IRANIAN JOURNAL OF CATALYSIS

# Eggshell: A green and efficient heterogeneous catalyst for the synthesis of pyrano[3,2-*c*]quinoline derivatives

Leila Youseftabar-Miri*[,a], Fatemeh Akbari[b], Farshid Ghraghsahar[b]

[a]*Department of Chemistry, Izeh Branch, Islamic Azad University, Izeh, Iran.*
[b]*Department of Chemistry, Khuzestan Science and Research Branch, Islamic Azad University, Ahwaz, Iran.*

Received 14 December 2013; received in revised form 7 January 2014; accepted 14 March 2014

ABSTRACT

Eggshell was found to be a versatile heterogeneous catalyst for the synthesis of pyrano[3,2-*c*]quinoline derivatives in good yields. This protocol has the advantages of environmental friendliness, short reaction time, low cost and convenient operation.

***Keywords****: Multicomponent reactions, Pyranoquinoline, Eggshell, Heterogeneous catalyst.*

## 1. Introduction

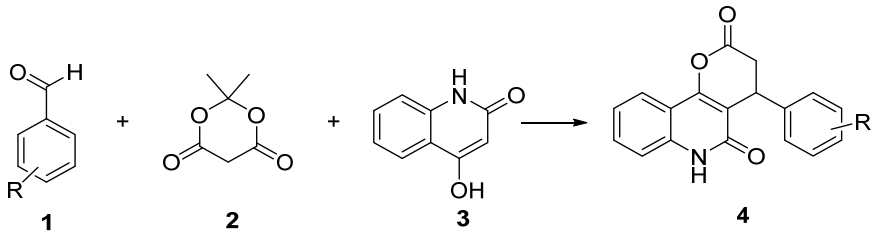
Designing of economical synthesis in direction to save the current chemical resources and the necessity to prevent the chemical impact on environment are the main objectives that inspire the recent researches in organic chemistry. To achieve these desirable synthesis, chemists have been and are being extending syntheses based on multicomponent reactions (MCRs) since they are combiners of more than two building blocks in usually practical manner, time-saving, atom economy, and one-pot operations [1]. Multicomponent reactions may give rise to complex structures by simultaneous formation of two or more bonds, a feature that highlights them as the promised means for quick generating a wide diversity of lead molecules required in preparation of libraries and associated high throughput screening programs [2]. Typically, purification of products resulting from MCRs is also simple since all the employed organic reactants are incorporated into the target compound so can offer far different physical properties than the individual starting materials [3]. The prospect of implementing MCRs without using toxic catalysts in solvent-free conditions as well as in water solutions is another existing strategy of laboratories since will complement the significant characters of MCRs to ideally satisfy the green chemistry's principles [4].

* Corresponding author: l.youseftabar@izehiau.ac.ir
Tel.: +986925224040, Fax: +986925231068

Pyran derivatives are of considerable interest in industry as well as in academia owing to their promising biological activity such as anticoagulant, anticancer, diuretic, spasmolytic and anti-anaphylactin agents [5]. Furthermore, recent studies have revealed several medicinal applications such as, for the treatment of alzheimer's disease, Huntington's disease, amyoprophic lateral sclerosis, Parkinson's diseases, AIDS associated dementia and Down's syndrome as well as for the treatment of schizophrenia and myoclonus [6].

Pyranoquinoline derivatives are found to possess a wide spectrum of biological activities, such as psychotropic, antiallergenic, anti-inflammatory and estrogenic activity. Furthermore, many of these alkaloids exhibit cancer cell growth inhibitory activity and are investigated as potential anticancer agents [7-14]. For examples, zanthosimuline, is active against multidrug resistant KB-VI cancer cells, while huajiaosimuline xhibits a selective cytotoxicity profile showing the greatest activity with estrogen receptor-positive ZR-75-1 breast cancer cells [15]. Therefore, preparation of this heterocyclic nucleus has gained great importance in organic synthesis. To the best of our knowledge, there are little reports in literature on the synthesis of pyran derivatives [16-18].

Heterogeneous catalyst have gained much importance in recent years due to economic and environmental benefits [19]. These catalysts make the synthetic processes clean, safe, high yielding and inexpensive.



**Scheme 1.** The model reaction.

In this research, we used eggshell as a heterogeneous, bioactive and biodegradable catalyst. Mosaddegh at el. described the characterization of eggshell [20].

## 2. Experimental

All chemicals were purchased from Merck or Fluka Chemical Companies. All known compounds were identified by comparison of their melting points and spectral data with those reported in the literature. Progress of the reactions was monitored by thin layer chromatography (TLC) using silica gel SIL G/UV 254 plates. IR spectra were recorded using a Shimadzu IR-470 spectrometer with KBr plates. $^{1}$HNMR and $^{13}$CNMR spectra were recorded on a Bruker Avance-400 MHz spectrometer.

### *2.1. General procedure*

A mixture aromatic aldehyde (1 mmol) and Meldrum's acid **2** (1 mmol) was added to a vial containing a magnetic stirring bar and 0.2 g of eggshell in 3 ml EtOH. The reaction mixture was sealed and stirred at 60 °C (oil bath) until created intermediate **5**, then added of 4-hydroxyquinolin-2(1H)-one **3** (1 mmol) to mixture of the starting materials. After completion, the reaction mixture was filtered and the obtained precipitate washed with hot ethanol (95.5%).

### *2.2. Catalyst preparation*

Empty chicken eggshells were collected from the household and washed with tap warm water. The adhering membrane is separated manually. Then, the eggshells are washed with distilled water and dried at room temperature [20–24].

### *Selected spectral data*

*4-(4-nitrophenyl)-3,4-dihydro-4H-pyrano[3,2-c] quinoline-2,5-dione* (***4a***):

$^{1}$HNMR (400 MHz, DMSO-$d_6$): $\delta$= 12.95 (1H, d, $^{2}J$ = 14.8 Hz, 3-Ha), 3.50 (1H, d.d, $^{3}J$ =7.6Hz, $^{3}J$ =7.6Hz, 3-Hb), 4.53 (1H, d, $^{3}J$= 6.8Hz), 4.53 (1H, d, $^{3}J$=6.8Hz, 4-H), 7.21-7.23 (2H, m), 7.30-7.33 (1H, m), 7.36-7.41 (3H, m), 7.60- 7.65 (1H, m), 7.83 (1H, d.d, $^{3}J$=8.0Hz, $^{3}J$=8.0Hz), 12.0 (1H, s, NH) ppm. $^{13}$CNMR (100 MHz, DMSO-$d_6$): $\delta$= 34.7 ($CH_2$), 35.5 (CH), 111.6, 112.8 (C), 116.0, 122.2, 122.7, 129.1, 129.3(2CH), 131.9, 132.3, 131.7, 140.3, 155.1, 161.3, 166.5 ppm. IR (KBr): $\bar{\nu}$ = 3426, 1782, 1661, 1580, 1498, 1390 cm$^{-1}$.

*4-(4-isopropylphenyl)-3,4-dihydro-4H-pyrano[3,2-c]quinoline-2,5-dione* (***4b***):

$^{1}$HNMR (400 MHz, DMSO-$d_6$): $\delta$= 1.15 (3H, s, $CH_3$), 2.85 (1H, m, $CH_{isopropyl}$), 2.93 (1H, d, $^{2}J$=14.8Hz, 3-Ha), 3.47 (1H, d.d, $^{3}J$=7.6Hz, $^{3}J$=7.2Hz, 3-$H_b$), 4.47 (1H, d, $^{3}J$=7.2Hz, 4-H), 7.09 (1H, d, $^{3}J$=7.2Hz), 7.09 (2H, d, $^{3}J$= 8.0Hz), 7.18 (2H, d, $^{3}J$=8.0Hz), 7.30 (1H, t, $J$=8.0Hz), 7.39 (1H, d, $^{3}J$=8.0Hz), 7.62 (1H, t, $^{3}J$=8.0Hz), 7.83 (1H, d, $^{3}J$=7.2Hz), 11.98 (1H, s, NH) ppm. $^{13}$CNMR (100 MHz, DMSO-$d_6$): δ 24.3 , 33.5, 34.6, 112.3, 112.8, 115.8, 122.1, 122.7, 127.0, 127.3, 131.8 , 138.7, 147.8, 154.9, 161.4, 166.8 ppm. IR(KBr): $\bar{\nu}$ = 3394, 1786, 1661, 1580, 1500 cm$^{-1}$.

*4-(4-chlorophenyl)-3,4-dihydro-4H-pyrano[3,2-c]quinoline-2,5-dione* (***4c***):

$^{1}$HNMR (400 MHz, DMSO-$d_6$): $\delta$= 2.98 (1H, d, $^{2}J$=14.8Hz, 3-Ha), 3.53 (1H, d.d, $^{2}J$=16.0Hz, $^{3}J$=7.2Hz, 3-$H_b$), 4.54 (1H, d, $^{3}J$=7.2Hz, 4-H), 7.15 (1H, d, $^{3}J$=7.6Hz), 7.26– 7.33 (2H, m), 7.40 (1H, d, $^{2}J$=8.4Hz), 7.47 (2H, d, $^{2}J$=8.4Hz), 7.62 (1H, t, $^{2}J$=6.8Hz), 7.83 (1H, d, $^{2}J$=7.2Hz), 12.0 (1H, s, NH) ppm. $^{13}$CNMR (100 MHz, DMSO-$d_6$): $\delta$= 34.7, 36.6, 111.4, 112.8, 116.0, 122.2, 122.6, 122.8, 125.9, 130.2, 130.7, 131.6, 132.0, 138.8, 144.1, 153.3 , 161.2, 166.5 ppm. IR (KBr): $\bar{\nu}$ = 3438, 1788, 1661, 1580, 1498, 1115, 863 cm$^{-1}$.

## 3. Results and Discussion

Recently, Rad-Moghadam at el. reported effect of several catalyst for synthesis of pyrano[3,2-*c*] quinolone [25], and introduced ionic liquids are efficient catalyst for this reaction. With this background in mind and our interest in the synthesis heterocyclic compounds [26,27], and use of biocatalyst in synthesis, we report an efficient and environmentally benign protocol for the synthesis of pyranoquinoline motifs compounds by multi-component condensation of aromatic aldehydes **1**, Meldrum's acid **2**, and 4- hydroxyquinolin-2(1H)-one **3** catalyzed by eggshell in ethanol. The products were obtained in high yields by a simple workup (Scheme 1). In order to optimize the reaction conditions, the condensation of 4-nitro-benzaldehyde **1a**, Meldrum's

acid **2**, and 4- hydroxyquinolin-2(1H)-one **3** and eggshell (0.2 g) was attempted in different solvent and temperature (Table 1). The condensation was performed in different solvent but the efficiency and the yield of the reaction in ethanol were higher than those in other solvent thereby making ethanol the most suitable reaction medium for successive reactions. In the same condition but without eggshell the yield of product was low even after 5h. This table also implies that water is potentially more effective medium for running the reaction. However, pure water appeared not so useful here presumably due to its less activity of catalyst [20].

Notably, the assistance of solvent is apparent in the table as the yield of reaction is very low in solvent-free conditions even when the reaction mixture stood at 60 °C for 6 h. To optimize the reaction temperature, the reactions were carried out at different temperatures ranging from 25 to 80 °C. The yield of product was improved and the reaction time was shortened as the temperature was increased to 60 °C. The yield did not improve when temperature was further increased to 80 °C. Therefore, the most suitable reaction temperature is 60 °C.

We also evaluated the amount of eggshell required for this reaction. It was found that when increasing the amount of the eggshell from 0.05 to 0.2 g, the yields increased from 54 to 85 respectively. Using 0.2 g eggshell in ethanol is sufficient to push this reaction forward. More amounts of the additive did not improve the yields or reaction time. Since almost 90% of eggshell is composed of $CaCO_3$ [20], we compared the catalytic activity between $CaCO_3$ and eggshell in the same conditions (Table 2, entry 14), this results same Mosaddegh at el. [20] reveals the activity of eggshell is higher than $CaCO_3$ [20].

After optimization of the reaction conditions, various aromatic aldehydes were subjected to reaction with Meldrum's acid 2 and 4- hydroxyquinolin-2(1H)-one **3** under the selected conditions. The reactions proceeded with different aldehydes substituted with electron-donating or electron-withdrawing groups giving excellent yields. These results are compiled in Table 2. As showed in Table 2, in all cases the reaction gives the products in good yields and easy work up.

A plausible mechanism for the formation of the selected product **4** in the presence of eggshell as a catalyst solvent is outlined in Scheme 2. The condensation of Meldrum's acid **1**, aldehyde **2** and 4-hydroxyquinolin-2(1*H*)-one **3** may occur by a mechanism of Knoevenagel condensation, Michael addition, intramolecular cyclization, and isomerization. Initially, intermediate **5** is formed by Knoevenagel condensation of Meldrum's acid **1** and aldehyde **2** by the action of eggshell. Then, the proton of 4- hydroxyquinolin-2(1*H*)-one **3** is abstracted by active sites of eggshell to form intermediate **5**. Michael addition of intermediate **6** on **5** leads to the formation of **7**, followed by cyclization and isomerization, affords the corresponding products **4** (Scheme 2).

**Table 1.** Optimization of reaction conditions.

| Entry | Solvent | Conditions | Time | Yield (%)[a] |
|---|---|---|---|---|
| 1 | EtOH | 60 °C/eggshell (0.2 g) | 30 | 85 |
| 2 | $CH_2Cl_2$ | 60 °C/eggshell (0.2 g) | 30 | 32 |
| 3 | $CH_3CN$ | 60 °C/eggshell (0.2 g) | 30 | 42 |
| 4 | $H_2O$ | 60 °C/eggshell (0.2 g) | 30 | 25 |
| 5 | EtOH | 25 °C/eggshell (0.2g) | 30 | Trace |
| 6 | EtOH | reflux/eggshell (0.2g) | 30 | 85 |
| 7 | EtOH | 60 °C/eggshell (0.1g) | 45 | 63 |
| 8 | EtOH | 60 °C/eggshell (0.05g) | 45 | 54 |
| 9 | EtOH | 60 °C/eggshell (0.15g) | 30 | 76 |
| 10 | EtOH | 45 °C/eggshell (0.2g) | 45 | 67 |
| 11 | - | 60 °C/eggshell (0.2g) | 6h | Trace |
| 12 | EtOH | 60 °C/eggshell (0.3g) | 30 | 85 |
| 13 | EtOH | 60 °C/- | 5h | Trace |
| 14 | EtOH | 60 °C/$CaCO_3$ (0.2g) | 30 | 62 |

[a]Isolated yields.

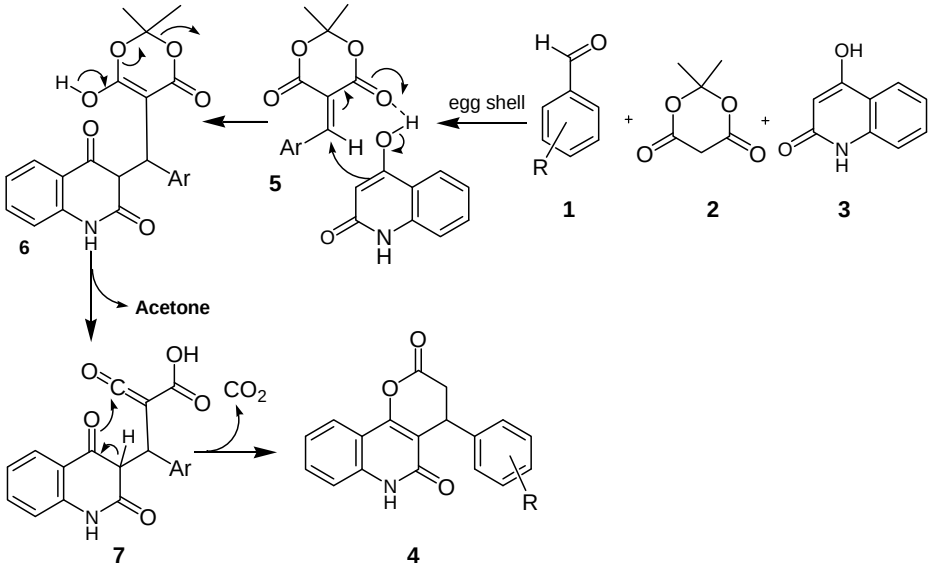
The known products have physical data consistent with those reported in literatures as well as the authentic samples prepared from previous reported methods. The structures of new compounds 4a-b were confirmed by IR, $^{1}H$ and $^{13}CNMR$.

In the next phase of study the viability of catalysis by the recycled eggshell was evaluated. In this regard preparation of **4a** was chosen as the model. After completion of the reaction catalyst washed with water and drying at room temperature [20] and then subjected to the next run with the same substrates and the same reaction time. Catalyst recycling showed that yield of reaction had not decreased after four runs (Yield decreased from 85 to 80%).

**Table 2.** Synthesis of pyranoquinoline motifs derivatives **4a-g** in the presence of eggshell after 30-35 min.

| Entry | Product | Ar | Time | Yield (%)[a] | m.p. (°C) | | Ref. |
|---|---|---|---|---|---|---|---|
| | | | | | Found | Reported | |
| 1 | **4a** | 4-$NO_2$–$C_6H_4$ | 30 | 85 | 328-330 | - | |
| 2 | **4b** | 4-isopropyl–$C_6H_4$ | 35 | 89 | 322-324 | - | |
| 3 | **4c** | 4-Cl–$C_6H_4$ | 35 | 89 | 330-332 | 333-335 | [25] |
| 4 | **4d** | 4-OMe–$C_6H_4$ | 30 | 90 | 324-326 | 335-337 | [25] |
| 5 | **4e** | 4-Me–$C_6H_4$ | 30 | 87 | 326-328 | 330-332 | [25] |
| 6 | **4f** | 2,4-Cl–$C_6H_4$ | 35 | 85 | 335-337 | 335-337 | [25] |
| 7 | **4g** | 3-Br- $C_6H_4$ | 35 | 86 | 328-330 | 305-307 | [25] |

[a]Isolated yields.




**Scheme 2.** Plausible mechanism for synthesis of pyranoquinoline ring systems **4** in the presence of eggshell as a catalyst.

## 4. Conclusions

In summary, an efficient method for the synthesis of the pyrano[3,2-*c*]quinolone drivatives by using simple and readily available starting materials under catalysis of the eggshell, was introduced here. The eggshell acts as a catalyst and can be recovered for reuse several times. Another advantage of the present method may be no requirement for metal catalysts and proceeding with similar rate with respect to the methods that gave the similar structure. We expect this method will find extensive applications in the field of combinatorial chemistry, diversity-oriented synthesis, and drug discovery.

## Acknowledgment

We gratefully acknowledge the financial support from the Research Council of University of Islamic Azad University, Izeh Branch.

## References


[1] N. Mont, J. Teixidoˊ, J.I. Borrell, C.O. Kappe, Tetrahedron Lett. 44 (2003) 5385-5387. (b) M.C. Bagley, J.W. Dale, J. Bower, Chem. Commun. (2002) 1682-1683. (c) C. Simon, T. Constantieux, J. Rodriguez, Eur. J. Org. Chem. 24 (2004) 4957-4980. (d) Y.J. Huang, F.Y. Yang, C.J. Zhu. J. Am. Chem. Soc. 127 (2005) 16386-16387.

[2] M.A.P. Martins, C.P. Frizzo, D.N. Moreira, N. Zanatta, H.G. Bonacorso, Chem. Rev. 108 (2008) 2015-2050.

[3] (a) J. Zhu, H. Bienayme, H. Multicomponent Reactions; Wiley: New York, (2005). (b) S.L. Cui, X.F. Lin, Y.G. Wang. J. Org. Chem. 70 (2005) 2866-2869.

[4] (a) C.J, Li, T.H Chan. Organic Reactions in Aqueous Media; Wiley: New York, (1997). (b) P.A. Grieco. Ed.; Thomson Science: Glasgow, Scotland, Organic Synthesis in Water. (1998). (c) C.J. Li. Chem. Rev.105 (2005) 3095-3166.

[5] S.K. Kulkarni, P.N. Kaul. Indian J. Exp. Biol. 18 (1980) 270-272.

[6] (a) H. Tomoda, Y.K. Kim, H. Nishida, R. Masuma, S. Omura, J. Antibiot. 47 (1994) 148-153. (b) M. Handa, T. Sunazuka, K. Nagai, R. Kimura, T. Shirahata, Z.M. Tian, K. Otoguro, Y. Harigaya, S. Omura, J. Antibiot. 54 (2001) 382-389.

[7] T.S., Chen, S.J. Wu, I.L. Tsai, T.S., Wu, J.M. Pezzuto, M.C. Lu, H. Chai, N. Suh, C.M. Teng, J. Nat. Prod. 57 (1994) 1206-1211.

[8] (a) T. Davion, B. Joseph, Y. Merour. Synlett (1998) 1051-1052. (b) L. F. Tietze, Y. F. Zhou. Angew. Chem. Int. Ed. 38 (1999) 2045-2047. (c) Y. Fujita, H. Oguri, H. Oikawa. J. Antibiot. 58 (2005) 425-427.

[9] F. Hanawa, N. Fokialakis, A.L. Skaltsounis, Planta Med. 70 (2004) 531-535.

[10] C.L. Cantrell, K.K. Schrader, L.K. Mamonov, G.T. Sitpaeva, T. S. Kustova, C. Dunbar, D.E. Wedge. J. Agric. Food Chem. 53 (2005) 7741-7748.

[11] J.J. Chen, P.H. Liao, C. H. Huang, S. Y. Chen. J. Nat. Prod. 70 (2007) 1444-1448.

[12] F. Koizumi, N. Fukumitsu, J. Zhao, R. Chanklan, T. Miyakawa, S. Kawahara, S. Iwamoto, M. Suzuki, S. Kakita, E.S. Rahayu, S. Hosokawa, K. Tatsuta, M. Ichimura. J. Antibiot. 60 (2007) 455-458.

[13] I.S. Chen, I.W. Tsai, C.M. Teng, J.J. Chen, Y.L. Chang, F.N. Ko, M.C. Lu. Phytochemistry 46 (1997) 525-529.

[14] C. Ito, M. Itoigawa, A. Furukawa, T. Hirano, T. Murata, N. Kaneda, Y. Hisada, K. Okuda, H. Furukawa. J. Nat. Prod. 67 (2004) 1800-1803.

[15] I.S. Chen, S.J. Wu, I.L. Tsai, T.S. Wu, J.M. Pezzuto, M.C. Lu, H. Chai, N. Suh, C.M. Teng. J. Nat. Prod. 57 (1994) 1206-1211.

[16] X. Wang, Z. Zeng, D. Shi, X. Wei, Z. Zong, Synth. Commun. 34 (2004) 3021-3027.

[17] M. Lei, L. Mab, L. Hu, Tetrahedron Lett. 52 (2011) 2597-2600.

[18] (a) I.V. Magedov, M. Manpadi, E. Rozhkova, N.M. Przheval'skii, S. Rogelj, S.T. Shors, W.F.A. Steelant, S. Van Slambrouck, A. Kornienko, Bioorg. Med. Chem. Lett. 17 (2007) 1381-1385. (b) I.V. Magedov, M. Manpadi, M.A. Ogasawara, A.S. Dhawan, S. Rogelj, S. Van slambrouck, W.F.A. Steelant, N.M. Evdokimov, P.Y. Uglinskii, E.M. Elias, E.J. Knee, P. Tongwa, M. Yu. Antipin, A. Kornienko, J. Med. Chem. 51 (2008) 2561-2570. (c) X. Fan, D. Feng, Y. Qu, X. Zhang, J. Wang, P.M. Loiseau, G. Andrei, R. Snoeck, E. Clercq, Bioorg. Med. Chem. Lett. 20 (2010) 809-813.

[19] (a) G. Rossini, R. Ballini, P. Sorrenti, Synthesis (1983) 1014-1016. (b) R. Ballini, G. Bosica, J. Org. Chem. 62 (1997) 425-427.

[20] E. Mosaddegh, A. Hassankhani, Catal. Commun. 33 (2013) 70-75.

[21] Y.C. Sharma, B. Singh, J. Korstad, Energy Fuels 24 (2010) 3223–3231.

[22] G. Krithiga, T.P. Sastry, Bull. Mater. Sci. 34 (2011) 177–181.

[23] W.N. Garnjanagoonchorn, A. Changpuak, Int. J. Food Prop. 10 (2007) 497–503.

[24] H.J. Park, S.W. Jeong, J.K. Yang, B.G. Kim, S.M. Lee, J. Environ. Sci. 19 (2007) 1436-1441.

[25] K. Rad-Moghadam, S.C. Azimi, E. Abbaspour-Gilandeh, Tetrahedron Lett. 54 (2013) 4633-4645.

[26] K. Rad-Moghadam, L. Youseftabar-Miri. J. Fluorine Chem. 135 (2012) 213-219.

[27] K. Rad-Moghadam, L. Youseftabar-Miri. Tetrahedron 67 (2011) 5693-5699.