Efficient and Green Synthesis of Mono- and Disubstituted 2,3-Dihydroquinazolin-4(1H)-Ones Using Squaric Acid as a New Organocatalyst in Water

Yeni Sulu Organokatalizör Skuarik Asit Varlığında Mono ve Disübstitüye 2,3-Dihidroksikuinazolin- 4(1H)-Ones'un Etkin ve Yeşil Sentezi

Research Article

Samad Khaksar[1]*, Sattar Arshadi[2], Fatemeh Ghanbari[2]

[1]Islamic Azad University, Department of Chemistry, Ayatollah Amoli Branch, Amol, Iran.

[2]Payame Noor University, Chemistry Department, Sari, Iran.

ABSTRACT

A simple and facile synthesis of mono- and disubstituted 2,3-dihydroquinazolin-4(1H)-one derivatives has been successfully developed by treatment of aldehydes, ammonium acetate, and isatoic anhydride under reflux conditions in the presence of a squaric acid organocatalyst. These catalytic condensation reactions represent green chemical processes and the squaric acid organocatalyst is air-stable, cost-effective, easy to handle, and easily removed from the reaction.

Key Words

Green chemistry, organocatalyst, squaric acid, quinazoline.

ÖZET

Aldehitler, amonyum asetat ve izotaktik anhidrit muameleleriyle skuarik asit organokatalizörü varlığında geri soğutucu altında, mono ve disübstitiye 2,3-dihidrokinazolin -4(1H) türevlerinin sentezi başarılı bir şekilde gerçekleştirilmiştir. Bu katalitik yoğuşma tepkimeleri yeşil kimya süreçlerini kapsamaktadır. Skuarik asit organokatalizörü havada kararlı, uygun maliyetli ve kullanımı kolaydır. Ayrıca tepkime ortamından kolaylıkla uzaklaştırılabilir.

Anahtar Kelimeler

Yeşil kimya, organokatalitik, skuarik asit, kuazolin.

Article History: Received: Jan 11, 2015; Revised: May 9, 2015; Accepted: June 12, 2015; Available Online: Jul 25, 2015.

DOI: 10.15671/HJBC.20154312554

Correspondence to: S. Khaksar, Islamic Azad University, Department of Chemistry, Ayatollah Amoli Branch, Amol, Iran.

Tel: +98 121 7098 Fax: +98- 121 251 7071 E-Mail: Samadkhaksar@yahoo.com

INTRODUCTION

Quinazoline and its derivatives are gaining importance in medicinal and organic chemistry. They have displayed broad spectrum of pharmacological and biological activities, such as antifertility, antibacterial, antitumor, antitremor, antifungle, and mono-amine oxidize inhibition [1-4]. Moreover, some of them are also known to act as selective inhibitors of the tyrosine-kinase activity of the epidermal growth factor receptor (EGFR) and as RNA binding reagents [5]. In particular, 3,4-dihydroquinazoline derivatives have been found to have excellent T-type calcium channel blocking activity [6]. For these reasons, much attention has been paid to the synthesis and biological evaluation of quinazoline derivatives. Several methods have been reported for the synthesis of 2,3-dihydroquinazolinone derivatives through one-pot condensation of isatoic anhydride and amines with aldehydes in organic solvent [7-14]. These methods show varying degrees of successes as well as limitations, such as the usage of hazardous, volatile solvents, toxic and expensive metal catalysts, cumbersome chromatographic separation procedures, high heating and low yields. Therefore, the development of novel methods toward focused libraries of such compounds is of great importance to both medicinal and synthetic chemists.

Owing to their unique physicochemical properties (a large temperature window in which it remains in the liquid state, extensive hydrogen bonding, high heat capacity, large dielectric constant, and optimum oxygen solubility to maintain aquatic life forms), the use of water as a solvent is attracting growing interest as green reaction media for various organic transformations [15-18]. Moreover, the high polarity of water has possibility to stabilize an ionic intermediate [19]. In recent years, organocatalysts have gained prominence, due to their significant advantages over the metallic catalysts, such as increased activity, selectivity, negligible equipment corrosion, ease of product separation, and reusability [20-26]. In recent years, squaric acid has proved to be very useful as a Brønsted acid catalyst in carrying out various organic transformations [27–29]. Squaric acid has received extensive recognitions in organic synthesis due to its unique properties of being readily affordable, water stability, operational simplicity, strong tolerance to oxygen, and nitrogen-containing substrates and functional groups, and it can often be used in catalytic amounts [30]. In a continuation of our interest in developing more efficient and environmentally benign methodologies [31–33], we report a new, convenient, mild, and efficient procedure for the synthesis of quinazoline derivatives, which are obtained through a one-pot three-component condensation reaction of of aldehydes, amines, and isatoic anhydride under reflux conditions using squaric acid as an efficient organocatalyst in water (Scheme 1).

MATERIALS and METHODS

Apparatus and analysis

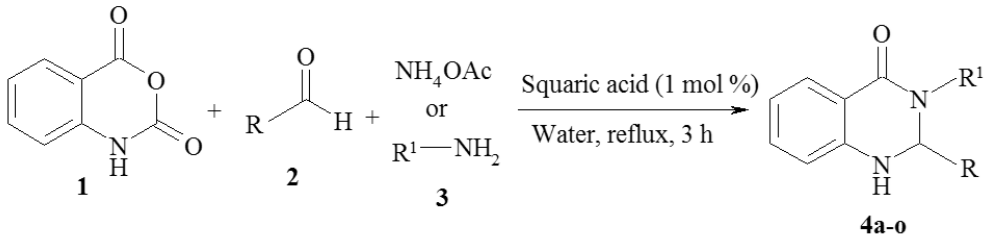
NMR spectra were determined on an FT-NMR Bruker AV-400 spectrometer in $CDCl_3$ and are expressed in δ values relative to tetramethylsilane; coupling constants (J) are measured in Hertz. Melting points were determined on an Electrothermal 9100 apparatus. Infrared spectra were recorded on a Rayleigh WQF-510 Fourier transform instrument. Commercially available reagents were used throughout without further purification.

General procedure for the synthesis of 2,3-dihydroquinazolin-4(1H)-ones:

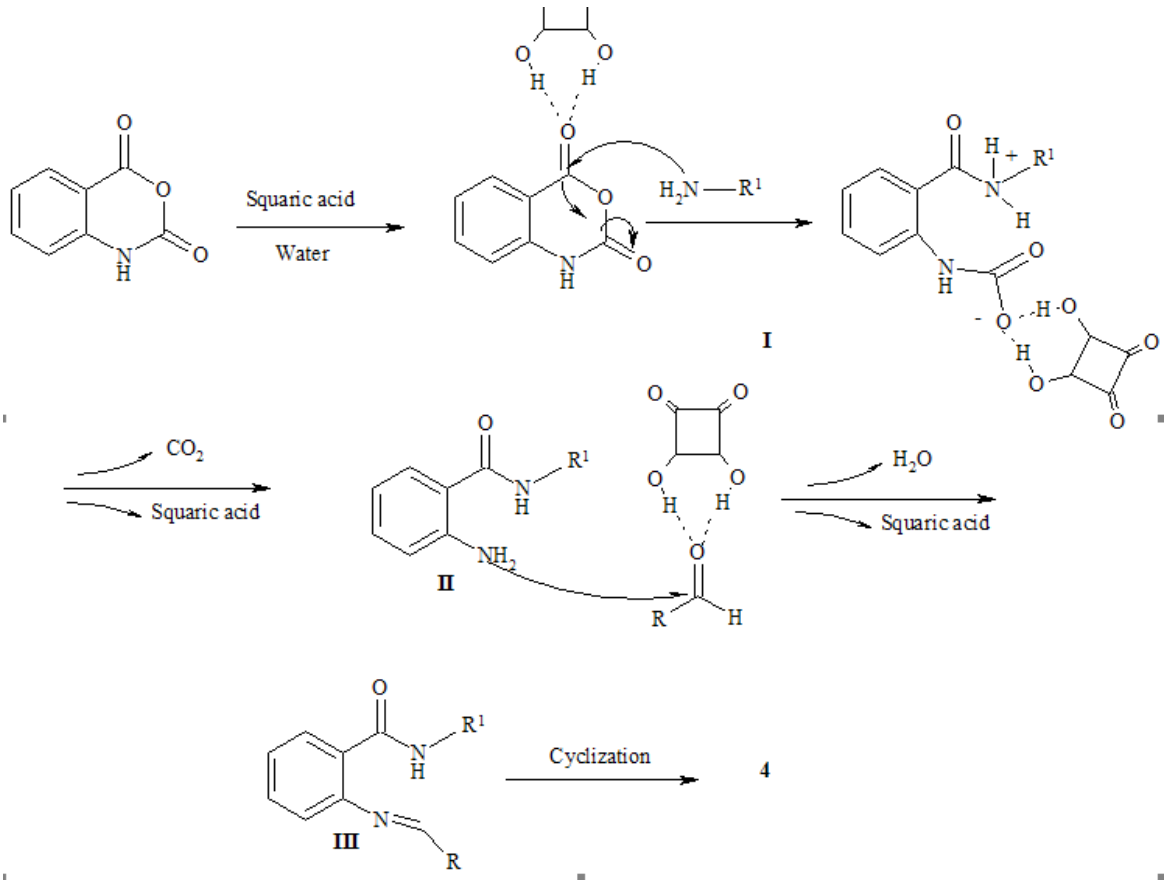
A mixture of isatoic anhydride (1 mmol), an aromatic aldehyde (1 mmol) and ammonium acetate (1.2 mmol) dissolved in 3 mL water, and squaric acid (1 mol%) was stirred for 3 h at 100°C. The reaction was monitored by TLC. The reaction mixture, after being cooled to room temperature was poured onto crushed ice and stirred for 5–10 min. The crystalline product was collected by filtration under suction (water aspirator), washed with ice-cold water (40 mL) and then recrystallized from hot ethanol to afford pure products.

Spectroscopic data for selected examples follow:

2,3-Dihydro-2-phenylquinazolin-4(1H)-one (4a) mp: 225–227°C; IR (KBr, cm^{-1}): 1508, 1610, 1653, 3062, 3302; ^1H NMR (400 MHz, $CDCl_3$): δ = 5.76(s, ^1H), 6.68 (t, *J* = 7.4 Hz, 1H), 6.76 (d, *J* = 8.09 Hz,



Scheme 1. Synthesis of 2,3- dihydroquinazolin-4(1H)-one derivatives.



Scheme 2. Proposed mechanism for quinazoline synthesis.

1H), 7.10 (br s, NH), 7.25 (t, *J* = 7.3 Hz, 1H), 7.33-7.41 (m, 3H), 7.50 (d, *J* = 7.44 Hz, 2H), 7.62 (d, *J* = 7.7 Hz, ^{1}H), 8.28 (br s, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 67.4, 115.2, 115.8, 117.9, 127.7, 128.2, 129.1, 129.3, 134.1, 142.5, 148.7, 164.4.

2-(4-Chlorophenyl)-2,3-dihydroquinazolin-4(1H)-one (4b) mp: 201-203°C; IR (KBr, cm^{-1}): 1292, 1483, 1650, 1667, 3025, 3307; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.77 (s, ^{1}H), 6.70 (t, *J* = 8.1 Hz, 1H), 6.95 (d, *J* = 6.4 Hz, ^{1}H), 7.15 (br s, ^{1}H, NH), 7.22-7.47 (m, 3H), 7.51 (d, *J* = 8.8 Hz, 2H), 7.61 (dd, J_1 = 7.8 Hz, J_2 = 1.3 Hz, ^{1}H), 8.34 (br s, NH); ^{13}C NMR (100 MHz, CDCl3): δ = 65.8, 114.4, 115.1, 117.27, 127.3, 128.3, 128.7, 132.9, 133.3, 140.7, 147.7, 163.4.

2-(4-Bromophenyl)-2,3-dihydroquinazolin-4(1H)-one (4e) mp: 201-203°C; IR (KBr, cm^{-1}): 1430, 1480, 1651, 1665, 3025, 3188, 3307; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.76 (s, ^{1}H), 6.67-6.77 (m, 2H), 7.15 (s, ^{1}H, NH), 7.25 (dt, J_1 = 7.7 Hz, J_2 = 1.5 Hz, ^{1}H), 7.45 (d, *J* = 8.6 Hz, 2H), 7.58-7.62 (m, 3H), 8.35 (br s, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 65.8, 114.4, 114.9, 117.3, 121.5,127.3, 129.1, 131.2, 133.4, 141.1, 147.6, 163.5.

3-Phenyl-2-(3,4,5-trimethoxy-phenyl)-2,3-dihydro-1H-quinazolin-4-one (4k) mp: 194–196 °C; IR (KBr): 1417, 1460, 1521, 1616, 1638, 2938, 3410 cm^{-1}; 1H NMR (400 MHz, $CDCl_3$): δ = 3.70 (s, 6H), 3.81(s, 3H), 4.84 (s, ^{1}H), 6.04 (s, ^{1}H), 6.55 (s, 2H), 6.67 (d, J = 8.0 Hz, 1H), 6.92 (t, J = 7.5 Hz, 1H), 7.20-7.24 (m, 3H), 7.30–7.36 (m, 3H), 8.03 (d, *J* = 7.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.8, 60.5, 74.6, 115.2, 116.8, 118.5, 120.3, 120.7, 126.6, 127.1, 129.2, 133.8, 136.1, 138.2, 140.3, 145.5, 154.2, 164.1.

2-(4-Methoxyphenyl)-3-p-tolyl-2,3-dihydro-1H-quinazolin-4-one (4o) mp 247–249°C; IR (KBr): 1393, 1480, 1585, 1605, 1635, 3413 cm^{-1}; 1H NMR (400 MHz, $CDCl_3$): δ = 2.28 (s, 3H), 3.75 (s, 3H), 4.80 (s, ^{1}H), 6.02 (s, ^{1}H), 6.65 (d, *J* = 8.0 Hz, ^{1}H), 6.76 (d, *J* = 8.0 Hz, 2H), 6.88 (t, *J* = 7.0 Hz, ^{1}H), 7.05 (d, *J* = 8.5 Hz, 2H), 7.07 (d, *J* = 8.5 Hz, 2H), 7.25–7.31 (m, 3H), 7.95-8.10 (m, ^{1}H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.2, 55.5, 74.1, 113.9, 114.5, 114.8, 117.1, 119.5, 120.6, 126.9, 128.2, 129.8, 130.1, 132.1, 133.7, 136.5, 138.1, 145.4, 158.9, 162.8.

3-(4-Methoxyphenyl)-2-m-tolyl-2,3-dihydro-1H-quinazolin-4-one (4p) mp 212-213°C; IR (KBr): 1485, 1510, 1610, 1635, 3135 cm-1; 1H NMR (400 MHz, CDCl3): δ = 2.25 (s, 3H), 3.75 (s, 3H), 5.97 (s, 1H), 6.59 (d, J = 8.0 Hz, 1H), 6.76 (d, J = 9.0 Hz, 2H), 6.83-6.92 (m, 1H), 7.06–7.08 (m, 3H), 7.13-7.16 (m,3H), 7.25-7.30 (m, 1H), 8.02 (dd, J = 7.5, 1.6 Hz, 1H); 13C NMR (100 MHz, CDCl3): δ = 22.1, 55.2, 74.7, 114.2, 114.8, 117.1, 119.5, 123.8, 127.5, 128.4, 128.6, 129.1, 129.7, 134.1, 138.4, 140.2, 145.4, 158.3, 163.6.

RESULT AND DISCUSSION

Initially, we explored the synthesis of 2,3-dihydroquinazolin-4(1H)-ones (4a) via a three-component condensation of benzaldehyde (1 mmol), isatoic anhydride (1 mmol), and ammonium acetate (1.2 mmol) in order to identify optimal reaction conditions (Table 1).

Reaction at 100°C in water in the presence of 1 mol% squaric acid afforded the product 4a in 90 % yield (Table 1, entry1). Increasing either the amount of catalyst and/or prolonging the reaction time did not improve the yield (Table 1, entry 10), while reducing these factors led to a reduction in product yield (Table 1, entry 3). Building upon this result, further studies were conducted and it was found that 1 mol% of squaric acid was optimum for this reaction and gave a product of 90 % yield in just 3 h (Table 1, entry 4). The reaction was also examined in solvents such as toluene, THF, CH_2Cl_2, ethanol, and diethyl ether. In the presence of solvents, the reaction was sluggish and the formation of byproducts was observed (Table 1, entries 5–9). Moreover, when the reaction was carried out in water medium, in most cases a solid product was separated at the end of the reaction.

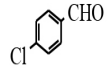
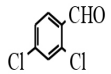
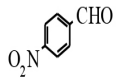
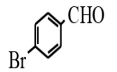
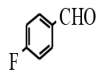
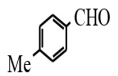
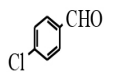
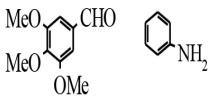
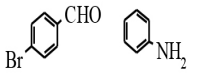
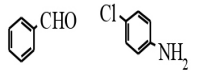
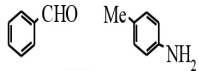
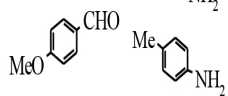
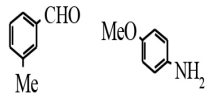
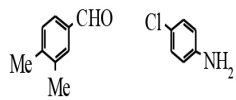
To establish the scope and generality of this three-component reaction, we extended our studies with a wide range of substrate combinations, and the desired substituted quinazolines were obtained in excellent yields (Table 2).

This protocol well tolerates aromatic aldehydes containing both electron donating and electron-withdrawing substituents. The electronic effect seemed to have a slight influence on the reaction since either the electron-withdrawing or the electron-donating groups on the different aromatic ring resulted in the scarcely discriminated yields from the reaction, as evidenced by benzaldehydes with either an o- or a p-Cl substituent (Table 2, entries 2, 3), which resulted in the corresponding products (95–92%). To expand the scope of amine substrates, ammonium acetate and primary aromatic amines including aniline, p-toluidine, p-methoxyaniline and 4-chloroaniline were applied to this protocol. In all cases, the desired reactions took place successfully to afford a series of 2,3-dihydroquinazolin-4 (1H)-one (4i-4q) in good yields. However, aliphatic aldehydes did not undergo condensation under this reaction condition, because of irreversible salt formation between aliphatic amines and squaric acid. The experimental procedure is very efficient, convenient, rapid and has the ability to tolerate a variety of other functional groups, such as alkyl, methoxyl, nitro, and halides under these reaction conditions. One of the major advantages of this protocol is the isolation and purification of the products, which have been achieved by simple filtration and crystallization of the crude products.

Table 1. Effect of different squaric acid (SA) and solvent on formation of 4.

Entry	SA amount (mol %)	Condition/solvent	Time (h)/yield
1	0	r.t/ H_2O	24/0
2	1	r.t/ H_2O	24/20
3	0.5	100°C / H_2O	5/70
4	1	100°C/ H_2O	3/90
5	1	r.t/CH_2Cl_2	24/0
6	1	r.t/THF	24/0
7	1	r.t/ethanol	24/10
8	1	r.t/toluene	24/0
9	1	r.t/diethyl ether	24/0
10	2	100°C / H_2O	3/90

Table 2. Squaric acid catalyzed synthesis of 2,3-dihydroquinazolin-4(1H)-ones.

Entry	Aldehyde	Amine	Product	Yield %	mp °C ref
1		NH_4OAc	4	90	224-225 [31]
2		NH_4OAc	4	95	200-202 [32]
3		NH_4OAc	4	90	142-184 [32]
4		NH_4OAc	4	95	300-301 [32]
5		NH_4OAc	4	92	200-202 [32]
6		NH_4OAc	4	95	236-238 [31]
7		NH_4OAc	4	88	227-229 [32]
8		NH_4OAc	4	90	182-185 [31]
9			4	90	202-204 [33]
10			4	95	216-218 [33]
11			4	85	193-195 [33]
12			4	90	186-188 [33]
13			4m	85	219-220 [33]
14			4	95	195-196 [33]
15			4o	90	245-246 [33]
16			4	85	210-211 [33]
17			4a	80	228-230 [33]

The results illustrate the high ability of this method for the synthesis of substituted 2,3-dihydroquinazolinones with different groups. A tentative mechanism for the formation of 2,3-dihydroquinazolin-4(1H)-ones was proposed (Scheme 2).

In this process, squaric acid acts as Brønsted acid and plays a significant role in increasing the electrophilic character of the electrophiles. In addition, the polar transition state of the reaction could be stabilized well by the water [18]. First, the isatoic anhydride is activated by squaric acid followed by the N-nucleophilic amine attacks on the carbonyl to form intermediate I. Then, decarboxylation occurs resulting in generation of 2-amino-N-substitued-benzamide (II). Subsequently, the reaction of activated aldehyde with II proceeds to afford intermediate III that is converted to product 4 via an intramolecular cyclization.

CONCLUSION

In conclusion, we have developed an efficient synthesis of quinazoline derivatives via the one-pot three-component coupling reaction of aldehydes, amines, and isatoic anhydride under reflux conditions using squaric acid as an efficient organocatalyst. The current method has the advantages of a avoiding the use of any base, metal or Lewis acid catalyst, ease of product isolation/purification by non-aqueous work-up, high chemoselectivity, no side reaction, low costs and simplicity in process and handling.

ACKNOWLEDGEMENT

This research is supported by the Islamic Azad University, Ayatollah Amoli Branch.

References

1. Y.S. Sadanadam, R.M. Reddy, A. Bhaskar, Eur. J. Med. Chem., 169 (1987) 22.
2. G. Bonola, E. Sianesi, J. Med. Chem., 329 (1970) 13.
3. M.L. Hour, L. Huang, S. Kuo, Y. Xia, K. Bastow, Y. Nakanishi, E. Hamel, K. Lee, J. Med. Chem., 4479 (2000) 43.
4. S. H. Lee, S. Y. Jung, H. A. Park, H. B. Kang, J. Kim, D. J. Choo, A. Handforth, J. Y. Lee, Bull. Korean. Chem. Soc., 2451 (2010) 31.
5. P. A. Ple, T. P.Green, L. F. Hennequin, J. Curwen, M. Fennell, J. Allen, Brempt, C. L. Costello, G. J. Med. Chem., 871 (2004) 47.
6. H. N. Seo, J. Y. Choi, Y. J. Choe, Y. Kim, H. Rhim, S. H. Lee, J. Kim, D. J. Joo and J. Y. Lee, Bioorg. Med. Chem. Lett., 5740 (2007) 17.
7. M. Baghbanzadeh, P. Salehi, M. Dabiri, G. Kozehgarya, Synthesis, (2006) 344.
8. M. Dabiri, P. Salehi,; S. Otokesh, M. Baghbanzadeh, G. Kozehgarya, A. A. Mohammadi, Tetrahedron Lett., 6123 (2005) 46.
9. P. Salehi, M. Dabiri, M. Baghbanzadeh, M. Bahramnejad, Synth.Commun., 2287 (2006) 36.
10. J. X. Chen, W. K. Su, H. Y. Wu, M. C. Liu, C. Jin. Green Chem., 972 (2007) 9.
11. J. Chen, D. Wu, F. He, M. Liu, H. Wu, J. Ding, W. Su. Tetrahedron Lett., 3814 (2008) 49.
12. P. Salehi, M. Dabiri, M. A. Zolfigol, M. Baghbanzadeh, Synlett., (2005) 1155.
13. H. L. J. Yale, Heterocycl. Chem., 1357 (1977), 14.
14. M. R. Mousavi, M. T. Maghsoodlou, J. Iranian. Chem. Soc., 743 (2015) 12.
15. A. Chanda, V. V. Fokin, Chem. Rev., 725 (2009) 109.
16. S. Minakata, M. Komatsu, Chem. Rev., 711 (2009) 109.
17. G. V. Oshovsky, D. N. Reinhoudt, W. Verboom, Angew. Chem. Int. Ed., 2366 (2007) 46.
18. C.J. Li, Chem. Rev., 3095 (2005) 105.
19. V. M. Dong, D. Fiedler, B. Cari, R. G. Bergmann, K. N. Raymond, J. Am. Chem. Soc., 14464 (2006) 128.
20. P.I. Dalko, L. Moisan, Angew. Chem. Int. Ed., 3726 (2001),40.
21. P.I. Dalko, L. Moisan, Angew. Chem. Int. Ed., 5138 (2004),43.
22. Y. Takemoto, Org. Biomol. Chem., 4299 (2005) 3.
23. P.R. Schreiner, Chem. Soc. Rev., 289 (2003) 32.
24. A.G. Doyle, E.N. Jacobsen, Chem. Rev., 5713 (2007) 107.
25. B. List, Chem. Commun., (2006) 819.
26. D. Enders, C. Grondal, M.R.M. Hüttl, Angew. Chem. Int. Ed., 1570 (2007) 46.
27. N. Azizi, A. Davoudpour, F. Eskandari, E. Batebi, Monatsh. Chem., 405 (2013) 144.
28. N. Azizi, E. Saki, M. Edrisi, C R Chimie., 973 (2011) 14.
29. N. Azizi, A. Davoudpour, Catalysis Lett., 1506 (2011) 141.
30. R. I. Storer, C. Aciroa, L. H. Jones, Chem. Soc. Rev., 40 (2011) 2330.
31. S. Khaksar, M. Yaghoobi, J. Fluorine. Chem., 41, (2012), 142.
32. S. Khaksar, A. Rouhollahpour, S.M. Talesh, J. Fluorine. Chem., 11 (2012) 141.
33. S. Khaksar, M. Tajbakhsh, M. Gholami, F. Rostamnezhad, Chin.Chem.Lett., 1287 (2014) 25.