Application of Arylglyoxals in Synthesis of Pyrrolo[2,3-d]pyrimidines via Multicomponent Reactions

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Abstract: This review provides an overview of the recent literature on application of arylglyoxals in the synthesis of pyrrolo[2,3-d]pyrimidines via multicomponent reactions in the period of 2008–2018. 1,2-Dicarbonyl compounds are attractive precursors for synthesis of various heterocyclic compounds, and arylglyoxals are frequently applied in synthesis of various organic compounds, and in particular of pyrrolo[2,3-d]pyrimidines derivatives, which are important due to their biological and pharmaceutical activities.

Keywords: Arylglyoxals, Pyrrolo[2,3-d]pyrimidines, Multicomponent reactions, Enamines

Biography: Ramin Javahershenas was born in Iran, in 1971. He received his B.Sc. degree in Applied Chemistry from Tabriz University, Tabriz, Iran, in 1993, his M.Sc. degree in Organic Chemistry from the Urmia University, Urmia, Iran, under the supervision of Professor Naser Ardabilchi in 1999 and his Ph.D. degree in Organic chemistry from Urmia University, Urmia, Iran under the supervision of Professor Jabbar Khalafy, in 2017. His research interests include organic synthesis, heterocyclic synthesis, asymmetric synthesis, natural products synthesis, synthetic methodology and applications of various catalysts in multicomponent reactions.
1. Introduction

There is a worldwide demand for design and preparation of heterocyclic compounds by reactions with more than two components, by forming more than one carbon-carbon or carbon-heteroatom bond by environmentally and economically useful one-pot procedures, usually referred to as multicomponent reactions (MCRs). These have been proved to be powerful synthetic methods for the synthesis of polycyclic heterocycles with pharmaceutical and biological activities [1-7]. More than 70% of drugs in common use are now synthetic heterocyclic compounds [8-12].

MCRs have many advantages in comparison with classical reactions, such as fewer isolation and purification steps, with high atom-economy, low cost and energy consumption, short reaction time, using green solvents, high selectivity, environmentally friendly chemical processes, easy operation and more productivity with excellent chemo- and regio-selectivities [13-23].

1,2-Dicarbonyl compounds are among the most attractive precursors for the design and synthesis of heterocyclic compounds. Arylglyoxals (AG) are aromatic α-keto aldehydes containing both aldehyde and ketone functional groups with different reactivity, and recently there has been a considerable literature on different reactions of AGs and their derivatives, such as alkylation [24], arylation [25], reductive amination [23], reductive coupling with dienes [27], Wittig [28], Cannizzaro [29], Mannich [30] and Henry [31] reactions. The main purpose of this short review is to show the application of AGs as precursors in reactions that lead to the synthesis of the pyrrolo[2,3-d]pyrimidine derivatives via multicomponent reactions in the period of 2008–2018.

Recently, fused-pyrimidine derivatives have received considerable attention due to their biological and pharmacological activities such as anti-AIDS [32], antifungal [33], antileishmanial [34], tuberculostatic [35], antimicrobial [36], antitumor [37], sedative [38], anti-inflammatory [39], antioxidant [40], analgesic [41] antiviral [42] anesthetic [43], acaricidal [44], anticancer [42], and antifolate [43]. These compounds are present in nucleosides such as pyrimidines, cytosine, uracil, guanine, thymine and purine adenine and their respective polymers, DNA and RNA [45,48].

![Scheme 1. Structures of few medicinally heterocyclic fused pyrimidines](image)
As the natural bases do not have any fluorescence, several groups have been attached or the base itself has been modified [49,50]. Although these heterocyclic compounds have been known since the middle of the twentieth century [51,52], they were not extensively studied until the last few decades. More recently, the interest of the chemical and pharmaceutical industry in heterocyclic fused pyrimidines, also named deazapurines, has increased notably, resulting in a large increase in the number of patents, research papers, and reviews, all of which led to the introduction of several drugs in the market or late clinical stages (Scheme 1) [53-54].

1.1. Arylglyoxals
Phenylglyoxal (PG), the simplest member of this family, is a yellow liquid that polymerizes upon standing. Upon heating, it loses a molecule of water and the polymeric material changes to the aldehyde form or anhydrous AG. To form the colorless crystalline hydrate, PG should be recrystallized in hot water. The AG-hydrate appears to contain one molecule of water (Scheme 2).

AGs contain aldehyde and ketone functional groups with different reactivity, the reactivity of the aldehyde group is greater than that of benzaldehyde because of the electron-withdrawing keto group and reacts quickly with different nucleophiles, the resulting product then undergoing cyclization in a number of ways. The resulting products have received considerable attention due to their biological and pharmacological activities, such as selective bronchodilators such as salbutamol and terbutaline, used for their selective and antiviral activity in the embryonated egg against several viruses, including influenza (PR-8) and newcastle disease (NJKD strain) viruses [55-57].

Table 1. Various methods for the synthesis of AGs

<table>
<thead>
<tr>
<th>Entry</th>
<th>Method</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Oxidation of aryl methyl ketones</td>
<td>SeO₂, dioxane-water, reflux</td>
</tr>
<tr>
<td></td>
<td></td>
<td>H₂SeO₃, dioxane-water, reflux, 4 h</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SeO₂, EtOH, 10% HNO₃(aq), 90 °C, 1h</td>
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<tr>
<td></td>
<td></td>
<td>(PhSe)₂, (NH₄)₂S₂O₅, MeOH, reflux, 1~4h</td>
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<td></td>
<td></td>
<td>48% HBr(aq), DMSO, 55 °C, 0.5–24 h</td>
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<td>DMSO, rt, 9 h</td>
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<tr>
<td>2</td>
<td>Oxidation of phenacyl bromides</td>
<td>α-picoline n-oxide, 0 °C, then Na₂CO₃, water</td>
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<tr>
<td></td>
<td></td>
<td>Et₂NOH, MeOH, reflux, 2 h</td>
</tr>
<tr>
<td>3</td>
<td>Oxidation of phenacyl nitrate esters</td>
<td>NaOAc·3H₂O, DMSO, 20-25 °C, 25-55 min</td>
</tr>
<tr>
<td>4</td>
<td>Oxidation of α-diazo ketones</td>
<td>DMDO, acetone, rt</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(HMPA)MoO(O₂), Hg(OAc)₂, DCE-MeOH, 0 °C, 15 min</td>
</tr>
<tr>
<td>5</td>
<td>Oxidation of aryl acetylenes</td>
<td>NBS, dry DMSO, rt, 20 h</td>
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<tr>
<td></td>
<td></td>
<td>(PhSe)₂, (NH₄)₂S₂O₅, water-CH₃CN, 60 °C, then chromatographed on SiO₂, DCM-ROH (99/1)</td>
</tr>
<tr>
<td>6</td>
<td>Reaction of methyl benzoates with KDMSO then oxidation</td>
<td>(1) DMSO, KOt-Bu, t-BuOH, rt, 4 h, then HCl, water, rt, 30 h</td>
</tr>
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<td></td>
<td></td>
<td>(2) Cu(OAc)₂·H₂O, CHCl₃, rt, 1 h</td>
</tr>
<tr>
<td>7</td>
<td>Reaction of organolithium compounds with diethoxyacetylpiperidine</td>
<td>piperidine-1-yl-COCH(OEt)₂, Ether, reflux, 2h, then HCl, water, N₂(atm.), rt, 41 h</td>
</tr>
<tr>
<td>8</td>
<td>Chlorination of aryl methyl ketones</td>
<td>1,3-Cl₂-5,5-Me₂-hydantoin, Cu(OTf)₂, CHCl₃, reflux, 5~8 h</td>
</tr>
</tbody>
</table>

1.2. Synthesis of Arylglyoxals
Various methods have been reported for synthesis of AGs in the literature. One of the most important methods for their preparation is by oxidation of aryl methyl ketones by SeO₂. A compilation of methods to synthesize AGs, along with experimental procedures are summarized in Table 1.
1.3. Pyrrolo[2,3-d]pyrimidine derivatives

Considerable effort has been made to synthesize a series of pyrrolo[2,3-d]pyrimidines and their derivatives, to optimize yield and purity. The major synthetic schemes are summarized in (Scheme 3) [55].

Quiroga and his coworkers reported the formation of several unexpected pyrrolo[2,3-d]pyrimidine derivatives 5 by a one-pot, three-component reaction of aminopyrimidines 3 or 4 with dimedone 2, and arylglyoxals 1 (Scheme 4) [76].

Shaker and his group designed the synthesis of new pyrrolo[2,3-d]pyrimidine-2,4-diones 8 or pyrimido[5,4-b]quinoline2,4,9(1H,3H,5H)-triones 9 by reaction of 5-aminouracil 3, dimedone 2 or barbituric acid 7 with phenylglyoxal hydrate 1 in DMF under controlled microwave heating for 20 min at 160 °C (Scheme 5) [77].

Rad-Moghadam investigated the synthesis of the oxindolylpyrrolo[2,3-d]pyrimidines 13, by a three-component reaction of the model substrates 6-aminomethyluracil 3 and acetophenone 11 instead of AG, the best yield of the product being obtained by the sequential use of piperidine (10 mol %) and p-toluenesulfonic acid (p-TSA, 40 mol %) in refluxing ethanol at 80 °C, which afforded the products 13 in good yields (Scheme 6) [78].

In another study, Azimi and his coworkers developed the synthesis of 1,3-dimethyl-5-(2-oxindolin-3-yl)-6-phenyl-1H-pyrrolo[2,3-d]pyrimidine-2,4(3H,7H)-dione analogues 15 under various reaction conditions and catalysts, by the reaction of acetophenone 11 and isatin 12 and 6-amino-1,3-dimethyluracil 3 as a model reaction (Scheme 7) [79].

Dommaraju and coworkers developed a methodology based on a two-step sequence using 4-methoxy-aniline 16, 1,3-dimethyl barbituric acid 7 and 4-methyl phenylglyoxal 1 with 1,3-indanedione 17 or dimedone 2 or 2-hydroxy-1,4-naphtaquinone 18 or 6-aminouracil 3 in equimolar quantities into a one-pot reaction in ethanol (Scheme 8) [80].
Naidu and co-workers reported the use of microwave irradiation for the three component reaction of N,N-dimethyl-6-aminouracil, phenylglyoxal, and aniline at 100 °C for 5 min, achieving an excellent yield of 84% when acetic acid was used as a solvent, without any added catalyst (Scheme 9) [81].

Choudhury’s group synthesized pyrrolo[2,3-d]pyrimidine derivatives by the reaction of phenylglyoxal, 6-aminocoumarin, and malononitrile or malononitrile under microwave heating conditions (Scheme 10) [82].

Yadav and co-workers reported a one-pot, four component biomimetic protocol for the synthesis of pyrrolo[2,3-d]pyrimidine for the first time, by employing 6-aminouracil, malononitrile, and arylglyoxal monohydrates in aqueous β-cyclodextrin (Scheme 11) [83].
In another study, Javahershenas and Khalafy reported an efficient procedure for the reaction of arylglyoxals 1 with 6-amino-1,3dimethyluracil 3 and barbituric acid derivatives 5 in the presence of TBAB (5 mol%) in ethanol at 50 °C, affording polyfunctionalized pyrrolo[2,3-d]pyrimidine derivatives 31 in high yields with no sign of any dihydropyrido[2,3-d:6,5-d']dipyrimidine derivatives 32 (Scheme 15) [87].

The new indole derivatives pyrrolo[2,3-d]pyrimidine 33 have been synthesized from arylglyoxals 1 with 6amino-uracil derivatives 5 and 5-methyl-2,4-dihydro-3H-pyrazol-3-one derivatives 28 in the presence of sulfamic acid as an efficient catalyst by Bayat and coworkers (Scheme 16) [88].

Khalafy and coworkers used TPAB as catalyst in the reaction between 1,4-phenylene-bis-glyoxal 35, 6aminouracil derivatives 3, and barbituric acid derivatives 5 or dimedone 2 in a one-pot, three-component reaction in EtOH under reflux conditions for the synthesis of bis-pyrrolo[2,3-d]pyrimidine derivatives 36 and 37 in high yields (Scheme 17) [89].

2. Conclusion

This study presented an overview of the recent literature on the application of the arylglyoxals for synthesis of the pyrrolo[2,3-d]pyrimidines via multicomponent reactions over the last decades. In the light of our studies, we found that, arylglyoxals have been frequently utilized for synthesis of various organic compounds including, pyrrolo[2,3-d]pyrimidine derivatives, which are influential because of their biological and medicinal characteristics.

Acknowledgment

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\[ p\text{-TsOH} \quad p\text{-toluenesulfonic acid} \\
rt \quad \text{room temperature} \\
TBAB \quad \text{tetrabutylammonium bromide} \\
TPAB \quad \text{tetrapropylammonium bromide} \\
\]

References


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