Four-Component Reaction between Ethyl Benzoylacetate, Hydroxylamine, Aldehydes and Malononitrile: Synthesis of Isoxazol-5(2*H*)-Ones

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ABSTRACT: *We present herein a new and efficient four-component synthesis of isoxazol-5(2H)-ones involving ring closing/Knoevenagel condensation/Michael addition sequential reactions.*

KEYWORDS: *Hydroxylamine; Aromatic aldehyde; Malononitrile; Isoxazol-5(2H)-ones; Multi-component reactions; Green chemistry*.

INTRODUCTION

Isoxazole derivatives are classified as one of the privileged useful synthetic building blocks in medicinal chemistry [1]. They are of considerable interest due to the diverse range of pharmaceutical properties such as antitumor [2], COX-2 and HDAC inhibitory [3], antimicrobial [4], antimycobacterial [5], anti-inflammatory [6], antiviral [7], antifungal [8], anticonvulsant [9], antioxidant [10], analgesic [11], antituberculosis [12], and antinociceptive [13]. In addition, isoxzolone unit have also considered as the basis for the design and construction of merocyanine dyes along with applications in optical recording and nonlinear optical research [14].

Isoxazol-5(2*H*)-ones are classified as an important class of isoxazole derivatives. Therefore, several synthetic strategies have been reported in the literature to produce isoxazol-5(2*H*)-ones derivatives in the past few years. The most common synthetic approaches involve: (*i*) reaction of ethyl benzoylacetate and alkyl chlorooximidoacetate in basic conditions [15], (*ii*) reaction of ethyl-2-(alkyl)carbamothioyl)-3-oxobutanoate and hydroxylamine [16], (*iii*) reactions of 4-arylidene-5(4*H*)-isoxazolones and nucleophiles [17], (*iv*) reduction of 4-arylidene-5(4*H*)-isoxazolones by sodium tetrahydroborate [18], 1,4-dihydropyridine [18] or *o*-phenylenediamines and aldehydes [19], (*v*) reaction of alkyl cyanoacetate and hydroxylamine [20]. However, Multi-Component Reactions (MCRs) are considered as one of the best routes to achieve functionalized isoxazol-5(2*H*)-ones.

Knowing the chemical and pharmacological importance of isoxazole derivatives and due to the environmental issues about utilizing green solvents [21, 22], we have focused on introducing a new, green and efficient reaction between ethyl benzoylacetate, hydroxyl amine, aromatic aldehyde and malononitrile in the presence of catalytic amount of *Para*-Toluene Sulfonic Acid (PTSA) in water.

EXPERIMENTAL SECTION

Apparatus

Commercially available reagents were used without further Purification. Melting points were measured with a Kofler hot stage apparatus and are uncorrected.

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1021-9986/2016/2/9-13 5/$/5.50

^{1}H and ^{13}C NMR spectra were recorded with a Bruker FT-400, 500, using TMS as an internal standard. IR spectra were obtained with a Shimadzu 470 spectrophotometer (KBr disks).

***General procedure for the preparation of compound 5a-h, exemplified on 5a*:**

A mixture of ethyl benzoylacetate **1** (0.192 g, 1 mmol), hydroxyl amine 2 (0.040 g, 1.2 mmol) and PTSA (0. 009 g, 5 mol %) was stirred in 5 mL of water for 5 min. Then, 4-methyl benzaldehyde **3a** (0.120 g, 1 mmol) and malononitrile **4** (0.066 g, 1 mmol) was added and the reaction mixture was stirred at 80 °C temperature for 5 min. The reaction mixture was cooled to r.t. and stirring was continued for another 10 min at ambient temperature. The white precipitate was filtered, washed with H_2O (3 × 2 mL), dried, and then recrystallized from EtOH to give **5a** as a white solid.

2-((5-Oxo-3-phenyl-2,5-dihydroisoxazol-4-yl)(p-tolyl) methyl) malononitrile (**5a**):

White solid; m.p. 120-122 °C; Yield 85%; IR (KBr) *ν* max (cm^{-1}): 3321, 2210, 1763, 1672, 1363, 1243, 739; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.64–7.57 (m, 3H), 7.52–7.49 (m, 2H), 7.38 (d, *J* = 8.0 Hz, 2H), 7.20 (d, *J* = 8.0 Hz, 2H), 5.69 (d, *J* = 11.2 Hz, 1H), 4.66 (d, *J* = 11.2 Hz, 1H), 2.28 (s, 3H), 2.29 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 171.2, 162.5, 138.1, 135.8, 132.0, 131.5, 130.0, 129.8, 128.4, 128.1, 114.1, 113.8, 40.5, 27.3, 21.1. MS *m/z* (%): 329 [M$^+$], 238, 161, 84, 77.

2-((5-Oxo-3-phenyl-2,5-dihydroisoxazol-4-yl)(phenyl)methyl) malononitrile (**5b**):

White solid; m.p. 131-133 °C; Yield 87%; IR (KBr) ν max (cm^{-1}): 3341, 2253, 1735, 1639, 1348, 1269, 748; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.64–7.58 (m, 3H), 7.52–7.49 (m, 4H), 7.42–7.38 (m, 2H), 7.36–7.34 (m, 1H), 5.73 (d, *J* = 11.2 Hz, 1H), 4.72 (d, *J* = 11.2 Hz, 1H), 2.27 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 168.9, 160.4, 136.6, 132.6, 129.7, 128.7, 127.7, 126.7, 126.1, 126.0, 124.3, 111.9, 38.6, 25.1. MS *m/z* (%): 315 [M$^+$], 250, 173, 83, 77.

2-((4-Chlorophenyl)(5-oxo-3-phenyl-2,5-dihydroisoxazol-4-yl)methyl)malononitrile (**5c**)

White solid; m.p. 125-126 °C; Yield 88%; IR (KBr) ν max (cm^{-1}): 3326, 2233, 1747, 1641, 1341, 1252, 823; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.64–7.58 (m, 3H), 7.54–7.47 (m, 6H), 5.73 (d, *J* = 11.2 Hz, 1H), 4.80 (d, *J* = 11.2 Hz, 1H), 2.11 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.9, 160.4, 135.8, 131.3, 130.3, 129.8, 128.0, 127.6, 126.2, 126.8, 124.2, 111.7, 111.4, 25.0. MS *m/z* (%): 349 [M$^+$], 241, 189, 161, 83, 77.

2-((3-Chlorophenyl)(5-oxo-3-phenyl-2,5-dihydroisoxazol-4-yl)methyl)malononitrile (**5d**)

White solid; m.p. 140-142 °C; Yield 85%; IR (KBr) ν max (cm^{-1}): 3318, 2251, 1749, 1639, 1349, 1207, 759; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.65–7.58 (m, 4H), 7.52–7.49 (m, 2H), 7.45–7.41 (m, 3H), 5.79 (d, *J* = 11.2 Hz, 1H), 4.81 (d, *J* = 11.2 Hz, 1H) 2.33 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 168.9, 160.4, 138.8, 131.6, 129.7, 126.7, 126.2, 125.8, 125.0, 124.2, 111.7, 111.4, 89.4, 37.9, 24.9. MS *m/z* (%): 349 [M$^+$], 238, 161, 84, 77.

2-((4-Fluorophenyl)(5-oxo-3-phenyl-2,5-dihydroisoxazol-4-yl)methyl)malononitrile (**5e**)

White solid; m.p. 117-119 °C; Yield 83%; IR (KBr) ν max (cm^{-1}): 3336, 2247, 1761, 1652, 1343, 1090, 819; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.59–7.64 (m, 3H), 7.53–7.58 (m, 2H), 7.51–7.48 (m, 2H), 7.27–7.22 (m, 2H), 5.71 (d, *J* = 11.2 Hz, 1H), 4.48 (d, *J* = 11.2 Hz, 1H), 2.16 (s, 1H) ^{13}C NMR (100 MHz, DMSO-d_6) δ: 168.9, 161.3, 158.8, 132.8, 131.8, 129.8, 128.3, 127.6, 126.1, 124.2, 114.2, 111.8, 90.1, 25.2. MS *m/z*: 333[M$^+$], 268, 191, 108, 77.

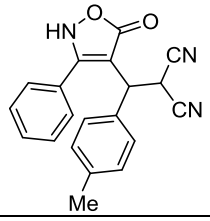
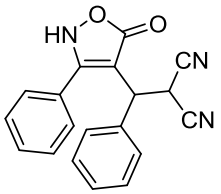
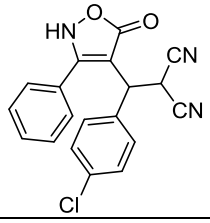
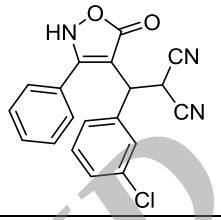
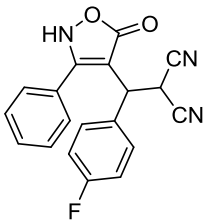
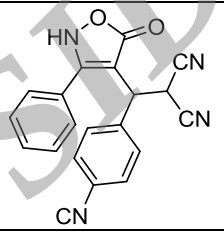
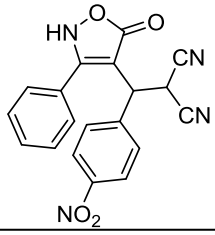
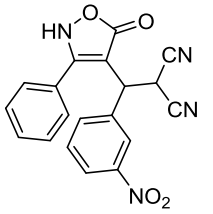
2-((4-Cyanophenyl)(5-oxo-3-phenyl-2,5-dihydroisoxazol-4-yl)methyl)malononitrile (**5f**)

White solid; m.p. 134-136 °C; Yield 88%; IR (KBr) ν max (cm^{-1}): 3320, 2241, 1728, 1639, 1361, 1234, 851; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.91–7.89 (m, 2H), 7.70–7.68 (m, 2H), 7.64–7.57 (m, 3H), 7.50–7.48 (m, 2H), 5.81 (d, *J* = 11.2 Hz, 1H), 4.92 (d, *J* = 11.2 Hz, 1H), 2.25 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 171.0, 162.7, 144.0, 133.4, 132.0, 129.8, 128.4, 126.4, 118.8, 113.8, 113.5, 111.7, 91.0, 40.3, 26.9. MS *m/z* (%): 340 [M$^+$], 275, 198, 83, 77.

2-((4-Nitrophenyl)(5-oxo-3-phenyl-2,5-dihydroisoxazol-4-yl)methyl)malononitrile (**5g**)

White solid; m.p. 128-129 °C; Yield 86%; IR (KBr) ν max (cm^{-1}): 3301, 2215, 1749, 1647, 1352, 1199, 865;

Table 1: Synthesis of isoxazol-5(2H)-one derivatives (Scheme 1)

Product	Structure	Yield (%)	Product	Structure	Yield (%)[a]
5a		85	5b		87
5c		88	5d		85
5e		83	5f		88
5g		86	5h		84

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.27 (d, J = 8.8 Hz, 2H), 7.78 (d, J = 8.8 Hz, 2H), 7.65–7.58 (m, 3H), 7.51–7.50 (m, 2H), 5.85 (d, J = 11.2 Hz, 1H), 5.01 (d, J = 11.2 Hz, 1H), 2.19 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.8, 160.5, 145.6, 143.6, 129.8, 129.6, 127.6, 126.2, 124.1, 122.4, 111.2, 88.6, 37.8, 24.6. MS *m/z* (%): 360 [M$^+$], 284, 160, 85, 78.

2-((3-Nitrophenyl)(5-oxo-3-phenyl-2,5- dihydroisoxazol-4-yl)methyl)malononitrile (**5h**)

White solid; m.p. 140-142 ºC; Yield 84%; IR (KBr) ν max (cm^{-1}): 3305, 2229, 1736, 1619, 1380, 1208, 750; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.43 (m, 1H), 8.23-8.20 (m, 1H), 7.96–7.94 (m, 1H), 7.74–7.70 (m, 1H), 7.76-7.57 (m, 3H), 7.51-7.49 (m, 2H), 5.87 (d, J = 11.2 Hz, 1H), 5.03 (d, J = 11.2 Hz, 1H), 2.21 (s, 1H); ^{13}C NMR (100 MHz, DMSO- d_6) δ 168.9, 160.5, 146.2, 138.5, 133.0, 129.8, 128.9, 127.6, 126.3, 124.1, 121.6, 120.9, 111.5, 111.3, 88.7, 24.9. MS *m/z* (%): 360 [M$^+$], 282, 161, 83, 77.

RESULTS AND DISCUSSIONS

Our endeavor began by mixing ethyl benzoylacetate **1** and hydroxylamine **2** in the presence of PTSA (5 mol%), then, aromatic aldehyde **3** and malononitrile **4** were added (Fig. 1). The reaction was completed at 80 °C in water within 10 minutes producing isoxazol-5(2*H*)-one derivatives **5a-h** in 83–88% yields (Table 1). All of the synthesized compounds are new and fully characterized.

The ^{1}H NMR spectrum of **5a** showed a broad signal for the NH group at δ = 3.63 ppm and two doublet signals for two CH (δ = 4.66 and 5.69 ppm, J = 11.0 Hz) along with the characteristic signals with appropriate chemical shifts and coupling constants for aromatic protons. The ^{1}H decoupled ^{13}C NMR spectrum of **5a** showed 16 distinct resonances in agreement with the proposed structure.

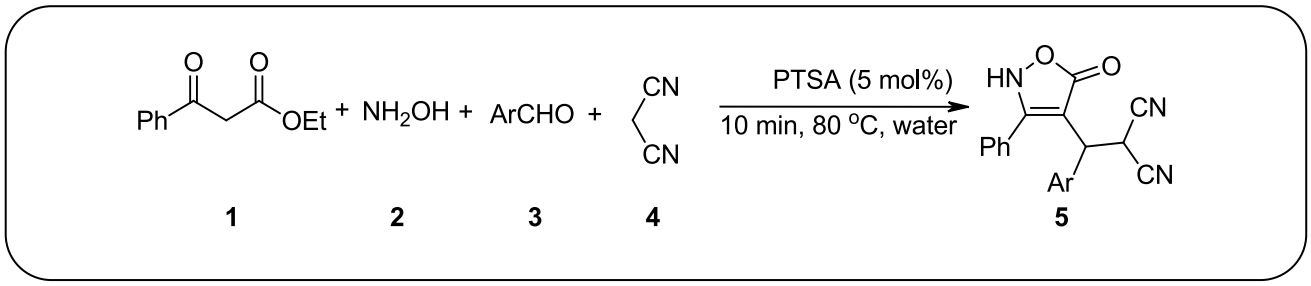


Fig. 1: Four-component synthesis of isoxazol-5(2H)-one.

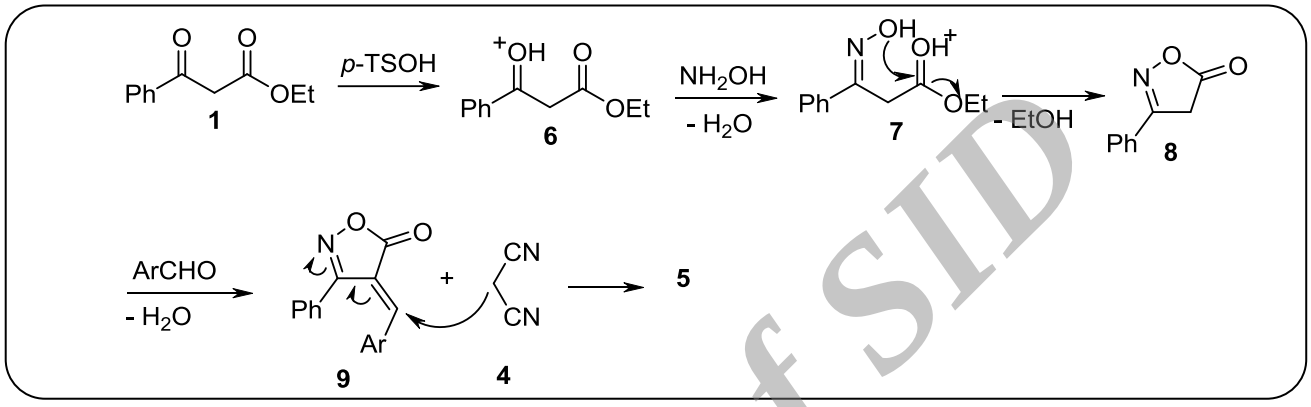


Fig. 2: Proposed mechanism.

A mechanistic rationalization for this reaction is provided in Fig. 2. At first, ethyl benzoylacetate **1** protonated by PTSA and condensed with hydroxylamine **2** to produce intermediate **7**, which is readily converted into isoxazol-5(4*H*)-ones **8** via the intramolecular cyclization which readily undergoes Knoevenagel condensation with aromatic aldehydes followed by the attack by malononitrile afforded isoxazol-5(2*H*)-one derivatives **5**.

CONCLUSIONS

In summary, we have reported a simple, efficient, and environmentally friendly approach for the synthesis of isoxazol-5(2*H*)-ones in the presence of PTSA in water. Aqueous media, excellent yields and simple purification step along with utilization of inexpensive starting materials are considered as the main advantages of this method.

Acknowledgements

This research was supported by the grant from University of Mazandaran.

Received : Jun 7, 2015 ; Accepted : Dec. 7, 2015

REFERENCES

[1] Baraldi P., Barco A., Benetti S., Pollini G.P., Simoni D., Synthesis of Natural Products *via* Isoxazoles, *Synthesis*, **10**:857-869 (1987).

[2] Patrizia D., Carbone A., Barraja P., Kelter G., Fiebig H.H., Cirrincione G., Synthesis and Antitumor Activity of 2,5-bis(3′-indolyl)-furans and 3,5-bis(3′-indolyl)-Isoxazoles, Nortopsentin Analogues, *Bioorg. Med. Chem.*, **18**(12):4524-4529 (2010).

[3] Talley J.J., Brown D.L., Carter J.S., Graneto M.J., Koboldt C.M., Masferrer J.L., Perkins W.E., Rogers R.S., Shaffer A.F., Zhang Y.Y., Zweifel B.S., Seibert K., 4-[5-Methyl-3-Phenylisoxazol-4-yl] -Benzene Sulfonamide, Valdecoxib: A Potent and Selective Inhibitor of COX-2, *J. Med. Chem.*, **43**(5): 775-777 (2000).

[4] Padmaja A., Payani T., Dinneswara Reddy G., Padmavathi V. Synthesis, Antimicrobial and Antioxidant Activities of Substituted Pyrazoles, Isoxazoles, Pyrimidine and Thioxopyrimidine Derivatives, *Eur. J. Med. Chem.*, **44**(11):4557-4566 (2009).

[5] Mao J., Yuan H., Wang Y., Wan B., Pak D., He R., Franzblau S.G., Synthesis and Antituberculosis Activity of Novel Mefloquine-Isoxazole Carboxylic Esters as Prodrugs, *Bioorg. Med. Chem. Lett*., **20**(3): 1263-1268 (2010).

[6] Karabasanagouda T., Adhikari A.V., Girisha M., Synthesis of Some New Pyrazolines and Isoxazoles Carrying 4-Methylthiophenyl Moiety as Potential Analgesic and Anti-inflammatory Agents, *Indian J. Chem.*, **48B**(3):430-437 (2009).

[7] Kamal A., Bharathi E.V., Reddy J.S., Janaki M., Ramaiah D., Reddy M.K., Viswanath A., Reddy T. L., Shaik T.B., Pushpavalli S.N.C.V.L., Bhadra M.P., Synthesis and Biological Evaluation of 3,5-Diaryl Isoxazoline/Isoxazole Linked 2,3-Dihydroquinazolinone Hybrids as Anticancer Agents, *Eur. J. Med. Chem*., **46**(2):691-703 (2011).

[8] Santos M.M.M., Faria N., Iley J., Coles S.J., Hursthouse M.B., Martins M., Moreira R., Reaction of Naphthoquinones with Substituted Nitromethanes. Facile Synthesis and Antifungal Activity of Naphtho[2,3-*d*]Isoxazole-4,9-Diones, *Bioorg. Med. Chem. Lett.*, **20**(1):193-195 (2010).

[9] Balalaie S., Sharifi A., Ahangarian B., Solid Phase Synthesis of Isoxazole and Pyrazole Derivatives under Microwave Irradiation, *Indian J. Heterocycl. Chem.*, **10**:149-150 (2000).

[10] Padmaja A., Rajasekhar C., Muralikrishna A., Padmavathi V., Synthesis and Antioxidant Activity of Oxazolyl/Thiazoly Sulfonyl Methyl Pyrazoles and Isoxazoles, *Eur. J. Med. Chem.*, **46**(10):5034-5038 (2011).

[11] Kano H., Adachi I., Kido R., Hirose K., Isoxazoles. xviii. Synthesis and Pharmacological Properties of 5-Aminoalkyl- and 3-Aminoalkylisoxazoles and Related Derivatives, *J. Med. Chem.*, **10**(3): 411-418 (1967).

[12] Lee Y.S., Park S.M., Kim B.H., Synthesis of 5-Isoxazol-5-yl-2-Deoxyuridines Exhibiting Antiviral Activity Against HSV and Several RNA Viruses, *Bioorg. Med. Chem. Lett*., **19**(4):1126-1128 (2009).

[13] Srinivas A., Nagaraj A., Reddy C.S., Synthesis and *in vitro* Study of Methylene-bis-Tetrahydro[1,3]Thiazolo[4,5-*c*]Isoxazoles as Potential Nematicidal Agents, *Eur. J. Med. Chem*., **45**(6):2353-2358 (2010).

[14] Zhang X.H., Wang L.Y., Zhan Y.H., Fu Y.L., Zhaia G.H., Wenc Z.Y., Synthesis and Structural Studies of 4-[(5-Methoxy-1*h*-Indole-3-yl)-Methylene]-3-Methyl-Isoxazole-5-One by X-Ray Crystallography, NMR Spectroscopy, and DFT Calculations, *J. Mol. Struct*., **994**(1-3):371-378 (2011).

[15] Zhang X.-H., Zhan Y.–H., Chen D., Wang F., Wang L.–Y., Merocyanine Dyes Containing An Isoxazolone Nucleus: Synthesis, X-ray Crystal Structures, Spectroscopic Properties and DFT Studies, *Dyes Pigments*, **93**(1-3):1408-1415 (2012).

[16] Azimi C., Sepehraddin F., Tahazadeh H., Net Rearrangements of 4-Acetyl-3-(4-Substituted Phenylamino)-2-(5-Nitropyridin-2-yl)Isoxazol-5(2*H*)-Ones to Imidazo [1,2-*a*]Pyridines by Flash-Vacuum-Pyrolysis (F.V.P), *Orient. J. Chem*., **29**(4):1443-1448 (2013).

[17] Batra S., Akhtar M.S., Seth M., Bhaduri A.P., Chemistry of 5(2*H*)-Isoxazolones: Novel Conversion of Positional Isomers, *J. Heterocycl. Chem.*, **27**(2):337-342 (1990).

[18] Liu Z., Han B., Liu Q., Zhang W., Yang L., Liu Z.–L., Yu W., Selective Reduction of The Exocyclic Double Bond of Isoxazolones and Pyrazolones by Hantzsch 1,4-Dihydropyridine, *Synlett*, **10**:1579-1580 (2005).

[19] Risitano F., Grassi G.; Foti F., An Efficient Preparation of 4-Arylmethylisoxazol-5-Ones by Selective Reduction of the 4-Arylmethyleneisoxazol-5-Ones, *Tetrahedron Lett*., **24**(52):5893-5896 (1983).

[20] Scobie M., Tennant G., A Convenient Synthesis of Otherwise Inaccessible 3-Aminocinnoline-4-Carboxylic Acid Derivatives, *J. Chem. Soc., Chem. Commun.*, **21**: 2451-2452 (1994).

[21] Baradajee G.R., Mohamadi A., Efficient and Practical Protocol for the Synthesis of Pyridopyrazines, Pyrazines and Quinoxalines Catalyzed by $La(OAc)_3$ in Water, *Iran. J. Chem. Chem. Eng. (IJCCE)*, **32**(3): 61-67 (2013).

[22] Shaabani A., Ghadari R., Rezayan A.H., Synthesis of Functionalized Coumarins, *Iran. J. Chem. Chem. Eng. (IJCCE)*, **30**(4):19-22 (2011).