isoquinolinium bromide **59**, benzo(1,3)dioxol-5-ol **22**, and aryl glyoxal **1** in water at reflux.

Further, a library of substrates was constructed by using different halo-, nitro-, and hydroxyl-substituted aryl glyoxals (Scheme 30).⁶¹

In 2020, Zhang *et al.* reported a simple and straightforward protocol for the quick synthesis of the benzofuran derivatives **63**



and **64**, which involved an FeCl₃-mediated intermolecular tandem reaction between anisole **61** and **1**, *via* a Friedel–Craft alkylation and oxidative annulation. This reaction offers a lot of benefits, like readily available starting materials, high atom economy, and strong functional group tolerance (Scheme 31).⁶² The mechanistic steps for the annulation reaction include the Friedel–Craft alkylation of **1** with anisole **61** forming the intermediate **1a**, which in turn is oxidized by FeCl₃ to generate the second radical cation intermediate **1b**. FeCl₃ is then reduced second time to further oxidize **1c** with a subsequent intramolecular cyclization followed by dehydration to yield the

By employing microwave irradiation in the presence of the $H_3PW_{12}O_{40}$ @Fe₃O₄–ZnO catalyst, Taheri and co-workers in 2021 developed an effective and convenient single-pot, threecomponent reaction (3CR) of 2-hydroxynaphthalene-1,4-dione **65**, aryl glyoxal **1**, and indoles **67** to produce benzo[*a*]furo[2,3-*c*] phenazine **68** derivatives with excellent yields. The facile and quick extraction of the products, short reaction time, mild reaction conditions, high product yield, solvent-free conditions, low energy demand, and economically affordable chemicals were the major advantages of this reaction protocol (Scheme 33).⁶³

Taheri and colleagues performed the same reaction in 2021 to develop an easy, efficient, and straightforward protocol for the synthesis of benzo[*a*]furo[2,3-*c*]phenazine **68** derivatives in excellent yields by the reaction of benzo[*a*]phenazin-5-ol **65**, **1**, and **67** utilizing the Fe₃O₄@rGO@ZnO-HPA catalyst and keeping the other conditions similar to the previous reaction (Scheme 34).⁶⁴

A one-pot multicomponent reaction leading to the synthesis of urea-substituted 2-arylfurans **71** was reported for the first time by Andrey N. Komogortsev's group by reacting numerous carbo and heterocyclic enols **69**, cyanamide **70**, and aryl glyoxal **1** under reflux conditions in the presence of the solvent acetonitrile and base triethylamine (Scheme 35).⁶⁵

2.3. Synthesis of pyran derivatives

A green nanoparticles-catalyzed strategy for the production of dihydropyrano(*c*)chromenes **74** was demonstrated by Khodabakhshi's group using aryl glyoxal **1**, 4-hydroxycoumarin **72**, and

annulated benzofuran 63 (Scheme 32).



 $R_1 = Ph, 2-BrC_6H_4, 4-BrC_6H_4, 4-CIC_6H_4, 4-FC_6H_4, 4-OMeC_6H_4, 4-MeC_6H_4, Cyclopronane$ $R_2 = H Br$





Scheme 21 Plausible mechanism for the calcium-catalyzed synthesis of naphthofuran 43.



Scheme 22 Synthesis of furylacetic acid 49 using Meldrum's acid 8 and 8-hydroxyquinoline 48.⁵⁵

malononitrile 73 in a single pot with an ethanol-water solvent system at reflux. The same reaction was tested against *p*-TSA, Na₂CO₃, FeCl₃, ZnCl₂, and AcOH and gave no significant yields of the desired products, except for the magnetically recyclable Fe₃O₄ nanoparticles (Scheme 36).⁶⁶

Again in 2014, Khodabakhshi and co-workers explored the use of nanosheets of graphene oxide with the same one-pot three-component combination under reflux in an ethanol/ water system with a little amount of loading of GO catalyst. The advantages of the above protocol were marked by the recyclable catalyst with a minimal loading of 0.005 g with a high yield and simple work-up procedure (Scheme 37).⁶⁷



Ar= 4-CH₃OC₆H₄,3-CH₃OC₆H₄,C₆H₅,4-BrC₆H₄,4-ClC₆H₄,3,4-(CH₃)₂,2,6-(CH₃)₂ C₆H₃CH₂O₂,C₆H₃(CH₂)₂O₂,(C₆H₅)₂, 4-C₆H₁,1C₆H₄

Scheme 23 Synthesis of 6,7-dihydrobenzo[9,10] heptaleno[3,2-*b*] furan-9(5*H*)-one 51 using Meldrum's acid 8 and colchiceine 50.⁵⁶



Scheme 24 Indium-catalyzed multicomponent protocol for the synthesis of 2-aryl-3-aminobenzofuran 53.⁵⁷



Scheme 25 Synthesis of furo[3,2-c]coumarin 56 via a [4 + 1] cyclo-addition reaction.⁵⁸

A synthetic library of multifunctional pyrano(*c*)chromenes 74 was developed by Saeed *et al.* by exploiting differently substituted aryl glyoxal 1 with malononitrile 73 and 4-hydroxycoumarin 72 in the presence of ammonium dihydrogen phosphate at room temperature, first for 30–40 min and then at reflux in an ethanol/water system to obtain the desired product (Scheme 38).⁶⁸





In 2015, a novel synthetic route was developed by Rimaz *et al.* to afford a library of biologically active substituted pyrano(2,3-d) pyrimidines 75. They obtained the desired products through an excess ammonium acetate-catalyzed one-pot condensation of aryl glyoxal monohydrate **1** with barbituric acid **19** using the greenest solvent water at room temperature (Scheme 39).⁶⁹

Rimaz and co-workers reported the synthesis of pyranofused pyrimidines derivatives 75 by the regioselective pseudothree-component condensation reaction of aryl glyoxal monohydrate **1** and 1-ethyl-2-thioxodihydropyrimidine-4,6(1*H*,5*H*)dione **19** under a catalytic system employing DABCO or ZrOCl₂·8H₂O in ethanol at 50 °C. The pyrano-fused-pyrimidine scaffold in the synthesized compound was identified as possessing HIV integrase inhibitor activity (Scheme 40).³⁵

The potassium phthalimide-*N*-oxyl (PPINO) organocatalyzed one-pot green reaction of aryl glyoxal monohydrate **1** with barbituric acid **19** or thiobarbituric acid and β -naphthol **42** at reflux in water yielded benzo[5,6]chromene **76** and derivatives was single-handedly reported by Etivand. The distinguishing features of the protocol as highlighted were the use of green solvents, short reaction time of only 30 min, and the product contained more than one heterocycle centre (Scheme **41**).⁷⁰

A convenient method for the synthesis of a novel series of 2-amino-4-aroyl-4*H*-benzo[*h*]chromene-3-carbonitriles **78** was developed by Marjani *et al.* under solvent-free micro-wave (MW) conditions, in high yields by using a multicomponent condensation reaction of aryl glyoxals **1**, 1-naphthol **77**, and malononitrile **73** in the presence of Mg–Al



Scheme 26 Mechanism to explain the synthesis of furo[3,2-c]coumarin 56 via a cycloaddition reaction.



Scheme 28 Mechanistic pathway representing the synthesis of 2-aryl-3-benzamido-benzofuran 58.



Scheme 29 Three-component DABCO-catalyzed synthetic protocol for the synthesis of *trans*-tetrahydrobenzofuran-4-ones **60**.⁶⁰



Ar= 4-NO₂C₆H₄,4-FC₆H₄,2-BrC₆H₄,4-OHC₆H₄,2-CIC₆H₄,4-CIC₆H₄

Scheme 30 Synthesis of trans-(4-chloroAryl)-7-aryl-6,7-dihydro(1,3) dioxolo(4,5-f)(1)benzofuran-6-yl)methanones 60 in a one-pot approach using DABCO.⁶¹

hydrotalcite (Scheme 42).⁷¹ A plausible outline of the scheme is starting from the Mg–Al hydrotalcite accelerated Knoevenagel reaction of 1 with C–H acid 73 to form an intermediate, namely 2-(2-oxo-2-arylethylidene)malononitrile **ma**. In the second step, α -naphthol is added as a C-nucleophile to **ma**, forming a new species with the C–C bond **mb**. The intermediate **mc** undergoes intramolecular cyclization to generate the species **md**, which tautomerizes to give the product 78 (Scheme 43).

Mishra and Choudhury investigated the possibility of using microwave irradiation as one of the synthetic routes with the assembly of aryl glyoxal monohydrate **1** along with malononitrile **73** and cyclic 1,3-dicarbonyls **79** to afford several pyrans fused with many functionalities, such as coumarins, quinolones, naphthoquinones, and pyrones **80**. This approach is a basic and simple way of obtaining functionalized pyrans without the need for a catalyst or column chromatographic purification (Scheme 44).⁷²

In addition, Mishra and Choudhury also explored the scope of this technique to obtain different fused pyrans 74 and 74a by changing 1,3-dicarbonyls to other cyclic functionalities, such as 4-hydroxy coumarin 72 and 4-hydroxy-6-methyl-2*H*-pyran-2-one 72a. The corresponding products were isolated in high yields (Scheme 45).⁷² The reaction pathway is outlined in Scheme 46.

Furthermore, Khalafy's group reported the nanocatalyzed synthesis of 2-amino-4-aroyl-5-oxo-5,6-dihydro-2*H*-pyrano[3,2-*c*] **80** *via* the reaction of aryl glyoxal **1**, active methylene group **73**, and 4-hydroxyquinolin-2(1*H*)-one **79** in a single-pot approach with the SBA-15 nanocatalyst in a green solvent. The simplicity of the work-up procedure, the use of an ethanol/water system as a green medium, and the good to extraordinary product yields represent the key benefits of this synthetic technique (Scheme 47).⁷³

Khalafy *et al.* extended the library of oxygen heterocycles in 2018 through 4-aroyl-4*H*-benzo[*g*]chromene **82** synthesis using **1**, 2-hydroxy-1,4-naphtoquinone(lawsone) **81**, and one active methylene species **73** with the effective use of a $\text{Zn}(\text{L-Pr})_2$ metal–amino acid complex. The $\text{Zn}(\text{L-Pr})_2$ is a water-soluble catalyst that shows Lewis acid behaviour together with significant reusability. The protocol was also tested with different acid catalysts, namely sulfanilic acid, *p*-toluene-sulfonic acid, the phase-transfer catalyst tetrabutylammonium bromide, and L-cystein, obtaining the target molecule **82** in high yields with 20% L-proline in ethanol/water at 50 °C (Scheme 48).⁷⁴

Next, in 2018, Nasri *et al.* successfully employed aryl glyoxal to obtain the biologically important oxygen heterocycle and



Scheme 31 Syntheses of benzofurans 63/64 via FeCl₃-mediated intermolecular tandem reactions.⁶²



Scheme 32 Plausible mechanism for the syntheses of benzofurans 63/64 in the presence of FeCl₃.

useful chemical synthon chromene. A chemical library of pyrano[3,2-c]chromene 74 and benzo[g]chromene 82 was constructed through a catalyst-free one-pot assembly of aryl

glyoxal monohydrate 1, malononitrile as the active methylene group 73, and 4-hydroxycoumarin 72/2-hydroxy 1,4-nephthaquinone 81 under reflux with ethanol as the solvent. Ethyl



Scheme 33 Synthesis of benzo[a]furo[2,3-c]phenazine 68 via microwave irradiation in the presence of $H_3PW_{12}O_{40}@Fe_3O_4-ZnO$ as a catalyst.63



R= CH₃, R'= NO₂, Ar= 4-Ph,4-PhCH₃,4-PhOCH₃,4-PhNO₂,4-PhBr.4-PhCl..

Scheme 34 Synthesis of benzo[a]furo[2,3-c]phenazine 68 using Fe₃-O4@rGO@ZnO-HPA as a catalyst.64



Scheme 35 One-pot protocol for the synthesis of urea-substituted 2arylfurans 71 by employing cyanamide 70 and heterocyclic enols 69.65



 $\label{eq:Area} \begin{array}{l} \mathsf{Are} \mathsf{C}_6\mathsf{H}_5,\!\mathsf{4}\!\!\cdot\!\!\mathsf{F}\!\!\cdot\!\!\mathsf{C}_6\mathsf{H}_4,\!\mathsf{4}\!\!\cdot\!\!\mathsf{Br}}_6\mathsf{H}_4,\!\mathsf{3}\!\!\cdot\!\!\mathsf{NO}_2\mathsf{C}_6\mathsf{H}_4,\!\mathsf{4}\!\!\cdot\!\!\mathsf{NO}_2\mathsf{C}_6\mathsf{H}_4,\\ \mathsf{3}\!\!\cdot\!\!\mathsf{OMe}\mathsf{C}_6\mathsf{H}_4,\!\mathsf{4}\!\!\cdot\!\!\mathsf{OMe}\mathsf{C}_6\mathsf{H}_4,1\!\!\cdot\!\!\mathsf{Naphthyl},\!\mathsf{2}\!\!\cdot\!\!\mathsf{Naphthyl} \end{array}$

Scheme 36 Nanocatalyzed synthesis of dihydropyrano(c)chromenes 74 by the reaction of aryl glyoxal 1 with 4-hydroxycoumarin 72, and malononitrile 73.⁶⁶



 $\begin{array}{l} {\rm Arr}={\rm C_6H_5,4\text{-}F\text{-}C_6H_4,4\text{-}CIC_6H_4,4\text{-}BrC_6H_4,3\text{-}NO_2\text{-}C_6H_4,4\text{-}NO_2\text{-}C_6H_4,3\text{-}NO_2\text{-}C_6H_4,4\text{-}NO_2\text{-}C_6H_4,3\text{-}NO_2\text{-}C_6H_4,4\text{-}NO_2\text{-}C_6H_4,4\text{-}NO_2\text{-}C_6H_4,3\text{-}NO_2\text{-}C_6H_4,4\text{-}NO_2\text{-}C_6H_4,3\text{-}NO_2\text{-}C_6H_4,4\text{-}NO_2\text{-}C_6H_4,3\text{-}NO_2\text{-}C_6H_4,4\text{-}NO_2\text{-}C_6H_4,3\text{-}NO_2\text{-}C_6H_4,4\text{-}NO_2\text{-}C_6H_4,3\text{-}NO_2\text{-}C_6H_4,3\text{-}NO_2\text{-}C_6H_4,4\text{-}NO_2\text{-}C_6H_4,3\text{-}NO_2\text{-}C_6H_4,3\text{-}NO_2\text{-}C_6H_4,3\text{-}NO_2\text{-}C_6H_4,3\text{-}NO_2\text{-}C_6H_4,3\text{-}NO_2\text{-}C_6H_4,3\text{-}NO_2\text{-}C_6H_4,3\text{-}NO_2\text{-}C_6H_4,3\text{-}NO_2\text{-}C_6H_4,3\text{-}NO_2\text{-}C_6H_4,3\text{-}NO_2\text{-}C_6H_4,3\text{-}NO_2\text{-}C_6H_4,3\text{-}NO_2\text{-}C_6H_4,3\text{-}NO_2\text{-}C_6H_4,3\text{-}NO_2\text{-$

Scheme 37 Graphene oxide-catalyzed synthesis of dihydropyrano(c) chromenes 74 by the reaction of aryl glyoxal 1 with 4- hydrox-ycoumarin 72 and malononitrile $73.^{67}$



Scheme 38 Pyrano(c)chromenes 74 synthesis in the presence of ammonium dihydrogen phosphate. 68

cyanoacetate and methyl cyanoacetate and cyanoacetamide favoured the enol product 83 (Scheme 49).⁷⁵ This assembly was also considered to follow the same mechanistic pathway as explained in the case of other equivalent functionalities starting from Knoevenagel condensation to form a Michael acceptor **oa** followed by 1–4 addition, thereby generating the open chain intermediates **ob** and **od**, which subsequently undergo cyclization intramolecularly to yield the desired products (Scheme 50).



Scheme 39 Synthesis of pyrano(c)chromenes 75 via ammonium acetate-catalyzed reaction in the presence of a green solvent.⁶⁹



Ar= Ph,4-BrC₆H₄,4-ClC₆H₄,4-FC₆H₄,4-MeOC₆H₄,4-NO₂C₆H₄,3-MeOC₆H₄,3-BrC₆H₄, 3,4-(MeO)₂C₆H₃,2,5-(MeO)₂C₆H₃,3,4-(OCH₂O)C₆H₃,4-OH-3MeOC₆H₃

Scheme 40 Pseudo-three-component reaction to yield the pyranofused pyrimidines derivative **75** under DABCO or ZrOCl₂·8H₂O catalysis.³⁵





Scheme 41 Organocatalyzed reaction of (PPINO) to yield benzo[5,6] chromene 76 using a green solvent.⁷⁰



 $Ar = C_6H_5, 4 - BrC_6H_4, 4 - CIC_6H_4, 4 - FC_6H_4, 4 - MeC_6H_4, 3 - MeOC_6H_4, 4 - O_2NC_6H_4$

Scheme 42 Microwave-assisted reaction to afford 2-amino-4-aroyl-4H-benzo[h]chromene-3-carbonitriles 78 using Mg–Al hydrotalcite.⁷¹

Khaligh in 2017 synthesized 2-amino-4*H*-benzo[g]chromenes 82 using the same tactic of a condensation–Michael addition reaction by stirring aryl glyoxal **1**, malononitrile 73, and 2 hydroxynephthaquinone **81** with the catalyst poly(N-vinylimidazole), *i.e.* PVIm, for 2 h in refluxing ethanol. The resulting



Scheme 43 Mechanism for the formation of 2-amino-4-aroyl-4H-benzo[h]chromene-3-carbonitrile 78.



Scheme 44 Microwave-assisted protocol for the synthesis of fused pyrone 80.⁷²



Scheme 45 Synthesis of fused pyrans 74/74a using a microwave technique in the presence of ethanol.⁷²

product showed antibacterial activity against *Escherichia coli* at 32 mg cm⁻³ (Scheme 51).²⁷

In 2014, Khodbakhshi's group successfully executed the three-component reaction of 4-hydroxycoumarin 72, aryl glyoxal 1, and malononitrile 73 to access pyrano[3,2-c]coumarins 74 with an aroyl group in excellent yield with a high degree of purity in the presence of Mohr's salt. The overall reaction process was simple, facile, atom economical, and environmentally beneficial (Scheme 52).⁷⁶

In the same year, Khodbakhshi's group repeated a similar three-component reaction protocol but replacing Mohr's salt with TiO_2 nanoparticles. Their process involved the coupling of **1** with malononitrile **73** and **72** in the presence of a catalytic amount of TiO_2 nanoparticles to give a novel family of

pyranochromenes 74 in excellent yield. Their reaction was both environmentally feasible and economically cost effective since it utilized a greener solvent, and reusable and safer catalyst (Scheme 53).⁷⁷

Marjani and co-workers revealed the synthetic utility of aryl glyoxal by bringing together substituted aryl glyoxal **1** in a reaction vessel with 4-hydroxyquinolin-2(1H)-one **79** and ethyl cyanoacetate **84** in the presence of the catalyst TPAB in a water/ ethanol system at reflux. This assembly yielded a series of ethyl 2-amino-4-benzoyl-5-oxo-5,6-dihydro-4*H*-pyrano[3,2-*c*] quinoline-3-carboxylate **85** compounds (Scheme 54).⁷⁸

Aryl glyoxal monohydrate as the same starting material was explored by Ahmad *et al.* in 2018, with malononitrile **73** and **1**,3-diketones **38** in the presence of the catalyst L-proline in ethanol solvent for the facile construction of *4H*-chromenes, namely 2-amino-4-aroyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile **86** (Scheme 55).⁷⁹

M. Taheri and R. Mohebat in 2020 proposed a unique greener and environmentally friendly one-pot four-component protocol for the synthesis of pyrazolo[4',3':5,6]pyrano[2,3-c]phenazin-15-yl)methanone 88 scaffolds in a solvent-free medium using nano Fe₃O₄(a)TiO₂-SO₃H as the catalyst under microwave monitoring at 75 °C. The major benefit of this green synthetic protocol was the mild reaction conditions, high product yield, fast reaction time, solvent-free condition, low energy demand, and economic affordability (Scheme 56).80 The underlying mechanism for the following protocol starts from the tautomerization of 2-hydroxy-1,4-naphthalene-1,4-dione 65 to form an intermediate, which then undergoes condensation with benzene-1,2-diamine 66 resulting in the formation of benzo[a]phenazine-5-ol pa. After this, Fe_3O_4 (a)TiO₂-SO₃H catalyzes the formation of pyrazolo[4',3':5,6]pyrano[2,3-c]phenazine-15-yl) pd, which after Michael addition with 1 undergoes cyclization-dehydration to finally give the desired product 88 (Scheme 57).



Scheme 46 Reaction pathway for the formation of fused pyran 74.



R=H, 4-CI, 4-Br, 4-F, 4-Me, 4-OMe, 4-OH, 3,4-(OMe)₂

Scheme 47 SBA-15-catalyzed green synthesis of 2-amino-4-aroyl-5oxo-5,6-dihydro-2*H*-pyrano[3,2-c] **80**.⁷³



Scheme 48 Three-component synthesis of 4-aroyl-4*H*-benzo[g] chromene 82.⁷⁴

2.4. Synthesis of furo-pyran

In 2020, Boris' group explored a new one-pot protocol for the synthesis of various substituted 2-aminofuran moieties **90** based on the multicomponent reaction of 3-hydroxy-4*H*-pyran-4-ones **89**, a-ketoaldehydes **1**, and methylene active nitriles **73**. The formation of 2-aminofuran was a distinguishing aspect of this protocol in contrast to the previously reported literature, which resulted in the formation of 2-aminopyrans. The excellent yield, high atom economy, simple work-up procedure, and maintenance of mild reaction conditions for the reaction to proceed were all major benefits of this protocol (Scheme 58).⁸¹ The suggested mechanism (Scheme 59) begins with the Michael acceptor generation from the C–H active site of malononitrile **73** reaction with **1**. The allomaltol anion (deprotonated by triethylamine) adds to

the intermediate, thus forming an adduct **qa**. This adduct undergoes deprotonation to form an oxoanion **qb** followed by cyclization at the nitriles **qc**, finally leading to furo-pyran as the final product **90**.

In 2021, Mirza and co-workers proposed a methodology for the synthesis of a novel, green, and highly efficient β -amidoaroyl carbonyl derivatives **91** *via* a three-component, one-pot reaction of dimedone **38**/barbituric acid **19** derivatives, aryl glyoxal **1**, and amides **57a** in a deep eutectic solvent of choline chloride/urea (DES). The utilization of biodegradable ingredients, rapid reaction times, and high product yields established this process as effective and ecologically friendly (Scheme 60).⁸²

In 2013, Karami and co-workers regiospecifically synthesized amido-substituted furo[4,5-c] coumarins **92** by reacting aryl glyoxal, 4-hydroxy coumarin **72**, and benzamide **57** in a single pot through coupling, followed by cyclization in acetic acid at reflux. The product showed selectivity over isoxazolo-substituted coumarin. The plausible mechanism for the reaction started from the condensation of **1** and **57** to generate an intermediate, followed by its intramolecular cyclization and then dehydration to give the final product (Scheme **61**).⁸³

Huang and co-workers reported an efficient Lewis acidcatalyzed reaction for synthesizing diverse furo[3,2-*c*]coumarins **93** and **94** by exploiting aryl glyoxal, 4-hydroxycoumarins **72**, and methylketone in 1,4-dioxane at 130 °C using 20mol% Zn(OTf)₂. The substrate scope of the protocol showed that both electron-rich and electron-neutral aryl glyoxal favoured an annulation reaction, while that with an electron-withdrawing group, such as the NO₂-bearing aryl ring of aryl glyoxal, did not yield any product. When the strategy was extended by involving aliphatic cyclic ketones, like cyclochexanone, to diversify the products, the use of Cu(OTf)₂ in the solvent dichloroethane (DCE) at 110 °C in a sealed vessel gave the best results, with a 76% yield (Scheme 62).⁸⁴ The proposed reaction design (Scheme 63) follows the pathway initially from the loss of a water molecule through the condensation reaction of **1** and **72** **RSC** Advances



Scheme 49 MCR-based synthesis of the different pyran derivatives 74, 82, and 83.75



Scheme 50 Mechanisms for 74 and 83 formation through Knoevenagel condensation with a subsequent intramolecular cyclization.

to give the intermediate **ra**, which reacts with the enol form of acetone in a Michael-type addition to produce the second intermediate **rb**. The electrophilicity of the condensed adduct **ra**



Scheme 51 Poly(*N*-vinylimidazole)-catalyzed synthesis of 2-amino-4*H*-benzo[*q*]chromenes 82.²⁷

is enhanced by the $Zn(OTf)_2$. Finally, dehydration preceded by an intramolecular cyclization leads to the formation of furo[3,2*c*]coumarin **93**.

Next, a facile and one-pot novel methodology was described by Melekhina's group for the synthesis of furan-2(5*H*)-one derivative **10** with indole **9** as a structural fragment. The reaction was carried out in two steps, starting with the interaction of 4-methoxy aryl glyoxal **1**, indole, and Meldrum's acid **8** in acetonitrile with triethylamine at reflux, followed by a further acidic reflux using acetic acid. The formation of a new oxygen heterocycle was considered to occur through the aryl glyoxal condensation with Meldrum's acid followed by Michael



Scheme 52 Three-component synthesis of pyrano[3,2-c]coumarins 74.⁷⁶



Ar= Ph,4-F-Ph,4-Cl-Ph,4-Br-Ph,3-NO₂-Ph,4-NO₂-Ph, 3-MeO-Ph,1-Naphthyl,2-Naphthyl

Scheme 53 TiO₂ nanoparticles-catalyzed synthesis of pyrano[3,2-c] coumarins 74.⁷⁷

addition to give the indole and finally cyclization occurs with the elimination of CO_2 (Scheme 64).⁴⁶

After this, Boris *et al.* replaced the indole with hydroxycoumarin derivative **95** to access the novel furylacetic acid moiety **96**. The pronounced advantage offered by the use of the photosensitizer and the biologically important furo-coumarin derivative synthesis is that the formation was possible through a single-pot approach using easily available staring materials with no harsh reaction conditions (Scheme 65).⁸⁵

In 2021, Lichitsky and co-workers described a simple one-pot approach for synthesizing a regiospecific 4H-furo[2,3-h]chromene **98** core using aryl glyoxal. The proposed method was based on a multicomponent reaction of aryl glyoxal, flavones **97**, and Meldrum's acid **8**. The mild reaction conditions, atom economy, and simple work-up procedure were all advantages of this method, which eliminated the need for chromatographic purification (Scheme 66).⁸⁶

In 2018, Chang *et al.* reported the formation of the highly functionalized furan derivatives **99** and **100** *via* aryl glyoxal, phenols **44**, and 4-hydroxycoumarin **72** in the presence of $MeSO_3H$ or $FeCl_3$ as a catalyst. By altering the reaction media, a range of furan derivatives with various substitution patterns were produced. This method's atom-economical traits and



 $A = 4 - OC_{6} - 14 + C_{6} - 14 + OMeC_{6} - 14 + OMeC_{6}$

Scheme 55 Formation of 2-amino-4-aroyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile **86**.⁷⁹

moderate conditions were consistent with the idea of contemporary green chemistry. In a short time, a substantial number of heterocycles of biological importance were created from this protocol (Scheme 67).⁸⁷

Chang *et al.* developed an effective method for synthesising furo[3,2-*c*]-coumarins utilizing **1** in multicomponent tandem reactions driven by FeCl₃ or ZnCl₂. As per the reports, this reaction between 4-hydroxycoumarin **72** and allyltrimethylsilane **101** in toluene produced two C–C bonds and one C–O bond in compounds **103** and **104**. This approach provided the desired furo [3,2-*c*]coumarin structures in good to outstanding yields. Some notable traits of the method include the ease with which the starting materials may be obtained, the great functional group tolerance, and the outstanding atom economy (Scheme 68).⁸⁸

Next in 2019, the synthetic application of aryl glyoxal was further explored to construct novel moieties of biological importance. Komogortsev *et al.* devised a new convenient method to obtain 7-oxo-7*H*-furo[3,2-*b*]pyran-3-ylacetic acid **106** through the reaction of pyranone **105**, Meldrum's acid **8**, and aryl glyoxal **1** as a carbonyl compound in one pot. The reaction was accomplished by the catalysis of Et_3N in the presence of MeCN at reflux, starting from the condensation of **1** with Meldrum's salt, thus setting the intermediate **sa** possessing an aroyl fragment as the starting material for the recyclization in acidic medium to form the substituted furan-3-acetic acid **106** (Scheme 69).⁸⁹ The distinguishing feature of the protocol was the application of the Kojic acid analogue 3 hydroxy-pyran-4-one **105**.

Lichitsky *et al.* in 2020 developed a systematic telescopic protocol to synthesize substituted furan 2(5H)-one derivatives containing the 4*H*-chromen-4-one fragment *via* the multicomponent reaction of 3-(dimethylamino)-1-(2-hydroxyaryl)prop-2en-1-one **37**, aryl glyoxal **1**, and Meldrum's acid **8**. The simultaneous production of 4*H*-chromen-4-one and furan-2(5*H*)-one fragments **107** in one synthetic stage was a distinguishing



Scheme 54 Synthesis of ethyl 2-amino-4-benzoyl-5-oxo-5,6-dihydro-4*H*-pyrano[3,2-c]quinoline-3-carboxylate 85 through 4-hydrox-yquinoline-2(1*H*)-one.⁷⁸





aspect of the suggested methodology. This approach was also atom economical along with having other virtues, such as mild reaction conditions and a simple work-up approach, which eliminates the need for chromatographic purification (Scheme 70).⁹⁰ In 2022, Ali *et al.* developed a straightforward, facile, and efficient approach for the synthesis of novel thioether-linked coumarin-fused furans *via* a $Sc(OTf)_3$ -catalyzed one-pot combination of aryl glyoxal **1**, 4-hydroxycoumarin **72**, and different aromatic thiols **108**. This approach could yield either

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19 R= H,CH_{3.} R₁= NO₂,Cl,Br,CH₃ R₂= CH₃,C₂H₅,Ph. X= O,S

Scheme 60 Synthesis of β -amido-aroyl carbonyl 91 in a deep eutectic solvent.⁸²

a three-component thioether-linked coumarin-fused furan **109** or a two-component furo-coumarin product **110**, depending on the thiols. The key attributes of this approach were its broad substrate range, good to exceptional yields, and products with multiple pharmaceutically significant motifs (Scheme 71).⁹¹

For the first time, the synthesis of substituted 2-aminooxazoles containing the 3-hydroxy-4*H*-pyran-4-one moiety **111** was accomplished by Komogortsev's group in a one-step method *via* the multicomponent condensation of allomaltol derivatives **105** with α -ketoaldehydes **1** and cyanamide **70**, followed by an acid-catalyzed recyclization into substituted furo [3,2-*b*]pyrans **112**. The formation of the 2-aminooxozole core as opposed to a urea-containing condensed furan was the distinctive feature of this approach (Scheme 72).⁹²

Ar= Ph,4-FC₆H₄,4-BrC₆H₄,4-NO₂C₆H₄,4-OMeC₆H₄,3-OMeC₆H₄, 1-naphthyl,2-naphthyl.

Scheme 61 Benzamide 57-derived amido-substituted furo[4,5-c]coumarin 92 synthesis.83

Scheme 62 Lewis acid-catalyzed protocols for yielding furo[3,2-c]coumarins 93 and 94.84

Scheme 63 Mechanism showing furo[3,2-c]coumarin synthesis through a condensation reaction followed by an intramolecular cyclization.

Scheme 67 Synthesis of 4-hydroxycoumarin 72-derived functionalized furans 99 and 100.87

Scheme 68 Tandem reactions leading to diverse furo[3,2-c] compounds 103 and 104 using allyltrimethylsilane 101 and toluene 102, respectively.⁸⁸

 $Ar = 4-OHC_6H_4, 4-OMeC_6H_4, 3, 4, (OCH_2O)C_6H_3$

 $Ar= C_6H_5, 4-Me-C_6H_4, 4-Cl-C_6H_4, 4-F-C_6H_4, 4-OMe-C_6H_4, 3-OMe-C_6H_4, 3-OMe-$

2.5. Miscellaneous reactions

A novel method was developed by Pogaku's team for the production of oxazoles **114** from methyl ketones **24** and TosMIC (tosyl methyl isocyanide) **113** using a self-sorting domino

reaction approach. TosMIC was used as an ammonium surrogate in contrast to its typical reactivity as a C–N C synthon in the production of oxazoles **114** (Scheme 73).⁹³ The technique is appealing due to its ease of operation, the wide availability of

Scheme 72 Synthesis of substituted furo[3,2-b]pyrans 112 derived from allomattol 111.92

the starting materials, absence of bases and metals, and the production of C–N and C–O bonds with excellent yields.

Nagarjuna Babu's group reported the simple and efficient syntheses of oxazoles **118** and furocoumarins **117**. The essential step in these transformations comprised the *in situ* formation of *N*-acyliminiumion (NAI) precursors **116** from aryl glyoxal and 2-pyrrolidinone **115** in the absence of a catalyst or solvent, followed by their further transformations aided by trifilic acid in the same vessel. It was demonstrated experimentally that the special exocyclic proto-solvated *N*-acyliminium ion was involved in the reaction. Additionally, the results of the fluorescence and UV-visible experiments revealed that a limited number of the compounds emitted blue light when exposed to light in EtOH in

4-FC₆H₄,4-ClC₆H₄,4-lC₆H₄,3MeSC₆H₄

Scheme 73 Synthesis of oxazole 114 under a domino reaction through tosyl methyl isocyanide 113.

the 404–422 nm wavelength range (Scheme 74).⁹⁴ An insight into the mechanism initially revealed the formation of the *N*acyliminium ion (NAI) precursor **ua** from **1** and 2-pyrrolodinone **115** under acid catalysis. There were two probable cyclization routes. In route **a**, the attack of acetonitrile on the iminium intermediate **ub** leads to the formation of the nitrilium ion **uc**, which undergoes cyclization to form the final product **118** through the involvement of an adjacent carbonyl group; while in route **b**, neutralization of the nitrilium ions by water molecules generate the bisamide **ud**, which subsequently undergoes cyclization, losing a water molecule to yield the desired product **118** (Scheme 75).

In 2008, Valverde *et al.* reported the use of aryl glyoxal **1** with aniline **119**, cyclohexyl-isocyanide **120**, and trichloroacetic acid **121** in dichloromethane, passing through a 3 Å molecular sieve to afford the oxazolone derivative **122** through the Ugi multicomponent reaction pathway group. The remarkable feature of the strategy was the carbonic acid function of the trichloroacetyl group (Scheme 76).⁹⁵

2.6. *In situ* domino reactions of aryl glyoxal to afford oxygen heterocycles

A facile, straightforward, novel, and highly efficient protocol was given by Borah and co-worker in 2016 to obtain

Scheme 75 Reaction pathway for the synthesis of the substituted oxazoles **118**.

functionalized furo[3,2-c] coumarins **123** from 4-hydroxy coumarins **72**. The reaction was allowed to proceed by reacting aldehyde/aryl methyl ketone **24** with **72** in the

 $R_2 = C_6H_5, p-MeC_6H_4, p-CIC_6H_4, C_4H_4S$

Scheme 77 Furo[3,2-c]coumarin 123 synthesis through *in situ*-generated phenyl glyoxal.⁹⁶

presence of molecular iodine in DMSO at 80 °C. DMSO here works as a solvent as well as an oxidizing agent to recycle the iodine during the reaction process (Scheme 77).⁹⁶ The plausible mechanism of the reaction is that initially phenylglyoxal 1 is formed from phenyl methyl ketone 24 *via* sp³-CH activation and oxidation, and is subsequently allowed to react with 4-hydroxycoumarin 72 in the presence of iodine to form the intermediate vb by eliminating a water molecule. Nucleophilic attack by the second molecule of 4-hydroxycoumarin on the intermediate vb yields the final product 123 (Scheme 78).

Cheng's group prepared the highly dense benzofuran 23 by bringing aryl glyoxal monohydrate 1, phenol derivatives 22, and indole 21 together in a reaction vessel with molecular iodine in a catalytic amount and DMSO as a solvent. Later, aryl glyoxal 1 was replaced with methylketones 24 and further tested by

Scheme 78 In situ domino synthesis of furo[3,2-c]coumarin 123 by sp³-CH activation and oxidation.

changing the nucleophiles to thiophenol and 1,2,4-trimethoxybenzene, etc. in place of indole (Scheme 79).7

In 2012 Jian and colleagues proposed a novel and highly efficient protocol to synthesize polysubstituted oxazole derivatives 125 from simple and easily available starting materials, that is by reacting methyl ketone 24, benzoin 124, and ammonium acetate via the convergent integration of two "self-labour domino sequences". This reaction has wide application in medicinal and life science chemistry (Scheme 80).97

Zhao and co-workers in 2018 proposed a novel path for the synthesis of fused heterocycles by employing an iodinepromoted fragment assembly method. They formulated

pyrazolone-oxepines-pyrazoles 128 by the reaction of phenylhydrazine 126, aryl methyl ketones 24, and acetoacetate ester 127 using molecular iodine at 140 °C in the presence of TfOH, and also explored the application of five-component reactions. Acetoacetate ester engaged in two crucial steps: formation of the 3-methyl-5-pyrazolone skeleton and formation of the C(sp³)-O bond (Scheme 81).98

An I₂-promoted domino oxidative cyclization method was proposed by Gao and colleagues in 2013 from easily available starting materials, methyl ketones 24, and benzylamines 12 at 100 °C in the absence of any metal or peroxide catalyst to afford

R= Ph,4-MeC₆H₄,4-NO₂C₆H₄,4-CIC₆H₄,2-Furyl,2-Thienyl

Scheme 80 Domino reaction leading to benzoin 124-derived oxazole Scheme 82 Oxazole 129 synthesis through methyl ketone 24 and benzylamine 12.98

Scheme 81 Synthesis of pyrazolone-oxepines-pyrazoles 128 through phenylhydrazine 126, acetoacetate ester 127, and in situ-generated phenyl glyoxal 1.98

125.97

Review

Scheme 83 Formation of oxazole 129 through a domino oxidative cyclization.

Scheme 84 Synthesis of 3-(furan-3-yl or4-yl) indole derivative 130 through 1,3-diketone 18, indole 15, and methylketone 24.99

2,5-disubstituted oxazole **129**. This reaction occurred with a metal-free catalyst and involved the breaking of C–H bond and the assembly of C–N and C–O bonds (Scheme 82).¹⁰⁰ As the reaction involved I₂-promoted dual sp³ C–H bond functionalization, its mechanism involved converting acetophenone into the α -iodoacetophenone intermediate **A** by utilizing I₂, which was further oxidized by DMSO to yield the phenylglyoxal intermediate **1**. Further, benzylamine **12** reacted with **1** to form the imino-derivative **wa** or its enolized form **wb**, which underwent intramolecular cyclization *via* an oxygen atom at the double bond, resulting in the formation of another intermediate **wc. wc** deprotonated in the presence of excess iodine to yield the disubstituted oxazole **129** (Scheme 83).

In 2011, Yang and colleague performed a convergent and linear domino reaction for the first time from easily available inexpensive substrates, like methyl ketone **24**, indole **15**, and 1,3-dicarbonyl **18**, to access the 3-(furan-3-yl or 4-yl) indole derivative **130** *via* a direct two-step process without the need for purification of the intermediate. This reaction has wide applications in synthetic and medicinal chemistry due to its operational simplicity (Scheme 84).⁹⁹

3. Conclusion

As a unique molecule with robust applications in organic synthesis, ranging from C–C bond formation reactions to the

synthesis of heterocycle libraries, aryl glyoxal is an efficient and easily accessible building block that has been extensively used in the past decade. Exploitation of this commercially available precursor all over the world by chemists has produced many novel functionalized moieties that are both pharmacologically and biologically beneficial to mankind. The different synthetic protocols of aryl glyoxal along with amines and nitrogen heterocycles in multicomponent reaction systems gives rise to highly complex synthetic diversity in the products, attracting researchers to think beyond the current ambit towards new horizons.

After the gigantic number of nitrogen heterocycles, oxygen heterocycles are the second category approved for clinical use as medicinal drugs. Their synthesis through different resources has raised the attention of researchers to a significant level, but there is still a huge gap between the synthetic methodologies and application patterns of nitrogen and oxygen scaffolds. The lower reactivity and somewhat complicated biomimicking process compared to nitrogen members are the possible reasons behind their limited number of applications to date in bio-systems. Further, researchers have brought phenyl glyoxal into action using it either as a substitute for mono-functional aldehydes for forming a structural backbone by adding carbon to the target structure or as an oxygen donor in the product molecule. The optimum use of phenyl glyoxal with new combinations of reagents possessing multiple functionalities is still awaited. The mounting up of oxygen heterocycles' applications is conditional on the proper execution of advanced tools and techniques for their strategic biosynthesis followed by extensive tests and trials.

Conflicts of interest

There is no conflict to declare.

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