

HETEROCYCLES, Vol. 96, No. 3, 2018, pp. 381 - 424. © 2018 The Japan Institute of Heterocyclic Chemistry
Received, 23rd October, 2017, Accepted, 19th January, 2018, Published online, 6th February, 2018
DOI: 10.3987/REV-17-872

4-HYDROXY-6-METHYL-2-PYRONE: A VERSATILE SYNTHON IN THE SYNTHESIS OF HETEROCYCLIC SCAFFOLDS VIA MULTICOMPONENT REACTIONS

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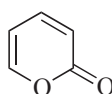
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Abstract – 4-Hydroxy-6-methyl-2-pyrone has been utilized in the synthesis of various heterocyclic compounds. It is a potential 1,3-dicarbonyl compound with diverse synthetic applications that have been extensively investigated. There is a wide range of multicomponent reactions that include 4-hydroxy-6-methyl-2-pyrone in the synthesis of heterocyclic compounds. This review highlights the advances in the use of this compound as starting material in the synthesis of various organic compounds.

1. INTRODUCTION

Pyrones; specifically 2-pyrones or α -pyrones (Figure 1), are among the most important heterocyclic structures in medicinal chemistry and can be found in a wide range of medicinally significant natural products such as orevactaene (anti-HIV),^{1,2} arisugacins (AChE inhibitors),³⁻⁵ and rosellisin (antibacterial agent)⁶ (Figure 2).

The multicomponent reactions (MCRs), referred to a chemical reaction in which three or more compounds react to form a single product,⁷ are an important tool in new drug discovery.⁸⁻¹¹ MCRs are used for developing new lead structures of active agents.¹² Recently, the synthesis of heterocyclic compounds via multicomponent reactions has been widely studied and reviewed by our group.¹³⁻¹⁸



α -pyrone or 2-pyrone

Figure 1. 2-Pyrones or α -pyrones

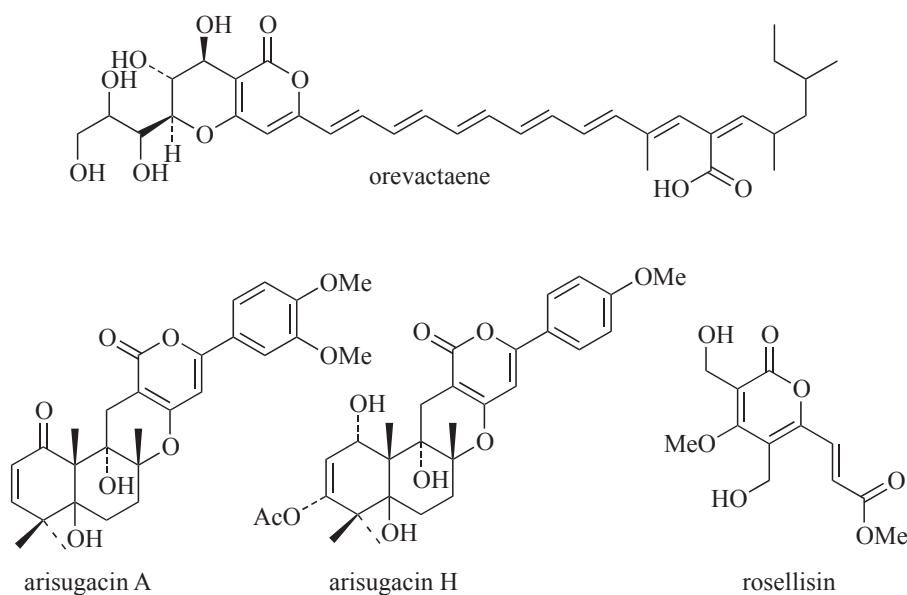


Figure 2. Medicinally significant natural products containing 2-pyrones

4-Hydroxy-6-methyl-2-pyrone or triacetic acid lactone, which can be obtained from natural sources (plants and bacteria) or be synthetically produced from acetic acid,¹⁹ plays an important role in the synthesis of heterocyclic compounds. This compound is a light yellow solid that is soluble in organic solvents and consists of two main tautomers (Figure 3). The tautomer on the left, having a 4-hydroxy group is dominant. Triacetic acid lactone is classified as a 2-pyrone compound owing to the ketone group on the C2 carbon in its dominant form. As yet no review article has been written on this subject, this review presents the application of 4-hydroxy-6-methyl-2-pyrone in the synthesis of different types of heterocyclic compounds by multicomponent reactions.

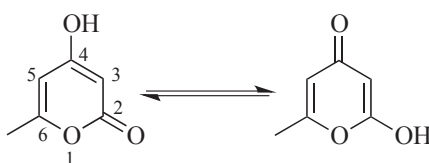
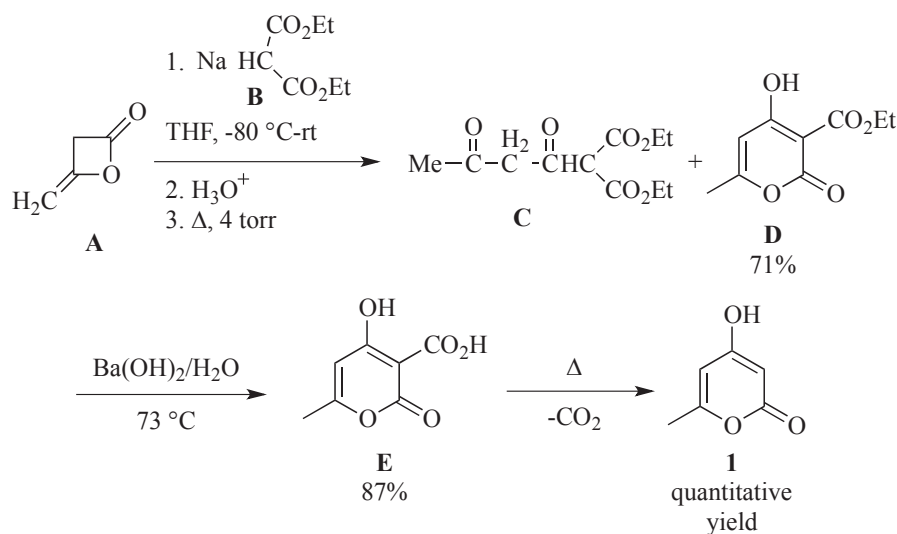


Figure 3. Two main tautomers of 4-hydroxy-6-methyl-2-pyrone

In 1962, Williams and co-workers isolated 4-hydroxy-6-methyl-2-pyrone **1** from the urine of rabbits.²⁰ Later, this compound was obtained from various synthetic routes. In 1975, Suzuki *et al.* reported the reaction of diketene **A** with diethyl sodium malonate **B** in tetrahydrofuran to afford an oily mixture containing the dioxodiester **C** and the pyrone ester **D**. Hydrolysis of 3-ethoxycarbonyl functional group in **D** was carried out for the synthesis of 3-carboxy-4-hydroxy-6-methyl-2-pyrone **E** in high yield. Compound **E** was finally decarboxylated to prepare 4-hydroxy-6-methyl-2-pyrone **1** (Scheme 1).²¹ There

are also other reported synthetic routes for preparation of 2-pyrone derivatives.²²

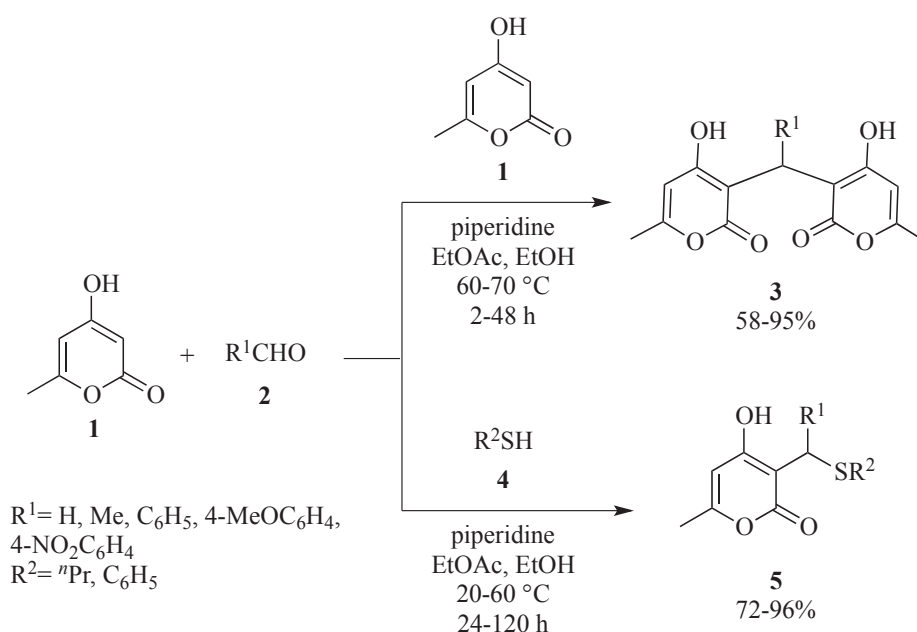


Scheme 1. Synthesis of 4-hydroxy-6-methyl-2-pyrone **1**

2. THREE-COMPONENT REACTIONS OF 4-HYDROXY-6-METHYL-2-PYRONE

2.1. Synthesis of arylmethane heterocycles

March *et al.* established the reaction of 4-hydroxy-6-methyl-2-pyrone **1** and aldehydes **2** in the presence or absence of thiols **4**, for the synthesis of bis(4-hydroxy-6-methyl-2-pyrone)methanes **3** and (4-hydroxy-6-methyl-2-pyrone)thiomethanes **5** using piperidine as the catalyst (Scheme 2).²³⁻²⁵



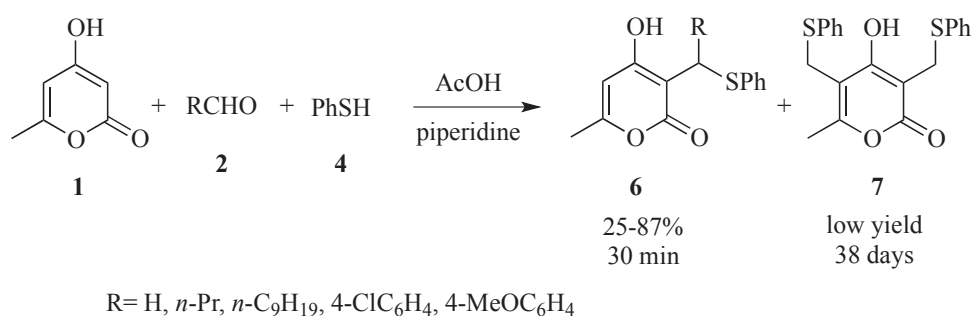
Scheme 2. Synthesis of bis(4-hydroxy-6-methyl-2-pyrone)methanes **3** and (4-hydroxy-6-methyl-2-pyrone)thiomethanes **5** from **1**

Zhang *et al.* synthesized the same products in the presence of $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ as the catalyst in 1-butyl-3-methylimidazolium tetrafluoroborate ($[\text{bmim}]\text{BF}_4$) in excellent yields (83-96%).²⁶ Shi and co-workers,²⁷ and Darwish *et al.*²⁸ in separate studies obtained the same products without any catalyst in good yields. Table 1 shows some results achieved with other catalysts for the synthesis of the products **3**.

Table 1. Different reported strategies for the synthesis of compounds **3**

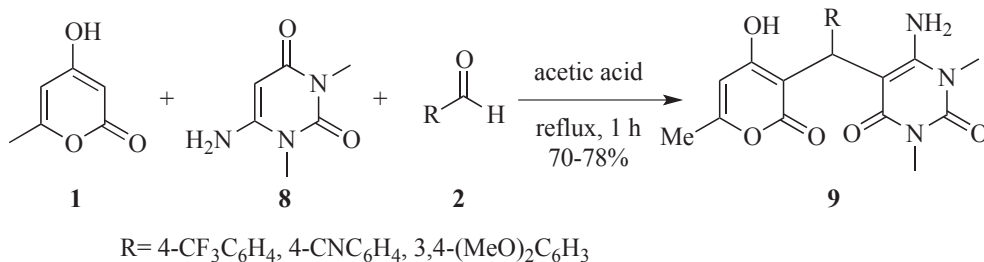
Entry	Solvent	Catalyst	Condition	Time (h)	Yield (%)
1	EtOAc/EtOH	piperidine	60-70 °C	2-48	58-95 ²³⁻²⁵
2	$[\text{bmim}]\text{BF}_4$	$\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$	80 °C	2-4	83-96 ²⁶
3	H_2O	-	MW	8-15 min	75-86 ²⁷
4	EtOH	-	78 °C	18	46 ²⁸
5	AcOH/EtOH	piperidine	70 °C	45-60 min	57-94 ²⁹

In another study, March *et al.* reported a three-component reaction of 4-hydroxy-6-methyl-2-pyrone **1**, aldehyde **2** and thiophenol **4** in acetic acid as solvent catalyzed by piperidine to produce two different products: 4-hydroxy-6-methyl-3-((phenylthio)methyl)-2*H*-pyran-2-one **6** in 30 minutes and 4-hydroxy-6-methyl-3,5-bis((phenylthio)methyl)-2*H*-pyran-2-one **7** in 38 days at room temperature (Scheme 3).³⁰



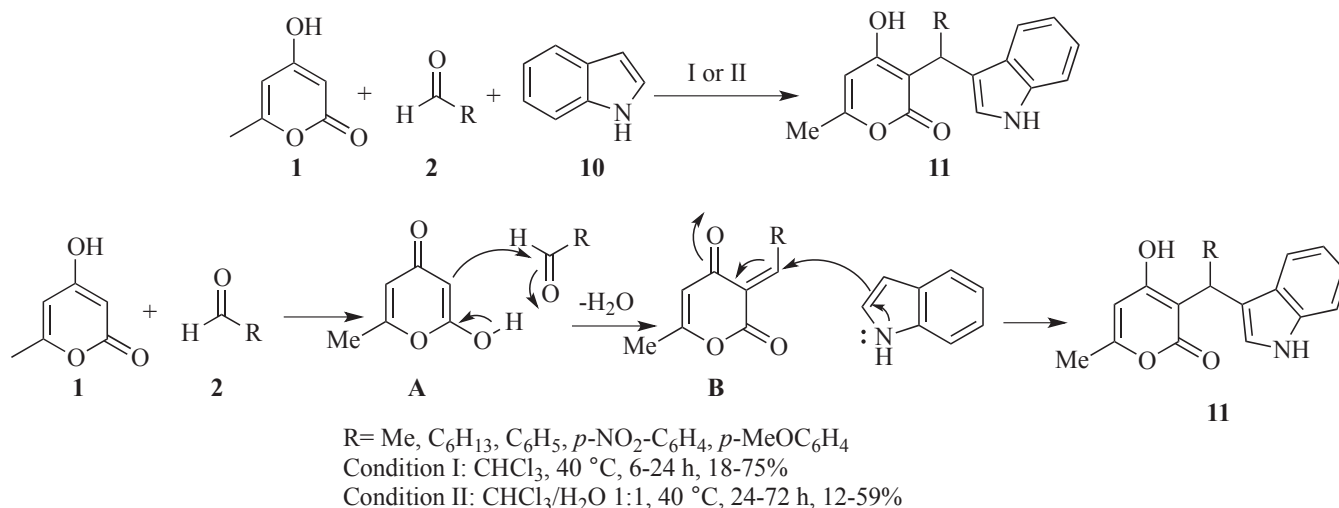
Scheme 3. Synthesis of ((phenylthio)methyl)pyran-2-one **6** and bis((phenylthio)methyl)pyran-2-one **7** from **1**

The anti-microbial and anti-biofilm active pyrimidine compounds **9** were prepared via a one-pot three-component regioselective reaction of 4-hydroxy-6-methyl-2-pyrone **1**, 6-amino-1,3-dimethyluracil **8** and different aldehydes **2** in acetic acid under reflux condition (Scheme 4).³¹



Scheme 4. Synthesis of pyrimidine compounds **9** from **1**

The multicomponent reaction of 4-hydroxy-6-methyl-2-pyrone **1** with aldehyde derivatives **2** and indole **10** was investigated to generate the *gem*-(β -dicarbonyl)arylmethanes **11** (Scheme 5).³² Two different conditions were used in this reaction. According to the possible mechanism, the carbonyl group in aldehyde is expected to react preferentially with the more localized nucleophilic double bond of an enol (Scheme 5). Conversely, the resulting Knoevenagel adduct is a softer electrophile, and should therefore react with an electron-rich aromatic nucleophile better than an enolized β -dicarbonyl.³³ Application of *L*-proline as a catalyst in this reaction was also reported by Brahmachari and Das³⁴ (4 h, 75%), and Li *et al.* (4 h, 81%).³⁵ Yamamoto *et al.* developed this reaction without any catalyst and obtained the products in good yields.³⁶ A comparison of different catalysts and experimental setups is given in Table 2.



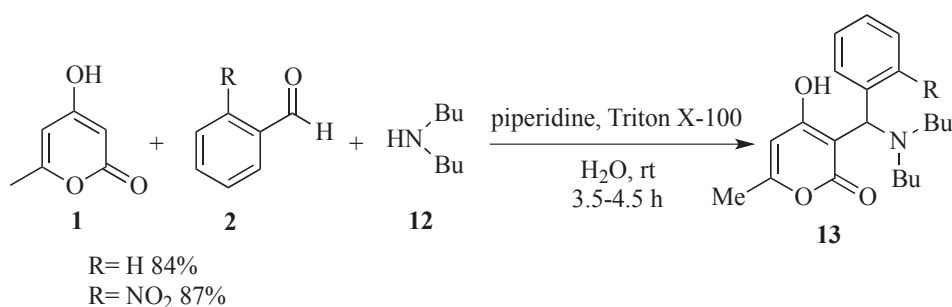
Scheme 5. Proposed mechanism for the synthesis of *gem*-(β -dicarbonyl)arylmethanes **11** from **1**

Table 2. Comparison of different conditions in the synthesis of compound **11**

Entry	Solvent	Catalyst	Condition	Time (h)	Yield (%)
1	A: CHCl ₃	-	40 °C	6-24	18-75 ³²
	B: CHCl ₃ /H ₂ O (1:1)	-	40 °C	24-72	12-59 ³²

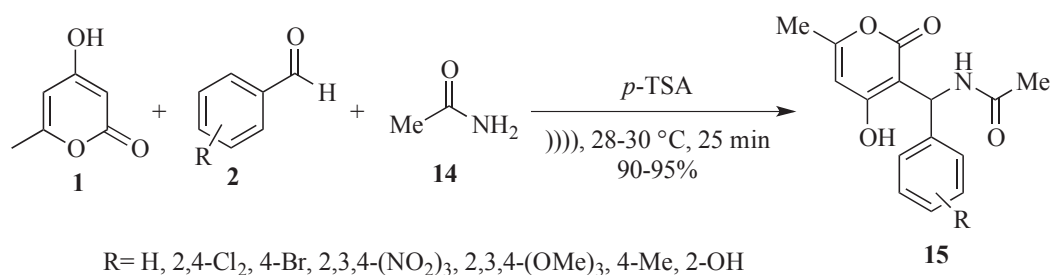
2	-	<i>L</i> -proline	rt	4-5	83-96 ³⁴
3	EtOH	<i>L</i> -proline	80 °C	4	81 ³⁵
4	AcOH	-	65 °C	10-20	87-90 ³⁶

A piperidine, triton X-100 catalyzed three-component Mannich type reaction³⁷ of 4-hydroxy-6-methyl-2-pyrone **1**, aldehyde derivatives **2** and secondary amine **12** was established in aqueous media and room temperature for the synthesis of novel 3-alkylated 4-hydroxypyrene derivatives **13** (Scheme 6).³⁸ In another study, Shi *et al.* employed *L*-proline as a catalyst in this reaction and obtained the main product in 90% yield.³⁹ The catalyst-free condition was also used and the same products were achieved in 69-94% yields.⁴⁰



Scheme 6. Synthesis of novel 3-alkylated 4-hydroxypyrene derivatives **13** from **1**

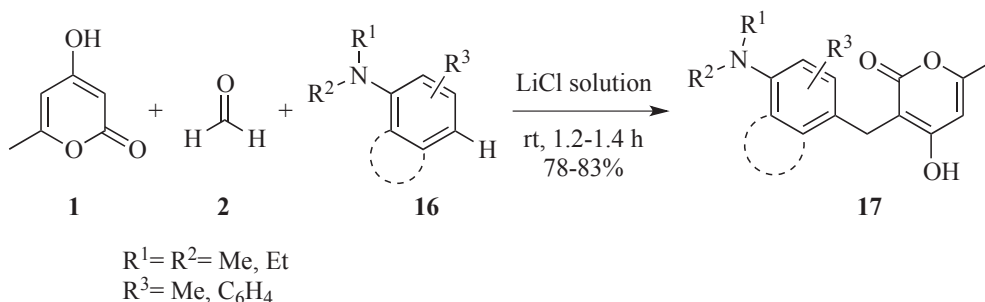
Bizhanpoor and Hassanabadi worked on a three-component one-pot reaction of 4-hydroxy-6-methyl-2-pyrone **1**, aryl aldehydes **2** and acetamide **14** in the presence of *p*-toluenesulfonic acid (*p*-TSA) as catalyst and under ultrasound irradiation to obtain 3-[(acetamido)(aryl)methyl]-4-hydroxy-6-methyl-2*H*-pyran-2-ones **15** in high yields (Scheme 7).⁴¹



Scheme 7. Synthesis of 3-[(acetamido)(aryl)methyl]pyran-2-ones **15** from **1**

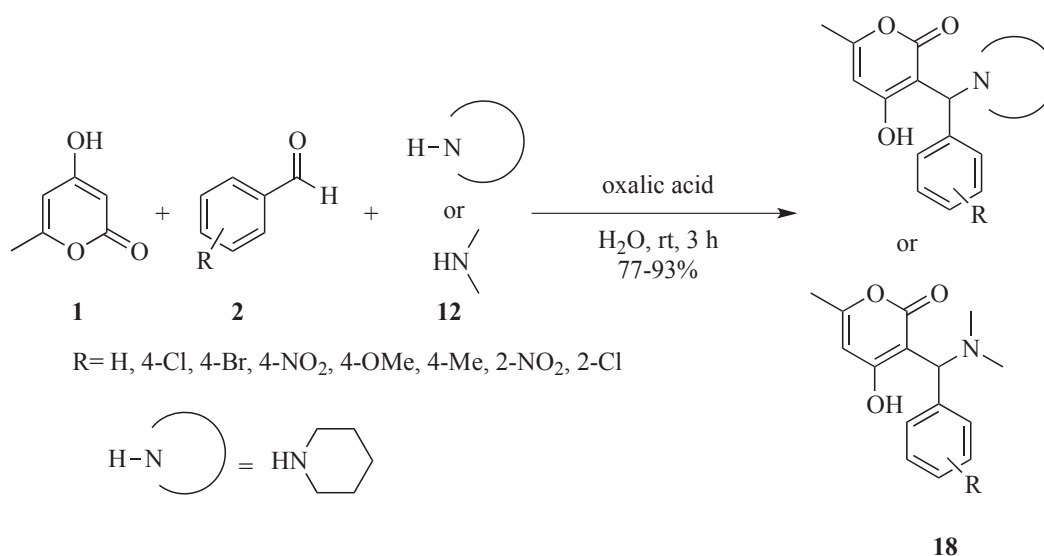
Kumar *et al.* accomplished a catalyst-free multicomponent reaction containing 4-hydroxy-6-methyl-2-pyrone **1**, formaldehyde **2** and *N,N*-dialkylaniline **16** in aqueous solution of LiCl at

room temperature to afford 3-alkylated 4-hydroxypyrrone derivatives **17** in good yields (Scheme 8).⁴²



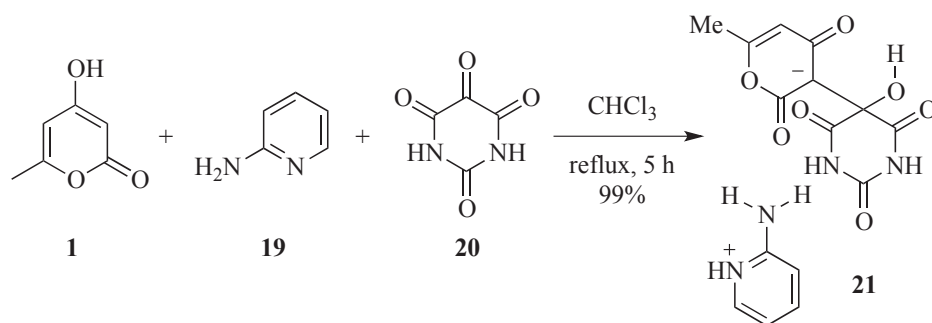
Scheme 8. Synthesis of 3-alkylated 4-hydroxypyrrone derivatives **17** from **1**

The three-component oxalic acid-catalyzed reaction of 4-hydroxy-6-methyl-2-pyrone **1**, aromatic aldehydes **2** and secondary amines **12** was developed to afford α -benzylaminopyrones **18** in H₂O as a green solvent in 3 hours (Scheme 9). This work was also reported by Sanchooli group.⁴³



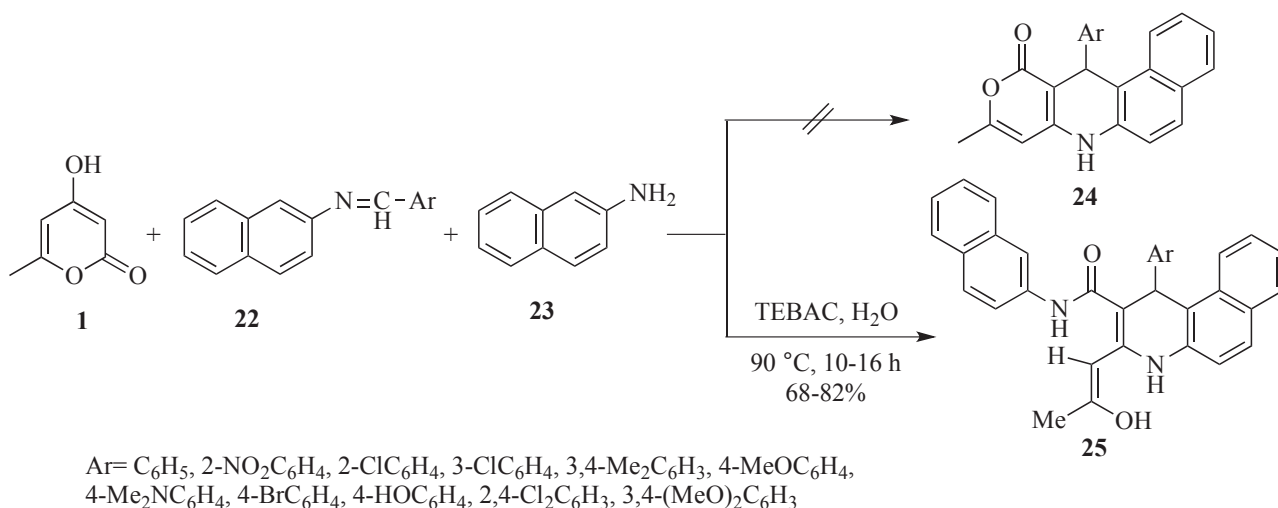
Scheme 9. Synthesis of α -benzylaminopyrones **18** from **1**

Three-component condensation reaction of 4-hydroxy-6-methyl-2-pyrone **1**, 2-aminopyridine **19** and pyrimidine-tetraone **20** in refluxing chloroform was carried out by Bazgir and co-workers to achieve a new barbiturate salt **21** in high yield (Scheme 10).⁴⁴



Scheme 10. Synthesis of new barbiturate salt **21** from **1**

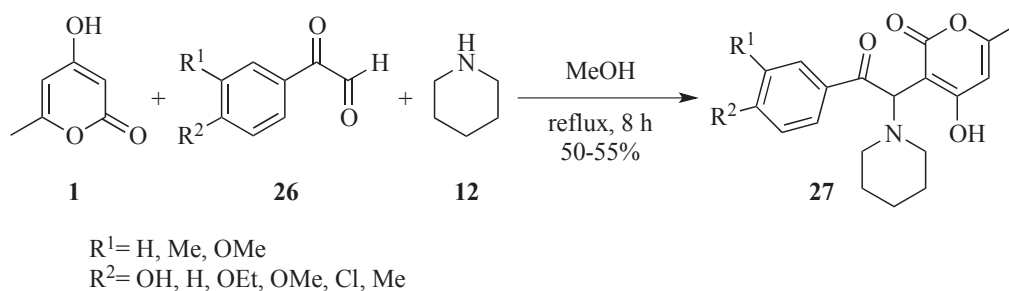
A three-component reaction of 4-hydroxy-6-methyl-2-pyrone **1**, *N*-arylidene-naphthalen-2-amine **22** and naphthalen-2-amine **23** in the presence of triethylbenzylammonium chloride (TEBAC) in aqueous media was carried out by Wang's group. The reaction, however, failed to produce the desired pyranobenzoquinolines **24** and unexpectedly, several 1-arylbenzo[*f*]quinoline-2-carboxamide derivatives (ring-opening product) **25** were obtained in good yields (Scheme 11).⁴⁵



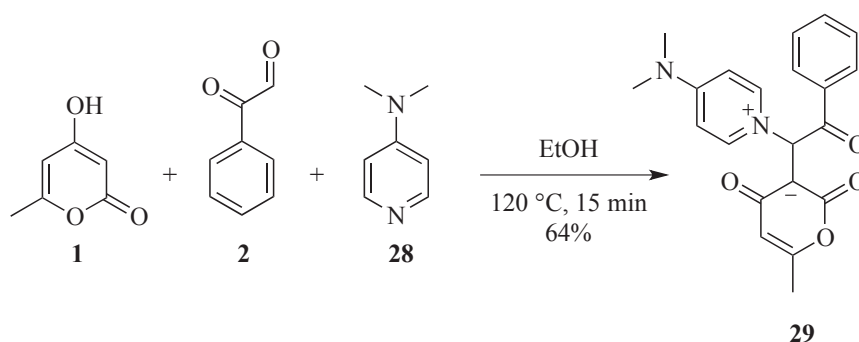
Scheme 11. Synthesis of 1-arylbenzo[*f*]quinoline-2-carboxamides **25** from **1**

3-(2-(4-Substituted phenyl)-2-oxo-1-(piperidin-1-yl)ethyl)-4-hydroxy-6-methyl-2*H*-pyran-2-ones **27** were synthesized through a three-component reaction of 4-hydroxy-6-methyl-2-pyrone **1**, substituted phenyl glyoxals **26** and piperidine **12** under reflux condition in methanol for 8 hours (Scheme 12).⁴⁶

Pereshivko *et al.* reported another reaction in which 4-hydroxy-6-methyl-2-pyrone **1**, 2-oxoaldehydes **2** and 4-aminopyridines **28** were put together in a three-component reaction and resulted in synthesis of zwitterionic Michael-type adduct **29** (Scheme 13).⁴⁷

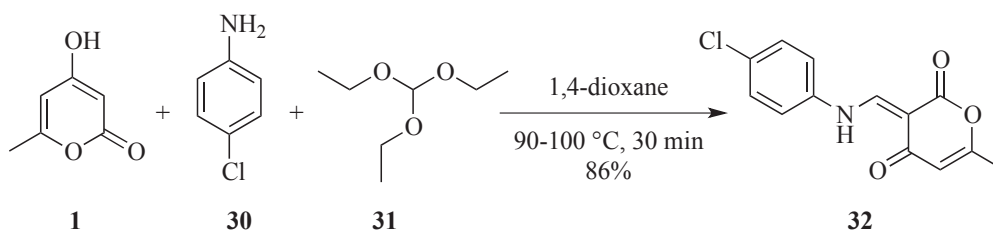


Scheme 12. Synthesis of substituted (piperidin-1-yl)ethyl-2*H*-pyran-2-ones **27** from **1**



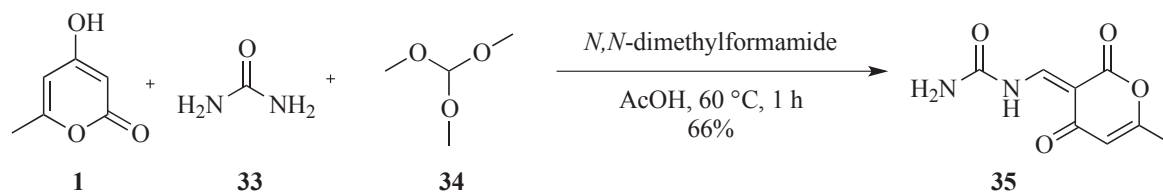
Scheme 13. Synthesis of zwitterionic Michael-type adduct **29** from **1**

(*E*)-3-(((4-Chlorophenyl)amino)methylene)-6-methyl-2*H*-pyran-2,4(3*H*)-dione **32** was synthesized by Zeigler's group via a three-component reaction of 4-hydroxy-6-methyl-2-pyrone **1**, 4-chloroaniline **30** and triethoxymethane **31** in 1,4-dioxane as solvent (Scheme 14).⁴⁸



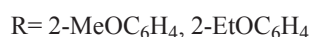
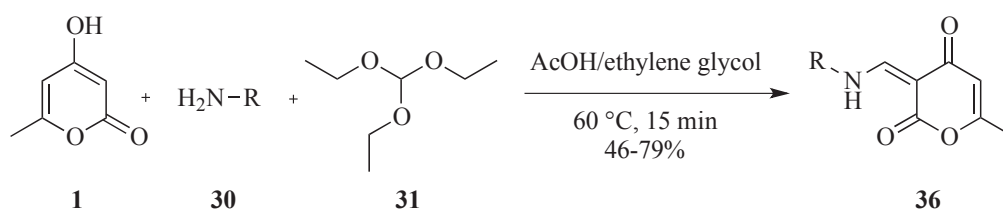
Scheme 14. Synthesis of (*E*)-3-(((4-chlorophenyl)amino)methylene)-2*H*-pyran-2,4-dione **32** from **1**

In another study, the same group developed a three-component reaction of 4-hydroxy-6-methyl-2-pyrone **1**, urea **33** and trimethoxymethane **34** in *N,N*-dimethylformamide/acetic acid leading to the formation of (*E*)-1-((6-methyl-2,4-dioxo-2*H*-pyran-3(4*H*)-ylidene)methyl)urea **35** as main product in good yield (Scheme 15).⁴⁹



Scheme 15. Synthesis of (*E*)-1-((6-methyl-2,4-dioxo-2*H*-pyran-3(4*H*)-ylidene)methyl)urea **35** from **1**

Trathnigg *et al.* developed a three-component reaction of 4-hydroxy-6-methyl-2-pyrone **1**, triethoxymethane **31** and primary amine **30** in acetic acid/ethylene glycol in 15 minutes to form (*Z*)-3-(aminomethylene)-6-methyl-2*H*-pyran-2,4(3*H*)-dione derivatives **36** (Scheme 16).⁵⁰

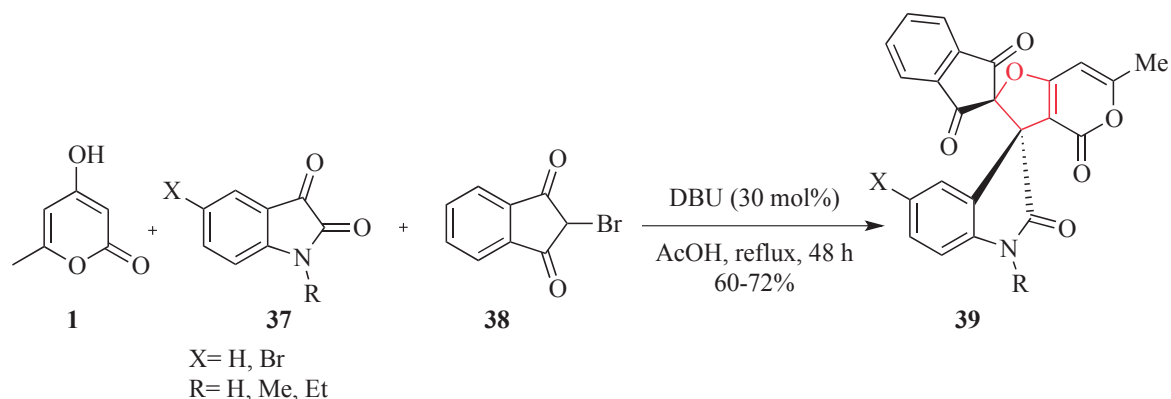


Scheme 16. Synthesis of (*Z*)-3-(aminomethylene)-2*H*-pyran-2,4(3*H*)-diones **36** from **1**

2.2. Synthesis of five-membered heterocycles

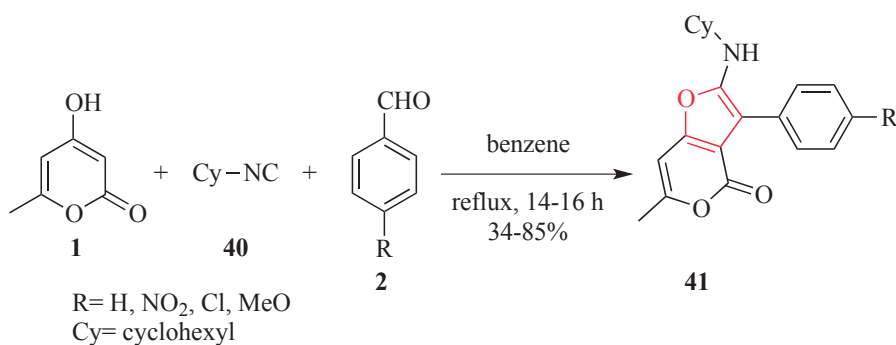
2.2.1. Five-membered heterocycles containing O atom

Bazgir and co-workers developed an effective method for the synthesis of bis-spirooxindole-fused dihydrofurans **39** containing two vicinal spiro centers, via the modified Feist–Benary^{51,52} reaction of 4-hydroxy-6-methyl-2-pyrone **1**, isatins **37** and cyclic α -bromodicarbonyl compound **38** in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as catalyst in AcOH (Scheme 17).⁵³



Scheme 17. Synthesis of bis-spirooxindole-fused dihydrofurans **39** from **1**

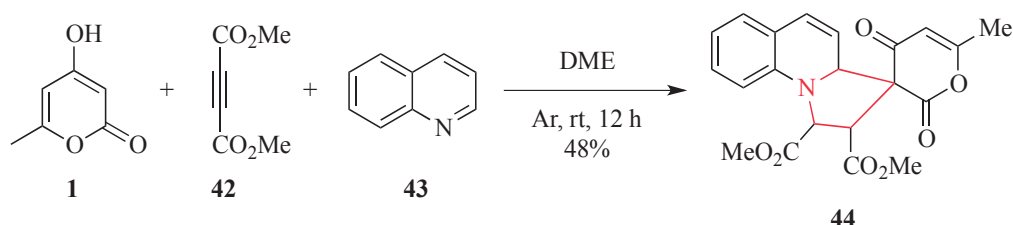
Furo[3,2-*c*]pyran-4-ones **41** were prepared in good yields (34-85%) via a facile three-component, catalyst-free reaction involving [4+1] cycloaddition of 4-hydroxy-6-methyl-2-pyrone **1** with cyclohexyl isocyanide **40** and aldehyde derivatives **2** (Scheme 18).⁵⁴ In other studies, Shaabani and Teimouri carried out this reaction in catalyst-free condition under microwave irradiation in 3 min (79-91% yields)⁵⁵ and also in the presence of Montmorillonite K10 (70-81% yields).⁵⁶



Scheme 18. Synthesis of furo[3,2-*c*]pyran-4-ones **41** from **1**

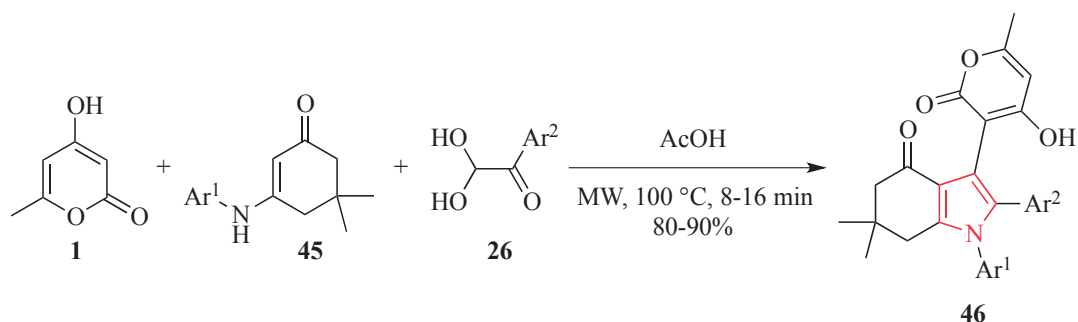
2.2.2. Five-membered heterocycles containing N atom

Three-component reaction of 4-hydroxy-6-methyl-2-pyrone **1**, dimethyl acetylenedicarboxylate **42** and quinoline **43** in 1,2-dimethoxyethane (DME) under argon atmosphere resulted in the formation of pyrroloquinoline **44** (Scheme 19).⁵⁷



Scheme 19. Synthesis of pyrroloquinoline **44** from **1**

Wang and co-workers designed the synthesis of a set of pyran-3-yl-substituted fused pyrroles **46** via a domino three-component reaction of 4-hydroxy-6-methyl-2-pyrone **1**, *N*-arylenaminones **45** and arylglyoxal monohydrates **26** promoted by AcOH under microwave irradiation (Scheme 20).⁵⁸ The attractive aspect of this domino reaction was shown by the fact that the construction of the pyrrole skeleton and the direct C3 pyranation were readily achieved in an intermolecular fashion in a single step. Furthermore, the reactions showed broad scopes of substrates which can employ a wide range of readily available arylglyoxal monohydrates and *N*-arylenaminones. In another study, the same products were obtained in 83-90% under catalyst-free conditions in refluxing ethanol.⁵⁹

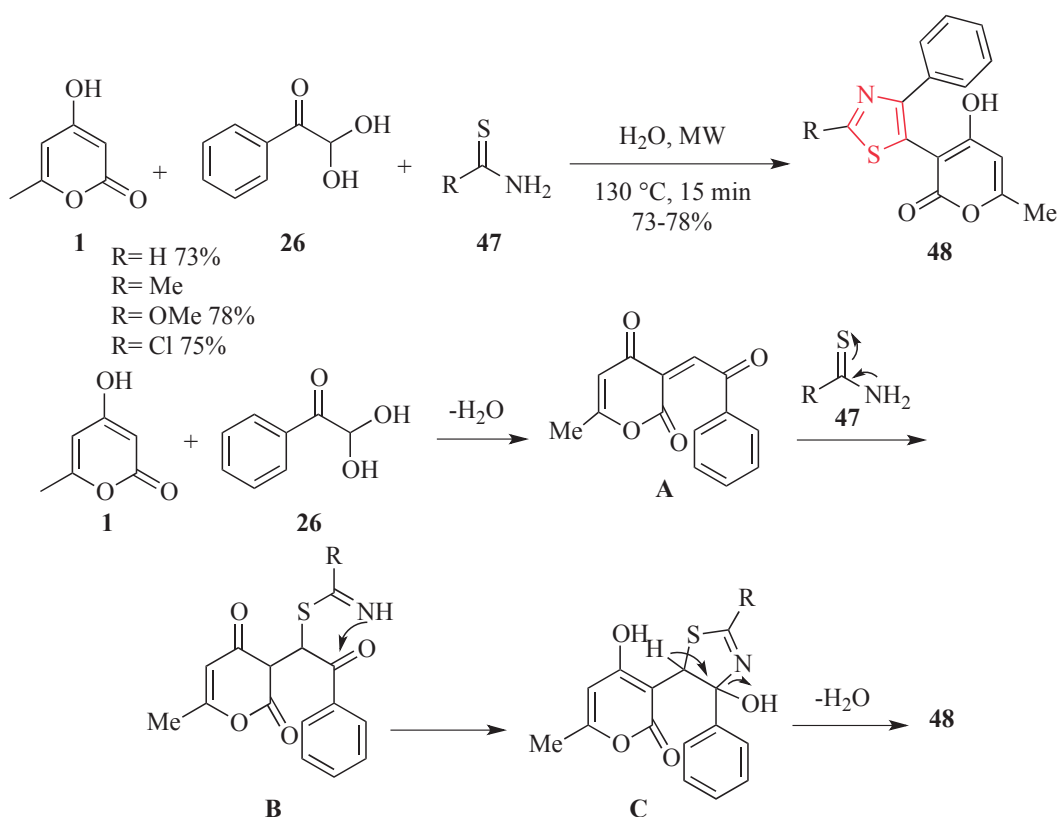


Ar¹ = C₆H₅, 4-FC₆H₄, 4-ClC₆H₄, 4-BrC₆H₄, 4-IC₆H₄, 4-MeC₆H₄,
 4-MeOC₆H₄, 3-BrC₆H₄, piperonyl
 Ar² = C₆H₅, 4-MeC₆H₄, 4-FC₆H₄, 4-ClC₆H₄, 4-BrC₆H₄, 4-MeC₆H₄

Scheme 20. Synthesis of pyran-3-yl-substituted fused pyrroles **46** from **1**

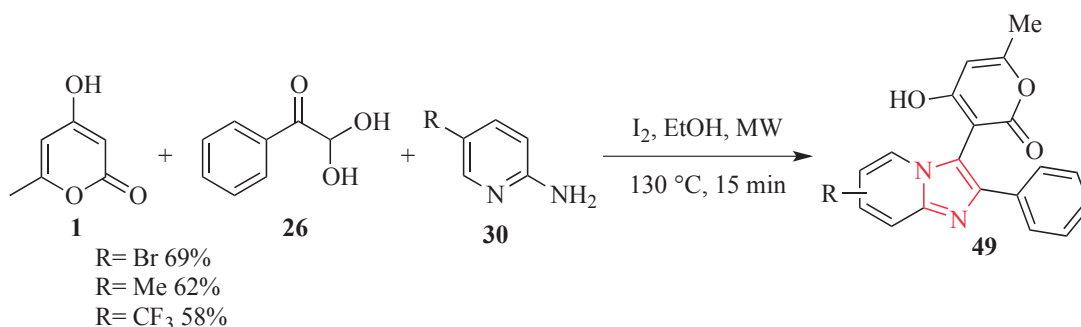
2.2.3. Five-membered heterocycles containing two hetero atoms

Karamthulla *et al.* reported the synthesis of novel trisubstituted 1,3-thiazoles **48** from the reaction of 4-hydroxy-6-methyl-2-pyrone **1**, arylglyoxals **26** and thioamides **47** via the microwave-assisted catalyst-free domino reaction.⁶² A plausible reaction mechanism was shown in Scheme 21. Initially, a Knoevenagel-type reaction⁶⁰ takes place for the preparation of intermediate **A** which was reacted with thioamide **47** via thia-Michael addition⁶¹ to afford intermediate **B**. This intermediate subsequently undergoes cyclization by the elimination of H₂O to form desired product **48** (Scheme 21).⁶²

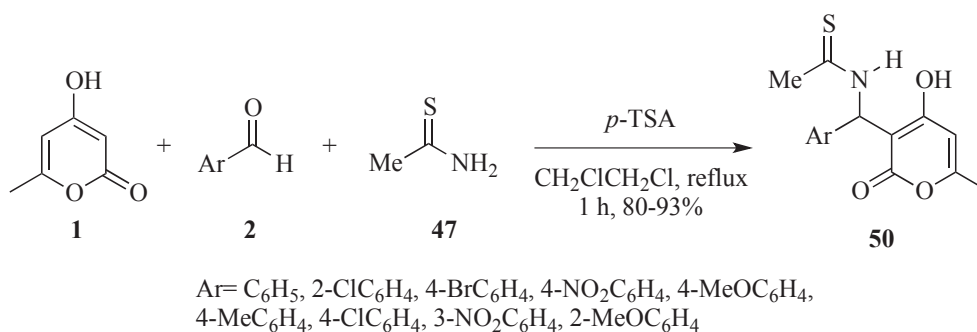


Scheme 21. Plausible reaction mechanism for the synthesis of trisubstituted 1,3-thiazoles **48** from **1**

In another study, the same group used I_2 as catalyst for the synthesis of 2,3-disubstituted imidazo[1,2-*a*]pyridines **49** when compound **47** was replaced with 2-aminopyridine **30** (Scheme 22).⁶³ Replacement of arylglyoxals **26** with aryl aldehyde **2** in this reaction leads to the synthesis of *N*-[aryl(4-hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl)methyl]thioacetamides **50** in high yields (Scheme 23).⁶⁴

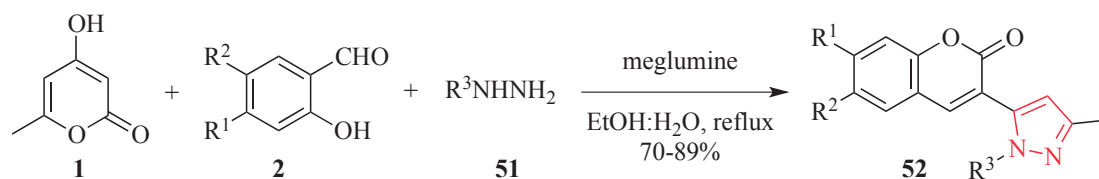


Scheme 22. Synthesis of 2,3-disubstituted imidazo[1,2-*a*]pyridines **49** from **1**



Scheme 23. Synthesis of *N*-[aryl(4-hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl)methyl]thioacetamides **50** from **1**

Li *et al.* accomplished a meglumine-catalyzed one-pot three-component protocol for the synthesis of pyrazolylcoumarins **52** from the reaction of 4-hydroxy-6-methyl-2-pyrone **1**, salicylaldehydes **2** and hydrazines **51** in aqueous-ethanol media (Scheme 24).⁶⁵ Various arylhydrazines bearing electron-donating groups and electron-withdrawing groups underwent the reaction with salicylaldehydes and 4-hydroxy-6-methyl-2-pyrone **1** to afford the desired products in good to high yields. The influence of substituents on the benzene ring of phenylhydrazine was also examined. In general, substituents possessing an electron-donating group tended to afford better yields than those bearing electron-withdrawing group. However, for phenylhydrazine with a strong electron-withdrawing group such as (4-nitrophenyl)hydrazine, no expected product was obtained.



$\text{R}^1 = \text{H, NO}_2, \text{Cl, Br}$

$\text{R}^2 = \text{H, OMe, OH, H}$

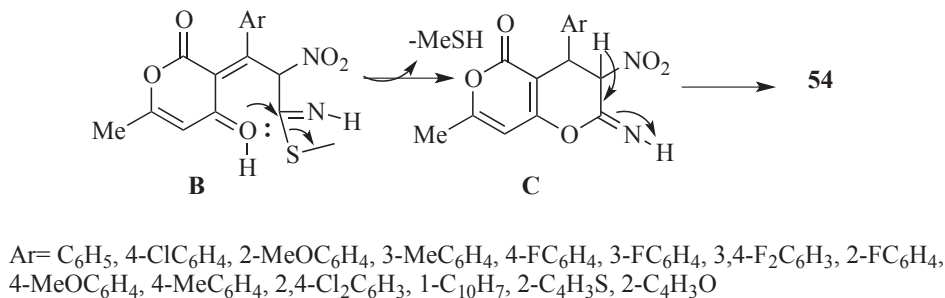
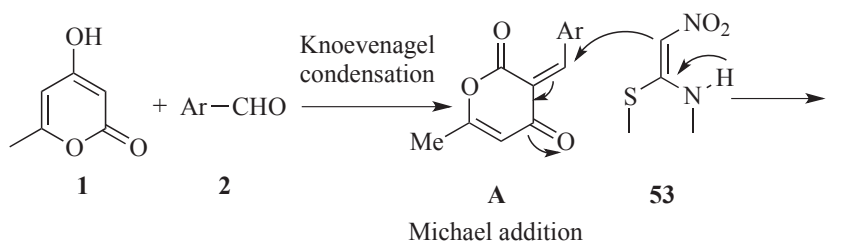
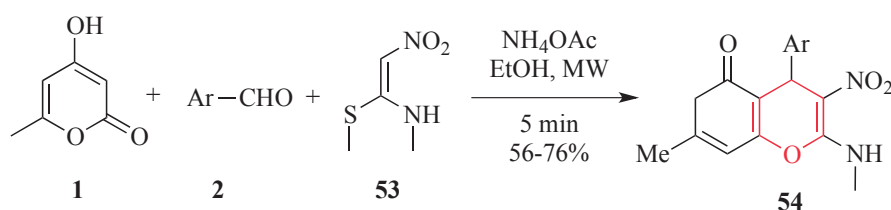
$\text{R}^3 = \text{C}_6\text{H}_5, 2\text{-MeOC}_6\text{H}_4, 2\text{-MeC}_6\text{H}_4, 3\text{-MeC}_6\text{H}_4, 3,4\text{-F}_2\text{C}_6\text{H}_3, 4\text{-BrC}_6\text{H}_4, \text{pyridine}$

Scheme 24. Synthesis of pyrazolylcoumarins **52** from **1**

2.3. Synthesis of six-membered heterocycles

2.3.1. Six-membered heterocycles containing O atom

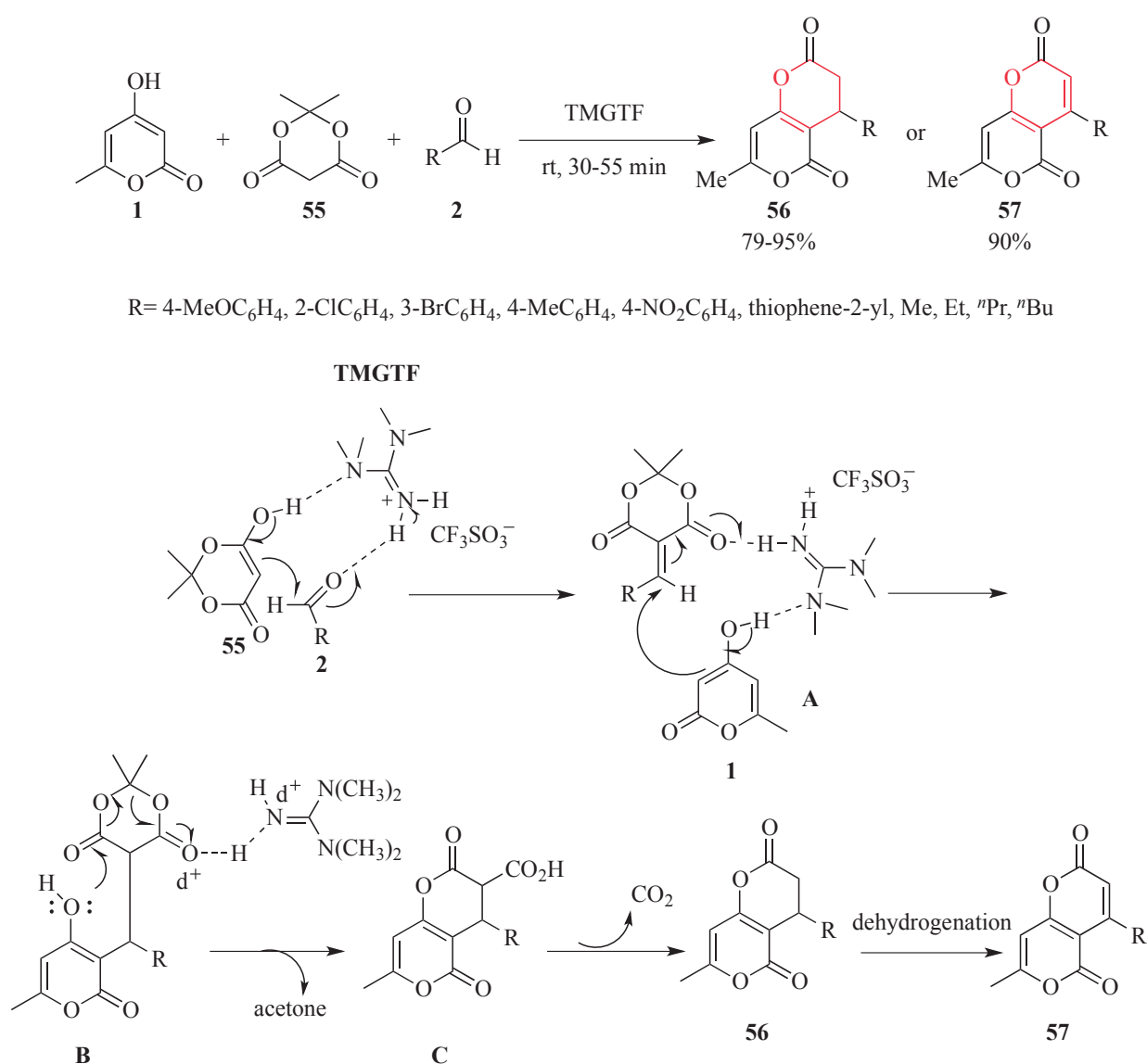
The synthesis of pyranopyran derivatives **54** has been developed through a domino reaction of 4-hydroxy-6-methyl-2-pyrone **1**, aromatic aldehydes **2** and *N*-methyl-1-(methylthio)-2-nitroethenamine (NMSM) **53** under microwave irradiation in the presence of ammonium acetate (Scheme 25).⁶⁶ Based on a plausible mechanism, the first step is the Knoevenagel condensation reaction between 4-hydroxy-6-methyl-2-pyrone **1** and aldehydes **2** which formed the adduct product **A**. Intermediate **A** then



Scheme 25. Proposed mechanism for the synthesis of pyranopyran derivatives **54** from **1**

acts as a Michael acceptor and immediately undergoes Michael-type addition with **53** to generate the open-chain intermediate **B** which undergoes intramolecular *O*-cyclization to give the compound **54** by elimination of MeSH (Scheme 25).

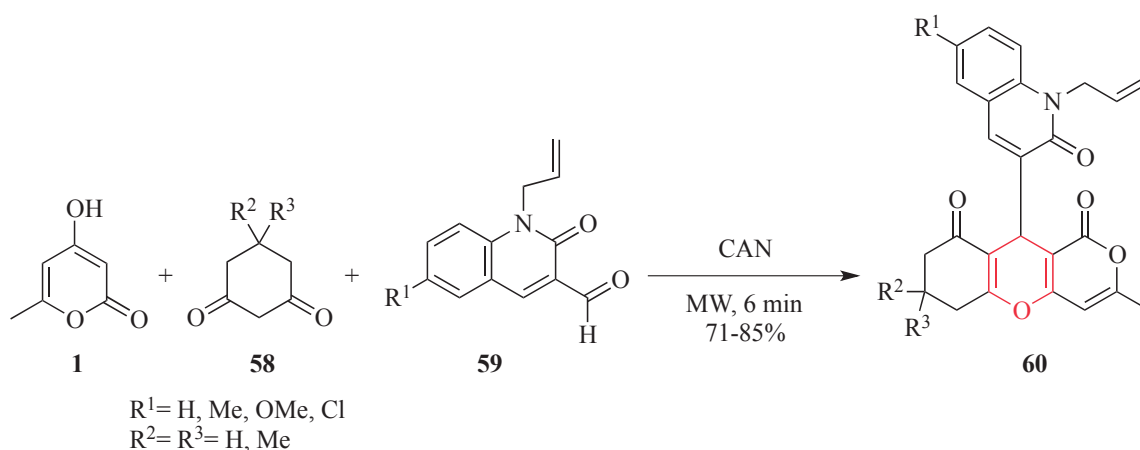
Treatment of 4-hydroxy-6-methyl-2-pyrone **1** and Meldrum's acid **55** with aldehydes **2** in ionic liquid *N,N,N,N*-tetramethylguanidinium triflate (TMGTF) solvent at room temperature resulted in novel pyrano[4,3-*b*]pyran-2,5-dione **56** or **57** in high yields (Scheme 26).⁶⁷ This reaction was also studied in the presence of piperidine as catalyst under reflux condition affording the related products in 79-95% yields.⁶⁸ According to the mechanism of the reaction, the synthesis is likely initiated by TMGTF, which



Scheme 26. Proposed mechanism for the preparation of pyrano[4,3-*b*]pyran-2,5-diones **56** or **57** from **1**

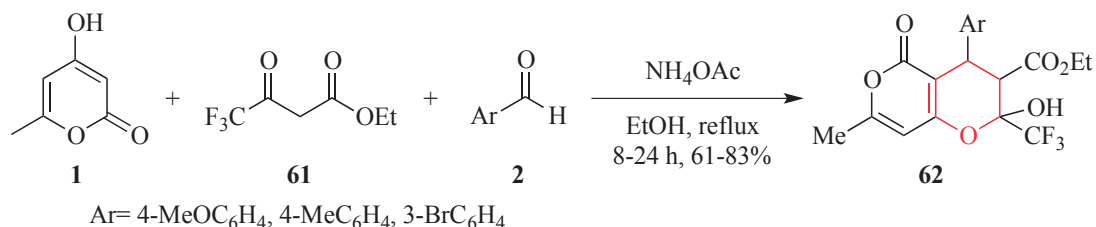
upon removing a proton from Meldrum's acid **55** promotes a Knoevenagel condensation with the aldehyde **2**, resulting in formation of the intermediate **A**. This intermediate subsequently undergoes a Michael-type addition with 4-hydroxy-6-methyl-2-pyrone **1** to produce **B**. Cyclization of **B** via a transactonization reaction leads to liberation of an acetone molecule leaving **C** bearing a carboxyl group at the 3-position. Spontaneous decarboxylation of **C** affords the 4-aryl-product **56** and after an aerobic dehydrogenation, product **57** is achieved.

The microwave-assisted one-pot, three-component reaction of 4-hydroxy-6-methyl-2-pyrone **1**, 1,3-cyclohexanedione/dimedone **58** and *N*-allylquinolones **59** in the presence of ceric ammonium nitrate (CAN) as catalyst under solvent-free condition resulted in the formation of some pyrano[4,3-*b*]chromene derivatives **60** (Scheme 27).⁶⁹



Scheme 27. Synthesis of pyrano[4,3-*b*]chromenes **60** from **1**

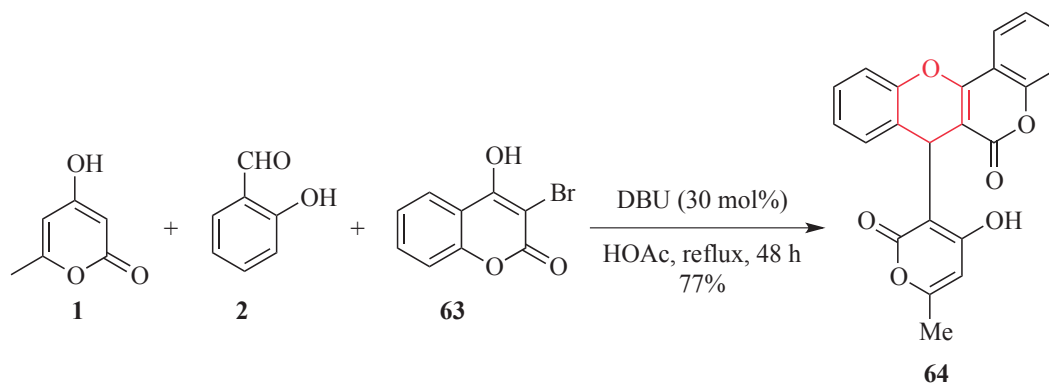
Song *et al.* reported the three-component reaction of 4-hydroxy-6-methyl-2-pyrone **1**, ethyl trifluoroacetoacetate **61** and aryl aldehyde **2** catalyzed by NH_4OAc in EtOH for the preparation of trifluoromethylated pyrano[4,3-*b*]pyrans **62** (Scheme 28).⁷⁰



Scheme 28. Synthesis of trifluoromethylated pyrano[4,3-*b*]pyrans **62** from **1**

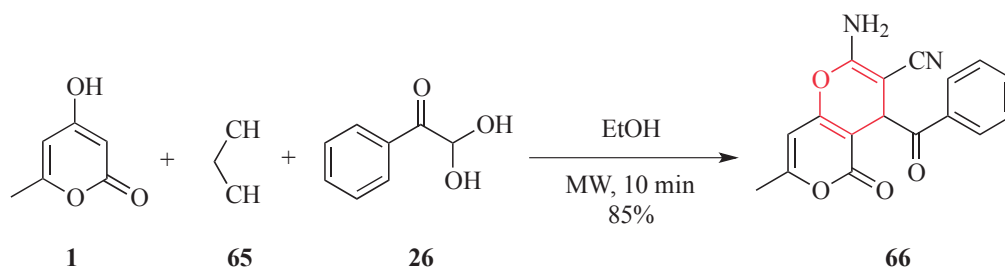
1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) was employed as catalyst in the one-pot three-component reaction of 4-hydroxy-6-methyl-2-pyrone **1** with salicylaldehyde **2** and 3-bromo-4-hydroxy-2*H*-chromen-

2-one **63** to prepare chromeno[4,3-*b*]chromenone **64** (Scheme 29).⁷¹



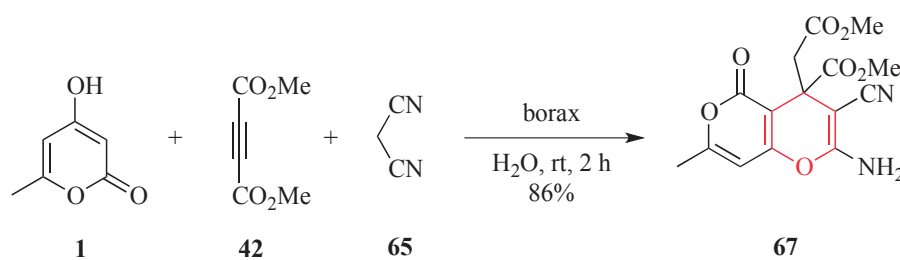
Scheme 29. Synthesis of chromeno[4,3-*b*]chromenone **64** from **1**

Mishra and Choudhury developed an efficient procedure for the synthesis of 2-amino-4-benzoyl-7-methyl-5-oxo-4*H*,5*H*-pyrano[4,3-*b*]pyran-3-carbonitrile **66** via three-component reaction of 4-hydroxy-6-methyl-2-pyrone **1**, malononitrile **65** and arylglyoxal monohydrate **26** in ethanol under microwave irradiation without any catalysts (Scheme 30).⁷²



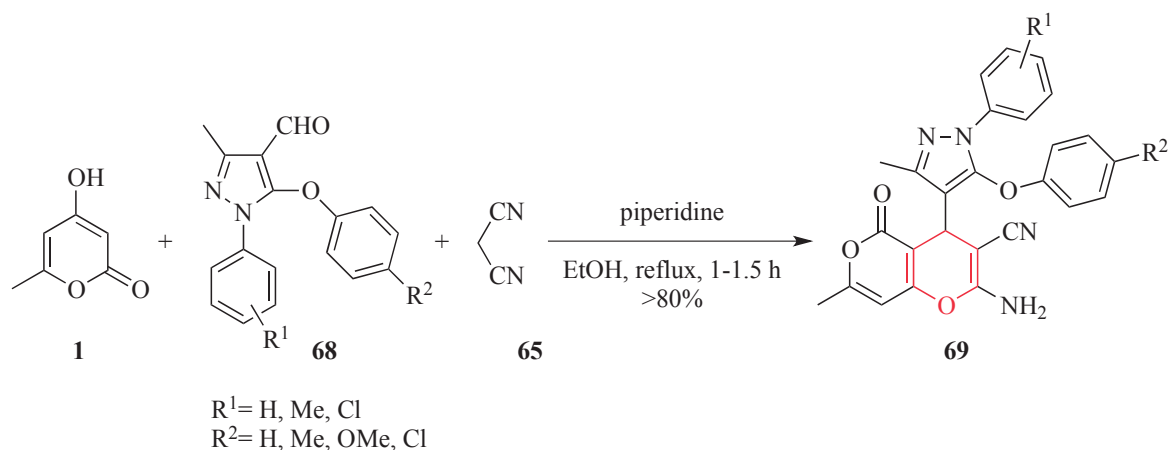
Scheme 30. Synthesis of pyrano[4,3-*b*]pyran-3-carbonitrile **66** from **1**

Dihydropyrano[3,2-*c*]chromene **67** was synthesized via a three-component reaction of 4-hydroxy-6-methyl-2-pyrone **1**, dimethyl acetylenedicarboxylate **42** and malononitrile **65** at room temperature in the presence of borax as catalyst (Scheme 31).⁷³



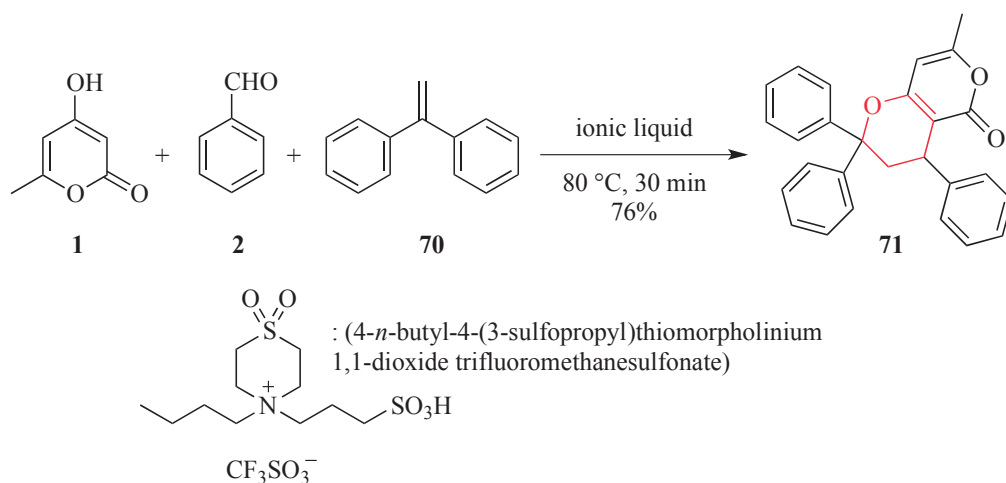
Scheme 31. Synthesis of dihydropyrano[3,2-*c*]chromene **67** from **1**

The one-pot synthesis of pyrano[4,3-*b*]pyran derivatives **69** was accomplished by Sangani *et al.* in which 4-hydroxy-6-methyl-2-pyrone **1**, 1*H*-pyrazole-4-carbaldehyde **68** and malononitrile **65** reacted in ethanol in the presence of a catalytic amount of piperidine (Scheme 32).⁷⁴ All the compounds **69** were screened for their antimicrobial activities and majority of compounds were found to be active against Gram-positive bacteria *B. subtilis*, *C. tetani* and a fungal pathogen *C. albicans*. It is worth mentioning that minor change in the molecular configuration of these compounds profoundly influences the activity.



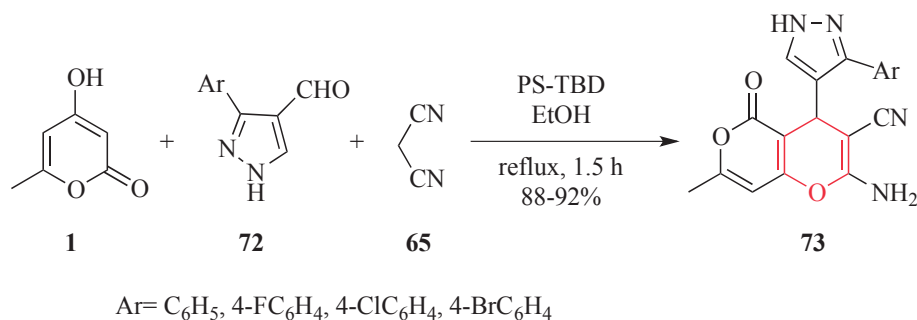
Scheme 32. Synthesis of pyrano[4,3-*b*]pyrans **69** from **1**

A facile strategy to form 7-methyl-2,2,4-triphenyl-3,4-dihydropyrano[4,3-*b*]pyran-5(2*H*)-one **71** via a three-component reaction of 4-hydroxy-6-methyl-2-pyrone **1**, benzaldehyde **2** and 1,1-diphenylethylene **70** in the presence of sulfonyl containing Brønsted acid ionic liquid (4-*n*-butyl-4-(3-sulfopropyl)thiomorpholinium 1,1-dioxide trifluoromethanesulfonate) under solvent-free conditions was reported by Taheri *et al.* (Scheme 33).⁷⁵



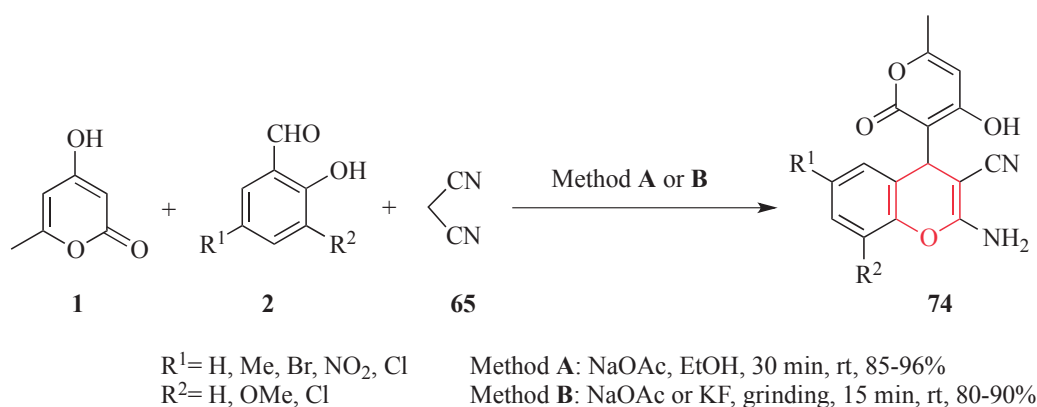
Scheme 33. Synthesis of 7-methyl-2,2,4-triphenyl-3,4-dihydropyrano[4,3-*b*]pyran-5(2*H*)-one **71** from **1**

A facile synthesis of pyrano[4,3-*b*]pyran derivatives **73** based on the polystyrene supported 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene (PS-TBD)-catalyzed three-component reaction of 4-hydroxy-6-methyl-2-pyrone **1**, 3-substituted phenyl-1*H*-pyrazole-4-carbaldehyde **72** and malononitrile **65** was described by Vala and co-workers (Scheme 34).⁷⁶



Scheme 34. Synthesis of pyrano[4,3-*b*]pyrans **73** from **1**

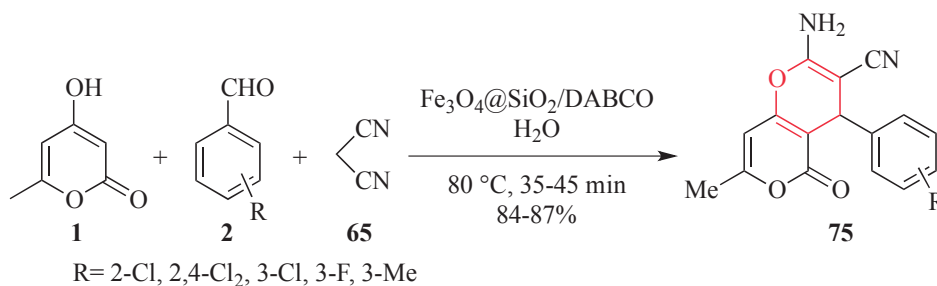
Vereshchagin *et al.* reported a sodium acetate-catalyzed three-component reaction of 4-hydroxy-6-methyl-2-pyrone **1**, salicylaldehydes **2** and malononitrile **65** through two different methods **A** and **B** which gave 2-amino-4*H*-chromene scaffolds **74** (Scheme 35).⁷⁷ In method **A** the reaction was taken place at room temperature under mild “on-solvent” condition, whereas in the second method, grinding was employed.



Scheme 35. Synthesis of 2-amino-4*H*-chromene scaffolds **74** from **1**

Davarpanah *et al.* published a study on the one-pot synthesis of pyrano[4,3-*b*]pyran-3-carbonitrile derivatives **75**⁷⁸ in the presence of Fe₃O₄@SiO₂/DABCO as catalyst via a three-component coupling reaction of 4-hydroxy-6-methyl-2-pyrone **1**, aromatic aldehydes **2** and malononitrile **65** in water (Scheme 36).⁷⁹ In another study, the synthesized products were evaluated for their potential antiviral and anti-leishmanial activities.⁸⁰ Shaabani *et al.* performed this reaction without any catalysts.⁸¹ This reaction was also developed using a variety of catalysts such as organocatalyst,⁸² NP-ZnO,^{83,84} [18-C-6K][OAc],⁸⁵

NH_4OAc ,⁸⁶ Alum,⁸⁷ $(\text{CTA})_3[\text{SiW}_{14}]\text{-Li-MMT}$,⁸⁸ nano-cellulose- OSO_3H ,⁸⁹ nano CaO,⁹⁰ SBSA,^{91,92} NCS,⁹³ $\text{HCO}_2\text{Na}/\text{HCO}_2\text{NH}_4$,⁹⁴ DBU,⁹⁵ Et_3N ,⁹⁶ PEG Ni-NPs,⁹⁷ $\text{BN}@\text{Fe}_3\text{O}_4$,⁹⁸ $\text{H}_6\text{P}_2\text{W}_{18}\text{O}_{62}\cdot 18\text{H}_2\text{O}$,⁹⁹ *p*-TSA,¹⁰⁰ ClSO_3H ,¹⁰¹ and DABCO.¹⁰² The efficiency of various catalysts in the synthesis of these skeletons was compared and the results were summarized in Table 3.



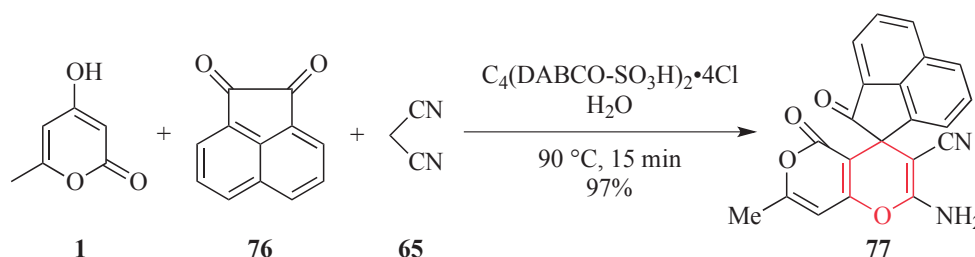
Scheme 36. Synthesis of pyrano[4,3-*b*]pyran-3-carbonitrile derivatives **75** from **1**

Table 3. Comparison of efficiency of various catalysts in synthesis of compound **75**

Entry	Solvent	Catalyst	Condition	Time	Yield (%)
1	H ₂ O	Fe ₃ O ₄ @SiO ₂ /DABCO	80 °C	35-45 min	84-87 ^{79,80}
2	H ₂ O	-	80 °C	9.5-11 h	61-66 ⁸¹
3	Et ₂ O	organocatalyst	rt	8 h	69-90 ⁸²
4	-	NP-ZnO	rt	5 h	78-80 ⁸⁴
5	-	NP-ZnO	rt	5 h	80 ⁸³
6	EtOH	[18-C-6K] [OAc]	reflux	13-30 min	85-91 ⁸⁵
7	-	NH ₄ OAc	rt	10-18 min	86-97 ⁸⁶
8	H ₂ O	Alum	A: MW B: 80 °C	A: 5-12 min B: 1-3 h	A: 79-95 B: 62-79 ⁸⁷
9	H ₂ O	(CTA) ₃ [SiW ₁₄]-Li	reflux	15-20 min	85-96 ⁸⁸
10	EtOH	nano-cellulose-OSO ₃ H	reflux	10 min	73-94 ⁸⁹
11	-	nano CaO	120 °C	5-45 min	93-95 ⁹⁰
12	-	SBSA	60 °C	1 h	88 ^{91,92}
13	H ₂ O	NCS	rt	3 h	58 ⁹³
14	H ₂ O	HCO ₂ Na/HCO ₂ NH ₄	rt	1 h	65-86 ⁹⁴
15	H ₂ O	DBU	reflux	10-15 min	86-90 ⁹⁵
16	EtOH	Et ₃ N	reflux	5-10 min	62-92 ⁹⁶

17	EG	PEG Ni-NP	rt	5-12 min	88-94 ⁹⁷
18	H ₂ O	BN@Fe ₃ O ₄	80 °C	10-20 min	86-97 ⁹⁸
19	H ₂ O	H ₆ P ₂ W ₁₈ O ₆₂ ·18H ₂ O	reflux	45-60 min	86-95 ⁹⁹
20	H ₂ O	<i>p</i> -TSA	80 °C	3 h	82-94 ¹⁰⁰
21	-	ClSO ₃ H	rt	1 h	89-95 ¹⁰¹
22	EtOH	DABCO	rt	12 h	80-85 ¹⁰²

Replacement of aldehyde **2** with acenaphthenequinone **76** in this reaction in the presence of C₄(DABCO-SO₃H)₂·4Cl as catalyst for the synthesis of spiro-acenaphthylenechromene **77** was reported by Goli-Jolodar *et al.* (Scheme 37).¹⁰³ DBU,¹⁰⁴ amino-appended β -cyclodextrin (ACD)¹⁰⁵ and β -cyclodextrin (β -CD)¹⁰⁶ were also used as catalysts in this reaction (Table 4). Elinson *et al.* developed this reaction in good yield (90%) without any catalyst (Table 4, entry 5).¹⁰⁷



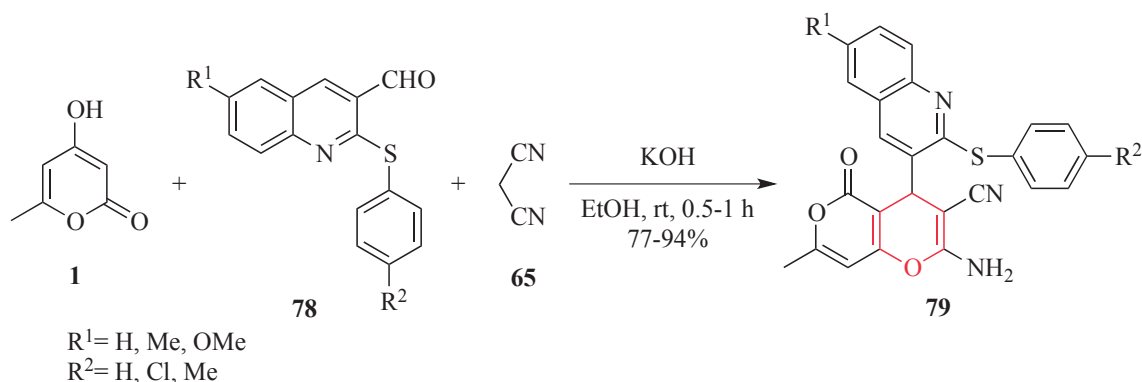
Scheme 37. Synthesis of spiro-acenaphthylenechromene **77** from **1**

Table 4. Comparison of different conditions in the synthesis of compound **77**

Entry	Solvent	Catalyst	Condition	Time (min)	Yield (%)
1	H ₂ O	C ₄ (DABCO-SO ₃ H) ₂ ·4Cl	90 °C	15	97 ¹⁰³
2	H ₂ O	DBU	rt	25	76 ¹⁰⁴
3	H ₂ O	ACD	rt	7 h	87 ¹⁰⁵
4	H ₂ O	β -CD	rt	5 h	87 ¹⁰⁶
5	H ₂ O	-	80 °C	15	90 ¹⁰⁷

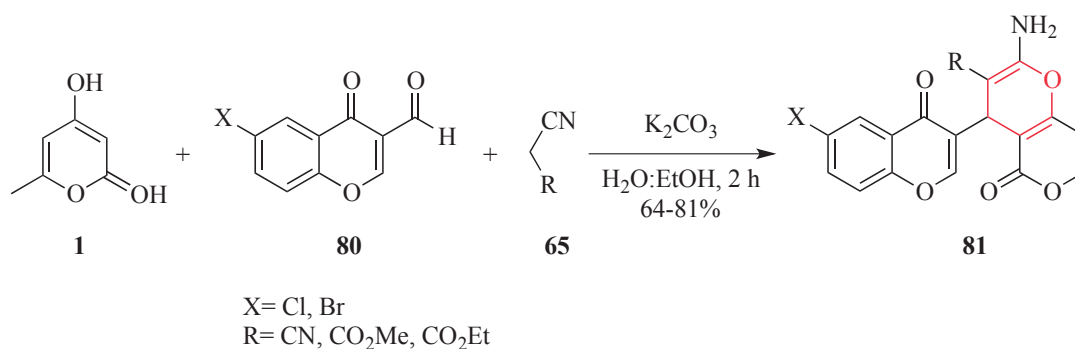
Synthesis of pyrano[4,3-*b*]pyran derivatives **79** via the reaction of 4-hydroxy-6-methyl-2-pyrone **1**, 2-(4-(un)-substituted thiophenoxy)quinoline-3-carbaldehydes **78** and malononitrile **65** was carried out at room temperature in the presence of KOH as basic catalyst (Scheme 38).¹⁰⁸ All compounds were screened against three Gram-positive bacteria, three Gram-negative bacteria, and two fungi and the majority of the

compounds were found to be active against *B. subtilis*, *C. tetani* and *C. albicans* as compared to standard drugs.



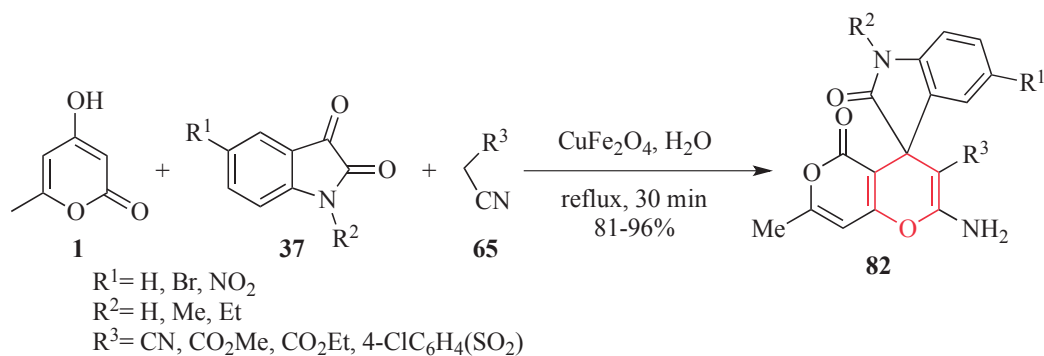
Scheme 38. Synthesis of pyrano[4,3-*b*]pyran derivatives **79** from **1**

Novel functionalized heterocyclic compounds containing the chromone skeleton **81** were obtained through domino Knoevenagel/Michael/cyclization reaction sequences using K₂CO₃ as catalyst in the three-component reaction of compound **1**, 3-formylchromone **80** and nitriles **65** in aqueous media (Scheme 39).¹⁰⁹ It should be mentioned that the reaction did not proceed in the absence of the basic catalyst.



Scheme 39. Synthesis of chromone derivatives **81** from **1**

Bazgir *et al.* have established spirooxindole fused heterocycles **82** via an efficient one-pot three-component reaction of 4-hydroxy-6-methyl-2-pyrone **1**, isatins **37** and active cyanomethanes **65** in refluxing water in the presence of the magnetically copper ferrite CuFe₂O₄ as nano-particle catalyst (Scheme 40).¹¹⁰ The synthesis of spirooxindole fused heterocycles **82** has been also reported under different conditions with several catalysts including *p*-TSA,¹¹¹ *L*-proline,¹¹² AcONa/KF,¹¹³ triethylamine,¹¹⁴ Ni-NPs,¹¹⁵ SSLP¹¹⁶ and sodium stearate.¹¹⁷ Some recent methods for the synthesis of corresponding products were compared in Table 5.

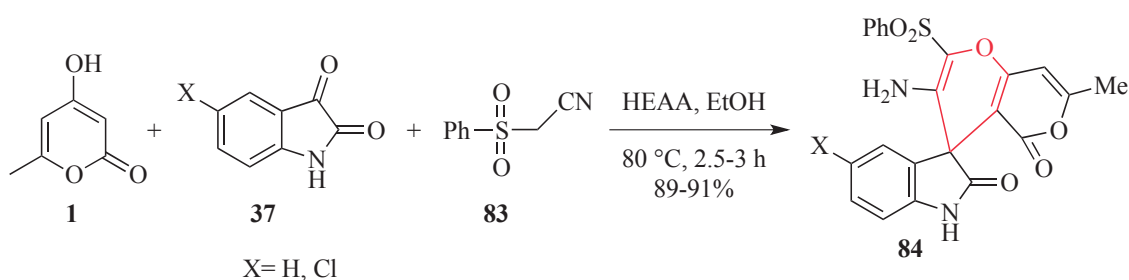


Scheme 40. Synthesis of spirooxindole fused heterocycles **82** from **1**

Table 5. Comparison of efficiency of various catalysts in synthesis of spirooxindole fused heterocycles **82**

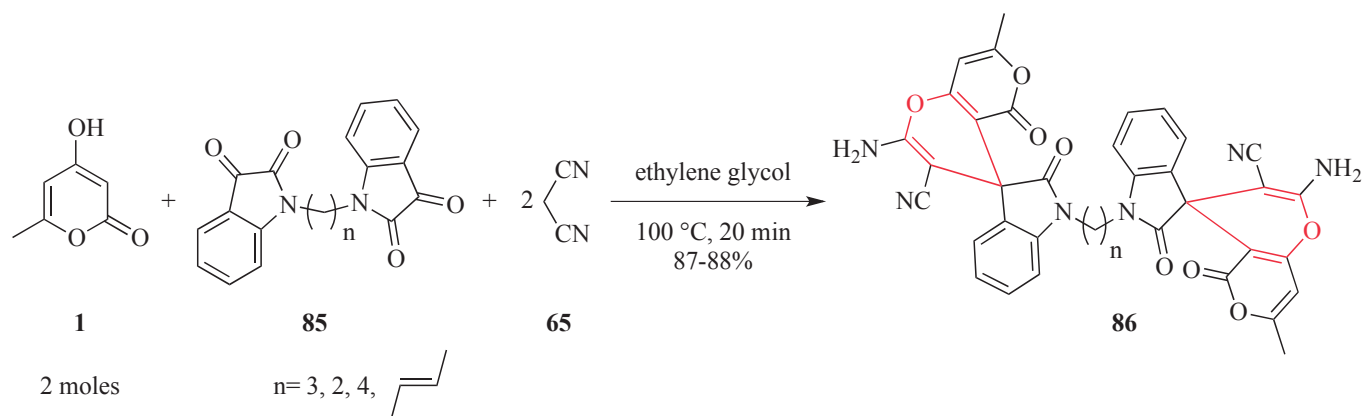
Entry	Solvent	Catalyst	Condition	Time (min)	Yield (%)
1	H ₂ O	CuFe ₂ O ₄	reflux	30	81-96 ¹¹⁰
2	H ₂ O	<i>p</i> -TSA	reflux	24 h	73-94 ¹¹¹
3	H ₂ O	<i>L</i> -proline	80 °C	11-45	76-94 ¹¹²
4	-	AcONa/KF	60-78 °C	1-15	67-95 ¹¹³
5	EtOH	triethylamine	reflux	5	76 ¹¹⁴
6	ethylene glycol	Ni-NPs	rt	10	90 ¹¹⁵
7	H ₂ O	SSLP	80 °C	1 h	94 ¹¹⁶
8	H ₂ O	sodium stearate	60 °C	3 h	89-93 ¹¹⁷

4-Hydroxy-6-methyl-2-pyrone **1** was reacted with isatins **37** and phenylsulfonylacetonitrile **83** in a one-pot reaction in EtOH using a novel basic ionic liquid (2-hydroxyethyl)ammonium acetate [H₃N⁺CH₂CH₂OH][MeCO₂⁻] (HEAA) as catalyst and some novel spiro-2-amino-3-phenylsulfonyl-4*H*-pyrans **84** were obtained in high yields (Scheme 41).¹¹⁸



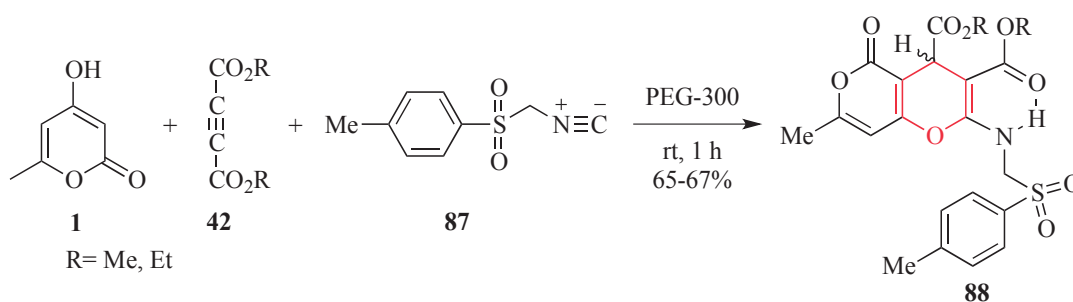
Scheme 41. Synthesis of spiro-2-amino-3-phenylsulfonyl-4*H*-pyrans **84** from **1**

A catalyst-free three-component reaction of 4-hydroxy-6-methyl-2-pyrone **1**, bis-isatins **85** and malononitrile **65** in ethylene glycol at 100 °C was reported by Khanna and co-workers to get access to bis-spirooxindoles **86** in high yields (Scheme 42).¹¹⁹ This protocol provides an easy and simple route for the synthesis of such complex compounds in short reaction times and high yields.



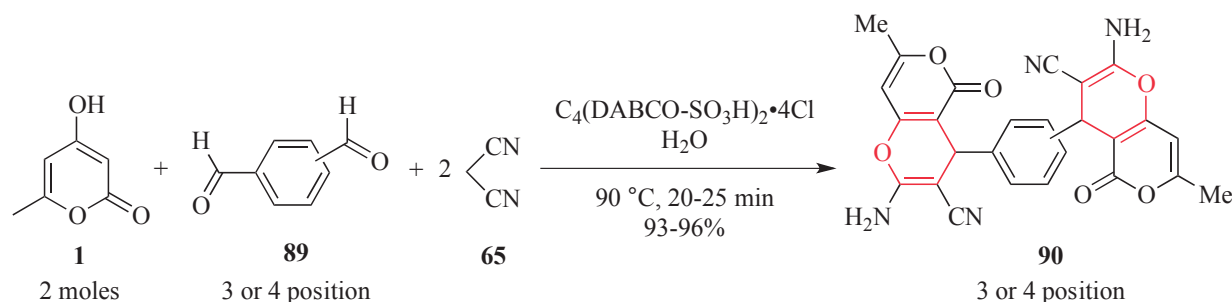
Scheme 42. Synthesis of bis-spirooxindoles **86** from **1**

Nasiri and Zolali studied the synthesis of new annulated polyfunctionalized 2-amino-4*H*-pyrans **88** from the reaction of 4-hydroxy-6-methyl-2-pyrone **1** with dialkyl acetylenedicarboxylates **42** and tosylmethyl isocyanides (TosMIC) **87** using polyethylene glycol (PEG-300) as solvent (Scheme 43).¹²⁰ Teimouri's group also performed this reaction in CH₂Cl₂ at room temperature to achieve the products in 58-72% yield.¹²¹



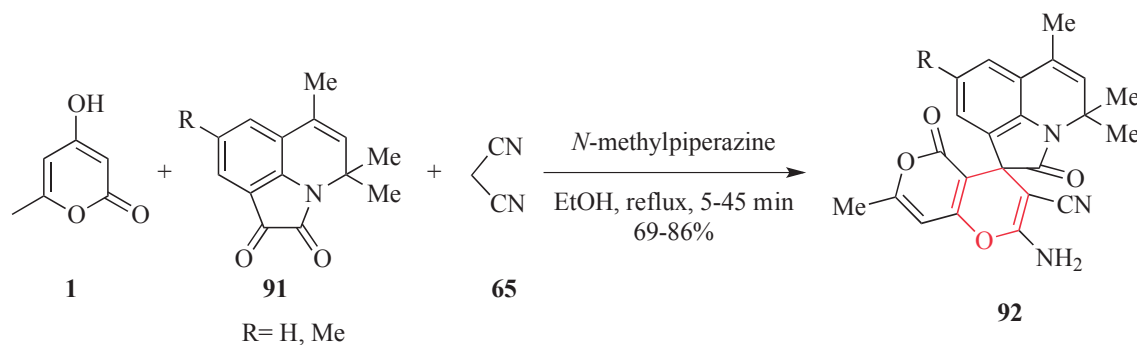
Scheme 43. Synthesis of annulated polyfunctionalized 2-amino-4*H*-pyrans **88** from **1**

Bis-2-amino-4*H*-pyran derivatives **90** were constructed using C₄(DABCO-SO₃H)₂·4Cl as a nano catalyst under homogeneous conditions. The products were obtained from the multicomponent reaction of 4-hydroxy-6-methyl-2-pyrone **1**, dialdehydes **89** and malononitrile **65** (Scheme 44).¹⁰³ In another study, Rao *et al.* used the Carbon-SO₃H as a solid acid catalyst in this reaction.¹²²



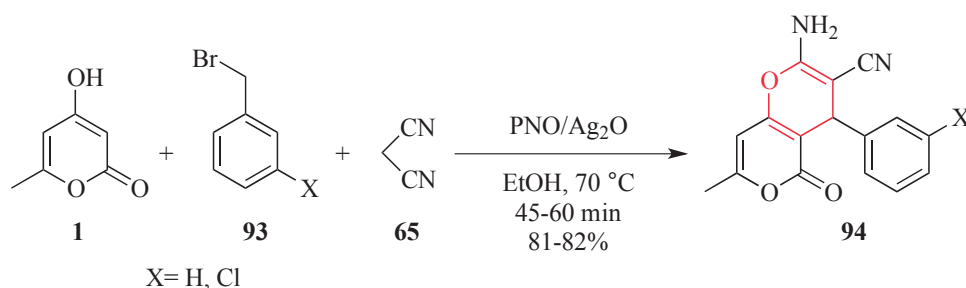
Scheme 44. Synthesis of bis-2-amino-4*H*-pyran derivatives **90** from **1**

Shikhaliev and co-workers applied a method for the synthesis of 4,4,6-trimethyl-4*H*-pyrrolo[3,2,1-*ij*]quinoline-1,2-diones **92** based on the reaction of 4-hydroxy-6-methyl-2-pyrone **1**, pyrroloquinolinediones **91** and malononitrile **65** in EtOH in the presence of *N*-methylpiperazine as catalyst (Scheme 45).¹²³



Scheme 45. Synthesis of 4,4,6-trimethyl-4*H*-pyrrolo[3,2,1-*ij*]quinoline-1,2-diones **92** from **1**

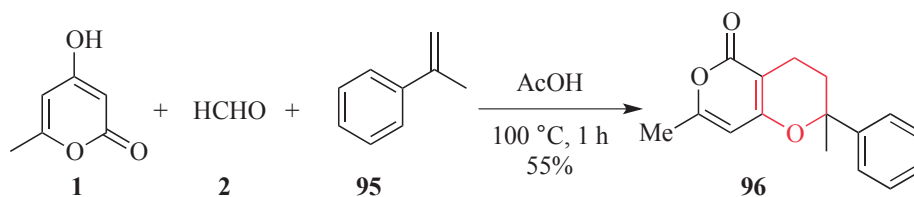
The pyran analogues **94** were synthesized via the tandem process involving oxidation, condensation and cyclization reaction of 4-hydroxy-6-methyl-2-pyrone **1**, benzyl halides **93** and malononitrile **65** in the presence of pyridine *N*-oxide (PNO) and silver oxide as catalyst at 70 °C (Scheme 46).¹²⁴



Scheme 46. Synthesis of pyran analogues **94** from **1**

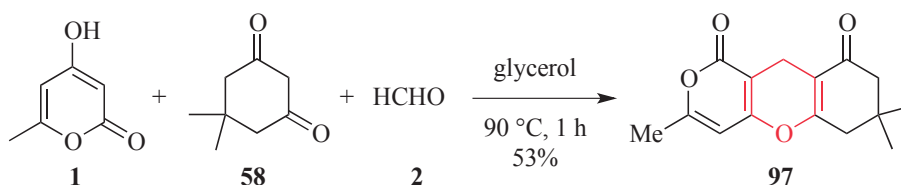
Gu *et al.* reported a novel method for the synthesis of pyranopyranone compound **96** via the one-pot three-component reaction of 4-hydroxy-6-methyl-2-pyrone **1**, formaldehyde **2** and α -methylstyrene **95** at

100 °C in acetic acid (Scheme 47).¹²⁵ In another study, lactic acid as a bio-based solvent was also used in this reaction which resulted in the formation of the product in 62% yield after 5 hours.¹²⁶



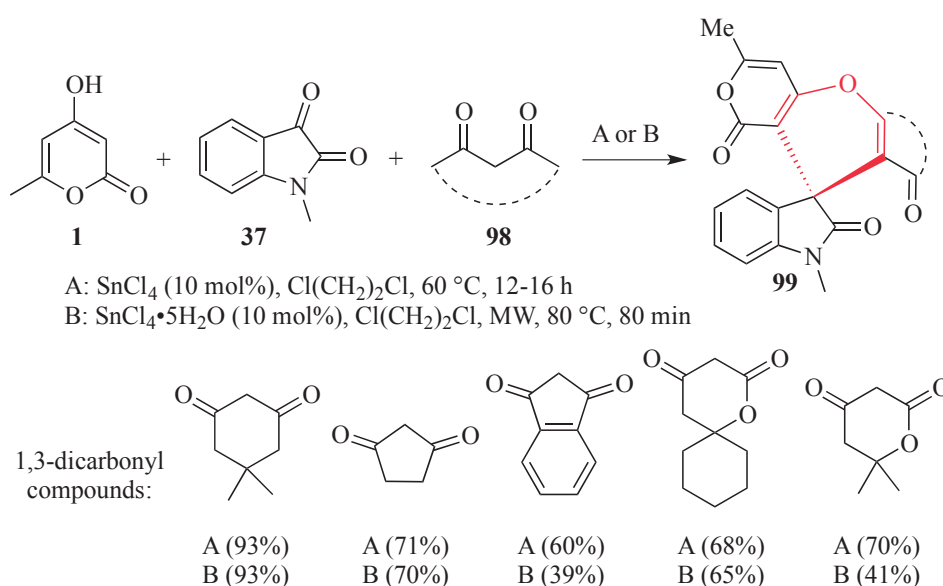
Scheme 47. Synthesis of pyranopyranone compound **96** from **1**

A three-component reaction of 4-hydroxy-6-methyl-2-pyrone **1**, dimedone **58** and formaldehyde **2** was performed in glycerol for the synthesis of pyranobenzopyrandione compound **97** (Scheme 48).¹²⁷



Scheme 48. Synthesis of pyranobenzopyrandione compound **97** from **1**

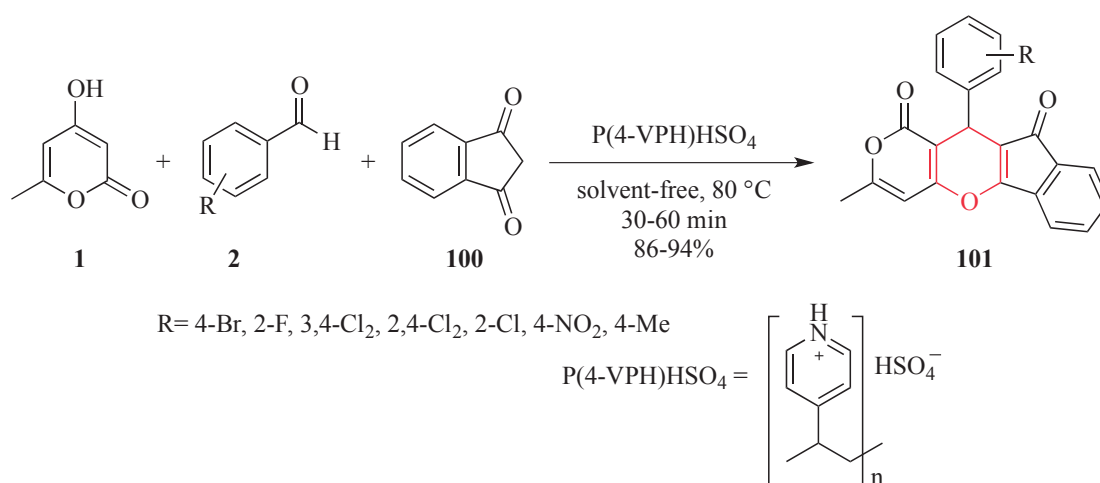
The Lewis acid-catalyzed three-component reaction of 4-hydroxy-6-methyl-2-pyrone **1**, *N*-methylisatin **37** and a number of 1,3-dicarbonyl compounds **98** was reported by Liang's group. The reactions proceed under mild reaction conditions in the presence of SnCl₄ as catalyst with good functional group tolerance



Scheme 49. Synthesis of spirooxindole derivatives **99** from **1**

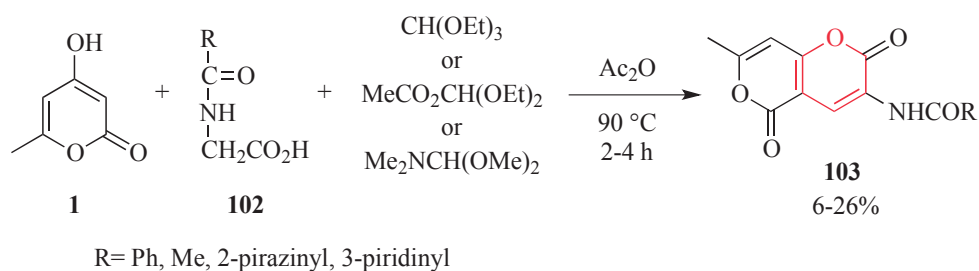
to afford spirooxindole derivatives **99** (Scheme 49).¹²⁸ In another study, $\text{H}_3\text{PW}_{12}\text{O}_{40}@/\text{SiO}_2$ was used as catalyst in this reaction and related products were obtained in 70-95% yield.¹²⁹

Ghashang *et al.* accomplished a one-pot, solvent-free condensation of 4-hydroxy-6-methyl-2-pyrone **1**, aldehyde **2** and 1,3-indandione **100** catalyzed by poly(4-vinyl)pyridinium hydrogen sulfate, as a facile protocol for the synthesis of 7-methyl-10-aryl-10*H*-5,8-dioxabenzob[*b*]fluorene-9,11-dione derivatives **101** in excellent yields (Scheme 50).¹³⁰ A range of aromatic aldehydes bearing electron-withdrawing and electron-donating substituents were subjected to this procedure and converted into the targeted molecules in high yields. Based on the obtained results, the electronic effects and the steric effects of the substituents played significant roles in the reaction rate. Aromatic aldehyde systems that possessed substitutions at the *ortho*, *meta*, or *para* positions had the yields, but the aromatic aldehydes containing electron-donating groups gave longer reaction times and lower yields than those with electron-withdrawing groups. When *ortho*-substituted aldehydes were used in this process, the corresponding products were obtained in good yields but in longer reaction times.



Scheme 50. Synthesis of 10-aryl-10*H*-5,8-dioxabenzob[*b*]fluorene-9,11-diones **101** from **1**

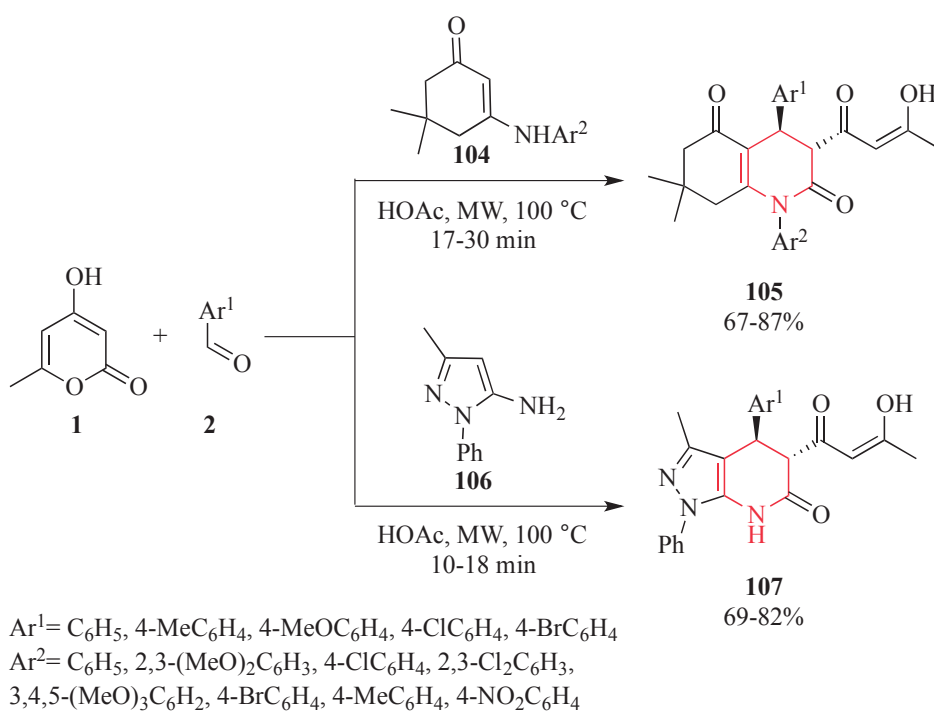
The reaction of 4-hydroxy-6-methyl-2-pyrone **1**, *N*-acylglycines **102** and one-carbon synthons, such as triethyl orthoformate (TOF), diethoxymethyl acetate (DEMA) or *N,N*-dimethylformamide dimethyl acetal (DMFDMA) in the presence of a large amount of acetic anhydride was studied by Kepe *et al.* in order to obtain some fused pyran-2-ones **103** (Scheme 51).¹³¹



Scheme 51. Synthesis of fused pyran-2-ones **103** from **1**

2.3.2. Six-membered heterocycles containing N atom

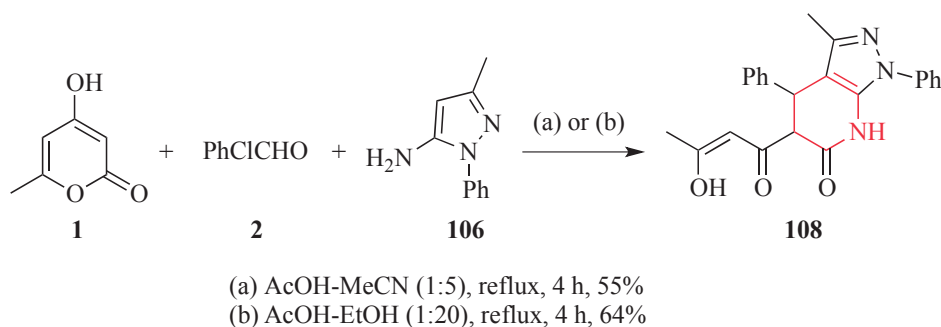
A series of bicyclic hexahydroquinoline-2,5-diones **105** and pyrazolo[3,4-*b*]pyridin-6(7*H*)-ones **107** were synthesized via three-component Knoevenagel condensation/Michael addition cyclization reaction of 4-hydroxy-6-methyl-2-pyrone **1**, aromatic aldehydes **2**, and *N*-arylenaminones **104**/5-aminopyrazole **106** under microwave irradiation (Scheme 52).¹³² The results exhibited the scope and generality of this reaction with respect to a range of enaminone and aldehyde substrates. When 5-aminopyrazole **106** was used to investigate the possibility of this transformation, the substituents on the aromatic ring of the aryl aldehydes **2** did not hamper the reaction process.



Scheme 52. Synthesis of bicyclic hexahydroquinoline-2,5-diones **105** and pyrazolo[3,4-*b*]pyridin-6(7*H*)-ones **107** from **1**

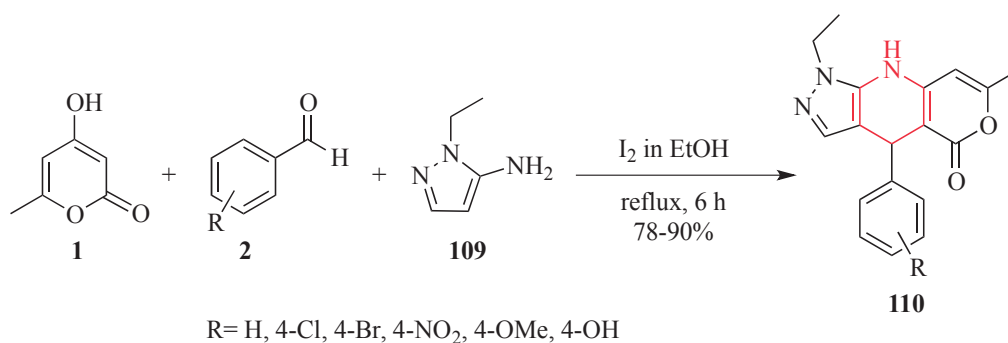
Yin and co-workers developed a three-component one-pot reaction in which 4-hydroxy-6-methyl-2-pyrone **1**, benzaldehyde **2** and 5-aminopyrazole **106** were reacted to form

pyrazolo[3,4-*b*]pyridin-6(7*H*)-one **108** through two different procedures (Scheme 53).¹³³



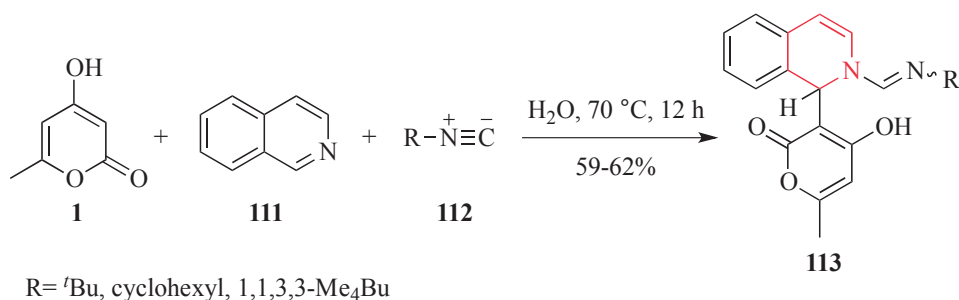
Scheme 53. Synthesis of pyrazolo[3,4-*b*]pyridin-6(7*H*)-one **108** from **1**

An efficient synthesis of a series of dihydropyrano[4,3-*b*]pyrazolo[4,3-*e*]pyridin-5(4*H*)-ones **110** was reported by condensation of 4-hydroxy-6-methyl-2-pyrone **1**, aryl aldehydes **2** and 1-ethylpyrazol-5-amine **109** in the presence of 10 mol% molecular I₂ in ethanol under reflux conditions through a one-pot reaction (Scheme 54).¹³⁴



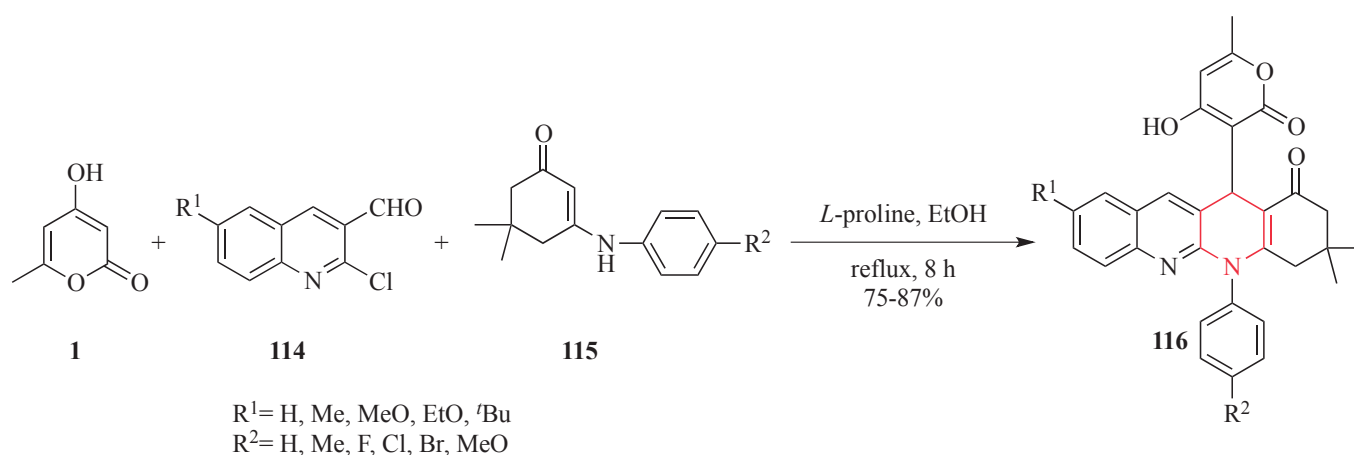
Scheme 54. Synthesis of dihydropyrano[4,3-*b*]pyrazolo[4,3-*e*]pyridin-5(4*H*)-ones **110** from **1**

The synthesis of 1,2-dihydroisoquinolines **113** has been developed through the one-pot three-component reaction of 4-hydroxy-6-methyl-2-pyrone **1**, isoquinoline **111**, and isocyanide **112** in aqueous medium without using any catalyst (Scheme 55).¹³⁵



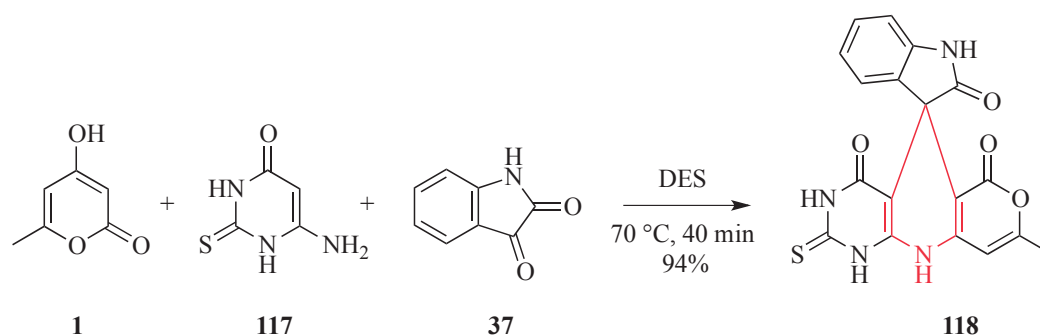
Scheme 55. Synthesis of 1,2-dihydroisoquinolines **113** from **1**

L-Proline catalyzed the multicomponent reaction of 4-hydroxy-6-methyl-2-pyrone **1**, 2-chloroquinoline-3-carbaldehydes **114** and enaminones **115** for the preparation of functionalized benzo[*b*][1,8]naphthyridine derivatives **116** in good yields (Scheme 56).¹³⁶ It was found that phenyl groups bearing either electron-withdrawing or electron-donating groups on the enaminone ring, were tolerated under the reaction conditions, leading to the final products in satisfactory yields (up to 87%).



Scheme 56. Synthesis of functionalized benzo[*b*][1,8]naphthyridines **116** from **1**

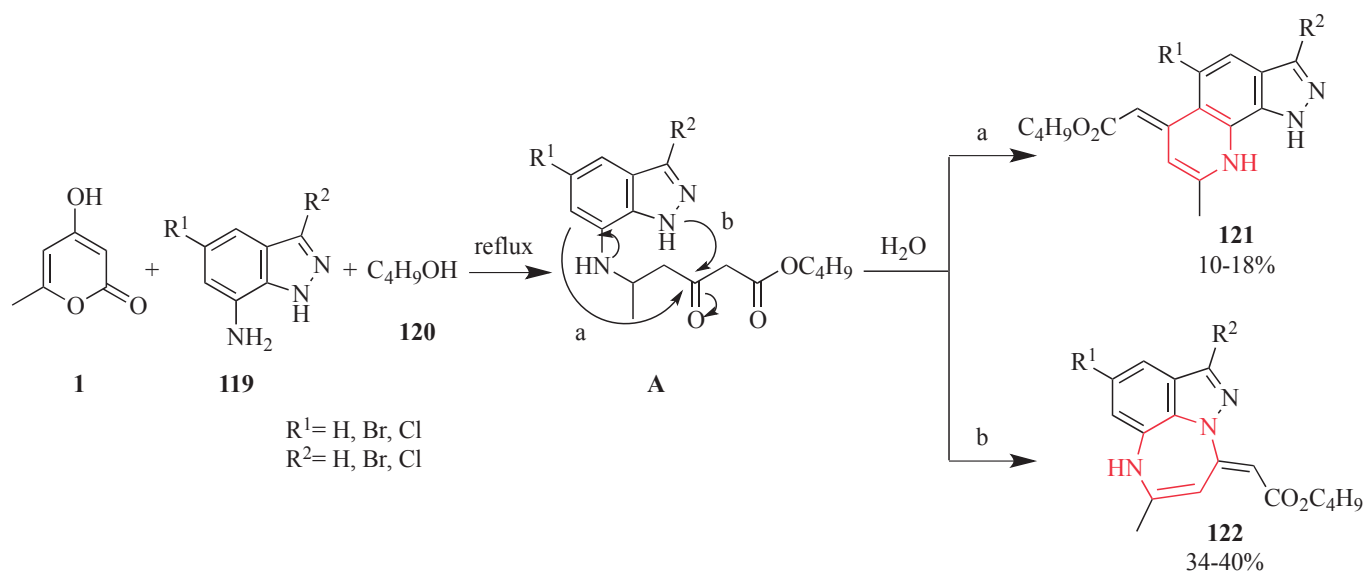
Three-component domino reaction of 4-hydroxy-6-methyl-2-pyrone **1**, 6-amino-2-thiouracil **117** and isatin **37** in the presence of choline chloride:oxalic acid (1:1) as deep eutectic solvent (DES) proceeded to furnish spiro[pyrano[4,3-*b*]pyrido[2,3-*d*]pyrimidine **118** in high yield (Scheme 57).¹³⁷



Scheme 57. Synthesis of spiro[pyrano[4,3-*b*]pyrido[2,3-*d*]pyrimidine **118** from **1**

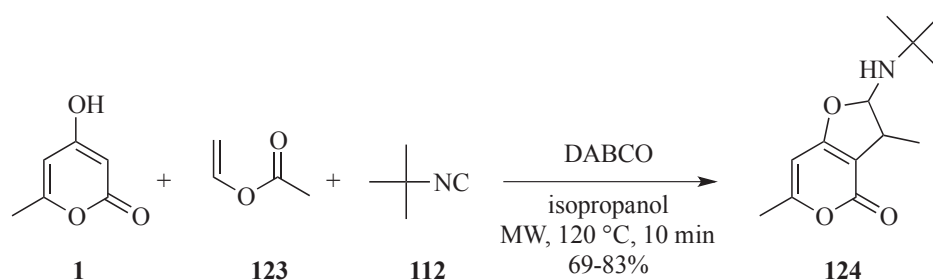
Rakib *et al.* reported a simple route for the synthesis of a mixture of pyrazolo[4,5-*h*]quinolones **121** and pyrazolo[1,5,4-*ef*][1,5]benzodiazepines **122** via a three-component reaction of 4-hydroxy-6-methyl-2-pyrone **1**, 7-aminoindazoles **119** and butanol **120** under reflux condition for 24 hours (Scheme 58).¹³⁸ According to the mechanism, initial attack of the amino group on C-6 of pyrone **1** followed by the opening of the pyranic cycle results in the formation of the intermediate **A**. Butanol

(weak nucleophile) can lead to cyclization in two different pathways (a and b) to give related compounds **121** and **122**.



Scheme 58. Synthesis of pyrazolo[4,5-*h*]quinolones **121** and pyrazolo[1,5,4-*ef*][1,5]benzodiazepines **122** from **1**

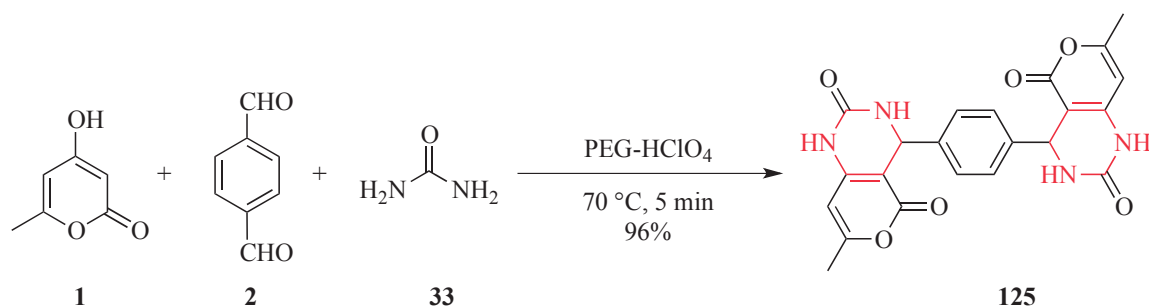
Three-component cascade reaction of 4-hydroxy-6-methyl-2-pyrone **1**, vinyl esters **123** and isocyanides **112** in the presence of DABCO as catalyst under microwave irradiation was developed by Kumar's group to synthesize the final product **124** (Scheme 59).¹³⁹



Scheme 59. Synthesis of compound **124** via three-component cascade reaction

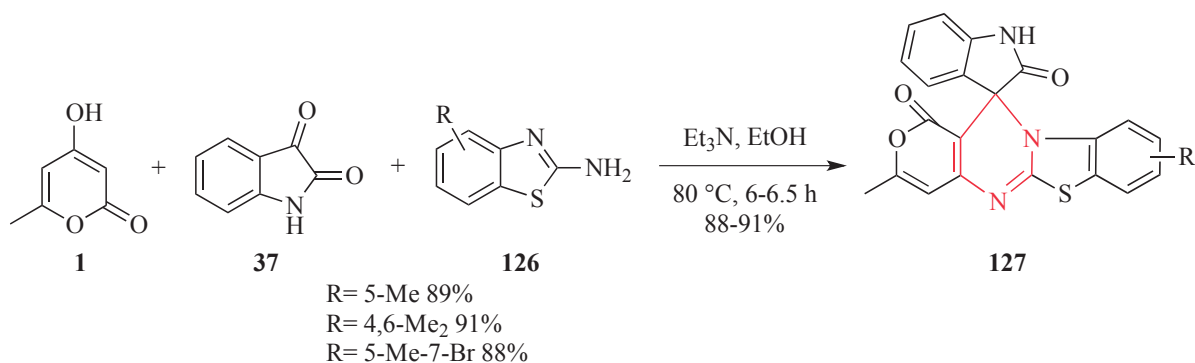
2.3.3. Six-membered heterocycles containing two heteroatoms

Siddiqui and Khan investigated three-component reaction of 4-hydroxy-6-methyl-2-pyrone **1**, terephthalaldehyde **2** and urea **33** in the presence of perchloric acid-modified PEG-6000 (PEG-HClO₄) as catalyst leading to the formation of bis-3,4-dihydropyrimidin-2(1*H*)-one **125** in 96% yield (Scheme 60).¹⁴⁰



Scheme 60. Synthesis of bis-3,4-dihydropyrimidin-2(1*H*)-one **125** from **1**

Structurally diverse spiroheterocycles **127** have been synthesized by a simple and convenient synthetic method involving triethylamine catalyzed multicomponent domino reaction of 4-hydroxy-6-methyl-2-pyrone **1**, isatin **37** and 2-aminobenzothiazoles **126** (Scheme 61).¹⁴¹ In another study, the same authors used the sulfamic acid as catalyst in this reaction (25-30 min, 90-93%).¹⁴² Furthermore, SFIL/H₂O was also used as catalyst and resulted in the formation of related products in 89-94% yield.¹⁴³



Scheme 61. Synthesis of spiroheterocycles **127** from **1**

2.3.4. Poly-membered heterocycles containing two heteroatoms

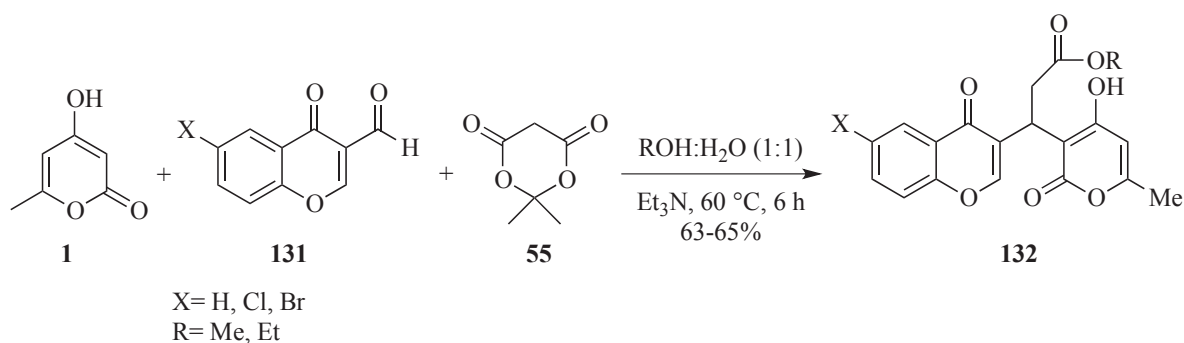
Multifunctionalized pyrano[3',2':2,3]indeno[2,1-*c*]quinolones **129** and ([3,4]furanoimino)benzo[*e*]pyrano[4,3-*b*]oxepines **130** have been synthesized by Jiang *et al.* via three-component domino annulations of 4-hydroxy-6-methyl-2-pyrone **1**, *o*-phthalaldehyde (OPA) **2**, and enaminones **45** and or **128** in HOAc as solvent under microwave irradiation (Scheme 62).¹⁴⁴ The reactions exhibited a good scope of enaminone substrates and several different *N* substituents with electron-withdrawing or electron-donating groups were all suitable substrates. This work provided an attractive strategy for construction of structurally diverse pentacyclic oxa-azaspiro and oxa-azabridged skeletons.



Scheme 62. Synthesis of multifunctionalized pyrano[3',2':2,3]indeno[2,1-*c*]quinolones **129** and ([3,4]furanoimino)benzo[*e*]pyrano[4,3-*b*]oxepines **130** from **1**

3. FOUR-COMPONENT REACTIONS OF 4-HYDROXY-6-METHYL-2-PYRONE

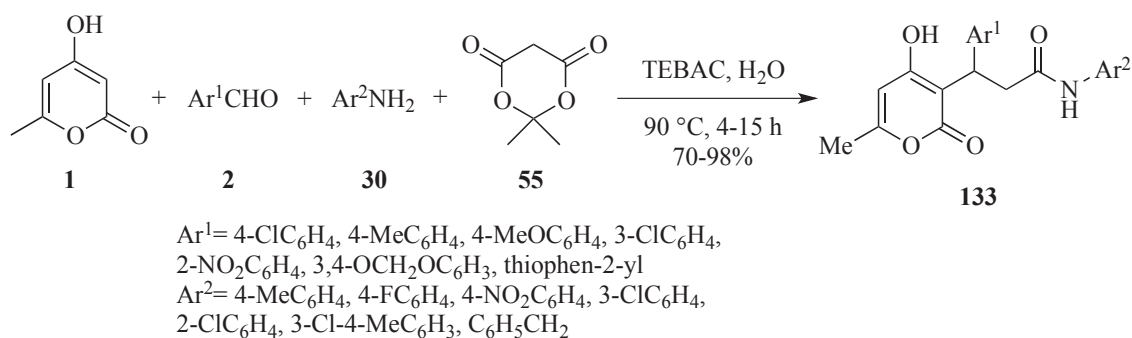
Mehrpavar *et al.* reported the four-component reaction of 6-methyl-4-hydroxy-2-pyrone **1**, 3-formylchromone **131** and Meldrum's acid **55** in the mixture of some primary alcohols and water (EtOH/H₂O 1:1) in the presence of triethylamine to construct the products containing chromone skeletons **132** (Scheme 63).¹⁴⁵



Scheme 63. Synthesis of chromone derivatives **132** from **1**

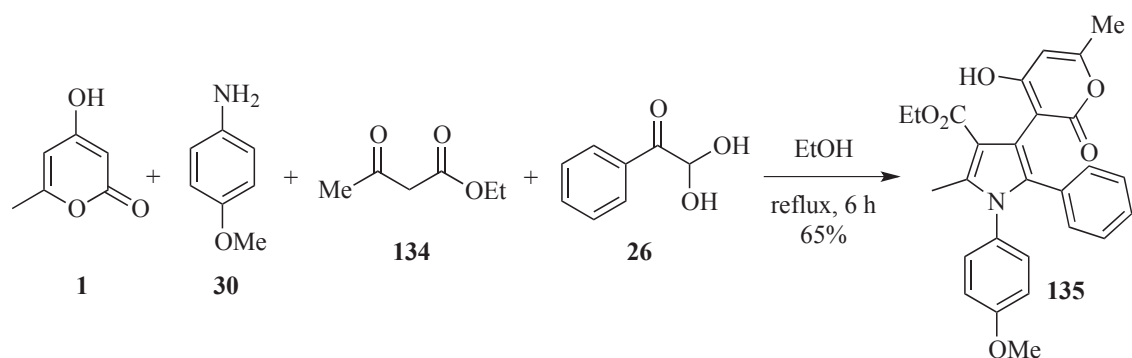
Wang's group described the four-component reaction of 6-methyl-4-hydroxy-2-pyrone **1**, aldehydes **2**, amines **30** and Meldrum's acid **55** in the presence of triethylbenzylammonium chloride (TEBAC) in aqueous medium for the preparation of *N*-substituted-3-aryl-3-(4-hydroxy-6-methyl-2-

oxo-2*H*-pyran-3-yl)propanamides **133** (Scheme 64).¹⁴⁶ Because TEBAC is soluble in water and the desired product is less soluble in water, the products can be directly separated by cooling to room temperature, and filtering after the reaction is completed.



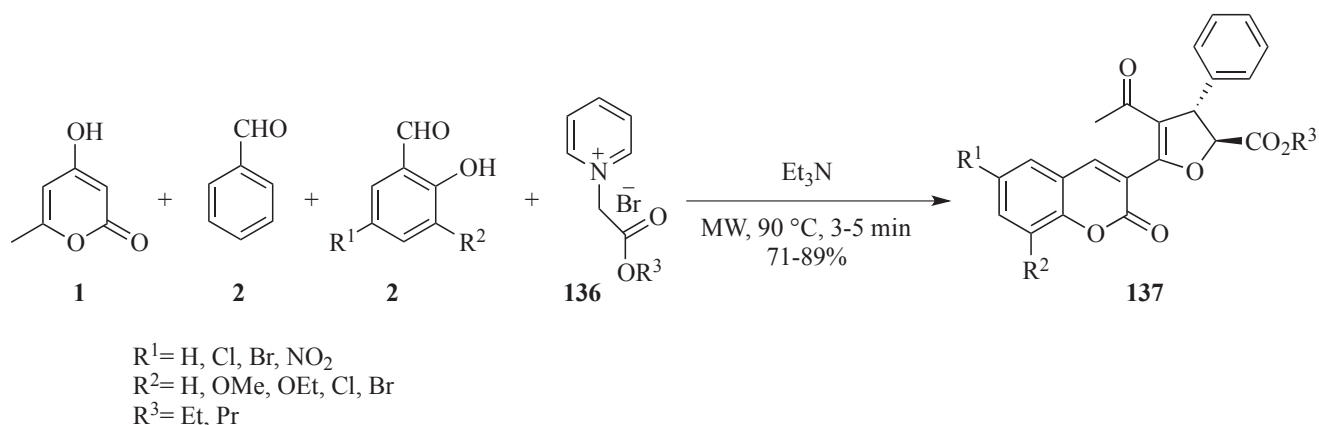
Scheme 64. Synthesis of aryl-3-(4-hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl)propanamides **133** from **1**

Choudhury and co-workers developed a one-pot four-component reaction of 4-hydroxy-6-methyl-2-pyrone **1**, *p*-methoxyaniline **30**, ethyl acetoacetate **134** and phenylglyoxal monohydrate **26** to provide the corresponding product **135** (Scheme 65).¹⁴⁷

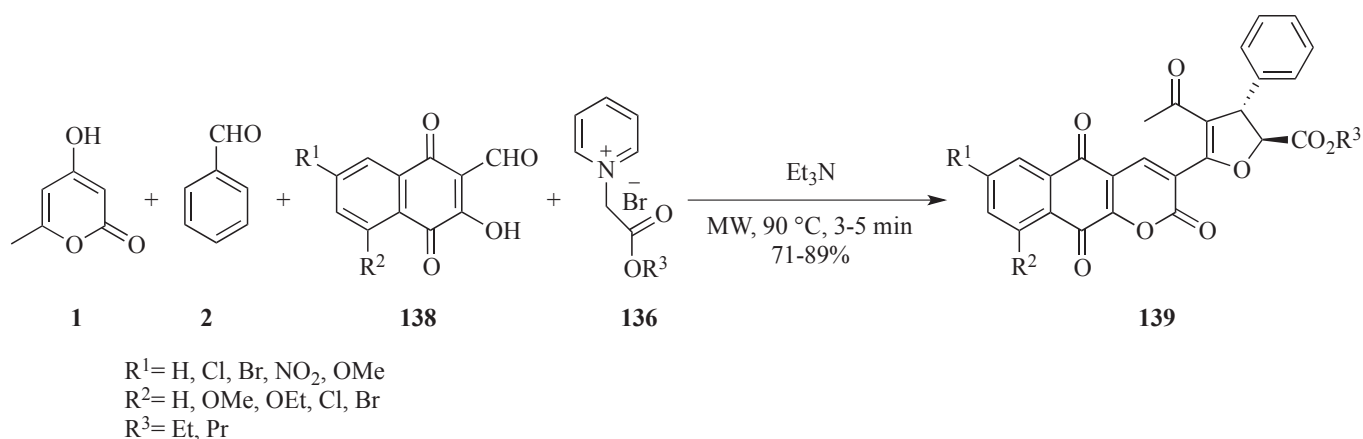


Scheme 65. Synthesis of compound **135** via one-pot four-component reaction

Tangeti and co-workers reported an efficient solvent-free microwave-assisted protocol for the preparation of dihydrofuran substituted coumarins **137** through a one-pot four-component reaction of 4-hydroxy-6-methyl-2-pyrone **1**, pyridinium ylide **136**, aromatic aldehydes and 2-hydroxy aromatic aldehydes **2** in the presence of triethylamine as catalyst (Scheme 66).¹⁴⁸ High yields and short reaction times were the advantageous of this reaction. In another study, the same group used 3-formyl-2-hydroxy-naphthoquinone derivatives **138** instead of 2-hydroxy aromatic aldehydes **2** to prepare 1*H*-benzo[*g*]chromene-2,5,10-triones **139** (Scheme 67).¹⁴⁹

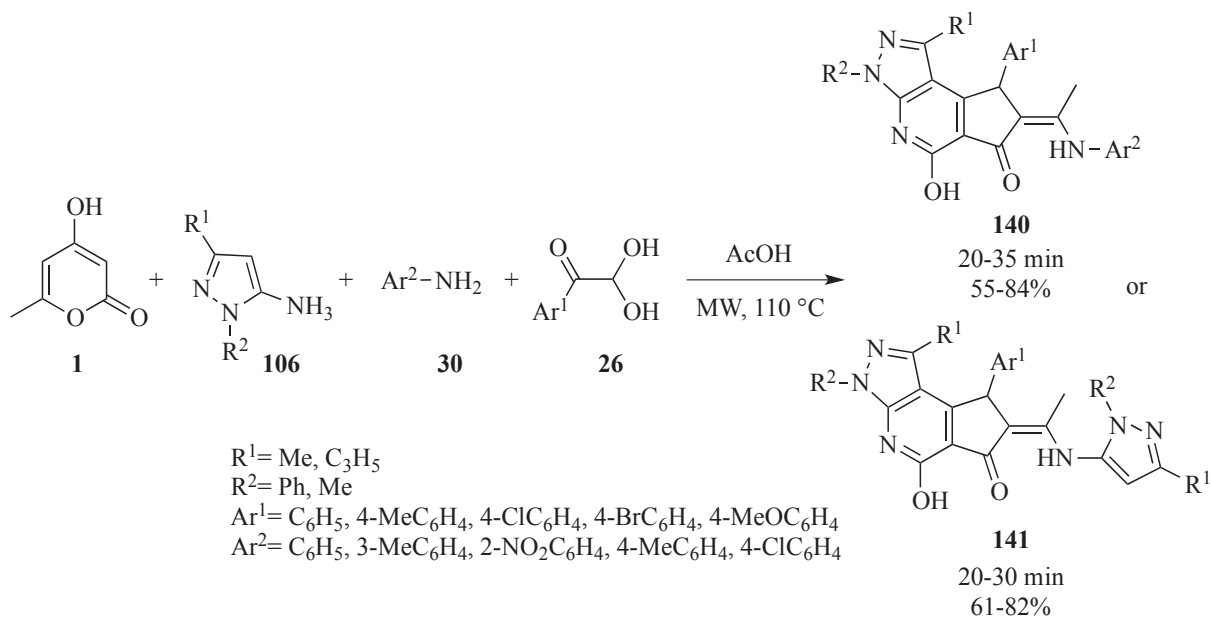


Scheme 66. Synthesis of dihydrofuran substituted coumarins **137** from **1**

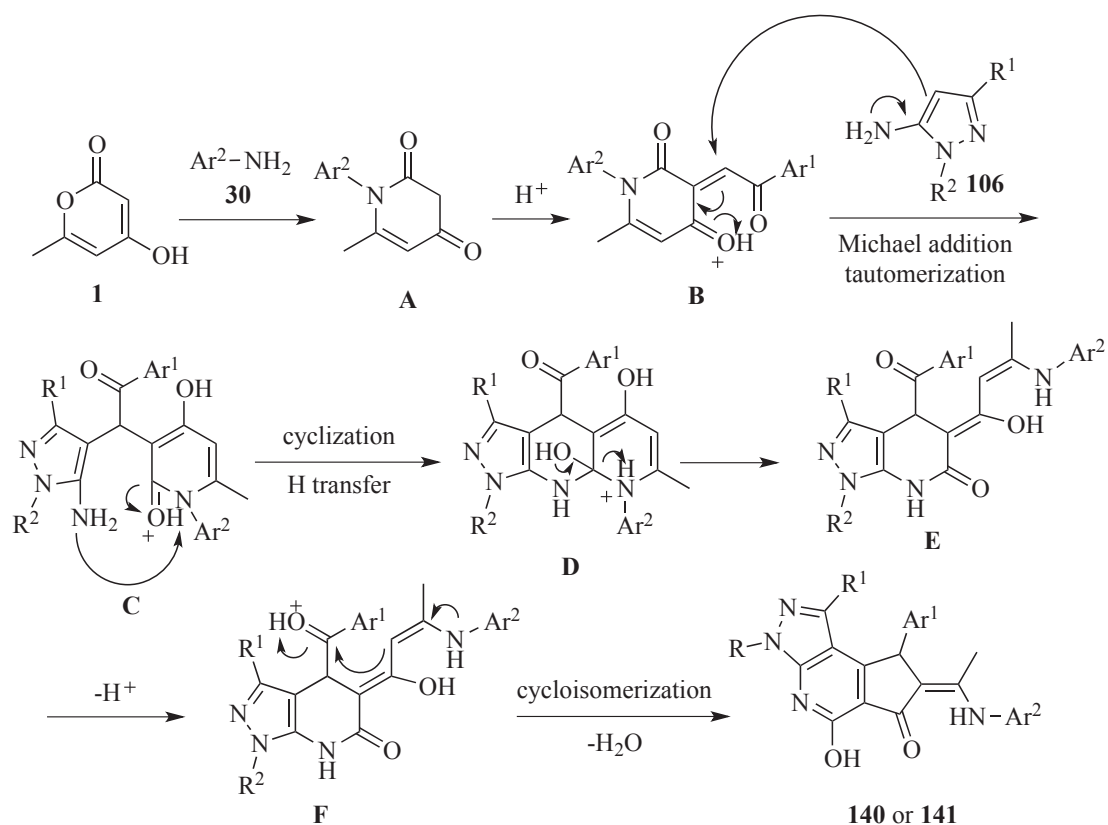


Scheme 67. Synthesis of *1H*-benzo[*g*]chromene-2,5,10-triones **139** from **1**

A four-component domino reaction was developed by Tu's group in order to obtain cyclopenta[*d*]pyrazolo[3,4-*b*]pyridines **140** and cyclopenta[*d*]pyrazolo[3,4-*b*]pyridines **141** from the reaction of 4-hydroxy-6-methyl-2-pyrone **1**, pyrazol-5-amines **106**, aromatic amines **30** and arylglyoxals **26** (Scheme 68).¹⁵⁰ It is noteworthy to mention here that the second product was formed in the same ratio of pyrazol-5-amines **106** and aromatic amines **30**. On the basis of proposed mechanism of the reaction, 4-hydroxy-6-methyl-2-pyrone **1**, initially reacted with aryl amines **30** to give intermediate **A**, which undergoes Knoevenagel condensation with arylglyoxals **26** to give **B**, followed by Michael addition and tautomerization to form intermediate **C**. Next, intramolecular cyclization occurs to afford fused pyrazolo[3,4-*b*]pyridines **D**. Subsequent ring opening of the pyridine skeleton and cycloisomerization yield the final tricyclic cyclopenta-fused pyrazolo[3,4-*b*]pyridines **140** or **141** (Scheme 69).



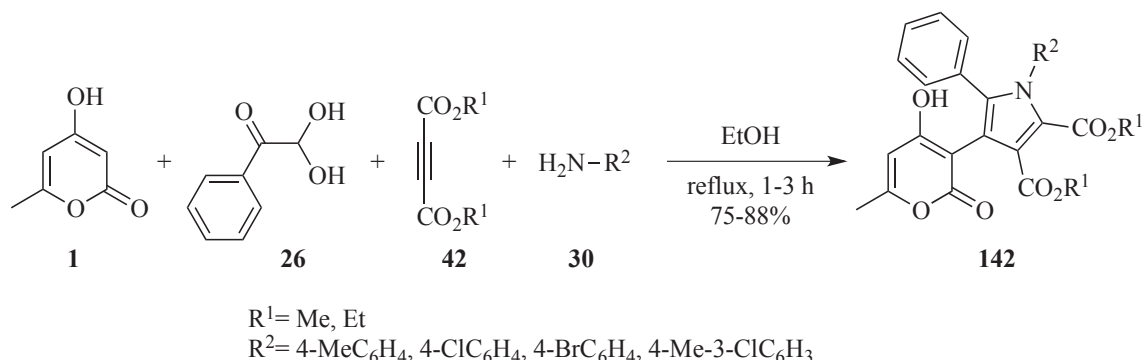
Scheme 68. Synthesis of tricyclic cyclopenta-fused pyrazolo[3,4-*b*]pyridines **140** or **141**



Scheme 69. Proposed mechanism for the synthesis of tricyclic cyclopenta-fused pyrazolo[3,4-*b*]pyridines **140** or **141**

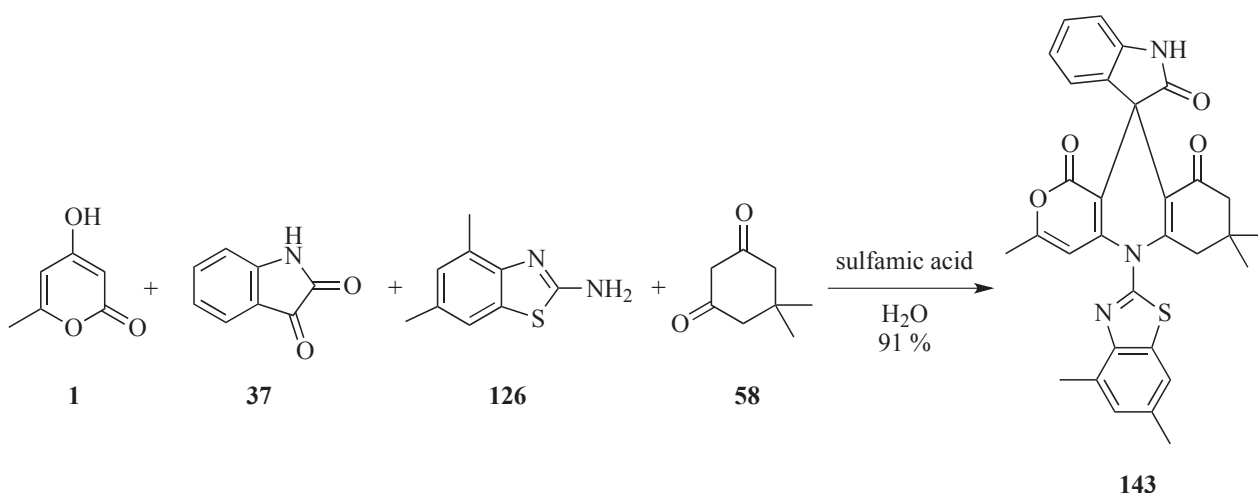
The synthesis of pyrrole derivatives **142** was achieved via a four-component reaction of 4-hydroxy-6-methyl-2-pyrone **1**, phenylglyoxal monohydrate **26**, dialkyl acetylenedicarboxylate **42** and

arylamines **30** under reflux condition in ethanol (Scheme 70).¹⁵¹



Scheme 70. Synthesis of pyrrole derivatives **142** from **1**

Kumar Arya *et al.* accomplished a four-component reaction of 4-hydroxy-6-methyl-2-pyrone **1**, isatin **37**, 2-amino-5,7-dimethyl-benzothiazole **126** and dimedone **58** in the presence of sulfamic acid as catalyst in water to obtain spiropyrano[3,4-*b*]-5,3'-indolinetrione **143** in 91% yield (Scheme 71).¹⁵²



Scheme 71. Synthesis of spiropyrano[3,4-*b*]-5,3'-indolinetrione **143** from **1**

4. CONCLUSION

This review surveyed the use of 4-hydroxy-6-methyl-2-pyrone in the synthesis of heterocyclic compounds with respect to the number of atoms in heterocyclic rings, taking into consideration the heteroatom. 4-Hydroxy-6-methyl-2-pyrone as an important structural unit can be used for the synthesis of a large variety of heterocyclic compounds. The reactions tolerate a wide variety of functional groups, leading to the formation of multiple heterocyclic frameworks.

ABBREVIATIONS

ACD: Amino-appended β -cyclodextrin

DABCO: 1,4-Diazabicyclo[2.2.2]octane

DBU: 1,8-Diazabicyclo[5.4.0]undec-7-ene

DME: 1,2-Dimethoxyethane

HEAA: Hydroxyethylammonium acetate

MW: Microwave

NCS: N-Chlorosuccinimide

NPs: Nanoparticles

PEG: Polyethylene glycol

PNO: Pyridine *N*-oxide

p-TSA: *p*-Toluenesulfonic acid

SBSA: Silica boron sulfonic acid

SSLP: Silica-supported organocatalyst system based on *L*-proline

TEBAC: Triethylbenzylammonium chloride

THF: Tetrahydrofuran

TMGTF: Tetramethylguanidinium triflate

ACKNOWLEDGEMENTS

We are grateful for financial support from the Research Council of Alzahra University and support of National Elites Foundation of Iran, Tehran.

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