Molecular diversity of four-component synthesis of pyrazole-based pyrido[2,3-d]pyrimidine-diones in water: a green synthesis

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Abstract
A novel one pot, four component synthesis of pyrazolo[4′,3′:5,6]pyrido[2,3-d]pyrimidine-diones, involving, hydrazine hydrate, ethyl acetoacetate, 6-amino-1,3-dimethyl uracil and an appropriate aryl aldehyde in the presence of two green catalysts in water, is reported.

Keywords: Pyrazole, pyrido[2,3-d]pyrimidine-diones, green synthesis, four-component reaction

Introduction

Malaria and tuberculosis (TB), both from the aspect of mortality and morbidity are the most destroying infectious diseases in the world. Plasmodium falciparum is the most virulent species of the malaria parasite and is responsible for most of the malaria-related deaths. A family of hybrid molecules involving pyrimidine were synthesized and screened for antimalarial potency against both chloroquine (CQ)-sensitive (D6) and chloroquine (CQ)-resistant (W2) strains of Plasmodium falciparum via an in vitro assay.3

Pyrimidines have been well-known as an important class of heterocyclic compounds with different pharmacological activity due to their presence in various naturally occurring cofactors and purine bases of DNA and RNA. The superiority of this antimalarial pharmacophore is mainly due the excellent observed clinical efficiency, ease of administration, low toxicity, and inexpensive production.4

Polyfunctionalized heterocyclic compounds play main and essential roles in the processes of drug discovery and development.5 Thus, they have attracted much attention and interest of synthetic organic chemists and pharmacists.6 Several fused pyrimidine systems, exhibit wide and divers range of bioactivities such as antiallergy,7 antiviral,8 anti-HIV activities9 and antimalarial.10

Due to these biological activities and importance of pyazole, pyridine and pyrimidine derivatives, in recent years, remarkable attempts have been focused on the synthesis of novel
heterocyclic systems derived from the aforementioned heterocycles and also the development of the already known strategies has attracted much attention. Particularly, the efficient, facile and green synthesis of pyrazolopyrimidine derivatives has stirred up the interest of synthetic organic chemists. In fact, several differently oriented and substituted pyrazolopyrimidines have been recognized, showing interesting biological activities. Addition, of another heterocycle to pyrazolopyrimindes may have increased the biological activities of the aforementioned bicyclic systems. For example several pyrazolopyridopyrimidines illustrate interesting divers biological potencies such as virucidal anticancer, hepatoprotective activity, antioxidant, and vasodilatory activities.

Nowadays, multi-component reactions (MCRs), sometimes referred to as a "Multi-component Assembly Process" (MCAP), have attracted enormous attention and have stirred up the interest of synthetic organic chemists due to their well-established advantages and merits. In multi-component reactions whereby more than two reactants combine in a sequential fashion affording highly selective products that retain majority of the atoms of the starting materials. Thus, MCRs are frequently considered as the first choice by synthetic organic chemists for the generation of molecular diversity. Due to their unique and significant features such as selectivity, atom-economy, high yielding in relative short times and being compatible with well–defined green chemistry principles, MCRs are the method of choice for building relatively complex targets.

In MCRs combination of several diverse elements in a unique chemical operation gives the desired compounds. Thus expanding this approach to the synthesis of already known organic and in particular heterocyclic compounds, synthesized via multi-step route, is still in much demand.

Pyrazole based pyrido[2,3-d]pyrimidine-diones are interesting compounds from both chemical and biological point of views, thus attracted the attention of several research groups. We are interested in green synthesis and heterocyclic chemistry. Synthesis of pyrazole based pyrido[2,3-d]pyrimidine-diones were reported by a three component reaction with barbituric acids, 1H-pyrazol-5-amines and aromatic aldehydes using p-TSA and Cell-IL, respectively.

Due to the importance of these compounds in medicinal chemistry, in this project, we decided to develop their synthesis by examination of a new four-component reaction, employing different starting materials, trying to catalyze the reaction with a superior catalyst and preferentially under environmentally benign conditions in order to promote the previously reported procedure from both chemical and molecular diversity points of view.

To the purpose, we used 6-amino-1,3-dimethyl uracil instead of aminopyrazole, as a nitrogen source. The uracil and its derivatives are well known by synthetic as well as biological chemists. In addition we tried to design our protocol using inexpensive starting materials being performed under green conditions. The pyrazol moiety can be prepared from two inexpensive commercially available starting materials (ethyl acetoacetate and hydrazine hydrate).
Thus after using different catalysts and solvents, we achieved the preparation of the target molecule via a one pot four component reaction of hydrazine hydrate, ethyl acetoacetate, 6-amino-1,3-dimethyl uracil and benzaldehyde in the presence of trimethylamine (TEA) in water as solvent. As a result the reaction proceeded smoothly, giving the desired products in excellent yields. (Scheme 1)

![Scheme 1](image)

**Scheme 1.** Model reaction for the synthesis of pyrazole based pyrido[2,3-d] pyrimidine-dione using TEA as a catalyst.

In this reaction water as greenest and most abundant solvent plays a vital role as a medium. Water is also is highly polar, thus immiscible with most organic solvents. Reaction in water are environmentally benign, devoid of any carcinogenic effects. It usually has a simple work up and especially are important in industrial fields as far as economical feasibility concerns.

In addition we used TEA as a commercially available basic catalyst, which is commonly used in catalyzed Knoevenagel-Michael addition reaction. Thus, it was used successfully in the synthesis of pyrazole based pyrido[2,3-d]pyrimidine-dione. As a weak base, triethylamine has been successfully used in the Knoevenagel condensation and Michael addition. After completion the reaction, 2-3 drops of HCl was added to neutralize the trimethylamine.

The scope of this new four component reaction was extended by using differently substituted aryl aldehydes bearing electron donating and electron withdrawing substituents to obtain successfully the corresponding desired compounds.

![Scheme 2](image)

**Scheme 2.** The proposed mechanism for reaction.
Results and Discussion

Initially, we examined the condensation of ethyl acetoacetate 1, hydrazine hydrate 2, benzaldehyde 3 and 1,3-dimethyluracil 4 in the presence of wide range of different solvents and catalysts, to achieve a one pot four components synthesis of the corresponding pyrazole based pyrido[2,3-d]pyrimidine-dione. First, we examined the un-catalyzed reaction in different solvents which were unsuccessful. Thus divergent combination of catalysts and solvents were tested for the above four component reaction. The results for optimization of reaction conditions were enlisted in Table 1.

Table 1. Optimization of the reaction conditions for the synthesis of pyrazole based pyrido[2,3-d]pyrimidine-diones under thermal conditions

| Catalyst (mol%) | Solvent | Time (h) | Yield (%) |
|----------------|---------|----------|-----------|
| $\text{H}_3\text{P}_2\text{W}_{18}\text{O}_{62}\cdot18\text{H}_2\text{O}$ (10) | Water | 2 | 60 |
| Sulfamic acid (20) | Water | 2.5 | 65 |
| DABCO (10) | Water | 3.5 | 85 |
| Morpholine (10) | Water | 3 | 80 |
| TEA (8) | Water | 2 | 92 |
| TEA (8) | EtOH | 2.5 | 65 |

In conclusion, when the reaction was performed in the presence of catalytic amount of TEA in different solvents under reflux conditions, including water, delightfully, we observed more the smooth progress of reaction in water, monitored by TLC. Upon completion of the reaction (indicated also by TLC) and conventional work up the corresponding pyrazolo-[4′,3′:5,6]pyrido[2,3-d]pyrimidine-dione, was obtained within 2 h in high yield. The generality of this method was established by using differently substituted aromatic aldehydes under optimal conditions (TEA as catalyst, refluxing water as green solvent). The results are represented in Table 2.

Thus there is neither need to use energy for evaporation nor organic solvents for extraction. It should be noted that due to the good efficiency of production and non-generated by product and also the possibility of complete neutralization of the catalyst from the reaction mixture, the remaining water is free of pollutants.

The structures of the new derivatives were elucidated by their IR, $^1\text{HNMR}$, and $^{13}\text{CNMR}$ spectra and by elemental analysis.

Over the last decade, organocatalysis in general, and asymmetric organocatalysis in particular, Have attracted much attention. For instance inexpensive commercially available $\text{L}$-proline has been found as an efficient catalyst in organic synthesis.
### Table 2. One pot, four-component synthesis of pyrazolo-[4',3',5,6]pyrido[2,3-d]pyrimidine-diones in refluxing water using a catalytic amount of TEA

| Comp. | Ar      | R     | Time (h) | Yield (%)<sup>a</sup> | Mp (°C)  | Mp rep. (°C)<sup>34</sup> |
|-------|---------|-------|----------|------------------------|----------|---------------------------|
| 5a    | C₆H₅    | H     | 2        | 92                     | 194-196  | 195-196                   |
| 5b    | 4-FC₆H₄ | H     | 1.5      | 90                     | 281-283  | ------                    |
| 5c    | 4-ClC₆H₄| H     | 1.5      | 91                     | 285-286  | 284-285                   |
| 5d    | 4-BrC₆H₄| H     | 2        | 90                     | 286-288  | 286-287                   |
| 5e    | 2,4-ClC₆H₃| H   | 1.8      | 89                     | 285-287  | 286-287                   |
| 5f    | 4-NO₂C₆H₄| H   | 1.8      | 89                     | 172-173  | 173-174                   |
| 5g    | 3-NO₂C₆H₄| H   | 2        | 87                     | 221-223  | 220-221                   |
| 5h    | 4-OHC₆H₄| H     | 3        | 82                     | 220-222  | 219-220                   |
| 5i    | 4-N(Me)₂C₆H₄| H | 2.5     | 80                     | 222-224  | 221-223                   |
| 5j    | C₆H₅    | Ph    | 3        | 90                     | 208-210  | 210-211                   |
| 5k    | 4-FC₆H₄ | Ph    | 2.2      | 88                     | 207-208  | 208-210                   |
| 5l    | 4-ClC₆H₄| Ph    | 2.2      | 86                     | 200-202  | ------                    |
| 5m    | 4-BrC₆H₄| Ph    | 2.5      | 85                     | 160-161  | 158-159                   |
| 5n    | 4-NO₂C₆H₄| Ph | 3        | 83                     | 155-157  | 156-157                   |
| 5o    | 4-CH₃C₆H₄| Ph | 3        | 85                     | 205-506  | 207-209                   |

<sup>a</sup> isolated yield.

This amino acid has been extolled as one of the simplest enzymes to catalyze several organic reactions with high stereoselectivity.⁴⁴ L-proline has been successfully asymmetrically catalyzed reactions such as reduction, oxidation, electrophilic α-fluorination, amination reactions, and most importantly C-C bond formation reactions.⁴⁵,⁴⁶ Thus when we should create a stereogenic center in our final product, we frequently used it. (Scheme 3)

**Scheme 3.** Model reaction for the synthesis of pyrazole based pyrido[2,3-d]pyrimidine-dione using L-proline.
In an attempt towards the asymmetric synthesis of our target molecule, initially the model reaction was conducted at 25 °C using l-proline as the catalyst. The progress of reaction was monitored which was found to proceed sluggishly. Thus the reaction was heated under reflux to afford compound 5a in satisfactory yield. The optical activity was measured by polarimeter, but unfortunately does not show any optical activity perhaps, due to reflux temperature. The scope of reaction, however studied using differently substituted aromatic aldehydes to obtain our target albeit as a racemic mixture. The results are summarized in Table 3.

Table 3. One pot, four-component synthesis of pyrazolo-[4',3':5,6]pyrido[2,3-d]pyrimidine-diones in refluxing water using a catalytic amount of l-proline

| Comp. | Ar       | R | Time (h) | Yield (%)<sup>a</sup> | Mp (°C) | Mp rep. (°C)<sup>34</sup> | Optical activity<sup>b</sup> |
|-------|----------|---|----------|------------------------|---------|--------------------------|-----------------------------|
| 5a    | C₆H₅     | H | 4        | 89                     | 193-195 | 195-196                  | 0                           |
| 5b    | 4-FC₆H₄  | H | 3.5      | 90                     | 280-281 | ------                   | 0                           |
| 5c    | 4-ClC₆H₄  | H | 3.5      | 89                     | 284-286 | 284-285                  | 0                           |
| 5d    | 4-BrC₆H₄  | H | 4        | 87                     | 283-286 | 286-287                  | 0                           |
| 5e    | 2,4-ClC₆H₃ | H | 4.2      | 85                     | 284-287 | 286-287                  | 0                           |
| 5f    | 4-NO₂C₆H₄ | H | 4        | 85                     | 171-173 | 173-174                  | 0                           |
| 5g    | 3-NO₂C₆H₄ | H | 4.2      | 86                     | 219-221 | 220-221                  | 0                           |
| 5h    | 4-OHC₆H₄  | H | 5        | 77                     | 221-224 | 219-220                  | 0                           |
| 5i    | 4-N(Me)₂C₆H₄ | H | 4.5      | 78                     | 220-224 | 221-223                  | 0                           |
| 5j    | C₆H₅     | Ph| 5        | 87                     | 207-210 | 210-211                  | 0                           |
| 5k    | 4-FC₆H₄  | Ph| 4.2      | 87                     | 206-208 | 208-210                  | 0                           |
| 5l    | 4-ClC₆H₄  | Ph| 4.4      | 86                     | 201-202 | ------                   | 0                           |
| 5m    | 4-BrC₆H₄  | Ph| 4.5      | 80                     | 160-163 | 158-159                  | 0                           |
| 5n    | 4-NO₂C₆H₄ | Ph| 5        | 78                     | 157-159 | 156-157                  | 0                           |
| 5o    | 4-CH₃C₆H₄ | Ph| 5        | 75                     | 206-508 | 207-209                  | 0                           |

<sup>a</sup> isolated yield.
<sup>b</sup> confirmed by polarimetry.

Conclusions

Herein, we report a completely new (using 6-amino-1,3-dimethyl uracil as a nitrogen source and other different material), versatile, simple, and eco-friendly approach for the one-pot, four-component synthesis of pyrazolo-[4',3':5,6]pyrido[2,3-d]pyrimidine-dione derivatives via
cyclocondensation of ethyl acetoacetate, hydrazine hydrate/ phenyl hydrazine, 6-amino-1,3-dimethyl uracil and differently substituted aromatic aldehydes catalyzed by TEA and l-proline under green conditions. The conditions are mild and a wide range of functional groups can be tolerated. This work will not only lead to establish a practical synthetic method but also expand the versatility of clean organic reactions in water.

**Experimental Section**

**General.** Melting points were measured by using the capillary tube method with an electro thermal 9200 apparatus. $^1$HNMR, $^{13}$CNMR spectra were recorded on a Bruker spectrometer at 400 MHz, respectively, using TMS as an internal standard (DMSO-d$_6$ solution). IR spectra were recorded from KBr disk on the FT-IR Bruker Tensor 27. The reactions were monitored by TLC. All solvents and reagents were purchased from Aldrich and Merck and were used as received. some products are new and were fully characterized by their spectral and physical data. Most of the products were known and identified by comparison of their melting points with those reported for authentic samples. The new compounds were identified by analyzing their physical and spectral data.

**General procedures**

**Synthesis of pyrazolo-[4′,3′:5,6]pyrido[2,3-d]pyrimidine-diones with TEA.** A mixture of Ethyl acetoacetate (1 mmol), hydrazine hydrate or phenyl hydrazine (1.2 mmol) 6-amino-1,3-dimethyl uracil (1mmol), and various benzaldehydes (1mmol), a catalytic amount of TEA (0.1 cc) was heated under reflux in H$_2$O (5 mL). The progress of the reaction was monitored by TLC (ethyl acetate: n-hexan: 7:3). Upon the completion the reaction, the mixture was cooled and HCl (0.05 cc) was added to neutralize the triethylamine. Upon this neutralization, the final product precipitates in the water and therefore the product was easily isolated by simple filtration. The pure corresponding product was obtained by recrystallization from CH$_2$Cl$_2$.

**Synthesis of pyrazolo-[4′,3′:5,6]pyrido[2,3-d]pyrimidine-diones using l-proline.** To a mixture of Ethyl acetoacetate (1 mmol), hydrazine hydrate or phenyl hydrazine (1.2 mmol) 6-amino-1,3-dimethyl uracil (1mmol), and benzaldehyde (1mmol), a catalytic amount of l-proline (0.03 g) was added and the resulting mixture was heated under reflux in H$_2$O (5 mL). The progress of the reaction was monitored by TLC (ethyl acetate: n-hexan: 7:3). On completion, the mixture was cooled and filtered. The precipitate was recrystallized from CH$_2$Cl$_2$ to give pure target compounds. All the products were identified by comparison of their physical and spectroscopic data with those reported for authentic samples. The physical and spectral data for the new products as well as their elemental analysis are given.

3,6,8-Trimethyl-4-phenyl-8,9-dihydro-1H-pyrazolo[4′,3′:5,6]pyrido[2,3-d]pyrimidine-5,7-(4H,6H)-dione (5a). Yield 92%, mp 194–196 °C; IR (KBr, $\nu_{\text{max}},$cm$^{-1}$): 3332, 2971, 1654, 1248;
**1H NMR (400 MHz, DMSO-d$_6$):** δ 2.22 (s, 3H, CH$_3$), 2.81 (s, 3H, CH$_3$), 3.07 (s, 3H, CH$_3$), 5.63 (s, 1H, CH), 7.006-7.084 (m, 3H, Ar–H), 7.158-7.196 (t, 2H, Ar–H), 10.46 (brs, 2H, 2-NH).

**4-(4-Fluorophenyl)-3,6,8-trimethyl-8,9-dihydro-1H-pyrazolo[4′,3′:5,6]pyrido[2,3-d]pyrimidine-5,7(4H,6H)-dione (5b).** Yield 90%, mp 281–283 °C; IR (KBr, ν$_{\text{max}}$, cm$^{-1}$): 3312, 2956, 1663, 1280; 1H NMR (400 MHz, DMSO-d$_6$): δ 1.96 (s, 3H, CH$_3$), 3.06 (s, 3H, CH$_3$), 3.46 (s, 3H, CH$_3$), 4.99 (s, 1H, CH), 7.14–7.16 (d, J= 7.6 Hz, 2H, Ar–H), 7.36–7.38 (d, J=7.6 Hz, 2H, Ar–H), 9.81 (s, 1H, NH), 11.99 (s, 1H, NH); 13C NMR (100 MHz, DMSO-d$_6$) δ: 10.02, 27.15, 30.28, 33.84, 88.63, 106.23, 125.06, 130.41, 134.57, 135.63, 137.31, 142.28, 149.62, 150.19, 158.24; calcd for C$_{17}$H$_{16}$FN$_5$O$_2$: C, 57.07; H, 4.51; N, 19.57; found: C, 57.12; H, 4.50; N, 20.02.

**3,6,8-Trimethyl-1,4-diphenyl-8,9-dihydro-1H-pyrazolo[4′,3′:5,6]pyrido[2,3-d]pyrimidine-5,7(4H,6H)-dione (5j).** Yield 90%, mp 208–210 °C; IR (KBr, ν$_{\text{max}}$, cm$^{-1}$): 3315, 2936, 1650, 1241; 1H NMR (400 MHz, DMSO-d$_6$): δ 1.55 (s, 3H, CH$_3$), 2.70 (s, 3H, CH$_3$), 2.82 (s, 3H, CH$_3$), 5.09 (s, 1H, CH), 7.42–7.46 (t, J= 8.0 Hz, 6H, Ar–H), 7.87–7.89 (d, J= 8.0 Hz, 4H, Ar–H), 11.77 (s, 1H, NH)

**4-(4-Chlorophenyl)-3,6,8-trimethyl-8,9-dihydro-1H-pyrazolo[4′,3′:5,6]pyrido[2,3-d]pyrimidine-5,7(4H,6H)-dione (5l).** Yield 86%, mp 200–202 °C; IR (KBr, ν$_{\text{max}}$, cm$^{-1}$): 3321, 2946, 1641, 1273; 1HNMR (400 MHz, DMSO-d$_6$): δ 1.96(s, 3H, CH$_3$), 2.88 (s, 3H, CH$_3$), 3.46 (s, 3H, CH$_3$), 4.86 (s, 1H, CH), 7.14–7.19 (m, 5H, Ar –H), 7.54–7.56 (d, 2H, J= 7.6 Hz, Ar–H), 7.96-7.98 (d, 2H, J= 7.6 Hz, Ar–H), 11.97 (s, 1H, NH); 13C NMR (100 MHz, DMSO-d$_6$) δ: 10.91, 26.55, 29.13, 32.69, 87.17, 101.45, 117.40, 122.81, 124.54, 126.33, 127.91, 128.17, 129.21, 134.52, 135.71, 145.43, 147.38, 149.09, 161.98; calcd for C$_{23}$H$_{20}$ClN$_5$O$_2$: C, 66.18; H, 4.83; N, 16.78; found: C, 66.34; H, 4.76; N, 16.18.

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**References**

1. World Malaria Report 2011 summary (Report). World Health Organization.
2. Russell, D. G.; Barry, C. E.; Flynn, J. L. *Science* 2010, 328, 852-856. [http://dx.doi.org/10.1126/science.1184784](http://dx.doi.org/10.1126/science.1184784)
3. Manohar, S.; Rajesh, U. C.; Khan, S. I.; Tekwani, B. L.; Rawat, D. S. *Med. Chem. Lett.* 2012, 3, 555–559. [http://dx.doi.org/10.1021/ml3000808](http://dx.doi.org/10.1021/ml3000808)
4. Cegielski, J. P.; Chin, D. P.; Espinal, M. A.; Frieden, T. R.; Cruz, R. R.; Talbot, E. A.; Weil, D. E. C.; Zaleskis, R.; Raviglione, M.C. *Infect. Dis. Clin. North. Am.* 2002, 16, 1-58. [http://dx.doi.org/10.1016/S0891-5520(03)00045-X](http://dx.doi.org/10.1016/S0891-5520(03)00045-X)
5. Selvam, T. P.; James, C. R.; Dniandev, P. V.; Valzita, S. K. *Drug. Res. Pharm.* **2012**, *2*, 01-09.

6. Dömling, A. *Chem. Rev.* **2006**, *106*, 17-89. 
   [http://dx.doi.org/10.1021/cr0505728]

7. Ozeki, K.; Ichikawa, T.; Takehara, H.; Tanimura, K.; Sato, M.; Yaginuma, H. *Chem. Pharm. Bull.* **1989**, *37*, 1780–1787. 
   [http://dx.doi.org/10.1248/cpb.37.1780]

8. Tenser, R. B.; Gaydos, A.; Hay, K. A. *Antimicrob Agents Chemother* **2001**, *45*, 3657-3659.

9. Gadhachanda, V. R.; Wu, B.; Wang, Z.; Kuhen, K. L.; Caldwell, J.; Zondler, H.; Walter, H.; Havenhand, M.; He, Y. *Bioorg. Med. Chem.* **2007**, *17*, 260–265. 
   [http://dx.doi.org/10.1016/j.bmcl.2006.09.047]

10. Shaifullah, A.Z.M.; Yasuyuki, S. *Chem. Pharm. Bull.* **2001**, *49*, 391-395. 
   [http://dx.doi.org/10.1248/cpb.49.391]

11. Youssif, S.; El-Kafravy, A.; Bayoumy, B.; El-Bahaie, S. *Bull. Korea. Chem. Soc.* **2002**, *23*, 374-384.

12. Bakavoli, M.; Heravi, M. M.; Germaninejad, H.; Rahimizadeh, M.; Ghassemzadeh, M. *Phosphorus Sulfur Silicon Relat. Elem.* **2006**, *181*, 381-385. 
   [http://dx.doi.org/10.1080/104265091000642]

13. Bishop, A.C.; Kung, C.Y.; Shah, K.; Shokat, K.M.; Liu, Y. *J. Am. Chem. Soc.* **2002**, *121*, 627–631. 
   [http://dx.doi.org/10.1021/ja983267v]

14. Capdeville, R.; Buchdunger, E.; Zimmermann, J.; Matter, A. *Nat. Rev. Drug Discov.* **2002**, *1*, 493–502. 
   [http://dx.doi.org/10.1038/nrd839]

15. Ram. V. J.; Goel, A.; Sarkhel, S.; Maulik, P. R. A. *Bioorg. Med. Chem.* **2002**, *10*, 1275-1280. 
   [http://dx.doi.org/10.1016/S0968-0896(01)00423-0]

16. Nizamuddin-Mishra, M.; Srivastava, M. K.; Khan, M. *Indian. J. Chem.* **2001**, *40*, 49-53.

17. Ahluwalia, V. K.; Dahiya, A.; Garg, V. J. *Indian. J. Chem* **1997**, *36B*, 88-90.

18. Sunderhaus, J. D.; Martin, S. F. *Chem. Eur. J.* **2009**, *15*, 1300-1308. 
   [http://dx.doi.org/10.1002/chem.200802140]

19. Hulme, C.; Gore, V. *Curr. Med. Chem.* **2003**, *10*, 51-80. 
   [http://dx.doi.org/10.2174/09298670333368600]

20. Dömling, A.; Ugi, I. *Angew. Chem. Int. Ed.* **2000**, *39*, 3169-3210. 
   [http://dx.doi.org/10.1002/1521-3773(20000915)39:18<3169::AID-ANIE3168>3.0.CO;2-U]

21. Zhu, J.; Bienaym, H. Multicomponent Reactions Wiley 2006.

22. Quiroga. J.; Portilla. J.; Serrano, H.; Abonia, R. Insuasty, B.; Nogueras, M.; Cobo, J. *Tetrahedron Lett.* **2007**, *48*, 1987-2243. 
   [http://dx.doi.org/10.1016/j.tetlet.2007.01.074]
23. Shi, C-L.; Shi, D-Q.; Kim, SH.; Huang, Z-B.; Ji, S-B.; Ji, M. *Tetrahedron* **2008**, *64*, 2425-2432. 
   [http://dx.doi.org/10.1016/j.tet.2007.12.053](http://dx.doi.org/10.1016/j.tet.2007.12.053)

24. Quiroga, J.; Insuasty, B.; Hormaza, A.; Saitz, C.; Jullian, C. *J Heterocycl. Chem.* **1998**, *35*, 575-578. 
   [http://dx.doi.org/10.1002/jhet.5570350313](http://dx.doi.org/10.1002/jhet.5570350313)

25. Heravi, M. M.; Bakhtiari, K.; Taheri, S. *Green Chem.* **2005**, *7*, 867-869. 
   [http://dx.doi.org/10.1039/b510855c](http://dx.doi.org/10.1039/b510855c)

26. Heravi, M. M.; Mousavizadeh, F.; Ghobadi, N.; Tajbakhsh, M. *Tetrahedron Lett.* **2014**, *55*, 1226-1228. 
   [http://dx.doi.org/10.1016/j.tetlet.2014.01.004](http://dx.doi.org/10.1016/j.tetlet.2014.01.004)

27. Heravi, M. M.; Behbahani, F.K.; Daraie, M.; Oskooie, H.A. *Mol. Divers.* **2009**, *13*, 375-378. 
   [http://dx.doi.org/10.1007/s11030-009-9118-z](http://dx.doi.org/10.1007/s11030-009-9118-z)

28. Heravi, M. M.; Sadjadi, S.; Oskooie, H. A.; Hekmat Shoar, R.; Bamoharram, F. F. *Molecules* **2007**, *12*, 255-262.

29. Heravi, M. M.; Alishiri, T. *Adv. Het. Chem.* **2014**, *113*, 1-66.

30. Heravi, M. M.; Khaghaninejad, S.; Nazari, N. *Adv. Het. Chem.* **2014**, *112*, 183-234.

31. Heravi, M. M.; Zadsirjan, V. *Adv. Het. Chem*. In Press, Corrected Proof, Available online 11 September 2015.

32. Tajbakhsh, M.; Mohajerani, B.; Heravi, M. M.; Ahmadi, A. N. *J. Mol. Catal. A: Chem.* **2005**, *236*, 216-219. 
   [http://dx.doi.org/10.1016/j.molcata.2005.04.033](http://dx.doi.org/10.1016/j.molcata.2005.04.033)

33. Bazgir, A.; Khanaposhtani, M. M.; Soorki, A. A. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 5800–5803. 
   [http://dx.doi.org/10.1016/j.bmcl.2008.09.057](http://dx.doi.org/10.1016/j.bmcl.2008.09.057)

34. Satasia, S. P.; Kalaria, P. N.; Raval, D. K. *Org. Biomol. Chem.* **2014**, *12*, 1751–1758. 
   [http://dx.doi.org/10.1039/c3ob42132e](http://dx.doi.org/10.1039/c3ob42132e)

35. Sasaki, T.; Minamoto, K.; Suzuki, T.; Yamashita, S. *Tetrahedron* **1980**, *36*, 865-870. 
   [http://dx.doi.org/10.1016/0040-4020(80)80036-6](http://dx.doi.org/10.1016/0040-4020(80)80036-6)

36. Griengl, R.; Wanek, E.; Schwarz, W.; Streicher, W.; Rosenwirth, B.; Clercq, E. D. *J. Med. Chem.* **1987**, *30*, 1199-1204. 
   [http://dx.doi.org/10.1021/jm00390a013](http://dx.doi.org/10.1021/jm00390a013)

37. Heravi, M. M.; Asadi, S. *Tetrahedron Asym.* **2012**, *23*, 1431-1465/ 
   [http://dx.doi.org/10.1016/j.tetasy.2012.10.002](http://dx.doi.org/10.1016/j.tetasy.2012.10.002)

38. Heravi, M. M.; Ghods, A.; Bakhtiari, K.; Derikvand, F. *Synth. Commun.* **2010**, *40*, 1927-1931. 
   [http://dx.doi.org/10.1080/00397910903174390](http://dx.doi.org/10.1080/00397910903174390)

39. Xiaoli, M.; Jianhua, Z.; Haixia, P. *Res. Chem. Intermed.* **2012**, *38*, 629-638. 
   [http://dx.doi.org/10.1007/s11164-011-0376-x](http://dx.doi.org/10.1007/s11164-011-0376-x)
40. Heravi, M. M.; Tehrani, M. H.; Bakhtiar, K.; Oskooie, H. A. Catal. Commun. 2007, 8, 1341-1344. [http://dx.doi.org/10.1016/j.catcom.2006.11.026]

41. Oskooie, H. A.; Roomizadeh, E.; Heravi, M. M. J. Chem. Res. 2006, 4, 246-247. [http://dx.doi.org/10.3184/030823406776894238]

42. Heravi, M. M.; Zadsirjan, V.; Kamjou, K. Curr. Org. Chem. 2015, 20, 167-1686.

43. Pandey, J.; Anand, N.T.; Rama, P. Tetrahedron 2009, 65, 9350-9356. [http://dx.doi.org/10.1016/j.tet.2009.09.002]

44. Movassaghi, M.; Jacobsen, E. N. Science 2002, 298, 1904-1905. [http://dx.doi.org/10.1126/science.1076547]

45. List, B. Tetrahedron 2002, 58, 5573-5590. [http://dx.doi.org/10.1016/S0040-4020(02)00516-1]

46. Steiner, D.D.; Mase, N.; Barbas, C.F. III. Angew. Chem. Int. Ed. 2005, 44, 3706-3710. [http://dx.doi.org/10.1002/anie.200500571]