Research on Chemical Intermediates
https://doi.org/10.1007/s11164-019-04072-z

Imin-based synthesis of polyfunctionalized dihydro-2-oxypyrroles catalyzed by glycine amino acid *via* tandem Michael–Mannich cyclocondensation reaction under ambient temperature

Farzaneh Mohamadpour[1]

Received: 27 September 2019 / Accepted: 30 December 2019

Abstract
An efficient and mild synthetic route to the convenient one-pot preparation of polyfunctionalized dihydro-2-oxypyrroles has been developed and catalyzed *via* glycine amino acid as a natural bio-based and biodegradable catalyst using imin-based four condensation domino reaction of amines, dialkyl acetylenedicarboxylates and formaldehyde *via* tandem Michael–Mannich cyclocondensation reaction under ambient temperature. The reactions complete in less time, but the products are obtained in outstanding yields. This environmentally friendly method includes the noticeable properties such as bio-based and green catalyst, direct workup without column chromatographic separation, cost-effective, mild and simple synthesis, one-pot procedure and high atom economy.

Keywords Polyfunctionalized dihydro-2-oxypyrroles · Glycine amino acid · Naturally bio-based and biodegradable catalyst · High atom economy · Imin-based synthesis

Introduction

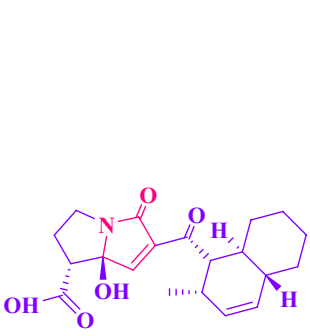
Biochemists and synthetic organic chemists have been fascinated by the structures comprising the pyrrole derivatives as a result of their biological and pharmaceutical activities (Fig. 1). There are reports in the literature regarding pyrrole derivatives as human cytomegalovirus protease (HCMV) [1] and human cytosolic carbonic anhydrase isozymes [2]; they were utilized as PI-091 [3], as well as

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s11164-019-04072-z) contains supplementary material, which is available to authorized users.

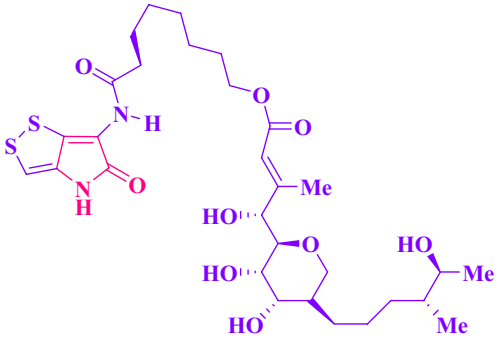
✉ Farzaneh Mohamadpour
mohamadpour.f.7@gmail.com

[1] School of Engineering, Apadana Institute of Higher Education, Shiraz, Iran

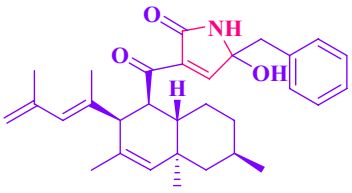
Published online: 11 January 2020



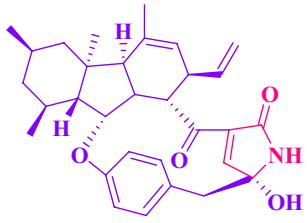
UCS1025A



Thiomarinol A 4



Oteromycin



Pyrrocidine A

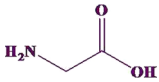
Fig. 1 Biologically active compounds with dihydro-2-oxypyrroles rings

cardiac cAMP phosphodiesterase [4]; most of the alkaloids possess pyrrole rings [5]. Also, these rings have the same usage as oteromycin [6]. They exhibit various biological activities, for example (imidazolylphenyl) pyrrol-2-one [4].

Considering the great prominence of pyrrole derivatives, recently, there are some reports of synthesizing polyfunctionalized dihydro-2-oxypyrroles utilizing reactions with multi-components in the existence of different catalysts such as I_2 [7], $InCl_3$ [8], [n-Bu_4N][HSO_4] [9], $Al(H_2PO_4)_3$ [10], AcOH [11], $Cu(OAc)_2{\cdot}H_2O$ [12], oxalic acid dihydrate [13], $ZrCl_4$ [14], Fe_3O_4@ nano-cellulose–OPO_3H [15], ethylenediammonium diformate [16], maltose [17], $BiFeO_3$ nanoparticles [18], nano-Fe_3O_4@SiO_2/$SnCl_4$ [19], graphene oxide [20] and $CoFe_2O_4$@SiO_2@IRMOF-3 [21]. Each of the these methods has its own merits, but some of these methods are limited in terms of the use of expensive catalysts, long reaction periods, low yields, harsh reaction conditions, tedious workup, and need of additional quantities of catalysts or reagents and hazardous or toxic catalysts with column chromatographic separation. Hence, finding the mild environmentally friendly and appropriate approaches for synthesizing these kinds of compounds is vital.

Since we partly aimed to develop efficient synthetic processes using green catalyst [22–24] and due to the above considerations, preparation of various

Fig. 2 Structure of glycine amino acid



biologically active polyfunctionalized dihydro-2-oxypyrroles is of considerable interest and herein, we have reported glycine amino acid (Fig. 2) as a naturally bio-based and biodegradable catalyst for synthesis of polyfunctionalized dihydro-2-oxypyrroles through imin-based four condensation domino reaction of amines, formaldehyde and dialkyl acetylenedicarboxylates in superb yields and short reaction periods. The advantages of glycine in synthesis of organic compounds are natural, green, easy control, low cost, trivial, simply accessible, non-toxic and ecofriendly. Also, in the present paper, the products were found *via* simple filtering and purified just by washing with ethanol without requiring column chromatographic separation.

Materials and methods

Materials

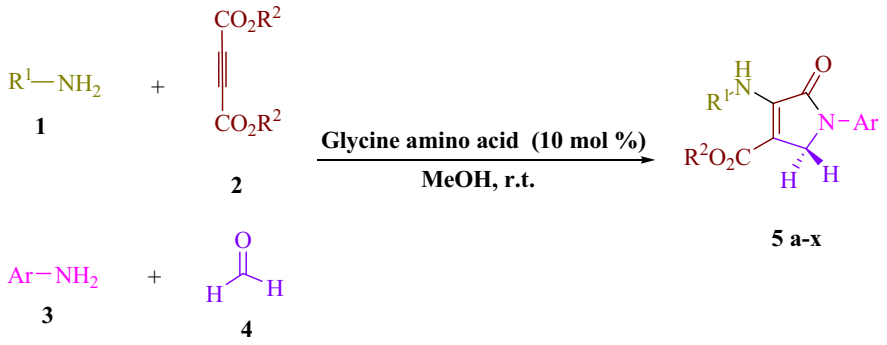
Utilizing an Electrothermal 9100 device, all compounds' melting points were found. Moreover, nuclear magnetic resonance, ^{1}H NMR, spectra were recorded on a Bruker DRX-400 and Bruker DRX-300 Avance tool with $CDCl_3$.

Overall process of preparing (5a-x)

A combination of amine **1** (1.0 mmol) and dialkyl acetylenedicarboxylate **2** (1.0 mmol) was agitated in MeOH (3 mL) for 15 min. Then, adding amine **3** (1.0 mmol) and formaldehyde **4** (1.5 mmol) and glycine amino acid (10 mol%), the reaction was agitated for apposite period (Scheme 1). The combination was filtered after completing the reaction (by thin-layer chromatography TLC), and then, the solid was rinsed with EtOH without column chromatographic separation to obtain pure compounds (**5a-x**). Comparing the spectroscopic information, the products were categorized (^{1}HNMR). Supporting Information associated with this article can be found in the online version.

Results and discussion

Primarily, glycine amino acid's catalytic activity was examined in a model system in the four-element reaction between a combination of formaldehyde (1.5 mmol), aniline (2 mmol) and dimethyl acetylenedicarboxylate (DMAD) (1 mmol). The enhanced circumstances were defined by changing the solvents and number of the catalyst equivalents. In the absence of a catalyst, only a trace of product was obtained at rt for a reaction time of about 12h (Table 1, entry 1). Inserting 5 mol%



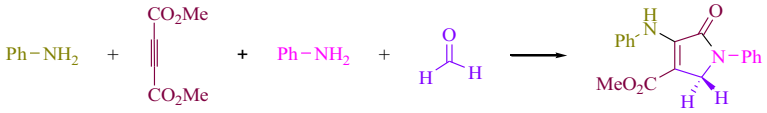
R^{1} = n-C_4H_9, $PhCH_2$, C_6H_5, 4-Cl-C_6H_4, 4-Br-C_6H_4, 4-Et-C_6H_4, 4-OMe-C_6H_4, 4-F-C_6H_4, 4-Me-C_6H_4.

R^{2} = CH_3, C_2H_5.

Ar = 4-Br-C_6H_4, 4-F-C_6H_4, 3,4-Cl_2-C_6H_3, C_6H_5, 4-Cl-C_6H_4, 4-Et-C_6H_4, 4-OMe-C_6H_4, 4-Me-C_6H_4.

Scheme 1 Synthesis of polyfunctionalized dihydro-2-oxypyrroles

Table 1 Optimizing the reaction circumstance in the existence of various quantities of glycine amino acid



Entry	Glycine (mol %)	Solvent	Time (h)	Isolated yields (%)
1	Catalyst free	MeOH	12	Trace
2	5	MeOH	5	67
3	**10**	**MeOH**	**3**	**93**
4	10	H_2O	7	17
5	10	EtOH	4	56
6	10	H_2O/EtOH	6	44
7	10	Solvent free	6	32
8	10	DMF	4	45
9	10	THF	4	50
10	10	$CHCl_3$	10	16
11	10	*n*-Hexane	9	21
12	10	CH_3CN	4	39
13	10	CH_2Cl_2	10	13
14	15	MeOH	3	94

of the catalyst, a considerable progress was found by the reaction, completing in around 5 h (Table 1, entry 2). When 10 mol% of catalyst was used, the reaction efficiently proceeded and completed in less reaction time (3h) (Table 1, entry 3). No considerable enhancement in the product yield and reaction period was found by additionally incrementing catalyst quantity (Table 1, entry 14). Some solvents like H_2O, MeOH, EtOH, H_2O/EtOH, DMF, THF, $CHCl_3$, *n*-hexane, CH_3CN and CH_2Cl_2 were also examined with catalytic quantity of glycine (10 mol %) and from the environmental and economic aspects; MeOH was chosen as medium for all additional reactions (Table 1, entry 3). As observed in Table 2, it was indicated that this technique can work with various substrates. It should be noted that for purifying the products (**5a-x**), a modest filtration and wash with ethanol are needed.

Recommended mechanism for synthesizing polyfunctionalized dihydro-2-oxypyrroles is demonstrated in Fig. 2. Originally, in the existence of glycine, a reaction happens between the amine **3** and formaldehyde **4** to create imine **A**. Furthermore, enamine **B** is obtained by the Michael reaction between amine **1** and dialkyl acetylenedicarboxylate **2**. Mannich kind of reaction happens between activated imine **A** and enamine **B** to create intermediate **C** transforming to more stable tautomeric form **D**. The intramolecular cyclization in intermediate **D** that in the final step, it tautomerizes into the corresponding polyfunctionalized dihydro-2-oxypyrroles **5** (Scheme 2).

Table 3 represents the comparison of the catalytic capability of some catalysts reported in the literature for synthesis of polyfunctionalized dihydro-2-oxypyrroles. Within this work, it is revealed that glycine amino acid possesses its amazing potential as a substitute green, bio-based, biodegradable and inexpensive catalyst for the one-pot mild synthesis of these naturally active heterocyclic compounds, and outstanding yields and short reaction periods are the remarkable benefits of this current procedure.

Conclusions

In conclusion, in the present work, it is demonstrated that a natural bio-based and biodegradable catalyst, glycine amino acid, can be used as a greatly efficient and available solid catalyst for one-pot mild imin-based 4-component synthesis of polyfunctionalized dihydro-2-oxypyrroles under ambient temperature. The use of the green, inexpensive and easy-to-handle catalyst, short reaction periods, excellent yields, high catalytic efficiency, mild reaction circumstances, simple workup,

Table 2 Glycine amino acid catalyzed synthesis of polyfunctionalized dihydro-2-oxypyrroles

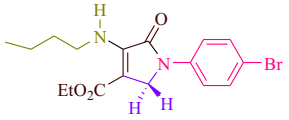
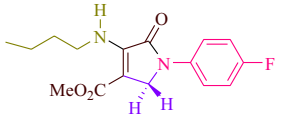
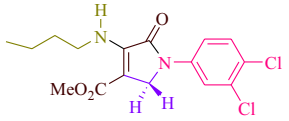
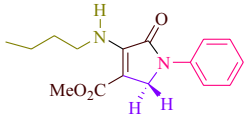
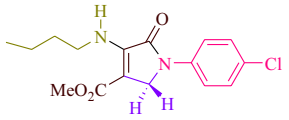
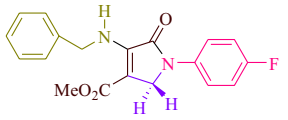
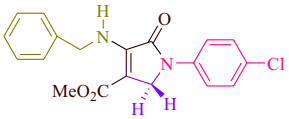
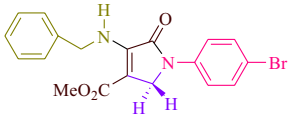
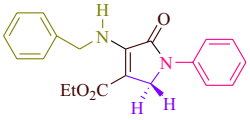
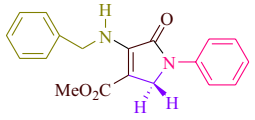
 **5a** (4h, 82%) Mp. 92-94 °C Lit. 94-96 °C **[10]**	 **5b** (2.5h, 91%) Mp. 83-85 °C Lit. 81-83 °C **[16]**
 **5c** (4h, 80%) Mp. 99-101 °C Lit. 97-99 °C **[10]**	 **5d** (3h, 84%) Mp. 58-60 °C Lit. 60 °C **[7]**
 **5e** (3.5h, 88%) Mp. 92-94 °C Lit. 91-93 °C **[16]**	 **5f** (3h, 86%) Mp. 164-166 °C Lit. 166-168 °C **[10]**
 **5g** (4h, 85%) Mp. 146-148 °C Lit. 147-148 °C **[7]**	 **5h** (5h, 82%) Mp. 121-123 °C Lit. 120-121 °C **[7]**
 **5i** (4h, 86%) Mp. 128-130 °C Lit. 130-132 °C **[11]**	 **5j** (4h, 89%) Mp. 139-141 °C Lit. 140-141 °C **[11]**

Table 2 (continued)

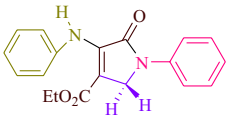
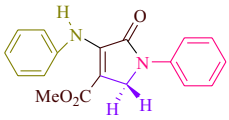
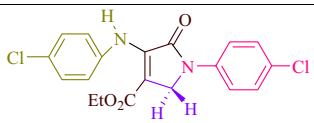
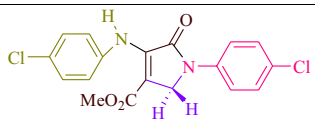
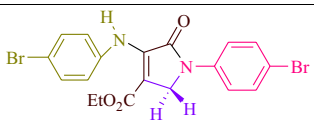
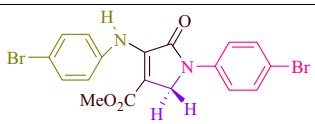
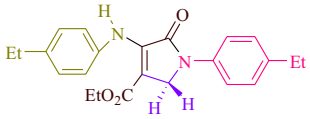
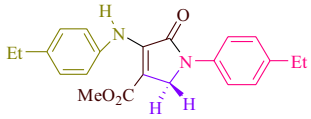
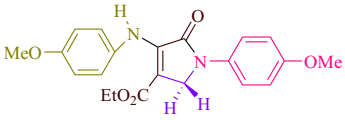
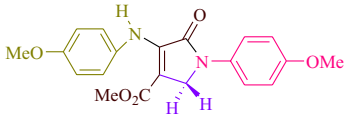
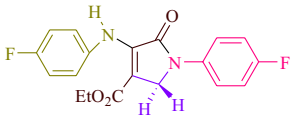
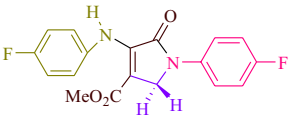
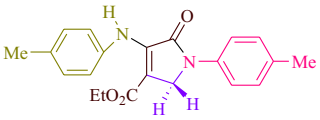
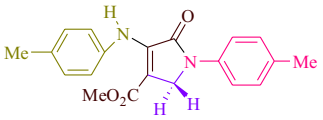
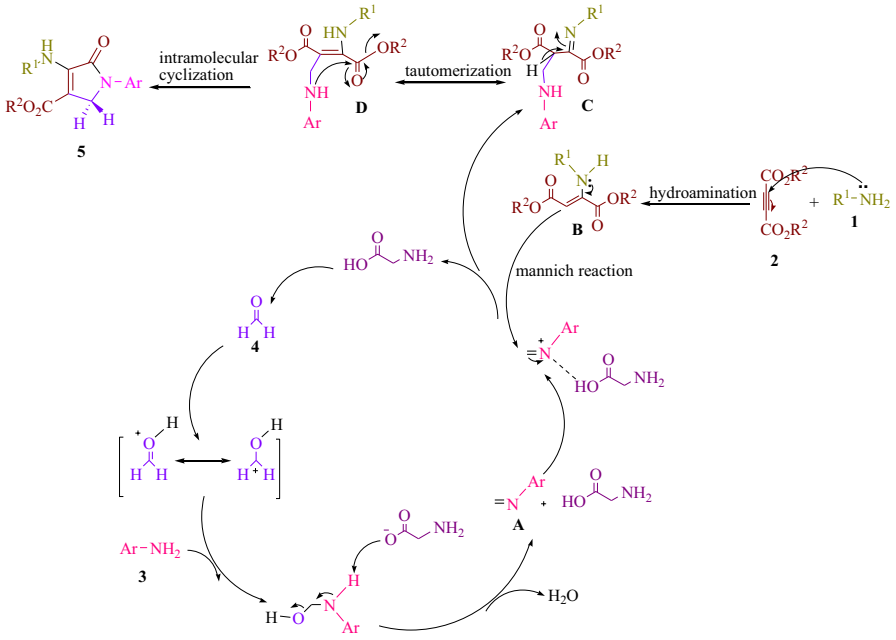
 **5k** (3h, 90%) Mp. 137-139 °C Lit. 138-140 °C **[11]**	 **5l** (3h, 93%) Mp. 155-157 °C Lit. 155-156 °C **[7]**
 **5m** (5h, 80%) Mp. 169-171 °C Lit. 168-170 °C **[9]**	 **5n** (5h, 82%) Mp. 173-175 °C Lit. 171-173 °C **[9]**
 **5o** (5.5h, 76%) Mp. 169-171 °C Lit. 169-171 °C **[11]**	 **5p** (5h, 79%) Mp. 173-175 °C Lit. 175-177 °C **[9]**
 **5q** (4h, 84%) Mp. 104-106 °C Lit. 102-104 °C **[15]**	 **5r** (4h, 82%) Mp. 123-125 °C Lit. 124-125 °C **[15]**
 **5s** (3h, 91%) Mp. 151-153 °C Lit. 152-154 °C **[10]**	 **5t** (3h, 89%) Mp. 173-175 °C Lit. 172-175 °C **[9]**

Table 2 (continued)

 **5u** (2h, 95%) Mp. 174-176 °C Lit. 172-174 °C [9]	 **5v** (2h, 96%) Mp. 162-164 °C Lit. 163-165 °C [8]
 **5w** (3h, 93%) Mp. 130-132 °C Lit. 131-132 °C [11]	 **5x** (3h, 92%) Mp. 178-180 °C Lit. 177-178 °C [10]



Scheme 2 Recommended mechanistic path for synthesizing polyfunctionalized dihydro-2-oxypyrroles

convenient and expedient procedure are the notable advantages of this eco-safe and simple protocol.

Table 3 Comparison of catalytic capability

Entry	Product	Catalyst	Conditions	Time/yield (%)	References
1	**5k**	I_2	MeOH, r.t.	1 h/81	[7]
2	**5k**	$InCl_3$	MeOH, r.t.	3 h/85	[8]
3	**5k**	$[n\text{-}Bu_4N][HSO_4]$	MeOH, r.t.	4 h/86	[9]
4	**5k**	$Al(H_2PO_4)_3$	MeOH, r.t.	5 h/80	[10]
5	**5k**	$Cu(OAc)_2{\bullet}H_2O$	MeOH, r.t.	5 h/85	[12]
6	**5k**	$ZrCl_4$	MeOH, r.t.	3.5 h/83	[14]
7	**5k**	EDDF	EtOH, reflux	3.5 h/84	[16]
8	**5k**	Maltose	MeOH, r.t.	6 h/73	[17]
9	**5k**	Glycine amino acid	MeOH, r.t.	3 h/90	This work
10	**5l**	I_2	MeOH, r.t.	1 h/82	[7]
11	**5l**	$InCl_3$	MeOH, r.t.	3 h/85	[8]
12	**5l**	$[n\text{-}Bu_4N][HSO_4]$	MeOH, r.t.	4 h/88	[9]
13	**5l**	$Al(H_2PO_4)_3$	MeOH, r.t.	5 h/81	[10]
14	**5l**	$Cu(OAc)_2{\bullet}H_2O$	MeOH, r.t.	6 h/91	[12]
15	**5l**	$ZrCl_4$	MeOH, r.t.	4 h/84	[14]
16	**5l**	EDDF	EtOH, reflux	3 h/89	[16]
17	**5l**	Maltose	MeOH, r.t.	3 h/82	[17]
18	**5l**	Glycine amino acid	MeOH, r.t.	3 h/93	This work

Acknowledgements We gratefully acknowledge financial support from the Research council of the Apadana Institute of Higher Education.

References

1. A.D. Borthwick, A.J. Crame, P.F. Ertl, A.M. Exall, T.M. Haley, G.J. Hart, A.M. Mason, M.K. Pennell, O.M.P. Singh, G.G. Weingarten, J.M. Woolven, J. Med. Chem. **45**, 1 (2002)
2. C. Alp, D. Ekinci, M.S. Gultekin, M. Senturk, E. Sahin, O. Kufrevioglu, Bioorg. Med. Chem. **18**, 4468 (2010)
3. R. Shiraki, A. Sumino, K. Tadano, S. Ogawa, Tetrahedron Lett. **36**, 5551 (1995)
4. Y.L. Lampe, R.G. Chou, R.G. Hanna, S.V. DiMeo, P.W. Erhardt, A.A. Hagedorn, W.R. Ingebretsen, E. Cantor, J. Med. Chem. **36**, 10410 (1993)
5. Y. Chen, D.X. Zeng, N. Xie, Y.Z. Dang, J. Org. Chem. **70**, 5001 (2005)
6. S.B. Singh, M.A. Goetz, E.T. Jones, G.F. Billes, R.A. Giacobbe, L. Herranz, J. Org. Chem. **60**, 7040 (1995)
7. A.T. Khan, A. Ghosh, M. Musawwer Khan, Tetrahedron Lett. **53**, 2622 (2012)
8. S.S. Sajadikhah, M.T. Maghsoodlou, N. Hazeri, Chin. Chem. Lett. **25**, 58 (2014)
9. S.S. Sajadikhah, N. Hazeri, Res. Chem. Intermed. **40**, 737 (2014)
10. S.S. Sajadikhah, N. Hazeri, M.T. Maghsoodlou, S.M. Habibi-Khorassani, A. Beigbabaei, A.C. Willis, J. Iran. Chem. Soc. **10**, 863 (2013)
11. Q. Zhu, H. Jiang, J. Li, S. Liu, C. Xia, M. Zhang, J. Comb. Chem. **11**, 685 (2009)
12. L. Lv, S. Zheng, X. Cai, Z. Chen, Q. Zhu, S. Liu, J. Acs. Comb. Sci. **15**, 183 (2013)
13. S.S. Sajadikhah, N. Hazeri, M.T. Maghsoodlou, J. Chem. Res. **37**, 40 (2013)
14. S.S. Sajadikhah, M.T. Maghsoodlou, N. Hazeri, S. Mohamadian-Souri, Res. Chem. Intermed. **42**, 2805 (2016)
15. N. Salehi, B.B.F. Mirjalili, RSC Adv. **7**, 30303 (2017)

16. M. Zarei, S.S. Sajadikhah, Res. Chem. Intermed. **42**, 7005 (2016)
17. N. Hazeri, S.S. Sajadikhah, M.T. Maghsoodlou, M. Norouzi, M. Moein, S. Mohamadian-Souri, J. Chem. Res. **37**, 550 (2013)
18. H. Singh, J.K. Rajput, J. Mater. Sci. **53**, 3163 (2018)
19. B.B.F. Mirjalilia, R. Araqia, S.A. Mohajeri, Iran J. Catal. **9**, 11 (2019)
20. M. Bavadi, K. Niknam, Mol. Divers. **22**, 561 (2018)
21. J.N. Zhang, X.H. Yang, W.J. Guo, B. Wang, Z.H. Zhang, Synlett **28**, 734 (2017)
22. F. Mohamadpour, Polycycl. Aromat. Comp. (2019)
23. F. Mohamadpour, M. Lashkari, J. Serb. Chem. Soc. **83**, 673 (2018)
24. F. Mohamadpour, Org. Prep. Proced. Int. (2019)