Article

JOURNAL OF THE CHINESE CHEMICAL SOCIETY

Condensation of Aryl Aldehydes, 2-naphthol, and Thioacetamide Catalyzed by *N*-halo Reagents in Neutral Media

Ardeshir Khazaei,[a]* Fatemeh Abbasi,[a] Ahmad Reza Moosavi-Zare,[b]* Marzieh Khazaei[a] and M. Hassan Beyzavi[c]

[a]*Faculty of Chemistry, Bu-Ali Sina University, Hamedan 6517838683, Iran*
[b]*Department of Chemistry, Sayyed Jamaleddin Asadabadi University, Asadabad, 6541835583, Iran*
[c]*Department of Chemistry and Chemical Biology, Harvard University, 12 Oxford St., Cambridge MA 02138, USA*

(Received: Apr. 1, 2015; Accepted: Jul. 31, 2015; Published Online: Sept. 7, 2015; DOI: 10.1002/jccs.201500125)

A new three-component, highly efficient and solvent-free approach for the synthesis of known and new 1-thioamido-alkyl-2-naphthol derivatives was investigated. This was achieved via a one-pot condensation by reacting aryl aldehydes, 2-naphthol, and thioacetamide in the presence of catalytic amount of 1,3,5-trichloro-1,3,5-triazinane-2,4,6-trione (TCCA) and 1,3-dichloro-5,5-dimethylhydantoin (DCDMH). Mechanistically, the in situ generation of Cl^+ ion from TCCA and DCDMH is proposed to catalyse the reactions in neutral media. In the presented work, most of the products have been reported for the first time.

Keywords: Multi-component condensation; 1,3,5-trichloro-1,3,5-triazinane-2,4,6-trione (TCCA); 1,3-dichloro-5,5-dimethylhydantoin (DCDMH); 1-thioamido-alkyl-2-naphthol; Solvent-free.

INTRODUCTION

Because of the ability of synthesizing target products with atom economy and higher efficiency by forming structural complexity in one pot step from three or more reactants, multi-component reactions (MCRs) play a significant role in the sustainable and diversity-oriented synthesis of organic materials. In addition, MCRs bear some advantages of synthetic efficiency and simplicity compared with conventional reactions.[1-3] 1-Amidoalkyl-2-naphthols and 1-thiomido-alkyl-2-naphthols are intersting molecules of choice as they can be easily converted to biologically important 1-aminoalkyl-2-naphthols via hydrolysis.[4] 1-Aminoalkyl-2-naphthols have been studied as bradycardiac and hypotensive agents.[4,5] 1-Amidoalkyl-2-naphthols can be also converted to 1,3-oxazine derivatives.[6] 1,3-Oxazines offer several pharmaceutical properties including antibiotic,7 antitumor[8] and analgesic activities.[9]

There are known procedures for the synthesis of 1-amido-alkyl-2-naphthols in the literatures. However, limited approaches have been reported to replace the amide with thioamide. The preparation of 1-amidoalkyl and thioamidoalkyl naphthols can be carried out by multi-component reactions using different catalysts such as [Msim]Cl, [Dsim]Cl, $[Msim]AlCl_4$,[10] $[Dsim]HSO_4$,[11] p-TSA,[12] H_2SO_4/SiO_2,[13] $Fe(HSO_4)_3$,[14] trityl chloride.[15] However, mostly the reported methods suffer from one or more of disadvantages such as using toxic, corrosive, expensive and/or large amount of catalysts, long reaction time, toxic and corrosive solvents, and strong acidic media. Because of the importance of 1-amido-alkyl-2-naphthols, the investigatioin for a milder, more eco-friendly and faster method with higher yields is still needed and challenging.

Trichloro-1,3,5-triazinane-2,4,6-trione (TCCA) (Scheme 1) is an easily available reagent and inexpensive compound which has been widely applied in organic synthesis.[16] On the other hand, 1,3-dichloro-5,5-dimethylhydantoin (DCDMH) (Scheme 1) is also a stable, commercially available and inexpensive heterocycle which has rarely utilized as a source of chlorine ion or radical in chlorination[17,18] or oxidation reactions.[19-21] To the best of our knowledge, there is no report of catalytic application of DCDMH and TCCA in the preparation of 1-thioacetamido-alkyl-2-naphthols.

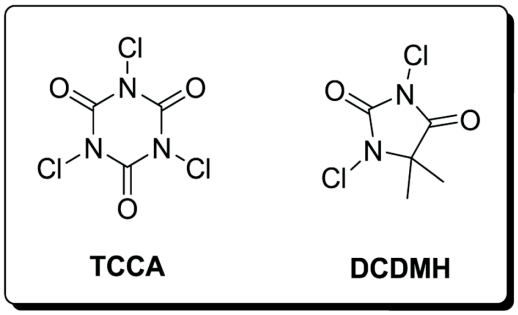
Having above facts, herein, we report DCDMH and TCCA as homogenous and neutral catalysts for the synthesis of 1-thioacetamido-alkyl-2-naphthols *via* a one-pot, multi-component reaction of 2-naphthol, aromatic aldehydes, and thioacetamide (Scheme 2).

Additionally, we report that TCCA and DCDMH can also catalyze the preparation of bis(1-thioacetamido-alkyl-2-naphthol) (Scheme 3).

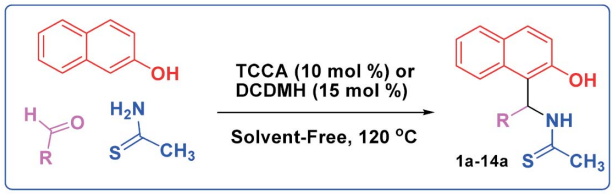
* Corresponding author. Email: moosavizare@yahoo.com & moosavi-zare@sjau.ac.ir

Supporting information for this article is available on the www under http://dx.doi.org/10.1002/jccs.201500125

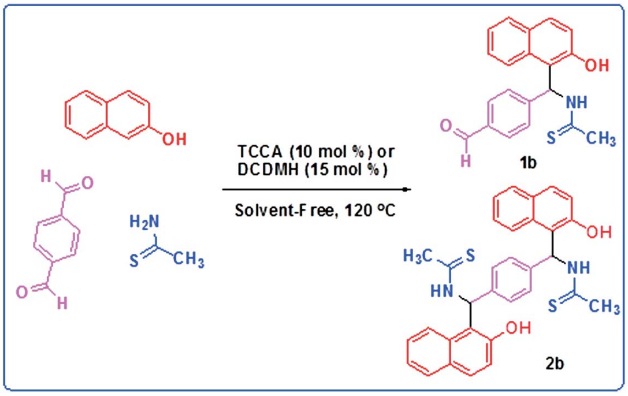
Scheme 1 The structure of trichloro-1,3,5-triazinane-2,4,6-trione (TCCA) and 1,3-dichloro-5,5-dimethylhydantoin (DCDMH).



Scheme 2. The synthesis of 1-thioacetamido-alkyl-2-naphthols.



Scheme 3. The synthesis of bis(1-thioacetamido-alkyl-2-naphthol).



RESULTS AND DISCUSSION

Initially, to optimize the reaction conditions (catalysts loading and temperature), the reaction of 2-naphthol (1 mmol), benzaldehyde (1 mmol) and thioacetamide (1.2 mmol) was chosen as the model reaction, and we investigated this model reaction in the presence of different amounts of catalysts (TCCA and DCDMH) under thermal solvent-free conditions. The results are summarized in Table 1 and 2. As Table 1 and 2 indicates, higher yield of purified product and shorter reaction time were obtained using 10 mol% of TCCA and 15 mol% of DCDMH at 120 °C under solvent-free conditions.

Table 1. Optimization of the amount of TCCA and the reaction temperature

Entry	Catalyst (mol%)	Temperature (°C)	Time (min)	Yield (%)[a]
1	5	120	50	65
2	10	120	25	85
3	15	120	25	84
4	10	80	60	60
5	10	90	50	67
6	10	100	45	71
7	10	110	30	75

[a] Yield of purified product.

Table 2. Optimization of the amount of DCDMH and the reaction temperature

Entry	Catalyst (mol%)	Temperature (°C)	Time (min)	Yield (%)[a]
1	5	120	60	60
2	10	120	50	65
3	13	120	40	69
4	15	120	35	80
5	20	120	35	80
6	15	80	70	52
7	15	90	55	60
8	15	100	50	64
9	15	110	40	70

[a] Yield of purified product.

To assess the efficiency and the scope of the organic catalyst in the synthesis of 1-thioacetamido-alkyl-2-naphthols, the reaction of 2-naphthol with a variety of arylaldehydes and thioacetamide was studied under optimized conditions. The corresponding results are summerized in Table 3. As it can be seen in Table 3, the reactions were carried out efficiently within 20-150 min and the expected products were obtained in moderate to excellent yields (40-82%). In addition, the influence of electron-releasing and electron-withdrawing substituents and halogens on the aromatic ring of arylaldehydes was studied (Table 3).

Based on these results, TCCA and DCDMH are considered as highly efficient and mild organic catalysts with a good substrate scope for the synthesis of 1-thioacetamido-alkyl-2-naphthol derivatives.

Moreover, the presented protocol was also examined on the condensation of 2-naphthol with bis-aldehyde

Table 3. The Preparation of 1-thioacetamido-alkyl-2-naphthols from 2-naphthol, aromatic aldehydes and thioacetamide using TCCA and DCDMH at 120 °C

Entry	R	Time (min)/Yield (%)[a,b]	Time (min)/Yield (%)[a,c]	M P °C (lit.)
1a	C_6H_5	25/80	35/73	180-182 (190-193)[15]
2a	2-$NO_2C_6H_4$	105/68	110/64	202-204
3a	3-$NO_2C_6H_4$	120/65	135/61	187-190
4a	2-ClC_6H_4	25/82	30/78	253-255
5a	4-ClC_6H_4	80/78	90/69	240-242 (246-248)[14]
6a	2,6-diClC_6H_3	45/65	60/59	241-242
7a	4-Cl-3-$NO_2C_6H_3$	35/70	45/62	246-249
8a	4-BrC_6H_4	80/79	85/72	190-193
9a	4-$CF_3C_6H_4$	55/70	70/60	230-231
10a	4-$CH_3C_6H_4$	150/55	155/51	192-195
11a	4-$OCH_3C_6H_4$	30/44	45/40	180-185 (192-194)[14]

[a] Yield of purified product, [b] TCCA, [c] DCDMH.

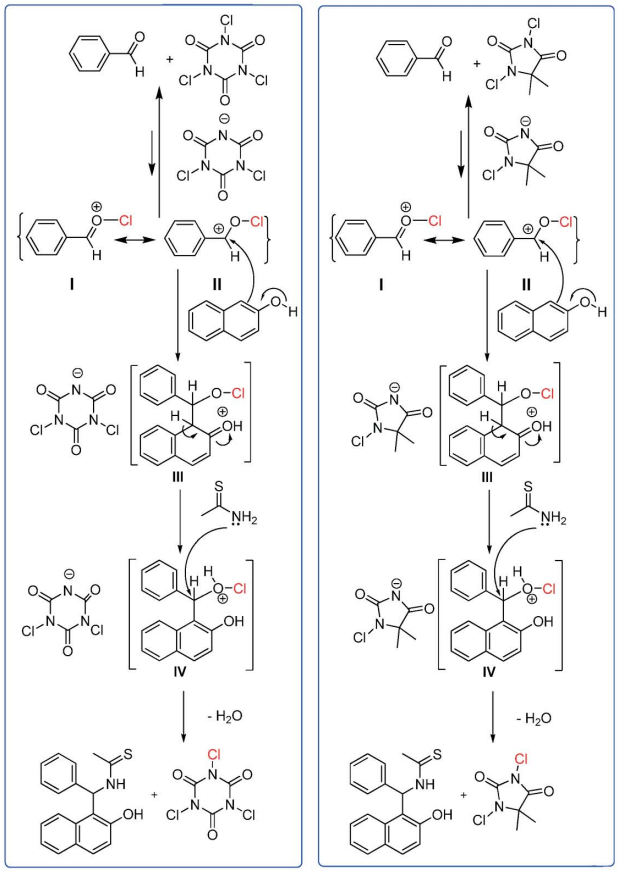
(terephthaldehyde) and thioacetamide in the presence of 10 mol% of TCCA and 15 mol% of DCDMH (Scheme 3). For this reaction, 1 equiv. of 2-naphthol, 1 equiv. of terephthalaldehyde and 1.2 equiv. of thioacetamide were utilized which beared purified 1-thioacetamido-alkyl-2-naphthol (**1b**) and bis(thioacetamido-alkyl-2-naphthol) (**2b**) in the ratio of 65%:16% yields in 7 min and ratio of 61%:14% yields in 8 min utililizing TCCA and DCDMH, respectively.

Once we changed the reaction conditions by utilizing 2 equiv. of 2-naphthol, 1 equiv. of terphetaldehyde and 2.4 equiv. of thioacetamide, the products were obtained in the ratio of 1b:2b as 13%:70% yields in 15 min and in ratio of 11%:67% yields in 17 min for TCCA and DCDMH, respectively.

Since TCCA and DCDMH contain chlorine atoms bonded to nitrogen atoms in heterocyclic ring, based on the literature,[16,22-25] it is speculated that the *in situ* generation of Cl^+ ion from the catalysts initiate the catalytic processes. in a way that Cl^+ ion from the catalysts (TCCA or DCDMH) is abstracted by the aldehyde and I and II as activated forms of aldehyde are generated (Scheme 4). Then, from attacking of 2-naphthol to the activated forms of **I** and **II** intermediate **III** is achieved and tautomerized to **IV**. Finally, followed by dehydration, the attacking of thioacetamide to **IV** intermediate is led to the corresponded products and the catalysts are regenerated for the next catalytic cycles.

In a separate experiment, to confirm that HCl could not be generated from TCCA and DCDMH to catalyze the reaction, the model reactions were performed in the presence of hydrochloric acid (10% and 20%). As shown in Table 4, TCCA and DCDMH were more effective than HCl to catalyze the reactions.

Scheme 4. The plausible mechanism for the synthesis of 1-thioacetamido-alkyl-2-naphthols catalyzed by TCCA and DCDMH.



To prove the formation of intermediate **I** and **II**, benzaldehyde was reacted with catalysts at 120 °C, and then IR and UV spectra of the aldehydic functional group in the reaction mixture were compared with those in benzaldehyde. Indeed, the carbonyl streching frequeccy of

Table 4. Comparison result of TCCA and DCDMH with HCl in the synthesis of *N*-((2-hydroxynaphthalen-1-yl) (phenyl) methyl) thioacetamide at 120 °C

Entry	Catalyst	Catalyst (mol%)	Time (min)	Yield (%)[a]	TOF (min^{-1})[b]
1	TCCA	10	25	85	0.34
2	DCDMH	15	35	80	0.23
3	HCl	10	300	32	0.015
4	HCl	20	300	36	0.009

[a] Yield of purified product, [b] Turn over frequency.

benzaldehyde (1703 cm^{-1}) was decreased to 1682 cm^{-1} in the reaction mixture. It is indicative of decreased nature of double bond and the formation of activated carbonyls. UV spectra were another evidence to confirm the formation of **I** and **II**. The maximum absorbance for benzaldehyde appeared at 243 nm and for TCCA at 234 nm and DCDMH at 231 nm. But the λ_{max} of the complexes of aldehyde and Cl^{+} ion which are formed by the addition TCCA and DCDMH to benzaldehyde was observed at 238 nm.[25]

Intermediates I and II act as activated carbonyl compounds to react with 2-naphthol to give III intermediate. 1-Thioacetamido-alkyl-2-naphthol is synthesized by reacting of this intermediate with thioacetamide. To examine that the catalyst was completely regained during the reaction the UV spectra of the catalyst and reaction mixture in dichloromethane were recorded. As Figure 1 indicates, the maximum of absorption for the catalysts in UV spectrum of the reaction mixture is similar to UV spectra of TCCA and DCDMH. Based on, it is clear that TCCA and DCDMH were recovered unchanged after the completion of the reaction and the proposed mechanisms were acceptable.

EXPERIMENTAL

General: Chemicals were purchased from Merck and Aldrich Chemical Companies and used without further purification. The known products were identified by comparison of their melting points and spectral data with those in the authentic samples. Infrared (IR) spectra were recorded on a Shimadzu IR 470 spectrophotometer. ^{13}C NMR and ^{1}H NMR spectra were recorded on a Bruker 400 and JEOL FT-NMR 90 MHz using TMS as an internal standard in dimthylsulfoxide (DMSO) as the solvent. Mass spectra were recorded on an Agilent technologies (HP) 5973 network mass selective detector (MSD). Melting points were determined in open capillaries with a Stuart Scientific melting point apparatus. TLC was performed on Silica–gel polygram SILG/UV 254 plates.

General procedure for the synthesis of 1-thioacetamido-alkyl-2-naphthol derivatives (Scheme 3): A mixture of 2-naphthols (0.29 g, 2.0 mmol), aldehydes (2.0 mmol), thioacetamide (0.18 g, 2.4 mmol) and TCCA (46.4 mg, 0.2 mmol, 10 mol%) or DCDMH (59.1 mg, 0.3 mmol, 15 mol%) in a 10 mL round-bottomed flask sealed with a stopper was stirred in an oil-bath (120 °C). After completion of the reaction, as monitored by TLC, the reaction was cooled to room temperature and washed with hot water. Subsequently, the crude products (compounds **1a-11a**) were purified by plate chromatography on silica gel eluted with EtOAc/*n*-hexane.

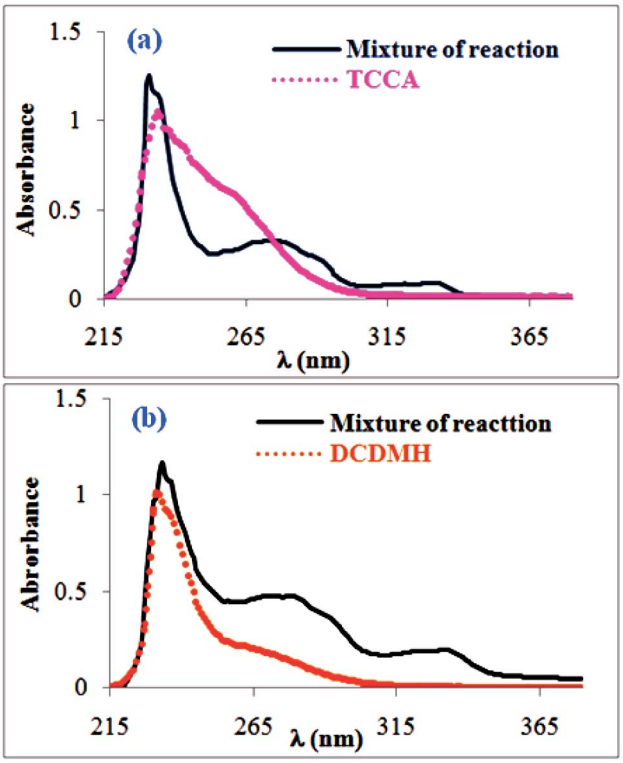


Fig. 1. UV spectra of TCCA, DCDMH and mixture of reaction with TCCA and DCDMH at 120 °C in dichloromethane respectively.

General procedure for the condensation between 2-naphthol, terephthaldehyde and thioacetamide (Scheme 3): To a mixture of 2-naphthols (0.29 g, 2.0 mmol), thioacetamide (0.18 g, 2.4 mmol) and TCCA (46.4 mg, 0.2 mmol, 10 mol%) or DCDMH (59.1 mg, 0.3 mmol, 15 mol%), in two 10 mL round-bottomed flask, was added terephthaldehyde (0.27 g, 2.0 mmol) and (134.0 mg, 1.0 mmol) respectively. The reaction mixtures were stirred in an oil-bath (120 °C) for approprate times. After completion of the reactions, as monitored by TLC, The reactions were cooled to room temperature, washed with hot water. Afterward, the crude products were purified by plate chromatography on silica gel eluted with EtOAc/*n*-hexane and 1-thioacetamido-

alkyl-2-naphthol (**1b**) and bis(1-thioacetamido-alkyl-2-naphtol) (**2b**) completely separated. **Note:** It should be mentioned that, in the above procedure, 2.0 mmol of terephthaldehyde gives 1b more than **2b** and 1.0 mmol of terephthaldehyde gives **2b** as the main product.

CONCLUSIONS

In conclusion, it has been reported a new procedure for the preparation of 1-thioacetamido-alkyl)-2-naphthol derivatives via a one-pot, three-component condensation of 2-naphthol with aromatic aldehydes and thioacetamide using TCCA and DCDMH as homogenous organic catalysts at 120 °C under the solvent-free and neutral conditions. The presented approach also is allowed for the preparation of bis(1-thioacetamido-alkyl-2-naphthol).

ACKNOWLEDGEMENT

The authors acknowledge to Bu-Ali Sina University Research Councils, Center of Excellence in Development of Chemistry Methods (CEDCM) and National Foundation of elites (BMN) for support of this work.

REFERENCES

1. Zhu, J.; Bienayme, H. *Multicomponent Reactions*; Wiley: Weinheim, 2005.
2. Moosavi-Zare, A. R.; Zolfigol, M. A.; Farahmand, S.; Zare, A.; Pourali, A. R.; Ayazi-Nasrabadi, R. *Synlett* **2014**, *25*, 193-196.
3. Khazae, A.; Zolfigol, M. A.; Moosavi-Zare, A. R.; Zare, A.; Khojasteh, M.; Asgari, Z.; Khakyzadeh, V.; Khalafi-Nezhad, A. *Catal. Commun*. **2012**, *20*, 54-57.
4. (a) Khazaei, A.; Zolfigol, M. A.; Moosavi-Zare, A. R.; Zare, A.; Parhami, A.; Khalafi-Nezhad, A. *Appl. Catal. A: Gen*. **2010**, *386*, 179-187; (b) Zolfigol, M. A.; Khazaei, A.; Moosavi-Zare, A. R.; Zare, A.; Asgari, Z.; Khakyzadeh, V.; Hasaninejad, A. *J. Ind. Eng. Chem*. **2013**, *19*, 721-726; (c) Moosavi-Zare, A. R.; Zolfigol, M. A.; Daraei, M. *Synlett* **2014**, *25*, 1173-1177; (d) Khazaei, A.; Abbasi, F.; Moosavi-Zare, A. R. *New J. Chem*. **2014**, *38*, 5287-5292.
5. Shen, A. Y.; Tsai, C. T.; Chen, C. L. *Eur. J. Med. Chem*. **1999**, *34*, 877-882.
6. Damodira, M.; Selvam, N. P.; Perumal, P. T. *Tetrahedron Lett*. **2009**, *50*, 5474-5478.
7. Kusakabe, Y.; Nagatsu, J.; Shibuya, M.; Kawaguchi, O.; Hirose, C.; Shirato, S. *J. Antibiot.* **1972**, *25*, 44-47.
8. Renullard, S.; Rebhun, L. I.; Havic, G. A.; Kupchan, S. M. *Science* **1975**, *189*, 1002-1005.
9. Lesher, G. Y.; Surrey, A. R. *J. Am. Chem. Soc*. **1955**, *77*, 636-641.
10. Zolfigol, M. A.; Khazae, A.; Moosavi-Zare, A. R.; Zare, A.; Khakyzadeh, V. *Appl. Catal. A: Gen*. **2011**, *400*, 70-81.
11. Zare, A.; Yousofi, T.; Moosavi-Zare, A. R. *RSC Adv.* **2012**, *2*, 7988-7991.
12. Zhang, Z. P.; Wen, J. M.; Li, J. H.; Hu, W. X. *J. Chem. Res*. **2009**, *3*, 162-172.
13. Srihari, G.; Nagaraju, M.; Murthy, M. M. *Helv. Chim. Acta* **2007**, *90*, 1497-1504.
14. Eshghi, H.; Zohuri, G. H.; Damavandi, S. *Synth. Commun*. **2012**, *42*, 516-525.
15. Khazaei, A.; Zolfigol, M. A.; Moosavi-Zare, A. R.; Abi, F.; Zare, A.; Kaveh, H.; Khakyzadeh, V.; Kazem-Rostami, M.; Parhami, A.; Torabi-Monfared, H. *Tetrahedron* **2013**, *69*, 212-218.
16. Yang, L. *E.-J. Chem*. **2012**, *9*, 2424.
17. Xu, Z.; Zhang, D.; Zou, X. *Synth. Commun*. **2006**, *36*, 255-258.
18. Skibinska, M.; Zahn, F. A.; Czarnocka, A.; Lewenstein, W. *Acta Pol. Pharm*. **1969**, *6*, 25-28.
19. Khazaei, A.; Amini-Manesh, A. *J. Chin. Chem. Soc*. **2005**, *52*, 1017-1020.
20. Khazaei, A.; Amini-Manesh, A. *Synthesis* **2005**, 1929-1931.
21. Khazaei, A.; Abbasi, F.; Kiani Borazjani, M.; Saednia, S. *J. Braz. Chem. Soc*. **2014**, *25*, 361-364.
22. Maleki, B.; Gholizadeh, M.; Sepehr, Z. *Bull. Korean Chem. Soc*. **2011**, *32*, 1697-1702.
23. Habibzadeh, S.; Ghasemnejad-bosra, H. *J. Chin. Chem. Soc*. **2012**, *59*, 193-198.
24. Hojati, S. F.; Gholizadeh, M.; Haghdoust, M.; Shafiezadeh, F. *Bull. Korean Chem. Soc*. **2010**, *31*, 3238-3240.
25. Khazaei, A.; Abbasi, F.; Moosavi-Zare, A. R. *RSC Adv.* **2014**, *4*, 1388-1392.

