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Review Article

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A CONCISE REVIEW ON SYNTHESIS OF PYRAN HETEROCYCLES

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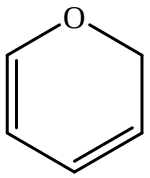
ABSTRACT

In this review, we report the different strategies for the synthesis of pyran heterocycles starting from different reactive substances. The strategies are either one pot or multi-stepped and may either occur in presence of catalyst or in absence of any precursor. Mostly these derivatives are synthesized conveniently by refluxing but some green procedures like ultra-sonication, microwave synthesis; solvent free methods are also involved. These pyrans are found to be biologically active as most of these are found as potential antiviral and anti-leishmanial agents.

KEYWORDS: Pyran; Active methylene, Electrocyclic ring, Catalyst.

Pyran is a six membered non-aromatic ring consisting of five carbon atoms, one oxygen atom and two double bonds. The molecular formula is C5H6O. The term pyran is also often applied to the saturated ring analog, which is more properly referred to as tetrahydropyran (oxane). The two isomers of pyran differ by the location of the double bonds. In 2H-pyran (**1**) and 4H-pyran (**2**), the saturated carbons are at position 2 and 4, respectively.



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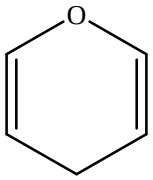
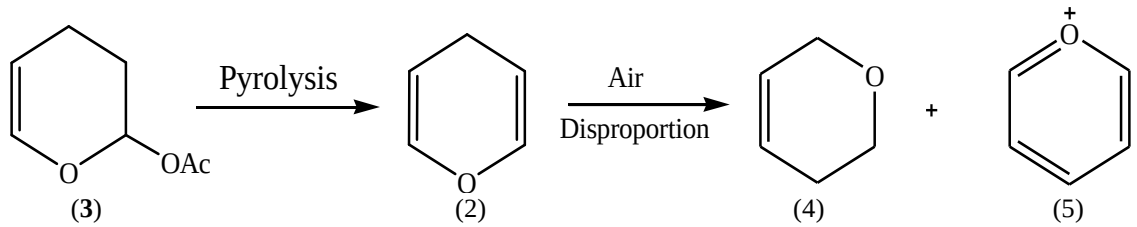


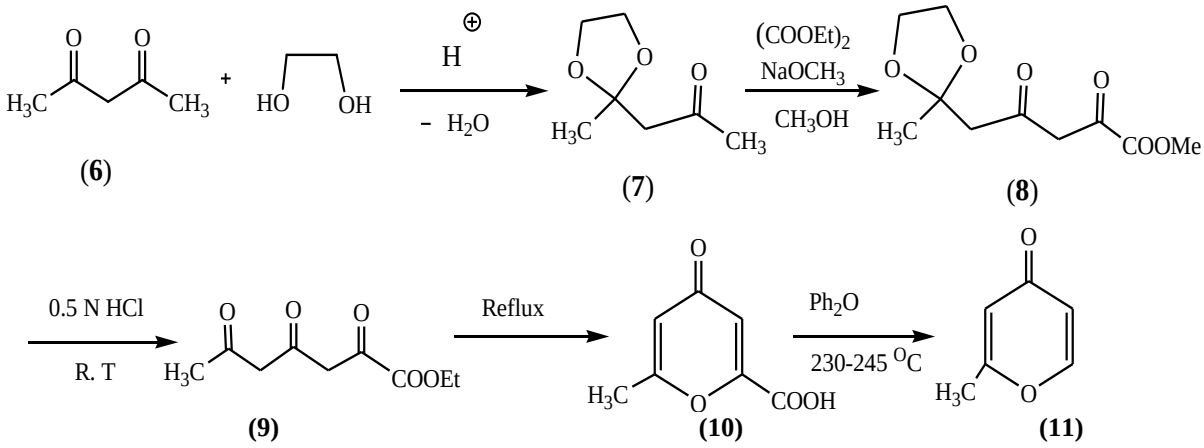
(2)

The pyrolysis of 2-acetoxy-3, 4-dihydro-2H-pyran (**3**). It was found too unstable, particularly in the presence of air and easily disproportionated to the corresponding dihydropyran (**4**) and the pyrylium ion (**5**).

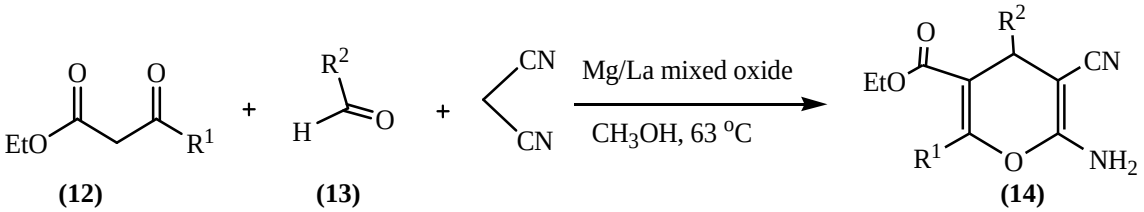


(**3**) (2) (4) (5)

Dorman[2] in 1967 reported the reaction of acetyl acetone (**6**) with ethylene glycol which gave 2-methyl-2-acetonyl-1, 3-dioxolan (**7**). The compound (**7**) was acylated with diethyl oxalate in presence of sodium methoxide formed methyl 5-(2-methyl-[1, 3] dioxolan-2-yl)-2, 4-dioxopentanoic acid methyl ester (**8**). The compound (**8**) was treated with 0.5 N HCl to give intermediate triketone (**9**). The compound (**9**) was refluxed to complete ring closure forming 6-methyl-4H-pyran-4-one-2-carboxylic acid (**10**) which on subsequent decarboxylation yielded 2-methyl-4H-pyran-4-one (**11**).

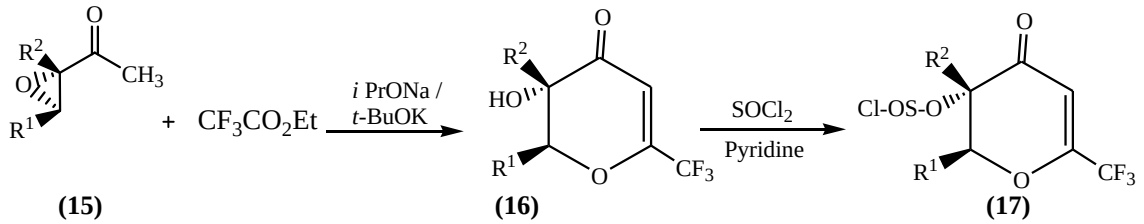


Lingaiah and co-workers[3] reported an efficient synthesis of polyfunctionalized 4H-pyrans (**14 a-h**) which involved one pot condensation of active methylenic diketo compounds (**12 a-h**), aldehydes (**13 a-h**) and malononitrile using basic Mg/La mixed oxide as catalyst.

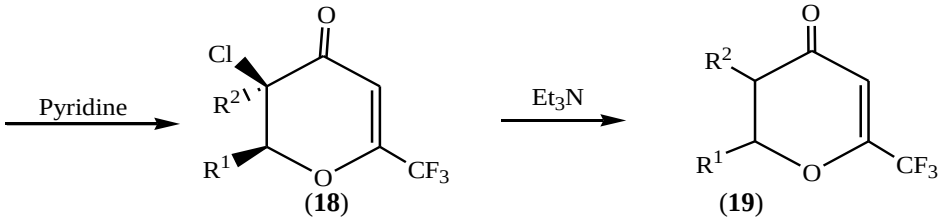


R^1	R^2	R^1	R^2
(**a**) C_2H_4Br	(**a**) C_6H_5	(**a**) C_2H_4Br	C_6H_5
(**b**) C_2H_5	(**b**) 4-NO_2-C_6H_4	(**b**) C_2H_5	4-NO_2-C_6H_4
(**c**) C_3H_7	(**c**) 3-NO_2-C_6H_4	(**c**) C_3H_7	3-NO_2-C_6H_4
(**d**) CH_2Cl	(**d**) 4-Cl-C_6H_4	(**d**) CH_2Cl	4-Cl-C_6H_4
(**e**) CH_2Br	(**e**) 4-CN-C_6H_4	(**e**) CH_2Br	4-CN-C_6H_4
(**f**) C_6H_4Cl	(**f**) 4-OH-C_6H_4	(**f**) C_6H_4Cl	4-OH-C_6H_4
(**g**) C_6H_4Br	(**g**) 4-Me-C_6H_4	(**g**) C_6H_4Br	4-Me-C_6H_4
(**h**) CH_2I	(**h**) 4-OMe-C_6H_4	(**h**) CH_2I	4-OMe-C_6H_4

Tyvorskii and co-workers[4] reported the reaction of oxiranes (**15 a-e**) with ethyl perfluoroalkanoate in presence of sodium *iso*-propoxide or potassium *tert*-butoxide that gave hydroxypyranones (**16 a-e**). The hydroxypyranones upon reaction with thionyl chloride in dry pyridine yielded chlorosulfites (**17 a-e**). These sulphites upon refluxing in presence of pyridine provided chlorosubstituted pyranones (**18 a-e**) which on reaction with triethyl amine yielded 2-perfluoroalkyl-4H-pyran-4-ones (**19 a-e**).

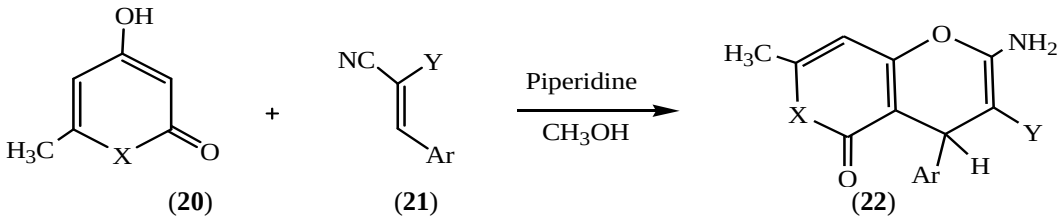


R^1	R^2	R^1	R^2	R^1	R^2
(**a**) H	CH_3	(**a**) H	CH_3	(**a**) H	CH_3
(**b**) H	Ph	(**b**) H	Ph	(**b**) H	Ph
(**c**) CH_3	CH_3	(**c**) CH_3	CH_3	(**c**) CH_3	CH_3
(**d**) CH_2Cl	CH_3	(**d**) CH_2Cl	CH_3	(**d**) CH_2Cl	CH_3
(**e**) CH_2I	Ph	(**e**) CH_2I	Ph	(**e**) CH_2I	Ph



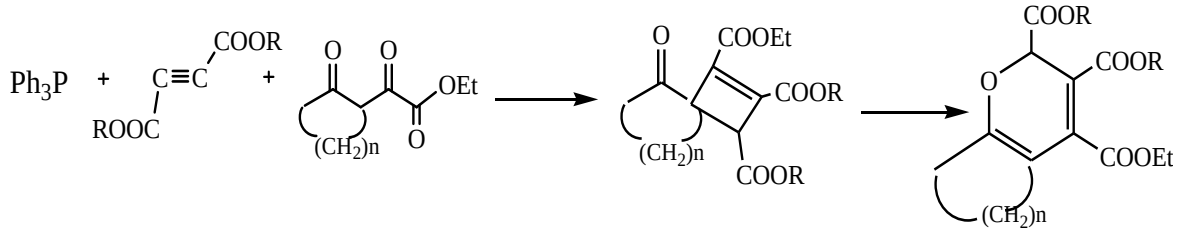
R^1	R^2	R^1	R^2
(**a**) H	CH_3	(**a**) H	CH_3
(**b**) H	Ph	(**b**) H	Ph
(**c**) CH_3	CH_3	(**c**) CH_3	CH_3
(**d**) CH_2Cl	CH_3	(**d**) CH_2Cl	CH_3
(**e**) CH_2I	Ph	(**e**) CH_2I	Ph

Ivanov and co-workers[5] reported the reaction of 4-hydroxy-6-methyl-pyranone and pyridinone derivatives (**20 a-c**) with Knoevenagel products (**21 a-c**) in presence of piperidine in methanol to yield substituted 2-amino-4H, 5H-pyrano [4, 3 - *b*] pyran-5-ones (**22 a-c**).



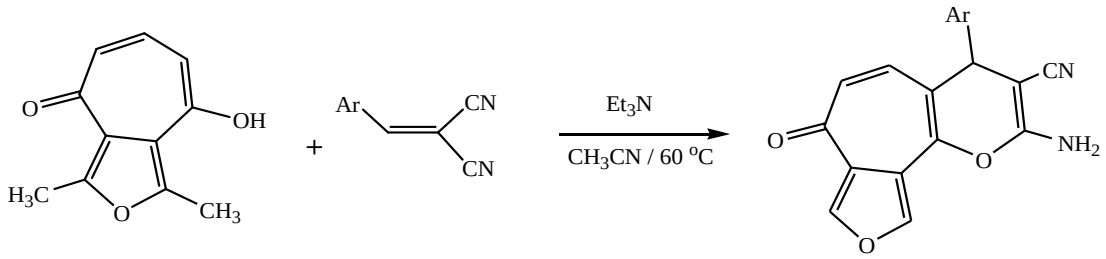
X	Ar	Y	X	Ar	Y
(**a**) O	(**a**) Ph	$COOCH_3$	(**a**) O	Ph	$COOCH_3$
(**b**) NH	(**b**) Ph	CN	(**b**) NH	Ph	CN
(**c**) NCH_2Ph	(**c**) NO_2Ph	$COOC_2H_5$	(**c**) NCH_2Ph	NO_2Ph	$COOC_2H_5$

Yavari and Bayat[6] reported that dialkylacetylenedicarboxylates (**23 a-d**) reacted smoothly with triphenylphosphine and ethyl oxo-(2-oxocycloalkyl)-ethanoates (**24 a-d**) via intramolecular Wittig reaction to produce *spiro*-cyclobutene derivatives (**25 a-d**). These *spiro* systems underwent electrocyclic ring-opening reaction to produce electron-deficient 1, 3-dienes which spontaneously cyclized to 2H-pyran derivatives (**26 a-d**).



R	n	R	n	R	N
(**a**) Me	(**a**) 3	(**a**) Me	3	(**a**) Me	3
(**b**) Et	(**b**) 4	(**b**) Et	4	(**b**) Et	4
(**c**) *i*Pr	(**c**) 5	(**c**) *i*Pr	5	(**c**) *i*Pr	5
(**d**) *i*Bu	(**d**) 9	(**d**) *i*Bu	9	(**d**) *i*Bu	9

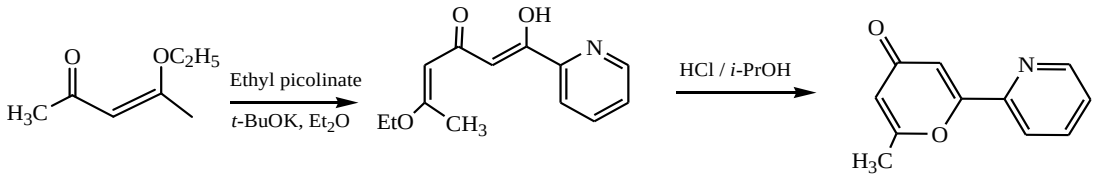
Arseneva and Arsenev[7] reported that 8-hydroxy-1, 3-dimethyl-4H-cyclohepta [*c*] furan-4-one (**27**) on reaction with arylidenemalononitriles (**28 a-h**) gave the corresponding condensed 2-amino-4H-pyrans (**29 a-h**) in good yields.



(**27**) (**28**) (**29**)

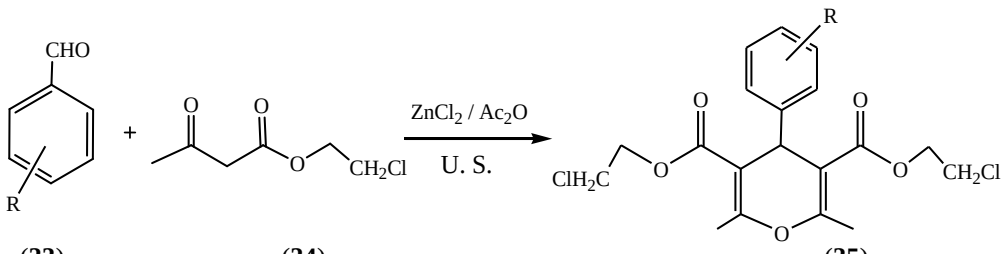
Ar	**Ar**
(**a**) Cl_2-C_6H_3	(**a**) Cl_2-C_6H_3
(**b**) F-C_6H_4	(**b**) F-C_6H_4
(**c**) Cl-C_6H_4	(**c**) Cl-C_6H_4
(**d**) Br-C_6H_4	(**d**) Br-C_6H_4
(**e**) EtO-C_6H_4	(**e**) EtO-C_6H_4
(**f**) MeO-C_6H_4	(**f**) MeO-C_6H_4
(**g**) MeS-C_6H_4	(**g**) MeS-C_6H_4
(**h**) Thienyl	(**h**) Thienyl

Bobrov and Tyvorskii[8] reported the synthesis of 6-methyl-2-(2-pyridyl)-4H-pyran-4-one (**32**). The pyranone precursor (5-ethoxy-1-hydroxy-1-pyridin-2-yl hexa-1, 4-dien-3-one) (**31**) was prepared by Claisen condensation of acetylacetone enol ether (**30**) with ethyl picolinate.



(**30**) (**31**) (**32**)

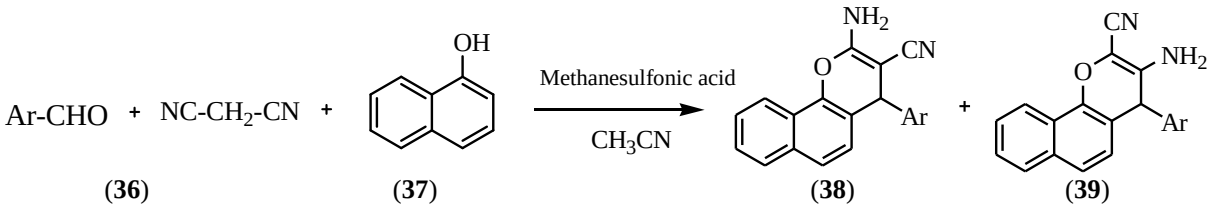
Yan and co-workers[9] reported the reaction of aromatic aldehydes (**33 a-j**) with 3-oxo-butyric acid-2-chloroethyl ester (**34**) in acetic anhydride in presence of zinc chloride, which was irradiated by an ultrasonic processor at 50 °C and 100 W to yield substituted 4-aryl-4H-pyran-3, 5-dicarboxylates (**35 a-j**).



(**33**) (**34**) (**35**)

R	**R**
(**a**) 2-F	(**a**) 2-F
(**b**) 2, 4-$(CH_3)_2$	(**b**) 2, 4-$(CH_3)_2$
(**c**) 4-Br	(**c**) 4-Br
(**d**) 4-OC_2H_5	(**d**) 4-OC_2H_5
(**e**) 2, 4-Cl, Br	(**e**) 2, 4-Cl, Br
(**f**) 2, 4-Cl, I	(**f**) 2, 4-Cl, I
(**g**) 4-F	(**g**) 4-F
(**h**) 2, 4-NO_2, CH_3	(**h**) 2, 4-NO_2, CH_3
(**i**) 2, 4-$(OH)_2$	(**i**) 2, 4-$(OH)_2$
(**j**) 3-Br	(**j**) 3-Br

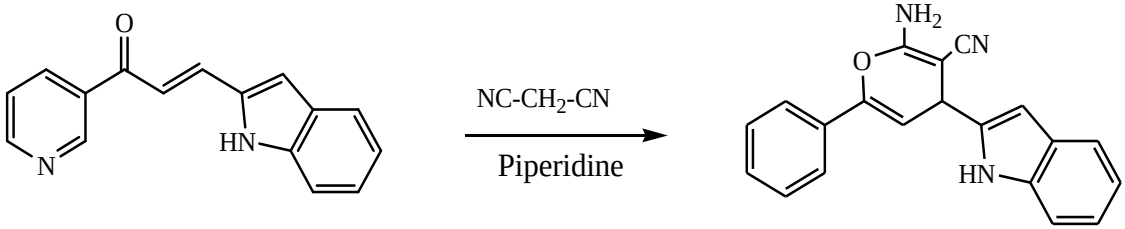
Heravi and co-workers[10] reported one-pot, three component reaction of aromatic aldehydes (**36 a-e**), malononitrile and α-naphthol (**37**) in presence of methanesulfonic acid to yield two isomers of 2-amino-4H-chromenes **38 (a-e)** and **39 (a-e)** in very good yields.



(**36**) (**37**) (**38**) (**39**)

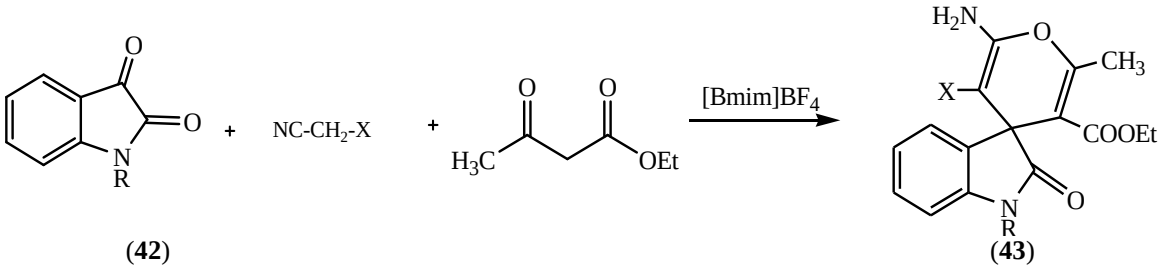
Ar	**Ar**	**Ar**
(**a**) $Cl_2C_6H_3$	(**a**) $Cl_2C_6H_3$	(**a**) $Cl_2C_6H_3$
(**b**) $(NO_2)_2C_6H_3$	(**b**) $(NO_2)_2C_6H_3$	(**b**) $(NO_2)_2C_6H_3$
(**c**) $(MeO)_2C_6H_3$	(**c**) $(MeO)_2C_6H_3$	(**c**) $(MeO)_2C_6H_3$
(**d**) $FClC_6H_3$	(**d**) $FClC_6H_3$	(**d**) $FClC_6H_3$
(**e**) $ClNO_2C_6H_3$	(**e**) $ClNO_2C_6H_3$	(**e**) $ClNO_2C_6H_3$

El-Latif and co-workers[11] reported the reaction of 3-*β*-indolylacryloylpyridine (**40**) with malononitrile in presence of piperidine to yield 2-amino-4-(3-indolyl)-6-(3-pyridyl)-pyran-3-carbonitrile (**41**).



(**40**) (**41**)

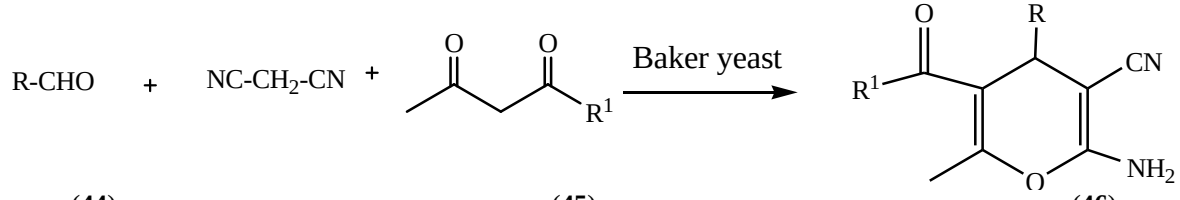
Moghadam and Miri[12] reported the reaction of isatins (**42 a-b**), malononitrile or ethyl cyano-acetate and 1, 3-dicarbonyl compound in the ionic liquid to yield *spiro* [4H-pyran-oxindole] derivatives (**43 a-d**) in better amounts.



(**42**) (**43**)

R	**X**	**R**	**X**
(**a**) H	CN	(**a**) H	CN
(**b**) Bu	COOEt	(**b**) H	COOEt
		(**c**) Bu	CN
		(**d**) Bu	COOEt

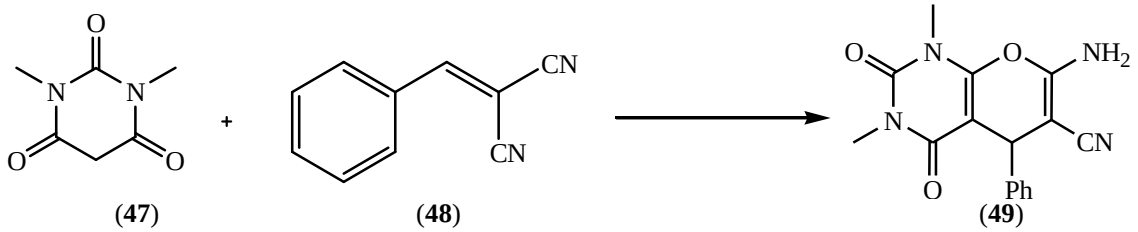
Mane and co-workers[13] reported the Baker's yeast catalyzed one-pot three-component cyclocondensation of aryl aldehydes (**44 a-g**), malononitrile and *β*-dicarbonyls (**45 a-c**) in dimethylacetamide solvent to obtain polyfunctionalized 4H-pyrans (**46 a-g**).



(**44**) (**45**) (**46**)

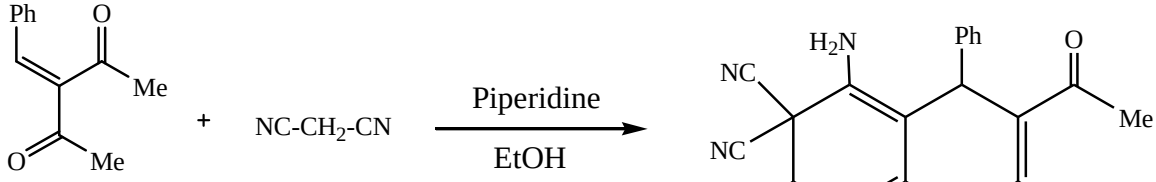
R	R^1	R	R^1
(**a**) $(MeO)_2C_6H_3$	(**a**) OEt	(**a**) $(MeO)_2C_6H_3$	OEt
(**b**) $Cl_2C_6H_3$	(**b**) Me	(**b**) $Cl_2C_6H_3$	Me
(**c**) $3\text{-}ClC_6H_4$	(**c**) OMe	(**c**) $3\text{-}ClC_6H_4$	OMe
(**d**) $4\text{-}OHC_6H_4$		(**d**) $4\text{-}OHC_6H_4$	OEt
(**e**) $4\text{-}FC_6H_4$		(**e**) $4\text{-}FC_6H_4$	Me
(**f**) 3-Pyridyl		(**f**) 3-Pyridyl	OMe (**g**) 4-
$CH_3C_6H_4$		(**g**) $4\text{-}CH_3C_6H_4$	OEt

Seeliger and co-workers[14] have reported the formation of dihydropyrano [2, 3 - *c*] pyrimidinedione (**49**) in 80% yields by the reaction of 1, 3-dimethylbarbituric acid (**47**) with arylidene malononitrile (**48**) upon protonation.



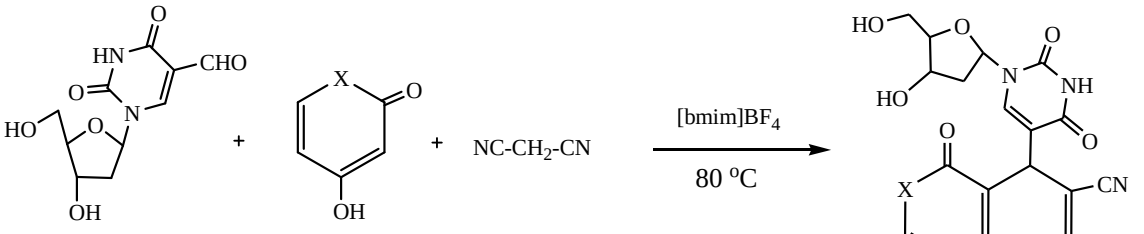
(**47**) (**48**) (**49**)

Martin and co-workers[15] reported the synthesis of pyrano [2, 3 - *b*] pyridine derivative (**51**) from malononitrile and 2-benylidene-1, 3-diketone (**50**). The compound **50** is easily accessible via Knoevenagel condensation of benzaldehyde and pentan-2, 4-dione.



(**50**) (**51**)

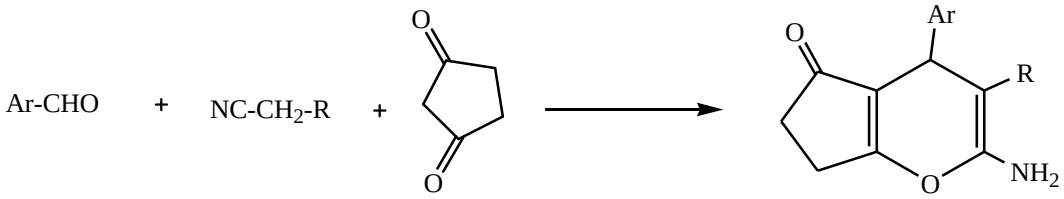
Feng and co-workers[16] reported the multi-component reactions of nucleoside (**52**), 4-hydroxy-2-pyranone (**53a**) or 4-hydroxy-pyridin-2(1H)-one (**53b**) and malononitrile in presence of ionic liquid to provide the efficient synthesis of pyrano [4, 3 - *b*] pyran nucleoside derivative (**54a**) and pyrano [3, 2 - *c*] pyridine nucleoside derivative (**54b**) which were also found as potential antiviral and anti-leishmanial agents.



(**52**) (**53**) (**54**)

X	X
(**a**) O	(**a**) O
(**b**) NH	(**b**) NH

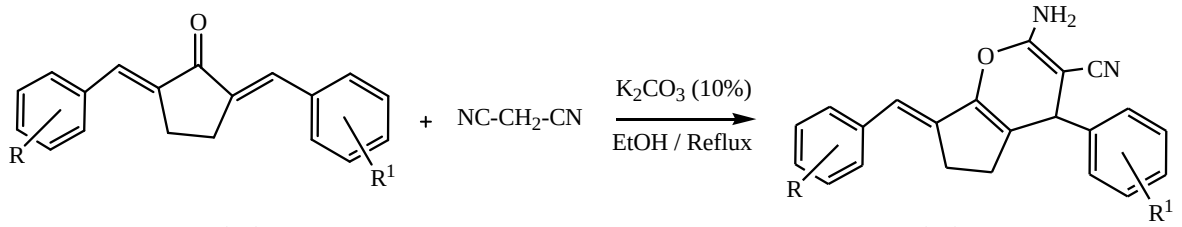
Yao and co-workers[17] reported a rapid and facile synthesis of cyclopenta [*b*] pyran derivatives namely, 2-amino-4-aryl-5-oxo-tetrahydrocyclopenta [*b*] pyran-3-carbonitriles (**57 a**, **c**) and ethyl-2-amino-4-aryl-5-oxo-tetrahydrocyclopenta [*b*] pyran-3-carboxylates (**57 b**, **d**) under solvent free conditions by triturating a mixture of the three components; aromatic aldehydes (**55 a**, **b**), malononitrile / ethyl cyanoacetate and cyclopentadione (**56**) at 80 °C.



(**55**) (**56**) (**57**)

Ar	**R**	**Ar**	**R**
(**a**) C_6H_5	CN	(**a**) C_6H_5	CN
(**b**) Cl-C_6H_4	COOEt	(**b**) C_6H_5	COOEt
(**c**) Cl-C_6H_4	CN		
(**d**) Cl-C_6H_4	COOEt		

Karimi-Jaberi and Pooladian[18] synthesized a series of substituted 2-amino-4H-pyran-3-carbonitriles (**59 a-s**) through a one-pot condensation of malononitrile and *α*, *α′-bis* (arylidene) cyclopentanones (**58 a-s**) in ethanol by using K_2CO_3 as a catalyst. Short experimental reaction times, excellent yields, no need to use cumbersome apparatus for purification of the products, inexpensiveness and commercially availability of the catalyst were the advantages of this method.



(**58**) (**59**)

R	**R^1**	**R**	**R^1**
(**a**) CH_2	2-Cl	(**a**) CH_2	2-Cl
(**b**) CH_2	H	(**b**) CH_2	H
(**c**) CH_2	2-Cl, 4-Cl	(**c**) CH_2	2-Cl, 4-Cl
(**d**) C_2H_4	2-Cl	(**d**) C_2H_4	2-Cl
(**e**) C_2H_4	H	(**e**) C_2H_4	H
(**f**) C_2H_4	2-Cl, 4-Cl	(**f**) C_2H_4	2-Cl, 4-Cl
(**g**) C_2H_4	4-F	(**g**) C_2H_4	4-F
(**h**) C_2H_4	4-Br	(**h**) C_2H_4	4-Br
(**i**) C_2H_4	4-OMe	(**i**) C_2H_4	4-OMe
(**j**) C_2H_4	4-Me	(**j**) C_2H_4	4-Me
(**k**) C_2H_4	2-Cl, 6-F	(**k**) C_2H_4	2-Cl, 6-F
(**l**) C_3H_6	H	(**l**) C_3H_6	H
(**m**) C_3H_6	2-Cl	(**m**) C_3H_6	2-Cl
(**n**) C_3H_6	2-Cl, 4-Cl	(**n**) C_3H_6	2-Cl, 4-Cl
(**o**) C_3H_6	4-F	(**o**) C_3H_6	4-F
(**p**) C_3H_6	4-Br	(**p**) C_3H_6	4-Br
(**q**) C_3H_6	4-OMe	(**q**) C_3H_6	4-OMe
(**r**) C_3H_6	4-Me	(**r**) C_3H_6	4-OMe
(**s**) C_3H_6	2-Cl, 6-F	(**s**) C_3H_6	2-Cl, 6-F

CONCLUSION

In this article we have mentioned the different routes for the synthesis of pyran derivatives. The steps included condensation followed by cyclization or multi component reaction (MCR), either in a step-wise manner or in one pot has been achieved successfully to obtain the aforementioned class of heterocycles under different conditions. Most of the preparative methods included diethyl oxalate, diethyl malonate, malononitrile and ethyl cyanoacetate as the common reagents for the synthesis of pyrimidines appended on different heterocyclic skeletons. Also many series of substituted pyrimidine six membered heterocycles possessing N-, Sand O- have been constructed in potential yields and with conventional methods. Hence these protocols provide convenient strategies to annelate different heterocyclic nuclei with widespread bioactive pyrimidines thereby extending the categories of heterocyclic systems. These strategies may also provide valuable information for the

further design and development of more active biological agents through various modifications and derivatizations.

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