Journal of Chemical Reviews, 2019, Volume 1, Issue 3, Pages 233-242

Short Review Article

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

Ramin Javahershenas [a,*], **Jabbar Khalafy** [a], **Rolf Herman Prager** [b]

[a] *Faculty of Chemistry, Urmia University, Urmia, Iran*
[b] *Department of Chemistry, Flinders University, Adelaide, Australia*

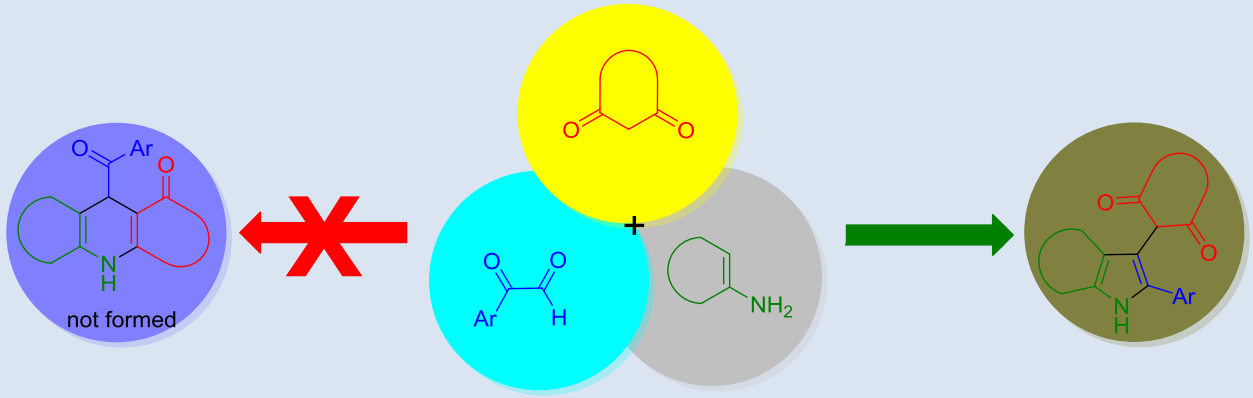
Receive Date: 18 July 2019, **Revise Date:** 20 July 2019, **Accept Date:** 25 July 2019

Abstract:
This review provides an overview of the recent literature on application of arylglyoxals 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.

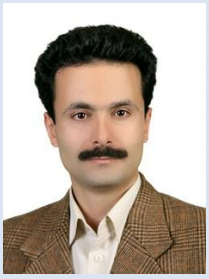
DOI: 10.33945/SAMI/JCR.2019.3.4

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

Graphical Abstract:



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.

*Corresponding author: Ramin Javahershenas, Email: jshbco@yahoo.com

Jabbar Khalafy was born in Iran, in 1952. He received his B.Sc. degree in Chemistry from Tabriz University, Tabriz, Iran, in 1975, his M.Sc. degree in Organic Chemistry from Manchester University, Manchester, England, in 1977 and his Ph.D. degree in Organic Chemistry from Manchester University, Manchester, England under the supervision of Professor J.M. Bruce, in 1979. He is Full Professor in the faculty of Chemistry at Urmia University, Urmia, Iran. His research interests include organic synthesis, heterocyclic synthesis, asymmetric synthesis, natural products synthesis, FVP, synthetic methodology and applications of various catalysts in multicomponent reactions.

Rolf Herman Prager was born in Australia, in 1937, and is a graduate of the University of Sydney and Imperial College, London. He is now Emeritus Professor in Chemistry at Flinders University, Adelaide. He has published widely in the fields of natural products, structure determination and synthesis, and in medicinal chemistry, particularly associated with pain relief.

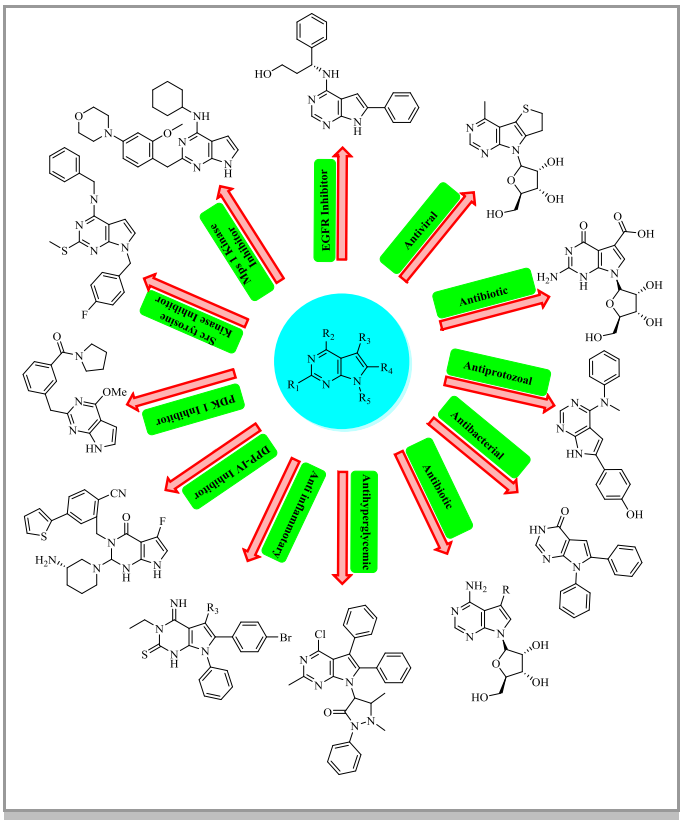
1. Introduction

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 allylation [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].

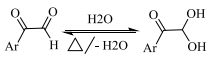


Scheme 1. Structures of few medicinally heterocyclic fused pyrimidines

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).



Scheme 2. Structures of Arylglyoxals

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

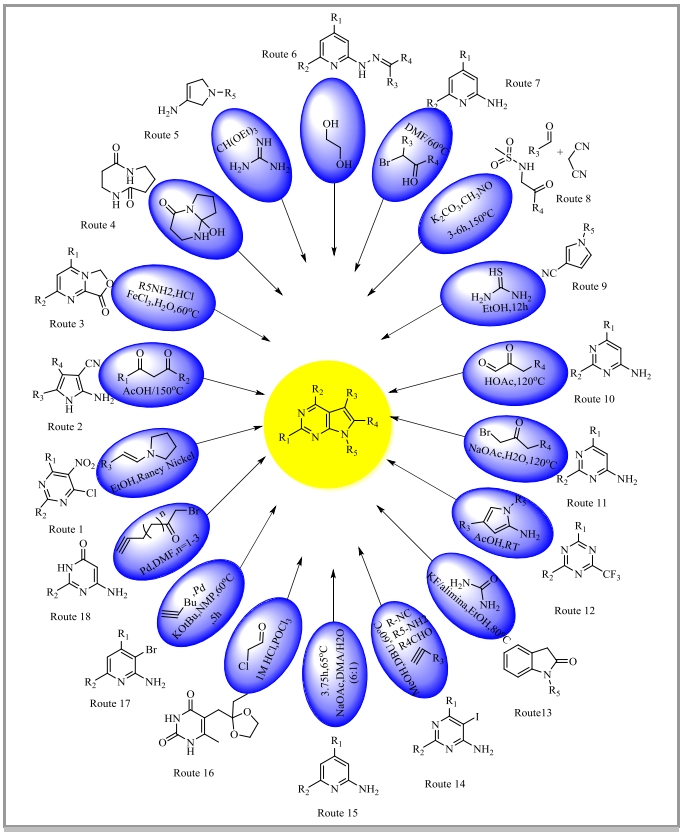
Entry	Method	Condition	Ref.
1	Oxidation of aryl methyl ketones	SeO_2, dioxane-water, reflux	[56], [58-61]
		H_2SeO_3, dioxane-water, reflux, 4 h	[62]
		SeO_2, EtOH, 10% HNO_3(aq), 90 °C ,1h	[63]
		$(PhSe)_2$, $(NH_4)_2S_2O_8$, MeOH, reflux, 1−4h	[64]
		48% HBr (aq), DMSO, 55 °C, 0.5−24 h	[65]
2	Oxidation of phenacylbromides	DMSO, rt, 9 h	[66]
		α-picoline n-oxide, 0 °C, then Na_2CO_3, water	[67]
		Et_2NOH, MeOH, reflux, 2 h	[68]
3	Oxidation of phenacyl nitrate esters	$NaOAc·3H_2O$, DMSO, 20-25 °C, 25-55 min	[69]
4	Oxidation of α-diazo ketones	DMDO, acetone, rt	[70]
5	Oxidation of aryl acetylenes	(HMPA)$MoO(O_2)$, $Hg(OAc)_2$, DCE-MeOH,0 °C, 15 min	[71]
		NBS, dry DMSO, rt,20 h	[72]
		$(PhSe)_2$, $(NH_4)_2S_2O_8$, water-CH_3CN, 60 °C,then chromatographed on SiO_2, DCM-ROH (99/1)	[73]
6	Reaction of methyl benzoates with KDMSO then oxidation	(1) DMSO, KOt-Bu, t-BuOH, rt, 4 h, then HCl, water, rt, 30 h (2) $Cu(OAc)_2·H_2O$, CHCl3, rt, 1 h	[74]
7	Reaction of organolithium compounds with diethoxyacetylpiperidine	piperidine-1-yl-$COCH(OEt)_2$, *p*-Me_2NC_6HLi, Ether, reflux, 2h,then HCl, water, N_2(atm.), rt, 41 h	[56]
8	Chlorination of aryl methyl ketones	1,3-Cl_2-5,5-Me_2hydantoin, $Cu(OTf)_2$, $CHCl_3$, reflux, 5−8 h	[75]

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 SeO_2. A compilation of methods to synthesize AGs, along with experimental procedures are summarized in Table 1.

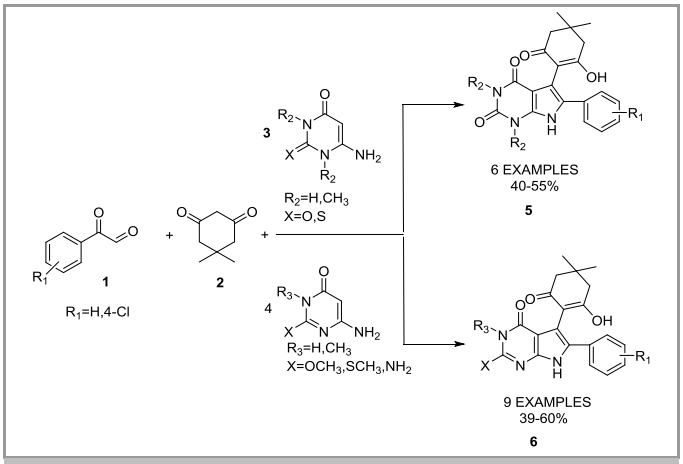
1.3. Pyrrolo[2,3-d]pyrimidine derivatives

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



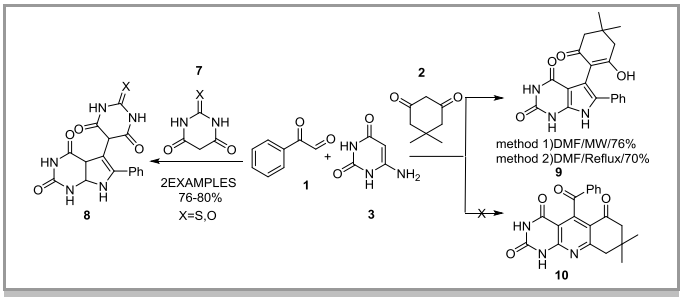
Scheme 3. Various synthetic schemes of Pyrrolo[2,3-*d*]pyrimidine derivatives

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].



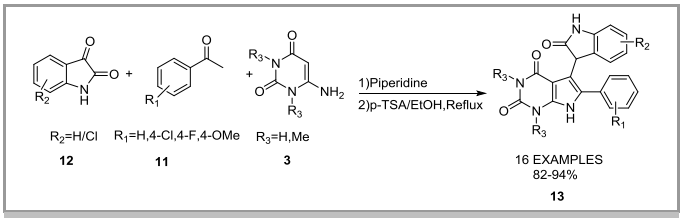
Scheme 4. Generation of pyrrolo[2,3-*d*]pyrimidines via multicomponent reaction of 6-aminopyrimidines, dimedone, and arylglyoxal

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(1*H*,3*H*,5*H*)-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].



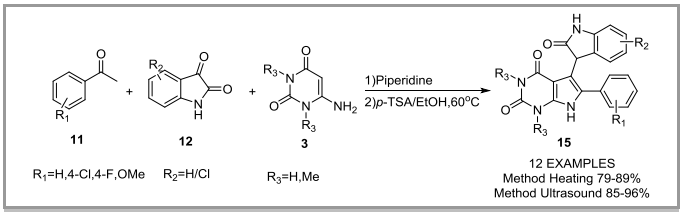
Scheme 5. One-pot Synthesis of 1H-Pyrrolo[2,3-*d*]pyrimidine-2,4(3*H*,7*H*)-dione Derivatives Using Controlled Microwave Heating

Rad-Moghadam investigated the synthesis of the oxindolylpyrrolo[2,3-*d*]pyrimidines **13**, by a three-component reaction of the model substrates 6-amino-1,3-dimethyluracil **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].



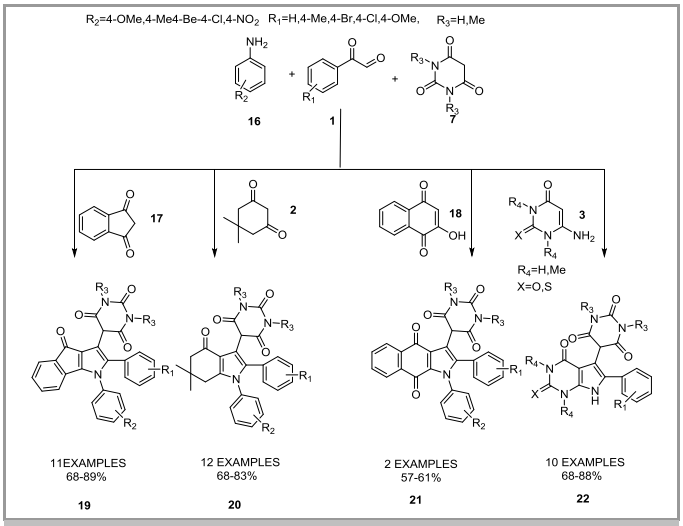
Scheme 6. Synthesis of oxindole substituted pyrrolo[2,3-*d*]pyrimidines under ultrasound irradiation

In another study, Azimi and his coworkers developed the synthesis of 1,3-dimethyl-5-(2-oxoindolin-3-yl)-6-phenyl-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4(3*H*,7*H*)-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].



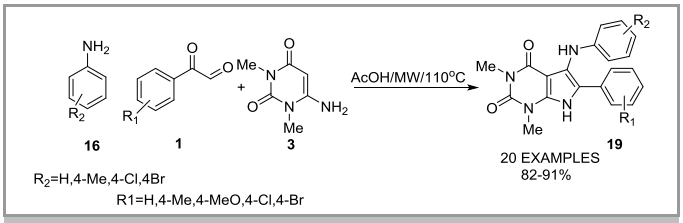
Scheme 7. Synthesis of bis-pyrrolo[2,3-*d*]pyrimidine derivatives with isatin

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].



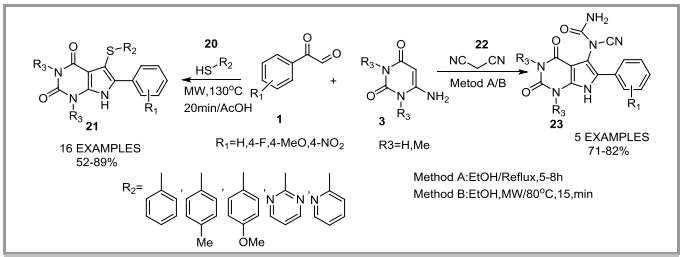
Scheme 8. Catalyst-free Multicomponent Reaction for the Synthesis of Pyrimidine Functionalized Pyrrolo-annelated Derivatives

Naidu and co-workers reported the use of microwave irradiation for the three component reaction of N,N-dimethyl-6-aminouracil **3**, phenylglyoxal **1**, and aniline **16** 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].



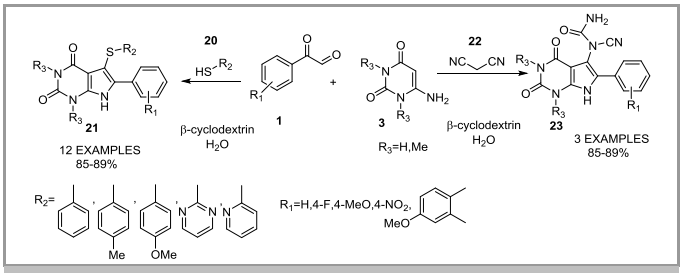
Scheme 9. Synthesis of bis-pyrrolo[2,3-*d*]pyrimidine derivatives under MW irradiations

Choudhury's group synthesized pyrrolo[2,3-*d*]pyrimidine derivatives **21** and **23** by the reaction of phenylglyoxal 1, 6-amino-1,3-dimethyluracil **3** and 2-mercaptopyrimidine **20** or malononitrile **22** under microwave heating conditions (Scheme 10) [82].



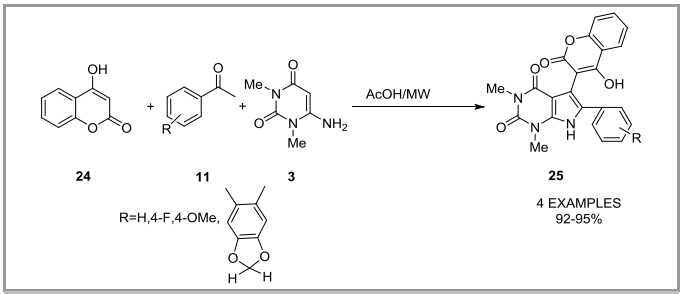
Scheme 10. Synthesis of Novel 5,6-Disubstituted Pyrrolo [2,3-*d*]Pyrimidine-2,4-Diones via One-Pot

Yadav and co-workers reported a one-pot, four component biomimetic protocol for the synthesis of pyrrolo[2,3-*d*]pyrimidine **23** for the first time, by employing 6-aminouracil **3**, malononitrile **22** and arylglyoxal monohydrates **1** in aqueous β-cyclodextrin (Scheme 11) [83].



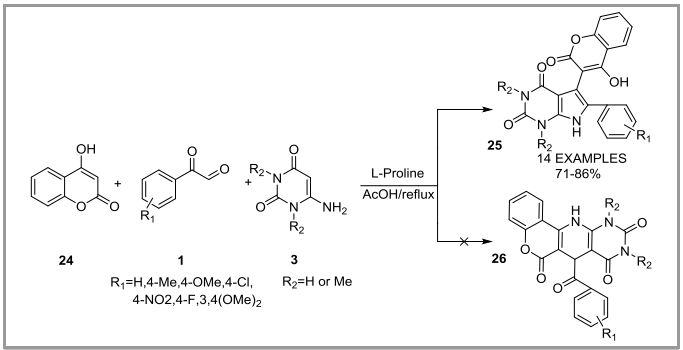
Scheme 11. Synthesis of Pyrrolo [2,3-*d*]Pyrimidine-2,4-Diones via One-Pot Three-Component Reactions

A simple and efficient method for the synthesis of a series pyrrolo[2,3-*d*]pyrimidine derivatives **25** with excellent yields was reported by Choudhury and co-workers. The reaction was performed between acetophenone **11** instead of AG **1**, 4-hydroxycoumarin **24**, and 6-aminouracil **3** under MW conditions in AcOH for the synthesis of to pyrrolo[2,3-*d*]pyrimidine derivatives **25** (Scheme 12) [84].



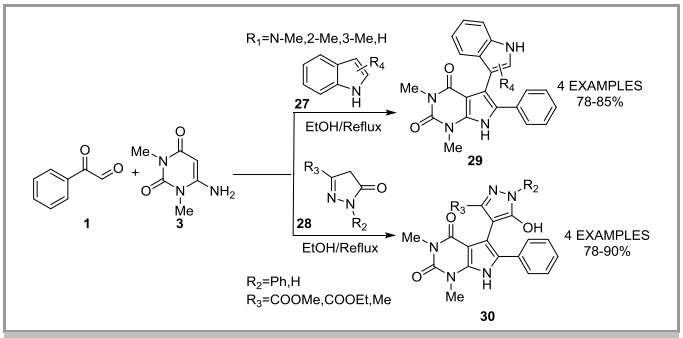
Scheme 12. Synthesis of bis-pyrrolo[2,3-*d*]pyrimidine derivatives under MW conditions

Javahershenas and Khalafy reported a new method for the synthesis of pyrrolo[2,3-*d*]pyrimidine derivatives **25** through the one-pot, three-component reaction of 4-hydroxycoumarin **24**, arylglyoxal **1** and 6-aminouracil **3** or 1,3- dimethyl-6-aminouracil **3** catalyzed by L-proline as catalyst (Scheme 13) [85].



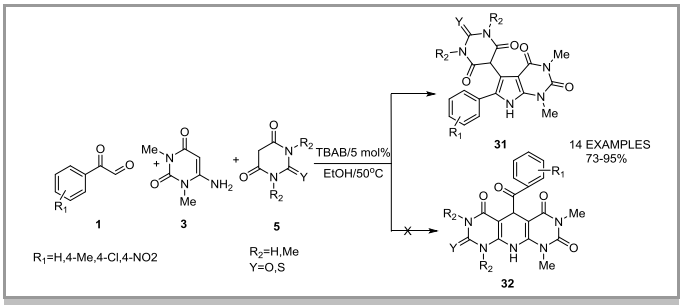
Scheme 13. Synthesis of pyrrolo[2,3-*d*]pyrimidine derivatives catalyzed by L-proline

Khurana and coworkers reported the microwave assisted synthesis of some novel 5-substituted 6-phenyl pyrrolo[2,3-*d*]-pyrimidine derivatives **29** and **30** by one-pot three-component condensation of arylglyoxal **1** , 6-amino-1,3dimethyluracil **3** and indole derivatives **27** or 1*H*-pyrazol-5(4*H*)-one derivatives **28** by refluxing in ethanol under catalyst-free conditions (Scheme 14) [86].



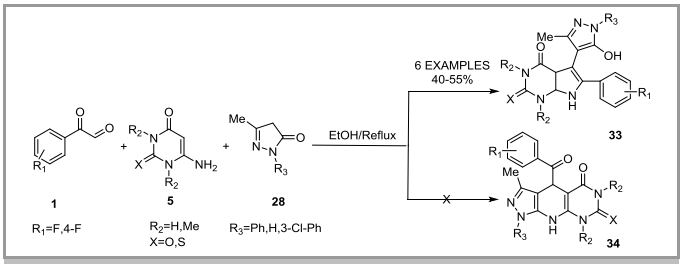
Scheme 14. Synthesis of [2,3-*d*]pyrimidine Derivatives via One-pot Three-Component Reactions Under Catalyst-Free Condition

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].



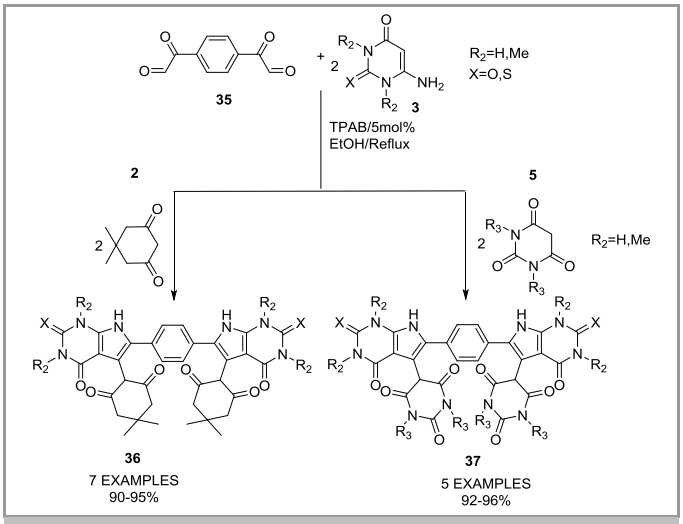
Scheme 15. TBAB catalyzed synthesis of bis-pyrrolo[2,3-*d*]pyrimidine derivatives

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



Scheme 16. Generation of pyrrolo[2,3-*d*]pyrimidines via multicomponent reaction of 6-aminopyrimidines, dimedone, and arylglyoxal

Khalafy and coworkers used TPAB as catalyst in the reaction between 1,4-phenylene-bis-glyoxal **35**, 6-aminouracil 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].



Scheme 17. Synthesis of pyrazolo substituted pyrrolo[2,3-*d*]pyrimidines

2. Conclusion

This study presented an overview of the recent literature on 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

We are grateful for financial support from the Research Council of Urmia University.

Abbreviations

AcOH	acetic acid
AGs	arylglyoxals
AcO	acetate
aq	aqueous
DMF	N,N-dimethylformamide
DMDO	dimethyldioxirane
DCE	1,2-dichloroethane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DMA	dimethylacetamide
DCM	dichloromethane
DMSO	dimethylsulfoxide
HMPA	hexamethylphosphoramide
HIV	human immunodeficiency virus
NMP	N-methyl-2-pyrrolidone
NBS	N-bromosuccinimide
MW	microwave
MCR	multicomponent reaction
PG	phenylglyoxal

p-TsOH	*p*-toluenesulfonic acid
rt	room temperature
TBAB	tetrabutylammonium bromide
TPAB	tetrapropylammonium bromide

References

[1] Parsons, P.J., Penkett, C.S., & Shell, A. (**1996**). Tandem Reactions in Organic Synthesis: Novel Strategies for Natural Product Elaboration and the Development of New Synthetic Methodology. *Journal of Chemical Review*, *96*, 195-206.

[2] Domling, A., Wang, W., & Wang, K. (**2012**). Chemistry and Biology of Multicomponent Reactions. *Chemical Reviews*, *112*, 3083-3135.

[3] Rotstein, B.H., Zaretsky, S., Rai V., & Yudin, A.K. (**2014**). Small Heterocycles in Multicomponent Reactions. *Chemical Reviews*, *114*, 8323-8359.

[4] Domling A. (**2006**). Recent Developments in Isocyanide Based Multicomponent Reactions in Applied Chemistry. *Chemical Reviews*, *106*, 17-89.

[5] Chanda, A., Fokin, V.V. (**2009**). Organic Synthesis "On Water". *Chemical Reviews*, *109*, 725-748.

[6] Mahmudov, K.T., Kopylovich, M.N., Maharramov, A.M., Kurbanova, M.M., Gurbanov, A.V., Pombeiro, A.J.L. (**2014**). Barbituric acids as a useful tool for the construction of coordination and supramolecular compounds. *Coordination Chemical Reviews*, *265*, 1-37.

[7] Estevez, V., Villacampa, M., Menendez, C.J. (**2010**). Multicomponent reactions for the synthesis of pyrroles. *Chemical Society Reviews*, *39*, 4402-4421.

[8] Ma, L.Y., Zheng, Y.C., Wang, S.Q., Wang, B., Wang, Z.R., Pang, L.P., Zhang, M., Wang, J. W., Ding, L., Li, J., Wang C., Hu, B., Liu, Y., Zhang, X. D., Wang, J. J., Wang, Z. J., Zhao, W., Liu, H. M. (**2015**). Design, Synthesis, and Structure–Activity Relationship of Novel LSD1 Inhibitors Based on Pyrimidine–Thiourea Hybrids As Potent, Orally Active Antitumor Agents. *Journal of Medicinal Chemistry*, *58*, 1705-1716.

[9] Allias, C., Grassot, J., Rodriguez, J., Constantieux, T. (**2014**). Metal-Free Multicomponent Syntheses of Pyridines. *Chemical Reviews*, *114*, 10829-10868.

[10] Jiang, S., Gao, J., Han, L. (**2016**). One-pot catalyst-free synthesis of 3-heterocyclic coumarins. *Research on Chemical Intermediates*, *2*, 1017-1028.

[11] Fu, Z., Qian, K., Li, S., Shen, T. (**2016**). MgCl2 catalyzed one-pot synthesis of 2-hydroxy-3-((5-methyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)(phenyl)methyl)naphthalene-1,4-dione derivatives in EG. *Tetrahedron Letter*, *57*, 1104-1108.

[12] Pałasz, A., Cież, D. (**2015**). In search of uracil derivatives as bioactive agents. Uracils and fused uracils: Synthesis, biological activity and applications. *European Journal of Medicinal Chemistry*, *97*, 582-611.

[13] Tolstoluzhsky, N., Nikolaienko, P., Gorobets, N., Van der Eycken, E. V., Kolos, N. (**2013**). Efficient Synthesis of Uracil-Derived Hexa- and Tetrahydropyrido[2,3-*d*]pyrimidines. *European Journal of Organic Chemistry*, *2013*, 5364-5369.

[14] Dhorajiya, B.D., Dholakiya, B.Z., Mohareb, R.M. (**2014**). Hybrid probes of aromatic amine and barbituric acid: highly promising leads for anti-bacterial, anti-fungal and anti-cancer activities. *Medicinal Chemistry Research*, *23*, 3941-3952.

[15] Yagi, K., Akimoto, K., Mimori, N., Miyake, T., Kudo, M., Arai, K., Ishii, S. (**2000**) Pest Management Science, 56, 65-73.

[16] El-Gazzar, A.R.B.A., Hafez, H.N. (**2009**). Synthesis of 4-substituted pyrido[2,3-*d*]pyrimidin-4(1*H*)-one as analgesic and anti-inflammatory agents. *Bioorganic & Medicinal Chemistry Letters*, *19*, 3392-3397.

[17] Siddiqui, Z. N. (**2015**). Chitosan catalyzed an efficient, one pot synthesis of pyridine derivatives. *Tetrahedron Letter*, *56*, 1919-1924.

[18] Abu-Hashem, A.A., Gouda, M.A., Badria, F.A. (**2010**). Synthesis of some new pyrimido[2′,1′:2,3]thiazolo[4,5-*b*]quinoxaline derivatives as anti-inflammatory and analgesic agents. *European Journal of Medicinal Chemistry*, *45*, 1976-1981.

[19] Kliethermes, C. L., Metten, P., Belknap, J. K., Buck, K. J., Crabbe, J.C. (**2004**). Selection for pentobarbital withdrawal severity: correlated differences in withdrawal from other sedative drugs. *Brain Research*, *1009*, 17-25.

[20] Rewcastle G.W., Bridges A.J., Fry, D.W., Rubin, J.R., Denny, W.A. (**1997**). Tyrosine Kinase Inhibitors. 12. Synthesis and Structure−Activity Relationships for 6-Substituted 4-(Phenylamino)pyrimido[5,4-*d*]pyrimidines Designed as Inhibitors of the Epidermal Growth Factor Receptor. *Journal of Medicinal Chemistry*, *40*, 1820-1826.

[21] Heravi, M.M., Oskooie, H.A., Karimi, N., & Hamidi, H. (**2011**). KAl (SO4) 2• 12H2O catalyzed efficient synthesis of 3, 4, 6-trisubstituted 2-pyridone in water. *Chinese Chemical Letters*, *22(9)*, 1059-1062.

[22] Shiri, M., Heravi, M.M., Hamidi, H., Zolfigol, M.A., Tanbakouchian, Z., Nejatinezhad-Arani, A., Shintre, S.A., & Koorbanally, N. A. (**2016**). Transition metal-free synthesis of quinolino

[2′,3′:3,4] pyrazolo [5,1-*b*] quinazolin-8 (6*H*)-ones via cascade dehydrogenation and intramolecular N-arylation. *Journal of the Iranian Chemical Society, 13(12)*, 2239-2246.

[23] Heravi, M.M., Hamidi, H., Karimi, N., & Amouchi, A. (**2018**). Caro's Acid-Silica Gel Catalyzed Regioselective Ring Opening of Epoxides with Indoles and Imidazoles under Solvent-Free Conditions. *Advanced Journal of Chemistry-Section A, 1(1)*, 1-6.

[24] Jin, Y.Z., Yasuda, N., Furuno, H., Inanaga, J. (**2003**). Organic synthesis in solid media. Silica gel as an effective and reusable medium for the selective allylation of aldehydes with tetraallyltin. *Tetrahedron Letter, 44*, 8765-8768.

[25] Zhang, Q., Xu, C.-M., Chen, J.X., Xu, X.L., Ding, J.C., Wu, H.Y. (**2009**). Palladium-catalyzed arylation of arylglyoxals with arylboronic acids. *Applied Organometallic Chemistry, 23*, 524-526.

[26] Itoh, T., Nagata, K., Miyazaki, M., Ishikawa, H., Kurihara, A., Ohsawa, A. (**2004**). A selective reductive amination of aldehydes by the use of Hantzsch dihydropyridines as reductant. *Tetrahedron, 60*, 6649-6655.

[27] Jang, H.-Y., Huddleston, R. R., Krische, M. J. (**2003**). A New Catalytic C□C Bond-Forming Hydrogenation: Reductive Coupling of Dienes and Glyoxals under Catalytic Hydrogenation Conditions. *Angewandte Chemie International Edition, 42*, 4074-4077.

[28] Wu, J., Sun, L., Dai, W.M. (**2006**). Microwave-assisted tandem Wittig–intramolecular Diels–Alder cycloaddition. Product distribution and stereochemical assignment. *Tetrahedron, 62*, 8360-8372.

[29] Schmitt, E., Schiffers, I., Bolm, C. (**2009**). Organocatalytic conversion of arylglyoxals into optically active mandelic acid derivatives. *Tetrahedron Letter, 50*, 3185-3188.

[30] Kobayashi, S., Araki, M., Yasuda, M. (**1995**). One-pot synthesis of β-amino esters from aldehydes using lanthanide triflate as a catalyst. *Tetrahedron Letter, 36*, 5773-57576.

[31] Blay, G., Hernández-Olmos, V., Pedro, J.R. (**2011**). The Construction of Quaternary Stereocenters by the Henry Reaction: Circumventing the Usual Reactivity of Substituted Glyoxals. *Chemistry European Journal, 17*, 3768-3773.

[32] Desai, J.T., Desai, C.K., Desai, K.R. (**2008**). A convenient, rapid and eco-friendly synthesis of isoxazoline heterocyclic moiety containing bridge at 2°-amine as potential pharmacological agent. *Journal of the Iranian Chemical Society, 5*, 67-73.

[33] Tangmouo, J.G., Meli, A.L., Komguem, J., Kuete, V., Ngounou, F.N., Lontsi, D., Beng, V.P., Choudhary, M.I., Sondengam, B.L. Crassiflorone, Crassiflorone, (**2006**) Tetrahedron Letter, 47, 3067-3069.

[34] Satti, N.K., Suri, K.A., Sun, O.P., Kapil, A. (**1993**). Synthesis and antileishemanial activity of some pyrido[1,2-a]pyrimidines and phennathrolines. *Indian Journal of Chemistry - Section B., 32B*, 978-980.

[35] Bystryakova, I., Burova, I., Chelysheva, G., Zhilinkova, S., Smirnova, N., Safonova, T. (**1991**). Synthesis of arylmethylureas and effects of their structure on anticonvulsant activity. *Khimiko-Farmatsevticheskii Zhurnal, 25*, 31-35.

[36] Emmadi, Atmakur, K., Bingi, C., Godumagadda, N.R., Kumar, C.G., Nanubolu, J.B. (**2014**). Regioselective synthesis of 3-benzyl substituted pyrimidino chromen-2-ones and evaluation of anti-microbial and anti-biofilm activities. *Bioorganic & Medicinal Chemistry Letters, 24*, 485-489.

[37] Ryota, M., Keisuke, A., Seijiro, M. (**2013**). Asymmetric Indoline Synthesis via Intramolecular Aza-Michael Addition Mediated by Bifunctional Organocatalysts. *Organic Letters, 15*, 3658-3661.

[38] Kliethermes, C.L., Metten, P., Belknap, J.K., Buck, K.J., Crabbe, J.C. (**2004**). Selection for pentobarbital withdrawal severity: correlated differences in withdrawal from other sedative drugs. *Brain Research, 1009*, 17-25.

[39] Isobe, Y., Tobe, M., Inoue, Y., Isobe, M., Tsuchiya, M., Hayashi, H. (**2003**). Structure and activity relationships of novel uracil derivatives as topical anti-inflammatory agents. *Bioorganic & Medicinal Chemistry, 11*, 4933- 4940.

[40] Berghot, M.A., Kandeel, E.M., Abdel-Rahman, A.H., Abdel-Motaal, M. (**2014**). Medicinal chemistry synthesis, antioxidant and cytotoxic activities of novel naphthoquinone. *Medicinal Chemistry, 4(3)*, 381-388.

[41] Abu-Hashem, A.A., Gouda, M.A., Badria, F.A. (**2010**). Synthesis of some new pyrimido[2′,1′:2,3]thiazolo[4,5-b]quinoxaline derivatives as anti-inflammatory and analgesic agents. *European Journal of Medicinal Chemistry, 45*, 1976- 1981.

[42] A. Cutignano, G. Bifulco, I., Bruno, A., Casapullo, L., Gomez-Paloma, R. Riccio, (**2000**). Dragmacidin F: A New Antiviral Bromoindole Alkaloid from the Mediterranean Sponge Halicortex sp. *Tetrahedron, 56*, 3743-3748.

[43] Sandberg, F. (**1951**). Anaesthetic Properties of Some New N-substituted and N,N'-disubstituted Derivatives of 5,5-Diallyl-Barbituric Acid. *Acta Physiologica Scandinavica, 24*, 7-26.

[44] Yagi, K., Akimoto, K., Mimori, N., Miyake, T., Kudo, M., Arai, K., Ishii, S. (**2000**). Synthesis

and insecticidal/acaricidal activity of novel 3-(2,4,6-trisubstituted phenyl)uracil derivatives. *Pest Management Science, 56*, 65-73.

[45] Elrazaz, E.Z., Serya, R. A.T., Ismail, N.S.M., Abou El Ella, D. A., Abouzid, K. A.M. (**2015**). Thieno[2,3-*d*]pyrimidine based derivatives as kinase inhibitors and anticancer agents. *Future Journal of Pharmaceutical Sciences, 1*, 33-41.

[46] Rosowsky, A., Mota, C.E., Queener, S.F. (**1995**). Synthesis and antifolate activity of 2,4-diamino-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine analogues of trimetrexate and piritrexim. *Journal of Heterocyclic Chemistry, 32*, 335-340.

[47] Limbach, P. A., Crain, P.F., McCloskey, J. A. (**1994**). Summary: the modified nucleosides of RNA. *Nucleic Acids Research, 22*, 2183-2196.

[48] Wojciechowski, F., Leumann, C.J. (**2011**). Alternative DNA base-pairs: from efforts to expand the genetic code to potential material applications. *Chemical Society Reviews, 40*, 5669-5679.

[49] Ranasinghe, R.T., Brown, T. (**2005**). Fluorescence based strategies for genetic analysis. *Chemical Communications*, 5487-5502.

[50] Greco, N.J., Sinkeldam, R.W., Tor, Y. (**2009**). An Emissive C Analog Distinguishes between G, 8-oxoG, and T. *Organic Letters, 11*, 1115-1118.

[51] Tanaka, K., Imai, K., Sanno, Y., Nakamori, R., Ando, Y., Sugawa, T. (**1964**). Studies on Nucleic Acid Antagonists. VI. Synthesis of 1, 4, 6-Triazaindenes(5*H*-Pyrrolo[3,2-*d*]pyrimidines). *Chemical and Pharmaceutical Bulletin, 12*, 1024-1030.

[52] Imai, K. (**1964**). Studies on Nucleic Acid Antagonists. VII. Synthesis and Characterization of 1, 4, 6-Triazaindenes (5*H*-Pyrrolo[3,2-*d*]pyrimidines). *Chemical and Pharmaceutical Bulletin, 12*, 1030-1042.

[53] De Coen, L.M., Heugebaert, T.S.A., García, D., Stevens, C.V. (**2016**). Synthetic Entries to and Biological Activity of Pyrrolopyrimidines. *Chemical Reviews, 116*, 80-139.

[54] Pathania, Sh., Rawal, R. K. (**2018**). Pyrrolopyrimidines: An update on recent advancements in their medicinal attributes. *European Journal of Medicinal Chemistry, 157*, 503-526.

[55] Takahashi, K. (**1968**). The Reaction of Phenylglyoxal with Arginine Residues in Proteins. *Journal of Biological Chemistry, 243*, 6171-6179.

[56] Tiffany, B.D., Wright, J.B., Moffett, R.B., Heinzelman, R. V., Strube, R. E., Aspergren, B. D., Lincoln, E. H., White, J. L. (**1957**). Antiviral Compounds. I. Aliphatic Glyoxals, α-Hydroxyaldehydes and Related Compounds. *Journal of the American Chemical Society*, 79, 1682-1687.

[57] Moffett, R.B., Tiffany, B.D., Aspergren, B.D., Heinzelman, R. V. (**1957**). Antiviral Compounds. II. Aromatic Glyoxals. *Journal of the American Chemical Society*, 79, 1687-1690.

[58] von Pechmann, H. (**1887**). For cleavage of isonitroso compounds. *Chemische Berichte , 20*, 2904-2906.

[59] Riley, H.L., Morley, J.F., Friend, N.A.C. (**1932**). Selenium dioxide, a new oxidising agent. Part I. Its reaction with aldehydes and ketones. *Journal of the Chemical Society*, 1875-1883.

[60] Riley, H.A., Gray, A.R. (**1935**). Phenylglyoxal. *Organic Syntheses, 15*, 67, (**1943**) *Organic Syntheses Collect. Vol., 2*, 509.

[61] Bousset, R. (**1939**) Bull. Soc. Chim. France, 6, 986-996.

[62] Saldabol, N.O., Popelis, J., Slavinska, V. (**2002**). 5-Methyl-2-furylglyoxal, 5-Methyl-4-nitro-2-furylglyoxal, and Their Derivatives. Nitration of 2-(5-Methyl-2-furyl)quinoxaline. *Chemistry Heterocyclic Compound, 38*, 783-788.

[63] Sharma, V.K., Chandalia, S.B. (**1986**). Liquid phase oxidation of acetophenone to phenylglyoxal by selenium dioxide alone or with aqueous nitric acid. *Journal of Chemical Technology & Biotechnology*, 36, 456-460.

[64] Tiecco, M., Testaferri, L., Tingoli, M., Bartoli, D. (**1990**). Selenium-catalyzed conversion of methyl ketones into .alpha.-keto acetals. *Journal of Organic Chemistry, 55*, 4523-4528.

[65] Floyd, M.B., Du, M. T., Fabio, P. F., Jacob, L.A., Johnson, B.D. (**1985**). The oxidation of acetophenones to arylglyoxals with aqueous hydrobromic acid in dimethyl sulfoxide. *Journal of Organic Chemistry, 50*, 5022-5027.

[66] Kornblum, N., Powers, J.W., Anderson, G.J., Jones, W.J., Larson, H. O., Levand, O., Weaver, W. M. (**1957**). A new and selective method of oxidation. *Journal of the American Chemical Society*, 79, 6562-6562.

[67] Kato, T., Goto, Y., Yamamoto, Y. (**1964**). A New Synthetic Method of α-Ketoaldehyde: Reaction of α-Picoline N-Oxide with α-Halo Ketone. *Yakugaku Zasshi, 84*, 287-289.

[68] Gunn, V.E., Anselme, J.P. (**1977**). The facile oxidation of phenacyl bromides with N,N-dialkylhydroxylamines. *Journal of Organic Chemistry, 42*, 754-755.

[69] Kornblum, N., Frazier, H. W. (**1966**) *Journal of the American Chemical Society*, 88, 865-866.

[70] Ihmels, H., Maggini, M., Prato, M., Scorrano, G. (**1991**). Oxidation of diazo compounds by dimethyl dioxirane: an extremely mild and

efficient method for the preparation of labile α-oso-aldehydes. *Tetrahedron Letter, 32*, 6215-6218.

[71] Ballistreri, F., Failla, S., Tomaselli, G. A., Curci, R. (**1986**). A new facile synthesis of α-dicarbonyl compounds by oxidation of alkynes with Mo(VI) peroxocomplex promoted by mercuric acetate. *Tetrahedron Letter, 27*, 5139-5142.

[72] Wolfe, S., Pilgrim, W.R., Garrard, T.F., Chamberlain, P. (**1971**). N-Bromosuccinimide-Induced Dimethyl Sulfoxide Oxidation of Acetylenes. *Canadian Journal of Chemistry, 49*, 1099-1105.

[73] Santoro, S., Battistelli, B., Gjoka, B., Si, C.-W. S., Testaferri, L.,Tiecco, M., Santi, C. (**2010**). Oxidation of Alkynes in Aqueous Media Catalyzed by Diphenyl Diselenide. *Synlett*, 1402-1406.

[74] Mikol, G. J., Russell, G. A. (**1968**). Phenylglyoxal. *Organic Syntheses 48*, 109, (**1973**) *Organic Syntheses Collect. Vol., 5*, 937.

[75] Jagdale, A.R., Chouthaiwale, P.V., Sudalai, A. (**2009**). Cu(OTf)2-catalyzed -halogenation of ketones with 1,3-dichloro-5,5′-dimethylhydantoin and N-bromosuccinimide. *Indian Journal of Chemistry, 48B*, 1424-1430.

[76] Quiroga, J., Acosta, P. A., Cruz, S., Abonía, R., Insuasty, B., Nogueras, M., Cobo, J. (**2010**). Generation of pyrrolo[2,3-d]pyrimidines. Unexpected products in the multicomponent reaction of 6-aminopyrimidines, dimedone, and arylglyoxal. *Tetrahedron Letter, 51*, 5443-5447.

[77] Raafat M. Shaker, R.M., Sadek, K.U., Hafez, E.A., Abd Elrady, M. Z. (**2011**). 5-Aminouracil as a Building Block in Heterocyclic Synthesis: Part IV. One-pot Synthesis of 1H-Pyrrolo[2,3-*d*]pyrimidine-2,4(3*H*,7*H*)-dione Derivatives Using Controlled Microwave Heating. *Naturforsch., 66b*, 843- 849.

[78] Rad-Moghadam, K., Azimi, S.C. (**2012**). Synthesis of novel oxindolylpyrrolo[2,3-*d*]pyrimidines via a three-component sequential tandem reaction. *Tetrahedron, 68*, 9706-9712.

[79] Rad-Moghadam, K., Azimi, S.C. (**2016**). A clean and highly efficient synthesis of oxindole substituted pyrrolo[2,3-*d*]pyrimidines under ultrasound irradiation. *Iran Chemical Communications, 5*, 156-166.

[80] Dommaraju, Y., Borthakur, S., Rajesh, N., Prajapati, D. (**2013**). An Efficient Catalyst-free Chemoselective Multicomponent Reaction for the Synthesis of Pyrimidine Functionalized Pyrrolo-annelated Derivatives. *RSC Advance, 00*, 1-3.

[81] Naidu, P.S., Bhuyan, P.J. (**2014**). A novel one-pot three-component reaction for the synthesis of 5-arylamino-pyrrolo[2,3-*d*]pyrimidines under microwave irradiation. *RSC Advance, 4*, 9942-9945.

[82] Shaik Karamthulla, S., Asim Jana, A., Choudhury, L.H. (**2017**). Synthesis of Novel 5,6-Disubstituted Pyrrolo [2,3-*d*]Pyrimidine-2,4-Diones Via One-Pot Three-Component Reactions. *ACS Combinatorial Science*, 19, 108-112.

[83] Yadav, V.B., Rai, P., Sagir, H., Akhilesh Kumar, A., Siddiqui, I.R. (**2018**). A greener route for the synthesis of Pyrrolo[2,3-*d*]pyrimidine derivatives catalyzed by β-cyclodextrin. *New Journal of Chemistry, 42*, 628-633.

[84] Panday, A.K., Choudhury, L.H., Jagannath Pal, J., Subramanian, R., Verm, R. (**2017**). Multicomponent Reactions of Arylglyoxal, 4-Hydroxycoumarin, and Cyclic 1,3-C,N-Binucleophiles: Binucleophile Directed Synthesis of Fused Five and Six Membered N-Heterocycles. *European Journal of Organic Chemistry, 2017*, 2789-2800.

[85] Javahershenas, R., Khalafy, J. (**2018**). A new synthesis of pyrrolo[3,2-*d*]pyrimidine derivatives by a one-pot, three-component reaction in the presence of L-proline as an organocatalyst. *Heterocyclic Communications, 24*, 37-41.

[86] Saroha, M., Khanna, G., Khurana, J. M. (**2017**). Synthesis of Novel 5-Substituted 6-Phenylpyrrolo[2,3-*d*]pyrimidine Derivatives via One-pot Three-Component Reactions Under Catalyst-Free Condition. *ChemistrySelect, 2*, 7263-7266.

[87] Javahershenas, R., Khalafy, J. (**2018**). One-pot three-component Synthesis of pyrrolo[2,3-d]pyrimidine Derivatives. *Journal of the Mexican Chemical Society, 62(1)*.

[88] Bayat, M., Nasri, Sh. J. (**2018**). Synthesis and dynamic ^{1}H NMR study of pyrazolo substituted pyrrolo[2,3-*d*]pyrimidines via a regioselective heterocyclization. *Journal of Molecular Structure, 1154*, 366-372.

[89] Ahmadi Sabegh, M., Khalafy, J., Etivand, N. (**2018**). One-pot, Three-component Synthesis of a Series of New Bis-pyrrolo[2,3-*d*]pyrimidines in the Presence of TPAB under Reflux Conditions. *Journal of Heterocyclic Chemistry, 55(11)*, 2610-2618.

How to cite this manuscript: Ramin Javahershenas, Jabbar Khalafy, Rolf Herman Prager . The Application of Arylglyoxals in the Synthesis of Pyrrolo[2,3-*d*]pyrimidines via Multicomponent Reactions. Journal of Chemical Reviews, 2019, 1(3), 233-242.