

Facile and convenient synthesis of 2-amino-5,10-dioxo-4-aryl-5,10-dihydro-4H-benzo[g]chromene-3-carbonitrile derivatives by electrocatalytically chemical transformation

Zahra Vafajoo^{a,b,c,*}, Davood Kordestani^a, Saba Vafajoo^b

^aDepartment of Chemistry, Shahr-e-Qods Branch, Islamic Azad University, Tehran, Iran

^bDepartment of Chemistry, Payame Noor University, P.O. BOX 19395-4697 Tehran, Iran

^cYoung Researchers and Elite Club, Kermanshah Branch, Islamic Azad University, Kermanshah, Iran

Received: 16 January 2017, Accepted: 05 July 2017, Published: 05 July 2017

Abstract

2-Amino-5,10-dioxo-4-aryl-5,10-dihydro-4H-benzo[g]chromene-3-carbonitrile derivatives are obtained in excellent yields with a simple and efficient procedure. This reaction can occur using electrocatalytic multicomponent chain transformation of aryl aldehydes, 2-hydroxynaphthalene-1,4-dione and malononitrile under neutral and mild conditions. Moreover, electrolysis is done in CH₃CN as solvent, Tetrabutylammonium fluoride (TBAF) as an effective supporting electrolyte and an iron electrode as the cathode and a graphite electrode as the anode in undivided cell. Also Excellent conversions of the starting materials were obtained under 10 mA/cm² current densities after 0.54 F/mol of electricity had been passed and I=50 mA at room temperature. The key advantages of this method are the high yields, simple work-up and the non-chromatographic purification of products.

Keywords: 2-Amino-4H-chromene; multicomponent; electrosynthesis; 2-hydroxynaphthalene-1,4-dione.

Introduction

Today, the multicomponent chemical reactions (MCRs) like domino reactions are valuable and interesting methods that have high importance in synthesis of various and relatively large organic structures. Obtained compounds have been synthesized through MCRs which have now been found as having various applications as functional chromophores [1], pharmaceutically active compounds [2-5] and marine alkaloids and derivatives [6].

The MCRs provide easy and rapid access to form a large library of various active macromolecules with different

and multiple substitution patterns while a number of synthetic steps can reduce. These convenient properties make the MCRs as appropriate candidate in green chemistry reactions category [7-8].

However, in many of these transformations, the use of hazardous and polluting solvents and catalysts cause ignoring the mentioned benefits.

4H-Benzo[g]chromene-5,10-dione derivatives show a variety of biological activities, including anti-inflammatory [9], anticancer [10-11], pesticide activities [12], antimalarial [13-15] and

*Corresponding author: Zahra Vafajoo

Tel: +98 (912) 8394279, Fax: +98 (83) 1 726 5130

E-mail: zahravafajoo@yahoo.com

antibacterial and anti-anaphylactic activities [16].

For synthesis of these important compounds, many methods with different conditions have been reported [17-19]. However, some of these protocols require long reaction times, multi-step reactions and complex synthetic pathways and afford products with only modest yields. So, it is necessary to introduce milder, faster and generally more green approaches accompanied with higher yields to the preparation of 4*H*-Benzo[g]chromene-5,10-dione derivatives.

The electro synthetically multicomponent reactions (EMCRs) can be defined as modified MCRs while previous disadvantages are not seen. In the EMCRs, the electron transfer between an electrode and the substrate molecules was occurred and followed by the formation of highly reactive intermediates which are achieved under mild conditions.

Therefore and according to the above-mentioned notes, It seems that EMCRs can be regarded as an appropriate technique in the synthesis of these organic compounds.

According to our previous studies [20-22], we evaluated synthesis of 2-amino-5,10-dioxo-4-aryl-5,10-dihydro-4*H*benzo[g]chromene-3-carbonitrile derivatives with EMCR method without the addition of base or any additive catalyst *via* the direct addition of only simple and available substrates such as various aromatic aldehydes, malononitrile and 2-hydroxynaphthalene-1,4-dione.

The structural evaluation studies of compounds were performed with various experimental techniques such as ¹H and ¹³C NMR spectroscopies. Notably, in examining their synthetic performance, it has been shown that

this method is capable of promoting organic synthesis of 2-amino-5,10-dioxo-4-aryl-5,10-dihydro-4*H*-benzo[g]chromene-3-carbonitrile derivatives in an environmentally friendly condition.

Experimental

All reagents were obtained from Merck and Aldrich and used without additional purification. All melting points were measured with an Electrothermal 9100 apparatus. The NMR spectra were recorded on a Bruker Avance DPX 400 and 300 MHz instrument with DMSO as solvent. Chemical shifts were recorded as δ values in parts per million (ppm). TLC was performed on silica-gel Poly Gram SIL G/UV 254 plates. Electrolysis were performed using a coulometry BHP2050 potentiostat/galvanostat.

Typical experimental procedure for electrocatalytic synthesis of 2-amino-5,10-dioxo-4-aryl-5,10-dihydro-4*H*-benzo[g]chromene-3-carbonitrile

A mixture of aryl aldehyde (2 mmol), malononitrile (3 mmol), 2-hydroxynaphthalene-1,4-dione (2 mmol), and tetrabutylammonium bromide (TBAB) (0.161g, 0.5 mmol) in acetonitrile (20 mL) was electrolyzed in an undivided cell equipped with a magnetic stirrer, a graphite anode, and an iron cathode at 25 °C under a constant current density of 10 mA/cm² [electrodes square 5 cm²] until the catalytic quantity of 0.54 F/mol of electricity was passed. After the electrolysis was finished, the precipitated products were separated by filtration which was then twice rinsed with an ice-cold ethanol/water solution (1:1, 5 mL), and dried under reduced pressure.

Analytical data for selected compounds (Table 2)

2-Amino-4-(2,4-dichlorophenyl)-5,10-dioxo-5,10-dihydro-4H-benzo[g]chromene-3-carbonitrile (4e, Entry 5)
m.p: 292-294°C, ¹H NMR (300 MHz, DMSO-*d*₆): δ = 4.6 (1H, s, CH), 7.30-7.33 (3H, m, 1H, ArH and 2H, NH₂), 7.82-7.84 (3H, m, ArH), 8.04-8.07 (1H, s, ArH) ppm.

2-Amino-4-(2-nitrophenyl)-5,10-dioxo-5,10-dihydro-4H-benzo[g]chromene-3-carbonitrile (4o, Entry 15)

m.p: 234-236°C, ¹H NMR (400 MHz, DMSO-*d*₆): δ = 5.40 (1H, s, CH), 7.46-7.60 (3H, m, 1H, ArH and 2H, NH₂), 7.80-7.82 (3H, m, ArH), 7.83-7.95 (1H, m, ArH), 8.02-8.07 (1H, m, ArH) ppm. ¹³C NMR (100 MHz, DMSO-*d*₆): δ = 31.5, 56.1, 119.2, 121.6, 124.5, 126.3, 126.6, 128.9, 131.1, 131.2, 131.8, 134.3, 138.8, 135.0, 149.0, 149.5, 159.4, 177.2, 183.1 ppm.

2-Amino-4-(2,6-dichlorophenyl)-5,10-dioxo-5,10-dihydro-4H-benzo[g]chromene-3-carbonitrile (4q, Entry 17)

m.p: 276-278 °C, ¹H NMR (400 MHz, DMSO-*d*₆): δ = 5.65 (1H, s, CH), 7.29-7.39 (2H, m, ArH), 7.52 (2H, s, NH₂), 7.56 (1H, d, ArH), 7.84-7.89 (3H, m, ArH), 8.05-8.07 (1H, m, ArH) ppm. ¹³C NMR (100 MHz, DMSO-*d*₆): δ = 33.9, 53.2, 119.0, 120.5, 126.4, 126.6, 129.2, 130.6, 130.5, 130.7, 131.1, 134.8, 135.0, 135.3, 136.0, 136.1, 150.2, 159.6, 177.1, 182.8 ppm.

2-Amino-4-(2,4-dimethoxyphenyl)-5,10-dioxo-5,10-dihydro-4H-benzo[g]chromene-3-carbonitrile (4r, Entry 18)

m.p: 249-251 °C, ¹H NMR (400 MHz, DMSO-*d*₆): δ = 3.72 (3H, s, OMe), 3.77

(3H, s, OMe), 4.83 (1H, s, CH), 6.43 (1H, d, ArH), 6.55 (1H, s, ArH), 7.10 (1H, d, ArH), 7.17 (2H, s, NH₂), 7.82-7.88 (3H, m, ArH), 8.044-8.065 (1H, s, ArH) ppm. ¹³C NMR (100 MHz, DMSO-*d*₆): δ = 31.2, 55.6, 56.2, 57.1, 99.2, 105.5, 120.0, 122.4, 124.1, 126.2, 126.5, 130.3, 130.9, 131.5, 134.5, 135.0, 149.8, 158.2, 159.2, 160.1, 177.5, 183.0 ppm.

Results and discussion

Our investigations on the electrocatalytic multicomponent chain transformation of aryl aldehydes, 2-hydroxynaphthalene-1,4-dione and malononitrile into 2-amino-5,10-dioxo-4-aryl-5,10-dihydro-4H-benzo[g]chromene-3-carbonitrile derivatives under neutral and mild conditions by electrolysis in an undivided cell began with the optimization of the reaction conditions. The synthetic pathway is shown in Scheme 1.

Table 1 lists the representative data obtained for the synthesis of 2-amino-5,10-dioxo-4-phenyl-5,10-dihydro-4H-benzo[g]chromene-3-carbonitrile **4a** from benzaldehyde, malononitrile and 2-hydroxynaphthalene-1,4-dione, and under various experimental conditions.

Initially, we evaluated the synthesis of compound **4a** as a model reaction in CH₃CN, in an undivided cell containing an iron electrode as the cathode and a graphite electrode as the anode at various constant current in the presence of electrolyte of NaBr at room temperature (Table 1, Entries 1-4). It could be seen that Excellent conversions of the starting materials were obtained under 10 mA/cm² current densities after 0.54 F/mol of electricity which had been passed and I=50 mA.

An increase in the current density up to 15 mA/cm² (I=75 mA) resulted in a slight decrease in the reaction yield, and

it may also be a result of the activation of the undesired direct electrochemical processes that lead to oligomerization of the starting material (Table 1, Entry 5).

On the other hand, the use of other solvents such as EtOH, MeOH, *n*-PrOH afforded lower yield of the desired product **4a** under similar conditions (Entries 6-8).

Then, we examined the effect of various electrolytes and found that when the electrolysis was supported by TBAF as the electrolyte; the yield of **4a** was satisfactory (Entry 9-11).

Finally, excellent conversions of the starting materials were obtained under 10 mA/cm² current densities after 0.54 F/mol of electricity which had been passed and I=50 mA, electrodes surface (5cm²) was found to be optimal for the electrochemically induced chain process and allowed for the highest yield of **4a** in solvent of CH₃CN and electrolyte of tetrabutyl ammonium fluoride.

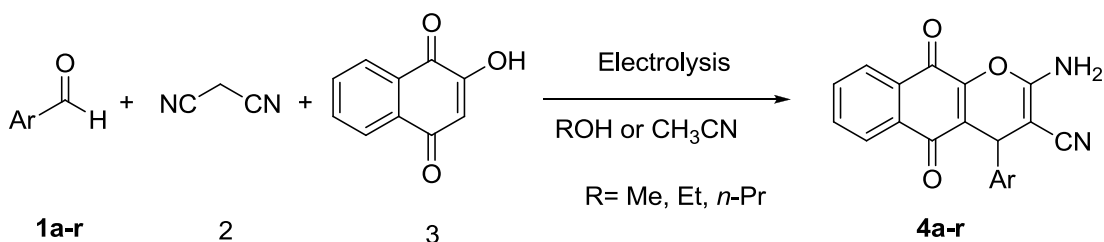
Using the optimized conditions, we also probed the scope and generality of the reaction of several aryl aldehydes

with malononitrile and 2-hydroxynaphthalene-1,4-dione for synthesis of 2-amino-5,10-dioxo-4-aryl-5,10-dihydro-4*H*-benzo[*g*]chromene-3-carbonitrile derivatives (Table 2, **4a-r**).

As shown in Table 2, products were obtained in excellent yields.

The proposed mechanism for the preparation of related products is depicted in scheme 2. As the initiation step of the catalytic cycle, deprotonation of a CH₃CN molecule at the cathode leads to formation of cyanomethyl anion [23].

Benzylidenemalononitrile (**4**), is formed quantitatively by Knoevenagel addition of malononitrile to the benzaldehyde. Then, the 2-benzylidenemalononitrile has been attacked by the 2-hydroxynaphthalene-1,4-dione (**3**) in the presence of cyanomethyl anion, which leads to the intermediate (**5**). Tautomerization and cyclization (**5**) gave the intermediate (**6**). The subsequent tautomerization produced the desired product.

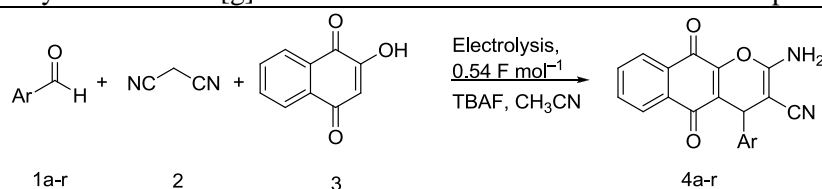


Scheme 1.

Table 1. Optimization of reaction conditions for synthesis of 2-amino-5,10-dioxo-4-phenyl-5,10-dihydro-4H-benzo[g]chromene-3-carbonitrile at room temperature

Entry	electrolyte	I (mA)	Current Density (mA/cm ²)	Time (h)	Solvent	Electricity passed (F mol ⁻¹)	Yield (%)
1	NaBr	5	1	5	CH ₃ CN	0.92	20
2	NaBr	10	2	3	CH ₃ CN	0.85	35
3	NaBr	20	4	2	CH ₃ CN	0.85	45
4	NaBr	50	10	1	CH ₃ CN	0.54	90
5	NaBr	75	15	1	CH ₃ CN	0.92	70
6	NaBr	50	10	1	EtOH	0.74	40
7	NaBr	50	10	1	MeOH	0.74	41
8	NaBr	50	10	1	<i>n</i> -PrOH	0.82	20
9	KBr	50	10	1	CH ₃ CN	0.54	50
10	KI	50	10	1	CH ₃ CN	0.54	65
11	TBAF	50	10	1	CH ₃ CN	0.54	95
12	TBAF	50	10	1	EtOH	0.74	60

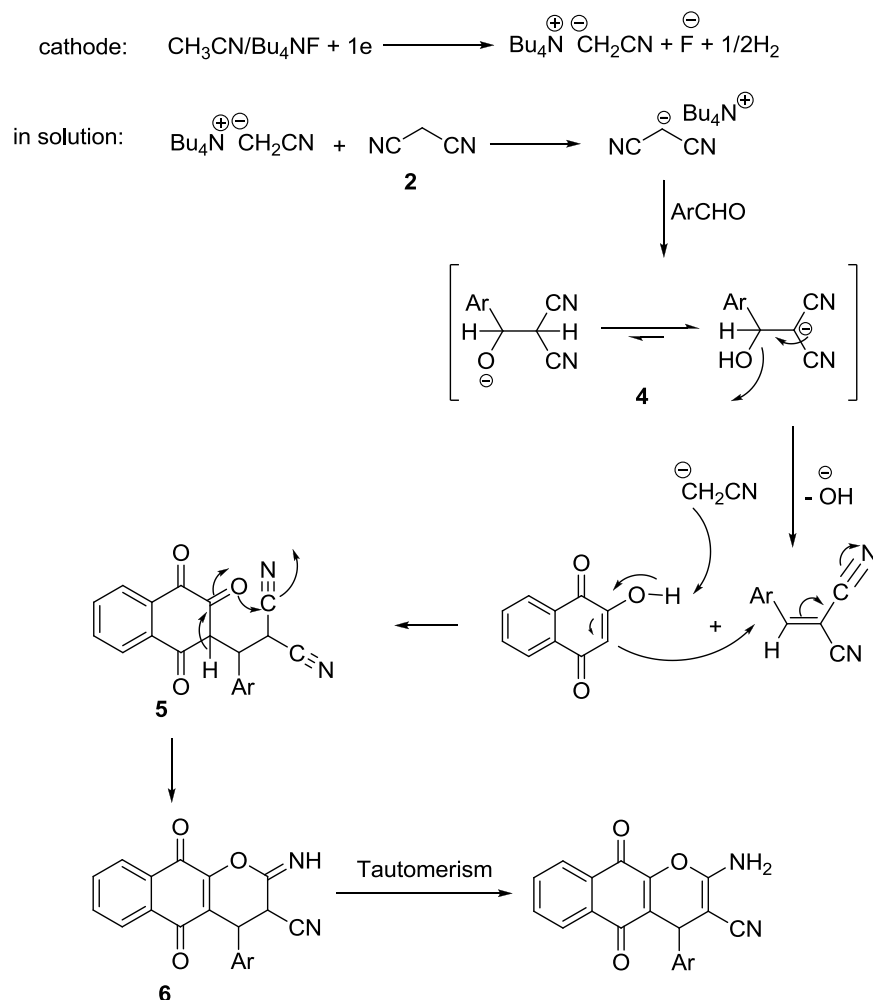
Table 2. Electrocatalytic multicomponent synthesis of 2-amino-5,10-dioxo-4-aryl-5,10-dihydro-4H-benzo[g]chromene-3-carbonitrile derivatives under optimized conditions



Entry	Aldehyde	Product	Yield (%)	M.p (°C)	Ref
1	Ph	4a	90	259-260	260-262 ²⁴
2	4-NO ₂ C ₆ H ₄	4b	91	233-236	234-235 ²⁵
3	3-NO ₂ C ₆ H ₄	4c	93	244-245	248-250 ²⁶
4	4-ClC ₆ H ₄	4d	90	270-272	278-280 ²⁴
5	2,4-Cl ₂ C ₆ H ₃	4e	91	292-294	293-295 ²³
6	3-BrC ₆ H ₄	4f	93	256-258	258-259 ²⁵
7	2-ClC ₆ H ₄	4g	90	239-241	236-239 ²⁵
8	4-OHC ₆ H ₄	4h	90	254-256	254-256 ²⁵
9	4-FC ₆ H ₄	4i	91	284-286	286-288 ²⁵
10	4-OCH ₃ C ₆ H ₄	4j	90	245-247	248 ²⁶
11	2,3,4-(OCH ₃) ₃ C ₆ H ₂	4k	93	287-289	291-292 ²⁶
12	3,4-(OCH ₃) ₂ C ₆ H ₃	4l	91	270-271	272-273 ²⁶
13	3-OCH ₃ C ₆ H ₄	4m	90	243-245	242-244 ²⁶
14	4-BrC ₆ H ₄	4n		251-253	252-253 ²⁶
15	2-NO ₂ C ₆ H ₄	4o	90	234-236	232-234 ²⁵
16	4-CH ₃ C ₆ H ₄	4p	90	242-244	241-243 ²⁵
17	2,6-Cl ₂ C ₆ H ₃	4q	91	276-278	278-280 ²⁵
18	2,4-(OCH ₃) ₂ C ₆ H ₃	4r	90	249-251	248-250 ²⁵

^aGeneral procedure: Aldehyde (2 mmol), malononitrile (3 mmol), 2-hydroxynaphthalene-1,4-dione (2 mmol), and tetrabutylammonium fluoride (0.5 mmol), Acetonitrile (20 mL), iron cathode (5 cm²), and graphite anode (5 cm²)

^bIsolated Yield



Scheme 2. Proposed mechanism for preparation 2-amino-5,10-dioxo-4-aryl-5,10-dihydro-4H-benzo[g]chromene-3-carbonitrile derivatives

Conclusion

In conclusion, we have described the synthesis of 2-amino-5,10-dioxo-4-aryl-5,10-dihydro-4H-benzo[g]chromene-3-carbonitrile derivatives in excellent yields by a simple and efficient procedure under neutral and mild conditions in the presence of tetrabutylammonium fluoride as an electrolyte. The key advantages of this method are the high yields, simple work up the non-chromatographic purification of products.

Acknowledgments

We are thankful to Shahr-e-Qods Branch, Islamic Azad University,

Tehran, Iran for partial support of this work.

References

- [1] A.M. Asiri, S.A. Khan, S.H. Al-Thaqafya, *J. Fluoresc.*, **2015**, *25*, 1203-1213.
- [2] S. Bhagat, A.K. Chakraborti., *J. Org. Chem.*, **2007**, *72*, 1263-1270.
- [3] M. Baumann, I. R. Baxendale, *Beilstein J. Org. Chem.*, **2016**, *11*, 1194-1219.
- [4] A. Domling, W. Wang, K. Wang, *Chem. Rev.*, **2012**, *112*, 3083-3135.
- [5] M.N. Elinson, V.M. Merkulova, A.I. Ilovaiskya, F. Barba, B. Batanero, *Electrochem. Acta.*, **2011**, *56*, 8219-8223.

- [6] L.V. Frolova, I.V. Magedov, A.E. Romero, M. Karki, I. Otero, K. Hayden, N.M. Evdokimov, L.M.Y. Banuls, Sh.K. Rastogi, W.R. Smith, Sh.-L. Lu, R. Kiss, Ch. B. Shuster, E. Hamel, T. Betancourt, S. Rogelj, A. Kornienko, *Journal of medicinal chemistry.*, **2013**, *56*, 6886-6900.
- [7] M.N. Elinson, A.S. Dorofeev, S.K. Feducovich, R.F. Nasybullin, S.V. Gorbunov, G.I. Nikishin, *Electrochem. Commun.*, **2006**, *8*, 1567-1571.
- [8] M.N. Elinson, A. S. Dorofeev, R.F. Nasybullin, G. I. Nikishin, *Synthesis*, **2008**; 1933-1937
- [9] D.O. Moon, Y.H. Choi, N.D. Kim, Y.M. Park, G.Y. Kim., *International Immunopharmacology.*, **2007**, *7*, 506-514.
- [10] M. Ough, A. Lewis, E.A. Bey, J. Gao, J.M. Ritchie, W. Bornmann, D.A. Boothman, L.W. Oberley, J.J. Cullen, *Cancer Biology and Therapy.*, **2005**, *4*, 102- 109.
- [11] J. Tiwari, M. Saquib, S. Singh, F. Tufail, M. Singh, J. Singh, J. Singh, *Green Chemistry.*, **2016**, *18*, 3221–3231.
- [12] A.M. Shestopalov, Y.M. Emelianova, V.N. Nesterov, *Russian Chemical Bulletin.*, **2003**, *52*, 1164-1171.
- [13] V.F. De Andrade-Neto, M.O.F. Goulart, J.F. Da Silva Filho, M.J. Da Silva, M.D.C.F.R. Pinto, A.V. Pinto, M.G. Zalis, L.H. Carvalho, A.U. Krettli, *Bioorganic and Medicinal Chemistry Letters.*, **2004**, *14*, 1145-1149.
- [14] P.S. Elisa, E.B. Ana, A.G. Ravelo, D.J. Yapu, A.G. Turba, *Chemistry and Biodiversity.*, **2005**, *2*, 264-274.
- [15] P. Sagar Vijay Kumar, L. Suresh, T. Vinodkumar, B. M. Reddy, G.V.P. Chandramouli, *ACS Sustainable Chem. Eng.*, **2016**, *4*, 2376-2386.
- [16] S. D. Dindulkar, D. Jeong, E. Cho, D. Kimb, S. Jung, *Green Chemistry.*, DOI: 10.1039/c6gc00137h.
- [17] A. Shaabani, R. Ghadari, S. Ghasemi, M. Pedarpour, A.H. Rezayan, A. Sarvary, S.W. Ng, *Journal of Combinatorial Chemistry.*, **2009**, *11*, 956–959.
- [18] X.-H. Wang, X.-H. Zhang, S.-J. Tu, F. Shi, X. Zou, S. Yan, Z.-G. Han, W.-J. Hao, X.-D. Cao, S.-S. Wua, *Journal of Heterocyclic Chemistry.*, **2009**, *46*, 832–836.
- [19] Y. Yu, H. Guo, X. Li, *Journal of Heterocyclic Chemistry.*, **2011**, *48*, 1264–1268.
- [20] Z. Vafajoo, H. Veisi, M. T. Maghsoodlou, H. Ahmadian; *Journal of Comptes Rendus Chimie.*, **2014**, *17*, 301-304.
- [21] H. Veisi, Z. Vafajoo, B. Maleki, M. Taher Maghsoodlou, *Sulfur, and Silicon and the Related Elements.*, **2013**, *188*, 672-677.
- [22] Z. Vafajoo, N. Hazeri, M. T. Maghsoodlou, H. Veisi, *Journal of Chinese Chemical Letters.*, **2015**, *26*, 973–976.
- [23] R. Kazemi-Rad, J. Azizian, H. Kefayati, *Tetrahedron Letters.*, **2014**, *55* 6887–6890.
- [24] Changsheng, Y. Chenxia, LI. Tuanjie, T. Shujiang, *Chinese Journal of Chemistry.*, **2009**, *27*, 1989–1994.
- [25] H.R. Shaterian, M. Kangani, *Scientia Iranica.*, **2013**, *20*, 571–579.
- [26] H.R. Shaterian, M. Mohammadnia, *Journal of Molecular Liquids*, **2013**, *177*, 353–360.