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Nano SnCl₂-SiO₂ Catalyzed Facile Synthesis of Aryloylamido Coumarins Derivatives

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Abstract

A highly efficient and general method for the synthesis of aryloylamido coumarins derivatives by a three-component condensation of 4-hydroxycoumarin or 4-hydroxy-6-methylpyran-1-one, aryl glyoxals and benzamide in the presence of nano silica supported tin (II) chloride as a heterogeneous catalyst is established. In this method, SnCl₂/nano SiO₂ was used as green and reusable catalyst. Excellent yields, short reaction times, simple workup, and inexpensiveness and commercial availability of the catalyst are the advantages of this method.

Keywords: *Multicomponent reaction, Aryl glyoxals, Benzamide, Nano SnCl₂-SiO₂, Heterogeneous catalyst.*

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Introduction

Multi-component reactions (MCRs) are important for generating high levels of diversity, as they allow more than two building blocks to be combined in a practical, time-saving, one-pot operation, giving rise to complex structures by simultaneous formation of two or more bonds. MCRs have received considerable attention because of their wide range of applications in pharmaceutical chemistry for the creation of structural diversity and combinatorial libraries for drug discovery [1-3]. Coumarin and its derivatives are an important class of heterocyclic compounds, which constitute the key core of various natural products [4,5]. They exhibit a wide range of biological activities such as anti-HIV, antimalarial, insecticidal, and antioxidant properties [6,7]. Most significant are 3-substituted-4-hydroxy coumarin derivatives which have important clinical applications [8-10] (Figure 1).

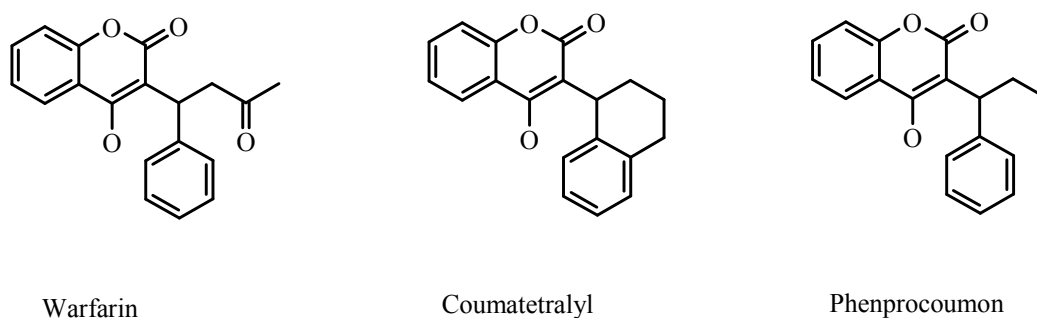
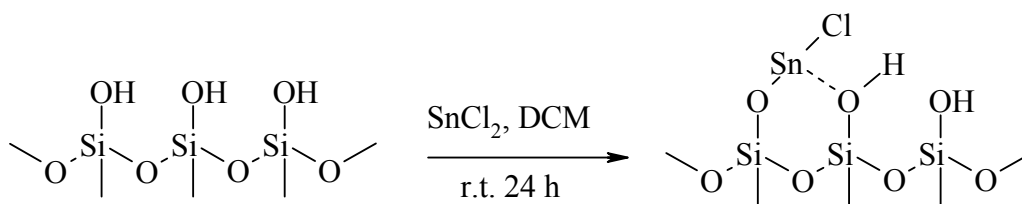


Figure 1. Coumarin derivatives.

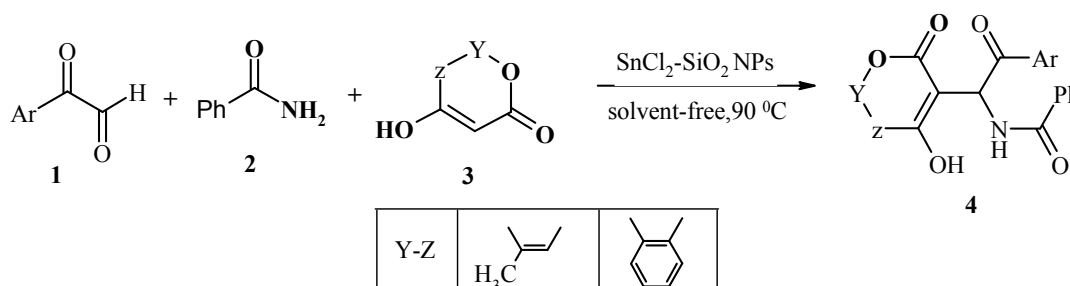
The literature survey reveals that tin salts show high Lewis acidity as compared to other transition metals and the order is $\text{Sn}^{2+} \gg \text{Zn}^{2+} > \text{Pb}^{2+} \approx \text{Hg}^{2+}$ [11]. Considering that Sn^{2+} salt has higher Lewis acidity in comparison to other metal salts, SnCl_2 was selected as homogeneous catalyst. Further, to improve upon the catalyst efficiency, catalyst loading, applicability and recyclability of the catalyst, silica nanoparticles was selected as it has high surface area, large pore volume, and recyclable tendency; hence, it may be useful as support for immobilization of Sn^{2+} salts. SnCl_2 was immobilized by reaction of hydroxyl groups on silica (Scheme 1), thus homogeneous SnCl_2 catalyst converted into heterogeneous catalyst with improved features for the synthesis of aryloylamido coumarins derivatives.



Scheme 1. Proposed structure for nano-SnCl₂-SiO₂.

Nanoparticles have undergone extensive examination in the past years. Recently, nanoparticle catalysts have emerged as an alternative method for the development of many considerable organic reactions. Nanocatalysts decrease reaction times and they can be easily recovered from the reaction mixture by standard techniques (filtration, centrifugation) and recycle without losing their activity [12–15].

Considering the above reports and in continuation of our research on multi-component reactions, we have researched for three-component coupling of 4-hydroxycoumarin, or 4-hydroxy-6-methylpyran-1-one **1**, aryl glyoxals **2**, and benzamide **3**, in the presence of SnCl₂-SiO₂ nanoparticles as heterogeneous catalyst to the synthesis of aryloylamido coumarins derivatives **4** (Scheme 2).



Scheme 2. Synthesis of aryloylamido coumarins derivatives catalyzed by SnCl₂-SiO₂ NPs nanoparticles (NPs) under solvent -free conditions.

Experimental

Melting points were determined with an electrothermal 9100 apparatus. Elemental analyses were performed using a Heraeus CHN-O-Rapid analyzer. Mass spectra were recorded on a FINNIGAN-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. IR spectra were recorded on a Shimadzu IR-470 spectrometer. ¹H and ¹³C NMR spectra were recorded on Bruker DRX-400 Avance spectrometer at solution in CDCl₃ using TMS

as internal standard. The chemicals used in this work were purchased from fluka (Buchs, Switzerland) and were used without further purification.

Preparation of nano silica-supported stannous chloride

Nano silica gel supported tin (II) chloride was prepared according to the procedure reported in the literatures with some modification [20, 21]. In a typical procedure, tin (II) chloridedihydrate (0.28 g) was added to a suspension of nano particles of silica gel (3.075 g) in dichloromethane (DCM) (25.0 mL). The mixture was stirred at room temperature overnight. Then the solvent was removed under reduced pressure and the residue was heated at 100 °C under vacuum for 5h to furnish SnCl₂/nano SiO₂. The prepared SnCl₂/nano SiO₂ has been structurally characterized SEM analysis and by IR spectrum. Figure 2 indicates that the original morphology of the particle was approximately spherical with the diameter varying between 30 and 60 nm.

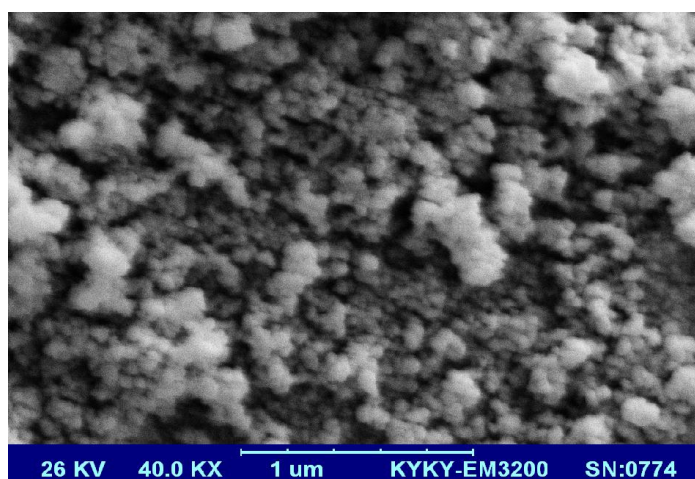


Figure 2. SEM image of synthesized Nano SnCl₂-SiO₂.

General procedure

A mixture of aryl glyoxal (1 mmol), benzamide (1.1 mmol), and Nano SnCl₂-SiO₂ (20 mol%) was stirred and heated at 70 °C for 30 min. Then the 4-hydroxycoumarin was added to the mixture and the reaction allowed stirring at 90 °C. The reaction progress was monitored by TLC (EtOAc/hexane, 1:1). After completion, the mixture was washed with MeOH. The precipitate was dissolved in hot EtOH:THF (3:1) and the catalyst was separated. The purification by silica gel column chromatography using *n*-hexane-EtOAc (1:1) as an eluent is needed to obtain pure product.

Selected spectral data

N-[1-(4-Hydroxy-6-methyl-2-oxo-2H-pyran-3-yl)-2-oxo-2-*p*-tolyl-ethyl]-*b*enzamide (**4g**)

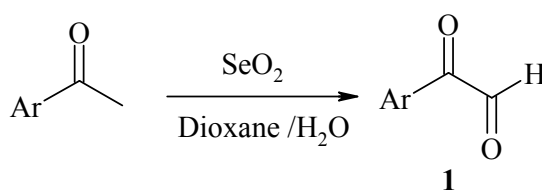
White powder, Yield: 80%; mp 195-198°C, IR (KBr) (ν_{\max} , cm^{-1}): 3288 (N-H), 1690, 1667 (C=O). Analyses: Calcd. for $\text{C}_{22}\text{H}_{19}\text{NO}_5$: C, 70.02; H, 5.07; N, 3.71, Found: C, 70.22; H, 5.12; N, 3.54 %. ^1H NMR (400 MHz, CDCl_3): δ = 2.06 (s, 3H), 2.30 (s, 3H), 5.93 (s, 1H), 6.76-8.08 (m, 11H), 8.52 (s, 1H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ = 21.16, 23.47, 50.62, 96.64, 101.07, 127.14, 128.77, 128.83, 129.16, 129.85, 133.84, 142.84, 162.28, 162.66, 171.13, 187.46 ppm.

N-[1-(4-Hydroxy-6-methyl-2-oxo-2H-pyran-3-yl)-2-oxo-2-phenyl-ethyl]-benzamide (**4h**)

White powder, Yield: 85%; mp 200-202°C, IR (KBr) (ν_{\max} , cm^{-1}): 3035 (N-H), 1691 (C=O). Analyses: Calcd. for $\text{C}_{21}\text{H}_{17}\text{NO}_5$: C, 69.41; H, 4.72; N, 3.85; Found: C, 69.33; H, 4.62; N, 3.73; %. ^1H NMR (400 MHz, CDCl_3): δ = 2.15 (s, 3H), 5.90 (s, 1H), 6.06 (s, 1H), 7.16-8.05 (m, 11H), 8.65 (s, 1H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ = 19.63, 51.24, 104.81, 116.54, 116.61, 124.13, 124.64, 128.20, 129.43, 131.49, 132.85, 144.75, 153.27, 162.04, 165.41, 173.44, 192.182 ppm.

Results and discussion

Aryglyoxals **1** was prepared by the reaction between their corresponding acetophenone and SeO_2 according to the reported procedures [18] (Scheme 3).



Scheme 3. Aryglyoxals synthesis.

Firstly, in order to optimize the reaction conditions, the model reaction was carried out by using 4-hydroxycoumarin, phenyl glyoxal, and benzamide under solvent-free conditions in the presence of different nanoparticle as catalysts and the results are listed in Table 1.

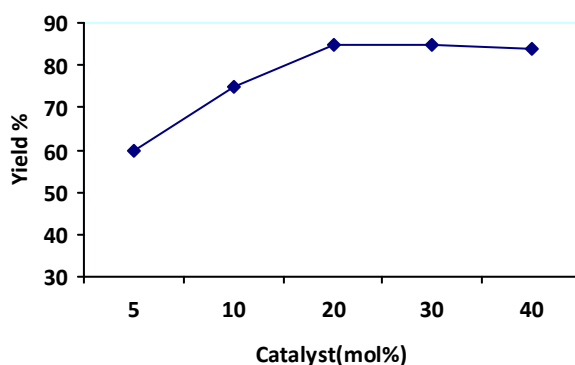
Table 1. Optimization of the nanoparticles catalysed model reaction for synthesis of *N*-[1-(4-Hydroxy-2-oxo-2H-chromen-3-yl)-2-oxo-2-phenyl-ethyl]-benzamide(**4a**) under solvent-free condition ^a.

Entry	Catalyst	Catalyst (mol%)	Time(h)	Yield ^b (%)
1	Non	-	3	trace
2	SiO ₂ bulk	20	2	30
3	Nano-SiO ₂	20	2	40
4	Nano-Al ₂ O ₃	20	2	45
5	HClO ₄ -SiO ₂ NP	20	2	50
6	SnCl ₂ -SiO ₂ NP	20	2	85

^a Reaction conditions: 4-hydroxy coumarin (1.0 mmol), benzamide (1.1 mmol), phenyl glyoxal (1.0 mmol), neat 90 °C.

^b Isolated yield

We examined this reaction in the presence of various nanoparticle catalysts in hand including Al₂O₃ nanoparticles, SiO₂ nanoparticles, HClO₄-SiO₂ nanoparticles, (Table 1). It was showed that SnCl₂-SiO₂ nanoparticle was the most efficient catalyst for the reaction in solvent-free condition (Table 1, entry 6). However, only a trace amount of the product was formed in the absence of catalyst (Table 1, entry 1). Afterward, optimization of catalyst amounts was carried out in the model study by using different amounts of the SnCl₂/nano SiO₂. A higher yield was obtained with increasing the amount of catalyst from 5 mol% to 20 mol%. However, further increase of the molar amount of the catalyst from 20 mol% to 40 mol% did not significantly increase the yield of the product (Figure 3). Hence, the optimum concentration of SnCl₂/nano SiO₂ NPs was chosen 20 mol% in the model reaction.

**Figure 3.** Influence of the amount of the catalyst on the model reaction.

To improve the yield of the target product, the test reaction was carried out in presence of various solvents and the results are presented in Table 2. As can be seen from this table, solvent- free conditions accelerated the rate of reaction and also high yields were obtained for all products.

Table 2. Solvent effect on the reaction between 4-hydroxycoumarin (1eq), phenyl glyoxal (1 eq) and benzamide (1 eq) catalyzed by SnCl₂/nano SiO₂ (20mol%).

Entry	Solvent	Temp(°C)	Time(h)	Yield(%)
1	Ethanol	Reflux	3	50
2	Methanol	Reflux	3	55
3	1,2 Dichloroethane	Reflux	3	50
4	THF	Reflux	3	50
5	H ₂ O	Reflux	3	55
6	Solvent- free condition	90	2	85

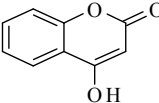
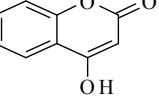
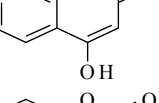
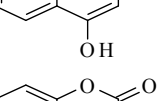
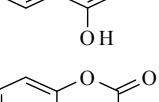
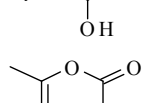
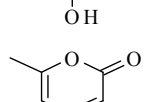
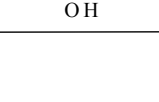
To study the scope of the reaction, a series of aryl glyoxals were employed. The results are shown in Table 3. In all cases, aromatic ring of the aryl glyoxal substituted with either electron-donating or electron-withdrawing groups underwent the reaction smoothly and gave the products in good yields. It could also be concluded that the aromatic ring of the aryl glyoxal bearing electron-withdrawing groups required shorter time and gave higher yields (Table 3).

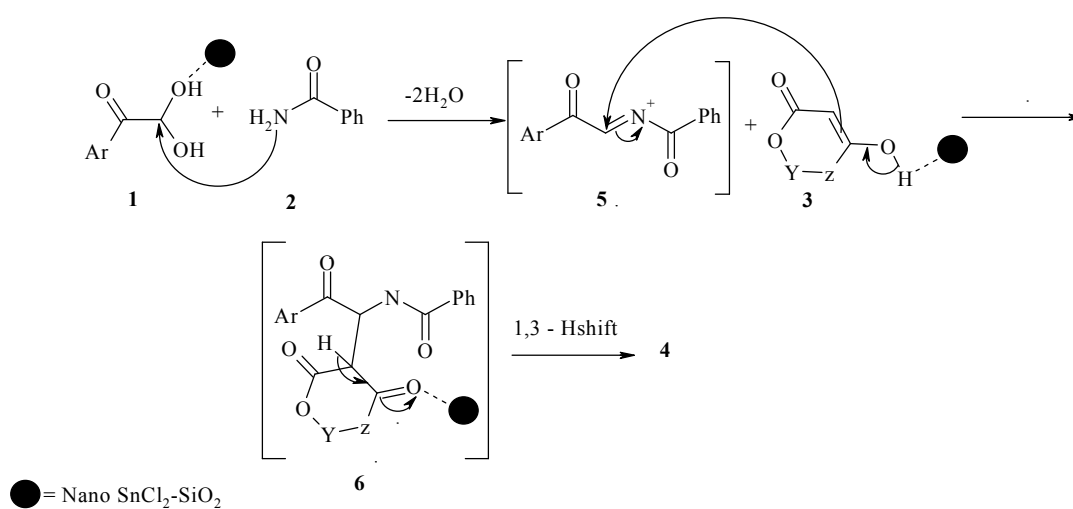
Compounds **4g-h** were new and their structures were deduced by elemental and spectral analysis. Other compounds (**4a-f**) were known and their structures were deduced by comparison of melting points and spectral data with authentic samples [19-21].

A possible mechanism for the formation of the products **4a-h** is proposed in Scheme 4.

The reaction of aryl glyoxal **1** with benzamide **2** in the presence of SnCl₂/nano SiO₂ catalyst is proposed to give corresponding iminium ion **5**. Next attack of 4-hydroxycoumarin or 4-hydroxy-6-methylpyran-1-one **3** to iminium ion **5** followed by 1,3-H shift leads to form final product **4**. (Scheme 4)

Table 3. Three-component reaction of aryl glyoxal, 4-hydroxycoumarin or 4-hydroxy-6-methylpyran-1-one and benzamide catalyzed by SnCl₂/nano SiO₂ (20 mol%).

Entry	Substrate	Ar	Time(min)	Yield(%)	mp °C
4a		C ₆ H ₅	120	85	222(220-224) ^[19-21]
4b		4-CH ₃ O-C ₆ H ₄	120	80	220(218-220) ^[19-21]
4c		3-CH ₃ O-C ₆ H ₄	130	82	285(>280) ^[19-21]
4d		4-NO ₂ -C ₆ H ₄	100	80	242(243-245) ^[19-21]
4e		4-Br-C ₆ H ₄	100	88	242-244(243-245) ^[19-21]
4f		4-F-C ₆ H ₄	110	80	250(248-250) ^[19-21]
4g		4-CH ₃ -C ₆ H ₄	120	80	195-198
4h		C ₆ H ₅	120	85	200-202

**Scheme 4.** Suggested pathway for the formation of compounds 4a-h.

The reusability of the catalyst was tested in the synthesis of aryloylamido coumarins derivatives, as shown in Figure 4. The catalyst was recovered after each run, washed with ethanol, dried in an oven at 100 °C for 20 min prior to use and tested for its activity in the subsequent run. The catalyst was tested for 3 runs. It was seen that the catalyst displayed very good reusability (Figure 4).

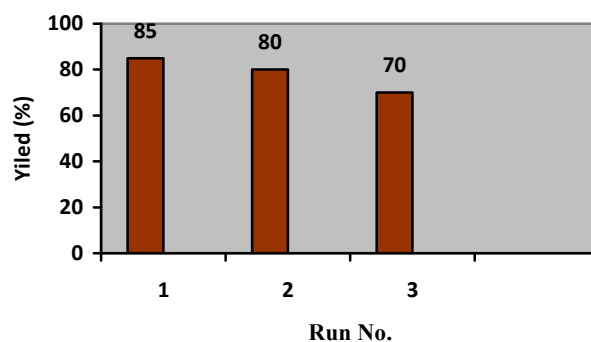


Figure 4. Reusability of the catalyst.

Conclusion

In conclusion, we have developed a convenient methodology for the synthesis of aryloylamido coumarins derivatives by the three-component coupling of 4-hydroxycoumarin or 4-hydroxy-6-methylpyran-1-one, aryl glyoxals and benzamide by using Nano SnCl₂-SiO₂ as a reusable, eco-friendly, inexpensive and efficient catalyst in solvent free conditions.

The attractive features of this protocol are simple procedure, cleaner reaction, use of reusable, nontoxic and inexpensive heterogeneous nano catalyst.

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References

- [1](a) Y. J. Huang, F. Y. Yang, C. J. Zhu, *J. Am. Chem. Soc.*, 127, 16387(2005). (b) D. J. Ramn, M. Yus, *Angew. Chem., Int. Ed.*, 44, 1602 (2005).
- [2] R. W. Armstrong, A. P. Combs, P. A. Tempest, S. D. Brown, T. A. Keating, *Acc. Chem. Res.*, 29, 123 (1996).

- [3] A. Domling, *Chem. Rev.*, 106, 17 (2006).
- [4] R. D. H. Murray, *Nat. Prod. Rep.*, 12, 477 (1995).
- [5] A. Lacy, R. O’Kennedy, *Curr. Pharm. Des.*, 10, 3797 (2004).
- [6] A. D. Patil, A. J. Freyer, D. S. Eggleston, R. C. Haltiwanger, M. F. Bean, P. B. Taylor, M. J. Caranfa, A. L. Breen, H. R. Bartus, R. K. Johnson, R. P. Hertzberg, J. W. Westley, *J. Med. Chem.*, 36, 4131 (1993).
- [7] D. Guilet, D. Guilet, J. J. Hélesbeux, D. Séraphin, T. Sévenet, P. Richomme, J. J. Bruneton, *Nat. Prod.*, 64, 563 (2001).
- [8] M. R. Hadler, R. S. Shadbolt, *Nature*, 253, 275 (1975).
- [9] M. Takumi, N. Ikuzo, H. Tsuneaki, K. Akiya, N. Kambe, N. Sonoda, *Synthesis*, 257 (1988).
- [10] C. Angelo, P. Ombretta, *Synthesis*, 99 (1993).
- [11] F. R. Abreu, D. G. Lima, E. H. Hamu, C. Wolf and P. A. Z. Suarez, *J. Mol. Catal. A: Chem.*, 209, 29 (2004).
- [12] K. Chanda, S. Rej, M.H. Huang, *Chem. Eur. J.* 19, 16036 (2013).
- [13] M.B. Gawande, A. Velhinho, I. D. Nogueira, et al., *RSC Adv.* 2, 6144 (2012).
- [14] A.R. Kiasat, J. Davarpanah, *J. Mol. Catal. A: Chem.* 373, 46 (2013).
- [15] A. Mobinikhaledi, H. Moghanian, S. Pakdel, *Chin. Chem. Lett.* 26, 557 (2015).
- [16] H.R. Darabi, K. Aghapoor, F. Mohsenzadeh, et al., *Bull. Korean Chem. Soc.*, 32, 213 (2011).
- [17] B.F. Mirjalili, A. Bamoniri, A. Akbari, *J. Iran Chem. Soc.*, 8, 135 (2011).
- [18] (a) B. Khalili, P. Jajarmi, B. Eftekhari-Sis, M. M. Hashemi, *J. Org. Chem.* 73, 2090 (2008). (b) H. A. Riley, A. R. Gray, *Organic Syntheses*; Wiley & Sons: NewYork, NY, 1943; Collect. Vol. II, 509.
- [19] S. Khodabakhshi, B. Karami, *Tetrahedron Letters* 55, 7136 (2014).
- [20] S. Khodabakhshi, B. Karami, K. Eskandari, *Res Chem Intermed*, 41, 7263 (2015).
- [21] S. Khodabakhshi, M. Khaleghi Abbasabadi, M. Baghrnejad, F. Marahel *J. Chin. Chem. Soc.*, 62, 9 (2015).