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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 used extensively 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.

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 an easy and efficient methodology 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 to a significant level of 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 a chemical library of novel moieties.⁶ MCRs are the

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only way to meet the intermittent demands of advanced technology-driven research, such as in 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, reagent- and substrate-based multicomponent reactions have recently been reported in high numbers.^{7,8}

Heterocycles occupy a key functional position in many living processes and therefore they 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 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 screened for antianaphylactic, diuretic, spasmolytic, anticoagulant and anticancer properties, *etc.*^{9–11} Alkaloids possessing pyranoquinoline as the structural unit feature anti-microbial 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 kallolides,¹⁵ in fragrances, and dye-like commercial products. The furan derivative furoquinolinone blocks the potassium channel Kv1.3, which is the target for

immunosuppressive therapy in the treatment of auto-immune diseases and transplantation.¹⁶ Likewise, the pyrazoline derivative containing a furan moiety shows anti-malarial activity against *Plasmodium falciparum*.¹⁷ Isoxazoles, as oxygen–nitrogen heterocycles, add to the synthetic utility of oxygen heterocycles as they offer anti-tubercular,¹⁸ anti-inflammatory,¹⁹ and COX-2 inhibitor properties,²⁰ and are thus a constituent of many therapeutic drugs. The newly synthesized chroman derivative was tested and found to show potential anti-convulsant²¹ activity. One of the benzopyranone derivatives, Enasculin, is a pharmacologically tested neuronal activator KA 672-HCl,²² which works as an antagonist by simultaneously activating several neurotransmitters that are deactivated in dementia. Furthermore, the structural presence of benzo[*g*]chromene in many useful natural products with reported anticancer activity and the synergistic effect of β -lapachone with taxol against tumour growth,^{23–25} *etc.*, are driving the search for newer strategies to synthesize oxygen heterocyclic moieties in economical and environmentally friendly conditions. Therapeutic functions of some O-heterocycles are illustrated in Fig. 1.

Revolutionary advancements in the physiological studies of living beings for the sake of mankind and the environment are due to the 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 molecules 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 a distinctive building block for the synthesis of heterocyclic and carbocyclic compounds. The electron-withdrawing ketone group makes aryl glyoxal more reactive than benzaldehyde and allows the site to be open to nucleophilic attack followed by cyclisation in various ways. Furthermore, 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-aryl chromene derived from phenyl glyoxal hydrate and naphthyl glyoxal, which has shown anti-bacterial properties by inhibiting *Escherichia coli* growth with a minimum inhibitory concentration (MIC) of 32 $\mu\text{g cm}^{-3}$.²⁷ 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 IC₅₀ value of 3.9 $\mu\text{g mL}^{-1}$.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 starting materials exhibits α -glucosidase



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Ambassador of India (2020); RSC Best Cited Author Certificate (2018); Start-up Research grant (UGC) (2012); Indian Academy of Sciences-Summer Research Fellowship 2012; Senior Research Fellowship (2009); Junior Research Fellowship (2007); DST- Pre-Doctoral Fellowship (2006); and Post Graduate Merit Scholarship (2002 and 2003). Dr Khan has published more than 40 research papers in various international refereed journals of repute, including *J. Org. Chem. (ACS)*, *ACS Omega (ACS)*, *Tetrahedron (Elsevier)*, *Tetrahedron Letters (Elsevier)*, *Carbohydrate Res. (Elsevier)*, *RSC Advances (RSC)*, *New J. Chem. (RSC)*, *ChemistrySelect (Wiley)*, *Synthetic Communication (Taylor & Francis)*, *Curr. Org. Chem. (Bentham Sciences)*, and *J. Heterocycl. Chem. (Wiley)*. His current research interests include diversity-oriented MCRs, the development of novel synthetic methodologies, heterocyclic chemistry, carbohydrate chemistry, and target-oriented synthesis for biologically significant molecules.

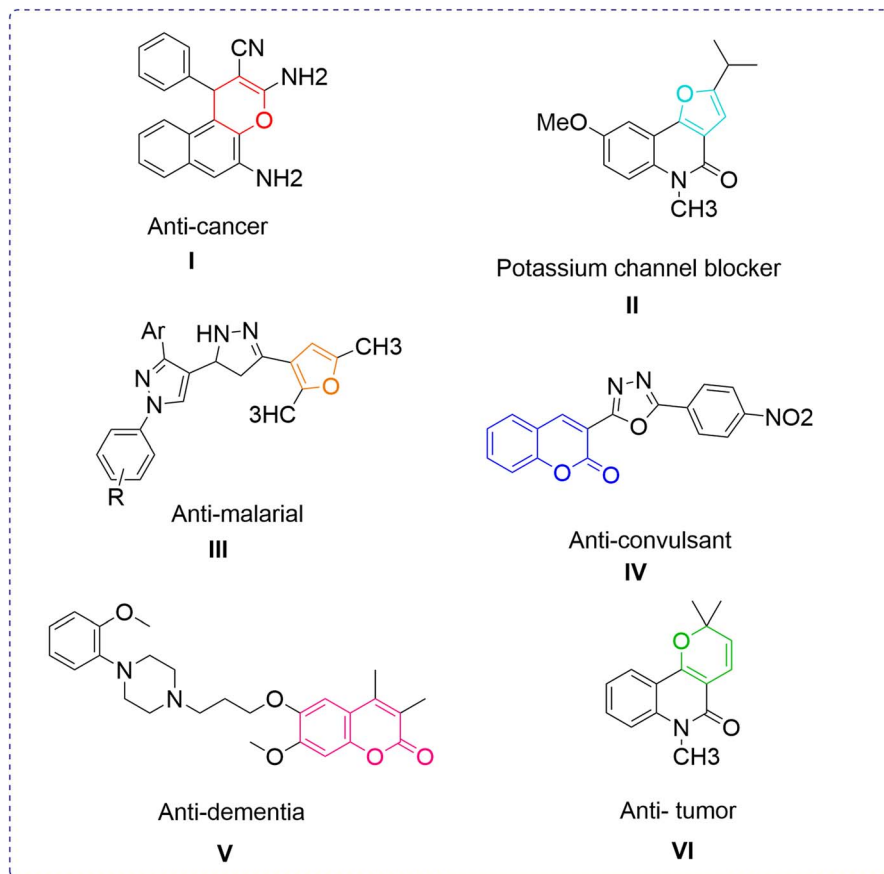


Fig. 1 Some biologically active O-heterocycles.

inhibitory activity,³¹ thus aiding the drug-development process for hyperglycemia and Type 2 diabetes mellitus (T2DM). 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 aryl group-substituted pyrano[3,2-*c*]chromene and benzo[*g*]chromene by employing phenyl glyoxal due to their divergent properties.³³ 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 precursor development.³⁴ Phenyl glyoxal was further used in the synthesis of a furo(2,3-*b*)furan moiety³⁵ mimicking drug candidates like BrecaNavir (GW640385), an HIV inhibitor,³⁶ and Darunavir (TMC-114),^{37,38} another HIV-1 protease inhibitor. A coumarin-glyoxal hybrid, namely the tartrate salt of a Mannich base bearing coumarin derivatives³⁹, was found to be an efficient contraceptive as it shows activity as both a spermicide and a microbicide. The compound was tested for spermicidal activity against non-oxynol (N-9),⁴⁰ 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 Metronidazole⁴¹ 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 as a key building block in multicomponent single-pot reactions.⁴²

In this review article, we intend to highlight the extensive use of the bifunctional building block known as aryl glyoxal monohydrate as the starting material in the construction of 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 cyclisation 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

Li *et al.* efficiently utilized aryl glyoxal **1** in the gold-catalysed three-component reaction with amine **2** and a terminal alkyne **3** to obtain substituted furans **4** through cyclisation in a nitrogen atmosphere with methanol as a solvent. This

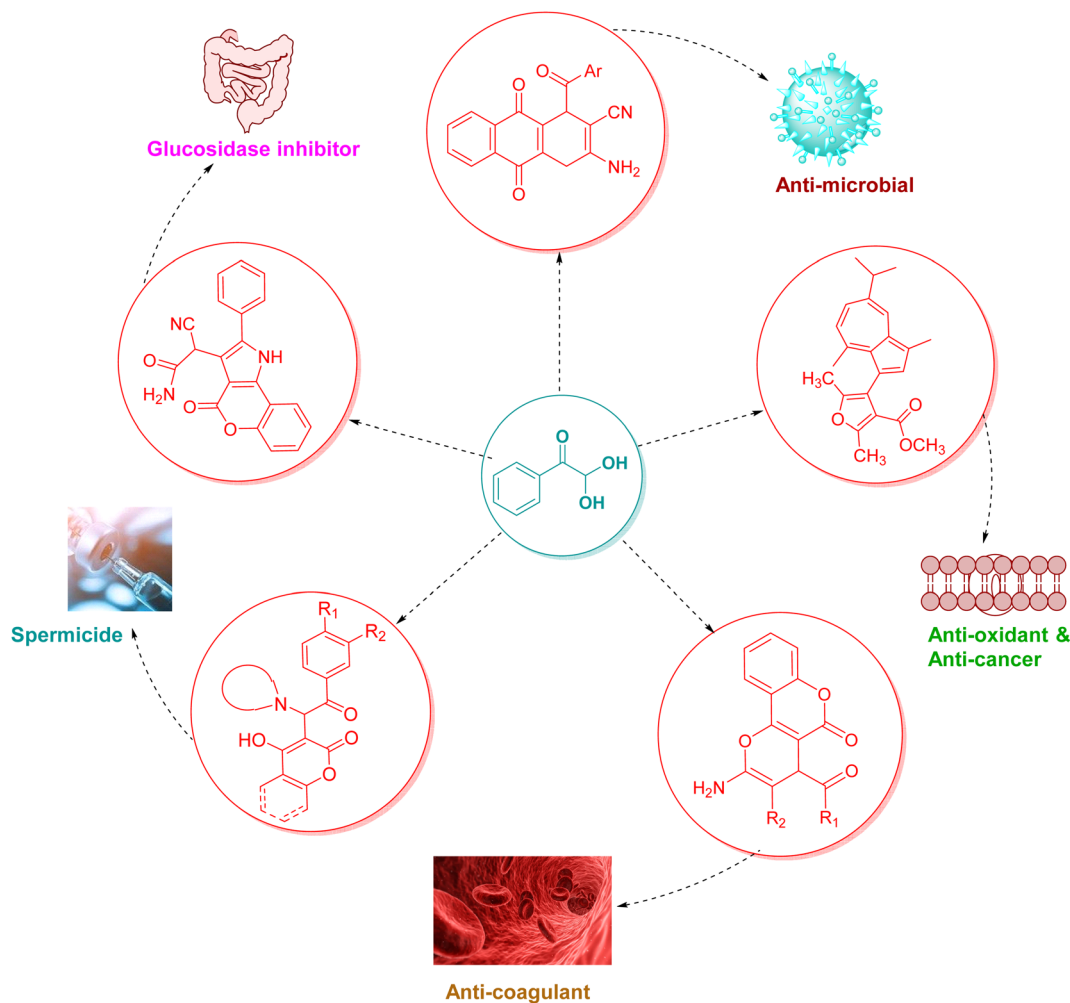
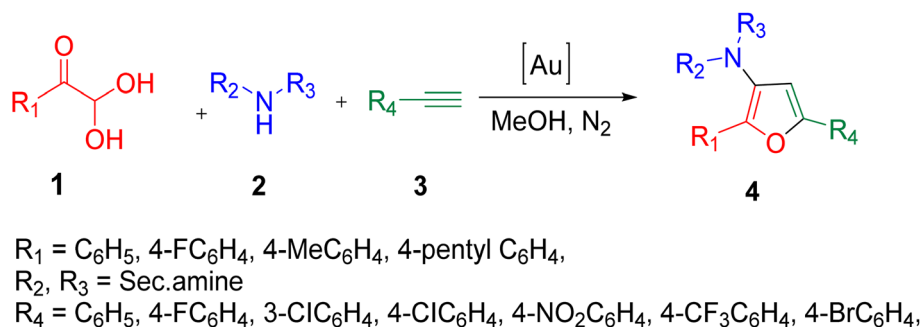


Fig. 2 Biologically active O-heterocycles obtained from phenyl glyoxal.

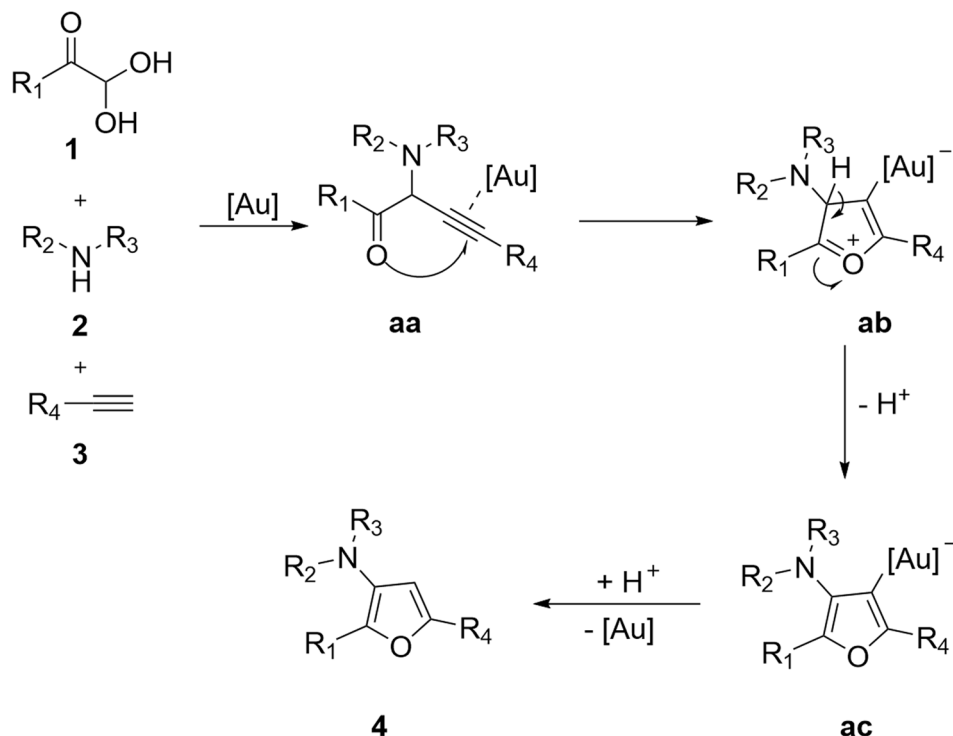
reaction provides an effective protocol for the preparation of synthetic and pharmacological derivatives of furan (Scheme 1).⁴³ The plausible mechanism of the protocol starts with the coupling of aryl glyoxal **1**, amine **2** and alkyne **3** in a Mannich–Grignard pattern to give a propargyl intermediate **aa**, which is followed by the attack of an oxygen lone pair on the electrophilic triple bond, forming a cation **ab**, leading to the final product

indolizines **4** through deprotonation and demetallation of **ac** (Scheme 2).

For the synthesis of isoxazolyl amino furo[3,2-*c*]quinolinone scaffolds **7**, Modugu and co-workers developed an efficient one-pot, three-component reaction of aryl glyoxal monohydrate, 4-hydroxy-1-methyl-2-quinolinone **6**, and 4-amino-3-methyl-5-styrylisoxazoles **5** under reflux conditions in an aqueous medium with a 5 mol% catalytic amount of *p*-TSA. The scheme



Scheme 1 Gold-catalysed three-component synthesis of furan derivatives **4**.



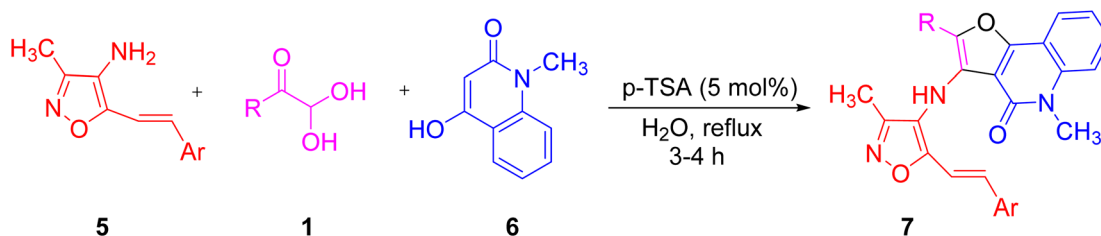
Scheme 2 Mechanism proposed to explain gold-catalysed furan synthesis.

was tested with different Lewis acids and organic acids, but *p*-TSA in water as the solvent was found to give the best results in terms of the time, yield and environmentally friendly protocol (Scheme 3).⁴⁴ The reaction mechanism (as shown in Scheme 4) starts from the *p*-TSA-catalysed 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 isomerisation with **bc**. The intermediate **bd** undergoes intramolecular cyclisation initiated by the acid to give the final product 7 through dehydration of **be** (Scheme 4).

For the synthesis of the furan-2(5*H*)-one derivative 10 with indole as a structural fragment, Komogortsev and his group

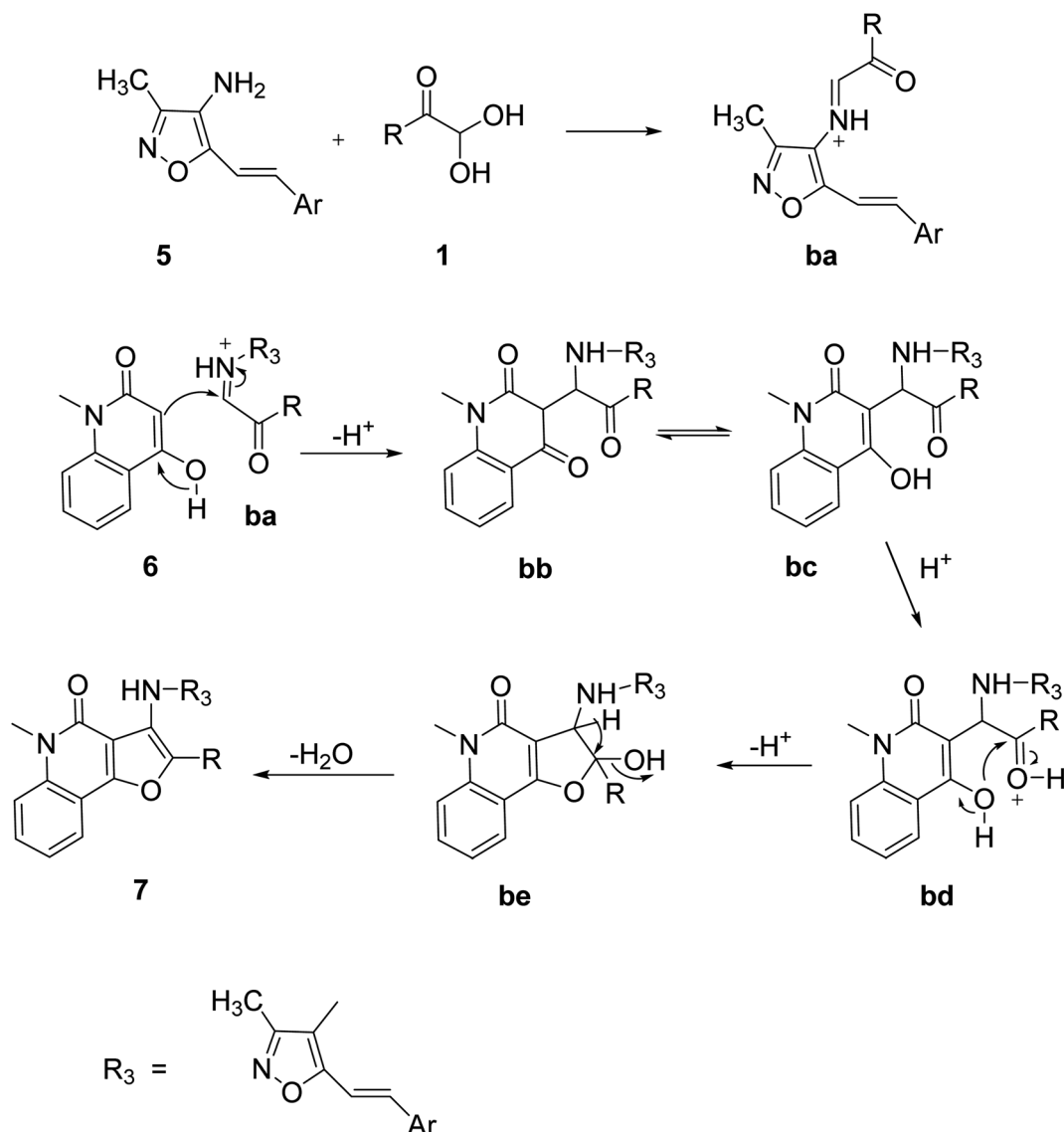
established a facile and one-pot novel methodology, which was completed in two steps starting with the interaction of aryl glyoxal 1, indole 9, and Meldrum's acid 8 in acetonitrile with triethylamine at reflux, followed by an acidic reflux using acetic acid (Scheme 5).⁴⁵ The formation of the new oxygen heterocycle is considered to go through the aryl glyoxal 1 condensation with Meldrum's acid to generate intermediate **ca** followed by Michael addition with the indole to give **cb** and finally cyclisation with the elimination of CO₂ to give 10 (Scheme 6).

Shahbazi-Alavi and co-workers demonstrated an environmentally friendly nano-catalysed synthesis of substituted furans. The target molecule 13 was afforded through the heterogeneous catalysis of aryl glyoxal 1, dimethylacetylenedicarboxylate 11, and primary amine 12 at room temperature

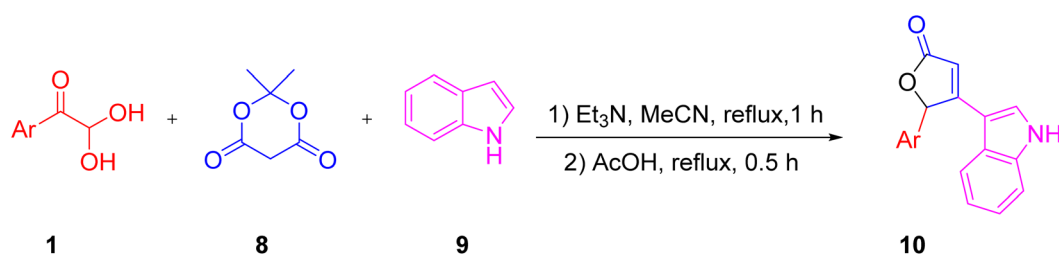


Ar = C₆H₅, 4-CH₃C₆H₄, 2-CH₃C₆H₄, 4-OCH₃C₆H₄, 2-OCH₃C₆H₄, 4-ClC₆H₄, 2-ClC₆H₄, 4-BrC₆H₄, 4-NO₂C₆H₄
 R = C₆H₅, 4-CH₃C₆H₄, 2-CH₃C₆H₄, 4-OCH₃C₆H₄, 4-ClC₆H₄, 2-ClC₆H₄, 4BrC₆H₄, 2-BrC₆H₄, 2-furyl, 2-thienyl, 3-pyridyl, CH₃, 4-OCH₃C₆H₄, 4-ClC₆H₄,

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



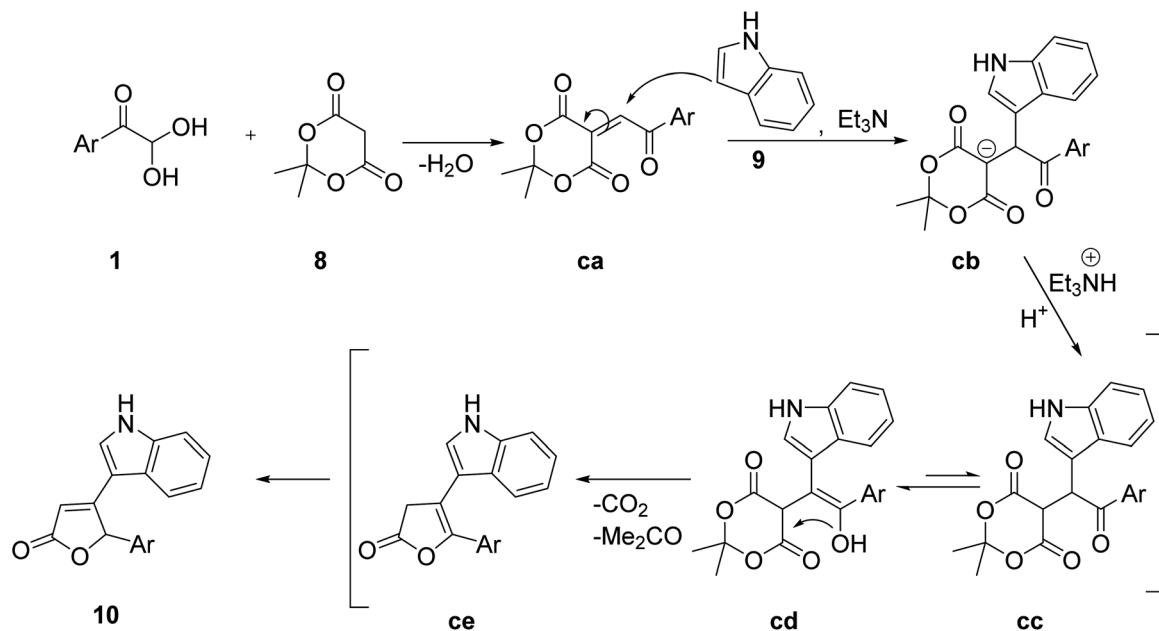
Scheme 4 Mechanistic explanation of the synthesis of isoxazolyl amino furo[3,2-c]quinolinone 7.



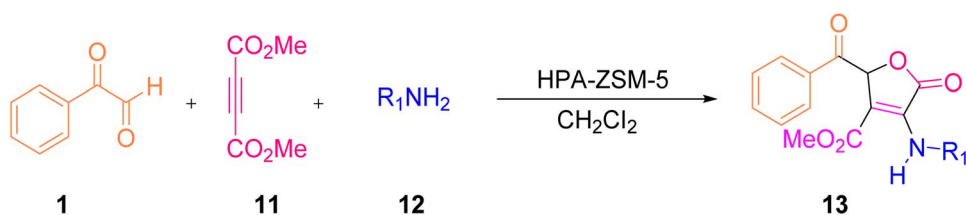
Scheme 5 Three-component synthesis of furan-2(5H)-one derivative 10 using Meldrum's acid 8.

using the HPA-ZSM-5 nano-catalyst in dichloromethane (Scheme 7).⁴⁶ 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 amino-butenedioate acts as a C-nucleophile and attacks the electron-

deficient 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). In 2021, the same protocol was also followed by Ebrahimi and co-workers,⁴⁷ this time using

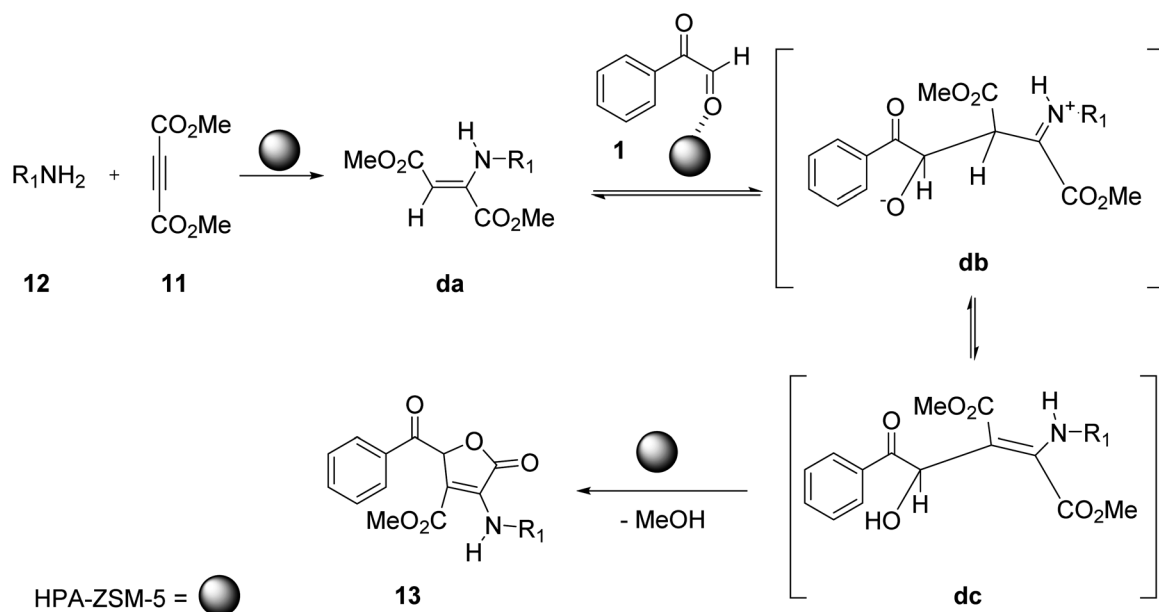


Scheme 6 Mechanism to explain the synthesis of furan-2(5H)-one **10** using indole **9**, Meldrum's acid **8**, and aryl glyoxal **1** as starting materials.



R_1 = 2-Methoxybenzylamine, 4-Methoxybenzylamine, 4-Methylbenzylamine, Benzylamine, 4-Fluorobenzylamine, Propylamine, 3,4-Dichlorobenzylamine.

Scheme 7 Nano-catalysed protocol for the synthesis of substituted furans **13**.



Scheme 8 Mechanistic pathway to explain the nano-catalysed synthesis of furan derivatives **13**.

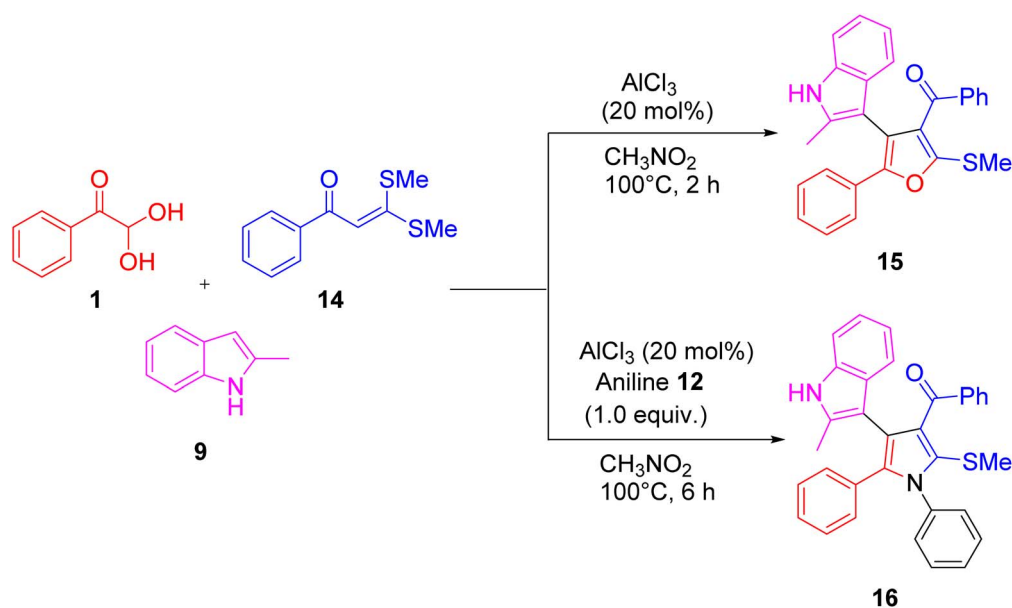
nano-CuO. This work gained popularity due to its ease of operation, facile and quick extraction of the product, quick response time, high yield, and low loading and re-utilisation of the catalyst.

Phenyl glyoxal **1** and α -oxoketene dithioacetals **14** with indoles **9** as the precursors were utilized by Liu *et al.* to create six multicomponent reactions, which were used to synthesize a variety of heterocycles, including quinolines, dihydrocoumarins, furans **15**, and pyrroles **16**. The discovery of these multicomponent reactions was made feasible by the coupling of bifunctional aldo-X reagents and α -oxoketene dithioacetals since these reagents contain a minimum of two reactive sites, therefore diverse substrates can be put together in different ways (Scheme 9).⁴⁸

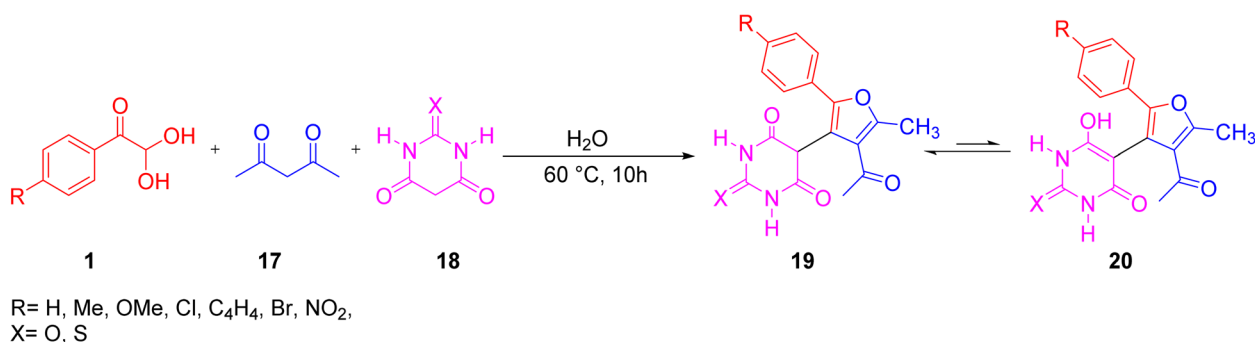
Dehghanzadeh and co-workers applied aryl glyoxal **1** for the fabrication of 5-(furan-yl)barbiturate and 5-(furan-3-yl)thiobarbiturate **19** *via* a one-pot assembly of **1** with

acetylacetone **17** and barbituric acid and thiobarbituric acid **18**, respectively, in water at 60 °C (Scheme 10).⁴⁹ The plausible mechanism starts with the Knoevenagel reaction between **1** and **17** to give intermediate **ea**, which undergoes a 1,4-conjugated addition with barbiturate **18** yielding 1,4-diketone **eb**, followed by a Paal-Knorr cyclisation **ec** to finally give 5-(furan-3-yl) barbiturate/thiobarbiturate **19** (Scheme 11).

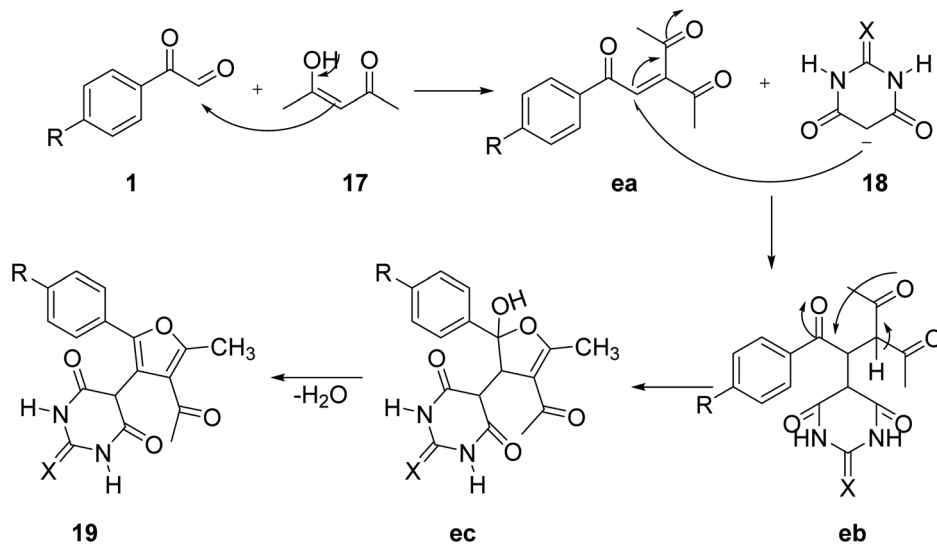
A further synthesis was done by Khoehiniha and his group using aryl glyoxal **1** as a building block for obtaining novel 4*H*-indeno[1,2-*b*]furan-4-ones **23** through its one-pot condensation with 2-aminopyridines **21** and 1,3-indandione **22** in water in the absence of any catalyst. In addition, by employing aryl glyoxal **1**, **21** and barbituric acid **18** under the same green conditions, they obtained furo[2,3-*d*]pyrimidine **24** derivatives in high yield (Scheme 12).⁵⁰ The reaction is believed to start from the aldol condensation of **1** and 1,3-indandione **22** generating intermediate **fa**. Amine **21** is added to this intermediate through



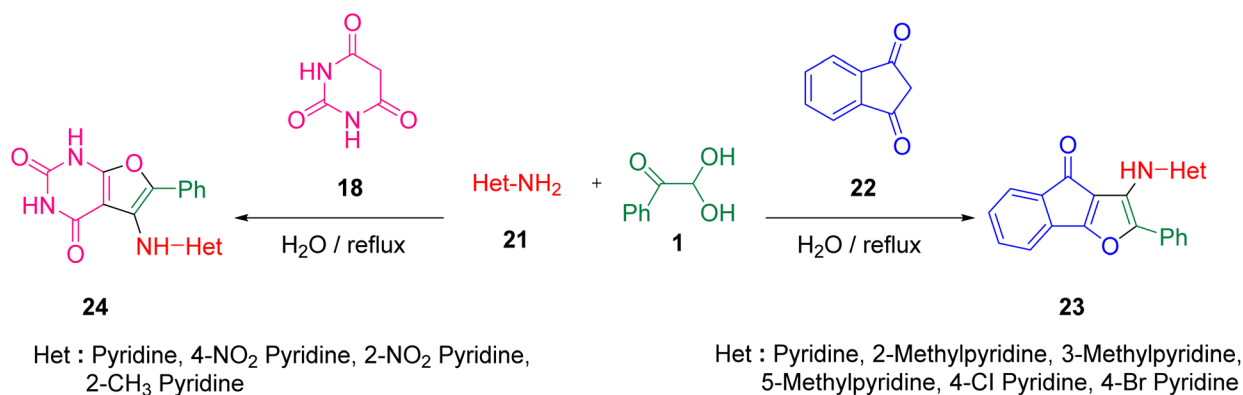
Scheme 9 Syntheses of furan **15** and pyrrole **16** derivatives *via* three-component reactions.



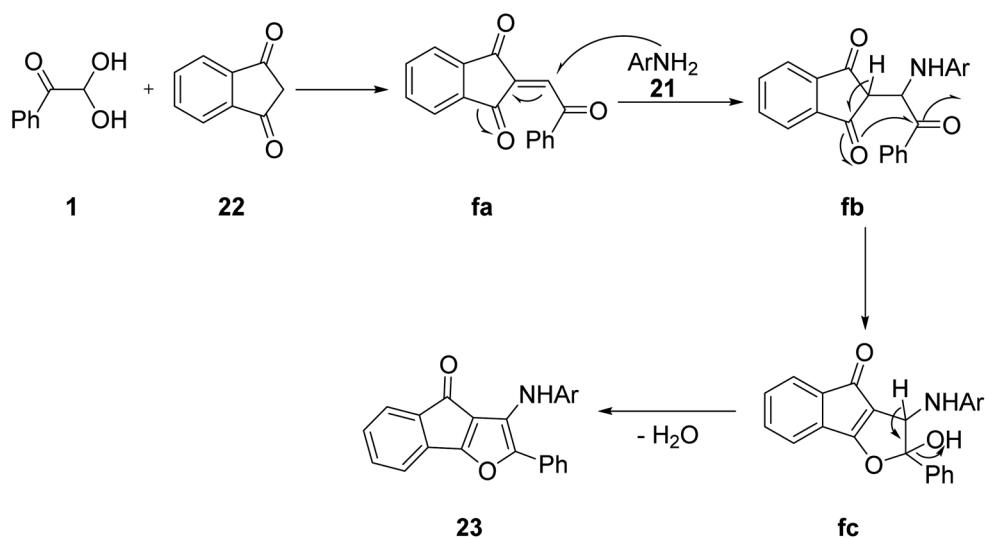
Scheme 10 Three-component synthesis of 5-(furan-yl)barbiturate and 5-(furan-3-yl)thiobarbiturate **19** from acetylacetone **17** and barbituric acid **18**.



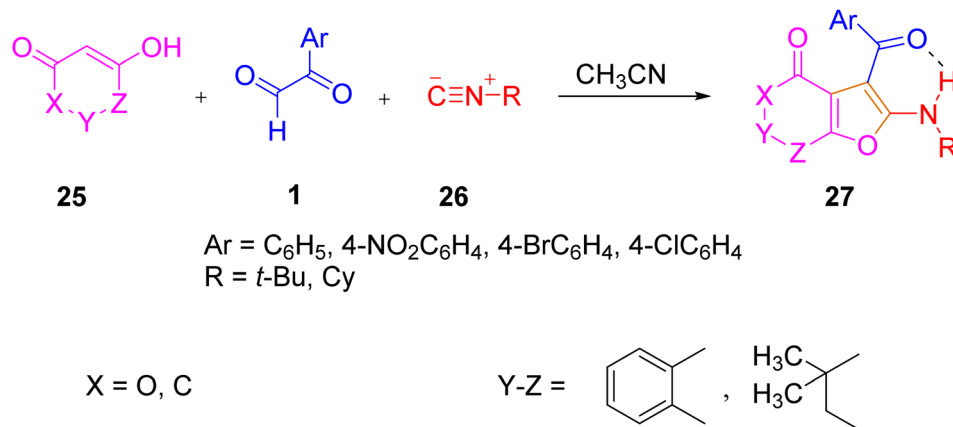
Scheme 11 Mechanism proposed to explain the formation of 5-(furan-3-yl)barbiturate/thiobarbiturate 19.



Scheme 12 Three-component synthesis of 4*H*-indeno[1,2-*b*]furan-4-ones 23 via aldol condensation.



Scheme 13 Plausible mechanism to represent the synthesis of 4*H*-indeno[1,2-*b*]furan-4-ones 23.



Scheme 14 Synthesis of furo[3,2-c]coumarin **27** via a [4 + 1] cycloaddition reaction.

a Michael addition **fb**, followed by intramolecular cyclisation **fc**, with subsequent dehydration to produce the final product **23**. When 1,3-indandione is replaced with barbituric acid following the same methodology, the furo-pyrimidine derivative **24** is obtained as the product (Scheme 13).

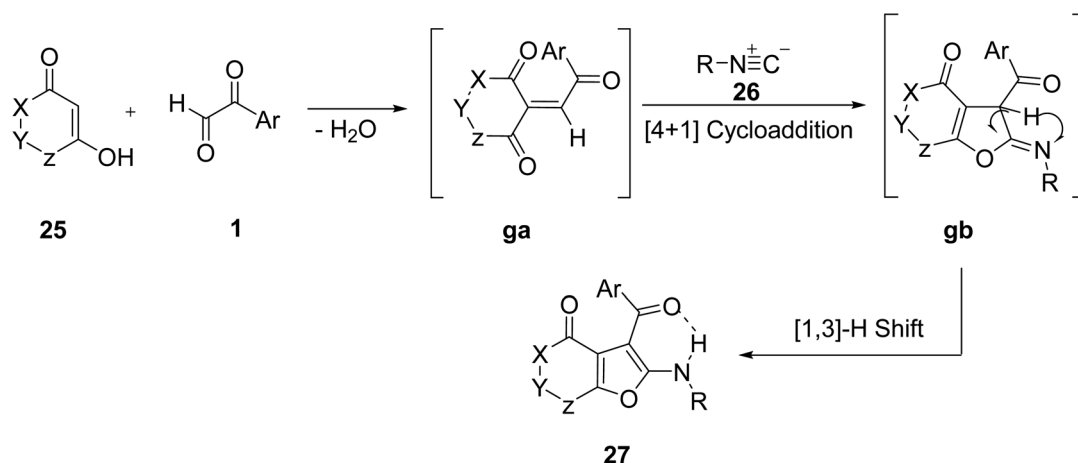
In 2009, Mosslemin's group reported the isocyanide-based formation of furo[3,2-c]coumarin **27** through a condensation-cycloaddition of the easily available 4-hydroxy coumarin **25** with the extensively used aryl glyoxal and alkyl isocyanides **26** in a neutral acetonitrile medium. The reaction also gave the same result when 4-hydroxycoumarin was substituted with dimethylcyclohexandione (Scheme 14).⁵¹ The underlying mechanism for the synthesis begins with the generation of the Knoevenagel adduct **ga** of 4-hydroxycoumarin **25** and **1** with a subsequent [4 + 1] cycloaddition reaction between the resulting hetero-diene **ga** and isocyanide **26** to form iminolactone **gb** as an intermediate. Lastly, a [1,3]-H shift in this iminolactone leads to furo[3,2-c]coumarin **27** (Scheme 15).

Chang *et al.* developed an effective method for synthesising furo[3,2-c]coumarins utilising **1** in multicomponent tandem reactions driven by FeCl_3 or ZnCl_2 . As per the reports, this

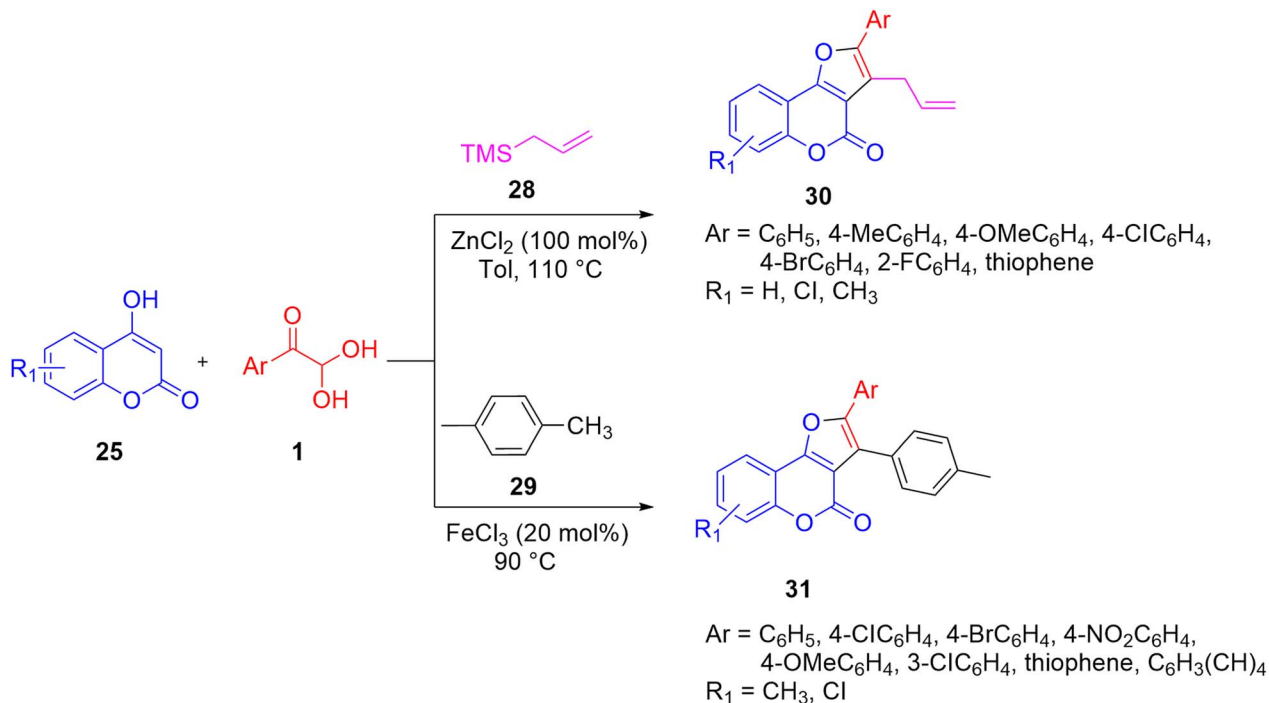
reaction between 4-hydroxycoumarin **25** and allyltrimethylsilane **28** or toluene **29** produced two C–C bonds and one C–O bond in compounds **30** and **31**, respectively. This approach provided the desired furo[3,2-c]coumarin structures in good to outstanding yields. Some notable traits of the method include the ease with which the starting materials may be obtained, the great functional group tolerance, and the outstanding atom economy (Scheme 16).⁵²

The use of aryl glyoxal **1** by Salari and co-workers set an efficient protocol for the synthesis of functionalized *trans*-tetrahydrobenzofuran-4-ones **34** via the condensation reaction of aryl glyoxal, *N*-(4-halophenacyl)-pyridinium bromide **33**, and cyclic 1,3-diketone **32** utilizing DABCO in a catalytic amount with water as the solvent under reflux conditions. Furthermore, 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 17).⁵³

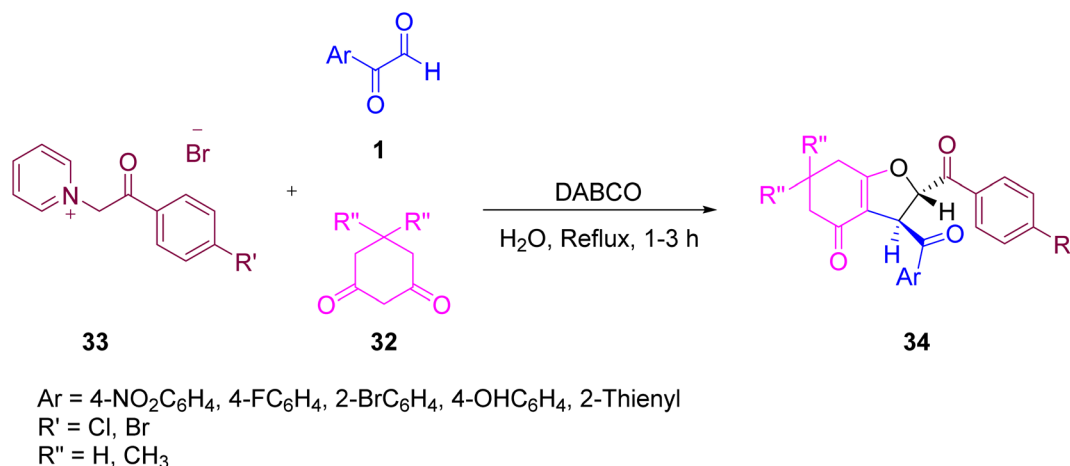
Next, in 2019, the synthetic application of aryl glyoxal was further explored to construct novel moieties of biological importance. Komogortsev *et al.* devised a new convenient



Scheme 15 Mechanism to explain the synthesis of furo[3,2-c]coumarin **27** via a cycloaddition reaction.



Scheme 16 Tandem reactions leading to diverse furo[3,2-c]coumarin compounds **30** and **31** using allyltrimethylsilane **28** and toluene **29**, respectively.



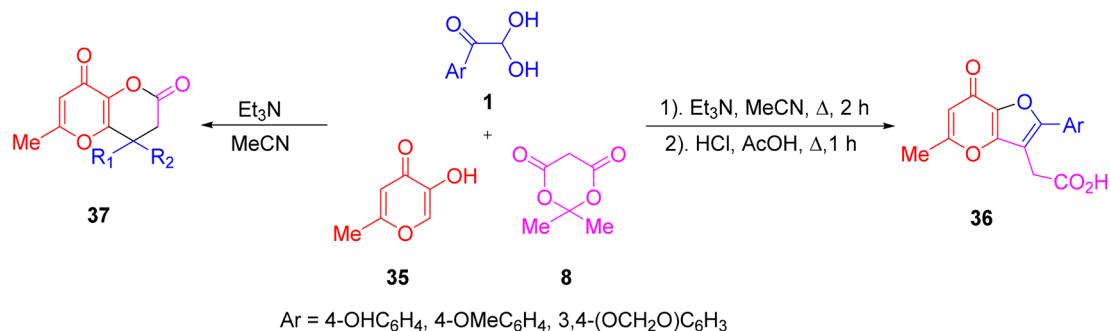
Scheme 17 Three-component DABCO-catalysed synthetic protocol for the synthesis of *trans*-tetrahydrobenzofuran-4-ones **34**.

method to obtain 7-oxo-7*H*-furo[3,2-*b*]pyran-3-ylacetic acid **36** through the reaction of pyranone **35**, Meldrum's acid **8** and aryl glyoxal **1** as the carbonyl compound in one pot. The reaction was accomplished by the catalysis of Et_3N in MeCN under reflux conditions (Scheme 18).⁵⁴ The distinguishing feature of the protocol is the application of the Kojic acid analogue 3-hydroxypyran-4-one **35**.

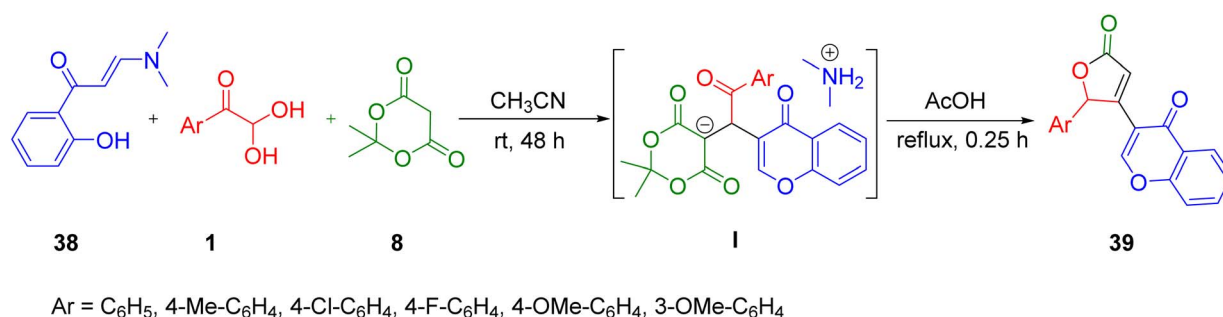
Lichitsky *et al.* in 2020 developed a systematic telescoping-synthesis protocol to synthesise substituted furan-2(5*H*)-one derivatives **39** containing a 4*H*-chromen-4-one fragment *via* the multicomponent reaction of 3-(dimethylamino)-1-(2-hydroxyaryl)prop-2-en-1-one **38**, aryl glyoxal **1**, and Meldrum's

acid **8**. The simultaneous production of 4*H*-chromen-4-one and furan-2(5*H*)-one fragments **39** in one synthetic stage is a distinguishing aspect of the suggested methodology. This approach is atom economical, and has other virtues, such as mild reaction conditions and a simple workup approach, which eliminates the need for chromatographic purifications (Scheme 19).⁵⁵

In 2020, Komogortsev *et al.* explored a new one-pot protocol for the synthesis of various substituted 2-aminofuran moieties **41** based on the multicomponent reaction of 3-hydroxy-4*H*-pyran-4-ones **35**, aryl glyoxal **1** and methylene active nitriles **40**. The formation of 2-aminofuran is a distinguishing aspect of



Scheme 18 Synthesis of 7-oxo-7H-furo[3,2-b]pyran-3-ylacetic acid **36** through a condensation reaction.



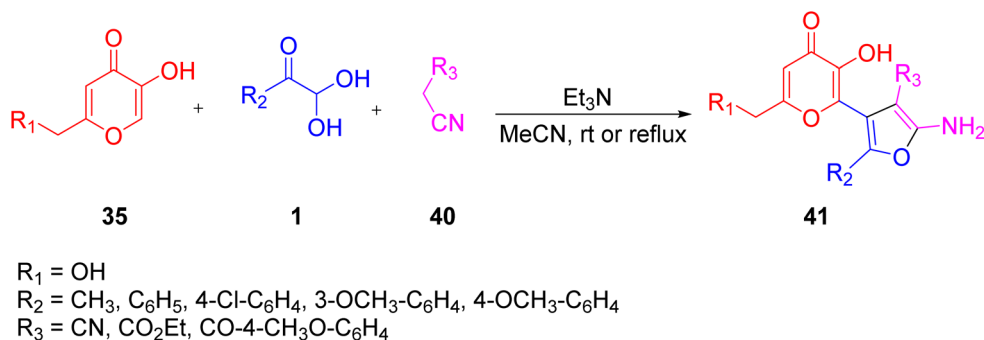
Scheme 19 3-(Dimethylamino)-1-(2-hydroxyaryl)prop-2-en-1-one **38**-derived formation of the substituted furan-2(5H)-one derivative **39**.

this protocol. The excellent yield, high atom economy, simple workup procedure and maintenance of mild reaction conditions for the reaction to proceed are all major benefits of this protocol (Scheme 20).⁵⁶ The suggested mechanism (Scheme 21) begins with the generation of a Michael acceptor from the reaction of the C-H active malononitrile **40** with **1**. The allomaltol anion (deprotonated by triethylamine) adds to the intermediate, thus forming the adduct **ha**. This adduct undergoes deprotonation to form an oxoanion **hb** followed by cyclisation at the nitriles **hc**, finally leading to furo-pyran as the final product **41**.

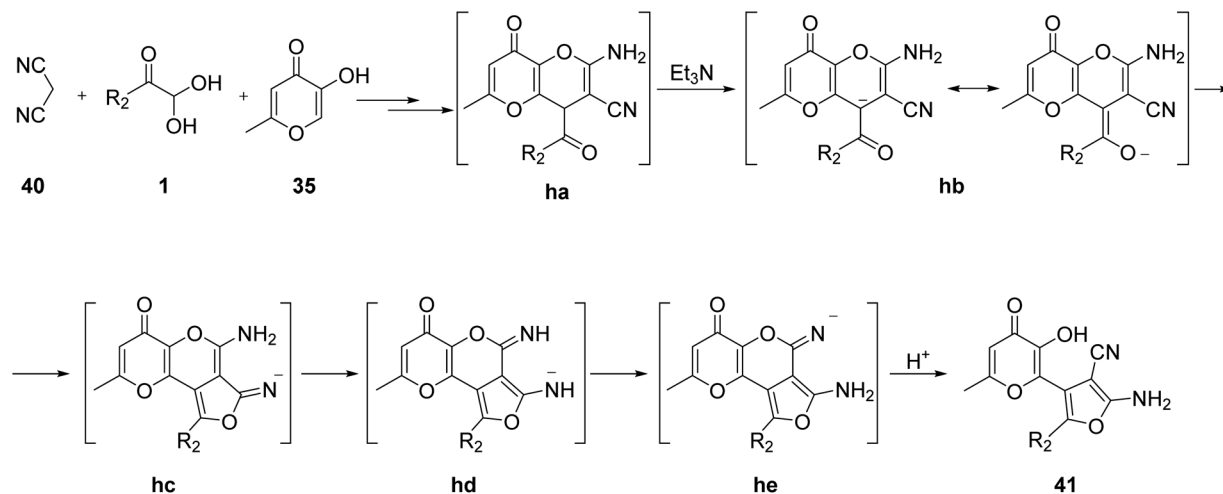
In 2013, Karami and co-workers regioselectively synthesized amido-substituted furo[4,5-*c*]coumarins **43** by reacting aryl glyoxal **1**, 4-hydroxycoumarin **25** and benzamide **42** in a single pot through coupling, followed by cyclisation in acetic acid at

reflux (Scheme 22).⁵⁷ The product showed selectivity over isoxazolo-substituted coumarin. The plausible pathway for the reaction is generation of the intermediate in the condensation reaction, followed by its intramolecular cyclisation and then dehydration to give the final product.

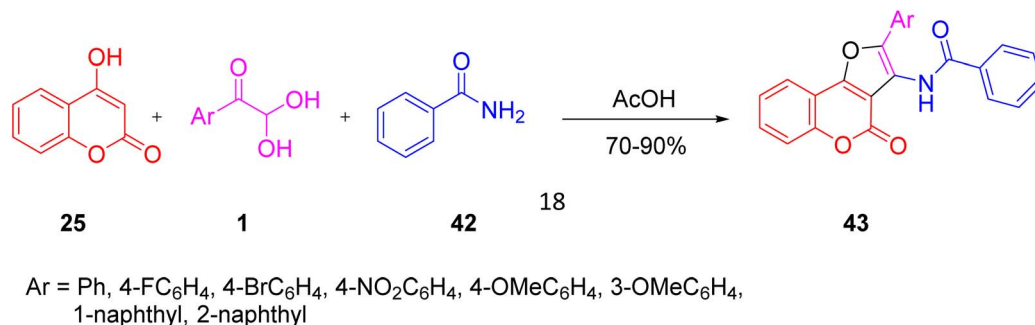
Huang and co-workers reported an efficient Lewis-acid-catalysed reaction for synthesizing diverse furo[3,2-*c*]coumarins **45** by exploiting aryl glyoxal, 4-hydroxycoumarins **25**, and methylketone **44** in 1,4-dioxane at 130 °C using 20 mol% Zn(OTf)₂. The substrate scope of the protocol showed that 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 (Scheme 23).⁵⁸ The proposed reaction design (Scheme 24) follows the pathway initially from the loss of



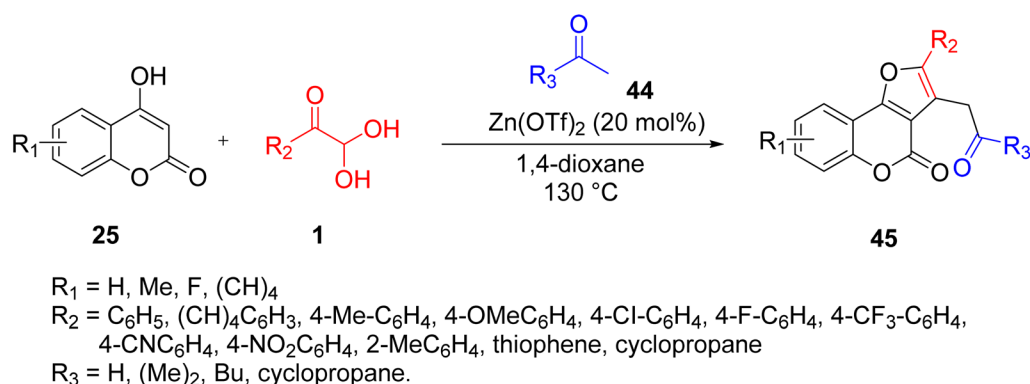
Scheme 20 3-Hydroxy-4H-pyran-4-ones-derived synthesis of 2-aminofuran **41**.



Scheme 21 Synthesis of 2-aminofuran **41** through a Michael reaction followed by cyclisation.



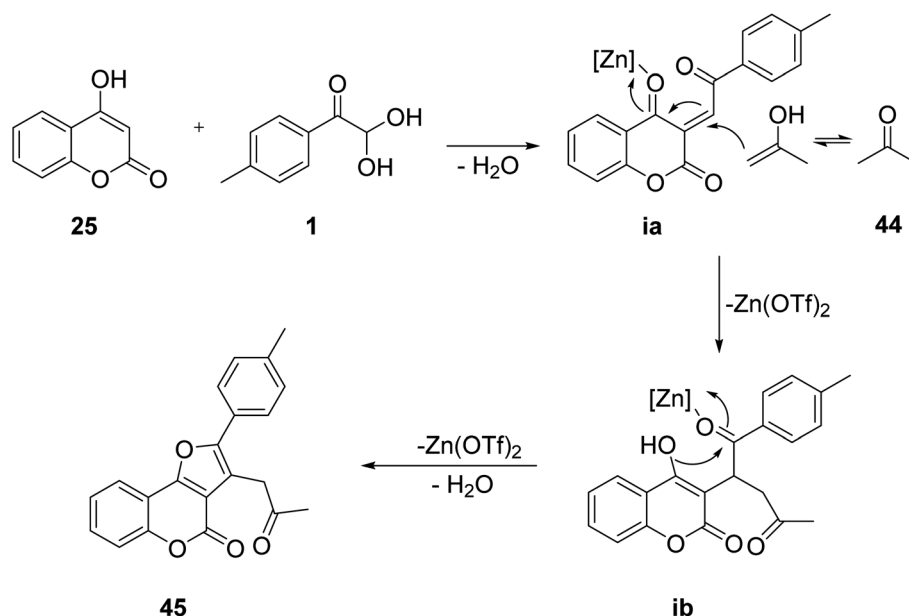
Scheme 22 Synthesis of benzamide **42**-derived amido-substituted furo[4,5-*c*]coumarin **43**.



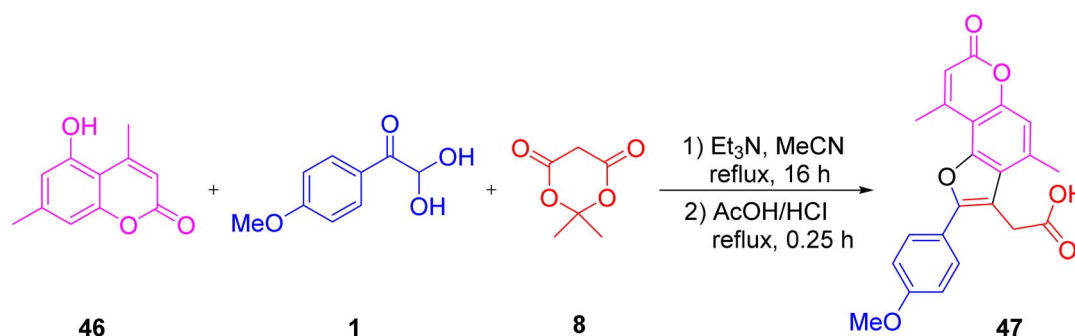
Scheme 23 Lewis-acid-catalysed protocol yielding furo[3,2-*c*]coumarins **45**.

a water molecule through the condensation reaction of **1** and **25** to give the intermediate **ia**, which reacts with the enol form of acetone in a Michael-type addition to produce the second intermediate **ib**. The electrophilicity of the condensed adduct **ia** is enhanced by the Zn(OTf)₂. Finally, dehydration preceded by an intramolecular cyclisation leads to the formation of furo[3,2-*c*]coumarin **45**.

After this, Lichitsky *et al.* used the Meldrum's acid **8** with hydroxycoumarin derivative **46** to access the novel furylacetic acid moiety **47**. The pronounced advantage of the biologically important furo-coumarin derivative synthesis is that the formation was possible through a single-pot approach using easily available starting materials with no harsh reaction conditions (Scheme 25).⁵⁹



Scheme 24 Mechanism showing furo[3,2-*c*]coumarin **45** synthesis through a condensation reaction followed by intramolecular cyclisation.



Scheme 25 Formation of the hydroxycoumarin **46**-derived furylacetic acid moiety **47**.

In 2022, Jana *et al.* developed a straightforward, facile and efficient approach for the synthesis of novel thioether-linked coumarin-fused furans **49** via the $\text{Sc}(\text{OTf})_3$ -catalysed one-pot combination of aryl glyoxal **1**, 4-hydroxycoumarin **25** and different aromatic thiols **48**. This approach can yield either a three-component thioether-linked coumarin-fused furan **49** or a two-component furo-coumarin product **50**, depending on the thiols. The key attributes of this approach are its broad substrate range, good to exceptional yields, and products with multiple pharmaceutically significant motifs (Scheme 26).⁶⁰

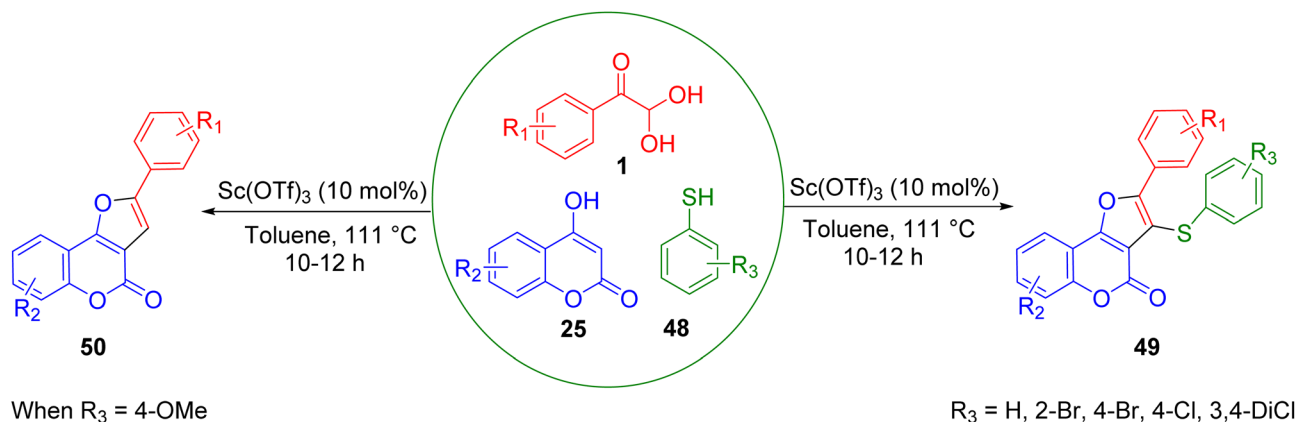
In 2020, Palanivel explored the combination of **1** and benzimidazole acetonitrile **51** with malononitrile **40** at room temperature in a triflic acid/acetonitrile system to afford tricyclic aza-cyclopenta(*cd*)diindene **54**. The above combination was also executed with benzoyl acetonitrile **53** at room temperature in ethanol/water to access the furo[2,3-*b*]furan derivative **55** in the presence of the organic base DABCO. Furthermore, he obtained the pyrrolo-pyridine carboxamide **57** and furo-pyrrolo imidazole carboxamide **56** when the aryl glyoxal **1** was made to react with two equivalents of benzimidazole acetonitrile **52** in

a pseudo-three-component reaction employing DABCO and NaO^tBu as additives, respectively, in ethanol/water at room temperature (Scheme 27).⁶¹

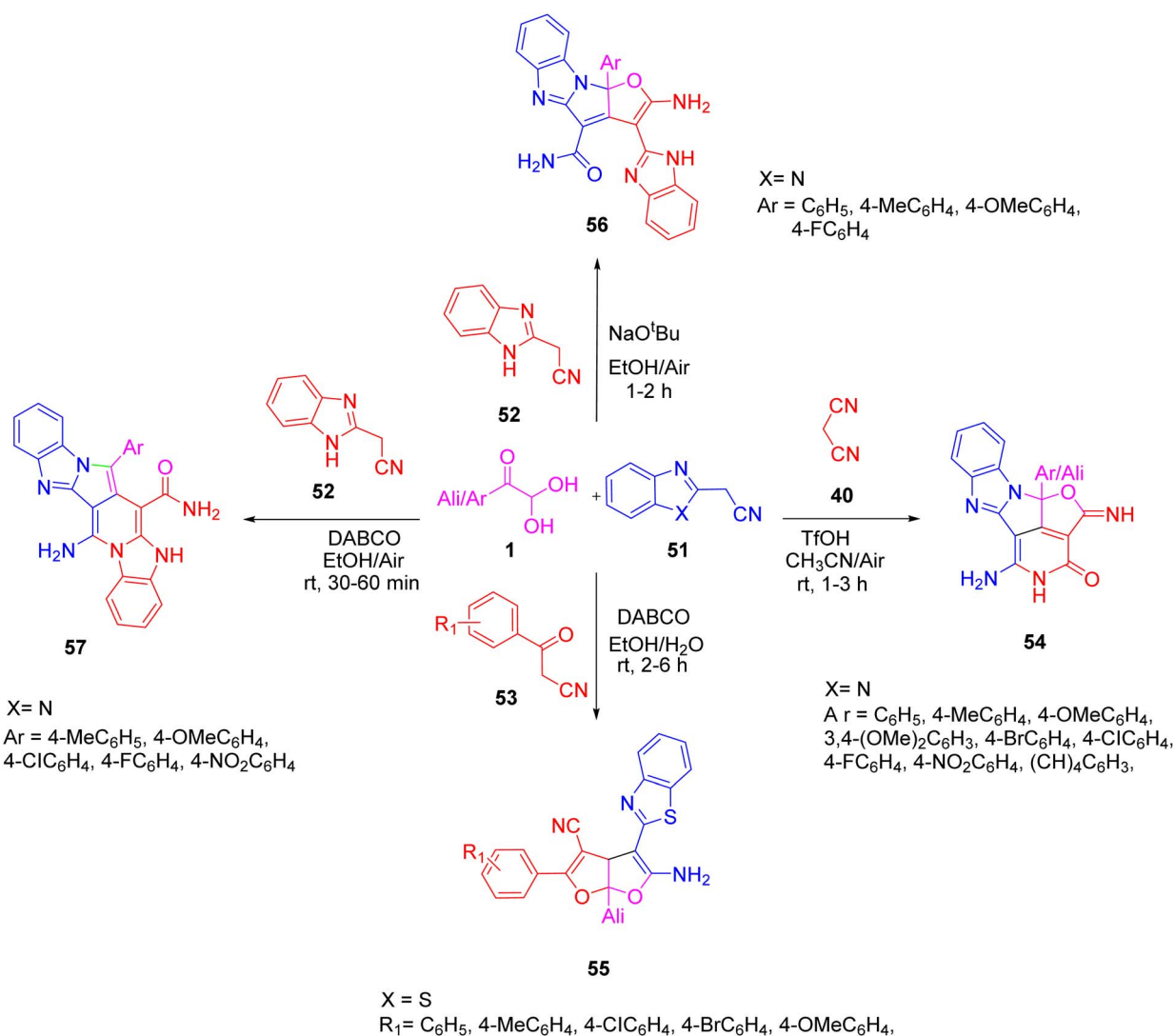
2.2. Synthesis of benzofuran derivatives

In 2019, El-Harairy *et al.* used aryl glyoxal for synthesizing functionalized benzofuran **59** through an ionic liquid catalysis. The desired product **59** was obtained by the assembly of aryl glyoxal hydrate **1**, sesamol **58**, and indole **9** in an imidazolium-based Brønsted acid ionic liquid/butyl acetate green system. The above catalyst was recovered and used for further reactions (Scheme 28).⁶²

In 2020, Lichitskii and co-workers effectively used aryl glyoxal for the preparation of terarylenes **60**, a starting material for the synthesis of naphtho[1,2-*b*]benzofuran-7(*8H*)-ones **61** 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 **38** and cyclic 1,3-diketone **32** in the presence



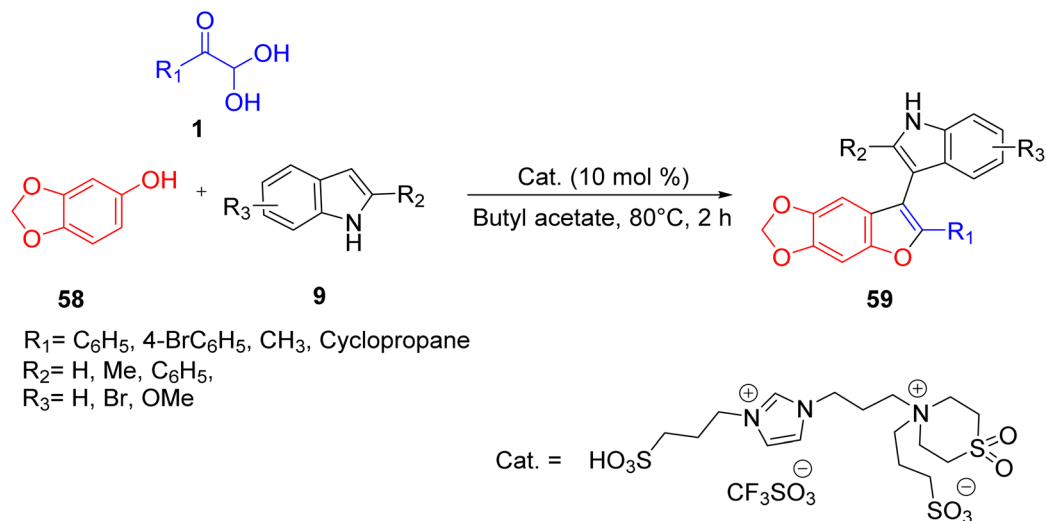
Scheme 26 Synthesis of the thioether-linked coumarin-fused furan **49** and the furo-coumarin product **50** through reaction with aromatic thiols **48**.



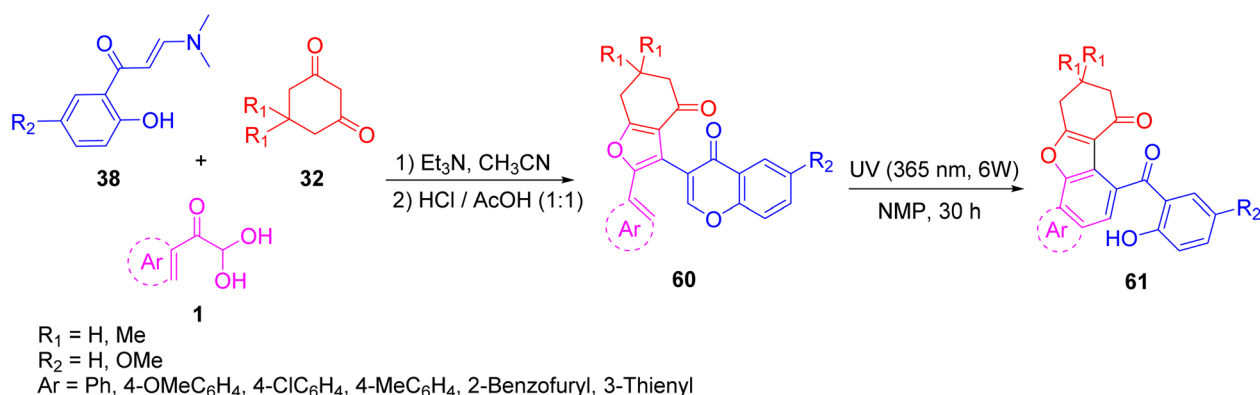
Scheme 27 Synthesis of polyheterocyclic hybrid scaffolds.

of an inert solvent and base at room temperature, followed by the subsequent addition of a hydrochloric acid and acetic acid mixture. The model reaction was optimized by using different

solvents and varying the system temperature. Terarylenes were best obtained in good yield at room temperature with acetonitrile and triethylamine as the solvent/base system. The



Scheme 28 Synthesis of benzofuran **59** using sesamol **58** and indole **9** in a Brønsted acid system.

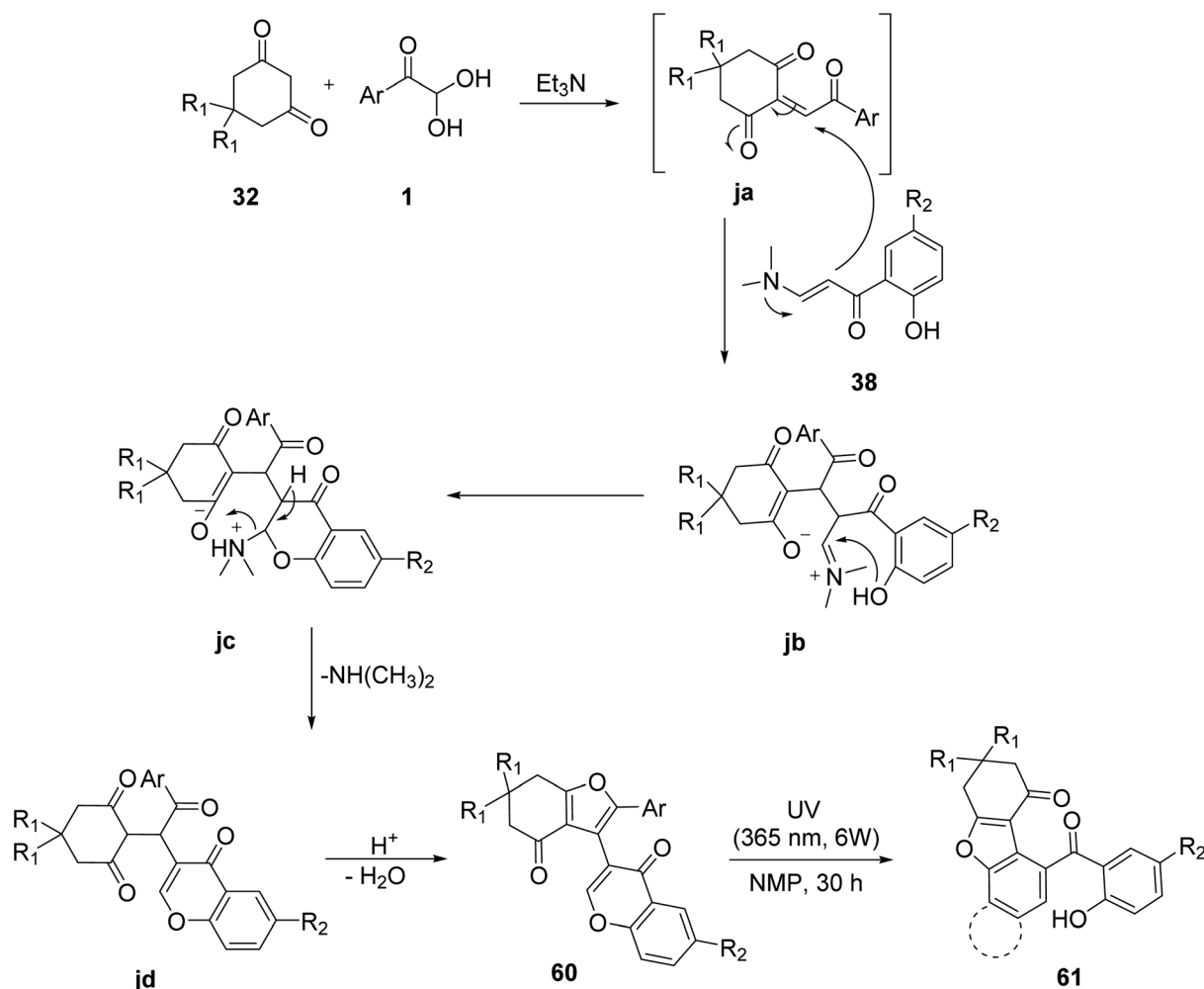


Scheme 29 Synthesis of naphtho[1,2-*b*]benzofuran-7(8*H*)-ones **61** via photochemical rearrangement reactions of the 4*H*-chromen-4-one derivative (terarylene) **60**.

limitation of the novel multicomponent methodology to cyclic diketones was also confirmed by the unsuccessful test reaction of 2,4-pentanedione (Scheme 29).⁶³ The plausible mechanism for this reaction includes the expected base-catalysed condensation reaction of 1,3-diketone **32** with **1**, followed by the subsequent addition of enaminone **38** to the generated Michael acceptor **ja**, forming the adduct **jb**. Intramolecular cyclisation through nucleophilic attack of the hydroxyl group to the iminium ion generates an intermediate **jc**, which finally undergoes acid-catalysed dehydration to form the desired terarylene **60** with a new furan moiety in the structure. This terarylene **60** was exposed to UV light of 365 nm for 30 hours and yielded the desired benzofuran derivative (Scheme 30).

Recently, Rajesh P. *et al.* successfully demonstrated a three-component calcium-catalysed approach for obtaining naphthofuran (3-aminofurans) **68** in good yield *via* annulation of the *in situ* intermediate *C,N*-diacyliminium ion generated as a result of a three-component reaction between a variety of aryl glyoxal **1** and lactams **62** with 2-naphthols **65** under solvent-free conditions at 100 °C (Scheme 31).⁶⁴ The proposed mechanism

includes formation of the Ca^{2+} -catalysed imine **ka** in the initial step followed by ligand metathesis between Ca^{2+} and the hydroxyl group of β -naphthol to form a C–C bond **kc**, and then an intermediate **kd** with a new C–O bond. Finally, **kd** undergoes aromatisation yielding the naphthofuran **68** (Scheme 32). 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 $\text{Ca}(\text{OTf})_2$ and Bu_4NPF_6 increases the acidity of the catalyst, making it more efficient and able to provide excellent yields. Interestingly, they also repeated the same protocol by changing the nucleophile source to mequinol (substituted phenol) **63** to access the corresponding benzofuran **66** and later glyoxal with the 9*H*-fluoren-3-ol derivative **64** and lactam-furnished fluorenofuran **67** in a good yield of 84%. Furthermore, 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.



Scheme 30 Mechanistic pathway representing the synthesis of naphtho[1,2-*b*]benzofuran-7(8*H*)-ones **61** via an acid-catalysed dehydration reaction.

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 **69** in acetonitrile followed by cyclisation in refluxing acetic acid to afford furylacetic acid **70**. Advantages of this protocol include a simple work-up route and high atom economy (Scheme 33).⁶⁵

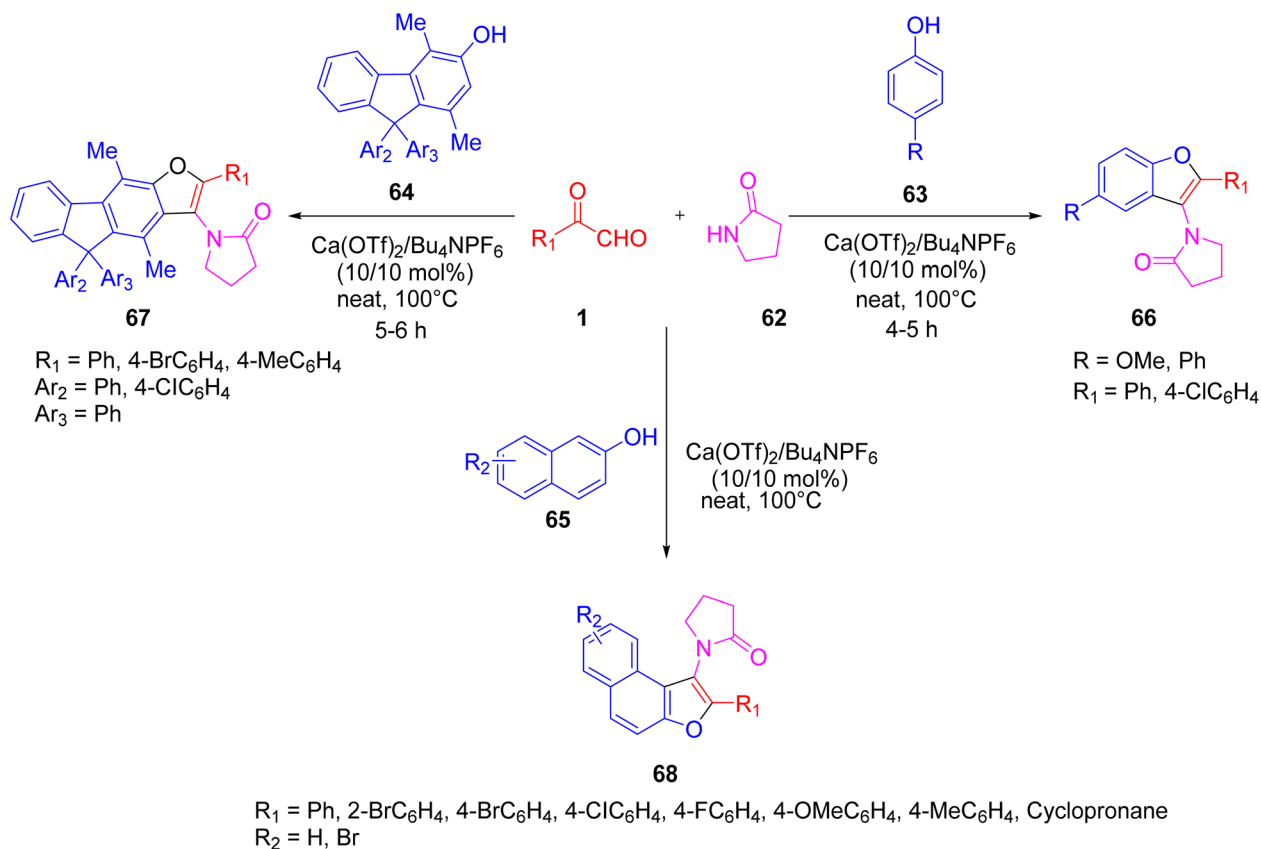
In 2021, Lichitsky and co-workers described a simple one-pot approach for synthesizing a regiospecific 4*H*-furo[2,3-*h*]chromene **72** core using aryl glyoxal. The proposed method was based on a multicomponent reaction of aryl glyoxal, flavones **71**, and Meldrum's acid **8**. The mild reaction conditions, atom economy, and simple workup procedure are all advantages of this method, which eliminates the need for chromatographic purification (Scheme 34).⁶⁶

In 2021, Komogortsev and co-workers performed a reaction involving **1**, Meldrum's acid **8**, and colchicine **73**, which led to a practical one-pot method to synthesize colchicine derivatives **74** with different substitutions. One of the distinctive aspects of the method is the production of the 2-(7-acetamido-1,2,3-trimethoxy-9-oxo-11-phenyl-5,6,7,9-tetrahydrobenzo[9,10]

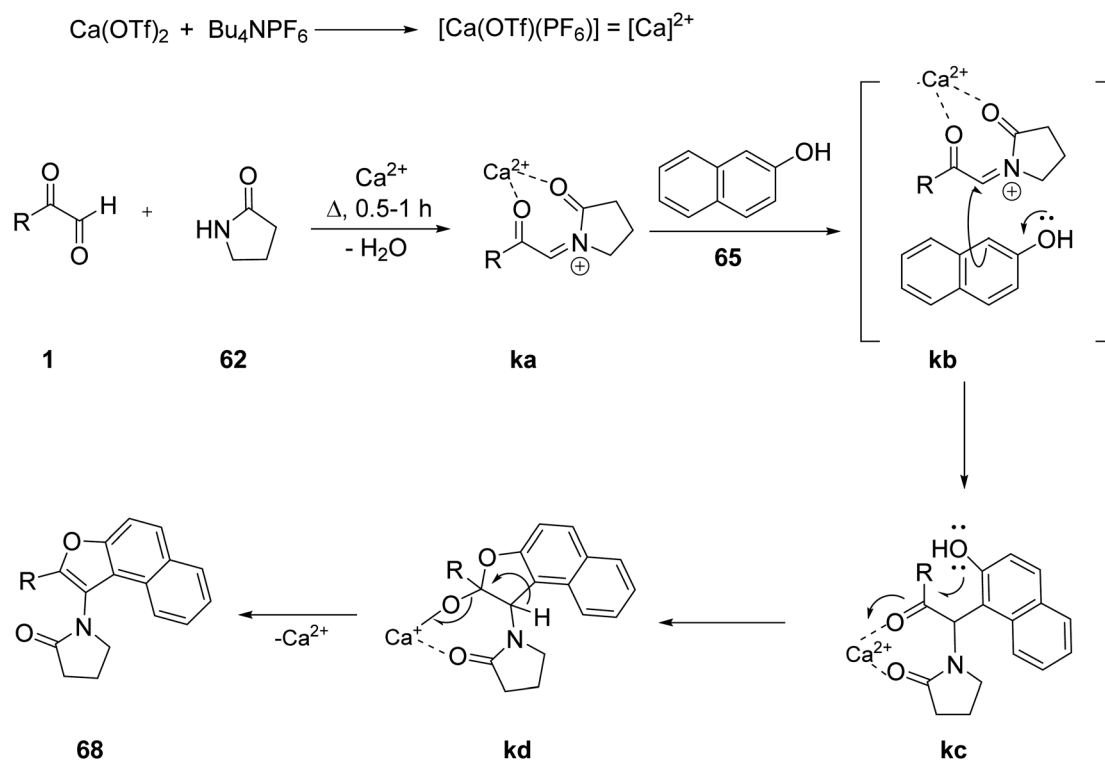
heptaleno[3,2-*b*]furan-12-yl)acetic acid. **74** moiety. Some of the key features of this method include the use of easily available precursors, facile execution of the protocol, and the ease with which the target products were separated. Two-dimensional NMR spectroscopy verified the structure of one of the furo-tropolone products (Scheme 35).⁶⁷

A multicomponent reaction protocol was developed by Chen *et al.* for the formation of 2-aryl-3-aminobenzofuran **75** derivatives by reacting aryl glyoxal monohydrates **1**, phenols **63**, and *para*-toluenesulfonamide **12**, catalysed by 10 mol% of indium trichloride in the presence of dichloromethane as the solvent to obtain an excellent yield (Scheme 36).⁶⁸

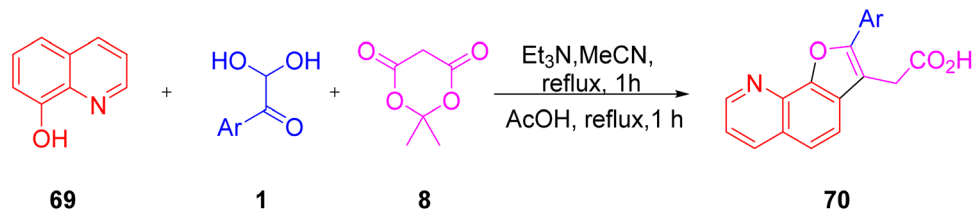
In 2018, Chang *et al.* reported the formation of the highly functionalized furan derivatives **76** and **77** via the reaction of aryl glyoxal, phenols **63** and 4-hydroxycoumarin **25** in the presence of MeSO₃H or FeCl₃ as a catalyst. By altering the reaction media, a range of furan derivatives with various substitution patterns were produced. This method's atom-economical traits and moderate conditions are consistent with the principles of contemporary green chemistry. In a short



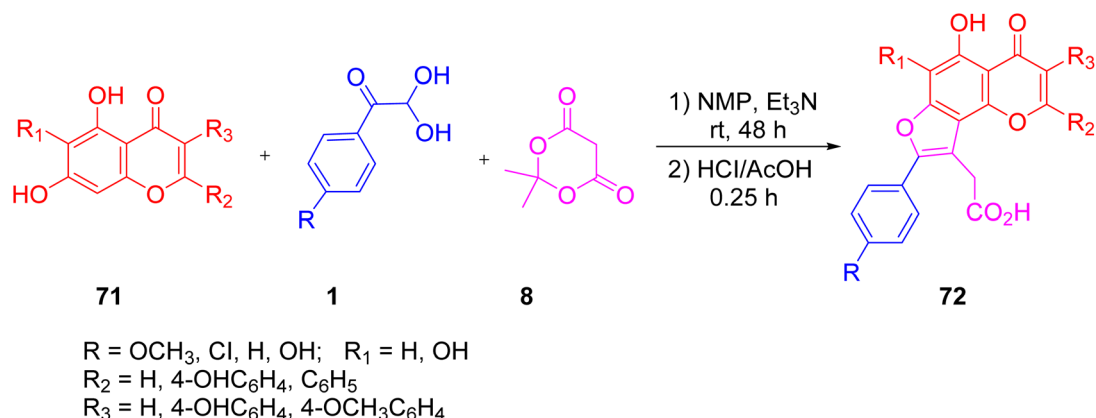
Scheme 31 Three-component calcium-catalysed protocol for syntheses of 3-aminofurans **68**, fluorenofuran **67** and benzofuran **66**.



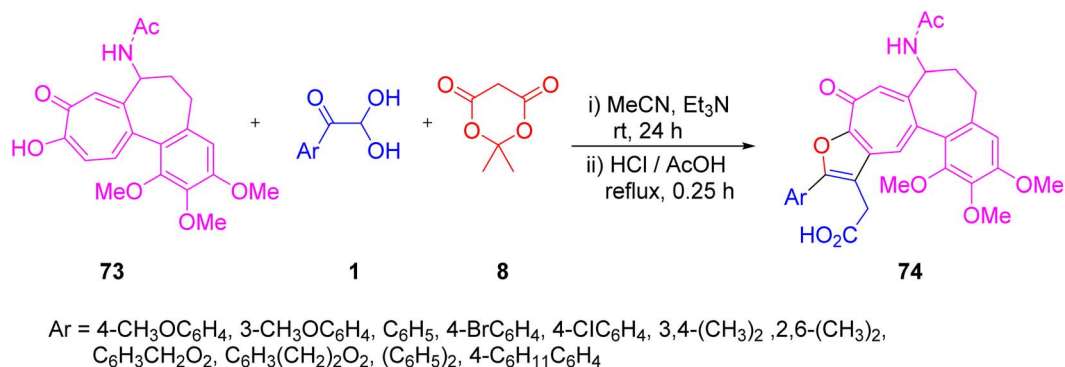
Scheme 32 Plausible mechanism for the calcium-catalysed synthesis of naphthofuran **68**.



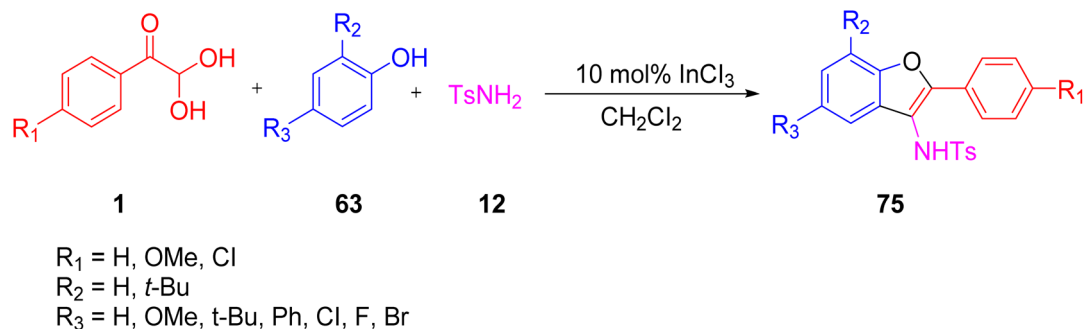
Scheme 33 Synthesis of furylactic acid **70** using Meldrum's acid **8** and 8-hydroxyquinoline **69**.



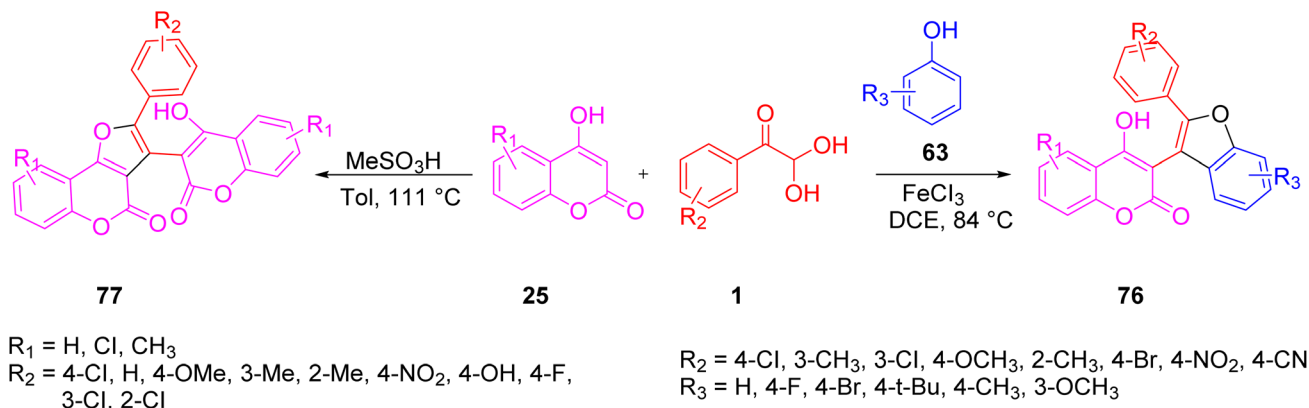
Scheme 34 Regiospecific synthesis of 4H-furo[2,3-h]chromene **72** from flavone **71**, Meldrum's acid **8** and aryl glyoxal **1**.



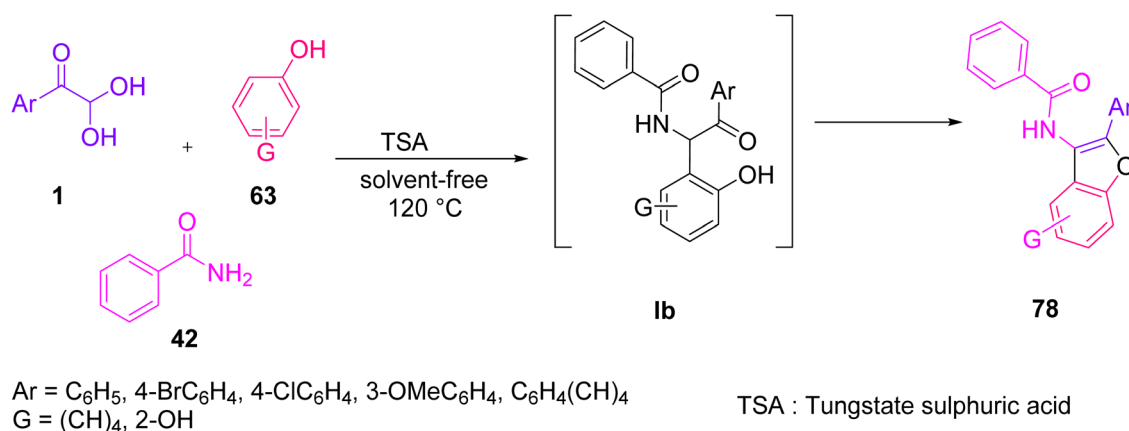
Scheme 35 Synthesis of 2-(7-acetamido-1,2,3-trimethoxy-9-oxo-11-phenyl-5,6,7,9-tetrahydrobenzo[9,10]heptaleno[3,2-b]furan-12-yl)acetic acid **74** using Meldrum's acid **8** and colchicine **73**.



Scheme 36 Indium-catalysed multicomponent protocol for the synthesis of 2-aryl-3-aminobenzofuran **75**.



Scheme 37 Synthesis of 4-hydroxycoumarin 25-derived functionalized furans 76 and 77.



Scheme 38 Three-component solvent-free TSA-catalysed protocol for the synthesis of 2-aryl-3-benzamido-benzofuran 78.

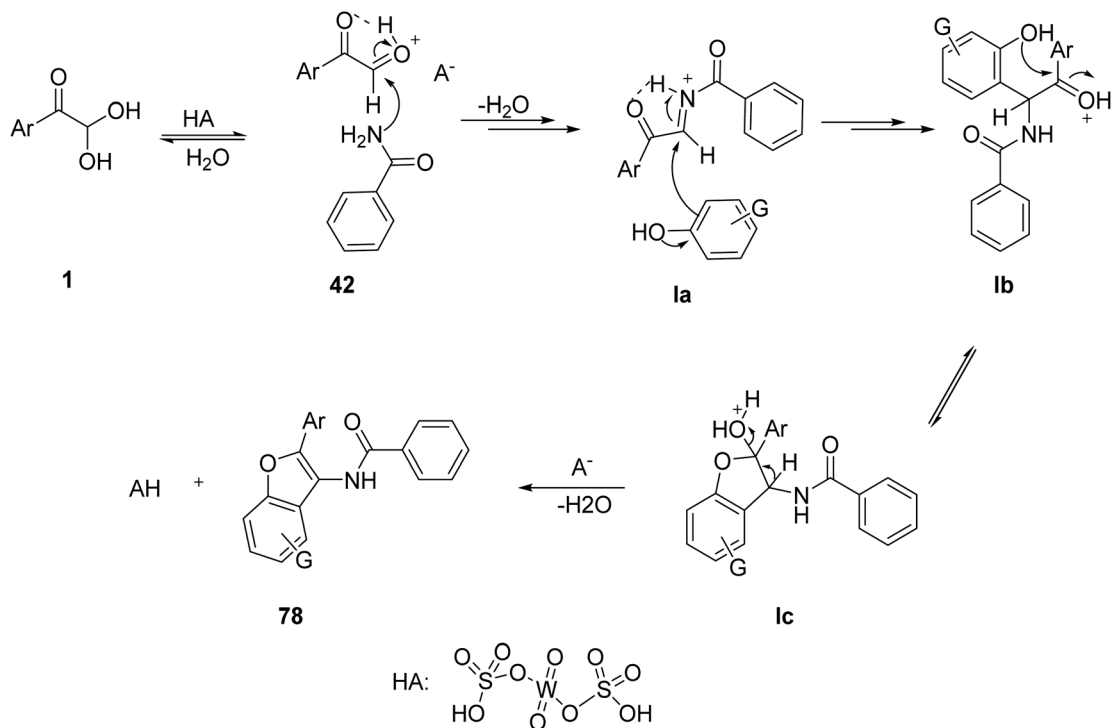
time, a substantial number of heterocycles of biological importance can be created using this protocol (Scheme 37).⁶⁹

Khodabakhshi and Hashemi demonstrated the application of aryl glyoxal in the construction of 2-aryl-3-benzamido-benzofurans 78 *via* a solvent-free three-component condensation reaction of 1 benzamide 42 and the phenolic substrate 63 with a catalytic amount of tungstate sulfuric acid (TSA) at 120 °C (Scheme 38).⁷⁰ The plausible mechanism for the formation of benzofuran consists of three steps, starting with the generation of the intermediate **la** through an *in situ* condensation of amide 42 and 1, followed by the regioselective formation of the oxygen-containing five-membered ring **lc** *via* the intramolecular cyclisation of **lb**, and finally dehydration leading to the final product 78 (Scheme 39).

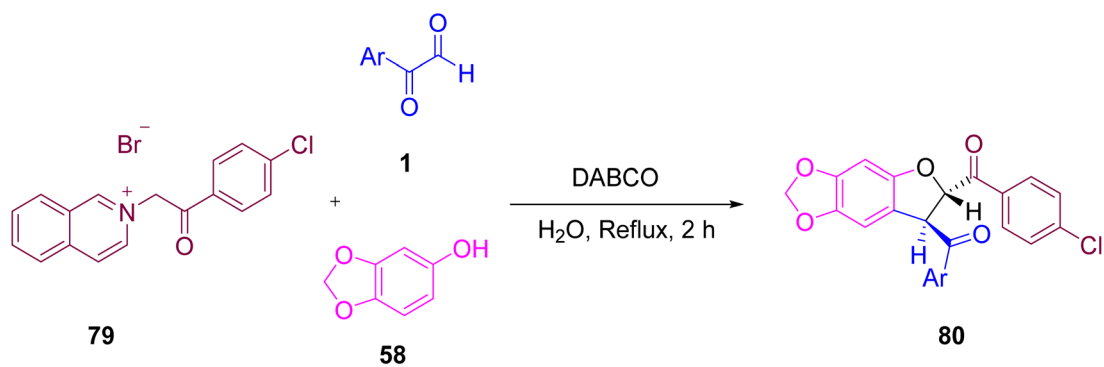
A pentacyclic product named as (7-benzoyl-6,7-dihydro-[1,3]dioxolo[4,5-*f*]benzofuran-6-yl)(4-chloroaryl)methanone **80** was afforded by Reza Salari *et al.* *via* a one-pot 1,4-diaza-bicyclo[2.2.2]octane (DABCO)-catalysed condensation of three components, namely 2-(2-(4-chloroaryl)-2-oxoethyl)isoquinolinium bromide 79, benzo(1,3)dioxol-5-ol 58, and aryl glyoxal 1 in water at reflux. Furthermore, a library of substrates was constructed by using different halo-, nitro- and hydroxyl-substituted aryl glyoxals (Scheme 40).⁷¹

In 2020, Zhang *et al.* reported a simple and straight-forward protocol for the quick synthesis of the benzofuran derivative **82**, that involved an FeCl_3 -mediated intermolecular tandem reaction between anisole **81** and 1 *via* a Friedel–Crafts alkylation and oxidative annulation. This reaction offers a lot of benefits, such as readily available starting materials, high atom economy, and strong functional group tolerance (Scheme 41).⁷² The mechanistic steps for the annulation reaction include the Friedel–Crafts alkylation of 1 with anisole **81** forming the intermediate **ma**, which in turn is oxidised by FeCl_3 to generate the second radical cation intermediate **mb**. FeCl_3 is then reduced a second time to further oxidise **mc** with a subsequent intramolecular cyclisation followed by deprotonation to yield the annulated benzofuran **82** (Scheme 42).

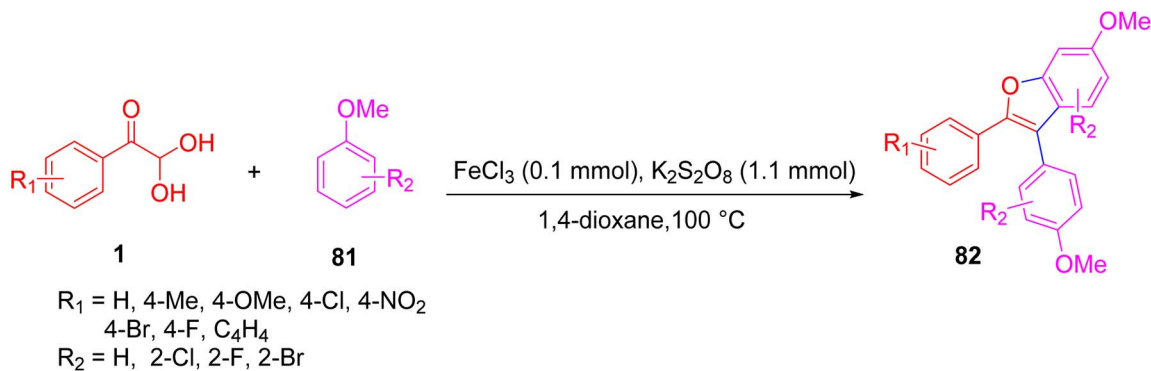
By employing microwave irradiation in the presence of the $\text{H}_3\text{PW}_{12}\text{O}_{40}/\text{Fe}_3\text{O}_4\text{-ZnO}$ catalyst, Taheri and co-workers in 2021 developed an effective and convenient single-pot reaction of benzo[*a*]phenazine **85** (synthesized from 2-hydroxynaphthalene-1,4-dione **83** and benzene 1,2-diamine **84**) a , aryl glyoxal 1, and indoles 9 to produce benzo[*a*]furo[2,3-*c*]phenazine **86** derivatives with excellent yields. The facile and quick extraction of the products, short reaction time, mild reaction conditions, high product yield, solvent-free conditions,



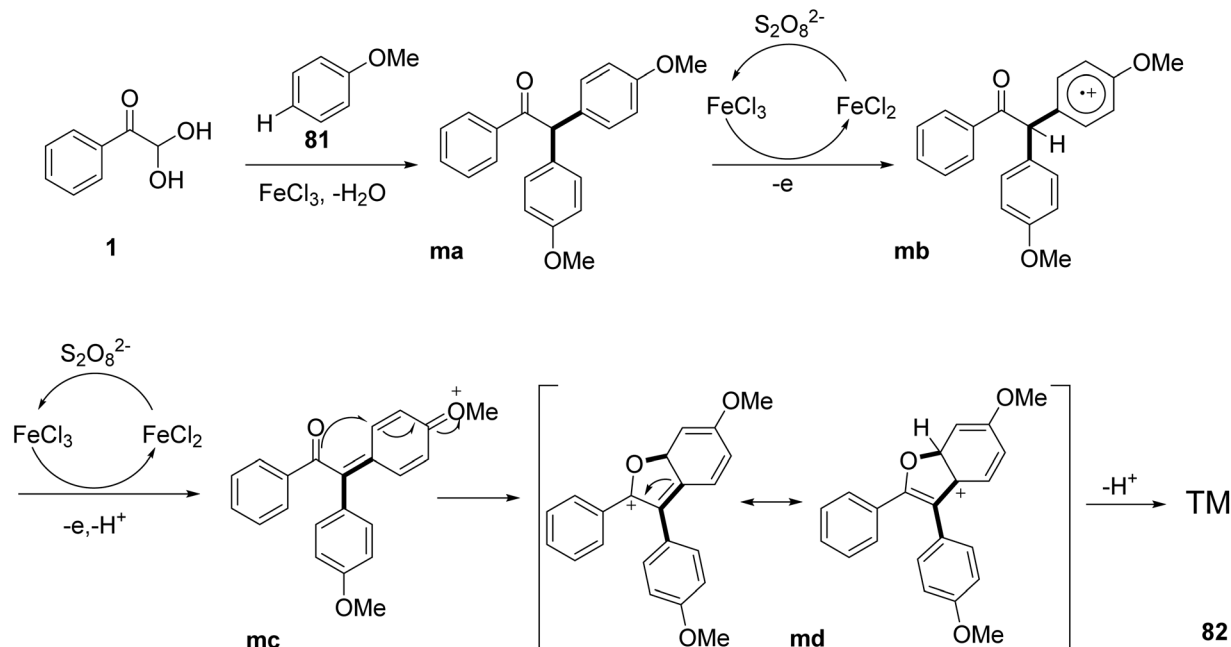
Scheme 39 Mechanistic pathway representing the synthesis of 2-aryl-3-benzamido-benzofuran **78**.



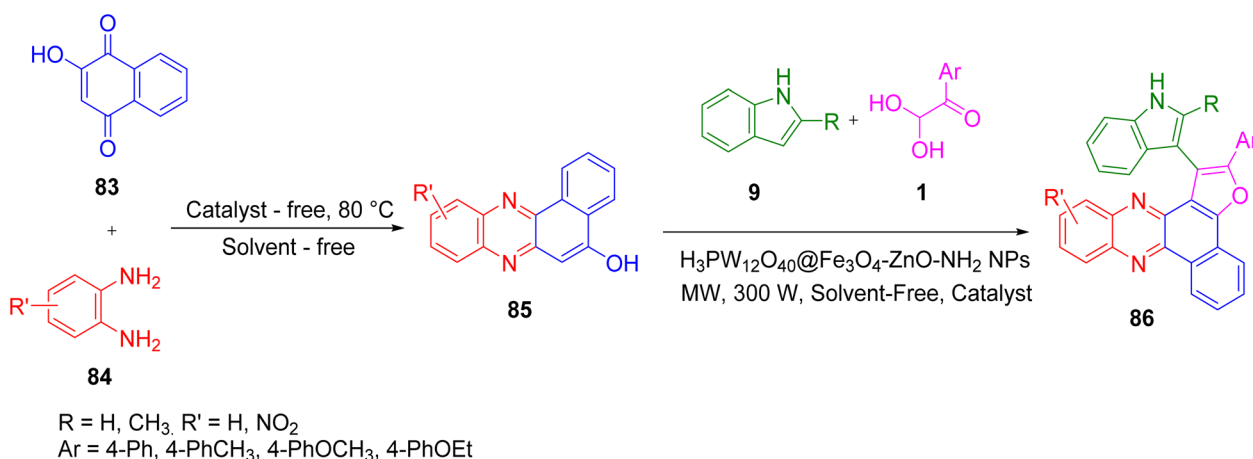
Scheme 40 Synthesis of (7-benzoyl-6,7-dihydro-[1,3]dioxolo[4,5-f]benzofuran-6-yl)(4-chloroaryl)methanone **80** in a one-pot approach using DABCO.



Scheme 41 Synthesis of benzofuran **82** via an FeCl₃-mediated intermolecular tandem reaction.



Scheme 42 Plausible mechanism for the synthesis of benzofuran **82** in the presence of FeCl_3 .



Scheme 43 Synthesis of benzo[*a*]furo[2,3-*c*]phenazine **86** via microwave irradiation in the presence of $\text{H}_3\text{PW}_{12}\text{O}_{40}@\text{Fe}_3\text{O}_4\text{-ZnO}$ as a catalyst.

low energy demand and economically affordable chemicals are the major advantages of this reaction protocol (Scheme 43).⁷³

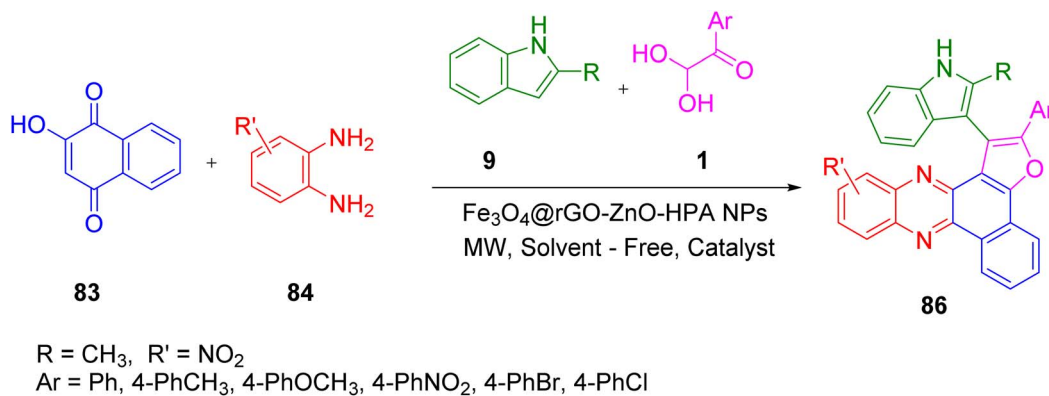
Taheri and colleagues performed the same reaction in 2021 to develop an easy, efficient and straight-forward protocol for the synthesis of benzo[*a*]furo[2,3-*c*]phenazine **86** derivatives in excellent yields by the reaction of benzo[*a*]phenazin-5-ol **85**, **1**, and **9** utilising the $\text{Fe}_3\text{O}_4@\text{rGO}@\text{ZnO-HPA}$ catalyst and keeping other the conditions similar to those in the previous reaction (Scheme 44).⁷⁴

A one-pot multicomponent reaction leading to the synthesis of urea-substituted 2-arylfurans **88** was reported for the first time by Komogortsev's group, and involved the reaction of numerous carbocyclic and heterocyclic enols **25** with cyanamide **87** and aryl glyoxal **1** under reflux conditions in the presence of the solvent acetonitrile, and the base triethylamine (Scheme 45).⁷⁵

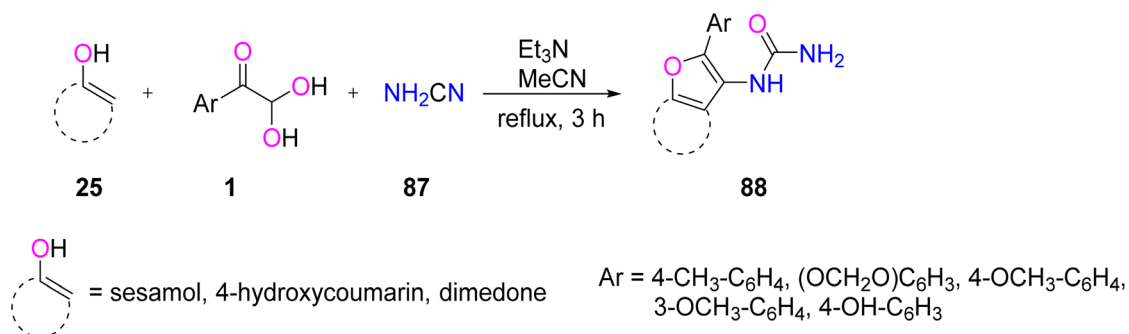
For the first time, the synthesis of substituted 2-amino-oxazoles containing the 3-hydroxy-4H-pyran-4-one moiety **89** was accomplished by Komogortsev's group in a one-step method *via* the multicomponent condensation of allomaltol derivatives **35** with aryl glyoxal **1** and cyanamide **87**, followed by an acid-catalysed recyclisation into substituted furo[3,2-*b*]pyrans **90**. The formation of the 2-aminooxazole core as opposed to a urea-containing condensed furan is the distinctive feature of this approach (Scheme 46).⁷⁶

2.3. Synthesis of pyran derivatives

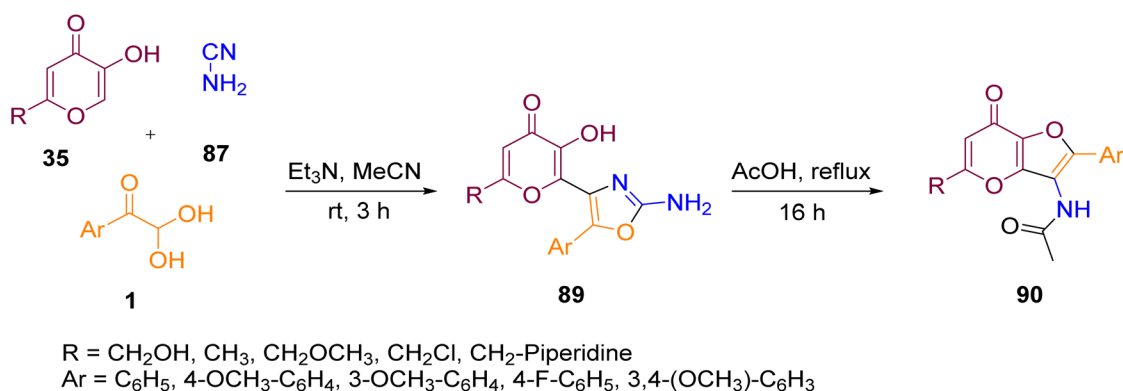
A green nanoparticle-catalysed strategy for the production of dihydropyrano[*c*]chromenes **91** was demonstrated by Khodabakhshi's group using aryl glyoxal **1**, 4-hydroxycoumarin **25**, and malononitrile **40** in a single pot with an ethanol-water



Scheme 44 Synthesis of benzo[a]furo[2,3-c]phenazine **86** using $\text{Fe}_3\text{O}_4@\text{rGO}@\text{ZnO-HPA}$ as a catalyst.



Scheme 45 One-pot protocol for the synthesis of urea-substituted 2-arylfurans **88** by employing cyanamide **87** and heterocyclic enols **25**.



Scheme 46 Synthesis of substituted furo[3,2-b]pyrans **90** derived from allomaltol.

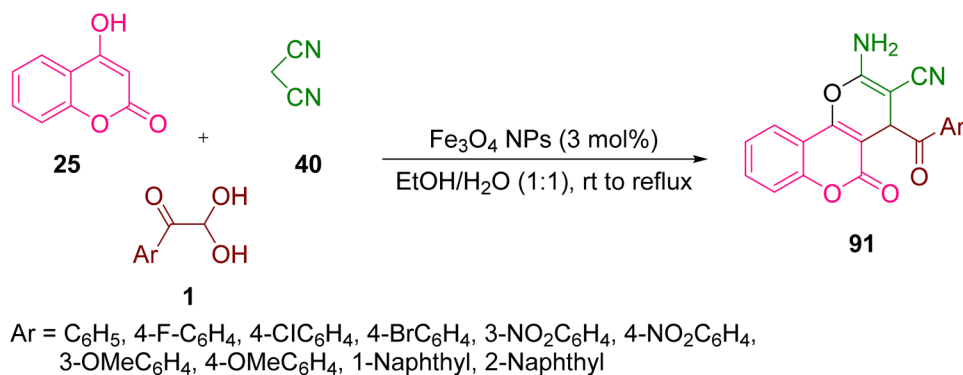
solvent system at reflux. The same reaction was tested against *p*-TSA, Na_2CO_3 , FeCl_3 , ZnCl_2 , and AcOH , and gave no significant yields of the desired products, except for the magnetically recyclable Fe_3O_4 nanoparticles (Scheme 47).⁷⁷

Also in 2014, Khodabakhshi and co-workers explored the use of nanosheets of graphene oxide with the same one-pot three-component combination under reflux conditions in an ethanol/water system with a low loading of GO catalyst. The advantages of the above protocol were marked by the recyclable catalyst with a minimum loading of 0.005 g, a high yield and a simple work-up procedure (Scheme 48).⁷⁸

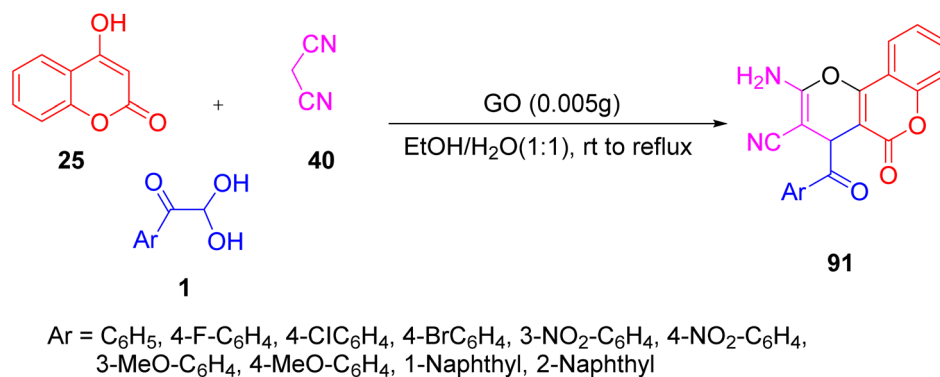
A synthetic library of multifunctional pyrano[c]chromenes **91** was developed by Khodabakhshi *et al.*, this time in the presence of ammonium dihydrogen phosphate at room temperature for the first 30–40 min, and then at reflux in an ethanol/water system (Scheme 49).⁷⁹

In 2014, Khodabakhshi's group successfully executed the same reaction in excellent yield with a high degree of purity in the presence of Mohr's salt (Scheme 50).⁸⁰

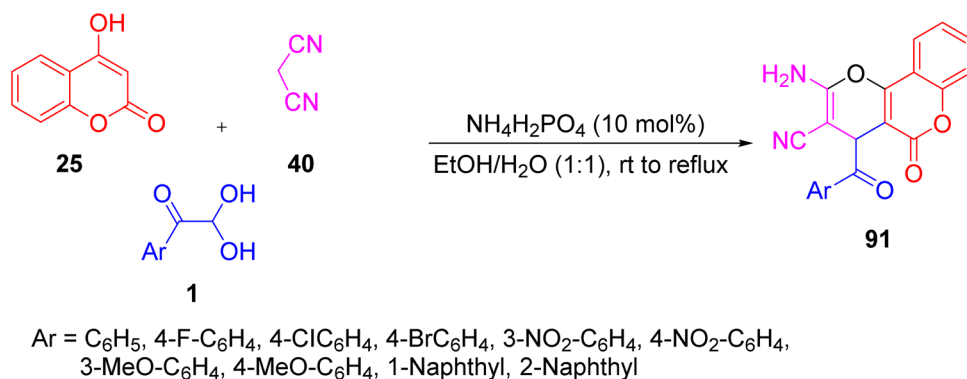
Afterwards, they reported a similar three-component reaction protocol where they replaced Mohr's salt with TiO_2 nanoparticles. Their process involved the coupling of **1** with malononitrile **40**,



Scheme 47 Nano-catalysed synthesis of dihydropyrano[c]chromenes **91** by reacting, 4-hydroxycoumarin **25** and malononitrile **40**.



Scheme 48 Graphene-oxide-catalysed synthesis of dihydropyrano[c]chromenes **91** by the reaction of 4-hydroxycoumarin and malononitrile.



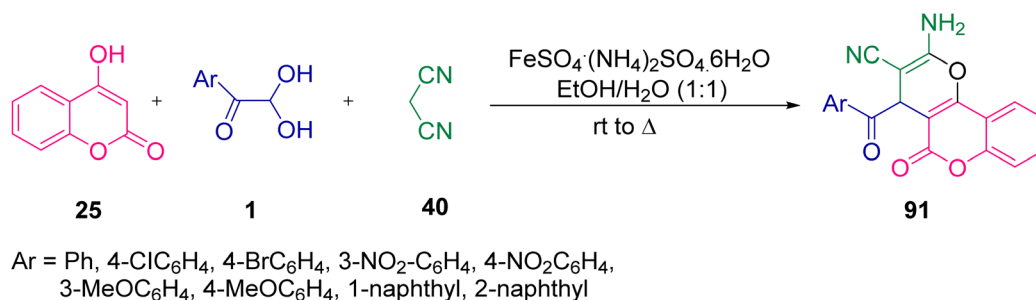
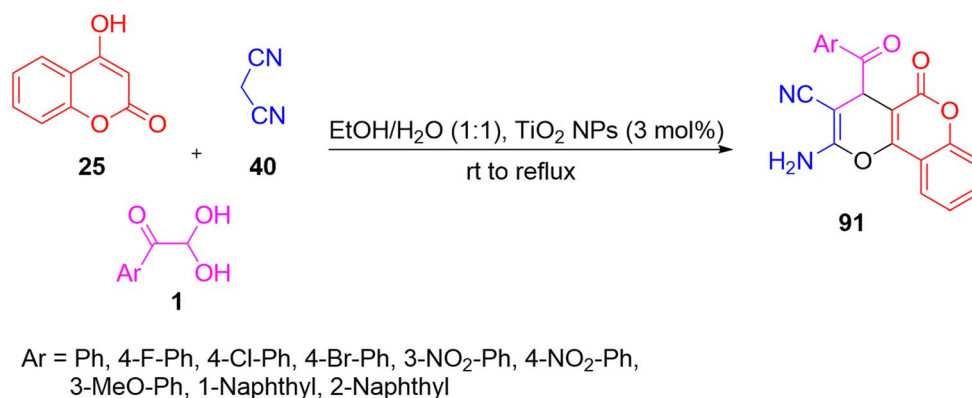
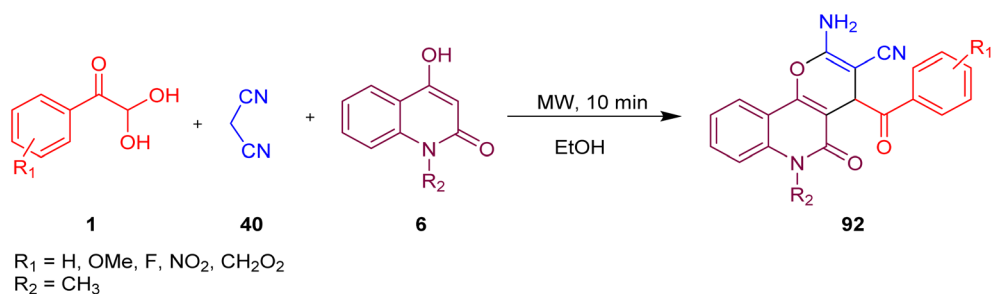
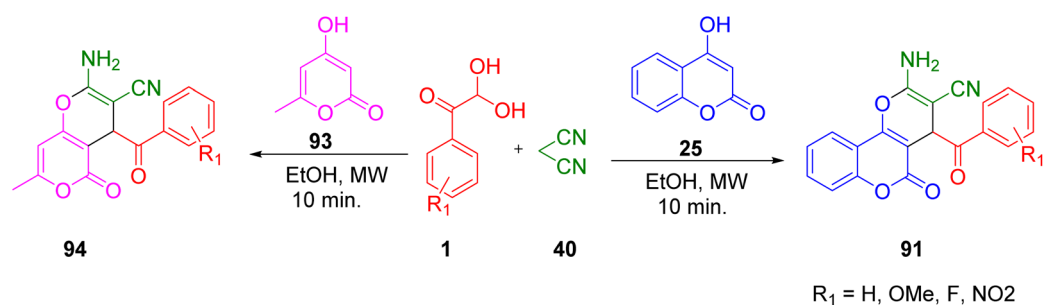
Scheme 49 Pyrano[c]chromenes **91** synthesis in the presence of ammonium dihydrogen phosphate.

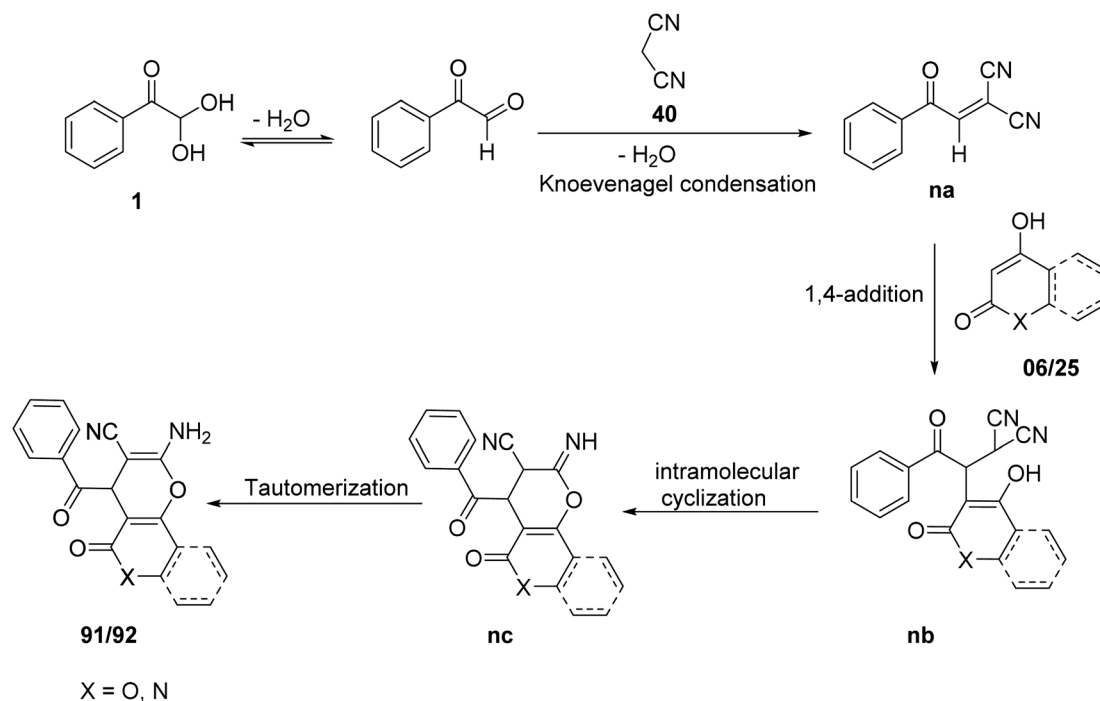
and **25** in the presence of a catalytic amount of TiO₂ nanoparticles to give a novel family of pyrano[3,2-*c*]chromenes **91** in excellent yield. Their reaction was both environmentally feasible and economically cost-effective since it utilised a greener solvent, and a reusable and safer catalyst (Scheme 51).⁸¹

Then in 2016, Mishra and Choudhury investigated the possibility of using microwave irradiation as one of the synthetic routes for the reaction of aryl glyoxal monohydrate **1**, malononitrile **40**, and cyclic 1,3-dicarbonyls **6** to afford several pyrans fused with many functionalities, such as coumarins,

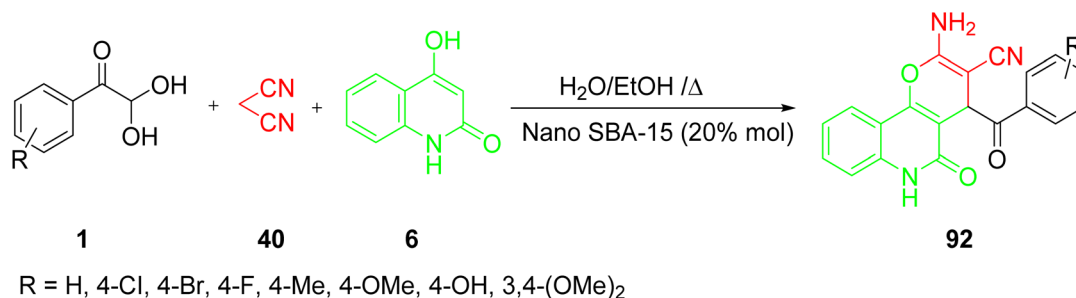
quinolones, naphthoquinones, and pyrones **92**. This approach is a basic and simple way of obtaining functionalized pyrans without the need for a catalyst or column chromatographic purification (Scheme 52).⁸²

In addition, Mishra and Choudhury also explored the scope of this technique to obtain the fused pyrans **91** and **94** by changing 1,3-dicarbonyls to other cyclic functionalities, such as 4-hydroxycoumarin **25** and 4-hydroxy-6-methyl-2*H*-pyran-2-one **93**. The corresponding products were isolated in high yields (Scheme 53).⁸² The reaction pathway is outlined in Scheme 54.

Scheme 50 Three-component synthesis of pyrano[3,2-c]coumarins **91**.Scheme 51 TiO₂-nanoparticle-catalysed synthesis of pyrano[3,2-c]chromenes **91**.Scheme 52 Microwave-assisted protocol for synthesis of fused pyrone **92**.Scheme 53 Synthesis of fused pyrans **91/94** using a microwave technique in the presence of ethanol.



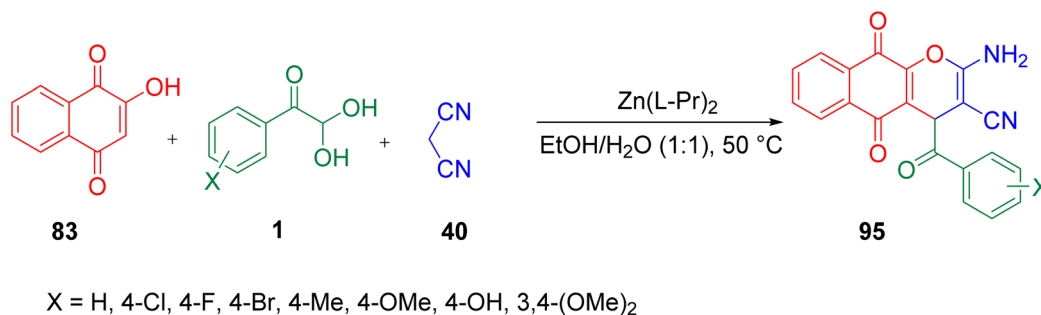
Scheme 54 Reaction pathway for the formation of fused pyran 91/92.



Scheme 55 SBA-15-catalysed green synthesis of 2-amino-4-aryl-5-oxo-5,6-dihydro-2H-pyrano[3,2-c]quinoline-3-carbonitrile 92.

Furthermore, Khalafy's group reported the nano-catalysed synthesis of 2-amino-4-aryl-5-oxo-5,6-dihydro-2H-pyrano[3,2-c]quinoline-3-carbonitrile **92** through the same combination of aryl glyoxal **1**, active methylene group **40** and 4-hydroxyquinolin-2(1H)-one **6** in a single-pot approach with the SBA-15

nanocatalyst in a green solvent. The simplicity of the workup procedure, the use of an ethanol/water system as the green medium, and the good to extraordinary product yields represent the key benefits of this synthetic technique (Scheme 55).⁸³



Scheme 56 Three-component synthesis of 4-aryl-4H-benzo[g]chromene 95.

Then Khalafy *et al.* extended the library of oxygen heterocycles in 2018 through 4-aryl-4*H*-benzo[*g*]chromene **95** synthesis using **1**, 2-hydroxy-1,4-naphthoquinone(lawsone) **83**, and one active methylene species **40** with the effective use of a Zn(L-Pr)₂ metal-amino acid complex. Zn(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*-toluenesulfonic acid, the phase-transfer catalyst tetrabutylammonium bromide, and L-cystein obtaining the target molecule **95** in a high yield with 20% L-proline in ethanol/water at 50 °C (Scheme 56).²⁵

Next, in 2018, Nasri *et al.* successfully employed aryl glyoxal to obtain the biologically important oxygen heterocycle and useful chemical synthon chromene. A chemical library of pyrano[3,2-*c*]chromene **91** and benzo[*g*]chromene **95** was constructed through a catalyst-free one-pot assembly of aryl glyoxal monohydrate **1**, malononitrile as the active methylene group **40**, and 4-hydroxycoumarin **25**/2-hydroxy-1,4-naphthoquinone **83**, respectively, under reflux conditions with ethanol as the solvent. Ethyl cyanoacetate, methyl cyanoacetate and cyanoacetamide favoured the enol product **95a** (Scheme 57).³³ This assembly is also considered to follow the same mechanistic pathway as explained in the case of other equivalent functionalities, starting from a Knoevenagel condensation to form the Michael acceptor **oa**, followed by 1-4 addition, thereby generating the open-chain intermediates **ob** and **od**, which subsequently undergo intramolecular cyclisation to yield the desired products **91** and **95** (Scheme 58).

In 2018, Khaligh synthesised 2-amino-4*H*-benzo[*g*]chromenes **95** using the same tactic of a condensation–Michael addition reaction by stirring aryl glyoxal **1**, malononitrile **40**, and 2-hydroxynaphthoquinone **83** with the catalyst poly(*N*-

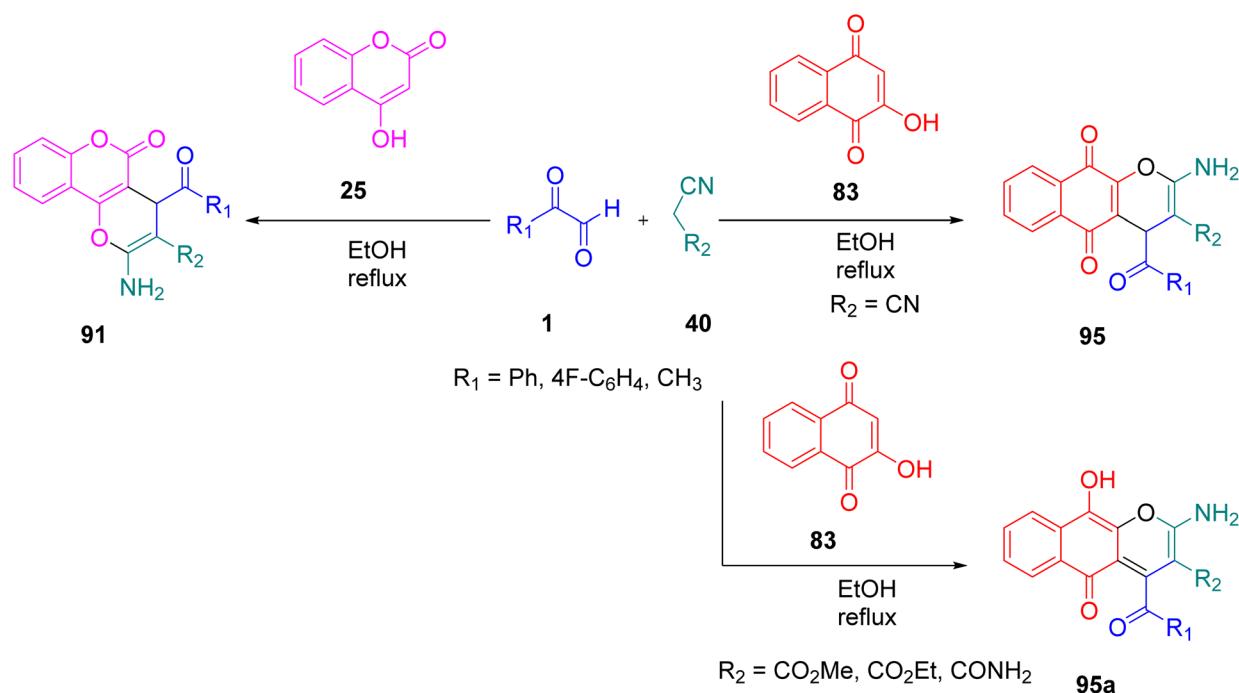
vinylimidazole) (PVIm) for two hours in refluxing ethanol. The resultant product **95** showed antibacterial activity against *Escherichia coli* at 32 mg cm^{−3} (Scheme 59).²⁷

Aryl glyoxal monohydrate as the same starting material was explored by Poursattar Marjani *et al.* in 2018, who reacted it with malononitrile **40** and 1,3-diketones **32** in the presence of the catalyst L-proline in ethanol solvent for the facile construction of 4*H*-chromenes, namely 2-amino-4-aryl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile **96** (Scheme 60).⁸⁴

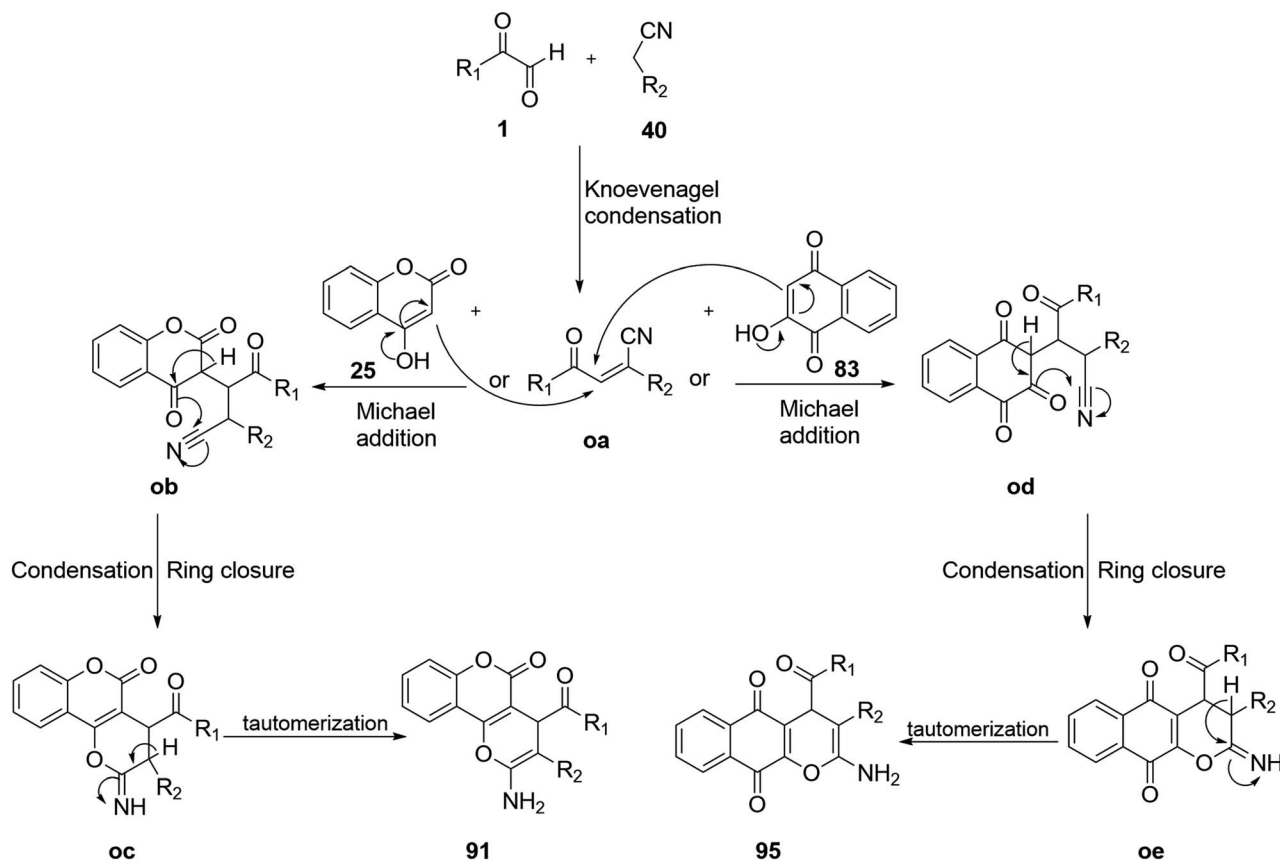
Poursattar Marjani and co-workers revealed the synthetic utility of aryl glyoxal by bringing together substituted aryl glyoxal **1** in a reaction vessel with 4-hydroxyquinolin-2(1*H*)-one **6** and ethyl cyanoacetate **40** in the presence of the catalyst TPAB in a water/ethanol system at reflux. This assembly yielded a series of ethyl 2-amino-4-benzoyl-5-oxo-5,6-dihydro-4*H*-pyrano[3,2-*c*]quinoline-3-carboxylate compounds **92** (Scheme 61).⁸⁵

A convenient method for the synthesis of a novel series of 2-amino-4-aryl-4*H*-benzo[*h*]chromene-3-carbonitriles **98** was developed by Poursattar Marjani *et al.* under solvent-free microwave (MW) conditions in high yields by using a multi-component condensation reaction of aryl glyoxals **1**, 1-naphthol **97**, and malononitrile **40** in the presence of Mg–Al hydrotalcite (Scheme 62).⁸⁶ A plausible outline of the scheme starts with the Mg–Al hydrotalcite-accelerated Knoevenagel reaction of **1** with C–H acid **40** to form an intermediate, namely 2-(2-oxo-2-arylethylidene)malononitrile **pa**. In the second step, α -naphthol is added as a C-nucleophile to the **pa**, forming a new species with the C–C bond **pb**. The intermediate **pc** undergoes intramolecular cyclisation to generate the species **pd**, which tautomerizes to give the product **98** (Scheme 63).

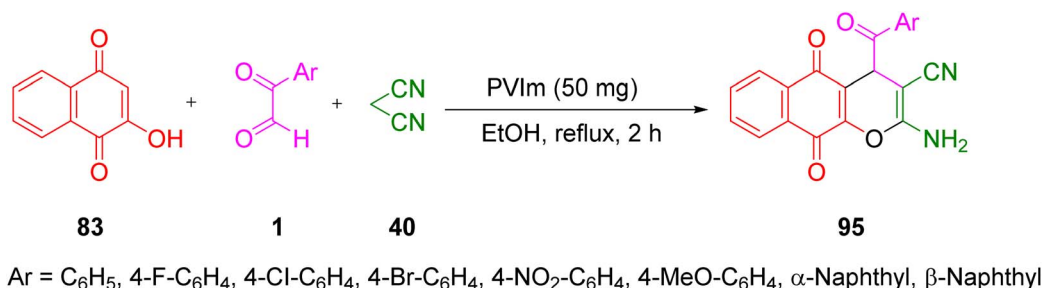
In 2015, a novel synthetic route was developed by Rimaz *et al.* to afford a library of biologically active substituted pyrano[2,3-*d*]



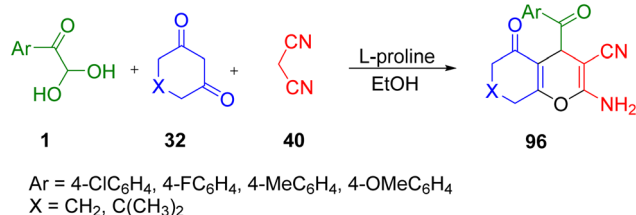
Scheme 57 MCR-based synthesis of the different pyran derivatives **91**, **95** and **95a**.



Scheme 58 Mechanisms for **91** and **95** formation through Knoevenagel condensation with a subsequent intramolecular cyclisation.



Scheme 59 Poly(*N*-vinylimidazole)-catalysed synthesis of 2-amino-4H-benzo[g]chromenes **95**.

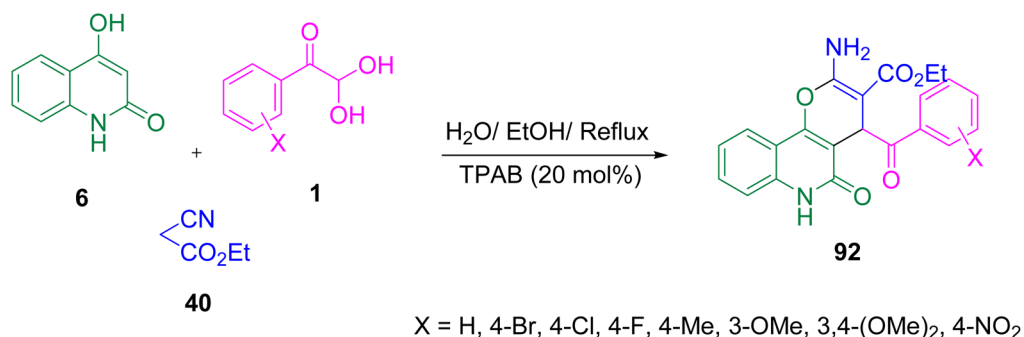


Scheme 60 Formation of 2-amino-4-aro-yl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile **96**.

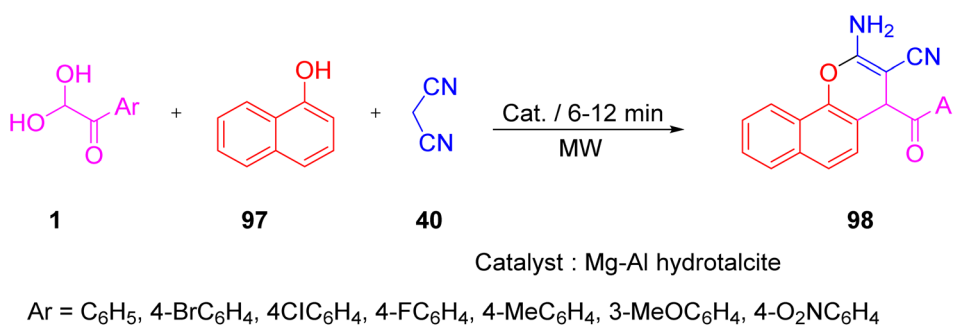
pyrimidines **99**. They obtained the desired products through an excess ammonium acetate-catalysed one-pot condensation of aryl glyoxal monohydrate **1** with barbituric acid **18** using the greenest solvent water at room temperature (Scheme 64).⁸⁷

Rimaz and co-workers also reported the synthesis of pyrano-fused pyrimidine derivatives **99** through the regioselective pseudo-three-component condensation reaction of aryl glyoxal monohydrate **1** and 1-ethyl-2-thioxodihydropyrimidine-4,6(1*H*,5*H*)-dione **18** in a catalytic system of DABCO or ZrOCl₂·8H₂O in ethanol at 50 °C. The pyrano-fused-pyrimidine scaffold in the synthesized compound was found to possess HIV integrase inhibitor activity (Scheme 65).³⁴

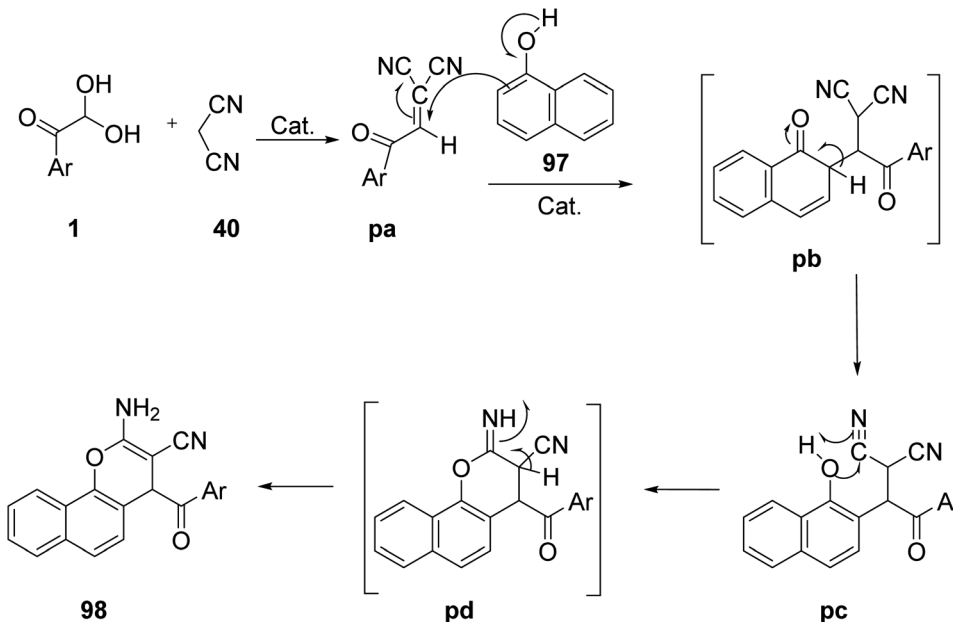
The potassium phthalimide-*N*-oxyl (PPINO)-organocatalysed one-pot green reaction of aryl glyoxal monohydrate **1** with barbituric acid **18** or thiobarbituric acid and β-naphthol **65** at reflux in water yielding benzo[5,6]chromene **100** and derivatives was single-handedly reported by Etivand *et al.* The distinguishing features of the protocol as highlighted were the use of green



Scheme 61 Synthesis of ethyl 2-amino-4-benzoyl-5-oxo-5,6-dihydro-4*H*-pyrano[3,2-*c*]quinoline-3-carboxylate **92** from 4-hydroxyquinoline-2(1*H*)-one **6**.



Scheme 62 Microwave-assisted reaction to afford 2-amino-4-aryl-4*H*-benzo[*h*]chromene-3-carbonitriles **98** using Mg–Al hydrotalcite.

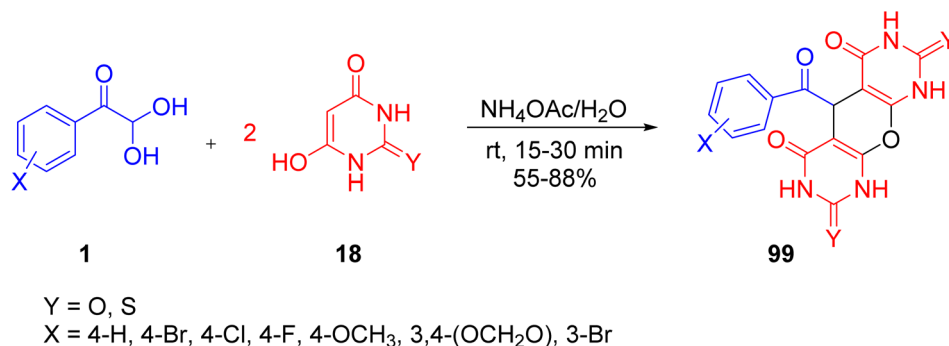


Scheme 63 Mechanism for the formation of 2-amino-4-aryl-4*H*-benzo[*h*]chromene-3-carbonitrile **98**.

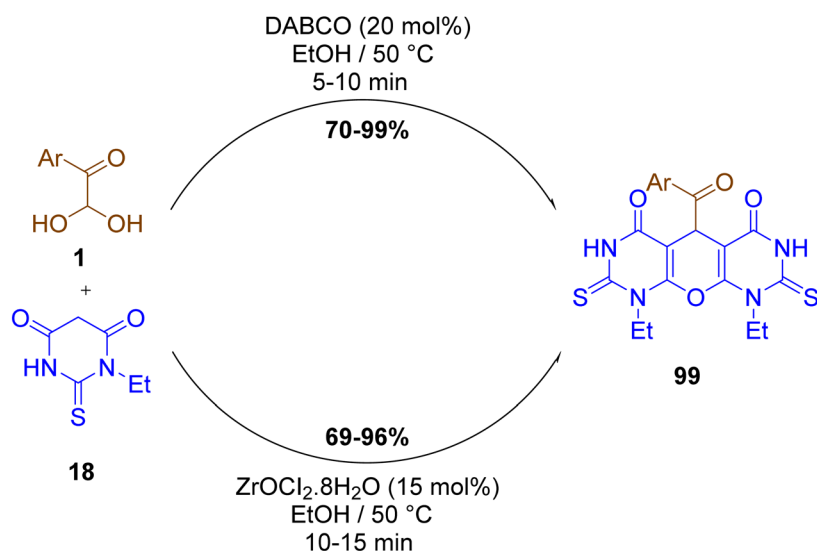
solvents, a short reaction time of only 30 minutes, and the product contained more than one heterocycle centre (Scheme 66).⁸⁸

In 2020, Taheri and Mohebat proposed a unique greener and environmentally friendly one-pot four-component protocol for

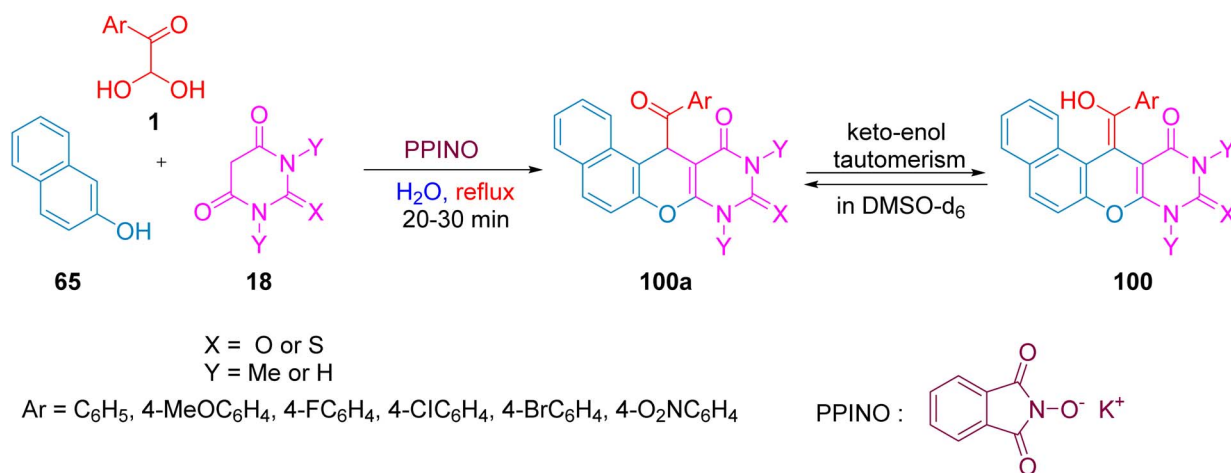
the synthesis of (1-methyl-3-phenyl-3,15-dihydrobenzo[*a*]pyrazolo[4',3':5,6]pyrano[2,3-*c*]phenazin-15-yl)methanone **102** scaffolds in a solvent-free medium using nano-Fe₃O₄@TiO₂-SO₃H as the catalyst under microwave monitoring at 75 °C. The major benefits of this green synthetic protocol were the mild



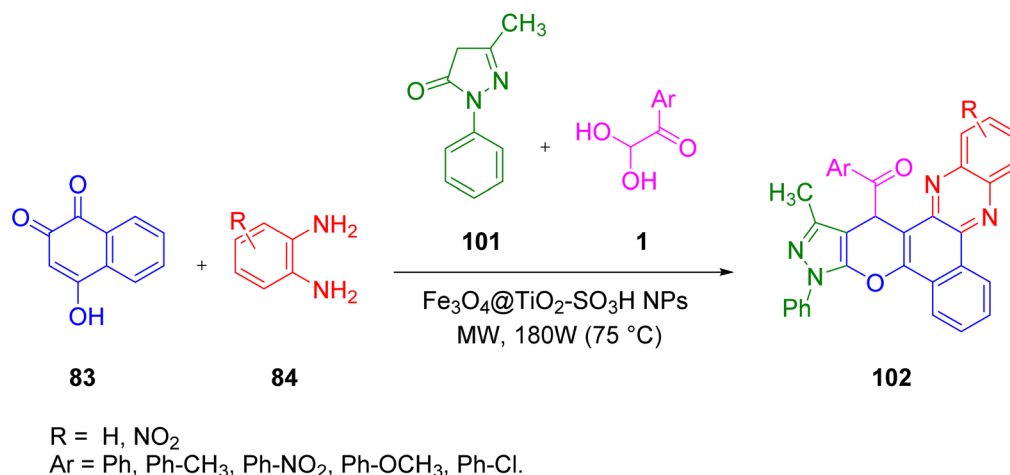
Scheme 64 Synthesis of pyrano[2,3-*d*]pyrimidines **99** via an ammonium acetate-catalysed reaction in the presence of a green solvent.



Scheme 65 Three-component reaction to yield pyrano-fused pyrimidine derivatives **99** using a catalytic system of DABCO or ZrOCl₂·8H₂O.



Scheme 66 Organocatalysed reaction of (PPINO) to yield benzo[5,6]chromene **100** using a green solvent.



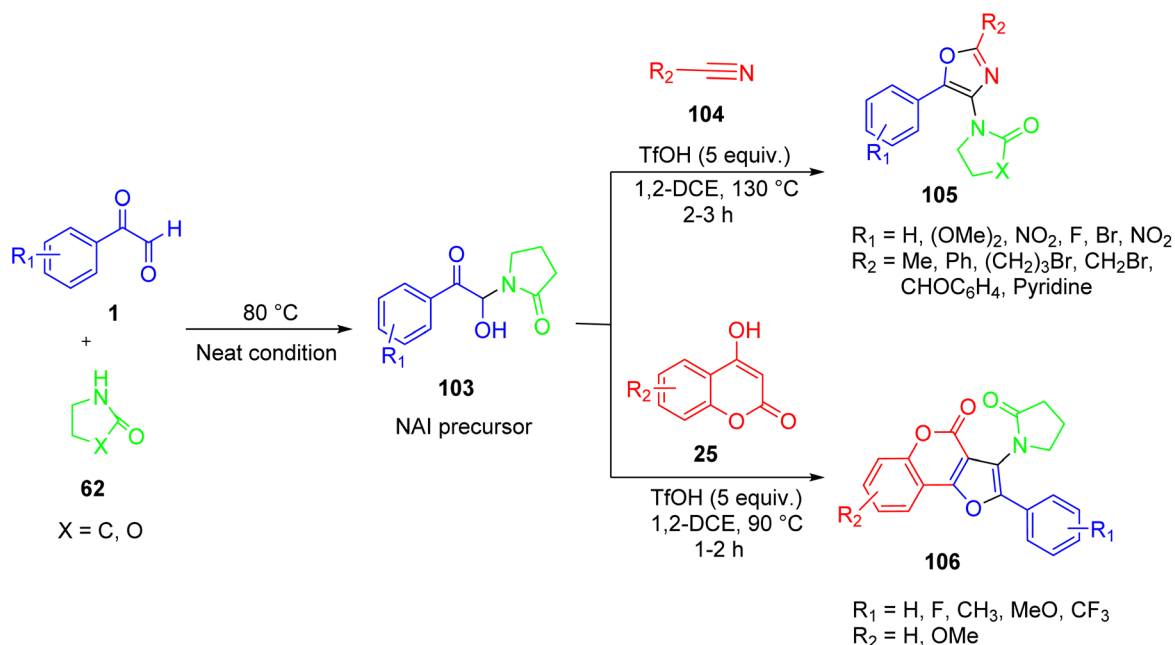
Scheme 67 Nano- $\text{Fe}_3\text{O}_4@\text{TiO}_2\text{-SO}_3\text{H}$ catalysed formation of (1-methyl-3-phenyl-3,15-dihydrobenzo[*a*]pyrazolo[4',3':5,6]pyrano[2,3-*c*]phenazin-15-yl)methanone **102**.

reaction conditions, a high product yield, fast reaction time, solvent-free condition, low energy demand and economic affordability (Scheme 67).⁸⁹

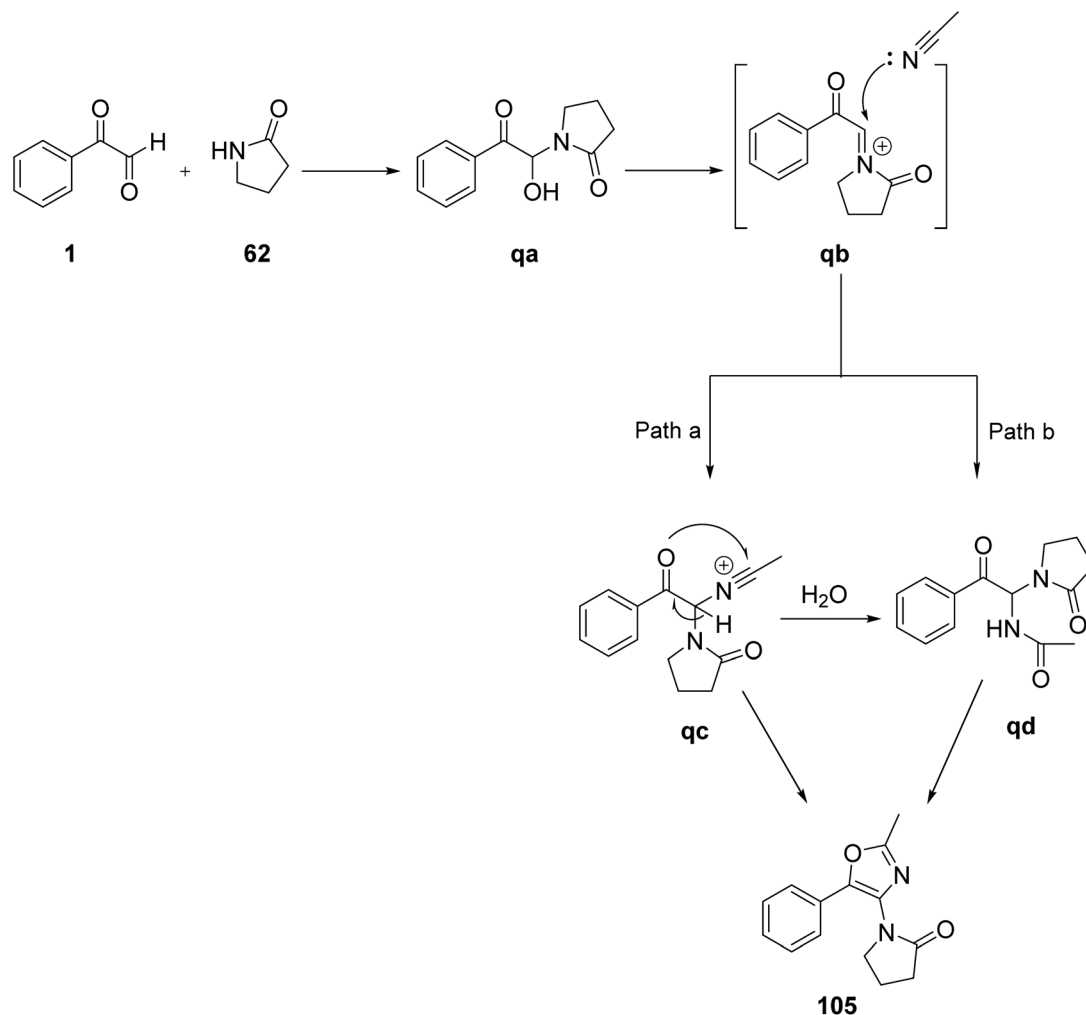
2.4. Miscellaneous reactions

Babu's group reported the simple and efficient synthesis of oxazoles **105** and furocoumarins **106**. The essential step in these transformations comprises the *in situ* formation of *N*-acyliminium ion (NAI) precursors **103** from aryl glyoxal and 2-pyrrolidinone **62** in the absence of a catalyst or solvent, followed by their further transformations aided by triflic acid in the same vessel. It was demonstrated experimentally that the special exocyclic proto-solvated *N*-acyliminium ion is involved in the

reaction. Additionally, the results of the fluorescence and UV-visible experiments revealed that a limited number of the compounds emit blue light when exposed to light in EtOH in the 404–422 nm wavelength range (Scheme 68).⁹⁰ An insight into the mechanism revealed that, at first, formation of the *N*-acyliminium ion (NAI) precursor **qa** from **1** and 2-pyrrolidinone **62** occurs under acid catalysis. There are two probable cyclisation routes. In route 'a', the attack of acetonitrile on the iminium intermediate **qb** leads to the formation of the nitrilium ion **qc**, which undergoes cyclisation to form the final product **105** through the involvement of an adjacent carbonyl group. While in route 'b', neutralisation of the nitrilium ion by a water molecule generates the bisamide **qd**, which subsequently



Scheme 68 Syntheses of oxazoles **105** and furocoumarins **106** via an *in situ* *N*-acyliminium ion (NAI) precursor.

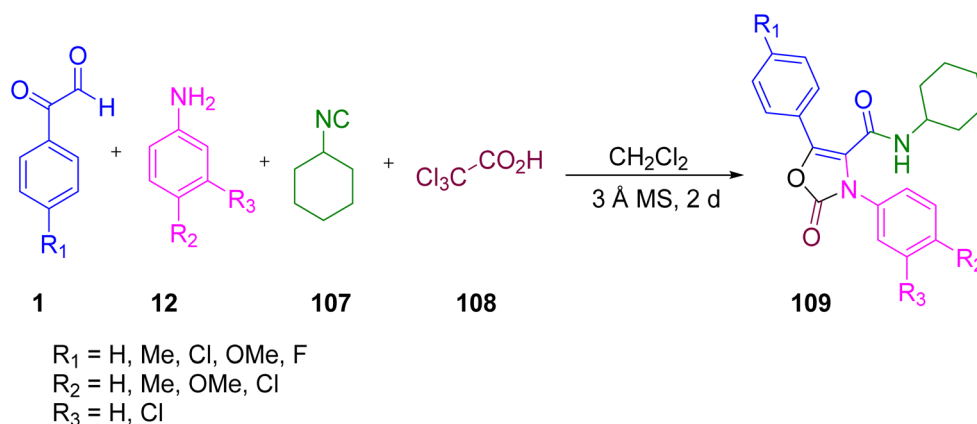


Scheme 69 Reaction pathway for the synthesis of substituted oxazoles **105**.

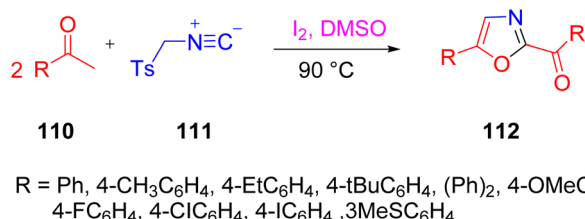
undergoes cyclisation, losing a water molecule to yield the desired product **105** (Scheme 69).

In 2008, García-Valverde *et al.* reported the reaction of aryl glyoxal **1** with aniline **12**, cyclohexyl-isocyanide **107**, and trichloroacetic acid **108** in dichloromethane, in the presence of a 3

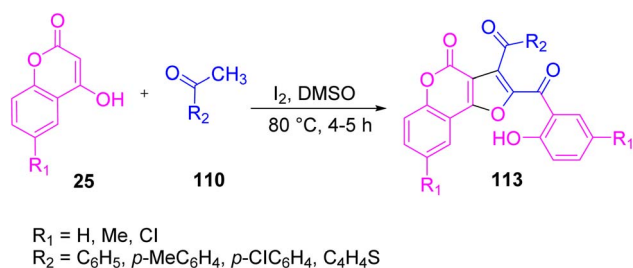
Å molecular sieve, to afford the oxazolone derivative **109** through the Ugi multicomponent reaction pathway group. The remarkable feature of the strategy is the carbonic acid function of the trichloroacetyl group (Scheme 70).⁹¹



Scheme 70 Synthesis of isoxazole **109** through an Ugi multicomponent reaction.



Scheme 71 Synthesis of oxazole **112** through a domino reaction using toluenesulfonylmethyl isocyanide **111**.



Scheme 72 Furo[3,2-c]coumarin **113** synthesis via *in situ*-generated phenyl glyoxal.

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

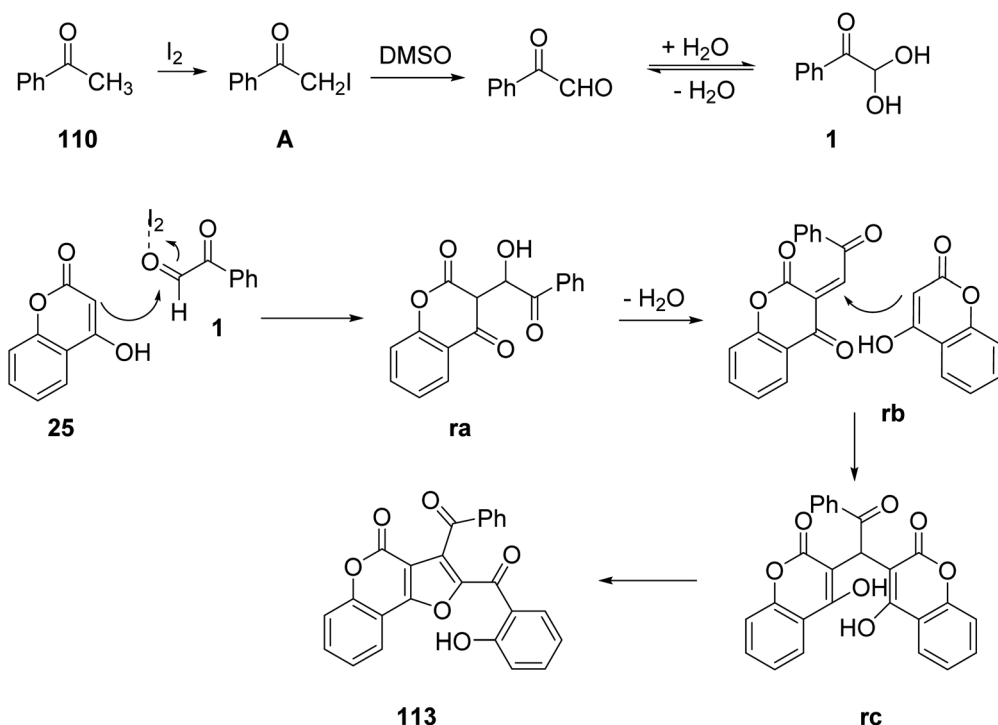
A novel method was developed by Pogaku *et al.* for the production of oxazoles **112** from methyl ketones **110** and TosMIC (toluenesulfonylmethyl isocyanide) **111** using a self-sorting domino reaction approach. TosMIC was used as an ammonium

surrogate in contrast to its typical reactivity as a C–N C synthon in the production of oxazoles **112** (Scheme 71).⁹² The technique is appealing due to its ease of operation, the wide availability of the starting materials, absence of bases and metals, and the production of C–N and C–O bonds with excellent yields.

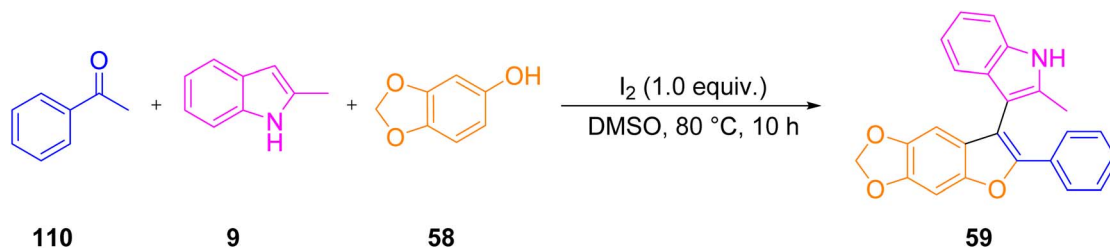
A facile, straightforward novel, and highly efficient protocol was reported by Kolita *et al.* in 2016 to obtain functionalized furo[3,2-c]coumarins **113** from 4-hydroxycoumarins **25**. The reaction was allowed to proceed by reacting aldehyde/aryl methyl ketone **110** with **25** in the presence 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 72).⁹³ The plausible mechanism of the reaction is that initially phenylglyoxal **1** is formed from phenyl methyl ketone **110** via $\text{sp}^3\text{-CH}$ activation and oxidation, and is subsequently allowed to react with 4-hydroxycoumarin **25** in the presence of iodine to form the intermediate **ra**. Species **ra** loses a water molecule, thereby generating **rb**. Nucleophilic attack by the second molecule of 4-hydroxycoumarin on the intermediate **rb** yields the final product **113** (Scheme 73).

Cheng's group prepared the highly dense benzofuran **59** by *in situ*-generating aryl glyoxal from methyl ketone **110**, phenol derivatives **58**, and indole **9** together in a reaction vessel with molecular iodine in a catalytic amount and DMSO as a solvent. Later, the nucleophile was changed to thiophenol and 1,2,4-trimethoxybenzene, *etc.*, in place of indole (Scheme 74).⁷

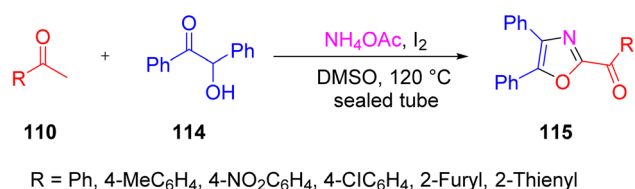
In 2012, Xue *et al.* proposed a novel and highly efficient protocol to synthesize polysubstituted oxazole derivatives **115** from simple and easily available starting materials, that is by reacting methyl ketone **110**, benzoin **114**, and ammonium



Scheme 73 *In situ* domino synthesis of furo[3,2-c]coumarin **113** by $\text{sp}^3\text{-CH}$ activation and oxidation.



Scheme 74 Synthesis of benzofuran **59** with the indole fragment **9** from methyl ketone **110**.

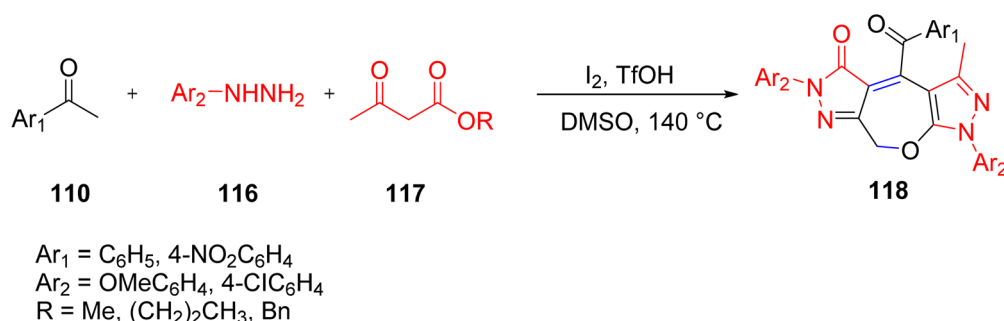


Scheme 75 Domino reaction leading to benzoin **114**-derived oxazole **115**.

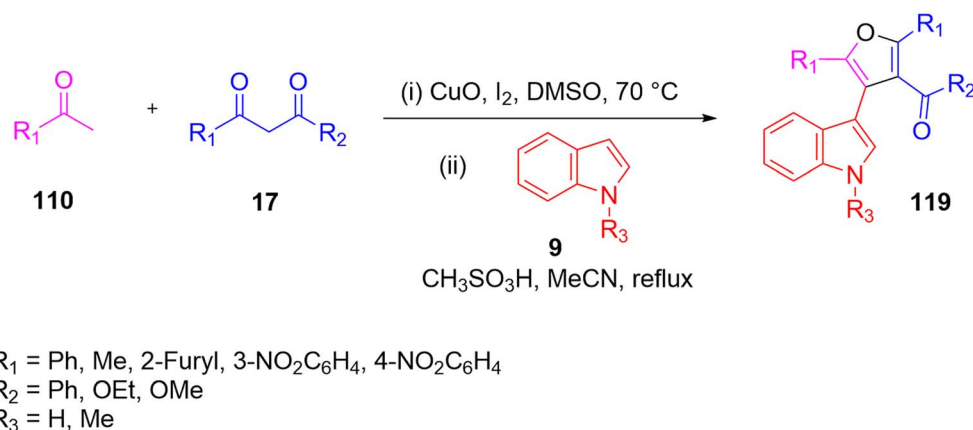
acetate *via* the convergent integration of two “self-labour domino sequences”. This reaction has wide application in medicinal and life science chemistry (Scheme 75).⁹⁴

In 2018, Zhao and co-workers proposed a novel path for the synthesis of fused heterocycles by employing an iodine-promoted fragment assembly method. They formulated pyrazolone-oxepine-pyrazoles **118** by the reaction of phenylhydrazine **116**, aryl methyl ketones **110**, and acetoacetate ester **117** using molecular iodine at 140 °C in the presence of TfOH, and also explored the application of a five-component reaction. Acetoacetate ester engages in two crucial steps, which are the formation of the 3-methyl-5-pyrazolone skeleton and the formation of the C(sp³)-O bond (Scheme 76).⁹⁵

In 2011, Yang *et al.* performed a convergent and linear domino reaction for the first time from easily available inexpensive substrates, like methyl ketone **110**, indole **9**, and 1,3-



Scheme 76 Synthesis of pyrazolone-oxepine-pyrazoles **118** from phenylhydrazine **116**, acetoacetate ester **117** and *in situ*-generated phenyl glyoxal **1**.



Scheme 77 Synthesis of 3-(furan-3-yl or 4-yl) indole derivative **119** from 1,3-diketone **17**, indole **9** and methyl ketone **110**.

dicarbonyl **17** to afford the 3-(furan-3-yl or 4-yl) indole derivative **119** via a direct two-step process without the need for purification of the intermediate. This reaction has a wide range of applications in synthetic and medicinal chemistry due to its operational simplicity (Scheme 77).⁹⁶

3. Conclusions

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 give rise to highly complex synthetic diversity in the products, inspiring researchers to think beyond the current scope 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 in biosystems. Furthermore, 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.

Data availability

No primary research results, software or code have been included and no new data were generated or analysed as part of this review.

Conflicts of interest

There are no conflicts to declare.

References

- 1 F. Wöhler, *Ann. Phys. Chem.*, 1828, **88**, 253–256.
- 2 A. Dömling, W. Wang and K. Wang, *Chem. Rev.*, 2012, **112**, 3083–3135.
- 3 S. Banerjee, A. Horn, H. Khatri and G. Sereda, *Tetrahedron Lett.*, 2011, **52**, 1878–1881.
- 4 I. Ugi, A. Dömling and W. Hörl, *Endeavour*, 1994, **18**, 115–122.
- 5 M. M. Khan, R. Yousuf, S. Khan and Shafiullah, *RSC Adv.*, 2015, **5**, 57883–57905.
- 6 R. C. Cioc, E. Ruijter and R. V. A. Orru, *Green Chem.*, 2014, **16**, 2958–2975.
- 7 C. Cheng, C. Liu and Y. Gu, *Tetrahedron*, 2015, **71**, 8009–8017.
- 8 M. M. Khan, S. Khan, S. Saigal and S. Iqbal, *RSC Adv.*, 2016, **6**, 42045–42061.
- 9 A. M. El-Agrody, A. M. Fouda and A.-A. M. Al-Dies, *Med. Chem. Res.*, 2014, **23**, 3187–3199.
- 10 A. Zonouzi, R. Mirzazadeh, M. Safavi, S. Kabudanian Ardestani, S. Emami and A. Foroumadi, *Iran. J. Pharm. Res.*, 2013, **12**, 679–685.
- 11 A. Poursattar Marjani, J. Khalafy and A. Farajollahi, *J. Heterocycl. Chem.*, 2019, **56**, 268–274.
- 12 P. Prasad, P. G. Shobhashana and M. P. Patel, *R. Soc. Open Sci.*, 2017, **4**, 170764.
- 13 D. Armesto, W. M. Horspool, N. Martin, A. Ramos and C. Seoane, *J. Org. Chem.*, 1989, **54**, 3069–3072.
- 14 M. Eghtedari, Y. Sarrafi, H. Nadri, M. Mahdavi, A. Moradi, F. Homayouni Moghadam, S. Emami, L. Firoozpour, A. Asadipour, O. Sabzevari and A. Foroumadi, *Eur. J. Med. Chem.*, 2017, **128**, 237–246.
- 15 S. A. Look, M. T. Burch, W. Fenical, Q. Zheng and J. Clardy, *J. Org. Chem.*, 1985, **50**, 5741–5746.
- 16 I. Butenschön, K. Möller and W. Hänsel, *J. Med. Chem.*, 2001, **44**, 1249–1256.
- 17 H. N. Akolkar, S. G. Dengale, K. K. Deshmukh, B. K. Karale, N. R. Darekar, V. M. Khedkar and M. H. Shaikh, *Polycyclic Aromat. Compd.*, 2022, **42**, 1959–1971.
- 18 A. Lilienkamp, M. Pieroni, S. G. Franzblau, W. R. Bishai and A. P. Kozikowski, *Curr. Top. Med. Chem.*, 2012, **12**, 729–734.
- 19 G. Daidone, D. Raffa, B. Maggio, F. Plescia, V. M. C. Cutuli, N. G. Mangano and A. Caruso, *Arch. Pharm.*, 1999, **332**, 50–54.
- 20 J. J. Talley, D. L. Brown, J. S. Carter, M. J. Graneto, C. M. Koboldt, J. L. Masferrer, W. E. Perkins, R. S. Rogers, A. F. Shaffer, Y. Y. Zhang, B. S. Zweifel and K. Seibert, *J. Med. Chem.*, 2000, **43**, 775–777.
- 21 P. Rawat and S. M. Verma, *Drug Des., Dev. Ther.*, 2016, **10**, 2779–2788.
- 22 H. Sourgens, R. Hoerr, A. Biber, H. Steinbrede and H. Derendorf, *J. Clin. Pharmacol.*, 1998, **38**, 373–381.
- 23 A. B. Pardee, Y. Li and C. J. Li, *Curr. Cancer Drug Targets*, 2002, **2**, 227–242.
- 24 C. J. Li, Y.-Z. Li, A. N. Pinto and A. B. Pardee, *Proc. Natl. Acad. Sci. U. S. A.*, 1999, **96**, 13369–13374.
- 25 J. Khalafy, S. Ilkhanizadeh and M. Ranjbar, *J. Heterocycl. Chem.*, 2018, **55**, 951–956.
- 26 P. Ravichandiran, B. Lai and Y. Gu, *Chem. Rec.*, 2017, **17**, 142–183.
- 27 N. G. Khaligh, *Monatsh. Chem.*, 2018, **149**, 33–38.

- 28 S.-T. Guo, J. Xu, X.-L. Zhang, X.-S. Xiong, L. Zhang, D.-L. Wang and S.-Q. Zhang, *Heterocycles*, 2021, **102**, 105.
- 29 M. Guarrera, L. Turbino and A. Rebora, *J. Eur. Acad. Dermatol. Venereol.*, 2001, **15**, 486–487.
- 30 A. S. Alqahtani, S. Hidayathulla, M. T. Rehman, A. A. ElGamal, S. Al-Massarani, V. Razmovski-Naumovski, M. S. Alqahtani, R. A. El Dib and M. F. AlAjmi, *Biomolecules*, 2019, **10**, 61.
- 31 M. Karami, A. Hasaninejad, H. Mahdavi, A. Iraj, S. Mojtavavi, M. A. Faramarzi and M. Mahdavi, *Mol. Diversity*, 2022, **26**, 2393–2405.
- 32 M. Hanefeld and F. Schaper, *Expert Rev. Cardiovasc. Ther.*, 2008, **6**, 153–163.
- 33 S. Nasri and M. Bayat, *J. Mol. Struct.*, 2018, **1164**, 77–88.
- 34 M. Rimaz, H. Mousavi, B. Khalili and L. Sarvari, *J. Iran. Chem. Soc.*, 2019, **16**, 1687–1701.
- 35 L. Palanivel and V. Gnanasambandam, *Org. Biomol. Chem.*, 2020, **18**, 3082–3092.
- 36 R. Hazen, R. Harvey, R. Ferris, C. Craig, P. Yates, P. Griffin, J. Miller, I. Kaldor, J. Ray, V. Samano, E. Furfine, A. Spaltenstein, M. Hale, R. Tung, M. St. Clair, M. Hanlon and L. Boone, *Antimicrob. Agents Chemother.*, 2007, **51**, 3147–3154.
- 37 A. K. Ghosh, Z. L. Dawson and H. Mitsuya, *Bioorg. Med. Chem.*, 2007, **15**, 7576–7580.
- 38 K. McKeage, C. M. Perry and S. J. Keam, *Drugs*, 2009, **69**, 477–503.
- 39 S. Gupta, B. Kushwaha, A. Srivastava, J. P. Maikhuri, S. N. Sankhwar, G. Gupta and A. K. Dwivedi, *RSC Adv.*, 2016, **6**, 76288–76297.
- 40 H. S. Whang, M. A. Hunt, N. Wrench, J. E. Hockney, C. E. Farin and A. E. Tonelli, *J. Appl. Polym. Sci.*, 2007, **106**, 4104–4109.
- 41 S. A. Dingsdag and N. Hunter, *J. Antimicrob. Chemother.*, 2018, **73**, 265–279.
- 42 B. Eftekhari-Sis, M. Zirak and A. Akbari, *Chem. Rev.*, 2013, **113**, 2958–3043.
- 43 J. Li, L. Liu, D. Ding, J. Sun, Y. Ji and J. Dong, *Org. Lett.*, 2013, **15**, 2884–2887.
- 44 N. R. Modugu and P. K. Pittala, *Tetrahedron Lett.*, 2017, **58**, 3859–3863.
- 45 A. N. Komogortsev, B. V. Lichitsky and V. G. Melekhina, *Molbank*, 2021, **2021**, M1292.
- 46 H. Shahbazi-Alavi, R. Teymuri and J. Safaei-Ghomi, *Nanochem. Res.*, 2021, **6**, 135–142.
- 47 S. M. Ebrahimi, B. Hamah-Ameen, A. Kareem Abbas, H. Shahbazi-Alavi, H. Gholamzadeh and J. Safaei-Ghomi, *Polycyclic Aromat. Compd.*, 2022, **42**, 6389–6397.
- 48 C. Liu, L. Zhou, D. Jiang and Y. Gu, *Asian J. Org. Chem.*, 2016, **5**, 367–372.
- 49 F. Dehghanzadeh, F. Shahrokhbabadi and M. Anary-Abbasinejad, *Arkivoc*, 2019, **2019**, 133–141.
- 50 R. Khoeiniha, A. Olyaei and M. Saraei, *Synth. Commun.*, 2018, **48**, 155–160.
- 51 M. H. Mosslemin, M. Anary-Abbasinejad, A. F. Nia, S. Bakhtiari and H. Anaraki-Ardakani, *J. Chem. Res.*, 2009, **2009**, 599–601.
- 52 X. Chang, P. Zeng and Z. Chen, *Eur. J. Org. Chem.*, 2019, **2019**, 6478–6485.
- 53 M. R. Salari, M. H. Mosslemin and A. Hassanabadi, *J. Chem. Res.*, 2017, **41**, 657–660.
- 54 A. N. Komogortsev, B. V. Lichitsky, A. D. Tretyakov, A. A. Dudinov and M. M. Krayushkin, *Chem. Heterocycl. Compd.*, 2019, **55**, 818–822.
- 55 B. V. Lichitsky, V. G. Melekhina, A. N. Komogortsev and M. E. Minyaev, *Tetrahedron Lett.*, 2020, **61**, 152602.
- 56 A. N. Komogortsev, V. G. Melekhina, B. V. Lichitsky and M. E. Minyaev, *Tetrahedron Lett.*, 2020, **61**, 152384.
- 57 B. Karami, S. Khodabakhshi and K. Eskandari, *Synlett*, 2013, **24**, 998–1000.
- 58 Z. Chen, P. Zeng, S. Zhang and X. Huang, *ChemistrySelect*, 2021, **6**, 4539–4543.
- 59 B. V. Lichitsky, A. N. Komogortsev and V. G. Melekhina, *Molbank*, 2021, **2021**, M1304.
- 60 A. Jana, D. Ali, P. Bhaumick and L. H. Choudhury, *J. Org. Chem.*, 2022, **87**, 7763–7777.
- 61 L. Palanivel and V. Gnanasambandam, *Org. Biomol. Chem.*, 2020, **18**, 3082–3092.
- 62 A. El-Hairry, Yiliqi, M. Yue, W. Fan, F. Popowycz, Y. Queneau, M. Li and Y. Gu, *ChemCatChem*, 2019, **11**, 4403–4410.
- 63 B. V. Lichitskii, V. G. Melekhina, A. N. Komogortsev, C. V. Milyutin, A. N. Fakhrutdinov, Y. O. Gorbunov and M. M. Krayushkin, *Org. Biomol. Chem.*, 2020, **18**, 2501–2509.
- 64 P. Rajesh, A. I. Almansour, N. Arumugam and S. Yaragorla, *Org. Biomol. Chem.*, 2021, **19**, 1060–1065.
- 65 B. V. Lichitsky, A. N. Komogortsev and V. G. Melekhina, *Molbank*, 2022, **2022**, M1315.
- 66 B. V. Lichitsky, V. G. Melekhina, A. N. Komogortsev, V. A. Migulin, Y. V. Nelyubina, A. N. Fakhrutdinov, E. D. Daeva and A. A. Dudinov, *Tetrahedron*, 2021, **83**, 131980.
- 67 A. N. Komogortsev, B. V. Lichitsky and V. G. Melekhina, *Tetrahedron Lett.*, 2021, **78**, 153292.
- 68 C. X. Chen, L. Liu, D. P. Yang, D. Wang and Y. J. Chen, *Synlett*, 2005, **13**, 2047–2051.
- 69 X. Chang, X. Zhang and Z. Chen, *Org. Biomol. Chem.*, 2018, **16**, 4279–4287.
- 70 B. Karami, S. Khodabakhshi and F. Hashemi, *Tetrahedron Lett.*, 2013, **54**, 3583–3585.
- 71 M. R. Salari, M. H. Mosslemin and A. Hassanabadi, *J. Chem. Res.*, 2019, **43**, 86–89.
- 72 X. Zhang, P. Zeng, S. Zhang and Z. Chen, *ChemistrySelect*, 2020, **5**, 3934–3938.
- 73 M. Taheri, R. Mohebat and M. H. Moslemin, *Artif. Cells, Nanomed., Biotechnol.*, 2021, **49**, 250–260.
- 74 M. Taheri, R. Mohebat and M. H. Moslemin, *Polycyclic Aromat. Compd.*, 2023, **43**, 586–596.
- 75 A. N. Komogortsev, V. G. Melekhina, B. V. Lichitsky, V. A. Migulin, T. T. Karibov and M. E. Minyaev, *Tetrahedron*, 2022, **111**, 132716.
- 76 A. N. Komogortsev, B. V. Lichitsky, T. T. Karibov and V. G. Melekhina, *Tetrahedron*, 2022, **117–118**, 132836.

- 77 S. Khodabakhshi, B. Karami and M. Baghernejad, *Monatsh. Chem.*, 2014, **145**, 1839–1843.
- 78 S. Khodabakhshi and B. Karami, *New J. Chem.*, 2014, **38**, 3586–3590.
- 79 S. Khodabakhshi, B. Karami, K. Eskandari and M. Farahi, *Tetrahedron Lett.*, 2014, **55**, 3753–3755.
- 80 S. Khodabakhshi, F. Jafari, F. Marahel and M. Baghernejad, *Heterocycl. Commun.*, 2014, **20**, 285–288.
- 81 S. Khodabakhshi, M. Shahamirian and M. Baghernejad, *J. Chem. Res.*, 2014, **38**, 473–476.
- 82 R. Mishra and L. H. Choudhury, *RSC Adv.*, 2016, **6**, 24464–24469.
- 83 J. Khalafy, F. M. Arlan and S. S. Chalanchi, *J. Heterocycl. Chem.*, 2018, **55**, 149–153.
- 84 A. Poursattar Marjani, B. E. Saatluo and F. Nouri, *Iran. J. Chem. Chem. Eng.*, 2018, **37**, 149–157.
- 85 A. Poursattar Marjani, J. Khalafy and A. Farajollahi, *J. Heterocycl. Chem.*, 2019, **56**, 268–274.
- 86 A. Poursattar Marjani, J. Khalafy, P. Eslamipour and M. A. Sabegh, *Iran. J. Chem. Chem. Eng.*, 2019, **38**, 51–57.
- 87 M. Rimaz, A. Mirshokraie, B. Khalili and P. Motiee, *Arkivoc*, 2015, **2015**, 88–98.
- 88 N. Etivand, J. Khalafy and M. G. Dekamin, *Synthesis*, 2020, **52**, 1707–1718.
- 89 M. Taheri and R. Mohebat, *Green Chem. Lett. Rev.*, 2020, **13**, 165–178.
- 90 V. N. Babu, A. Murugan, N. Katta, S. Devatha and D. S. Sharada, *J. Org. Chem.*, 2019, **84**, 6631–6641.
- 91 M. García-Valverde, S. Macho, S. Marcaccini, T. Rodríguez, J. Rojo and T. Torroba, *Synlett*, 2008, **1**, 33–36.
- 92 N. Pogaku, P. R. Krishna and Y. L. Prapurna, *Synth. Commun.*, 2018, **48**, 1986–1993.
- 93 S. Kolita, P. Borah, P. S. Naidu and P. J. Bhuyan, *Tetrahedron*, 2016, **72**, 532–538.
- 94 W. J. Xue, Q. Li, Y. P. Zhu, J. G. Wang and A. X. Wu, *Chem. Commun.*, 2012, **48**, 3485–3487.
- 95 P. Zhao, X. Wu, X. Geng, C. Wang, Y. D. Wu and A. X. Wu, *Tetrahedron*, 2018, **74**, 4323–4330.
- 96 Y. Yang, M. Gao, L. M. Wu, C. Deng, D. X. Zhang, Y. Gao, Y. P. Zhu and A. X. Wu, *Tetrahedron*, 2011, **67**, 5142–5149.