I.A.U
Karaj branch

Journal of
A p p l ied
C hemical
R esearch
jacr.kiau.ac.ir

*Journal of Applied Chemical Research, 16, 1, 48-56 (2022)*

# Choline Chloride-Oxalic Acid as a Deep Eutectic Solvent Promoted Synthesis of Aroylamido Coumarin Derivatives in Excellent Yields

**Hamed Asadi , Hossein Anaraki-Ardakani*, Parviz Torabi, Narges Taheri**

*Department of Chemistry, Mahshahr Branch, Islamic Azad University, Mahshahr, Iran*

*(Received 27 Jun. 2021; Final revised received 12 Sep. 2021)*

**Abstract**

An efficient and green protocol for synthesis of title compounds has been achieved via a one pot, three component reaction of 4-hydroxycoumarin or 4-hydroxy-6-methylpyran-1-one, aryl glyoxals and amides in choline chloride/oxalic acid as a deep eutectic solvent (DES) has been described. The DES system offers advantages in terms of environmentally benign, biodegradable, short reaction times, high yield and the use of safe and inexpensive components. DES can be easily recovered and can be reused for other runs without any reduction in the activity.

**Keywords:** Choline chloride, Aryl glyoxal, Deep eutectic solvents, Oxalic acid.

*Corresponding author: *Hossein Anaraki-Ardakani, Department of Chemistry, Mahshahr Branch, Islamic Azad University, Mahshahr, Iran. Email:Hosseinanaraki@yahoo.com.*

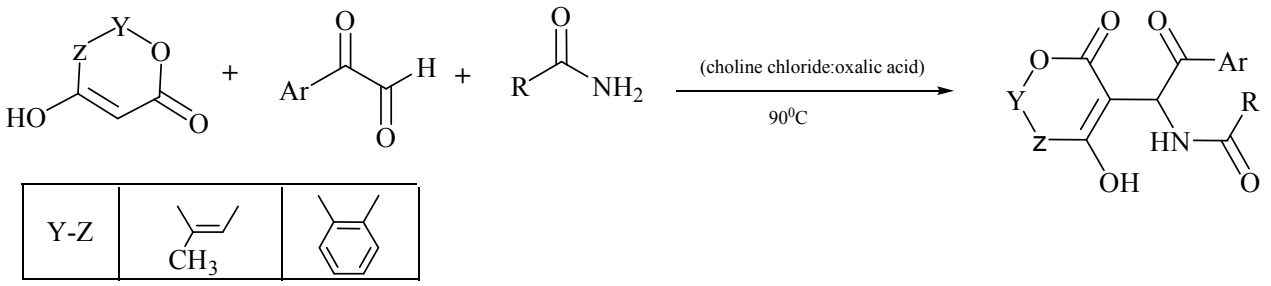
## Introduction

Multi-component reactions (MCRs) are important for generating high levels of diversity, as they allow more than two building blocks to be combined in a practical, time-saving, one-pot operation, giving rise to complex structures by simultaneous formation of two or more bonds. MCRs have received considerable attention because of their wide range of applications in pharmaceutical chemistry for the creation of structural diversity and combinatorial libraries for drug discovery [1,2]. Coumarin and its derivatives are an important class of heterocyclic compounds, which constitute the key core of various natural products [3,4]. They exhibit a wide range of biological activities such as anti-HIV, antimalarial, insecticidal, and antioxidant properties [5,6].

A new generation of green solvents, namely deep eutectic solvents (DESs) had emerged as an environmentally- benign media alternative to hazardous organic solvents in a variety of applications [7–8]. A Deep eutectic solvent is defined as a mixture of two or more components that are capable of self-association through hydrogen-bond interactions, which result in a large melting-point depression at a particular composition (the eutectic composition)[9]. DESs have some advantages, such as low price, negligible vapor pressure, non-flammability, simple reaction workup, low volatility, biodegradability and renewability. DESs are widely used in electrochemical applications and are promising alternatives for common organic solvents in industrial applications [10, 11] . One of the most widespread components used for the formation of DES is choline chloride (ChCl), an inexpensive, chemically and thermally stable, biodegradable, nontoxic and recyclable quaternary ammonium salt [12,13]. ChCl is capable of rapidly forming a DES in combination with hydrogen donors such as acids [14], alcohols [15], amines [16] or amides [17]. DES based on ChCl and organic Brønsted acid is a well-known system for synthesizing different heterocycles acting both as a solvent and a Brønsted- acidic catalyst [18].

Recently Khodabakhshi et al. reported a three-component process for the synthesis of aryloylamido coumarins derivatives from reaction of aryl glyoxal, benzamide, and 4-hydroxycoumarin in the presence of molybdate sulfuric acid, Tungstate sulfuric acid, Zirconium Oxychloride, and $Fe_3O_4$ nanoparticles [19-22]. Also we have reported the reaction of 1,3-dicarbonyl compounds, arylglyoxal and amides (thioacetamide), in the presence of $BF_3$-$SiO_2$ NP to produce 3-(α-aroylamido)-4-hydroxycoumarin derivatives[23], However, some of these methods displayed drawbacks such as require long reaction times [17,23], acidic conditions [20,23] , need for column chromatography to purify the products [19-21], expensive catalyst and also catalysts is not recyclable[19,21,23]. Therefore, it is necessary to further develop an efficient, milder and convenient method to synthesis of coumarin derivatives.

Considering the above reports and in continuation of our studies on one-pot multi-component reactions[24-27] we here reported an efficient approach for one-pot synthesis of 3-($\alpha$-aroylamido)-4-hydroxycoumarin derivatives (**4**) using a three-component reaction of 4-hydroxycoumarin or 4-hydroxy-6-methylpyran-1-one (**1**), arylglyoxals (**2**) and amides (**3**), in the presence of choline chloride/ oxalic acid as a deep eutectic solvent (DES) (Scheme 1).

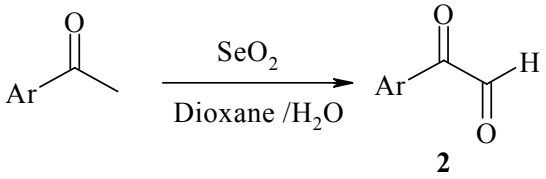



Ar: $C_6H_5$, 4-Me-$C_6H_4$, 4-Cl-$C_6H_4$

R: $CH_3$, $C_2H_5$

**Scheme 1**. Reaction between 4-hydroxycoumarin or 4-hydroxy-6-methylpyran-1-one, arylglyoxals and amides in DES as solvent and catalyst.

Aryglyoxals **2** were synthetized by the reaction between their corresponding acetophenone and selenium dioxide according to the reported procedures [28](Scheme 2).




**2**

**Scheme 2.**

## Experimental

*Materials and methods*

Products were characterized by comparison of their spectroscopic data (NMR and IR) and physical properties with those reported in the literature. Melting points were determined with an Electrothermal 9100 apparatus. Elemental analyses were performed using a Heraeus CHN-O-Rapid analyzer. Mass spectra were recorded on a FINNIGAN-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. IR spectra were recorded on a Shimadzu IR-470 spectrometer. $^1H$ and $^{13}C$ NMR spectra were recorded on Bruker DRX-500 AVANCE spectrometer at solution in

DMSO-$d_6$ or $CDCl_3$ using TMS as internal standard. Chemicals used in this work were purchased from Fluka (Buchs, Switzerland) and were used without further purification. Yields refer to isolated pure products.

*Preparation of choline chloride-based deep eutectic solvents*

Choline chloride-based deep eutectic solvents were prepared according to the literature [29, 30] and were used without further purification.

*General procedure*

A mixture of 4-hydroxycoumarin (0.25 mmol), arylglyoxal (0.25 mmol), and amide (0.25 mmol) were added to choline chloride/ oxalic acid (1mL). The resulting mixture was stirred and heated 90 ℃ for 55-65 min. (Table 2). After reaction completion, (TLC, ethyl acetate/n-hexane, 2:1), the reaction mixture was washed with water (10 mL) and the solid residue recrystallized from ethanol to obtain the pure product. All the products identified by IR, $^1$H NMR and $^{13}$C NMR spectral data and by comparison of their melting points with literature reports.

*N-[1-(4-Hydroxy-2-oxo-2H-chromen-3-yl)-2-oxo-2-P-tolyl-ethyl]-acetamide* **(4a)**

white powder, m.p. 205 °C. IR (KBr) ($\nu_{max}$, cm$^{-1}$): 3309 (N–H), 1690 (C=O). Anal. calcd for $C_{20}H_{17}NO_5$ : C, 68.37; H, 4.88; N, 3.99 %. Found: C, 68.59; H, 4.75; N, 3.90%. MS (m/z, %): 351 (7). $^1$HNMR (300 MHz, $CDCl_3$) $\delta$ = 2.21 (3 H, s, $CH_3$), 2.35 (3 H, s, $CH_3$), 6.03 (1 H, d, $^3J_{HH}$ = 6 Hz, C*H*-NH), 7.16-8.01 (8 H, m, arom), 8.08 (1H, d, $^3J_{HH}$ = 6 Hz, N*H* ), 12.78 (1H, broad, OH) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 21.70 (*C*$H_3$), 22.54 (*C*$H_3$), 51.73 (*C*H-NH), 104.81, 116.54, 116.60, 124.13, 124.64, 128.20, 129.43, 131.49, 132.85, 144.75, 153.27, 161.64 (C arom and olfine ), 165.41, 173.44, 192.18 (3*C*=O) ppm.

*N-[2-(4-Chloro-phenyl)-1-(4-hydroxy-2-oxo-2H-chromen-3-yl)-2-oxo-ethyl]-propionamide* **(4b)**

white powder, m.p. 192 °C. IR (KBr) ($\nu_{max}$, cm$^{-1}$): 3351 (N–H), 1694 (C=O). Anal. calcd for $C_{20}H_{16}ClNO_5$: C, 62.26; H, 4.18; N, 3.63%. Found: C, 62.32; H, 4.06; N, 3.51 %. MS (m/z, %): 385 (7). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 1.23 (3 H, t, $^3J_{HH}$ = 7.5 Hz, $CH_3$), 2.48 (2 H, q, $^3J_{HH}$ = 7.5 Hz, $CH_2$), 6.02 (1 H, d, $^3J_{HH}$ = 6 Hz, CH-NH), 7.14-8.11 (9 H arom and OH), 8.02 (1 H, d, $^3J_{HH}$ = 6.5 Hz, NH) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 9.51($CH_3$), 28.85 ($CH_2$), 51.77 (CH-NH) 104.24, 116.53, 124.26, 124.65, 128.70, 129.01, 129.38, 132.57, 132.85, 134.26, 140.02, 153.20 (C arom and olfine ), 167.75, 177.24, 191.86 (3*C*=O) ppm.

*N-[1-(4-Hydroxy-2-oxo-2H-chromen-3-yl)-2-oxo-2-phenyl-ethyl]-acetamide* **(4c)**

white powder, m.p. 199 °C. IR (KBr) ($\nu_{max}$, $cm^{-1}$): 3376 (N–H), 1695 (C=O). Anal. calcd for $C_{19}H_{15}NO_5$: C, 67.65; H,4.48; N, 4.15%. Found: C, 67.55; H,4.32; N, 4.23 %. MS (m/z, %): 337 (9). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 2.21(3 H, s, $CH_3$), 6.08 (1 H, d, $^3J_{HH}$ = 6.5 Hz, C*H*-NH), 7.09-7.82 (9 H, m, arom), 8.06 (1 H, d, $^3J_{HH}$ = 6.5 Hz, NH) ), 12.82 (1H, broad, OH) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 23.42 ($CH_3$), 50.12 (CH), 101.12, 121.54, 125.52, 126.82, 128.41, 128.78, 129.85, 130.81, 133.24, 143.17, 152.11, 161.19 (C arom and olfine ), 163.93, 171.15, 187.46 (3*C*=O).

## Results and discussion

At first, the reaction 4-hydroxycoumarin, *p*-methey phenyl glyoxal and acetamide were selected as model reaction. The model reaction was carried in various choline chloride (ChCl) - based DESs system like ChCl:PTSA, ChCl:$ZnCl_2$, ChCl:malonic acid, ChCl: citric acide, ChCl:oxalic acid and ChCl:urea in different temperatures and the results are listed in Table 1. As indicated the best yield was obtained in choline chloride and oxalic acid at 90 $^o$C (Table 1, entry 9). A decrease in temperature gave lower yields (entry 8), and in the absence of the DES, only trace of the product was obtained (entry 6).

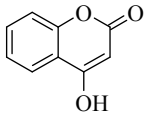
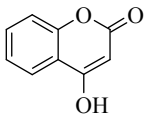
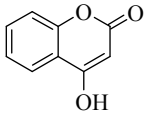
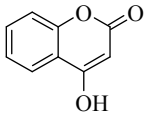
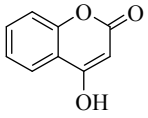
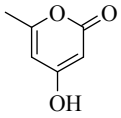
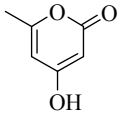
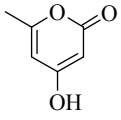
**Table1.** Optimization of reaction in various choline chloride-based $DES_S$[a]

| Entry | DES | Temp($^0$C) | Time (min) | Yield (%)[b] |
|---|---|---|---|---|
| **1** | Choline chloride:$ZnCl_2$(1:2) | 90 | 60 | 35 |
| **2** | Choline chloride:PTSA(1:1) | 90 | 60 | 42 |
| **3** | Choline chloride:citric acide(1:1) | 90 | 60 | 48 |
| **4** | Choline chloride:malonic acid(1:1) | 90 | 60 | 50 |
| **5** | Choline chloride: urea (1:1) | 90 | 60 | 55 |
| **6** | ------ | 100 | 220 | trace |
| **7** | Choline chloride:oxalic acid(1:1) | 90 | 60 | 65 |
| **8** | Choline chloride: oxalic acid (1:2) | 90 | 60 | 89 |
| **9** | Choline chloride: oxalic acid (1:2) | 90 | 55 | 89 |
| **10** | Choline chloride: oxalic acid (1:2) | 80 | 55 | 80 |
| **11** | Choline chloride: oxalic acid (1:2) | 100 | 55 | 89 |

[a] Reaction condition: 4-hydroxycoumarin, (0.25mmol), *p*-methey phenyl glyoxal (0.25mmol) and acetamide (0.25 mmol) in DES (1 mL).
[b] Isolated yield.

To study the scope and limitations of the reaction, various substituted arylglyoxal, cyclic 1,3-diketone and amides were employed. The results are shown in Table 2. In all cases, aromatic ring of the arylglyoxal substituted with either electron-donating or electron-withdrawing groups underwent the reaction smoothly and gave the products in good yields (Table 2).

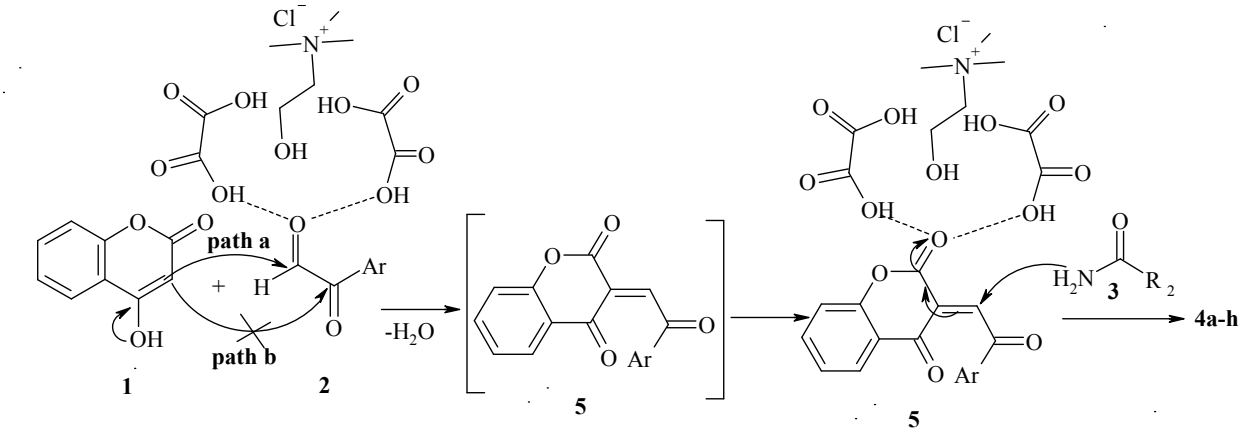
**Table 2.** Three-component reaction between 4-hydroxycoumarin or 4-hydroxy-6-methylpyran-1-one, aryl glyoxales and amides in deep eutectic solvent (DES).

| Entry | Substrate | Ar | X | Time(min) | Yield(%)[a] | mp °C |
|---|---|---|---|---|---|---|
| **4a** |  | 4-$CH_3$-$C_6H_4$ | $CH_3$ | 55 | 89 | 205(202-204)[23,27] |
| **4b** |  | 4-Cl-$C_6H_4$ | $C_2H_5$ | 60 | 82 | 192(190)[23,27] |
| **4c** |  | $C_6H_5$ | $CH_3$ | 60 | 85 | 199(196-198)[23,27] |
| **4d** |  | 4-$CH_3$-$C_6H_4$ | $C_2H_5$ | 65 | 78 | 197-200 (198-200)[23,27] |
| **4e** |  | $C_6H_5$ | $C_2H_5$ | 65 | 80 | 202-204(200)[23,27] |
| **4f** |  | 4-Cl-$C_6H_4$ | $CH_3$ | 65 | 82 | 202(201)[23,27] |
| **4g** |  | 4-$CH_3$-$C_6H_4$ | $C_2H_5$ | 65 | 87 | 200(200-202)[23,27] |
| **4h** |  | $C_6H_5$ | $CH_3$ | 60 | 86 | 193(190-192)[23,27] |

[a] Isolated Yield

All the products were known and their structures were deduced by comparison of melting points and spectral data with authentic samples [23,27]. A plausible mechanism for the synthesis of 3-(*α*-aroylamido)-4-hydroxycoumarin on the basis of the previously reported [23,27] is presented in Scheme 3. At first, the Knoevenagel condensation of enolic form of 4-hydroxycoumarin 1 with more electrophilic formyl group of the arylglyoxal **2** (path a) in the presence of DES is proposed to give intermediate **5** [23]. Then Michael addition of amide **3** to intermediate **5** forms the 3-(*α*-

aroylamido)-4-hydroxycoumarin derivatives products. DES activates all carbonyl groups via hydrogen bonding (Scheme 3).




**Scheme 3.** Suggested pathway for the formation of compounds 4a-h.

The reusability of the catalyst for the synthesis of *N-[1-(4-Hydroxy-2-oxo-2H-chromen-3-yl)-2-oxo-2-P-tolyl-ethyl]-acetamide* (**4a**) was investigated (Figure1). The DES was recovered from the aqueous phase by evaporation at 90C under vacuum and tested for its activity in the subsequent run was recycled for the next reaction. DES was tested for 4 runs. It was seen that the catalyst activity displayed very good reusability (Figure 1).

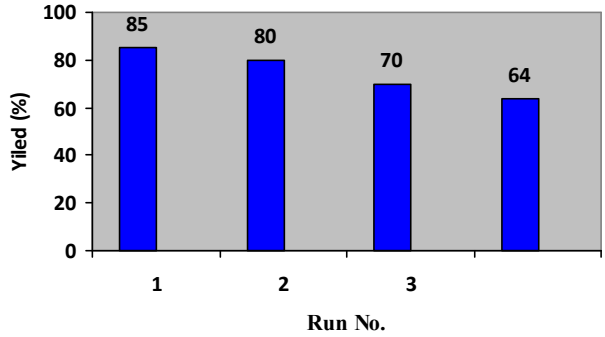



**Figure1.** Reusability of the DES.

Finally, in order to access the efficiency and generality of this methodology, we compared this method with previous reported catalysts in the synthesis of compound **4a** (Table 3). From comparison with the results depicted in Table 3, it was found that a deep eutectic mixture of Choline chloride-oxalic acid in a molar ratio of 1:2 is the most efficient catalyst with respect to reaction times, temperature and yield of the products and reusability of the catalyst.

**Table 3.** Comparison of different methodology for the synthesis of compound **4a.**

| Entry | Conditions | Temp($^0$C) | Time(min | Yield (%)[a] | Ref |
|---|---|---|---|---|---|
| **1** | $BF_3$-$SiO_2$ NP (0.04g), in Water | reflux | 60 | 78 | [23] |
| **2** | $SnCl_2$-$SiO_2$ NP, Solvent-free | 110 | 120 | 82 | [27] |
| **3** | This work | 90 | 55 | 89 | - |

[a] Isolated yield.

## Conclusion

In summary, a simple and efficient methodology for the synthesis of 3-($\alpha$-aroylamido)-4-hydroxycoumarin derivatives was successfully developed by three-component reaction between 4-hydroxycoumarin or 4-hydroxy-6-methylpyran-1-one, arylglyoxals, and amides in the presence of choline chloride/ oxalic as a green and eco-friendly catalyst and solvent. This method has advantages for example the use of metal-free strategy makes this method environmentally friendly in comparison with previous results. Also, the deep eutectic solvent (DES) could be easily recycled and reused in at least four consecutive runs without significant loss of catalytic activity. Furthermore, all products were obtained through simple filtration with no need for column chromatography, which reduces the waste as well as environmental pollution.

## References

[1]. Y. J. Huang, F. Y. Yang and C. J. Zhu, *J. Am. Chem. Soc.,* 127, 16387 (2005).

[2]. R. W. Armstrong, A. P. Combs, P. A.Tempest, S. D. Brown, T. A. Keating, *Acc. Chem. Res.,* 29, 123 (1996).

[3]. R. D. H. Murray, *Nat. Prod. Rep*., 12, 477 (1995).

[4]. A. Lacy and R. O'Kennedy, *Curr. Pharm. Des.,* 10, 3797 (2004).

[5]. D. Guilet, D. Guilet, J. J. Hélesbeux, D. Séraphin, T. Sévenet, P. Richomme , J. J. Bruneton, *Nat. Prod.*, 64, 563 (2001) .

[6]. S. Emami and S. Dadashpour, *Eur J. Med. Che.,* 102, 611 (2015).

[7]. Y. Cui, C. Li, J. Yin, S. Li, Y. Jia, M. Bao, *J. Mol. Liq.,* 236,338 (2017).

[8]. Q. Zhang, K. De. Oliveira Vigier, S. Royer, F. Jerome, *Chem. Soc. Rev*., *41*, 7108 (2012).

[9]. N. Azizi, T. Soleymani Ahooi, M. Mahmoudi Hashemi , *Journal of Molecular Liquids,* 246, 221 (2017).

[10]. M. Francisco, A. Van den Bruinhorst , M. C. Kroon, *Angew Chem Int Ed.,* 52, 3074 (2013).

[11]. A. Shaabani, S. E. Hooshmand, A. T. Tabatabaei , *Tetrahedron Lett,*.57, 351 (2016).

[12] H. R. Lobo, B. S. Singh, G. S. Shankarling, *Catal. Commun.*, 27, 179 (2012).

[13] A. Shaabani, S. E. Hooshmand, A. Tavousi Tabatabaei, *Tetrahedron Lett.* 57, 351 (2016).

[14] A. K. Sanap, G. S. Shankarling, *RSC Adv., 4*, 34938 (2014).

[15] A. P. Abbott, R. C. Harris, K. S. Ryder, C. D'Agostino, L. F. Gladden, M. D. Mantle, *Green Chem. 13*, 82 (2011).

[16] S. Khandelwal, Y. K. Tailor, M. Kumar, *J. Mol. Liq.*, 215, 345 (2016**)**.

[17] E. L. Smith, A. P. Abbott, K. S. Ryder, *Chem. Rev.,* 114, 11060(2014).

[18] M. Bakavoli, H. Eshghi, M. Rahimizadeh, M. R. Housaindokht, A. Mohammadi, H. Monhemi, *Res. Chem. Intermed.*, 41, 3497 (2015).

[19]. S. Khodabakhshi and B. Karami, *Tetrahedron Letters,* 55, 7136 (2014).

[20]. S. Khodabakhshi, B. Karami and K. Eskandari, Res. *Chem. Intermed.*, 41, 7263(2015).

[21]. S. Khodabakhshi, M. Khaleghi Abbasabadi, M. Baghrnejad and F. Marahel, *J. Chin. Chem. Soc.,* 62, 9 (2015).

[22]. S. Khodabakhshi, M. Khaleghi Abbasabadi, S. Heydarian, S. Gharehzadeh Shirazi, F. Marahel, *Letters in Organic Chemistry*, 12,465 (2015).

[23]. M. Arfavi-Safari, H. Anaraki-Ardakani, R. Badri, E. Tahanpesar, *Journal of Applied Chemical Research*, 13, 3, 27 (2019).

[24]. H. Anaraki-Ardakani, M. H. Mosslemin, M. Anary-Abbasinejad, N. Shams, S. H. Mirhosseini, *Arkivoc* xi, 343 (2010).

[25]. H. Anaraki-Ardakani, M. Noei and A.Tabarzad, *Chinese Chemical Letters,* 23, 45 (2012).

[26]. H. Asai, H.Anaraki-Ardakani,P. Torabi , N.Taheri, *Rev. Roum. Chim*., 65(9), 795 (2020).

[27]. M. Arfavi-Safari, H. Anaraki-Ardakani, R. Badri, E. Tahanpesar, *Journal of Chemical Research*, 41, 6, 321 (2017).

[28]. B. Khalili, P. Jajarmi, B. Eftekhari-Sis and M. M. Hashemi, *J. Org. Chem*., 73, 2090 (2008).

[29]. A. P. Abbott, D. Boothby, G. Capper, D. L. Davies, R. K. Rasheed , *J. Am. Chem. Soc.,* 126, 9142 (2004).

[30]. A. P. Abbott, G. Capper, D. L. Davies, R. K. Rasheed, V. Tambyrajah, *Chem. Commun.,* 70(2003).