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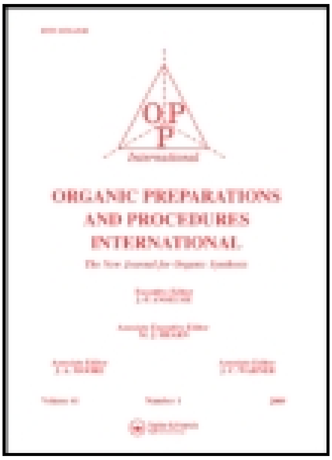

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One-pot Synthesis of 2-Amino-2-chromene and 2-Amino-3-cyano-4H-pyran Derivatives Promoted by Potassium Fluoride

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One-pot Synthesis of 2-Amino-2-chromene and 2-Amino-3-cyano-4H-pyran Derivatives Promoted by Potassium Fluoride

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Pyrans and chromenes are important classes of heterocycles because their core fragments are incorporated in a large variety of natural products and biologically active compounds. They are of considerable interest as they display a broad range of pharmaceutical properties such as anti-tumor,[1] anti-cancer,[2] anti-microbial,[3] anti-fungal,[4] and anti-HIV character.[5] They are widely used as pigments,[6] in cosmetics and as potential biodegradable agrochemicals.[7] Because of the wide range of pharmacological activities and industrial applications, several methods for their preparation have been reported in the literature. 2-Amino-2-chromene and 2-amino-3-cyano-4H-pyrane are generally prepared by the condensation of malononitrile, aldehydes and ethyl acetoacetate (or phenols) in the presence of catalysts such as basic ionic liquid [1-(*n*-butyl)-3-methylimidazolium hydroxide ([bmim]OH)],[8] *p*-dimethylaminopyridine (DMAP),[9] Triton B,[10] K_2CO_3,[11] triethylbenzylammonium chloride (TEBACl),[12] cetyltrimethylammonium chloride (CTACl),[13] cetyltrimethylammonium bromide (CTABr),[14] Na_2CO_3,[15] NH_4OAc,[16] tetramethylguanidine,[17] Mg/La mixed oxide,[18] $H_{14}[Na\ P_5W_{30}O_{110}]$,[19] $CuSO_4.5H_2O$,[20] methanesulfonic acid,[21] KF-Al_2O_3,[22,23] NH_3,[24] NH_4OH,[25] and potassium phthalimide-*N*-oxyl.[26] However, these methods suffer from some draw-backs such as prolonged reactions times, utilization of hazardous organic solvents, tedious work-ups and the use of large amounts of catalyst.

Potassium fluoride (KF) is an inexpensive, commercially available, and water-soluble salt that has been utilized in various organic syntheses.[27–29] Organic reactions performed under solvent-free conditions have attracted much attention, particularly from the viewpoint of green chemistry. Green chemistry approaches are most important due to the reduction in the generation of by-products and of waste products.[30–34] As a continuation of our work on the development of methods using efficient and environmentally benign reagents and catalysts,[35–42] we now report that potassium fluoride is an excellent reagent for the synthesis of 2-amino-2-chromene and 2-amino-2-cyano-4H-pyran derivatives (Scheme 1).

Initially, the reaction of 1-naphthol (1 mmol), benzaldehyde (1 mmol), and malononitrile (1.2 mmol) and potassium fluoride (0.2 mmol) was carried out under solvent-free conditions at 110°C (*Table 1*, *Entry 1*). The corresponding product **7a** was obtained

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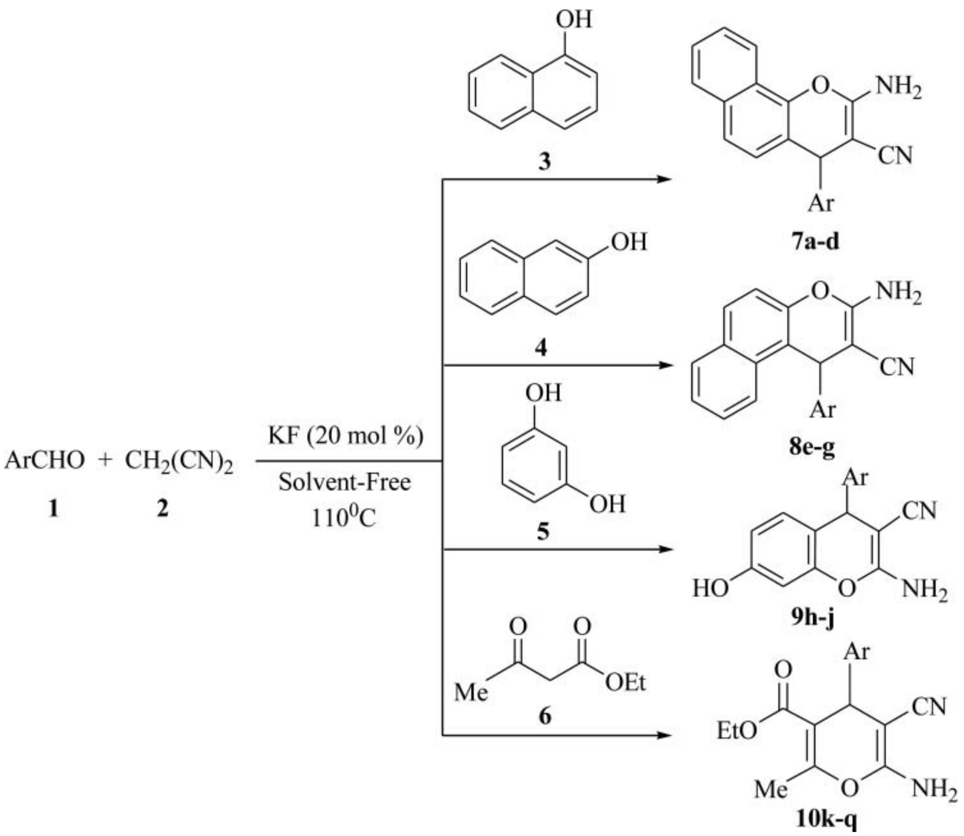


Scheme 1

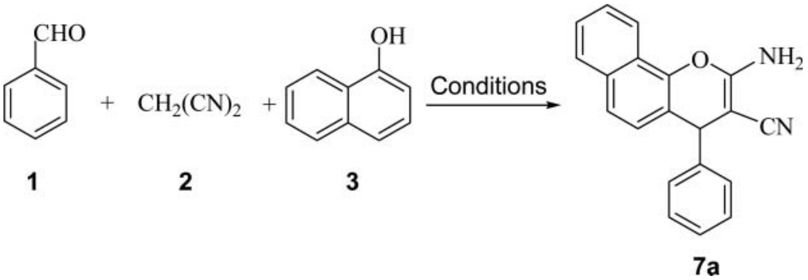
rapidly in excellent yield. Encouraged by this result, we then employed this reaction as a template to optimize the reaction conditions. The results were summarized in (*Table 1*, *Entries 2–6*). To evaluate the effect of potassium fluoride, the reaction was examined in the absence KF under solvent-free condition at 110°C; no product was formed after 60 min at 110°C (*Entry 7*).

The scope and generality of the present method were then further established by the reaction of various aromatic aldehydes with malononitrile and phenol derivatives under solvent-free condition at 110°C. In all of the cases, the corresponding 2-amino-2-chromene derivatives (**7a–d, 8e–g, 9h–j**) were obtained in good yields (Table 2).

To illustrate the applicability of our method, the preparation of 2-amino-3-cyano-4H-pyran derivatives (**10k–q**) was also investigated. First, the reaction of benzaldehyde (1 mmol), malononitrile (1.2 mmol) with ethyl acetoacetate (1 mmol) in the presence of potassium fluoride under different conditions was chosen as model reaction. The best yield was obtained with 0.2 mmol of KF at 110°C under solvent-free conditions. Under these parameters, various aromatic aldehydes were successfully condensed with malononitrile and ethyl acetoacetate in the presence of KF (*Table 2*).

A possible mecanism for these reactions may involve initial abstraction of an α-hydrogen of malononotrile by fluoride ion to give the anion of malononitrile and simultaneous activation of the carbonyl group of the aldehyde by coordination by potassium ion. This would then be followed by nucleophilic attack by malononitrile ion on the

Table 1
Optimization Process



Entry	Amount of KF (mmol)	Temperature (°C)	Time (min)	Yield (%)
1	0.2	110	5	95
2	0.2	100	10	85
3	0.2	120	3	88
4	0.2	90	15	75
5	0.1	110	10	58
6	0.3	110	4	90
7	–	110	60	–[a]

[a] No reaction.

aldehyde, followed by loss of water to produce the arylidenemalononitriles. In the final step, addition of the phenolates or acetoacetate ions (generated by attack of fluoride ion) on the arylidenemalononitrile followed by cyclization would lead to the observed products.

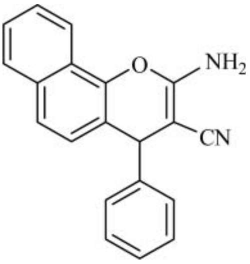
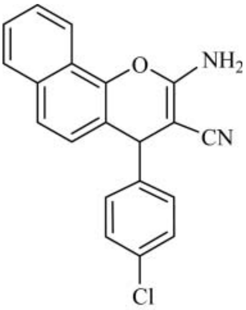
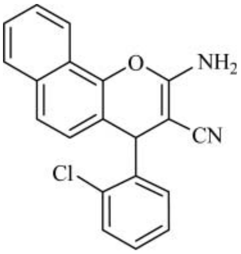
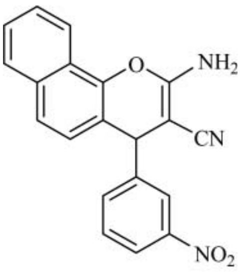
In order to illustrate the efficiency of our procedure, results for the preparation of 2-amino-2-chromenes and 2-amino-3-cyano-4H-pyrans previously reported are compared with our data (Table 3). The present method using KF as reagent offers several advantages such as excellent yields, a simple procedure, short reaction times, and facile work-up.

In conclusion, we have developed a simple and green protocol for the synthesis of 2-amino-2-chromene and 2-amino-3-cyano-4H-pyran derivatives *via* a one-pot three-component condensation reaction in the presence of KF. The new method is inexpensive, eco-friendly and convenient.

Experimental Section

All reagents were obtained from commercial sources and were used without purification. IR spectra were recorded as KBr pellets on a Shimadzu 435-U-04 spectrophotometer. ^{1}H and ^{13}C NMR spectra were determined on a Bruker DRX-300 Avance spectrometer in DMSO-d_6 or $CDCl_3$, and shifts are given in δ downfield from tetramethylsilane (TMS) as an internal standard. Melting points were determined using an Electrothermal 9200 apparatus and are uncorrected. ***CAUTION: Although potassium fluoride is relatively less***

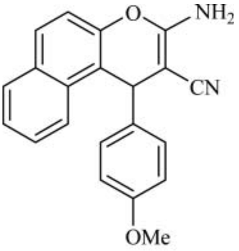
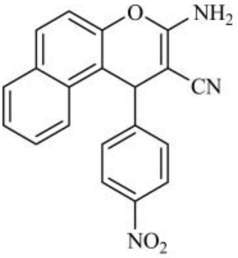
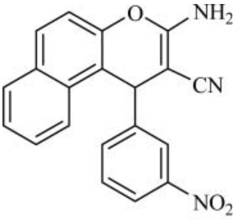
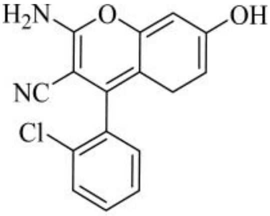
Table 2
One-Pot synthesis of 2-Amino-2-chromene and 2-Amino-3-cyano-4H-pyran Derivatives

			mp (°C)	
Products	Time(min)	Yield (%)	Found	Lit.
 **(7a)**	5	95	211–209	210–211[14]
 **(7b)**	4	90	232	231–232[14]
 **(7c)**	5	89	238–240	236–237[14]
 **(7d)**	5	91	213–214	212–214[14]

(*Continued on next page*)

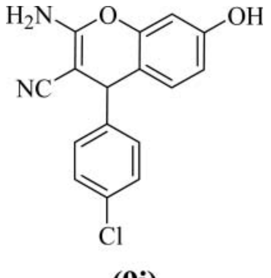
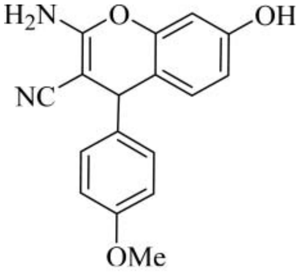
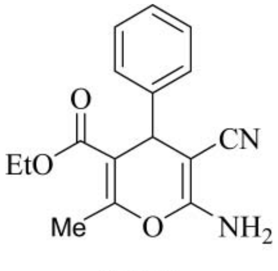
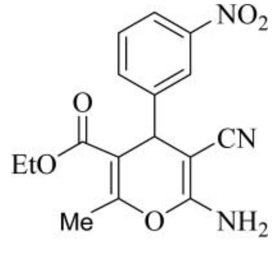
Table 2

One-Pot synthesis of 2-Amino-2-chromene and 2-Amino-3-cyano-4H-pyran Derivatives *(Continued)*

Products	Time(min)	Yield (%)	mp (°C)	
			Found	Lit.
Products	Time(min)	Yield (%)	mp (°C)	
			Found	Lit.
 **(8e)**	13	89	119–120	116–117[14]
 **(8f)**	10	90	186	185–186[14]
 **(8g)**	7	93	283–284	280–282[14]
 **(9h)**	35	76	96–97	94–95[14]

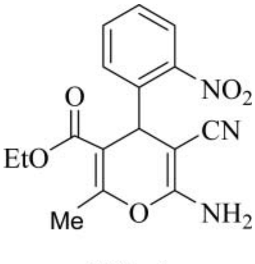
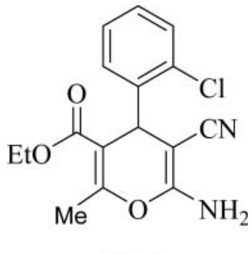
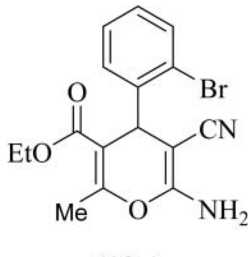
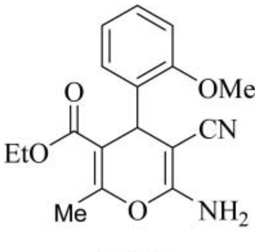
(*Continued on next page*)

Table 2
One-Pot synthesis of 2-Amino-2-chromene and 2-Amino-3-cyano-4H-pyran Derivatives *(Continued)*

Products	Time(min)	Yield (%)	mp (°C)	
			Found	Lit.
 **(9i)**	30	82	162–163	161–162[14]
 **(9j)**	30	80	111–112	112–114[14]
 **(10K)**	10	90	194–195	190–192[24]
 **(10l)**	5	95	187–188	187–188[24]

(*Continued on next page*)

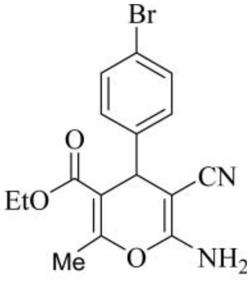
Table 2
One-Pot synthesis of 2-Amino-2-chromene and 2-Amino-3-cyano-4H-pyran Derivatives
(Continued)

			mp (°C)	
Products	Time(min)	Yield (%)	Found	Lit.
 **(10m)**	7	91	177–178	177–178[24]
 **(10n)**	10	89	190–191	191–192[24]
 **(10o)**	10	83	182–183	183–184[24]
 **(10p)**	15	75	197–198	196–197[24]

(*Continued on next page*)

Table 2

One-Pot synthesis of 2-Amino-2-chromene and 2-Amino-3-cyano-4H-pyran Derivatives *(Continued)*

			mp (°C)	
Products	Time(min)	Yield (%)	Found	Lit.
 **(10q)**	10	84	179–180	180–181[24]

***hazardous than many reagents, it is corrosive and toxic and care should be exercized in its use*.**

General Procedure for the Synthesis of 2-Amino-2-chromenes

A mixture of the aldehyde (1 mmol), malononitrile (0.08 g, 1.2 mmol) and α- or β-naphthol (0.14 g, 1 mmol) or 1,3-dihydroxybenzene (0.11 g, 1 mmol), was stirred at room temperature for two minutes, then 0.012 g (0.2 mmol) of KF was added and the mixture was heated on an oil bath at 110°C with stirring for the time show in Table 2. Upon completion of the reaction as indicated by TLC (hexane:ethyl acetate, 8:2), hot EtOH (96%, 1 ml) was added to the mixture which was stirred for 2 min. Then the reaction mixture was poured onto crushed ice and the precipitated solid was collected, recrystallized from ethanol (96%, 3 ml) to afford the pure 2-amino-2-chromene derivatives (**7a–d, 8e–g, 9h–j**).

General Procedure for the Synthesis 2-Amino-3-cyano-4H-pyrans

A mixture of the aldehyde (1 mmol), malononitrile (0.08 g, 1.2 mmol), and ethyl acetoacetate (0.13 ml, 1 mmol) was stirred at room temperature for two minutes, then KF (0.012 g, 0.2 mmol) was added and the mixture was heated in an oil bath at 110°C with stirring for the time shown in Table 2. Upon completion of the reaction as indicated by TLC (hexane:ethyl acetate, 8:2), hot EtOH (96%, 1 ml) was added and the mixture stirred for 2 min. Then the resulting crude reaction mixture was poured onto crushed ice and the precipitated solid was collected and recrystallized from ethanol (96%, 3 ml) to afford the pure 2-amino-3-cyano-4H-pyran derivatives (**10k–q**).

Table 3
Comparison of Methods for the Synthesis of 2-Amino-2-chromene and 2-Amino-3-cyano-4H-pyran Derivatives

Entry	Conditions	Time (min)	Yield (%)
7a	Present work	5	95
	$CTABr/H_2O$/ultrasonic/rt[14]	150	92
	Triton B/Ethanol/rt[10]	85	87
	$CuSO_4.5H_2O$/water/reflux[20]	60	95
	methanesulfonic acid/CH_3CN/reflux[21]	180	90
7c	Present work	5	89
	KF-Al_2O_3/EtOH/reflux[22]	300	73
	$CTABr/H_2O$/ultrasonic/rt[14]	360	86
	$CuSO_4.5H_2O$/water/reflux[20]	150	80
10k	Present work	10	90
	KF-Al_2O_3/EtOH/reflux[23]	180	85
	NH_3/ethanol/rt[24]	4	90
	NH_4OH/IR/Reflux[25]	10	98

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References

1. C. Lagisetti, A. Pourpak, Q. Jiang, X. Cui, T. Goronga, S. W. Morris, and T. R. Webb, *J. Med. Chem.*, **51**, 6220 (2008).
2. A. H. Banskota, Y. Tezuka, K. Q. Tran, I. Saiki, Y. Miwa, T. Taga, and S. Kadota, *Bioorg. Med. Chem. Lett.*, **8**, 3519 (1998).
3. A. M. El-Saghier, M. B. Naili, B. K. Rammash, N. A. Saleh, and K. M. Kreddan, *Arkivoc*, **16**, 83 (2007).
4. T. Suresh, V. Arunima, K. Atin, G. Sandeep, V. R. Prarthana, and R. K. Ganesh, *Acta Pol. Pharm.*, **67**, 423 (2010).
5. C. K. Denish, K. P. Hetal, and K. G. Nilesh, *Asian J. Biochem. Pharm. Res.*, **2**, 126 (2012).
6. G. P. Ellis, E. C. Weissberger, and E. C. Taylor, *The Chemistry of Heterocyclic Compounds: Chromene, Chromanes and Chromones*, John Wiley & Sons, New York, NY, Chapter **II**, 1977, 11–139.
7. E. A. A. Hafez, M. A. Elnagdi, A. A. Ali. Elagamey, and F. M. A. El-Taweel, *Heterocycles*, **26**, 903 (1987).
8. K. Gong, H. L. Wang, D. Fang, and Z. L. Liu, *Catal. Commun.*, **9**, 650 (2008).
9. K. R. Desale, K. P. Nandre, and S. L. Patil, *Org. Commun.*, **5**, 179 (2012).

10. G. Sabitha, M. Bhikshapathi, S. Nayak, R. Srinivas, and J. S. Yadav, *J. Heterocyclic Chem.*, **48**, 267 (2011).
11. M. Kidwai, S. Saxena, M. K. Rahman Khan, and S. S. Thukral, *Bioorg. Med. Chem. Lett.*, **15**, 4295 (2005).
12. L. Rong, X. Li, H. Wang, D. Shi, S. Tu, and Q. Zhuang, *Synth. Commun.*, **36**, 2363 (2006).
13. R. Ballini, G. Bosica, M. L. Conforti, R. Maggi, A. Mazzacani, P. Righi, and G. Sartori, *Tetrahedron*, **57**, 1395 (2001).
14. T. S. Jin, J. C. Xiao, S. J. Wang, T. S. Li, *Ultrason. Sonochem.*, **11**, 393 (2004).
15. M. R. Naimi-Jamal, S. Mashkouri, and A. Sharifi, *Mol. Divers.*, **14**, 473 (2010).
16. A. Moshtaghi Zonouz, I. Eskandari, and D. Moghani, *Chem. Sci. Trans.*, **1**, 91 (2012).
17. R. M. N. Kalla, S. J. Byeon, M. S. Heo, and I. Kim, *Tetrahedron*, **69**, 10544 (2013).
18. N. S. Babu, N. Pasha, K. T. V. Rao, P. S. S. Prasad, and N. Lingaiah, *Tetrahedron Lett.*, **49**, 2730 (2008).
19. M. M. Heravi, K. Bakhtiari, V. Zadsirjan, F. F. Bamoharram, and O. M. Heravi, *Bioorg. Med. Chem. Lett.*, **17**, 4262 (2007).
20. F. K. Behbahani, and M. Sadeghi, *J. Korean Chem. Soc.*, **57**, 357 (2013).
21. M. M. Heravi, B. Baghernejad, and H. A. Oskooie, *J. Chin. Chem, Soc.*, **55**, 659 (2008).
22. X. S. Wang, D. Q. Shi, H. Z. Yu, G. F. Wang, and S. J. Tu, *Synth. Commun.*, **34**, 509 (2004).
23. I. Kharbangar, R. Rohman, H. Mecadon, and B. Myrboh, *Inter. J. Org. Chem.*, **2**, 282, (2012).
24. A. A. Moshtaghi Zonouz, D. Moghani, and S. Okhravi, *Curr. Chem. Lett.*, **3**, 71 (2014).
25. A. Sánchez, F. Hernández, P. C. Cruz, Y. Alcaraz, J. Tamariz, F. Delgado, and M. A. Vázquez, *J. Mex. Chem. Soc.*, **56**, 121 (2012).
26. M. G. Dekamin, M. Eslami, and A. Maleki, *Tetrahedron*, **69**, 1074 (2013).
27. S. Bahadorikhalili, and A. R. Sardayyan, *Monatsh. Chem.*, **143**, 841 (2012).
28. B. L. Blass, *Tetrahedron*, **58**, 9301 (2002).
29. L. Yin, and S. Liebscher, *Chem. Rev.*, **107**, 133 (2007).
30. A. Zare, *Org. Prep. Proced. Int.*, **44**, 82 (2012).
31. G. Kumaraswamy, N. Raghu, and R. S. Kumar, *Org. Prep. Proced. Int.*, **46**, 435 (2014).
32. M. Wang, J. L. Song, S. Zhao, and X. Wan, *Org. Prep. Proced. Int.*, **46**, 457 (2014).
33. M. Wang, Z. G. Song, and Y. Liang, *Org. Prep. Proced. Int.*, **43**, 484 (2011).
34. J. Safaei-Ghomi, M. Taheri, and M. A. Ghasemzadeh, *Org. Prep. Proced. Int.*, **42**, 485 (2010).
35. B. Maleki, and F. Taimazi, *Org. Prep. Proced. Int.*, **46**, 252 (2014).
36. B. Maleki, S. Sedigh Ashrafi, *RSC Advances*, **4**, 42873 (2014).
37. B. Maleki, E. Rezaee-Seresht, and Z. Ebrahimi, *Org. Prep. Proced. Int.*, **47**, 149 (2015).
38. B. Maleki, *Org. Prep. Proced. Int.*, **47**, 173 (2015).

39. H. Veisi, B. Maleki, M. Hamelian, and S. Sedigh Ashrafi, *RSC Advances*, **5**, 6365 .

40. B. Maleki, F. Mohammadi Zonoz, and H. A. Akhlaghi, *Org. Prep. Proced. Int.*, **47**, DOI:10.1080/00304948.2015.1066646) (2015).

41. H. Veisi, A. Naeimi, B. Maleki, S. Sedigh Ashrafi, and A. Sedrpoushan, *Org. Prep. Proced. Int.*, **47**, 309 (2015).

42. B. Maleki, S. Sedigh Ashrafi, and R. Tayebee, *RSC Advances*, **4**, 41521 (2014).