

POLYSTYRENE RESIN FUNCTIONALIZED WITH PIPERAZINE FOR SYNTHESIS OF 4H-PYRAN DERIVATIVES

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Abstract

In this study, a novel and environmentally benign method for the synthesis of polyfunctionalized 4H-pyran derivatives has been developed using piperazine-functionalized polystyrene resin as a heterogeneous catalyst. These six-membered fused heterocycles are of immense pharmacological and industrial interest, exhibiting applications ranging from anticancer and antibacterial agents to uses in cosmetics, photonics, and agriculture. The catalyst, a modified solid acid polymer, offers significant advantages including reusability, simple separation, and minimal environmental impact. Various one-pot multicomponent reactions were reviewed, emphasizing the superiority of our approach in terms of efficiency, simplicity, and green chemistry principles. Our method eliminates the need for extensive purification steps and avoids toxic reagents or solvents, making it a promising route for the scalable production of bioactive 4H-pyran scaffolds. This research contributes to the growing field of sustainable catalysis and underscores the potential of polymer-supported reagents in modern synthetic methodologies.

Keywords: 4H-pyran derivatives, multicomponent reaction, polystyrene resin, piperazine, heterogeneous catalyst, green chemistry, fused heterocycles, sustainable synthesis, solid acid catalyst, pharmacologically active compounds.

Introduction:

Polyfunctionalized 4H-pyran (1, Figure.80), synthesized in this work are six membered fused heterocyclic compounds which gained enormous attention of both synthetic chemists as well as pharmacists for its plethora of diversified applications of its possibility of for their derivatives.

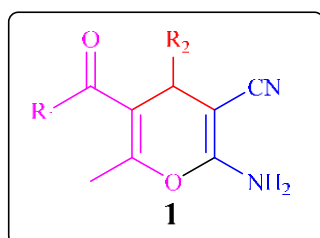


Figure 1: polyfunctionalized 4H-pyran

4H-pyran derivatives that are polyfunctionalized have emerged as compelling synthetic objectives due to their significant biological and pharmacological properties.¹ These compounds contain heterocyclic moieties with addition of countless additives and modifiers. The applications ranging from cosmetics, reprography, information storage and plastics heavily depend upon the heterocyclic residues. One of the striking structural features inherent to heterocycles, which is continued to be exploited to a great advantage by the drug industry, lies in their ability to manifest substituent around a core scaffold in well-defined three-dimensional representations. Based upon these considerations in recent years, a family of new heterocyclic scaffolds has come into existence having wide range of applications such as switching on /and off devices, photo catalysis, etc.²

Applications of polyfunctionalized 4H-pyrans:

Polyfunctionalized 4H- pyrans have recently attracted attention as an important class of heterocyclic scaffolds in the field of drugs and pharmaceuticals due to their wide range of applications (Figure 2).

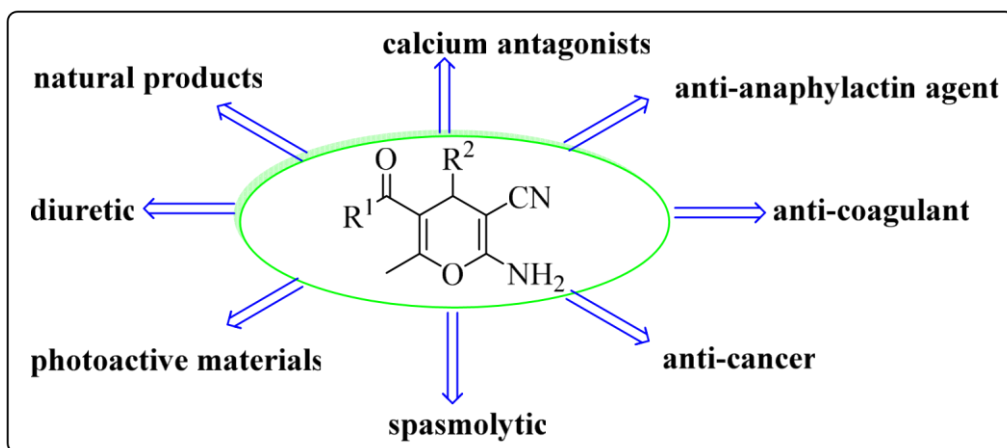


Figure 2: Applications of polyfunctionalized 4H-pyran

These substances serve various purposes, including functioning as anti-coagulants, acting as anticancer agents, providing spasmolytic effects, serving as antianaphylactic solutions, inhibiting insulin-regulated amino peptidase (IRAP) to boost memory and learning capabilities, and acting as antibacterial agents, among other applications. Moreover, 4H-pyrans that incorporate heterocyclic rings are being utilised more frequently due to their therapeutic properties. A variety of 4H-pyran derivatives have been synthesised and examined, including several 2-amino-4H-pyran derivatives that serve as effective photoactive substances.³⁻⁶ Compounds have demonstrated notable hypolipidemic effects and exhibited inhibitory activities against 5 α -reductase, respectively.⁷⁻⁸ Pyrans and benzocondensed derivatives form a fundamental structural component within a range of natural products (2-10, Figure 82).⁷⁻⁸ are commonly utilised in cosmetics, colouring agents, and are being explored as possible biodegradable agricultural chemicals.⁹⁻¹¹

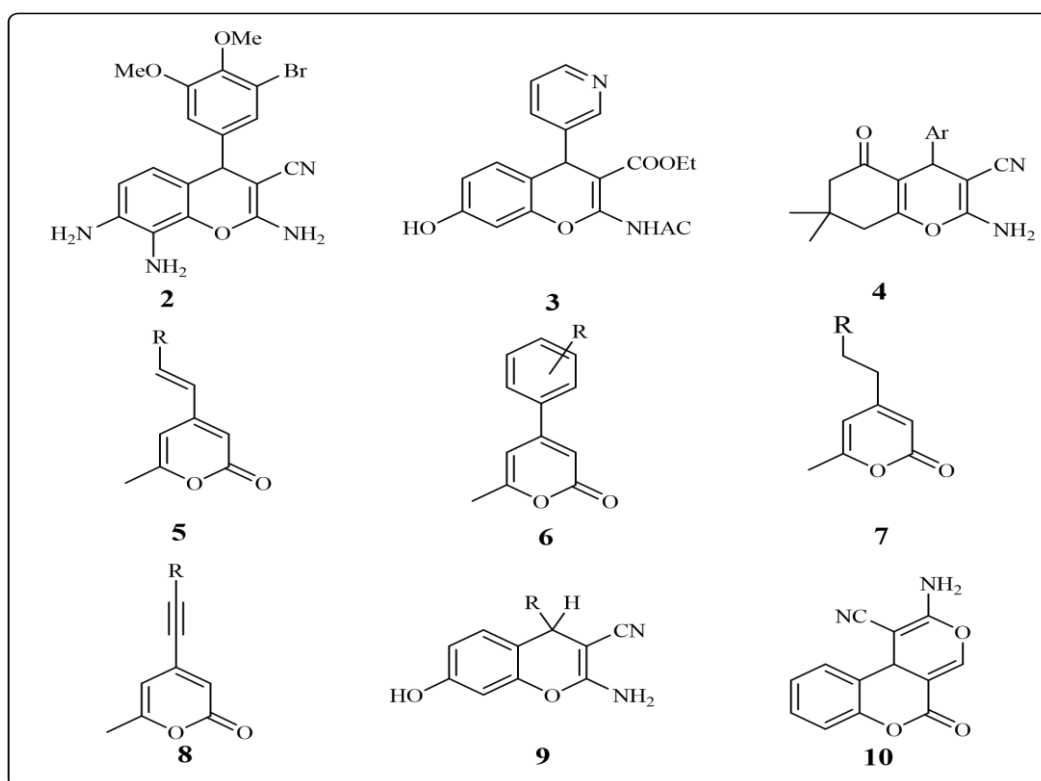


Figure 3: 4H-chromene derivatives of pharmacological and biological activity

Given the significant relevance of 4H-pyran and 2-pyridone derivatives, there is a revitalised focus on their extensive

appeal in the advancement of innovative methodologies for synthesising these compounds.

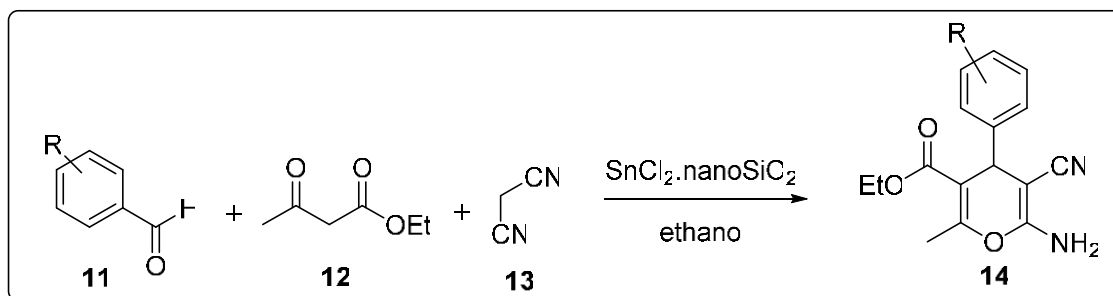
Reviews on Synthetic Approaches of Polyfunctionalized 4H-pyran derivatives.

Multi-component reactions (MCRs) have attracted considerable attention since they are performed without need to isolate any intermediate during their processes which reduces time as well as saves energy and raw materials.¹² These are superior to two component reactions in several aspects including the simplicity of a one-pot procedure, possible structural variations and building up complex molecules. Taking in to consideration these advantages, an efficient and convenient synthesis of poly functionalized 4H-pyrans can generally be carried out via a one-pot, three component condensation of an aromatic aldehyde, an active methylene compound and methyl acetoacetate or ethyl acetoacetate under influence of acidic/basic or phase transfer catalysts¹³ are reported in literature. The advantage of this multicomponent method over multistep synthesis is to achieve complex synthetic goals with maximum simplicity and brevity.¹⁴ some recent synthetic methods for these compounds are mentioned below

Javad Safaei-Ghomi et al Approach¹⁵

Javad Safaei-Ghomi and colleagues have successfully created a highly effective one-pot multicomponent synthesis through the reaction of substituted aromatic aldehydes, malononitrile, and ethyl acetoacetate, utilising nano silica supported tin (II) chloride as a catalyst.

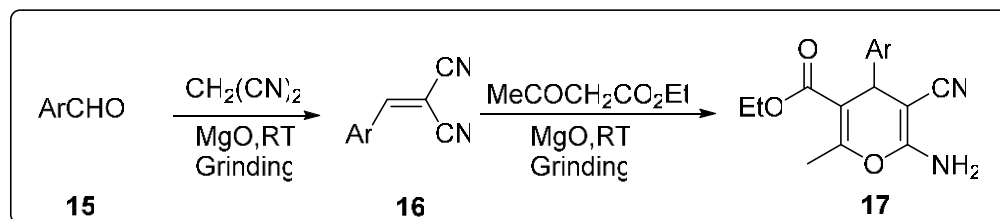
(Scheme 1)



Scheme 1: SnCl₂.nanoSiO₂ catalysed synthesis of substituted 2- amino, 3-cyano pyran derivatives.

Kumar et al Approach¹⁶

Kumar and colleagues have reported a highly effective method for the synthesis of 2-amino-4H-pyrans and 2-amino-5-oxo-5, 6, 7, 8-tetrahydro-4H-chromenes, achieved under solvent-free conditions with the utilisation of magnesium oxide as a catalyst. (Scheme 2)

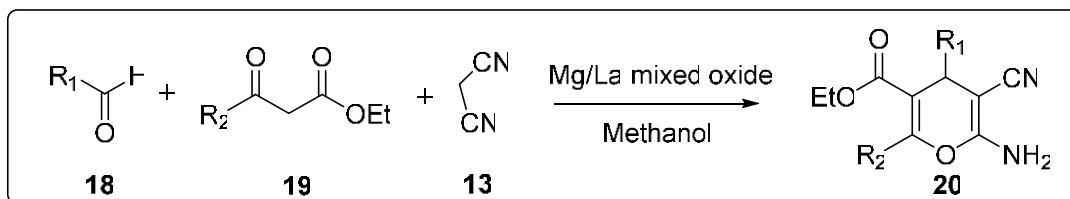


Scheme2: MgO catalysed synthesis of substituted 2- amino, 3-cyano pyran derivatives.

Seshu Babu et al Approach¹⁷

Seshu Babu et al., reported an efficient synthesis of polyfunctionalized 4H-pyrans is carried out in one pot through condensation of an aldehyde, malononitrile, and an active methylenic diketo compound using a heterogeneous strong

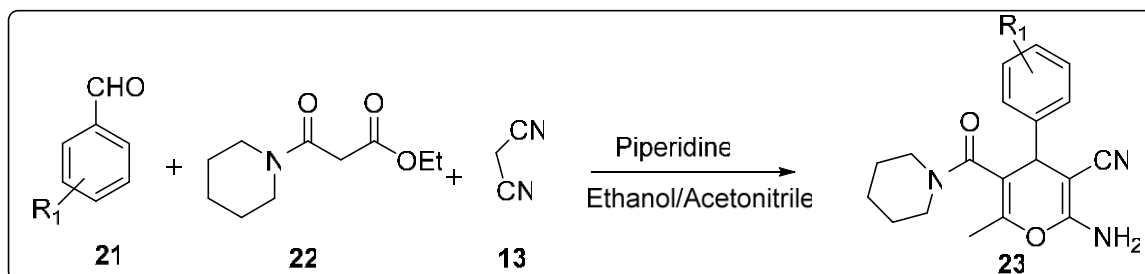
basic Mg/La mixed oxide catalyst. (Scheme 3)



Scheme 3: Mg/La mixed oxide catalysed synthesis of substituted 2- amino, 3cyano pyran derivatives.

Yadlapalli et al Approach¹⁸

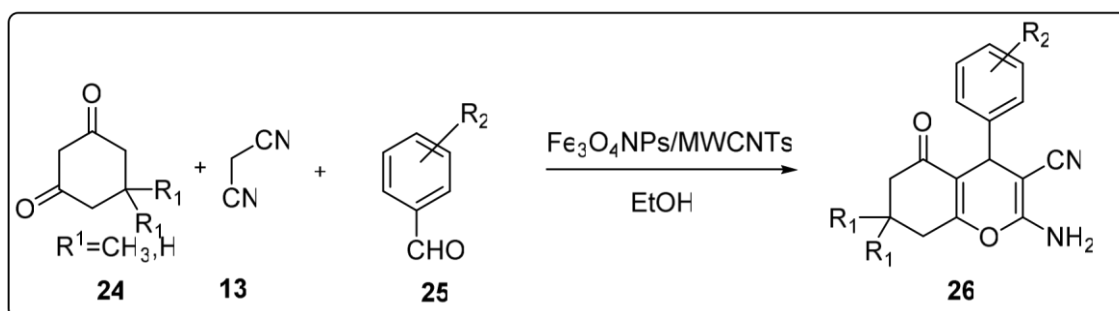
Yadlapalli et al., reported an efficient synthesis of one-pot multicomponent synthesis of aromatic aldehydes with CH acids, malononitrile and 1-(piperidin-1-yl) butane-1,3dione using piperidine as a catalyst. (Scheme 4)



Scheme 4: Piperidine catalysed synthesis of substituted 2- amino, 3-cyano pyran derivatives.

Abdollah Fallah-Shojaei et al Approach¹⁹

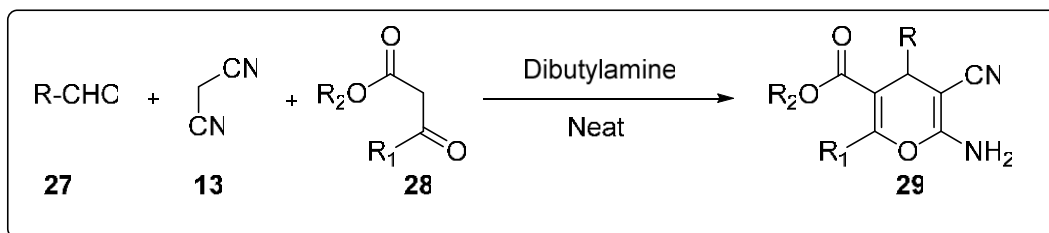
Abdollah Fallah-Shojaei et al., have developed as an efficient catalyst for the promotion of the synthesis of 4H-pyran derivatives via a one-pot multicomponent reaction of an substituted aldehyde, malononitrile and β -diketones using carbon nanotube supported Fe_3O_4 nanoparticles. (Scheme 5)



Scheme 5: Fe_3O_4 nanoparticles catalysed synthesis of substituted 2- amino, 3cyano pyran derivatives.

Kalla et al. Approach²⁰

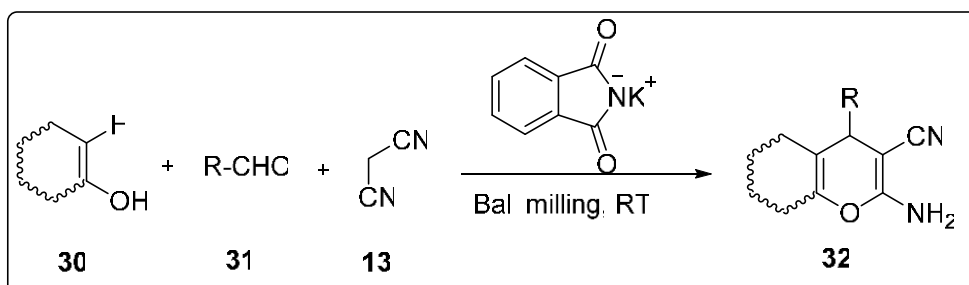
Kalla et al. have presented a convenient, environmentally sustainable, and effective method for synthesising innovative pyran derivatives. This approach involves a solvent-free, one-pot reaction utilising a range of aldehydes, malononitrile, and either methylacetoacetate or ethyl benzoylacetate, facilitated by dibutylamine at ambient temperature. (Scheme 6)



Scheme 6: Dibutylamine catalysed synthesis of substituted 2- amino, 3-cyano pyran derivatives.

Mohammad G. Dekamin et al., Approach²¹

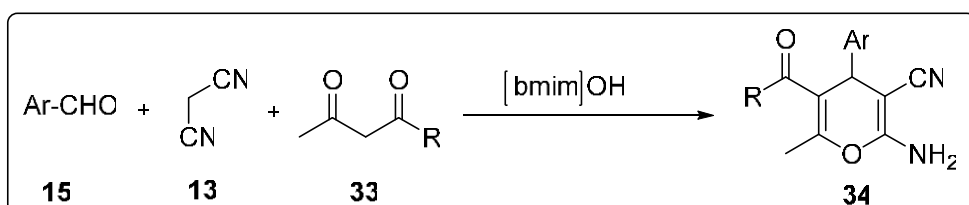
Mohammad G. Dekamin et al., has been described by the reaction of aryl aldehydes, malononitrile and diverse electron-rich phenolic or enolizable carbonyl compounds under mechanochemical ball milling conditions in the presence of potassium phthalimide, as a mild basic organocatalyst, at ambient temperature. (Scheme 7)



Scheme 7: potassium phthalimide (POPI) catalysed synthesis of substituted 2- amino, 3-cyano pyran derivatives.

Khurana et al. Approach²²

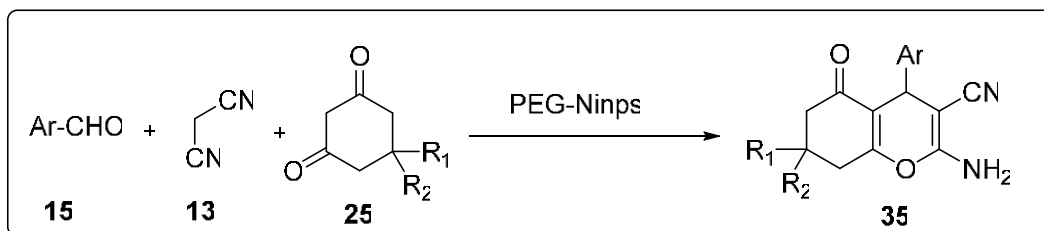
Khurana et al., has been described a facile and convenient procedure for the synthesis of 4H-pyrans from aldehydes, malononitrile, and ethyl acetoacetate/acetylacetone using [bmim]OH as task-specific ionic liquid. (Scheme 8)



Scheme 8: [bmim]OH catalysed synthesis of substituted 2- amino, 3-cyano pyran derivatives.

Khurana et al. Approach²³

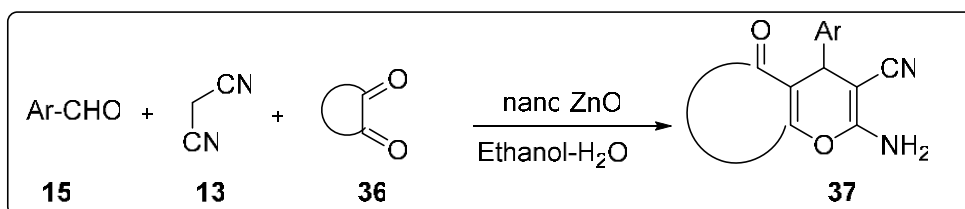
Khurana et al., has been reported an efficient route for the synthesis of 2- amino-4Hpyrans and pyran annulated heterocyclic moieties via one-pot tandem Knoevenagel– cyclocondensation of aldehydes, malononitrile, and carbocyclic/heterocyclic 1,3diones in the presence of stabilized nickel nanoparticles in ethylene glycol at room temperature. (Scheme 9)



Scheme 9: Nickel nanoparticles in ethylene glycol catalysed synthesis of substituted 2- amino, 3-cyano pyran derivatives.

Bhattacharyya et al. Approach²⁴

Bhattacharyya et al., has been reported A green and highly efficient protocol has been developed for the synthesis of 4H-pyran scaffolds installing a one-pot threecomponent coupling reaction of an aldehyde, malononitrile and a 1,3-diketo compound using nano structured ZnO as the catalyst in aqueous alcoholic medium.



Scheme 10: nano structured ZnO catalysed synthesis of substituted 2- amino, 3-cyano pyran derivatives.

We have reviewed above various methods for the synthesis of tetrahydrobenzopyrans, tetrahydrocyclopentapyrans, pyran annulated heterocycles and penta-substituted 4Hpyrans. All these compounds show a variety of biological activities besides other functions. In view of their importance and the fact that reported methods have their own merits and demerits, we decided to investigate another novel route for their synthesis.

The aim of the current research was to create a diverse catalyst for the effective synthesis of 2-substituted polyfunctionalized 4H-pyrans. A piperazine-functionalized polystyrene resin serves as an effective heterogeneous solid acid catalyst, allowing for straightforward handling and removal from the reaction mixture through simple filtration methods. Twenty-five to twenty-eight Driven by our continuous fascination with the role of heterogeneous catalysts in organic synthesis, we embarked on an exploration of polystyrene resin modified with a piperazine resin, aiming to synthesise a variety of substituted and fused 4H-pyran derivatives. A notable benefit of insoluble polymer catalysts lies in their straightforward retrieval from the reaction system, effectively mitigating the risk of harmful chemicals being discharged into the environment. Therefore, their increased utilisation could prove advantageous from an ecological perspective.

Conclusion:

In conclusion, the development of a piperazine-functionalized polystyrene resin as a heterogeneous catalyst provides a highly efficient, eco-friendly, and reusable platform for the synthesis of polyfunctionalized 4H-pyran derivatives. This method not only simplifies the reaction process through one-pot multicomponent condensation but also aligns with green chemistry principles by minimizing waste, avoiding harmful solvents, and enabling easy catalyst recovery. The synthesized compounds exhibit significant potential for pharmaceutical and industrial applications, affirming the versatility and sustainability of this catalytic system in modern organic synthesis.

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