

Cite this: *RSC Adv.*, 2019, 9, 14477

Received 24th January 2019

Accepted 17th April 2019

DOI: 10.1039/c9ra00630c

rsc.li/rsc-advances

Nitroketene *N,S*-acetals: synergistic building blocks for the synthesis of heterocycles

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The development of novel heterocyclic compounds from simple and easily accessible starting components is of significant importance in medicinal chemistry. Due to the presence of active chromophores and potent pharmacological activities, nitroketene *N,S*-acetals have emerged as a fascinating building block in organic synthesis. The synergistic skeleton of these acetals and the presence of electron-donating as well as electron-withdrawing groups lead to the generation of distinctive structural features and are highly useful for building diverse heterocyclic rings. This review highlights the preparation of different nitroketene *N,S*-acetals and their applications in the synthesis of diverse heterocyclic compounds.

1. Introduction

The novel inventions of small drug-like heterocycles are a challenging task for an organic and medicinal researcher. Among all known organic compounds, heterocycles occupy a central place because of their enormous presence in natural products, hormones, vitamins, antibiotics, dyes, agrochemicals, pharmaceuticals, *etc.*,^{1,2} moreover, due to their well-established therapeutic properties, heterocycles are significantly needed for counteracting various infectious diseases to achieve a healthy human life. They show a broad spectrum of biological activities such as antitumor,³ antibiotic,⁴ antidepressant,⁵ antimalarial,⁶

anti-HIV,⁷ antimicrobial,⁸ antiviral,⁹ anticancer,¹⁰ antitubercular,¹¹ antidiabetic¹² and anti-inflammatory activities.¹³ Some examples of pharmacologically and biologically potent heterocycles are depicted in Fig. 1.^{14–16} In addition, the molecules having a heterocycle as a subunit exhibit enhanced solubility and salt formation; this enables their oral absorption and bioavailability;¹⁷ therefore, both the development of a novel methodology and the strategic replacement of known methodology for the preparation of these heterocycles remain the active areas of research. The development of an innovative, environmentally benign, sustainable and practical method to carry out organic reactions demands certain regulations and guidelines.¹⁸ The common tactics to improve the synthetic methods for the synthesis of heterocycles are either to design a distinctive precursor or to develop novel catalysts.¹⁹ However, organic building blocks are important in a number of chemical protocols and play a key role in the reaction medium for chemical transformation to create molecular diversity.

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Sarfaraz Khan was born in Delhi, India in 1991. He received his B.Sc. (Hons.) in Chemistry from the University of Delhi, India in 2012, and in 2014, he obtained his M.Sc. degree with Organic Chemistry specialization from the same university. Currently, he is pursuing his Ph.D. under the supervision of Dr Md. Musawwer Khan as a UGC-SRF research fellow in

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In the present scenario, different kinds of ketene *N,S*-acetals, which contain electron-releasing and electron-withdrawing substituents, lead to unique structural features and are of significant interest to synthetic chemists due to their utility as useful starting materials in organic chemistry.^{20,21}

In addition, ketene *N,S*-acetal derivatives are as such used as drugs for the treatment of hypertension diseases and usually employed as probes for nucleic acids to investigate the interaction between G4 (G-quadruplex) and its ligands (Fig. 2).²²

Interestingly, the cyclic nitroketene *N,S*-acetal nithiazine **IV** was the first reported compound of neonicotinoid insecticides²³ and is currently used as a common insecticide all over the world. Recently, Rao and his co-workers have described the *in silico* evaluation of acyclic nitroketene *N,S*-acetals, *i.e.*, (*E*)-*N*-methyl-1-(methylthio)-2-nitroethenamine (NMSM) derivatives, against Alzheimer's disease.²⁴

Presently, five types of ketene acetals are mainly known: *S,S*-acetals (**V**), *O,O*-acetals (**VI**), *N,S*-acetals (**VII**), *N,N*-acetals (**VIII**)

and silyl acetals (**IX**), as depicted in Fig. 3. Among these, ketene *N,S*-acetals are the most abundant family in the world of ketene acetal chemistry. Furthermore, the ketene *O,O*; *N,N*; *S,S*; and *N,S* and ketene silyl acetals have been well studied and reviewed.^{25,26} However, according to our survey, to date, a review article summarizing the preparation and synthetic utilities of nitroketene *N,S*-acetals has not been reported in the literature.

In the present review, we tried to cover the chemistry of nitroketene *N,S*-acetals in terms of their interesting structures, reactivity patterns, general and special methods of preparation and applications in the synthesis of heterocycles; moreover, we focused on the actions and reactions related to their exceptional behaviour and the unique arrangement of their reactive sites towards attack by nucleophiles and electrophiles. These features of nitroketene *N,S*-acetals make them highly flexible and easy to use in the Michael addition, cyclization, annulation and multicomponent reactions. Nowadays, multicomponent reactions (MCRs) have become a prominent strategy and are chosen over stepwise synthesis due to the following reasons: reduced waste, minimal usage of toxic and harmful chemicals, short synthetic time period, simple workup of compounds, high yields, operational simplicity and economic viability;²⁷ therefore, MCRs are a powerful tactic to attain the aim of green and sustainable chemistry by reducing the formation of vast quantities of waste for the promotion of green chemistry.

2. Nitroketene *N,S*-acetal chemistry

2.1 Characteristic structure and reactive sites

The acyclic simple nitroketene *N,S*-acetals, such as (*E*)-*N*-methyl-1-(methylthio)-2-nitroethenamine (NMSM) and its derivatives, are flexible molecules. On the other hand, the cyclic nitroketene *N,S*-acetals have a rigid structure and behave as a Michael donor-type 1,3-*N,C* di-nucleophilic precursor for the construction of *N*-heterocyclic compounds. They contain three



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Dr. Shafiullah was born in 1966 and grew up in the district of West Champaran in Bihar, India. He received his M.Sc. degree from Aligarh Muslim University (AMU), India in 1988 with Organic Chemistry specialization. After completing his M.Sc., he successfully completed his Ph.D. degree under the supervision of Professor M. Ilyas in 1994 from

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Dr. Md. Musawwer Khan was born and grew up in the district of Deoria, Uttar Pradesh in India. He obtained his B.Sc. (Chemistry) and M.Sc. (Organic Chemistry) in 2001 and 2003, respectively, from Aligarh Muslim University (AMU), India. He also completed a B.Ed. in 2004 from AMU, Aligarh. He joined Professor Abu T. Khan's

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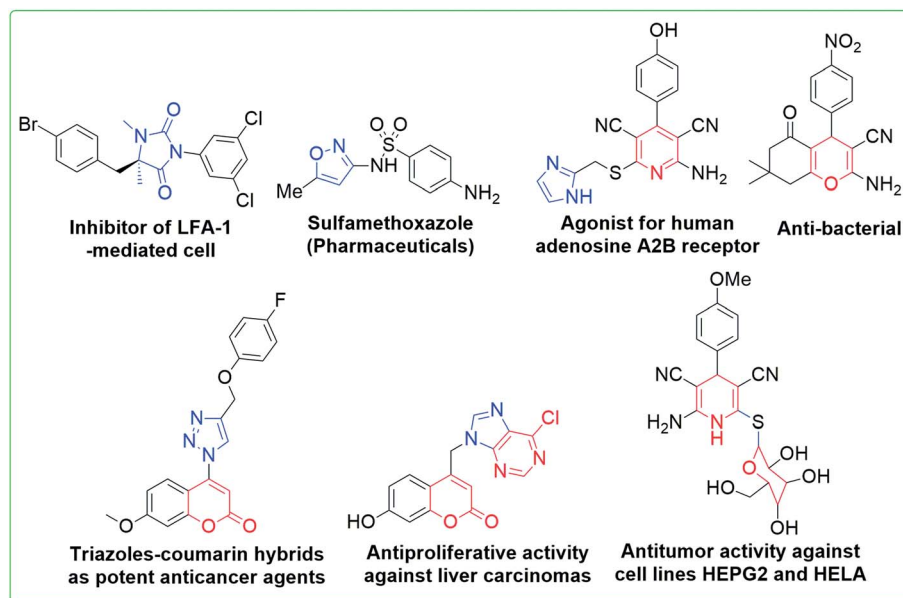


Fig. 1 Some biologically active heterocycle-containing compounds.

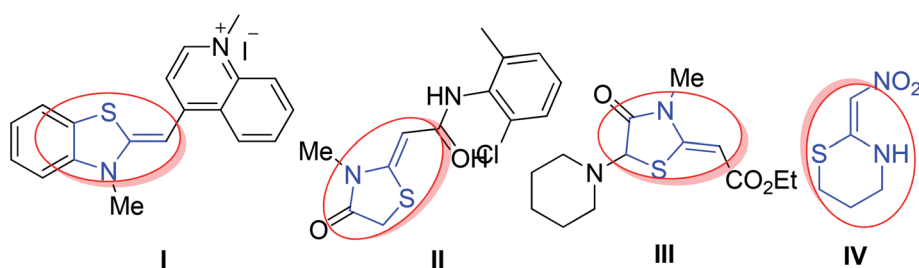


Fig. 2 Examples of drugs, insecticides and probes having the ketene *N,S*-acetal structure.

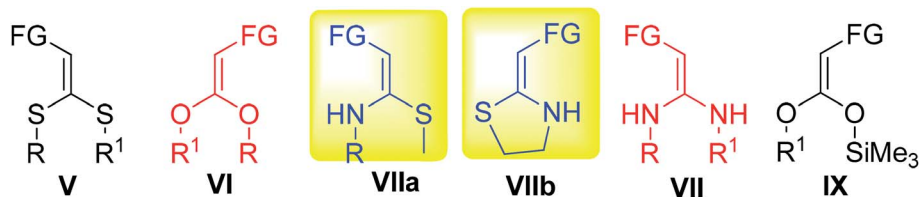


Fig. 3 The structures of different kinds of ketene acetals.

specific functional groups, *i.e.* nitro, methylamine and sulfanyl, on the ethylene skeleton, and each of these functional groups bonds well and play a significant role in the reaction media for the formation of products; the acyclic nitroketene *N,S*-acetals possess a distinguished feature: the methylsulfanyl group acts as a good leaving group and also possesses electron releasing capacity. Moreover, this methylsulfanyl group can be substituted with a different kind of nucleophile following the substitution nucleophilic vinyl (SNV) mechanism. The ethylene motif has a polarized push-pull type of alkene, and due to this, the one end develops an electrophilic character, whereas the other end develops a nucleophilic character with electron movement stemming from the methylsulfanyl-/methyl amino

group towards the nitro group. The interesting structural features of these two types of nitroketene *N,S*-acetals are shown in Fig. 4.

These features of NMSMs make them a multi-faceted precursor that can be used to explore the creation of more diverse and interesting complex molecules.

2.2 General methods for the preparation of acyclic and cyclic nitroketene *N,S*-acetals

This section covers the general methods used for the preparation of cyclic/acyclic ketene *N,S*-acetals possessing a $-\text{NO}_2$ group at the acceptor end. In 1967, Gompper and Schaefer synthesized



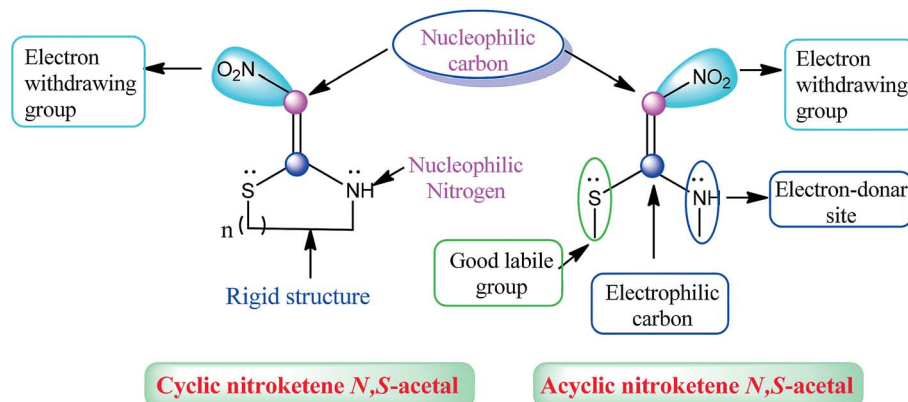
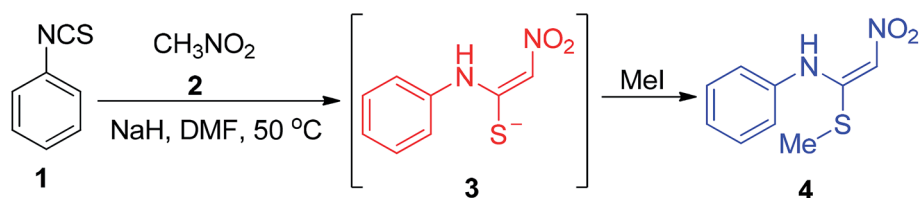


Fig. 4 Characteristic structural features of cyclic and acyclic nitroketene *N,S*-acetals.



Scheme 1 One-pot synthesis of nitroketene *N,S*-acetals.

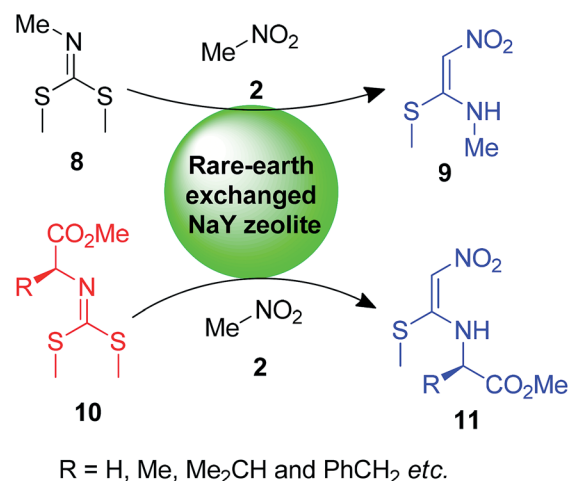
the nitroketene *N,S*-acetal derivatives **4** via the one-pot reaction of phenyl isothiocyanate **1** with nitromethane **2** followed by *S*-methylation by MeI using sodium hydride (NaH) as a base in DMF to afford good yields.

This synthetic method provides efficient access to **4** on a gram scale under mild conditions from simple starting materials (Scheme 1).²⁸ In 1988, Young and his co-workers developed a new approach for the synthesis of the unsymmetrical nitroketene *N,S*-acetal **7** via the amination of monosulfoxide **5** of 1,1-bis(methylthio)-2-nitroethene (Scheme 2).²⁹

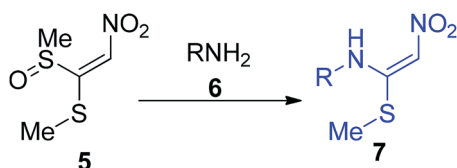
On the other hand, a new tactic was adopted for the synthesis of the compounds **9** and **11** by Deshmukh *et al.*, where nitromethane **2** was allowed to react with dimethyl methylcarbonimidodithioate **8** and **10** under catalysis by a rare-earth (La, Pr and Sm)-exchanged NaY zeolite (Scheme 3).^{30,31}

Maybhat and his group treated *N*-sulfonyl carbonimidodithioates **12** with the nitroethane derivatives **13** in the presence of anhydrous K₂CO₃ in DMSO to obtain 1-methylthio-*l*-sulfonamido-2-nitroethenes **14** (Scheme 4).³² Then, the same group utilized **15** for the synthesis of compound **17** in the presence of different primary and secondary amines **16** at 30 °C (Scheme 5).³³

Contreras and his co-workers synthesized a new analogue of nitroketene *N,S*-acetals **19** by the reaction between **15** (1,1-bis(methylthio)-2-nitroethene) and aminoethyl morpholine **18** (Scheme 6).³⁴



Scheme 3 New approach for the synthesis of the compounds **9/11** using zeolite.

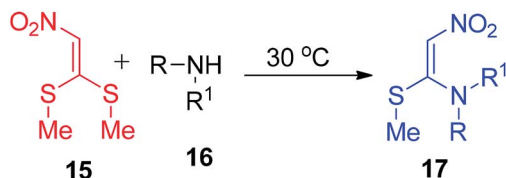


Scheme 2 Synthesis of nitroketene *N,S*-acetals by the amination of **5**.



Scheme 4 New kinds of nitroketene *N,S*-acetal derivatives **14**.



Scheme 5 Synthesis of the nitroketene *N,S*-acetal derivatives from 15.

The same starting component 15 was explored by Sangi and Correa to generate a short library of nitroketene *N,S*-acetals 21 *via* the reaction of 15 with one equivalent of a number of primary amines 20 under microwave irradiation with high yields (Scheme 6).³⁵ Again, similar conditions were utilized for the synthesis of the cyclic and acyclic nitroketene *N,S*-acetals 23 and 25 by the same group (Scheme 7).³⁶

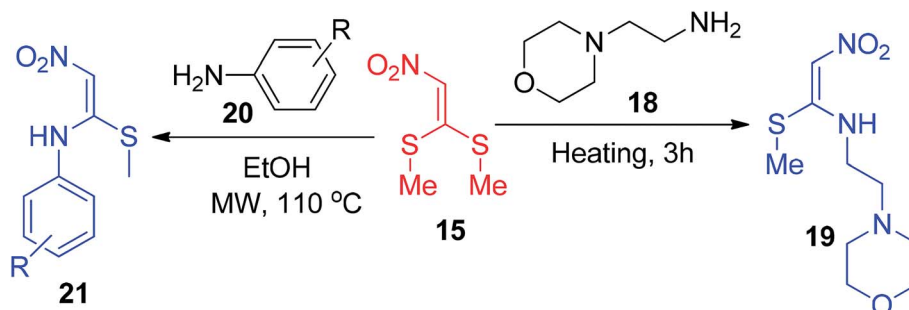
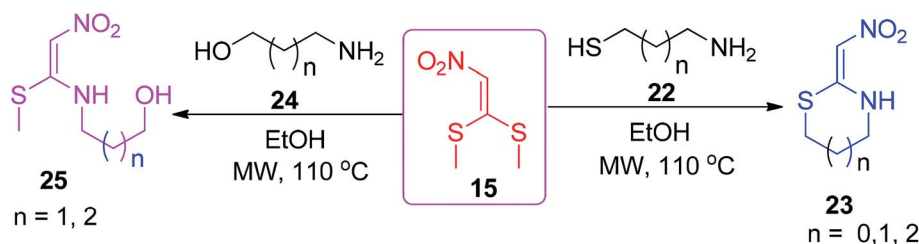
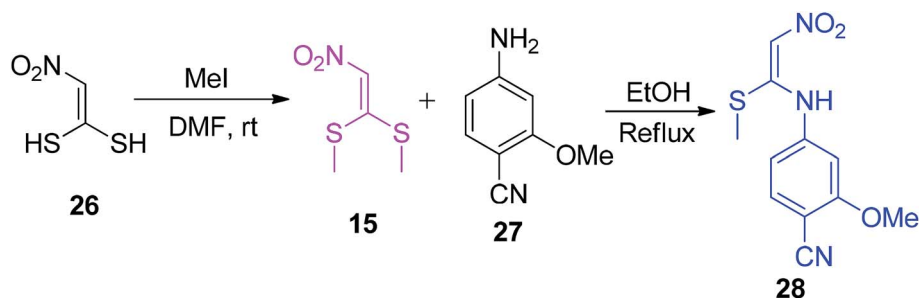
Dunkern *et al.* described a slightly modified protocol for the synthesis of the nitroketene *N,S*-acetal derivatives 28 from 15, as depicted in Scheme 8.³⁷ The precursor 15 was prepared by mixing 26 with MeI in DMF at room temperature.

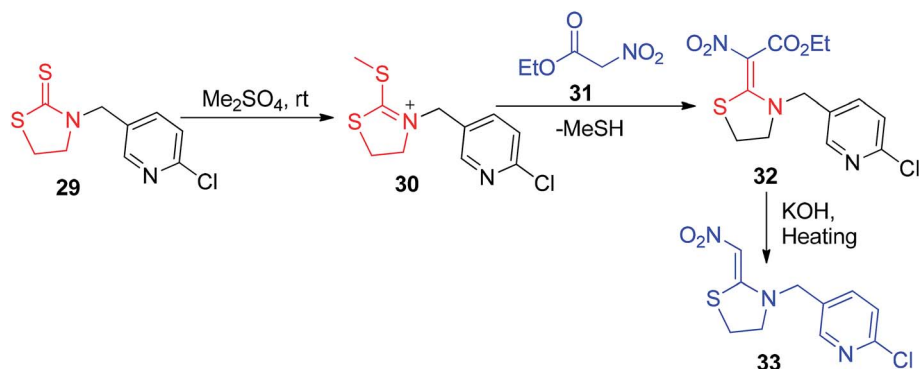
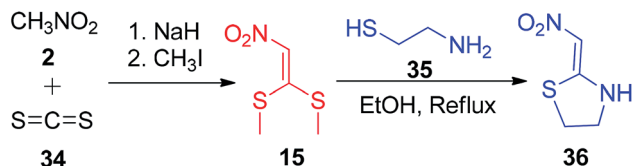
The five-membered cyclic nitroketene *N,S*-acetal 33 was prepared by Shiokawa *et al.* *via* a three-step process involving the *S*-methylation of 29, followed by condensation with the ethyl nitroacetate 31 to form 32, which generated 33 upon hydrolysis and decarboxylation (Scheme 9).³⁸

Huang and Shi described a two-step method for the formation of the five-membered simple nitroketene *N,S*-acetals 36. In the first step, nitromethane 2 and carbon disulfide 34 were combined in the presence of sodium hydride followed by *S*-methylation using MeI to form the compound 15. In the next step, 36 was generated by the reaction of 2-aminoethanethiol 35 with 15 under ethanol reflux conditions (Scheme 10).³⁹

3. Applications of nitroketene *N,S*-acetal in the synthesis of heterocycles

Heterocycles are compounds that contain a cyclic ring along with one or more heteroatoms such as nitrogen, sulfur, oxygen, phosphorus, *etc.* Moreover, acyclic and cyclic nitroketene *N,S*-

Scheme 6 Synthesis of the nitroketene *N,S*-acetals 19/21 from 1,1-bis (methylthio)-2-nitroethene.Scheme 7 Synthesis of new cyclic/acyclic nitroketene *N,S*-acetal derivatives.Scheme 8 Synthesis of the nitroketene *N,S*-acetal derivatives 26.

Scheme 9 Synthesis of cyclic nitroketene *N,S*-acetal derivatives.Scheme 10 Synthesis of five-membered cyclic nitroketene *N,S*-acetals.

acetals have different structural firmness. Thus, depending upon the type of nitroketene-*N,S*-acetal used, the applications can be classified into two major sections.

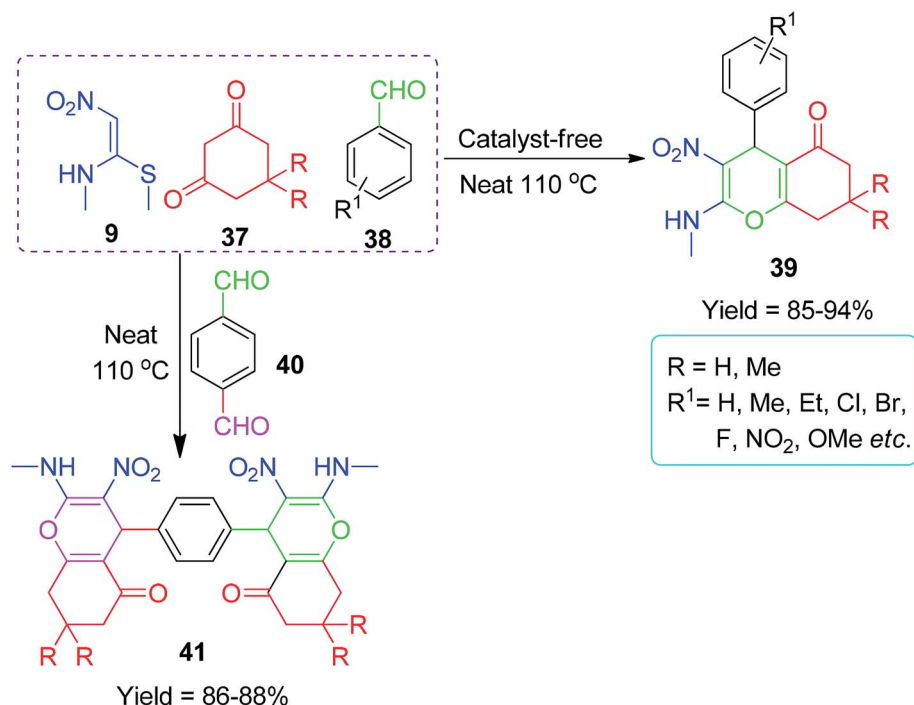
3.1 Applications of acyclic nitroketene *N,S*-acetals

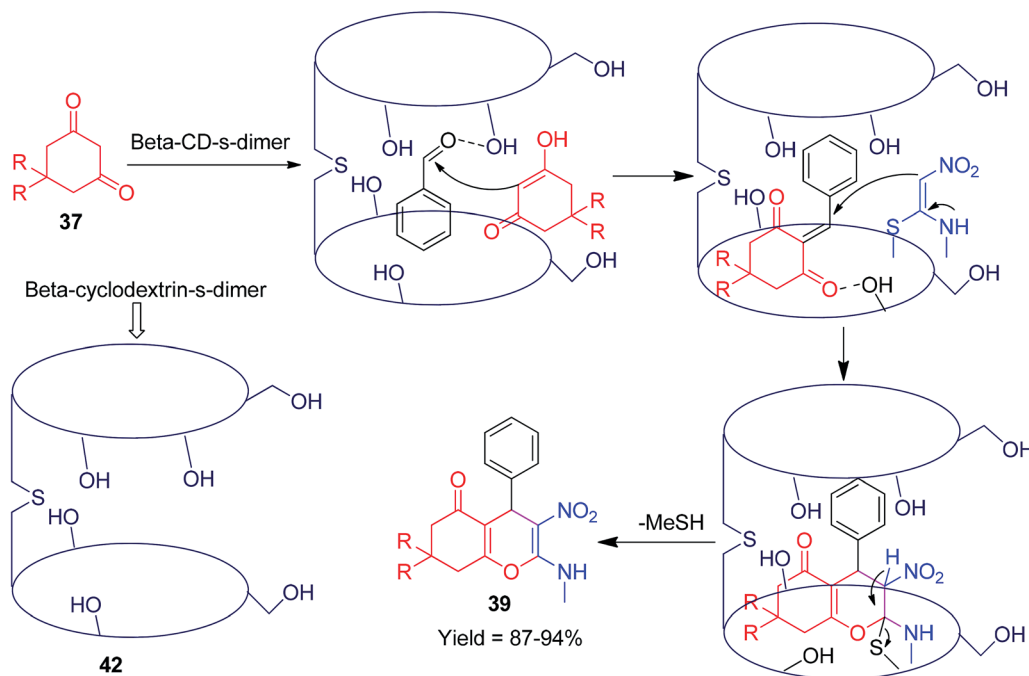
The structural flexibility of acyclic nitroketene-*N,S*-acetals allow them to be utilized in the construction of various oxygen, nitrogen and sulfur atom-containing cyclic compounds.

3.1.1 Synthesis of oxygen-containing heterocycles.

Recently, our group demonstrated the synthesis of a short combinatorial library of 4*H*-chromen-5-ones **39** and their bis derivatives **41** using catalyst- and solvent-free conditions *via* a one-pot MCR at 110 °C. The reaction occurred between cyclic β -dicarbonyl **37**, aryl aldehydes **38** and NMSM **9** in a short time with high yields. This convenient and green method has several advantages such as the avoidance of expensive catalysts, hazardous solvents and chromatographic purification (Scheme 11).⁴⁰

Furthermore, Shinde and his co-workers used NMSM for the construction of biologically active 4*H*-chromenone compounds *via* a three-component reaction using the 6,6'-thiobis(-methylene)- β -cyclodextrin dimer **42** as a reusable promoter in aqueous media.⁴¹ They have also described the synthetic procedures of dimeric β -cyclodextrin linked by a thio-methylene bridge as a supramolecular host. The reaction mechanism was described through molecular complexation and proposed based

Scheme 11 Synthesis of the 4*H*-chromen-6-ones **39** and bis-4*H*-chromen-6-ones **41**.



Scheme 12 The proposed reaction mechanism occurring *via* supramolecular host complexation.

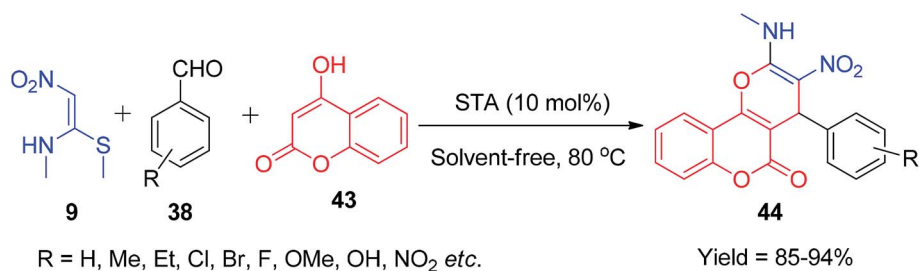
on the 2D ROESY NMR spectroscopic techniques (Scheme 12). Similarly, Perumal *et al.* developed a convenient method for the regioselective synthesis of chromenones **39** by the one-pot three-component condensation of various aromatic aldehydes **38**, dimedone **37** and NMSM **9** in the presence of 20 mol% piperidine in ethanol.⁴²

Next, Jadhav and his co-workers reported a new approach for the synthesis of coumarin-fused oxygen-containing heterocycles, pyrano[3,2-*c*]chromen-5-ones **44**, using NMSM. The reaction was carried out under solvent-free conditions using 4-hydroxycoumarin **43**, aryl aldehydes **38** and NMSM **9**, and silica-supported tungstic acid (STA) was employed in a catalytic amount; they showed recyclability of the catalyst up to the 4th cycle and achieved an 89% yield (Scheme 13).⁴³ Similarly, the β -CD-S dimer and piperidine have also been used as catalysts for the synthesis of **44**.^{41,42} Moreover, Mao *et al.* developed a sustainable method for the synthesis of the new type of coumarin-fused pyrano[4,3-*b*]pyran-5-one derivatives **46** using **9** as a building block. The compounds were synthesized by irradiating all the starting components (**9**, **45** and **38**) in a microwave oven in the presence of ammonium acetate in EtOH (Scheme 14).⁴⁴

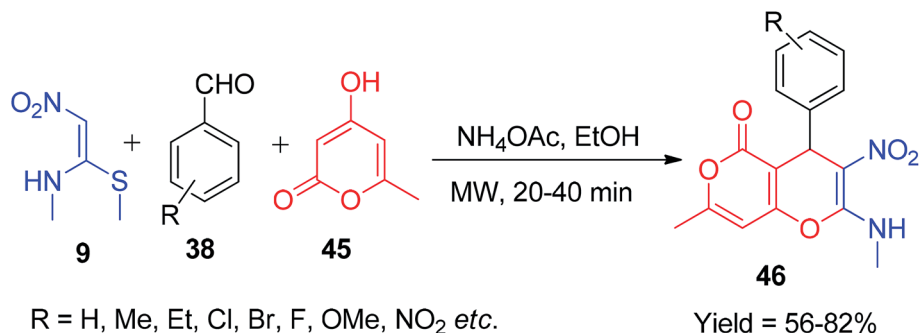
After this, Gunasekaran *et al.* applied NMSM for the construction of quinoline-fused pyran moieties. The pyranoquinolinone framework is a privileged sub-structure widely spread in several natural products.^{45,46} This fascinating compound was synthesised *via* the ZnCl₂-catalyzed three-component reactions of 4-hydroxy-1-methylquinolin-2(1*H*)-one **47**, NMSM **9**, and the aromatic aldehydes **38** in ethanol.

This method afforded the pyrano[3,2-*c*]quinolin-5(6*H*)-ones **48** in good yields (85–93%) (Scheme 15).⁴⁷ Next, the NMSM **9** was also chosen as a starting material by Reddy *et al.* for the synthesis of benzo[*f*]chromen-3-amine derivatives under mild aqueous conditions. *Via* this protocol, the compound **50** was afforded by a one-pot cascade reaction between various aromatic aldehydes **38**, naphthalen-2-ol **49** and **9** under catalyst-free conditions using a greener medium (ethanol-water mixture) (Scheme 16).⁴⁸

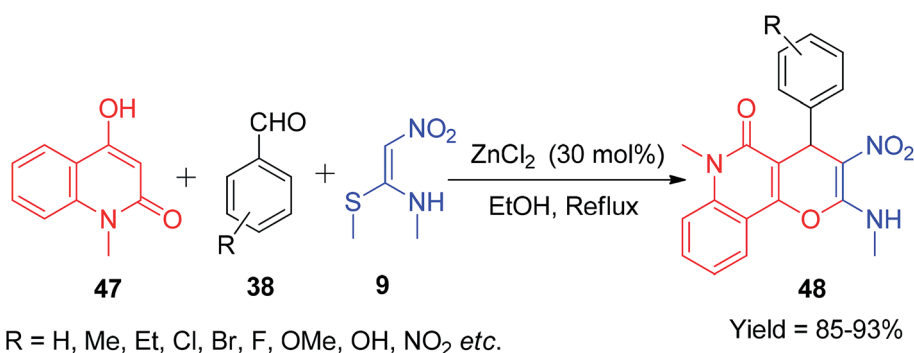
In addition, NMSM was explored by Sivakumar and his co-workers for the synthesis of simple 4*H*-pyrans. They synthesized a series of novel 2-(1*H*-indol-3-yl)-6-(methylamino)-5-nitro-4-aryl-4*H*-pyran-3-carbonitriles **53** and 6-(methylamino)-4-(aryl)-5-nitro-2-phenyl-4*H*-pyran-3-carbonitriles **54** in the presence of



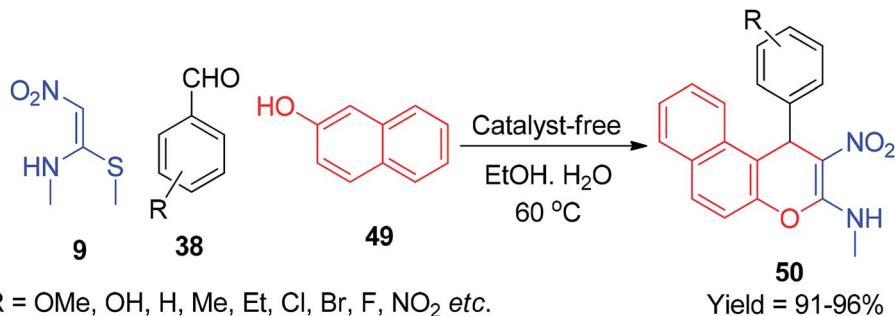
Scheme 13 Synthesis of functionalized pyranochromen-5-one derivatives.



Scheme 14 Synthesis of functionalized coumarin-fused pyran derivatives.



Scheme 15 Synthesis of quinoline-fused pyran derivatives 48.



Scheme 16 Synthesis of functionalized benzochromen derivatives.

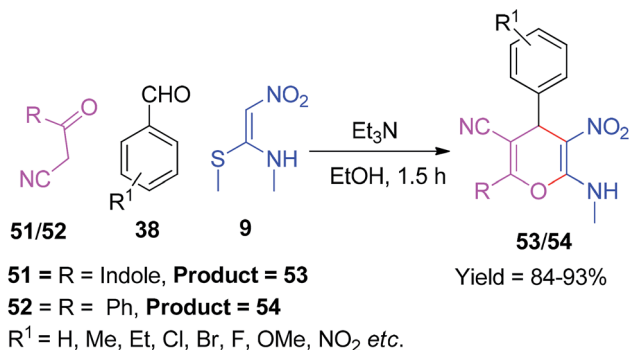
Et_3N as a catalyst *via* the three-component domino reactions of **51** and **52**, aryl aldehydes **38** and NMSM **9**, respectively (Scheme 17).⁴⁹

Kamalraja and Perumal demonstrated an environmentally friendly and sustainable method for the synthesis of the indole-containing *4H*-pyrans **56** using NMSM **9** as one of the building blocks. The indole ring system is a well-known heterocycle present in nature and an important structural motif in many pharmaceutically active compounds.⁵⁰ The reaction was conducted in the presence of InCl_3 as a catalyst *via* the microwave irradiation of the aromatic aldehydes **38** and 3-cyanoacetylindoles **55** with NMSM **9** under solvent-free conditions. Furthermore, they described its chemical transformation to indolyltriazolopyran **59** hybrids, as shown in Scheme 18.⁵¹

In 2018, Wang and co-workers synthesized the penta-substituted *4H*-pyran motifs **61** using NMSM. This multicomponent domino reaction was performed using the aromatic aldehydes **38**, pivaloylacetonitrile **60** and NMSM **9** in the presence of NH_4OAc under microwave irradiation in ethanol. The synthesized compounds exhibited good fluorescence intensity with the excitation wavelength of 300 nm (Scheme 19).⁵²

Kanchithalaivan and his group developed an effective one-pot four-component protocol for the synthesis of novel 1,4-dihydropyrano[2,3-*c*]pyrazol-6-amines **64/66** and benzochromenes **68** using NMSM. They described a simple synthesis of novel 1,4-dihydropyrano[2,3-*c*]pyrazol-6-amines *via* the domino condensation reactions of ethyl acetoacetate/ethyl benzoylacetate **65** and diethyl acetylenedicarboxylate **62** with hydrazines



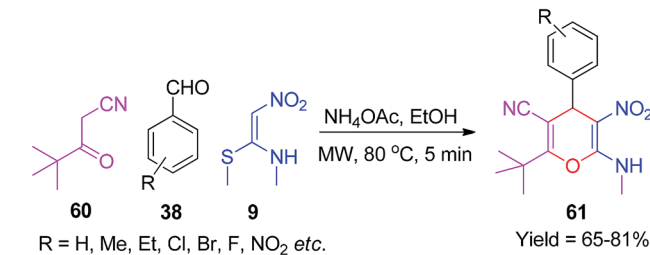


Scheme 17 Synthesis of indole-containing 4H-pyran derivatives.

63, aryl aldehydes **38**, and NMSM **9** in the presence of diisopropylethylamine (DIPEA) (Scheme 20).⁵³

The scope of the abovementioned protocol was also envisaged in the cyclic system (2-hydroxy-1,4-naphthoquinone) **67** with aromatic aldehydes and NMSM using ethanol under reflux conditions. This reaction afforded the corresponding products even in the absence of a base. The benzo[*g*]chromene-5,10-diones **68** were achieved in excellent yields, as represented in Scheme 21. In 2018, Krishnammagari and his group reported a similar reaction under solvent-free conditions using poly(oligo ethylene glycol methacrylate)-*g*-supported coated double hydroxides (LDHs-*g*-POEGMA) as a reusable heterogeneous catalyst.⁵⁴

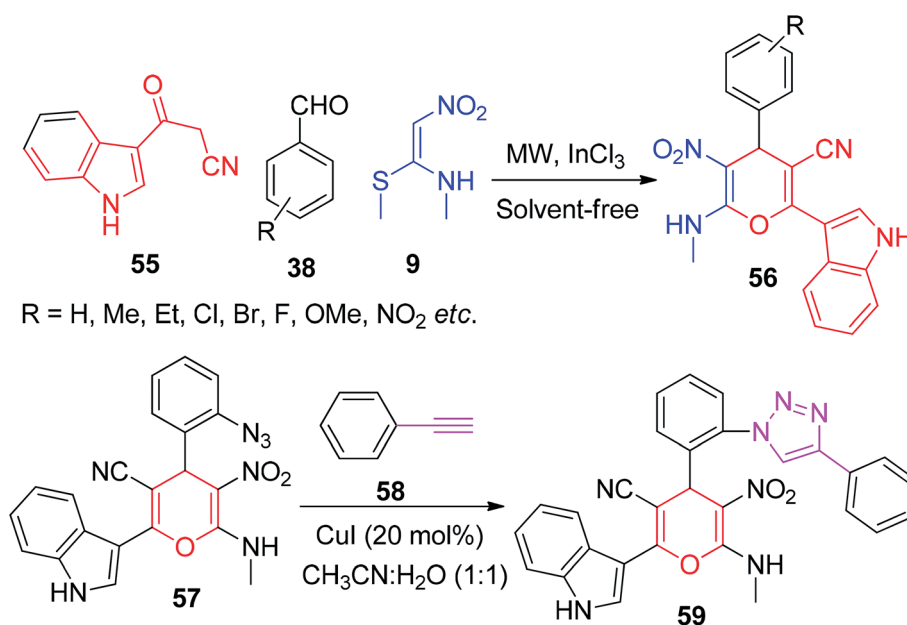
After this, Poomathi *et al.* described a new class of spiro 1,4-dihydropyridine derivatives using NMSM as a building block. They developed a high-yielding InCl₃-mediated regioselective method for the synthesis of spiro-pyrans **71a** via a domino, one-pot reaction of isatins **69**, pyrazolones **70** and NMSM **9**; on the other hand, Survase *et al.* also used a similar combination of

Scheme 19 Synthesis of penta-substituted 4H-pyran derivatives **61**.

pyrazolones **70** and NMSM **9** with aromatic aldehydes **38** in the presence of the abovementioned catalyst in aqueous ethanol for the synthesis of pyrazole-fused 4H-pyrans **71b** (Scheme 22).^{55,56}

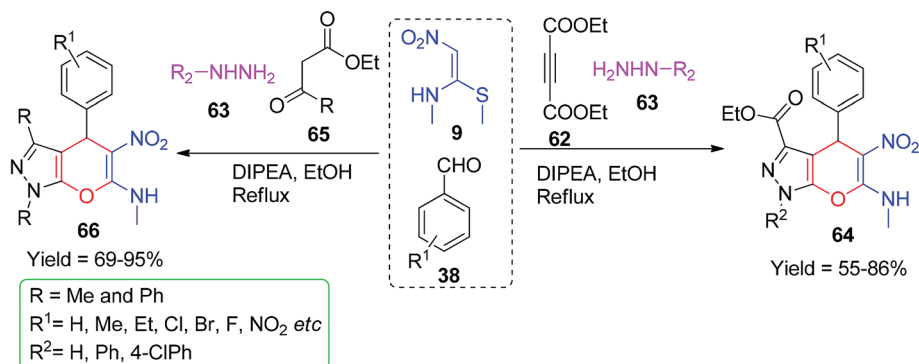
As a continuation of the exploration of NMSM derivatives to develop new type of 4H-chromenes **73/75**, Rao *et al.* described a two-component approach based on Michael-type addition followed by *O*-cyclization. The synthesis was achieved via a base-catalyzed reaction of **7** with 2-hydroxybenzaldehydes **72**, and 2-alkylamino-3-nitro-4-alkylsulfanyl 4H-chromenes **73** were afforded in excellent yields. The subsequent displacement of the -SMe group of **73** with different thiol nucleophiles **74** yielded the 4H-chromenes **75**, having more structural diversity in the molecules (Scheme 23).⁵⁷

Furthermore, the reaction was carried out between **7** and the simple 2-hydroxybenzaldehyde **72a** in the presence of NaH in THF, where they isolated the final products containing **73a** (1 : 1 adduct) in major amount and 4H-chromenes **76** (1 : 2 adduct) in minor amount, as depicted in Scheme 24. Next, the same research group extended the utility of **73a** to the construction of various chromene- and coumarine-based derivatives (**77–81**) under suitable reaction conditions in a two-step sequence (Scheme 25).⁵⁸

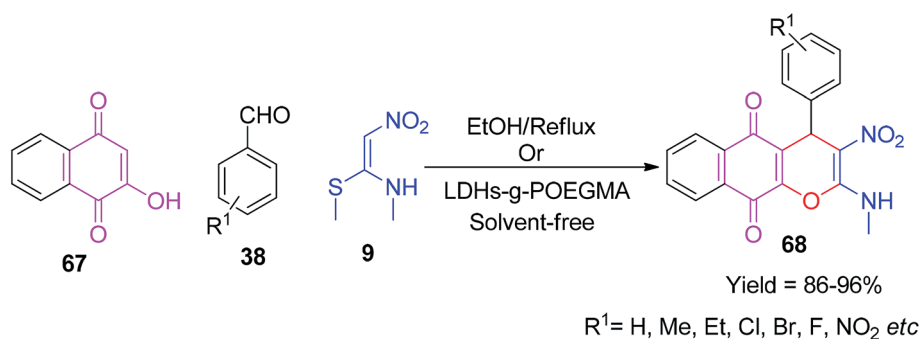


Scheme 18 Synthesis of indole-containing 4H-pyran derivatives and their functionalization.

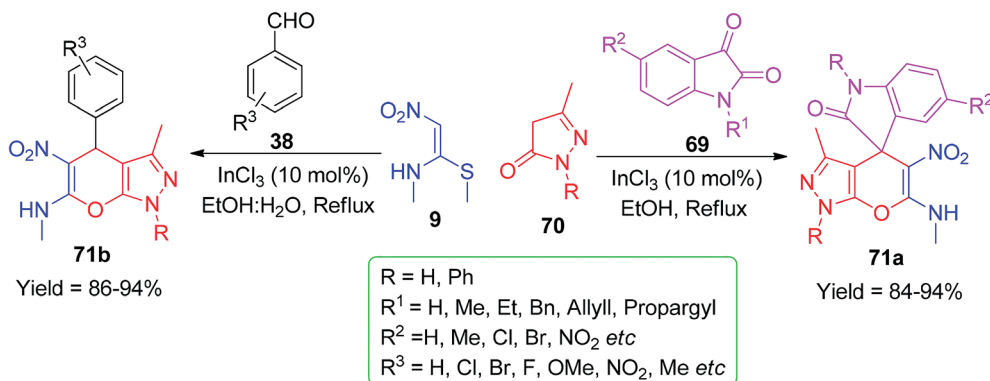




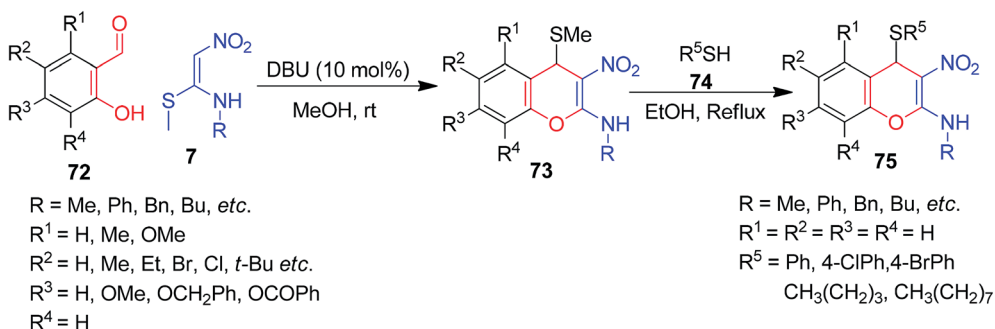
Scheme 20 Synthesis of the functionalized pyrazole-fused 4H-pyrans 64/66.

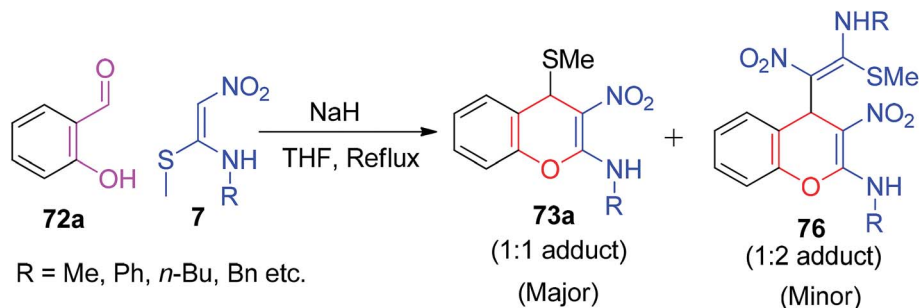
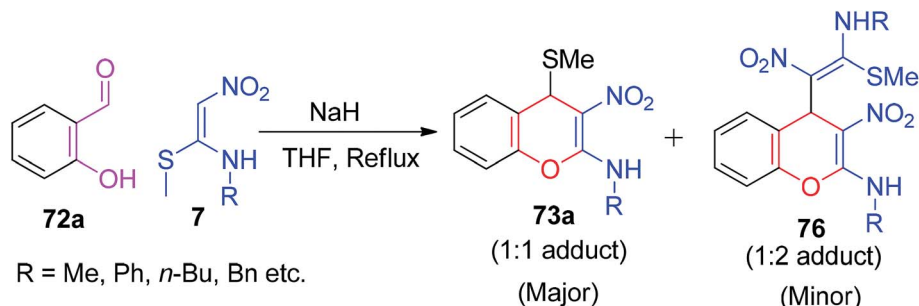


Scheme 21 Synthesis of the functionalized benzo[g]chromene-5,10-diones 68.



Scheme 22 Synthesis of functionalized pyrazole-fused spiro pyran derivatives.

Scheme 23 Synthesis of functionalized 4H-chromenes from nitroketene *N,S*-acetals.

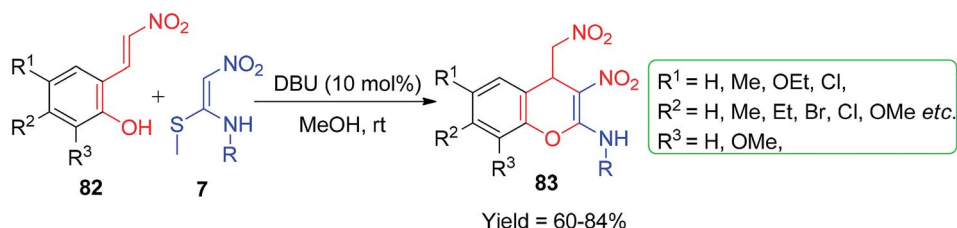
Scheme 24 Synthesis of the major 1 : 1 adduct 4*H*-chromenes from nitroketene *N,S*-acetals.Scheme 25 Synthesis of methylsulfanyl 4*H*-chromenes and their transformation.

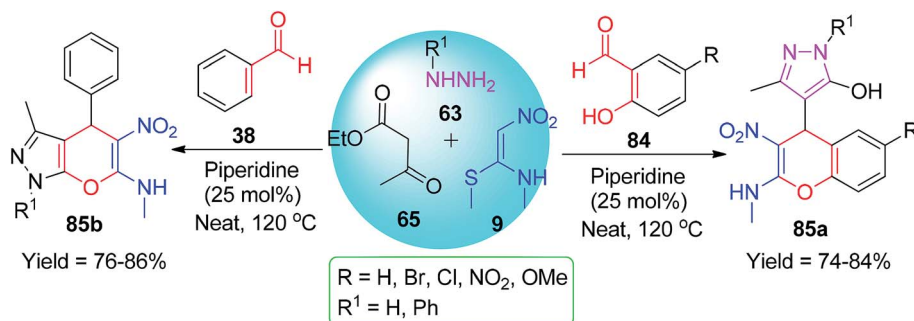
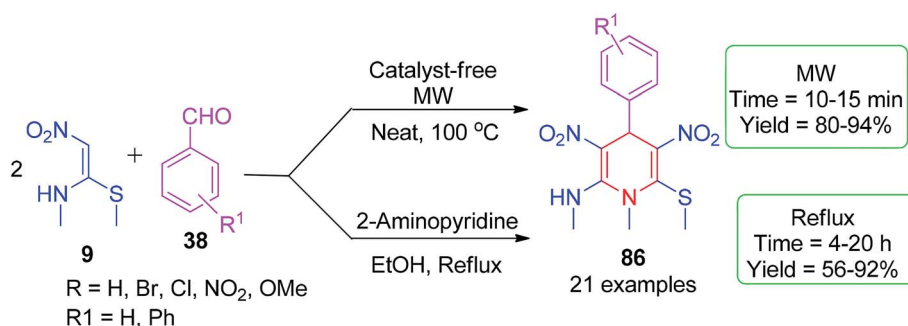
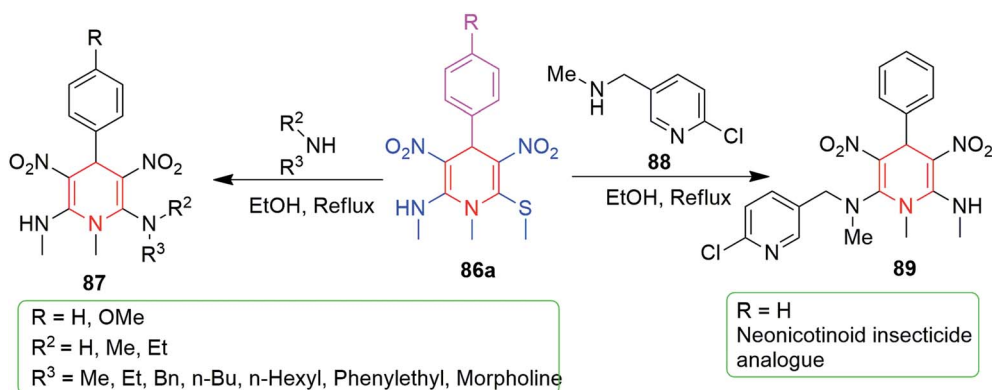
After this, 2-hydroxybenzaldehydes were replaced by 2-((*E*)-2-nitrovinyl)phenol **82** for the construction of new kinds of compounds. A number of *N*-methyl-3-nitro-4-(nitromethyl)-4*H*-chromen-2-amines **83** were synthesized by the reaction of 2-((*E*)-2-nitrovinyl)phenols **82** and NMSM **7** derivatives in the presence of 10 mol% DBU in MeOH (Scheme 26).⁵⁹ The synthesized compounds were tested for anticancer activity, which displayed moderate to good activity against two cancer cell lines, namely HeLa (cervical cancer) and HEP-2 (epidermoid laryngeal carcinoma).

Next, Jayabal and Paramasivan explored the combination of 2-hydroxybenzaldehydes **84** and NMSM **9** for the synthesis of pyrazole-containing chromene **85a** rings under SF conditions.⁶⁰ The one-pot four-component reaction was carried out by heating the mixture of all the starting components at 120 °C in the presence of 25 mol% piperidine for 1 h. They also used the aromatic aldehydes **38** instead of 2-hydroxybenzaldehydes under similar conditions, and the pyrazole-fused chromenes **85b** were obtained (Scheme 27).

3.1.2 Synthesis of nitrogen-containing heterocycles. The research interest in nitrogen-containing heterocyclic compounds can be attributed to their profound medicinal properties. These skeletons are well-known subunits in different alkaloids, pharmaceuticals and agricultural chemicals.⁶¹

3.1.2.1 Six-membered *N*-heterocycles. In 2014, Rao and Parthiban developed a protocol for the synthesis of diverse, functionalized *N*-methyl-substituted 1,4-dihydropyridines (**1,4-DHPs**) **86**. The pseudo three-component reaction was carried out by the reaction of NMSM **9** (2 mmol) and aromatic aldehydes **38** (1 mmol) using 2-aminopyridine (10 mol%) as a catalyst in ethanol (Scheme 28).⁶² The product isolated by simple filtration was further subjected to the nucleophilic substitution of the -SMe group by different kinds of primary and secondary amines; this afforded the structurally diverse 1,4-dihydropyridines **87**. They also synthesised the neonicotinoid insecticide analogue **89**, as shown in Scheme 29. Very recently, our group developed an improved and greener method for the synthesis of

Scheme 26 Synthesis of the functionalized 4*H*-chromene-2 amines **83**.

Scheme 27 Synthesis of pyrazole-containing chromene from nitroketene *N,S*-acetals.Scheme 28 Synthesis of the highly substituted 1,4-dihydropyridines **86**.Scheme 29 Functionalized 1,4-dihydropyridines **88/89**.

86 using microwave irradiation under catalyst- and solvent-free conditions within 10–15 min, and a yield of 80–94% was obtained, as depicted in Scheme 28.⁶³

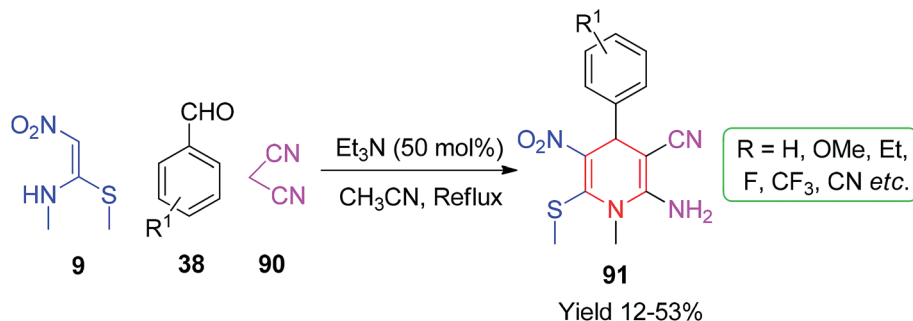
Next, Hajiyevea and his co-workers described the synthesis of a new type of *N*-heterocyclic compounds containing the NMSM scaffold using the Knoevenagel condensation product of malononitrile and aromatic aldehydes. A short library of poly-functionalized 2-amino-1-methyl-6-(methylthio)-5-nitro-4-aryl-1,4-dihydropyridine-3-carbonitriles **91** was synthesised through the multicomponent condensation of aryl aldehydes **38**, malononitrile **90**, and **9** in the presence of Et₃N in acetonitrile, as depicted in Scheme 30.⁶⁴

In 2014, Gunasekaran and his co-worker used NMSM for the formation of a pyrazolo[3,4-*b*]pyridine **92** ring system. The synthesis of the compounds **93** was achieved by the reaction of NMSM **9**, aryl aldehydes **36** and 3-methyl-1-phenyl-1*H*-pyrazol-5-amine **92** in the presence of the bio-catalyst *L*-proline in refluxing ethanol (Scheme 31).⁶⁵

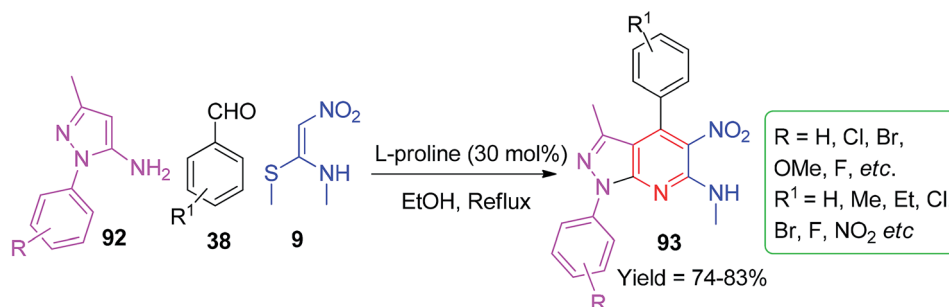
Next, Poomathi *et al.* synthesized the six-membered nitrogen-containing heterocycles 2-pyridinones **95** using NMSM and chromone derivatives possessing an aldehydic group at an appropriate position.

This well-organized and flexible route provides the functionalized compounds **95** in the presence of indium triflate by





Scheme 30 Synthesis of the substituted 2-amino-1,4-DHPs.



Scheme 31 Synthesis of functionalized pyrazole-fused pyridines.

the reaction of 3-formylchromones **94** and NMSM **9** in refluxing ethanol. The simple workup, usage of inexpensive and easily available starting materials, high yields, *etc.* are some of the advantages associated with this method (Scheme 32).⁶⁶ They have also established and discussed the mechanistic aspects for the formation of products, which are shown in Scheme 33.

Next, the use of a heterocyclic amine and NMSM by Jadhav and his co-workers led to the development of a new protocol for the construction of a novel benzoimidazopyrimidine ring system **97**. In this method, 2-aminobenzimidazole **95**, aldehydes and NMSM **9** were allowed to react in the presence of the *p*-TSA catalyst in ethanol under refluxing conditions (Scheme 34).⁶⁷

The plausible mechanism for the formation of *N*-methyl-3-nitro-aryl-benzo[4,5]imidazo[1,2-*a*]pyrimidin-2-amine **97** involved Knoevenagel condensation, Michael addition, then *N*-cyclization and tautomerisation, as shown in Scheme 35.

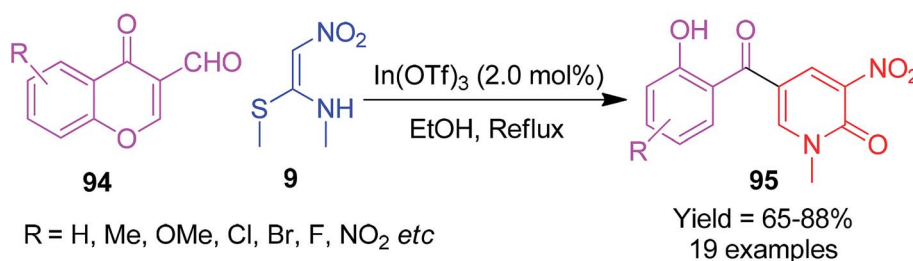
The next application of NMSM in the construction of *N*-heterocycles was demonstrated by Chakrabarti *et al.* based on

the substantial reactivity of itaconic anhydride. A new class of pyridinone derivatives **99** having a carboxylic acid group was synthesized by the reaction of itaconic anhydride **98** with the NMSM derivatives **7** in refluxing MeCN (Scheme 36).⁶⁸

Further functionalization of the phenyl derivatives **99a** using the MeMgI/CuI reagent afforded the compound **100** in a 76% yield. The proposed mechanism of product formation is outlined in Scheme 37.

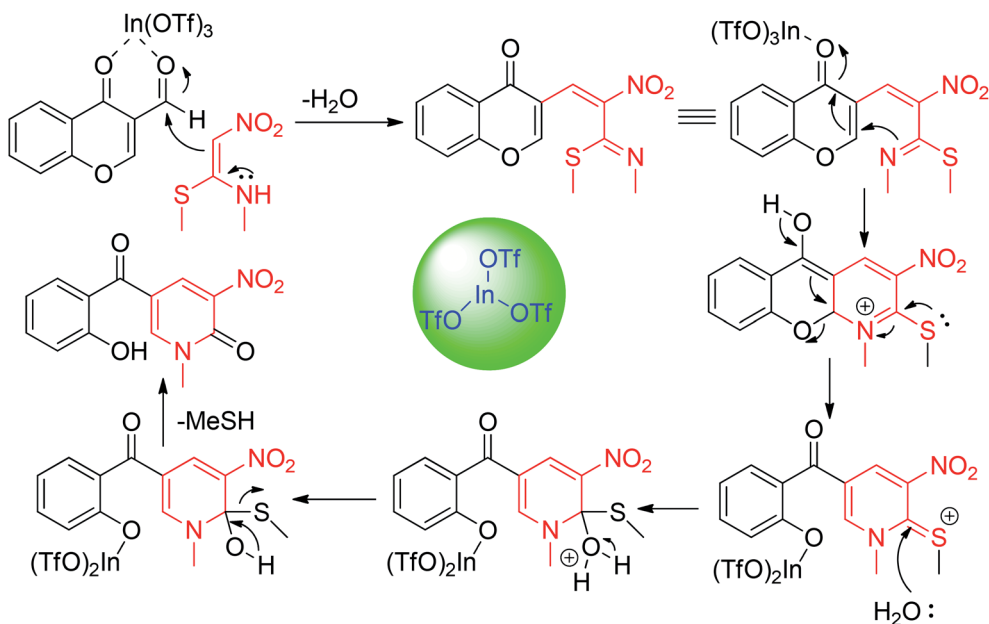
For the preparation of pyrimidine-2-one derivatives containing NMSM scaffolds, Sukach and his group described the [3 + 3] annulation approach. They synthesized a series of 3,4-dihydropyridine-2-ones **102** by the reaction between 1-chlorobenzyl isocyanates **101** and **7** in DCM under reflux conditions (Scheme 38).⁶⁹ The methylthio group present in the compound **102** was further substituted by primary and secondary amines.

A different reaction profile of the NMSM derivative was shown when they were mixed with POCl_3 to generate the quinoxaline derivatives **104**.

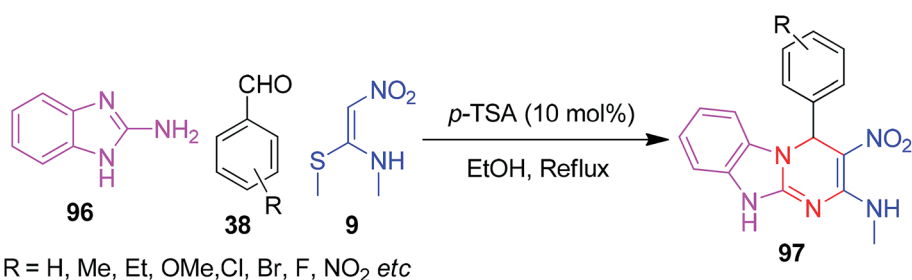


Scheme 32 Synthesis of functionalized 2-pyridinone derivatives from NMSM.





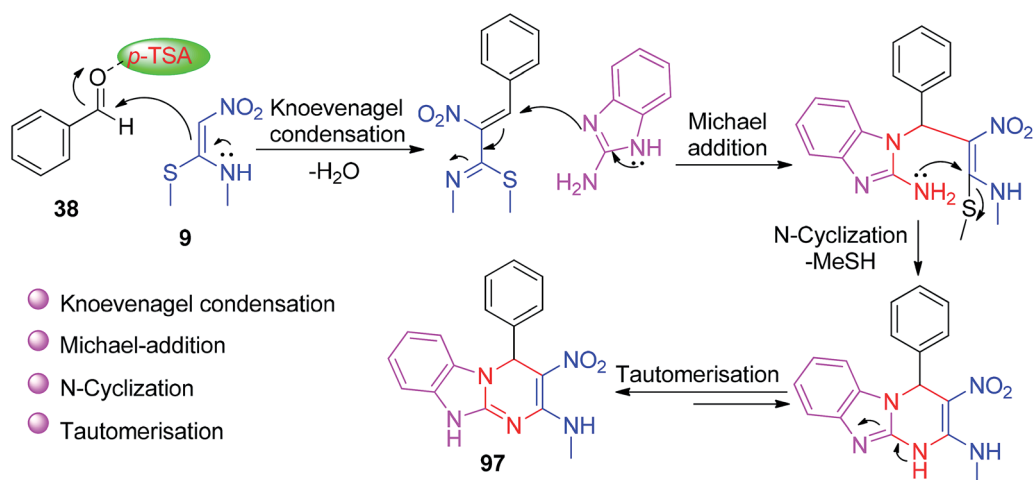
Scheme 33 Synthesis of functionalized 2-pyridinone derivatives from NMSM.



Scheme 34 Synthesis of functionalized benzoimidazole-fused pyrimidines.

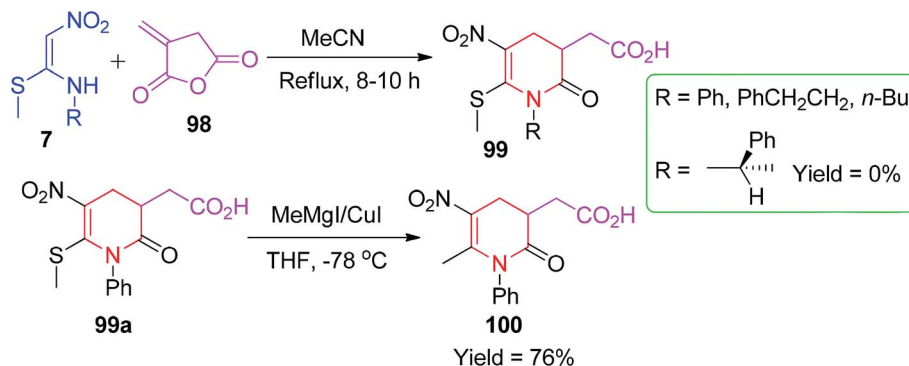
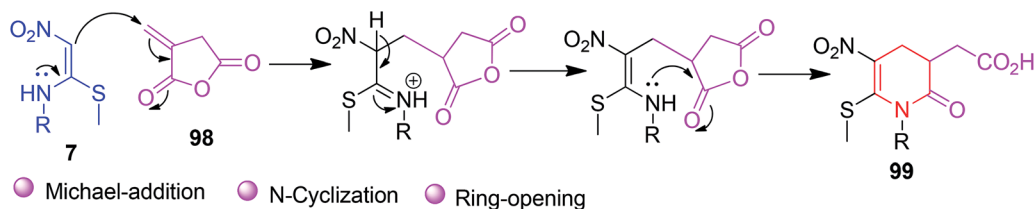
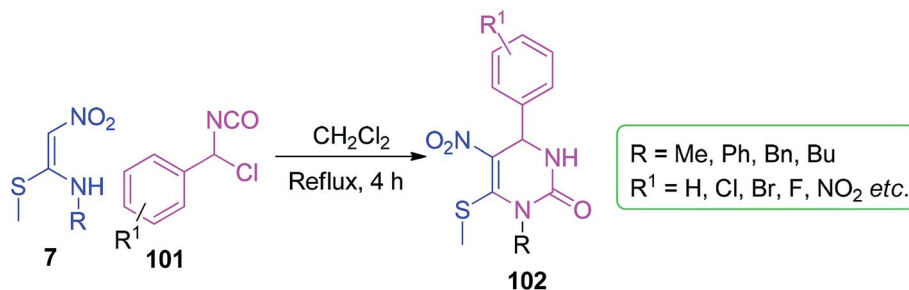
This was carried out by Venkatesh and his co-workers through the hetero-annulation reaction of the corresponding NMSM derivative **103** in the presence of POCl_3 in MeCN. They

also found that the formation of **104** by the reaction of **103** with POCl_3 unexpectedly produced quinoxaline instead of 3-nitro-quinoline **105** (Scheme 39).^{70,71}



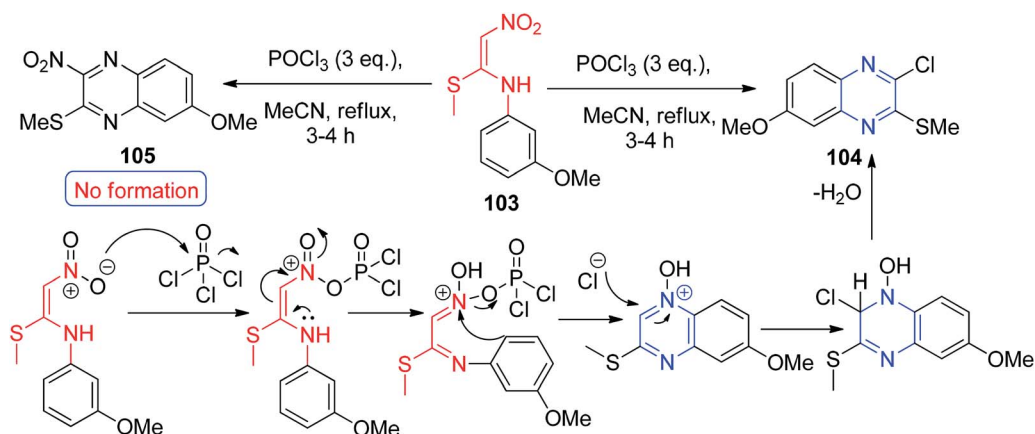
Scheme 35 Plausible mechanism for the formation of benzoimidazole-fused pyrimidines.

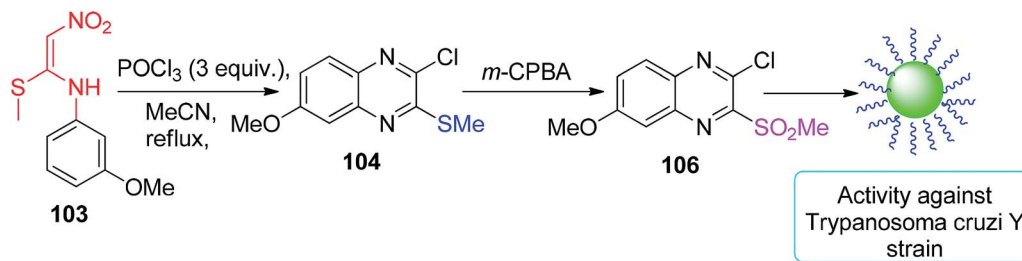


Scheme 36 Synthesis of pyridinone from nitroketene *N,S*-acetals.Scheme 37 Plausible mechanistic outline for the formation of pyridinone **99**.Scheme 38 Synthesis of the pyrimidinones **102** from nitroketene *N,S*-acetals.

Using the same tactic, Nakamura and his group prepared **104** in a 54% yield. In the presence of *m*-CPBA, **104** was further converted to **106**, which was tested against *Trypanosoma cruzi* Y

strain (the cause of Chagas disease). The outcome reveals that the compound **106** is active against the abovementioned strain (Scheme 40).⁷²

Scheme 39 Synthesis of functionalized quinoxalines from nitroketene *N,S*-acetals.



Scheme 40 Synthesis of the functionalized quinoxalines 106.

3.1.2.2 Five-membered N-heterocycles. Among the five-membered N-heterocycles, pyrroles are considered as a privileged scaffold as they are found in natural products such as heme, chlorophyll, and vitamin B₁₂.^{73,74} These are the most likely five-membered rings that can be constructed using NMSM. Therefore, this section has been devoted to the synthetic application of NMSM in the formation of five-membered nitrogen-containing heterocyclic systems.

Very recently, Chaudhary *et al.* described GAP-assisted chemistry for the synthesis of novel pyrroles using NMSM.

The three-component catalyst-free reaction of arylglyoxal monohydrate **108**, **9** and the barbituric acid derivatives **107** in one pot was performed in aqueous media. The methanethiol functionality present in the synthesized pyrroles **109** makes them easily accessible to further functionalization, thereby leading to a new type of heterocycles (Scheme 41).⁷⁵ The substrate scope, time and yields are shown in Scheme 42.

In 2018, Rahimi and co-workers synthesised a new class of polysubstituted heterocyclic ring systems **112** using NMSM **9** with indanetrione **110** and aryl amines **111** in EtOH at ambient temperature *via* a one-pot MCR (Scheme 43).⁷⁶

Similarly, by performing the reaction of ninhydrin **113** and **7** in the presence of ethanol at room temperature, Jeyachandran *et al.* synthesised the novel dihydroindeno[1,2-*b*]pyrrol-4(3*aH*)-ones **114** (Scheme 44).⁷⁷

In 2015, Balachandra and co-workers reported a protocol for the synthesis of a new class of substituted pyrroles **116**. The reaction of **7** and β -nitrostyrenes **115** under SF and metal-free conditions at 55 °C followed the iodine-catalyzed [3 + 2] annulation route.

Again, the pyrrole derivatives **116** were synthesised *via* an MCR strategy by the reaction of NMSM **9** and aromatic

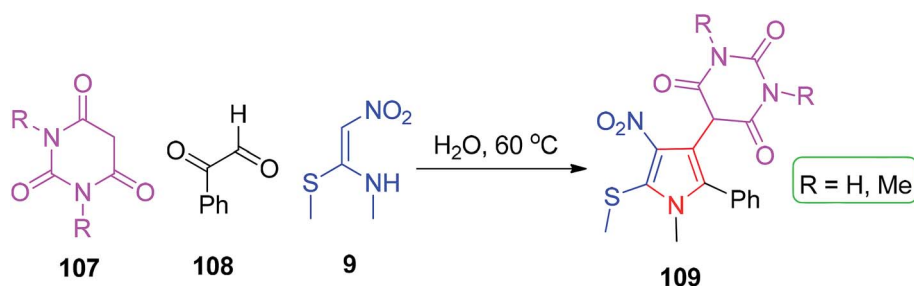
aldehydes **38** with nitromethane **2** in the presence of the same amount of molecular iodine at 90 °C (Scheme 45).⁷⁸ The synthesized pyrrole derivatives were tested for *in vitro* antibacterial activity against Gram-negative and Gram-positive infectious pathogens, and most of the compounds displayed good inhibitory properties.

Very recently, Balachandra and his co-worker established two different protocols for the synthesis of two different pyrroles **117/119**. They synthesised 2-(2-argio-1-methyl-5-(methylthio)-4-nitro-1*H*-pyrrol-3-yl)-2-cyanoacetamide **117** by the reaction of NMSM **9**, arylglyoxals **108** and malononitrile **90** using the H₂O/PEG-400 solvent combination.

They also synthesised the pyrrole derivatives **119** under neat conditions using methyl cyanoacetate **118** in place of the malononitrile **90** *via* the decarboxylative elimination reaction (Scheme 46).⁷⁹ Cytotoxicity studies of some of the selected newly synthesized compounds were also conducted on the L929 cells, and the test compounds exhibited good cell viability at lower concentrations.

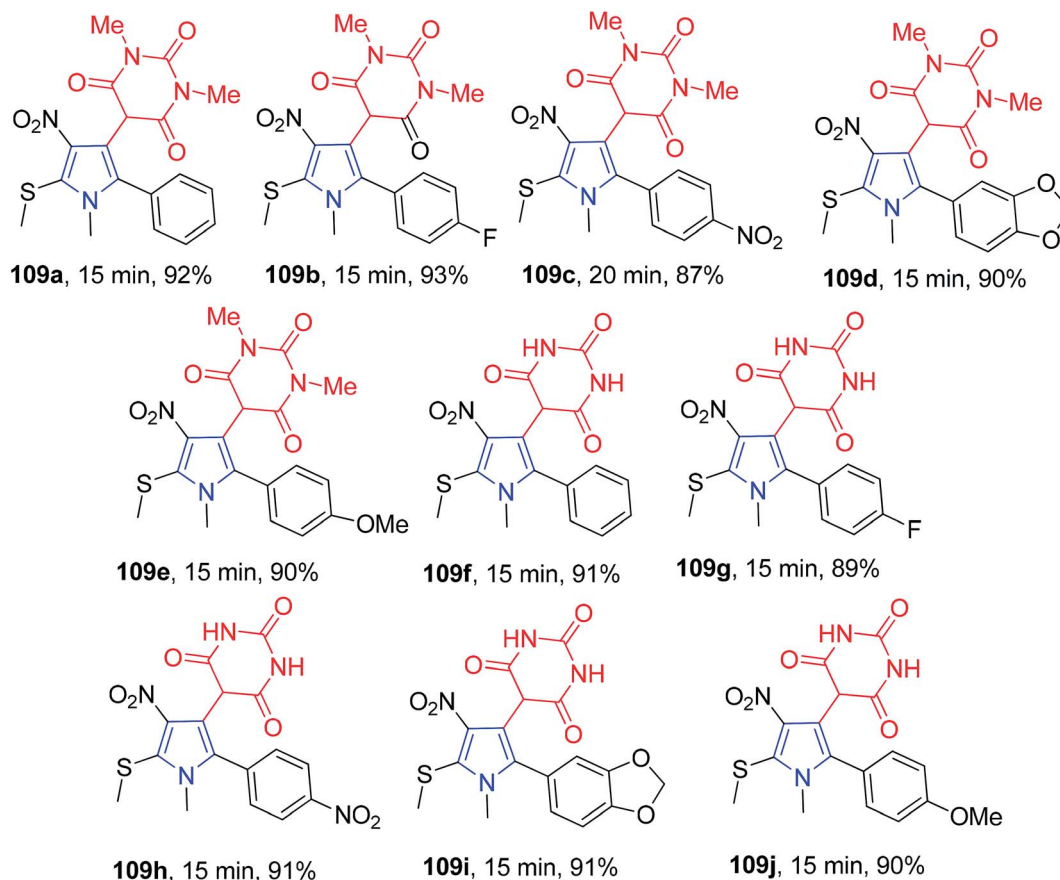
Misra and his group described an interesting route for the synthesis of the substituted pyrroles **122** by the 1,3-dipolar cycloaddition of the readily available NMSM derivative **120** with the active methylene ethyl isocyanoacetate **121** to provide the desired pyrroles (Scheme 47).⁸⁰

3.1.3 Synthesis of sulfur-containing heterocycles. In literature, to date, only one method has been reported for the synthesis of S-heterocycles using NMSM derivatives. In 2015, Kumar and his co-workers developed a protocol for the synthesis of the 2-amino-3-nitrothiophen derivatives **124** by the reaction of **7** with the 1,4-dithiane-2,5-diol **123** using K₂CO₃ as a base under refluxing ethanol (Scheme 48).⁸¹ A plausible mechanism leading to the construction of **124** is outlined in Scheme 49.

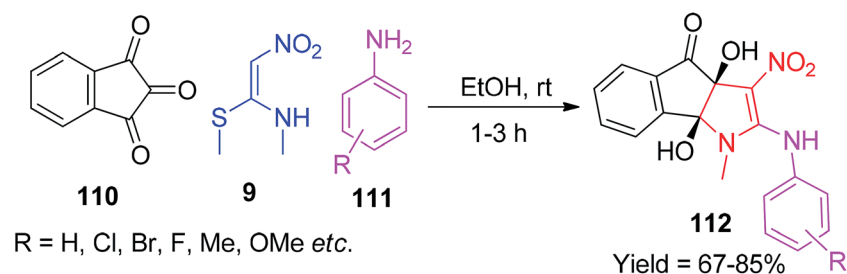


Scheme 41 Synthesis of the functionalized pyrrole derivative 109.





Scheme 42 The substrate scope of the pyrrole derivatives 109.

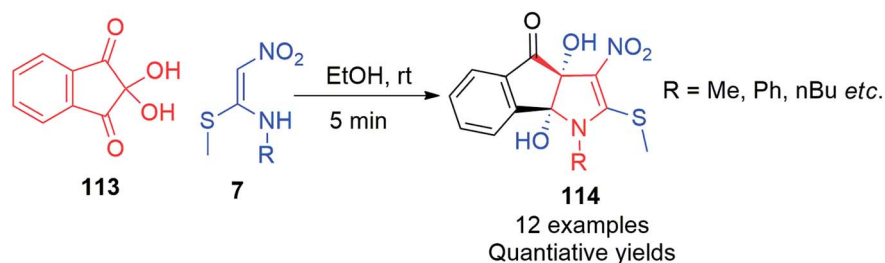


Scheme 43 Synthesis of the functionalized pyrrole derivatives 112.

3.2 Applications of cyclic nitroketene *N,S*-acetals

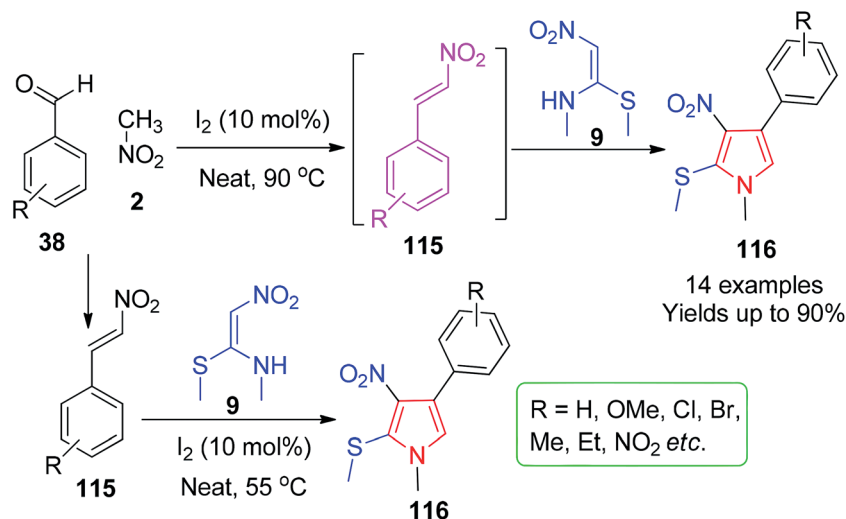
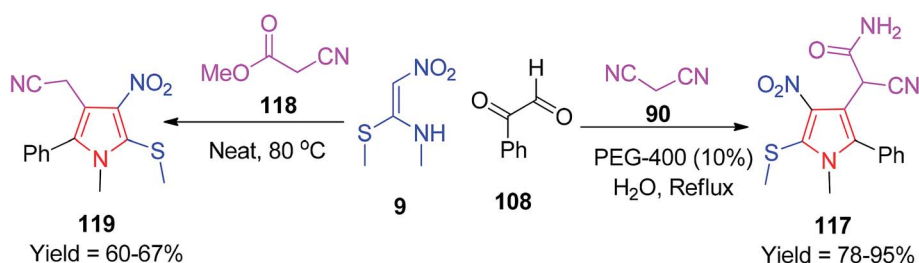
Owing to structural rigidity in cyclic nitroketene *N,S*-acetals, they behave as 1,3-*N,C*-dinucleophiles and generate only

nitrogen-containing heterocyclic compounds in their reactions. The commercially available six-membered nithiazine and five-membered cyclic nitroketene *N,S*-acetals have been



Scheme 44 Synthesis of the functionalized pyrroles 114.



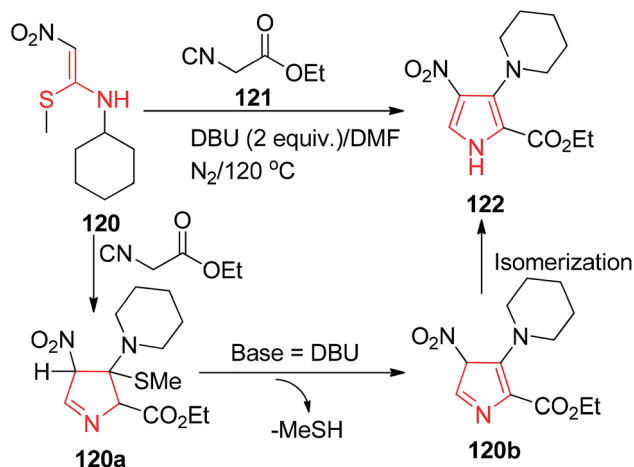
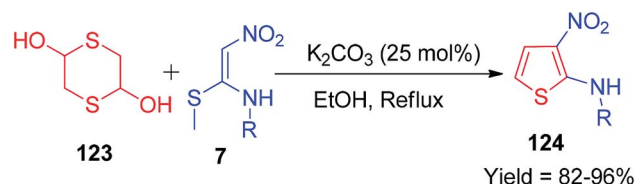
Scheme 45 Synthesis of the functionalized pyrroles **115** from NMSM.

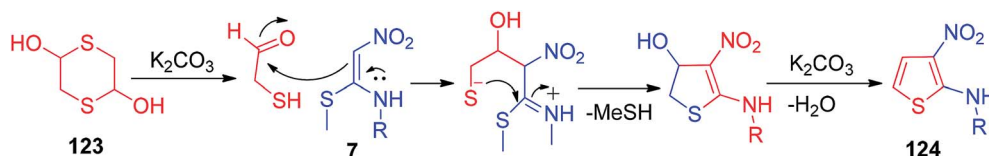
Scheme 46 Synthesis of functionalized pyrroles from NMSM.

significantly explored in the literature and act as Michael donors; therefore, their reaction with a Michael acceptor in the reaction medium is most anticipated. In this context, Altug and his group utilized 2-nitromethylenethiazolidine **36** for the formation of the functionalised fused *N*-substituted 1,4-DHPs **125**.

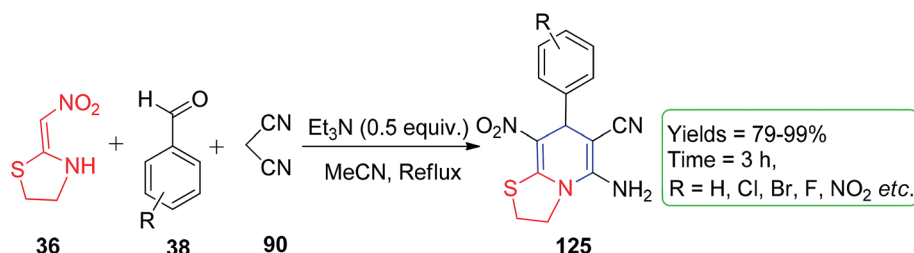
The Et₃N-catalyzed one-pot reaction was executed using active methylene compounds (*i.e.*, malononitrile **90**), ethyl cyanoacetate **126** and the aryl aldehydes **38** with **36** under mild conditions (Scheme 50).⁸² When the ethyl cyanoacetate **126** was used, only 1,4-dihydropyridine **127** was formed *via* grinding using a mortar for 10 min under neat conditions (Scheme 51). Moreover, the ratios of the enamine and imine tautomers **129** and **130**, respectively, were observed in an active methylene compound bearing a sulfoxide group, 2-phenyl sulfonylacetonitrile **128** (Scheme 52).

All the synthesized products were tested for *in vitro* anti-cancer activity using the MTT assay towards four human cancer cell lines, *i.e.* PC3 prostate, LoVo colorectal, A549 lung and MCF-7 breast cancer cell lines, and the compounds showed moderate to good activity.

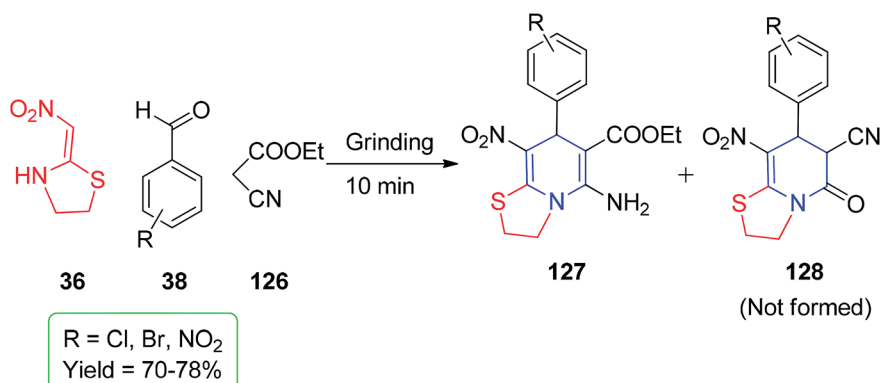
Scheme 47 Synthesis of the functionalized pyrroles **122**.Scheme 48 Synthesis of the functionalized thiophene **124**.



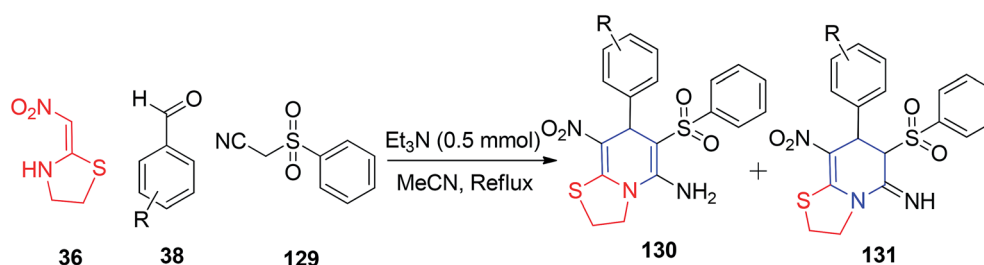
Scheme 49 The proposed mechanism for the formation of the 3-nitrothiophen-2-amines 124.



Scheme 50 Synthesis of the functionalized fused dihydropyridines 125.



Scheme 51 Synthesis of the highly substituted 1,4-DHPs 127.



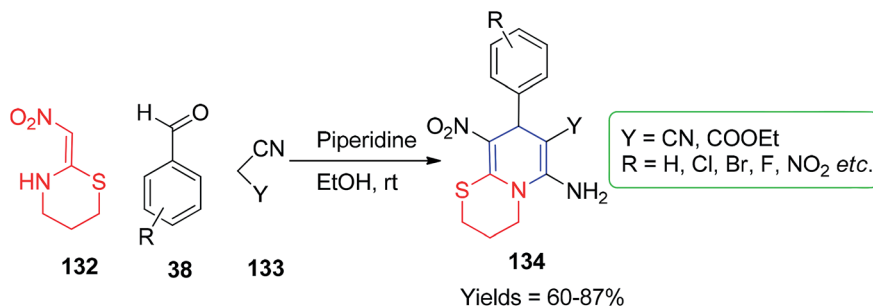
Scheme 52 Synthesis of the functionalized enamine imine tautomers 130 and 131.

Similarly, the preparation of the dihydropyridine motif was explored using nithiazine by Tian *et al.* The six-membered fused *N*-substituted 1,4-DHPs **134a-j** were obtained by mixing the active methylene compounds **133** and the aromatic aldehydes **38** with **132** in the presence of piperidine (10 mol%) under mild conditions (Scheme 53).⁸³ Furthermore, the replacement of malononitrile with the malononitrile dimer **136** was conducted by Sun and his co-workers for the synthesis of pyridine-fused 1,4-DHPs ring system.

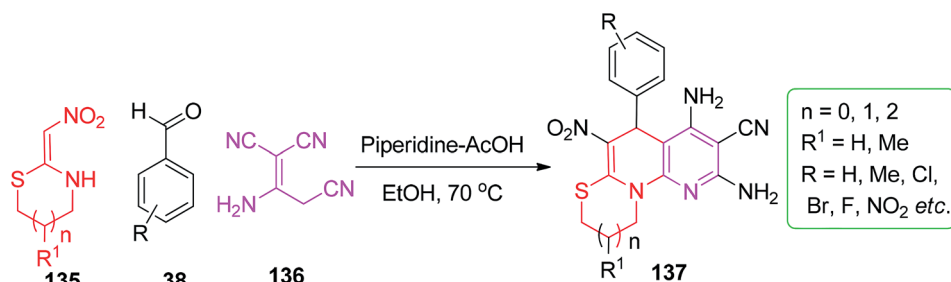
The tricyclic pyridine-fused 1,4-DHPs **137** were obtained by the condensation of the malononitrile dimer **136** with the aromatic aldehydes **38** under the piperidine/AcOH catalytic conditions using ethanol as a solvent (Scheme 54).⁸⁴

On the other hand, Bayat and his group synthesized fused 1,4-DHPs utilizing the five-membered cyclic nitroketene *N*,*S*-acetal **36**, which was prepared *via* the one-pot reaction of **15** with cysteamine hydrochloride **138** in the presence of the Et₃N catalyst. Then, the 1,4-DHP derivatives **140** were synthesized by





Scheme 53 Synthesis of functionalized six-membered fused 1,4-dihydropyridine.



Scheme 54 Synthesis of the tricyclic pyridine-fused 1,4-DHPs 137.

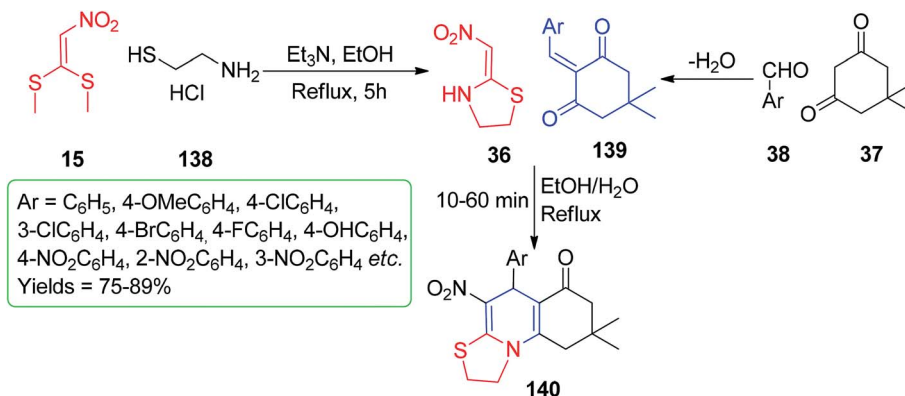
refluxing an aqueous ethanolic solution of compound **36**, dimedone **37** and different aromatic aldehydes **38** (Scheme 55).⁸⁵ The reaction proceeded *via* the Michael addition of the intermediate **139** to afford a short library of the fused 1,4-DHPs **140** in 75–94% yields. The Michael addition approach was also adopted by Yildirim and his group for the synthesis of different kinds of pyridinones (Scheme 56).⁸⁶

The base-promoted [3 + 3] cyclisation of the nitroketene *N,S*-acetals **36** with acryloyl or cinnamoyl chlorides **141** (1,3-dielectrophiles) provided the compounds **142** and **143** in good to excellent yields. However, they observed that (*E*)-3-methylbut-2-enoyl chloride and (*E*)-but-2-enoyl chloride afforded only the *N*-acylation products **143a** and **143b** and not the desired cyclic pyridinone compounds shown in Scheme 57.

Similarly, a new class of pyridinone derivatives having a carboxylic acid group was constructed by Chakrabarti and his co-workers by the reaction of the itaconic anhydride **98** with the five- and six-membered cyclic nitroketene *N,S*-acetals **36/145** in MeCN (Scheme 58).⁶⁸

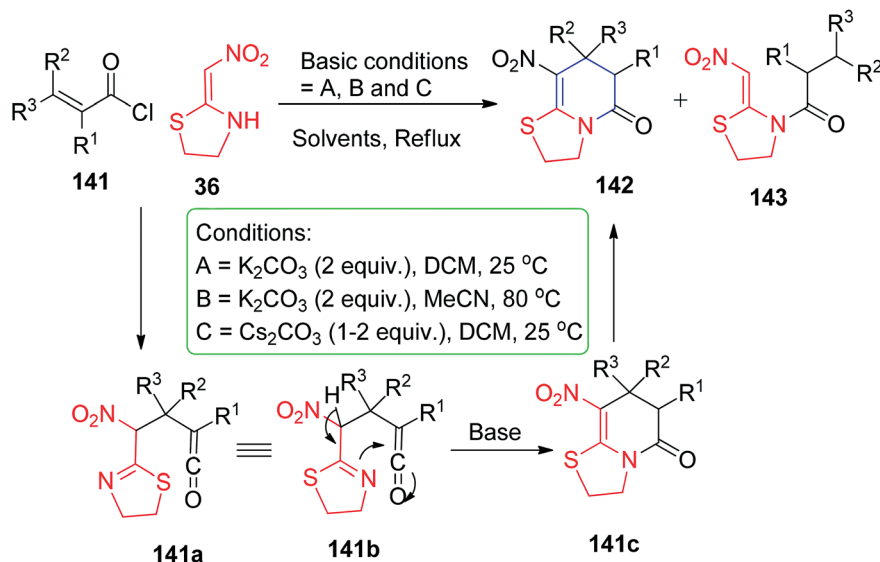
Further investigation on the –COOH group-containing pyridinone derivatives was conducted by Zou and his group *via* a two-step procedure. In the first step, the compound **148** was synthesized by the reaction of the phthalic anhydride **147** with the ethyl cyanoacetate **126** using diisopropylamine (DIPA) as a catalyst in THF followed by reaction with SOCl₂ in DCM.

In the next step, the starting materials **147** were heated in DMF at 70 °C with **36**, and the expected cyclic products **149** were obtained in good to excellent yields (Scheme 59).⁸⁷ Next, Yildirim *et al.* synthesized fused pyrimidine derivatives by green

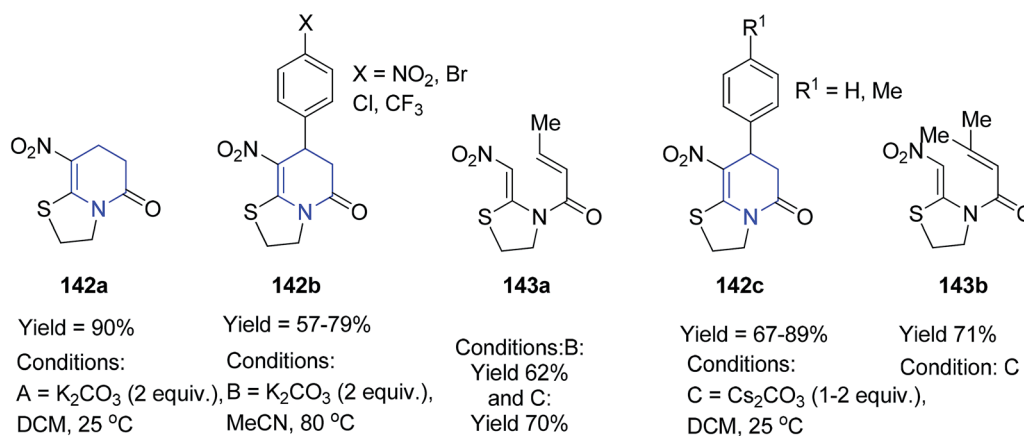


Scheme 55 Synthesis of the fused 1,4-DHPs 140.

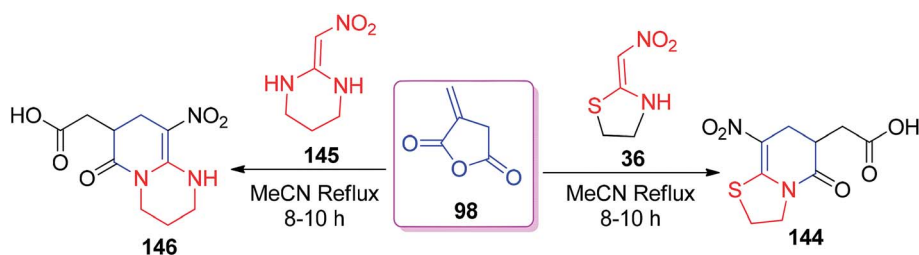




Scheme 56 Synthesis of the functionalized pyridinone 142.



Scheme 57 Diversity-oriented synthesis of functionalized pyridinones.



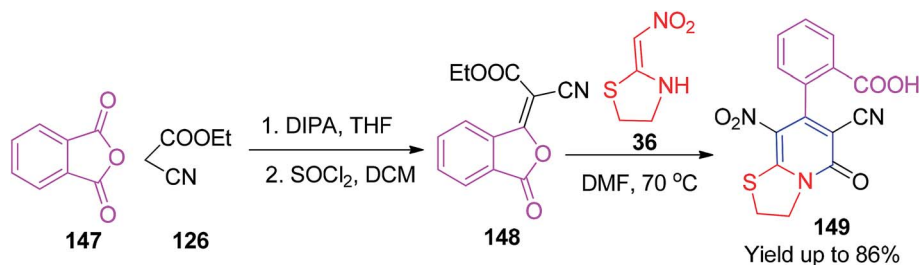
Scheme 58 Synthesis of the functionalized pyridinone 144 from the itaconic anhydride 98.

approaches using the five-membered cyclic nitroketene *N,S*-acetals **36**. These pseudo-four-component reactions were prompted by microwave/conventional heating using **36** with the aromatic/aliphatic amines **151** and formaldehyde **150** in water (Scheme 60).⁸⁸ In terms of yield and reaction time, MW heating provided better results than thermal heating. The synthesis of the bis pyrimidine **156** was also conducted with the yield of

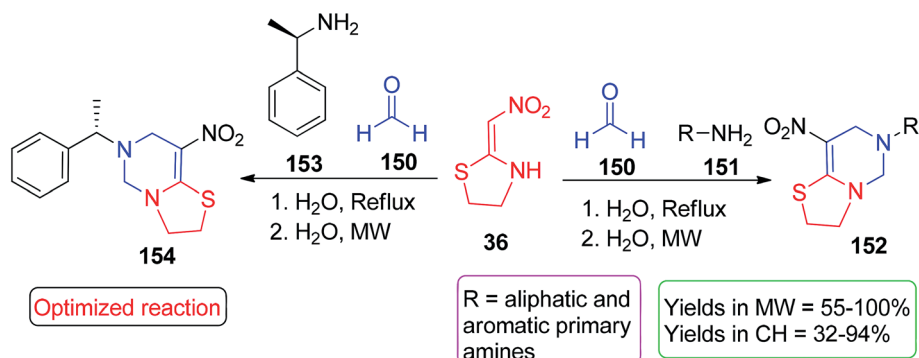
100% upon MW heating of the aromatic diamine **155**, formaldehyde and **36** (Scheme 61).

They also described a plausible mechanism, in which the imine **157** was formed by the reaction of formaldehyde **150** with the primary amine **151**, and the imine intermediate reacted with **36** *via* Mannich addition to generate the intermediate **157a**. This intermediate upon condensation with formaldehyde

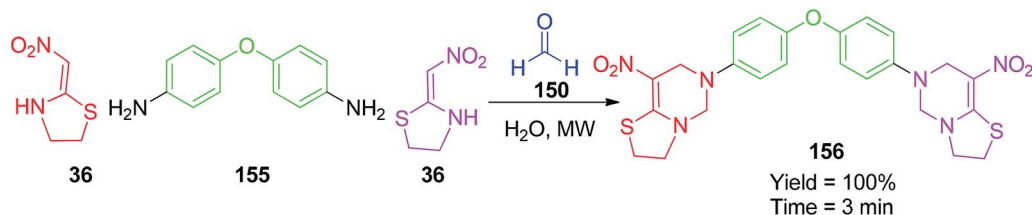




Scheme 59 Synthesis of the functionalized 2-oxo-1,2-dihydropyridinone 149.



Scheme 60 Synthesis of the functionalized pyrimidine derivatives 152/154.

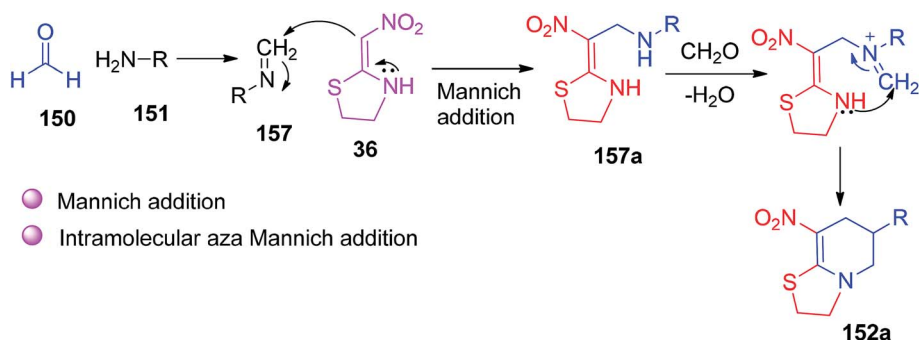


Scheme 61 Synthesis of the functionalized bis pyrimidine derivative.

and intramolecular aza-Mannich addition reaction afforded the final product (Scheme 62).

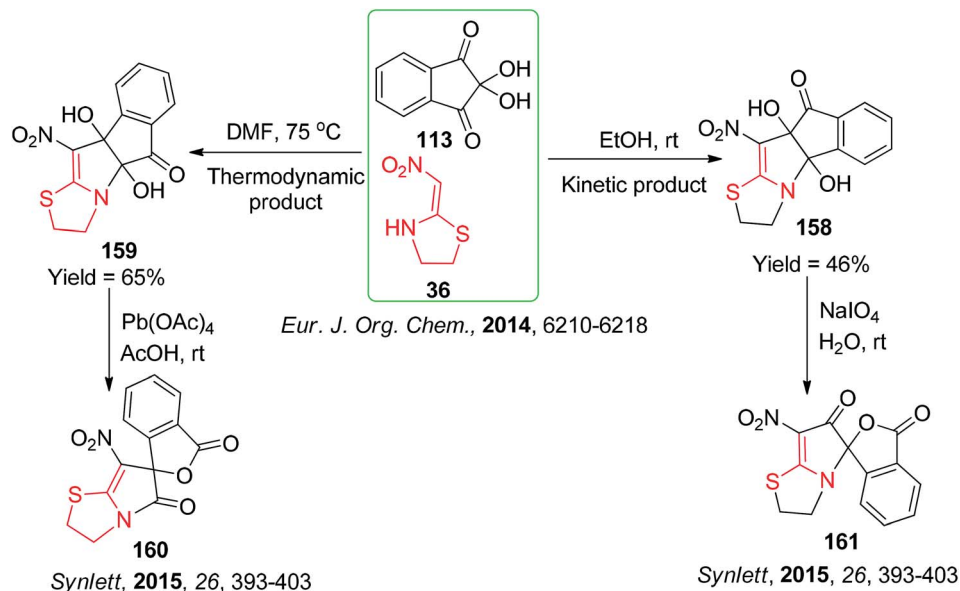
Next, an interesting approach was reported by Fan and his group for the synthesis of the kinetic and thermodynamically fused pyrroles **158/159** by the condensation of the ninhydrin

derivatives **113** with the cyclic nitroketene *N,S*-acetals **36** in ethanol at rt and in DMF at 75 °C, respectively (Scheme 63).⁸⁹ The kinetic and thermodynamic products were further subjected to oxidation using NaIO₄ and Pb(OAc)₄ at room temperature to obtain the compounds **161** and **160**, respectively.⁹⁰



Scheme 62 The proposed mechanism for product formation via Mannich addition.





Scheme 63 Synthesis of functionalized fused pyrroles and their functionalization.

4. Conclusions

Due to the synthetic and biological importance of nitroketene *N,S*-acetals, significant attention has been paid to their methods of preparation and applications. They are a robust building block for the construction of simple and fused heterocycles. The construction of highly stereo- and regioselective heterocycles *via* green synthetic procedures remains a vital challenge to chemists in recent times. Cyclic and acyclic functionalized nitroketene *N,S*-acetals take part in several commonly known reactions, such as Michael addition, 1,3-dipolar cycloaddition, heteroannulation reaction and also many cascade reactions, to afford novel *N*-, *O*- and *S*-containing heterocycles with high stereo- and regioselectivities. The formation of five-membered aromatic heterocycles, including pyrroles, thiophenes and non-aromatic dihydropyrroles, and six-membered 4*H*-pyran, chromene, chromenone, pyrazole-containing pyran, 1,4-DHP, pyrazole-fused pyridine, pyridinone and fused *N,S*-containing heterocycles, *etc.* from nitroketene *N,S*-acetals lead to outstanding functional group diversity, and these functional groups can be further functionalized to create complexity in the molecules; the graceful and original transformations have been recently reported along with the development of milder and safer access to heterocycles, and it is apparent that more of the scientific community will be enticed by this multitasking functional group.

We believe that these unique structural features have motivated organic chemists to explore nitroketene *N,S*-acetals to further heights, and the current overview is profoundly anticipated to boost the ongoing developments in this area of study.

Conflicts of interest

There are no conflicts to declare.

List of abbreviations

1,4-DHP	1,4-Dihydropyridine
AIBN	Azobisisobutyronitrile
β-CD	β-Cyclodextrin
CH	Conventional heating
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCM	Dichloromethane
DIPA	Diisopropylamine
DIPEA	Diisopropylethylamine
DMF	<i>N,N</i> -Dimethylformamide
DMSO	Dimethyl sulfoxide
GAP	Group-assisted purification
HIV	Human immunodeficiency viruses
<i>m</i> -CPBA	<i>m</i> -Chloroperbenzoic acid
MCR	Multicomponent reaction
MW	Microwave
NaH	Sodium hydride
NMR	Nuclear magnetic resonance
NMSM	(<i>E</i>)- <i>N</i> -Methyl-1-(methylthio)-2-nitroethenamine
PEG	Polyethyleneglycol
ROESY	Rotating-frame nuclear overhauser effect correlation spectroscopy
SF	Solvent-free
SNV	Substitution nucleophilic vinyl
STA	Silica-supported tungstic acid
TBTH	Tributyltin hydride
THF	Tetrahydrofuran
TSA	Toluenesulfonic acid

Acknowledgements

Saigal and S. K. are grateful to the CSIR and UGC, respectively, for their Senior Research Fellowship (SRF). We are grateful to



the referees and editors for their valuable comments and suggestions.

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