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

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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.\(^13\)\(^-\)\(^18\)

![Figure 1. 2-Pyrones or α-pyrones](image-url)
4-Hydroxy-6-methyl-2-pyrene or triacetic acid lactone, which can be obtained from natural sources (plants and bacteria) or be synthetically produced from acetic acid,\textsuperscript{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-pyrene 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-pyrene in the synthesis of different types of heterocyclic compounds by multicomponent reactions.

In 1962, Williams and co-workers isolated 4-hydroxy-6-methyl-2-pyrene 1 from the urine of rabbits.\textsuperscript{20} Later, this compound was obtained from various synthetic routes. In 1975, Suzuki \textit{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-pyrene E in high yield. Compound E was finally decarboxylated to prepare 4-hydroxy-6-methyl-2-pyrene 1 (Scheme 1).\textsuperscript{21}
are also other reported synthetic routes for preparation of 2-pyrone derivatives.\textsuperscript{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 \textit{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).\textsuperscript{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 FeCl$_3$·6H$_2$O as the catalyst in 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim]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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Catalyst</th>
<th>Condition</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>EtOAc/EtOH</td>
<td>piperidine</td>
<td>60-70 °C</td>
<td>2-48</td>
<td>58-95$^{23,24}$</td>
</tr>
<tr>
<td>2</td>
<td>[bmim]BF$_4$</td>
<td>FeCl$_3$·6H$_2$O</td>
<td>80 °C</td>
<td>2-4</td>
<td>83-96$^{26}$</td>
</tr>
<tr>
<td>3</td>
<td>H$_2$O</td>
<td>-</td>
<td>MW</td>
<td>8-15 min</td>
<td>75-86$^{27}$</td>
</tr>
<tr>
<td>4</td>
<td>EtOH</td>
<td>-</td>
<td>78 °C</td>
<td>18</td>
<td>46$^{28}$</td>
</tr>
<tr>
<td>5</td>
<td>AcOH/EtOH</td>
<td>piperidine</td>
<td>70 °C</td>
<td>45-60 min</td>
<td>57-94$^{29}$</td>
</tr>
</tbody>
</table>

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)-2H-pyran-2-one 6 in 30 minutes and 4-hydroxy-6-methyl-3,5-bis((phenylthio)methyl)-2H-pyran-2-one 7 in 38 days at room temperature (Scheme 3).$^{30}$

\[
\begin{array}{cccc}
\text{RCHO} \text{ PhSH} & \text{OH} & \text{O} \\
\text{O} & \text{OH} & \text{SPh} \text{SPh} \\
\text{OH} & \text{O} & \text{SPh} \\
\end{array}
\]

\[
\begin{array}{cccc}
\text{AcOH} \text{ piperidine} & \text{OH} & \text{R} \\
\text{SPh} & \text{SpH} & \text{SPh} \\
\text{OH} & \text{O} & \text{SpH} \\
\end{array}
\]

\[
R= \text{H, n-Pr, n-C}_9\text{H}_{19}, 4-\text{ClC}_6\text{H}_4, 4-\text{MeOC}_6\text{H}_4
\]

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).$^{31}$
The multicomponent reaction of 4-hydroxy-6-methyl-2-pyrene 1 with aldehyde derivatives 2 and indole 10 was investigated to generate the gem-(β-dicarbonyl)arylmethanes 11 (Scheme 5). 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. Application of L-proline as a catalyst in this reaction was also reported by Brahmachari and Das (4 h, 75%), and Li et al. (4 h, 81%). Yamamoto et al. developed this reaction without any catalyst and obtained the products in good yields. A comparison of different catalysts and experimental setups is given in Table 2.

Table 2. Comparison of different conditions in the synthesis of gem-(β-dicarbonyl)arylmethanes 11 from 1

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Catalyst</th>
<th>Condition</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>A: CHCl₃</td>
<td>-</td>
<td>40 °C</td>
<td>6-24</td>
<td>18-75</td>
</tr>
<tr>
<td></td>
<td>B: CHCl₃/H₂O (1:1)</td>
<td>-</td>
<td>40 °C</td>
<td>24-72</td>
<td>12-59</td>
</tr>
</tbody>
</table>

R= 4-CF₃C₆H₄, 4-CNC₆H₄, 3,4-(MeO)₂C₆H₃

Scheme 4. Synthesis of pyrimidine compounds 9 from 1

Scheme 5. Proposed mechanism for the synthesis of gem-(β-dicarbonyl)arylmethanes 11 from 1
A piperidine, triton X-100 catalyzed three-component Mannich type reaction\textsuperscript{37} of 4-hydroxy-6-methyl-2-pyrone \textbf{1}, aldehyde derivatives \textbf{2} and secondary amine \textbf{12} was established in aqueous media and room temperature for the synthesis of novel 3-alkylated 4-hydroxypyrone derivatives \textbf{13} (Scheme 6).\textsuperscript{38} In another study, Shi \textit{et al.} employed \textit{L}-proline as a catalyst in this reaction and obtained the main product in 90\% yield.\textsuperscript{39} The catalyst-free condition was also used and the same products were achieved in 69-94\% yields.\textsuperscript{40}

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|c|}
\hline
   &  &  &  &  \\
2  & -  & \textit{L}-proline  & rt  & 4-5  & 83-96\textsuperscript{34} \\
3  & EtOH  & \textit{L}-proline  & 80 °C  & 4  & 81\textsuperscript{35} \\
4  & AcOH  & -  & 65 °C  & 10-20  & 87-90\textsuperscript{36} \\
\hline
\end{tabular}
\end{table}

\textbf{Scheme 6.} Synthesis of novel 3-alkylated 4-hydroxypyrone derivatives \textbf{13} from \textbf{1}

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

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|}
\hline
   &  &  &  \\
R\= H 84\%  &  &  &  \\
R\= NO\textsubscript{2} 87\%  &  &  &  \\
\hline
\end{tabular}
\end{table}

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

Kumar \textit{et al.} accomplished a catalyst-free multicomponent reaction containing 4-hydroxy-6-methyl-2-pyrone \textbf{1}, formaldehyde \textbf{2} and \textit{N},\textit{N}-dialkylaniline \textbf{16} in aqueous solution of LiCl at
room temperature to afford 3-alkylated 4-hydroxypyrone derivatives 17 in good yields (Scheme 8).\textsuperscript{42}

![Scheme 8. Synthesis of 3-alkylated 4-hydroxypyrone derivatives 17 from 1](image)

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 H\textsubscript{2}O as a green solvent in 3 hours (Scheme 9). This work was also reported by Sanchooli group.\textsuperscript{43}

![Scheme 9. Synthesis of α-benzylaminopyrones 18 from 1](image)

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).\textsuperscript{44}
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

3-(2-(4-Substituted phenyl)-2-oxo-1-(piperidin-1-yl)ethyl)-4-hydroxy-6-methyl-2H-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)-2H-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-2H-pyran-2,4(3H)-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)-2H-pyrandione 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-2H-pyran-3(4H)-ylidene)methyl)urea 35 as main product in good yield (Scheme 15). 49
Scheme 15. Synthesis of (E)-1-((6-methyl-2,4-dioxo-2H-pyran-3(4H)-ylidene)methyl)urea 35 from 1

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

Scheme 16. Synthesis of (Z)-3-(aminomethylene)-2H-pyran-2,4(3H)-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-pyrene 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-pyrene 1 with cyclohexyl isocyanide 40 and aldehyde derivatives 2 (Scheme 18).\textsuperscript{54} In other studies, Shaabani and Teimouri carried out this reaction in catalyst-free condition under microwave irradiation in 3 min (79-91% yields)\textsuperscript{55} and also in the presence of Montmorillonite K10 (70-81% yields).\textsuperscript{56}

![Scheme 18. Synthesis of furo[3,2-c]pyran-4-ones 41 from 1](image)

### 2.2.2. Five-membered heterocycles containing N atom

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

![Scheme 19. Synthesis of pyrroloquinoline 44 from 1](image)

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-pyrene 1, \(N\)-arylenaminones 45 and arylglyoxal monohydrates 26 promoted by AcOH under microwave irradiation (Scheme 20).\textsuperscript{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.\textsuperscript{59}
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.\textsuperscript{62} A plausible reaction mechanism was shown in Scheme 21. Initially, a Knoevenagel-type reaction\textsuperscript{60} takes place for the preparation of intermediate A which was reacted with thioamide 47 via thia-Michael addition\textsuperscript{61} to afford intermediate B. This intermediate subsequently undergoes cyclization by the elimination of H$_2$O to form desired product 48 (Scheme 21).\textsuperscript{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\textsubscript{2} as catalyst for the synthesis of 2,3-disubstituted imidazo[1,2-\textit{a}]pyridines \textit{49} when compound \textit{47} was replaced with 2-aminopyridine \textit{30} (Scheme 22).\textsuperscript{63} Replacement of arylglyoxals \textit{26} with aryl aldehyde \textit{2} in this reaction leads to the synthesis of \textit{N}-aryl(4-hydroxy-6-methyl-2-oxo-2\textit{H}-pyran-3-yl)methyl]thioacetamides \textit{50} in high yields (Scheme 23).\textsuperscript{64}

![Scheme 22. Synthesis of 2,3-disubstituted imidazo[1,2-\textit{a}]pyridines \textit{49} from 1](image)

\textbf{Scheme 22. Synthesis of 2,3-disubstituted imidazo[1,2-\textit{a}]pyridines \textit{49} from 1}

![Scheme 23. Synthesis of \textit{N}-aryl(4-hydroxy-6-methyl-2-oxo-2\textit{H}-pyran-3-yl)methyl]thioacetamides \textit{50} from 1](image)

\textbf{Scheme 23. Synthesis of \textit{N}-aryl(4-hydroxy-6-methyl-2-oxo-2\textit{H}-pyran-3-yl)methyl]thioacetamides \textit{50} from 1}

Li \textit{et al.} accomplished a meglumine-catalyzed one-pot three-component protocol for the synthesis of pyrazolylcoumarins \textit{52} from the reaction of 4-hydroxy-6-methyl-2-pyrole \textit{1}, salicylaldehydes \textit{2} and hydrazines \textit{51} in aqueous-ethanol media (Scheme 24).\textsuperscript{65} Various arylhydrazines bearing electron-donating groups and electron-withdrawing groups underwent the reaction with salicylaldehydes and 4-hydroxy-6-methyl-2-pyrole \textit{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.
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). 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 undergoes a Michael addition and elimination of the sulfur-containing group to give product 54.

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

**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). This reaction was also studied in the presence of piperidine as catalyst under reflux condition affording the related products in 79-95% yields. According to the mechanism of the reaction, the synthesis is likely initiated by TMGTF, which

\[
\begin{align*}
\text{OH} & \quad + \quad \text{O} \quad + \quad \text{O} \quad + \quad \text{O} \\
\text{O} \quad \text{O} & \quad \text{O} \quad \text{O} \quad \text{O} \quad \text{O} \\
1 & \quad 55 & \quad 2 \quad \text{TMGTF} \\
& \quad \text{rt, 30-55 min} \quad & \quad \text{Me} \quad \text{or} \quad \text{Me} \\
& \quad 56 & \quad 57 \quad 90\% \\
R & = 4-\text{MeOC}_6\text{H}_4, 2-\text{ClC}_6\text{H}_4, 3-\text{BrC}_6\text{H}_4, 4-\text{MeC}_6\text{H}_4, 4-\text{NO}_2\text{C}_6\text{H}_4, \text{thiophene-2-yl}, \text{Me, Et, } \text{^nPr, ^tBu}
\end{align*}
\]

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 trans lactonization 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](image)

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$_4$OAc 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](image)

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-2H-chromen-
2-one 63 to prepare chromeno[4,3-b]chromenone 64 (Scheme 29).\(^1\)

**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).\(^2\)

**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).\(^3\)

**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, 1H-pyrazole-4-carbaldehyde 68 and malononitrile 65 reacted in ethanol in the presence of a catalytic amount of piperidine (Scheme 32). 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(2H)-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 sulfonoyl 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).

Scheme 33. Synthesis of 7-methyl-2,2,4-triphenyl-3,4-dihydropyrano[4,3-b]pyran-5(2H)-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-1H-pyrazole-4-carbaldehyde 72 and malononitrile 65 was described by Vala and co-workers (Scheme 34).76

\[
\text{1} + \text{72} + \text{65} \rightarrow \text{73}
\]

\( \text{Ar} = \text{C}_6\text{H}_5, \text{4-FC}_6\text{H}_4, \text{4-ClC}_6\text{H}_4, \text{4-BrC}_6\text{H}_4 \)

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-4H-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.

\[
\text{1} + \text{2} + \text{65} \rightarrow \text{74}
\]

\( \text{R}^1 = \text{H, Me, Br, NO}_2, \text{Cl} \)

\( \text{R}^2 = \text{H, OMe, Cl} \)

Method A: NaOAc, EtOH, 30 min, rt, 85-96%

Method B: NaOAc or KF, grinding, 15 min, rt, 80-90%

Scheme 35. Synthesis of 2-amino-4H-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 7578 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
NH₄OAc,⁸⁶ Alum,⁸⁷ (CTA)₃[SiW₁₄]-Li-MMT,⁸⁸ nano-cellulose-OSO₃H,⁹⁹ nano CaO,⁹⁹ SBSA,⁹¹-⁹² NCS,⁹³ HCO₂Na/HCO₂NH₄,⁹⁴ DBU,⁹⁵ Et₃N,⁹⁶ PEG Ni-NPs,⁹⁷ BN@Fe₃O₄,⁹⁸ H₆P₂W₁₈O₆₂·18H₂O,⁹⁹ p-TSA,¹⁰⁰ ClSO₃H,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](image)

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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Catalyst</th>
<th>Condition</th>
<th>Time</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H₂O</td>
<td>Fe₃O₄@SiO₂/DABCO</td>
<td>80 °C</td>
<td>35-45 min</td>
<td>84-87%⁷⁹,⁸⁰</td>
</tr>
<tr>
<td>2</td>
<td>H₂O</td>
<td>-</td>
<td>80 °C</td>
<td>9.5-11 h</td>
<td>61-66%⁴¹</td>
</tr>
<tr>
<td>3</td>
<td>Et₂O</td>
<td>organocatalyst</td>
<td>rt</td>
<td>8 h</td>
<td>69-90%⁴²</td>
</tr>
<tr>
<td>4</td>
<td>-</td>
<td>NP-ZnO</td>
<td>rt</td>
<td>5 h</td>
<td>78-80%⁴³</td>
</tr>
<tr>
<td>5</td>
<td>-</td>
<td>NP-ZnO</td>
<td>rt</td>
<td>5 h</td>
<td>80%⁴³</td>
</tr>
<tr>
<td>6</td>
<td>EtOH</td>
<td>[18-C-6K] [OAc]</td>
<td>reflux</td>
<td>13-30 min</td>
<td>85-91%⁴⁵</td>
</tr>
<tr>
<td>7</td>
<td>-</td>
<td>NH₄OAc</td>
<td>rt</td>
<td>10-18 min</td>
<td>86-97%⁴⁶</td>
</tr>
<tr>
<td>8</td>
<td>H₂O</td>
<td>Alum</td>
<td>A: MW</td>
<td>A: 5-12 min</td>
<td>A: 79-95%</td>
</tr>
<tr>
<td>9</td>
<td>H₂O</td>
<td>(CTA)₃[SiW₁₄]-Li</td>
<td>reflux</td>
<td>15-20 min</td>
<td>85-96%⁴⁸</td>
</tr>
<tr>
<td>10</td>
<td>EtOH</td>
<td>nano-cellulose-OSO₃H</td>
<td>reflux</td>
<td>10 min</td>
<td>73-94%⁴⁹</td>
</tr>
<tr>
<td>11</td>
<td>-</td>
<td>nano CaO</td>
<td>120 °C</td>
<td>5-45 min</td>
<td>93-95%⁴⁹</td>
</tr>
<tr>
<td>12</td>
<td>-</td>
<td>SBSA</td>
<td>60 °C</td>
<td>1 h</td>
<td>88%⁹¹,⁹²</td>
</tr>
<tr>
<td>13</td>
<td>H₂O</td>
<td>NCS</td>
<td>rt</td>
<td>3 h</td>
<td>58%⁹³</td>
</tr>
<tr>
<td>14</td>
<td>H₂O</td>
<td>HCO₂Na/HCO₂NH₄</td>
<td>rt</td>
<td>1 h</td>
<td>65-86%⁴⁴</td>
</tr>
<tr>
<td>15</td>
<td>H₂O</td>
<td>DBU</td>
<td>reflux</td>
<td>10-15 min</td>
<td>86-90%⁴⁵</td>
</tr>
<tr>
<td>16</td>
<td>EtOH</td>
<td>Et₃N</td>
<td>reflux</td>
<td>5-10 min</td>
<td>62-92%⁴⁵</td>
</tr>
</tbody>
</table>
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-acenaphthylenecromene 77 was reported 
by Goli-Jolodar et al. (Scheme 37). DBU, amino-appended β-cyclodextrin (ACD) and 
β-cyclodextrin (β-CD) 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).

![Scheme 37. Synthesis of spiro-acenaphthylenecromene 77 from 1](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Catalyst</th>
<th>Condition</th>
<th>Time (min)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H₂O</td>
<td>C₄(DABCO-SO₃H)₂•4Cl</td>
<td>90 °C</td>
<td>15</td>
<td>97</td>
</tr>
<tr>
<td>2</td>
<td>H₂O</td>
<td>DBU</td>
<td>rt</td>
<td>25</td>
<td>76</td>
</tr>
<tr>
<td>3</td>
<td>H₂O</td>
<td>ACD</td>
<td>rt</td>
<td>7 h</td>
<td>87</td>
</tr>
<tr>
<td>4</td>
<td>H₂O</td>
<td>β-CD</td>
<td>rt</td>
<td>5 h</td>
<td>87</td>
</tr>
<tr>
<td>5</td>
<td>H₂O</td>
<td>-</td>
<td>80 °C</td>
<td>15</td>
<td>90</td>
</tr>
</tbody>
</table>

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). 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 K$_2$CO$_3$ as catalyst in the three-component reaction of compound 1, 3-formylchromone 80 and nitriles 65 in aqueous media (Scheme 39).

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 CuFe$_2$O$_4$ as nano-particle catalyst (Scheme 40). The synthesis of spirooxindole fused heterocycles 82 has been also reported under different conditions with several catalysts including *p*-TSA, *L*-proline, AcONa/KF, triethylamine, Ni-NPs, SSLP and sodium stearate. Some recent methods for the synthesis of corresponding products were compared in Table 5.
Table 5. Comparison of efficiency of various catalysts in synthesis of spirooxindole fused heterocycles 82

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Catalyst</th>
<th>Condition</th>
<th>Time (min)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H&lt;sub&gt;2&lt;/sub&gt;O</td>
<td>CuFe&lt;sub&gt;2&lt;/sub&gt;O&lt;sub&gt;4&lt;/sub&gt;</td>
<td>reflux</td>
<td>30</td>
<td>81-96</td>
</tr>
<tr>
<td>2</td>
<td>H&lt;sub&gt;2&lt;/sub&gt;O</td>
<td>p-TSA</td>
<td>reflux</td>
<td>24 h</td>
<td>73-94</td>
</tr>
<tr>
<td>3</td>
<td>H&lt;sub&gt;2&lt;/sub&gt;O</td>
<td>L-proline</td>
<td>80 °C</td>
<td>11-45</td>
<td>76-94</td>
</tr>
<tr>
<td>4</td>
<td>-</td>
<td>AcONa/KF</td>
<td>60-78 °C</td>
<td>1-15</td>
<td>67-95</td>
</tr>
<tr>
<td>5</td>
<td>EtOH</td>
<td>triethylamine</td>
<td>reflux</td>
<td>5</td>
<td>76</td>
</tr>
<tr>
<td>6</td>
<td>ethylene glycol</td>
<td>Ni-NPs</td>
<td>rt</td>
<td>10</td>
<td>90</td>
</tr>
<tr>
<td>7</td>
<td>H&lt;sub&gt;2&lt;/sub&gt;O</td>
<td>SSLP</td>
<td>80 °C</td>
<td>1 h</td>
<td>94</td>
</tr>
<tr>
<td>8</td>
<td>H&lt;sub&gt;2&lt;/sub&gt;O</td>
<td>sodium stearate</td>
<td>60 °C</td>
<td>3 h</td>
<td>89-93</td>
</tr>
</tbody>
</table>

4-Hydroxy-6-methyl-2-pyrone 1 was reacted with isatins 37 and phenylsulfonfylacetonitrile 83 in a one-pot reaction in EtOH using a novel basic ionic liquid (2-hydroxyethyl)ammonium acetate [H<sub>3</sub>N<sup>+</sup>CH<sub>2</sub>CH<sub>2</sub>OH][MeCO<sub>2</sub>]<sup>-</sup> (HEAA) as catalyst and some novel spiro-2-amino-3-phenylsulfonyl-4H-pyran 84 were obtained in high yields (Scheme 41).<sup>118</sup>
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). 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-4H-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). Teimouri’s group also performed this reaction in CH2Cl2 at room temperature to achieve the products in 58-72% yield.

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

Bis-2-amino-4H-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). In another study, Rao et al. used the Carbon–SO3H as a solid acid catalyst in this reaction.
Shikhaliev and co-workers applied a method for the synthesis of 4,4,6-trimethyl-4H-pyrrolo-[3,2,1-ij]quinoline-1,2-diones 92 based on the reaction of 4-hydroxy-6-methyl-2-pyrone 1, pyrroloquinolininediones 91 and malononitrile 65 in EtOH in the presence of N-methylpiperazine as catalyst (Scheme 45).  

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).

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). 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.

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).

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). In another study, H$_3$PW$_{12}$O$_{40}$@SiO$_2$ was used as catalyst in this reaction and related products were obtained in 70-95% yield.

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-10H-5,8-dioxabenzo[b]fluorene-9,11-dione derivatives 101 in excellent yields (Scheme 50). 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-10H-5,8-dioxabenzo[b]fluorene-9,11-diones 101 from 1](image)

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).
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). 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.

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(7H)-one 108 through two different procedures (Scheme 53).\textsuperscript{[133]}

\[
\begin{align*}
\text{OH} & + \text{PhClCHO} + \text{H}_2\text{N} & \text{N} \quad \text{Ph} \\
\text{1} & \text{2} & \text{106} & \text{108} \\
(a) & \text{AcOH-MeCN (1:5), reflux, 4 h, 55\%} \\
(b) & \text{AcOH-EtOH (1:20), reflux, 4 h, 64\%}
\end{align*}
\]

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

An efficient synthesis of a series of dihydropyrano[4,3-b]pyrazolo[4,3-e]pyridin-5(4H)-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 I\(_2\) in ethanol under reflux conditions through a one-pot reaction (Scheme 54).\textsuperscript{[134]}

\[
\begin{align*}
\text{OH} & + \text{C}=\text{O} + \text{N} \quad \text{R} \\
\text{1} & \text{2} & \text{109} & \text{110} \\
\text{I}_2 & \text{EtOH, reflux, 6 h, 78-90\%}
\end{align*}
\]

\(R=\text{H, 4-Cl, 4-Br, 4-NO}_2\), 4-OME, 4-OH

\textbf{Scheme 54.} Synthesis of dihydropyrano[4,3-b]pyrazolo[4,3-e]pyridin-5(4H)-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).\textsuperscript{[135]}

\[
\begin{align*}
\text{OH} & + \text{C}=\text{N} \quad \text{R} \quad \text{H}_2\text{O, 70 °C, 12 h} \\
\text{1} & \text{111} & \text{112} & \text{113} \\
\text{R= tBu, cyclohexyl, 1,1,3,3-Me}_4\text{Bu}
\end{align*}
\]

\textbf{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 enamiones 115 for the preparation of functionalized benzo[b][1,8]naphthyridine derivatives 116 in good yields (Scheme 56).\textsuperscript{136} It was found that phenyl groups bearing either electron-withdrawing or electron-donating groups on the enamione 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](image)

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).\textsuperscript{137}

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

Rakib \textit{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).\textsuperscript{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).

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(1H)-one 125 in 96% yield (Scheme 60).
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-pyrones 1, isatins 37 and 2-aminobenzothiazoles 126 (Scheme 61). In another study, the same authors used the sulfamic acid as catalyst in this reaction (25-30 min, 90-93%). Furthermore, SFIL/H2O was also used as catalyst and resulted in the formation of related products in 89-94% yield.

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-pyrones 1, o-phthalaldehyde (OPA) 2, and enaminones 45 and or 128 in HOAc as solvent under microwave irradiation (Scheme 62). 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.
Mehrparvar 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/H$_2$O 1:1) in the presence of triethylamine to construct the products containing chromone skeletons 132 (Scheme 63).

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-2H-pyran-3-yl)propanamides 133 (Scheme 64). 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-2H-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).

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-pyrene 1, pyridinium ylide 136, aromatic aldehydes and 2-hydroxy aromatic aldehydes 2 in the presence of triethylamine as catalyst (Scheme 66). 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 1H-benzo[g]chromene-2,5,10-triones 139 (Scheme 67).
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). 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
arylarnines 30 under reflux condition in ethanol (Scheme 70).\textsuperscript{151}

\begin{equation}
\text{OH} + \text{OH} + \text{CO}_2\text{R}^1 + \text{H}_2\text{N}-\text{R}^2 \xrightarrow{\text{EtOH, reflux, 1-3 h}} 75-88\% \text{ yield}
\end{equation}

\text{R}^1 = \text{Me, Et}
\text{R}^2 = 4-\text{MeC}_6\text{H}_4, 4-\text{ClC}_6\text{H}_4, 4-\text{BrC}_6\text{H}_4, 4-\text{Me}-3-\text{ClC}_6\text{H}_3

\textbf{Scheme 70.} Synthesis of pyrrole derivatives 142 from 1

Kumar Arya \textit{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 spiropyano[3,4-b]-5,3'-indolinetrione 143 in 91\% yield (Scheme 71).\textsuperscript{152}

\begin{equation}
\text{OH} + \text{H}_2\text{O} + \text{N} = \text{S} + \text{O} + \text{OH} \xrightarrow{\text{sulfamic acid}} 91\% \text{ yield}
\end{equation}

\textbf{Scheme 71.} Synthesis of spiropyano[3,4-b]-5,3'-indolinetrione 143 from 1

\textbf{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-cycloextrin
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

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REFERENCES


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