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$Fe_3O_4@SiO_2/BiPy^{2+}2Cl^-$ nanocomposite Promoted Rapid Synthesis of Pyranopyrazole and Octahydroquinazoline Derivatives

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Abstract

$Fe_3O_4@SiO_2$/bipyridinium chloride nanocomposite, $Fe_3O_4@SiO_2/BiPy^{+2}2Cl^-$, as a magnetically separable and recyclable heterogeneous catalyst was used for the one-pot synthesis of pyranopyrazole and octahydroquinazoline derivatives via multi-components cyclocondensation reaction under solvent free conditions. The catalyst was recovered by simple magnetic decantation and can be recycled several times with no significant loss of its catalytic activity. The results showed that the desired products were obtained with high efficiency, rapid, simple, and eco-friendly.

Keywords: Pyranopyrazole, Octahydroquinazoline, Magnetically separable catalyst, $Fe_3O_4@SiO_2$/bipyridinium nanocomposite

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Introduction

The highly reported biological and medicinal properties of heterocyclic compounds have encouraged chemists to try to find effective and easy methods for their easy synthesis. The most useful way to achieve these goals requires multicomponent reactions that are used as a powerful tool for this purpose.

In recent years, many heterocyclic compounds with valuable components have been developed in the area of chemical and pharmaceutical biology and pharmaceuticals under environmental-friendly synthetic methods. Among them, pyranopyrazoles and octahydroquinazolines have received special attention due to their wide range of activities such as anti-inflammatory, anti-cancer and analgesic [1-6]. Although several methods and catalysts have been reported for the synthesis of pyropyrazoles and octahydroquinazolines, methods that are more efficient are still needed [7-9].

The synthesis of iron oxide-based magnetic catalysts has become increasingly important over the past decade due to its several applications in pharmaceuticals, biotechnology, and materials science engineering. These magnetic nanocatalysts, due to their ease of preparation, high active surfaces and abundant active sites, are a suitable substrate that can be easily separated from the reaction mixture by an external magnetic field for recovery and reuse. By keeping these facts in mind and continuing our research on the use of nanomagnetic catalysts in organic synthesis [10-12], recently we reported facile synthesis of $Fe_3O_4@SiO_2/BiPy^{+2}2Cl^-$, and its effective application in the synthesis of highly substituted imidazoles via multi-component condensation strategy [13]. Also, an attempt was made to expand the catalytic activity of $Fe_3O_4@SiO_2/BiPy^{+2}2Cl^-$ in the synthesis of pyranopyrazole and octahydroquinazoline derivatives via multi-components cyclocondensation reaction under solvent free conditions.

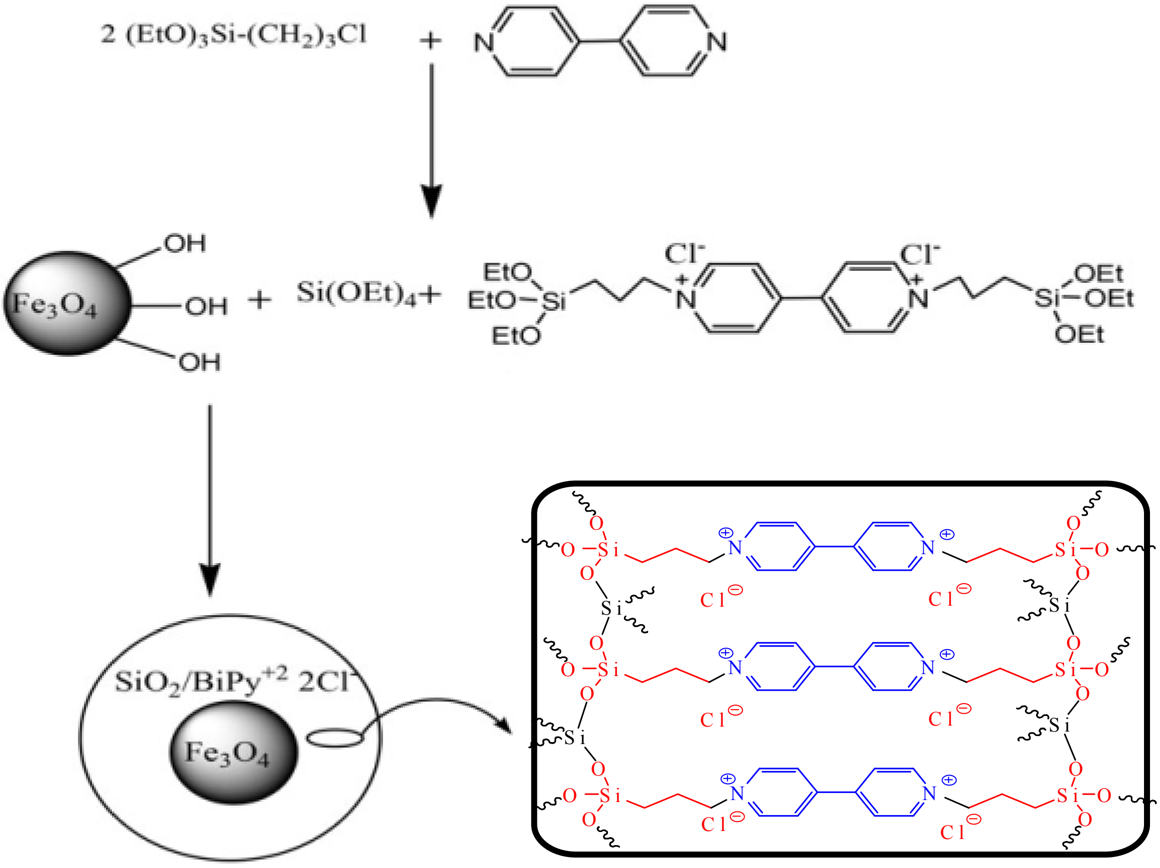
Experimental

General

General Chemical reagents and solvents were purchased from the Merck and Aldrich Chemical Company. Melting points were determined in open capillaries using an Electrothermal Mk3 apparatus, which are uncorrected. ^1H and ^{13}C NMR spectra were recorded with a Bruker DPX-400 spectrometer. FT-IR spectra were obtained with potassium bromide pellets in the range 400–4000 cm^{-1} with a Perkin–Elmer spectrometer. $Fe_3O_4@SiO_2/BiPy^{2+}2Cl^-$ nanocomposite was prepared according to the previously reported method. [13]

General procedure for the preparation of Pyranopyrazole derivatives

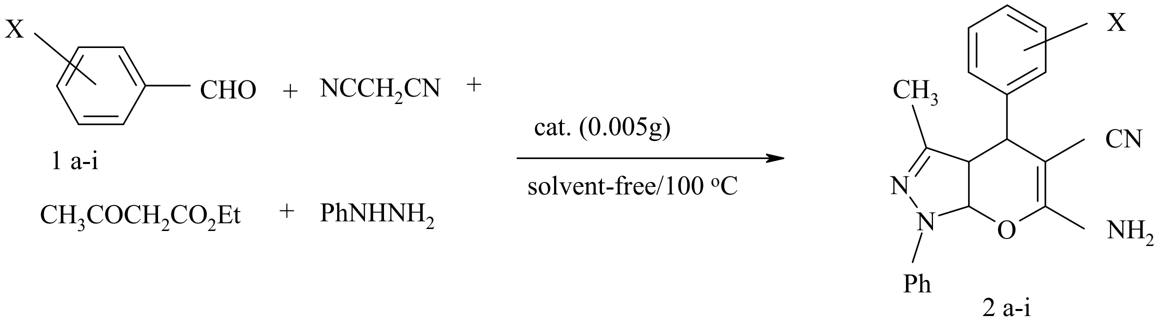
A mixture of malononitrile (1 mmol), aldehyde (1 mmol), ethyl acetoacetate (1 mmol), phenyl hydrazine (1mmol) and $Fe_3O_4@SiO_2/BiPy^{2+}2Cl^-$ (0.005 g) was mixed at 100 ˚C under solvent free conditions. The progress of the reaction was monitored using TLC using hexane and ethyl acetate (7:3) as eluents. After the satisfactory completion of the reaction and cooling, 5 mL hot ethanol was added to the reaction mixture and then an external magnet separated the magnetic catalyst. The crude product was purified by recrystallization in hot ethanol and identified by comparing the spectral data and melting point with those of the authentic samples scheme 1.



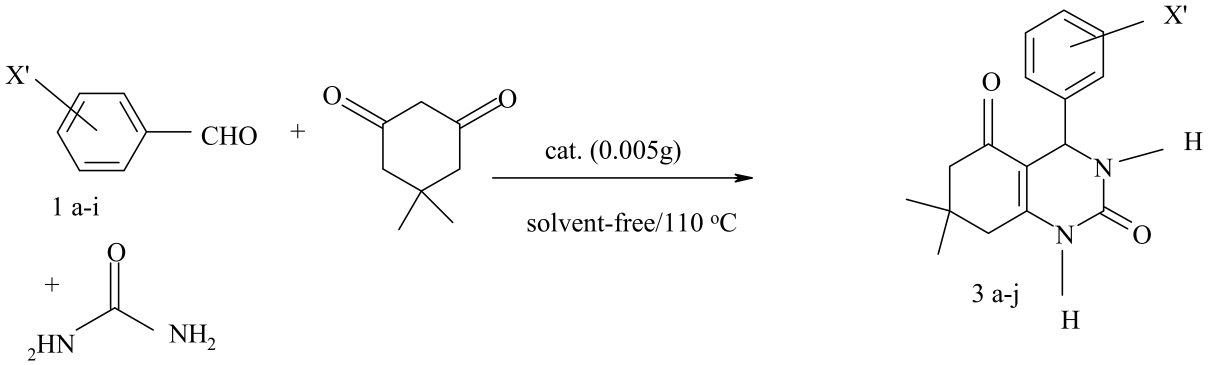
Scheme 1. Systematic approach for the preparation of $Fe_3O_4@SiO_2/BiPy^{2+}2Cl^-$ nanocomposite.

General procedure for the preparation of Octahydroquinazoline derivatives

A mixture of urea (5 mmol), benzaldehyde (1 mmol), dimedone (1 mmol), and 0.05 g of catalyst was prepared at 110 ˚C under solvent free conditions. TLC monitored the progress of reaction. After satisfactory completion of the reaction and cooling, 5 mL hot ethanol was added to the reaction mixture and then an external magnet separated the magnetic catalyst. The crude product was filtered and recrystallized with hot ethanol to get pure product. The desired pure products were characterized by comparison of spectral data and melting point with those of the authentic samples scheme 2.



X: 4-NO_2 (2**a**), H (2**b**), 4-CH_3 (2**c**), 4-CH_3O (2**d**), 4-Cl (2**e**), 2,4-Cl_2 (2**f**), 4-Br (2**g**), 2-Cl (2**h**)



X': 4-NO_2 (3**a**), H (3**b**), 4-CH_3 (3**c**), 4-CH_3O (3**d**), 3-CH_3O (3**e**), 4-Cl (3**f**), 3-NO_2 (3**g**),

4-Br (3**h**), 2-Cl (3**i**)

Scheme 2. The one-pot synthesis of Pyranopyrazole and Octahydroquinazoline derivatives.

Results and discussion

After successful preparation of $Fe_3O_4@SiO_2/BiPy^{2+}2Cl^-$ magnetic nanocomposite according to previously reported method [13] (Scheme 1), we examined its catalytic ability as a magnetically separable and recyclable heterogeneous catalyst in the one-pot synthesis of pyranopyrazole and octahydroquinazoline derivatives via multi-components cyclocondensation reaction under solvent free conditions (Scheme 2).

Initially, the one-pot four-component condensation reaction of malononitrile, benzaldehyde, ethyl acetoacetate, phenyl hydrazine (in a molar ratio of 1:1:1:1) was studied as a model for the synthesis of corresponding pyranopyrazol in the presence of $Fe_3O_4@SiO_2/BiPy^{2+}2Cl^-$. TLC analysis of the reaction mixture interestingly showed that this catalyst acts veried efficiently under solvent free thermal conditions. In addition, the optimum value of the catalyst was found to be 0.005 g at 100 ° C.

In order to optimize the reaction conditions, the condensation of benzaldehyde (1 mmol), dimidone (1–2 mmol) and urea (1–5 mmol) were selected as model reaction. According to the results, the best conditions were obtained in the presence of 0.005 g of catalyst and application of 5 mmol urea, 1 mmol benzaldehyde and 1 mmol dimedon at 110 ° C (Table 1).

Table 1. Synthesis of 4-(4-phenyl)-7,7-dimethyl-1,2,3,4,5,6,7,8 octahydroquinazoline-2,5-dione (2**b**) in different solvents.

Entry	Dimedone (mmol)	Urea (mmol)	T (^{o}C)	Cat. (g)	Solvent (mL)	Time (min)	(%)Yelid
1	1	1	100	0.03	Solvent-free	60	30
2	2	2	100	0.03	Solvent-free	60	45
3	1	1.5	100	0.01	Solvent-free	56	70
4	1	5	110	without	Solvent-free	45	30
5	1	5	110	0.005	Solvent-free	20	91
6	2	5	110	0.01	Solvent-free	25	80
7	2	5	110	0.03	Solvent-free	35	73
8	1	5	reflux	0.005	Water	90	66
9	1	5	reflux	0.005	Ethanol	83	75
10	1	5	reflux	0.005	Acetonitrile	110	52

In the following in order to investigate the effect of solvent on the conversion rate and reaction time, the desired reaction with the optimal value catalyst (0.005 g) in the absence of solvent and in different solvents ethanol, acetonitrile, water was investigated. Examination of The best results (91% yield, 20 min) were obtained in solvent free for this multi-component reaction (Table 1, Entry 5).

Table 2. One-pot preparation of pyranopyrazoles promoted by $Fe_3O_4@SiO_2/BiPy^{2+}2Cl^{-}$ under solvent-free conditions at 100℃.

Entry	Product	Time (min)	(%)Yield	Observed M.p	Reported M.p
1	2**a**	10	95	190-192	194-196[14]
2	2**b**	20	91	167-169	170-172[14]
3	2**c**	22	93	178-180	180-182[12]
4	2**d**	17	83	171-172	174-175[14]
5	2**e**	19	95	170-172	172-174[14]
7	2**f**	15	90	180-183	185-186[14]
8	2**g**	17	90	181-183	183-184[14]
9	2**h**	30	92	145-147	144-146[14]

The generality and synthetic scope of this multicomponent condensation reaction were demonstrated by synthesizing a series of pyranopyrazole derivatives, which contained different steric and electronic substituents. As shown in Table 2 in all cases, aromatic aldehydes with electron either donating or electron-withdrawing groups reacted successfully and gave the expected products in good to excellent yields in short reaction times. After successful application of $Fe_3O_4@SiO_2/BiPy^{2+}2Cl^{-}$ as promoter in the synthesis of pyranopyrazole derivatives, its catalytic ability as a magnetically separable and recyclable heterogeneous catalyst was also investigated in the one-pot synthesis of octahydroquinazoline derivatives via multi-components cyclocondensation reaction under solvent free conditions. The generality of the method was studied by application of aromatic aldehyde with electron donating and withdrawing groups.

Table 3. One-pot preparation of octahydroquinazolines promoted of $Fe_3O_4@SiO_2/BiPy^{2+}2Cl^-$ under solvent-free conditions at 110℃.

Entry	Product	Time (min)	(%)Yield	Observed M.p	Reported M.p
1	3**a**	20	88	302-304	302-304[15]
2	3**b**	25	90	290-292	290-292[16]
3	3**c**	35	81	298-299	>300[15]
4	3**d**	26	88	241-243	244-247[16]
5	3**e**	30	85	246-249	247-249[17]
6	3**f**	15	86	300-302	304-306[15]
7	3**g**	17	95	298-299	299-300[15]
8	3**h**	12	86	283-284	284-283 [18]
9	3**i**	12	87	286-288	282-285[16]

As shown in Table 3, aromatic aldehydes with substitutes carrying either electron-withdrawing or electron-donating groups reacted successfully and gave the expected products in good to excellent yields in short reaction times. The desired pure products were characterized by comparison of their physical and spectral data (melting points, IR, and ^1H NMR) with those of known compounds.

The reusability of the recovered catalyst has been studied as another efficient and important aspect of this protocol (Figure 1).

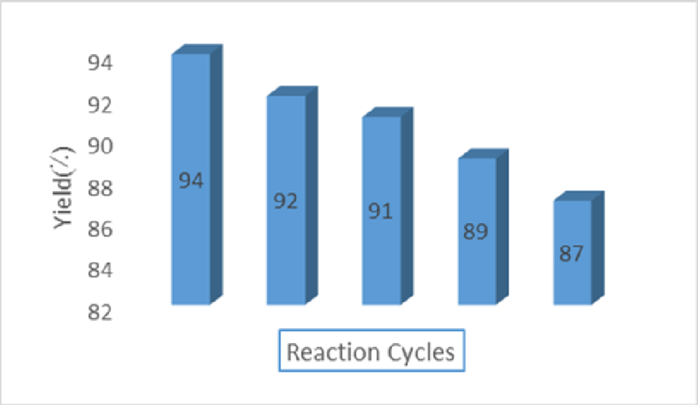


Figure 1. Reusability of the catalyst in the reaction of malononitrile, benzaldehyde, ethyl acetoacetate and phenyl hydrazine.

The procedure described here appeared to be highly efficient and competitive with other methods reported in the literature. We were compared the results of $Fe_3O_4@SiO_2/BiPy^{2+}2Cl^-$ nanocomposite with reported catalysts in the synthesis of Pyranopyrazole and Octahydroquinazoline derivatives.

The time and efficiency of the $Fe_3O_4@SiO_2/BiPy^{2+}2Cl^-$ is better than the other catalysts (Tables 4 and 5).

Table 4. Comparison of various catalysts for the multicomponent condensation of benzaldehyde, dimidone and urea

Entry	Cat.	Time(min)	Yield (%)	Ref.
1	Conc.H_2SO_4/Ethanol/80 °C	540	70	[19]
2	Conc.H_2SO_4/H_2O/rt	180	85	[20]
3	$HClO_4$-SiO_2(0.025 mmol)/CH_8CN/Reflux	360	54	[21]
4	VCl_3/CH_3CN/Reflux	120	67	[22]
5	TMSCl/CH_8CN/Reflux	300	15	[23]
6	$Fe_3O_4@SiO_2$/bipyridinium	25	90	Present work

Table 5. Comparison of various catalysts for the multicomponent condensation of malononitrile, benzaldehyde, ethyl acetoacetate and phenyl hydrazine.

Entry	Cat.	Time(min)	Yield (%)	Ref.
1	Sulfamic acide (5%mol)	600	82	[24]
2	Bovine serum albumin (60mg)	90	94	[25]
3	FSM-16-SO_3H (40 mg)	40	88	[26]
4	γ-Alumina	50	80	[27]
5	$Fe_3O_4@SiO_2$/bipyridinium	20	90	Present work

Selected spectral data

4-Phenyl-3,3-dimethyl-1,2,3,4,5,6,7,8-octahydroquinazoline-2,5-dione (3**b**)

Yield 90%.- M. p. 290-292 °C.- IR (KBr): ν = 3310, 2958 (NH), 1720, 1650 (CO), 1606 (C=C) cm^{-1}.- ^1H NMR (400 MHz, DMSO-d6): δ = 2.2 (S, 3H, CH_3), 2.4 (s, 3H, CH_3), 2.20 (s, CH_2), 3.73 (s, 1H, CH), 5.42 (NH), 7.29-7.46 (m, H, Ar).- ^{13}C NMR (100 MHz, DMSO-*d*6): δ = 192.31 (CO).- 153.28 (CO).- 146.28, 143.72, 129.93-126.41 (aromatic carbons).- 101.39, 79.30, 76.14, 64.38(CH).- 34.98, 24.32 (CH_3).- 22.30 (CH_3).

6-Amino-4-(2,4-di-(2,3-dicholorohenyl)-3-methyl-1-phenyl-1,4-dihydropyrano[2,3c] pyrazole-3-carbonitrile (2**f**)

Yield 90%.- M. p. 194-196 °C.- IR (KBr): ν = 3454, 3321 (NH_2), 2199 (C≡N), 1659 (C=C) cm^{-1}.- ^1H NMR (400 MHz, DMSO-d6): δ = 2.08 (s, 3H, CH_3), 4.80 (s, 1H, CH), 7.6 (2H, NH_2), 7.20-7.68 (m, 14H, Ar).

Conclusions

In conclusion, we reported a one-pot synthesis of functionalized Pyranopyrazole and octahydroquinazolinone derivatives in the presence of $Fe_3O_4@SiO_2$/bipyridinium as an environmentally safe and heterogeneous catalyst. These methods offered several advantages including recyclable catalyst, increase reaction speed, high yields short reaction times, easy work-up and performing the reaction under green conditions.

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References

[1] S. C. Kuo, L. J. Huang, H. Nakamura, *J. Med. Chem.*, 27, 539 (1984).

[2] J. L. Wang, D. Liu, Z. J. Zheng, S. Shan, X. Han, S. M. Srinivasula, C. Croce, E. S. Alnemri, Z. Huang, *Proc. Natl. Acad. Sci., U.S.A.* 97, 7124 (2000).

[3] M. E. A. Zaki, H. A. Soliman, O. A. Hiekal, A. E. Z. Rashad, *Naturforsch.,* 61, 1 (2006).

[4] D. Das, R. Banerjee, A. Mitra, *J. Chem. Pharmaceut. Res*., 6, 108 (2014).

[5] R. Sakhuja, S. S. Panda, L. Khanna, S. Khurana, S.C. Jain, *Bioorg. Med. Chem. Lett*., 18, 5465 (2011).

[6] M. Kidwai, S. Saxena, M. K. R. Khan, S. S. Thukral, *Eur. J. Med. Chem*., 40, 816 (2005).

[7] S. Sikandar, A. F. Zahoor, *J. Heterocyclic. Chem.,* 58, 685 (2021)

[8] O. I. el-Sabbagh [1], M. A. Shabaan, H. H. Kadry, E. Saad Al-Din, *Eur. J. Med. Chem*., 45, 5390 (2010).

[9] S. Zheng, S. Zhong, Z. Chen, W. Chen, Q. Zhu, *ACS Comb. Sci.*, 8, 475 (2016).

[10] M. Ghobadi, M. Kargar Razi., R. Javahershenas, M. Kazemi, *Synth. Commun.*, 51, 647 (2020).

[11] K. K. Gangu, S. Maddila, S. N. Maddila, S .B. Jonnalagadda, *RSC Advances*, 7, 423 (2017).

[12] B. Shaabani, H. Maleki, J. Rakhtshah, *J. Organomet. Chem.,* 897, 139 (2019).

[13] S. Hosseini, A.Kiasat, A Farhadi, *Polycyclic Aromatic Compounds*, 40, 1 (2019).

[14] J. Etemad Gholtash, M. Farahi, *RSC.,* 8, 40962 (2018).

[15] S. Kantevari, R. Bantu, L. Nagarapu, *ARKIVOC xvi.,* 3, 136 (2006).).

[16] S. B. Kamble, A.S.Kumbhar, S.N. Jadhav, R. S. Salunkhe, *Procedia Materials Science,* 6, 1850 (2014

[17] M. M. Candan, E. Kendi, M. Yarim, S. Sarac. M. Ertan, *Anal. Sci.,* 17, 1023 (2001).

[18] P. Movaheditabar, M. Javaherian, V. Nobakht, *Appl. Organomet. Chem*., 36, e6602 (2022).

[19] N. N. Tonkikh, A. Strakovs, M. V. Petrova, *Chem. Heterocycl. Compds*., 2444, 43 (2004).

[20] Z. Hassani, M. R. Islami, M. *Bio. Med. Chem. Lett*., 16, 4479 (2017).

[21] S. N.Kirti, B. Shingate, S.S. Murlidhar, *Tetrahedron Lett*., 51, 3616 (2010).

[22] O. Wolfgang, W. Fröstl, *Tetrahedron Lett*., 23, 361 (2006).

[223] S. N. Kantevari, V. S. Vuppalapati, O. Biradar, D. L Nagarapu, *J. Mol. Cata. A: Chem*., 211, 649 (2007).

[24] S. Hashemi-Uderji, M. Abdollahi- Alibeik, *J. Iran. Chem. Soc*., 15, 135 (2018).

[25] K. S. dalal, Y. A. Tayade, Y. B. Wagh, D.R. Trivedi, D. S. Dalal, B. L. Chaudhari, *RSC Adv*., 6, 14868 (2016).

[26] S. Hashemi-Uderji, M. Abdollahi-Alibeik, *J. Iran. Chem. Soc*., 15, 311 (2018).

[27] H. Mecadon, M. R. Rohman, M. Rajbangshi, B. Myrboh, *Tetrahedron Lett*., 52, 2523 (2011).