HETEROCYCLES, Vol.89, No. 7, 2014, pp. 1670 - 1677. © 2014 The Japan Institute of Heterocyclic Chemistry
Received, 17th April, 2014, Accepted, 28th May, 2014, Published online, 5th June, 2014
DOI: 10.3987/COM-14-13006

ONE-POT SYNTHESIS OF NOVEL PYRANO-FUSED COUMARINS CATALYZED BY ZINC OXIDE NANOPARTICLES

Saeed Khodabakhshi,*[a] Bahador Karami,[b] and Khalil Eskandari[c]

[a]Young Researchers and Elite Club, Gachsaran Branch, Islamic Azad University, Gachsaran, Iran; E-mail: saeidkhm@yahoo.com
[b]Department of Chemistry, Yasouj University, Yasouj, Zip Code: 75918-74831 P.O.Box 353, Iran
[c]Young Researchers and Elite Club, Shahrekord Branch, Islamic Azad University, Shahrekord, Iran

Abstract – A new class of pyrano[3,2-*c*]coumarins containing an aryloylgroup was synthesized via the three-component reactions of 4-hydroxycoumarin with arylglyoxals and malononitrile. The reactions are efficiently catalyzed by zinc oxide nanoparticles as powerful and recyclable catalyst. The green chemistry principles were also considered and the present method has some advantages, such as simplicity, low catalyst loading, and high yields.

From the perspective of environmental problems, the avoidance of harmful organic solvents is one of the efficient ways to decrease the concerns in chemical research and industry. In regard of the fundamental principles of the green chemistry, the elimination of toxic solvents and the generation of waste are important items.[1-3] In chemical reactions, transition metal oxides are commonly used due to their catalytic activity.[4,5] Among the nano-sized transition metal oxides, zinc oxide nanoparticles (ZnO NPs) have gained tremendous importance as they exhibit interesting catalytic properties which cannot be achieved by their bulk counterparts. ZnO nanomaterials are non-toxic and water-insoluble material which can be recovered and reused, therefore, it can help to reduce the waste.[6-8]

The pyranocoumarins possess several types of pharmacological properties, such as anti-HIV, antibacterial, insecticidal, anticancer, and anti-inflammatory activities, thus, they have received considerable attention.[9,10] Among pyranocoumarins, the pyrano[3,2-*c*]coumarins are the most synthetically feasible.[11] Generally, pyrano[3,2-*c*]coumarins are affordable from commercially available 4-hydroxycoumarin with

the suitable electrophiles. For example, pyrano[3,2-*c*]coumarins were prepared via the one-pot, three component reaction of 4-hydroxycoumarins with carbonyl compounds and active methylenes.[12-15]

To the best of our knowledge, there is no report describing the synthesis of pyrano[3,2-*c*]coumarins containing aryloyl group starting from arylglyoxals via a three-component reaction.

ZnO nanoparticles were prepared through the thermal decomposition method and characterized by scanning electron microscopy (SEM), transmission electron microscopy (TEM) and selected area electron diffraction (SAED). The morphology of the ZnO NPs was investigated by scanning electron microscopy (SEM). The typical SEM image of ZnO NPs shows that the nanoparticles have an average diameter of 20 nm (Figure 1, A). In addition, transmission electron microscopy (TEM) analyses and selected area electron diffraction (SAED) pattern were used for more investigation (Figure 1, B).

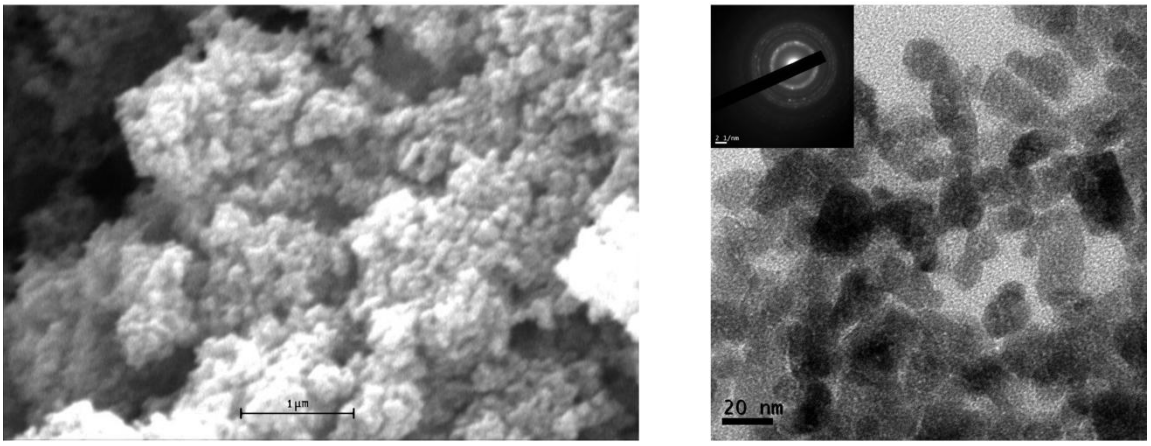
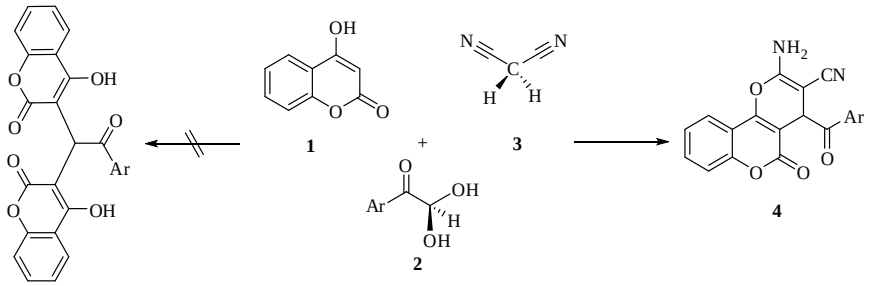


Figure 1

The TEM image reveals that the spherical ZnO nanoparticles have granular nature with the average size of 20 nm and clearly shows that the ZnO nanoparticles are in the form of wurtzite crystal structure. The rings with a dotted pattern in SAED (shown in the inset of Figure 1B) confirm the wide size distribution of ZnO nanoparticles.

In continuation of our previous studies on synthesis of organic compounds by the use of safe catalysts,[16-20] in this work, we report the three-component synthesis of new pyrano[3,2-*c*]coumarins **4** using ZnO NPs as powerful catalyst based the condensation reaction of 4-hydroxycoumarin (**1**) with aryl-glyoxals **2** and malononitrile (**3**) (Scheme 1). It is noteworthy to mention that these ZnO-catalyzed reactions showed the chemoselectivity toward pyranocoumarins **4** instead of biscoumarins **5** which was reported in the previous literature.[21]

To determine suitable conditions, the preparation of **4a** was selected as a model. In the first attempt, compound **4a** was not produced in absence of catalyst even after 180 min. When ZnO (3 mol%) was added, the compound **4a** was formed in good yield (85%)



Conditions: EtOH:H_2O (50/50), ZnO NPs (3 mol%), rt to reflux

Scheme 1

Subsequently, the amount of catalyst was varied. As shown in Figure 2, when 6 mol% of ZnO NPs was employed, the desired product **4a** was isolated in 85% yield and no appreciable effect observed on the reaction rate. In order to compare the ZnO nanoparticles with bulk case, an experiment was also investigated. However, it was found that the model reaction proceeds slowly using ZnO bulk and needs 140 min to be completed.

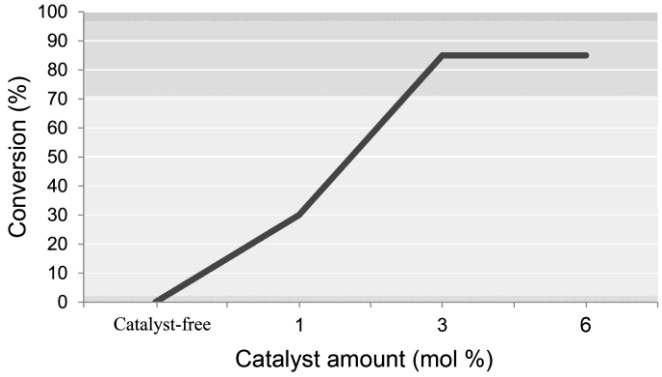


Figure 2

A series of common solvents (THF, CH_2Cl_2, H_2O, EtOH, and MeOH) was also investigated. Amongst the solvents experimented, an equal mixture of EtOH and H_2O provided the best yield.

Using the optimized conditions, we studied the domino Knoevenagel-Michael type reaction of 4-hydroxycoumarin, malononitrile and different arylglyoxals. It should be noted that both electron donating/withdrawing groups on arylglyoxal reacted well. The results are summarized in Table 1.

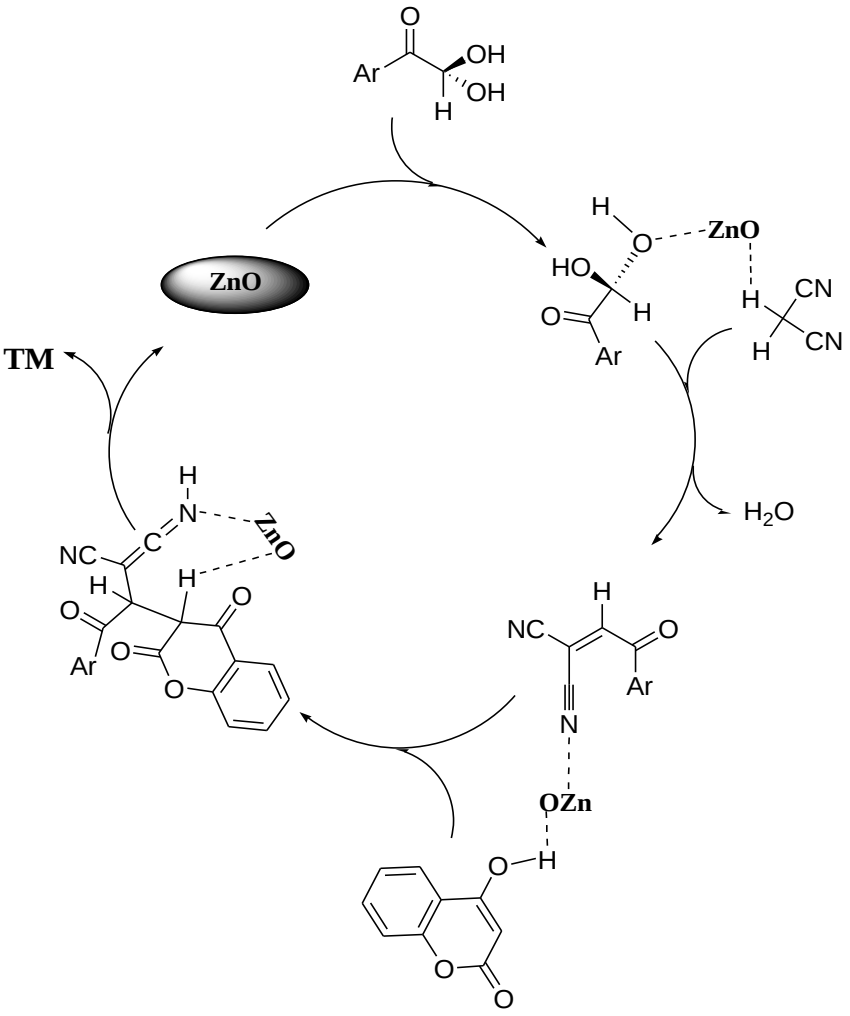
During our experiments, it was found that the reactions are independent from electron donating/withdrawing substitutions on the phenyl ring.

As a mechanistic pathway, Scheme 2 indicates a catalytic cycle for synthesis of compounds **4**. It seems that in the first step, the reaction undergoes the Knoevenagel condensation between arylglyoxal and malononitrile in which ZnO can promote the condensation as the versatile catalyst. In the next step, Michael type addition of 4-hydroxycoumarin to the corresponding aroylidene malononitriles followed by interamolecular heterocyclization reaction lead to the formation of **4**.

Table 1. Synthesis of pyrano fused coumarins catalyzed by ZnO NPs (3 mol%) in H_2O/EtOH (1:1)

Entry	Product	Ar	Time (min)	Yield (%)[a]	Mp (ºC)
1	**4a**	C_6H_5	85	80	272-274
2	**4b**	4-F-C_6H_4	85	85	253-255
3	**4c**	4-Cl-C_6H_4	90	80	263-265
4	**4d**	4-Br-C_6H_4	85	85	263-265
5	**4e**	3-NO_2-C_6H_4	80	100	248-250
6	**4f**	4-NO_2-C_6H_4	95	80	273-275
7	**4g**	3-MeO-C_6H_4	80	95	268-270
8	**4h**	4-MeO-C_6H_4	80	90	266-268
9	**4i**	1-naphthyl	95	75	271-273
10	**4j**	2-naphthyl	97	75	278-280

[a]Isolated yields.



Scheme 2

To investigate the recyclability of ZnO NPs, a recycling experiment was conducted by the use of above mentioned model reaction. After separation, the catalyst was reused in the next run. It was revealed that the ZnO NPs could be reused at least three times without the apparent loss of catalytic activity (Figure 3).

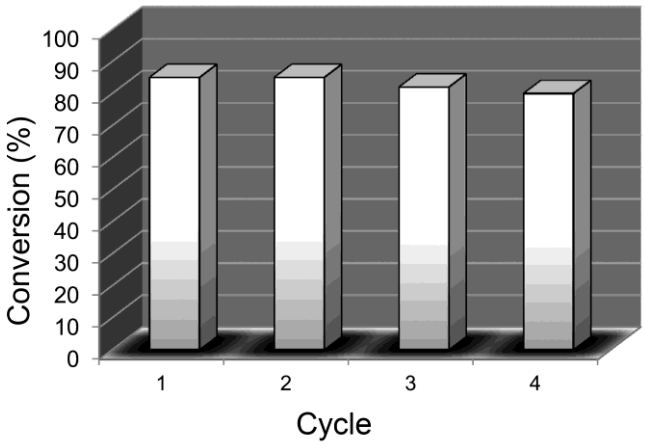


Figure 3

In summary, we developed the first method for synthesis of novel pyrano[3,2-*c*]coumarins by employing arylglyoxals. This research presents a green and efficient method catalyzed by ZnO NPs as safe and recyclable catalyst. It should be mentioned that the present strategy enables the access to a wide variety of pyranocoumarins bearing an aryloyl group which are unexplored compounds with a high potential for synthetic and biological applications.

EXPERIMENTAL

The reactions were monitored by TLC (silica gel 60 F_{254}). IR spectra (in KBr discs) were recorded on a FTIR Shimadzu-470 spectrometer (Shimadzu, Japan) in the scanning range of 400–4000 cm^{-1} and the ^1H NMR spectra (300 MHz) were obtained on a Bruker Avance DPX-300 NMR spectrometer (Bruker, USA).

Starting Materials. Arylglyoxals were prepared as detailed in the previous paper.[22] All other chemicals used in this study were commercially available.

General procedure for the preparation of ZnO nanoparticles

In a typical two step procedure, firstly, zinc acetate dihydrate (2.19 g, 0.01 mol) and oxalic acid (1.08 g, 0.012 mol) were combined by grinding in an agate mortar for 30 min at room temperature. Afterwards, in the second step, the prepared $ZnC_2O_4{\cdot}2H_2O$ nanoparticles were calcinated at 450 ºC for 30 min to produce ZnO nanoparticles (0.78 g) under thermal decomposition conditions.

General procedure for the synthesis of compounds 4

To a 25 mL round-bottomed flask, 4-hydroxycoumarin (1.0 mmol), arylglyoxal (1.2 mmol), malononitrile (1.2 mmol), EtOH/H_2O (1:1, 10 mL) and ZnO NPs (0.03 mmol) were added. The reaction was stirred at

room temperature for 30 min, then, vigorously stirred under reflux conditions for a special time. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was cooled to room temperature and the precipitates were filtered, dried and dissolved in THF to separate the catalyst. The solvent was removed under reduced pressure and the pure product was obtained after recrystallization from EtOH/THF (3:1).

2-Amino-4-(benzoyl)-3-cyano-4*H*,5*H*-pyrano[3,2-*c*]chromen-5-one (4a): mp 272-274 ºC; IR 3402, 3292, 2201, 1708, 1678, 1606, 1373, 1064 cm^{-1}; ^1H NMR: δ8.16 (d, 2H, J = 7.2 Hz), 7.90 (dd, 1H, J_1 = 8.2, J_2 = 1.6 Hz), 7.81-7.73 (m, 2H), 7.69 (s, 2H), 7.62 (t, 2H, J = 8.2 Hz), 7.57-7.53 (m, 2H), 5.42 (s, 1H); ^{13}C NMR: δ198.1, 160.0, 159.5, 154.7, 152.1, 135.3, 134.1, 133.3, 129.1, 128.8, 125.0, 122.1, 118.5, 116.8, 112.5, 101.9, 51.9, 37.1. Anal. Calcd for $C_{20}H_{12}N_2O_4$: C, 69.76; H, 3.51; N, 8.14. Found: C, 69.55; H, 3.41; N, 8.09.

2-Amino-4-(4-fluorobenzoyl)-3-cyano-4*H*,5*H*-pyrano[3,2-*c*]chromen-5-one (4b): mp 253-255 ºC; IR 3474, 3404, 2205, 1712, 1677, 1595, 1371, 1218, 1061 cm^{-1}; ^1H NMR: δ8.27 (m, 2H), 7.90 (dd, 1H, J = 8.2, 1.8 Hz), 7.82-7.76 (m, 1H), 7.70 (s, 2H), 7.58-7.53 (m, 2H), 7.46 (t, 2H, J = 8.8 Hz), 5.44 (s, 1H); ^{13}C NMR: δ196.7, 160.0, 159.5, 154.7, 152.1, 133.3, 132.3, 132.1, 125.0, 122.1, 118.5, 116.8, 116.1, 115.8, 112.5, 101.7, 51.8, 37.1. Anal. Calcd for $C_{20}H_{11}FN_2O_4$: C, 66.30; H, 3.06; N, 7.73. Found: C, 66.37; H, 3.00; N, 7.61.

2-Amino-4-(4-chlorobenzoyl)-3-cyano-4*H*,5*H*-pyrano[3,2-*c*]chromen-5-one (4c): mp 263-265 ºC; IR 3319, 3186, 3027, 2871, 2205, 1713, 1673, 1587, 1375, 1058, 759 cm^{-1}; ^1H NMR: δ8.20 (d, 2H, J = 8.4 Hz), 7.89 (dd, 1H, J_1 = 8.2, J_2 = 1.4 Hz), 7.81-7.69 (m, 5H), 7.57-7.52 (m, 2H), 5.43 (s, 1H); ^{13}C NMR: δ 197.2, 160.0, 159.5, 154.7, 152.1, 139.2, 134.1, 133.3, 130.9, 129.0, 125.0, 122.1, 118.4, 116.8, 112.5, 101.6, 51.7, 37.2. Anal. Calcd for $C_{20}H_{11}ClN_2O_4$: C, 63.42; H, 2.93; N, 7.40. Found: C, 63.61; H, 2.99; N, 7.35.

2-Amino-4-(4-bromobenzoyl)-3-cyano-4*H*,5*H*-pyrano[3,2-*c*]chromen-5-one (4d): mp 263-265 ºC; IR 3316, 3186, 3027, 2871, 2203, 1715, 1673, 1582, 1374, 1057, 620 cm^{-1}; ^1H NMR: δ8.10 (d, 2H, J = 8.6 Hz), 7.91-7.76 (m, 4H), 7.71 (s, 2H), 7.58-7.53 (m, 2H), 5.42 (s, 1H); ^{13}C NMR: δ197.5, 159.5, 154.7, 152.1, 134.4, 133.4, 132.0, 131.0, 125.0, 122.1, 116.8, 112.5, 101.6, 51.7, 37.2. Anal. Calcd. for $C_{20}H_{11}BrN_2O_4$: C, 56.76; H, 2.62; N, 6.62. Found: C, 56.89; H, 2.51; N, 6.58.

2-Amino-4-(3-nitrobenzoyl)-3-cyano-4*H*,5*H*-pyrano[3,2-*c*]chromen-5-one (4e): mp 248-250 ºC; IR 3415, 3086, 2928, 2197, 1712, 1673, 1609, 1525, 1385, 1352, 1063 cm^{-1}; ^1H NMR: δ8.83 (t, 1H, J = 1.8 Hz), 8.65 (d, 1 H, J = 7.8 Hz), 8.61-8.57 (m, 1H), 7.98-7.89 (m, 2H), 7.82-7.77 (m, 3H), 7.59-7.53 (m, 2H), 5.57 (s, 1H); ^{13}C NMR: δ197.0, 160.1, 159.5, 154.8, 152.1, 148.1, 136.6, 135.2, 133.5, 130.9, 128.3,

125.1, 123.1, 122.2, 118.5, 116.8, 112.5, 101.3, 51.2, 37.6. Anal. Calcd for $C_{20}H_{11}N_3O_6$: C, 61.70; H, 2.85; N, 10.79. Found: C, 61.88; H, 2.77; N, 10.83.

2-Amino-4-(4-nitrobenzoyl)-3-cyano-4*H*,5*H*-pyrano[3,2-*c*]chromen-5-one (4f): mp 273-275 ºC; IR 3461, 3336, 2192, 1720, 1681, 1613, 1517, 1383, 1326, 1070, 1064 cm^{-1}; ^1H NMR: δ 8.46-8.38 (m, 4H), 7.90 (dd, 1H, J = 8.2, 1.4 Hz), 7.82-7.77 (m, 3H), 7.59-7.54 (m, 2H), 5.51 (s, 1H); ^{13}C NMR: δ 197.7, 160.1, 159.5, 154.8, 152.1, 150.4, 140.2, 133.5, 130.4, 125.1, 124.0, 122.2, 116.8, 112.5, 101.3, 51.2, 37.9. Anal. Calcd for $C_{20}H_{11}N_3O_6$: C, 61.70; H, 2.85; N, 10.79. Found: C, 61.79; H, 2.72; N, 10.71.

2-Amino-4-(3-methoxybenzoyl)-3-cyano-4*H*,5*H*-pyrano[3,2-*c*]chromen-5-one (4g): mp 268-270 ºC; IR 3477, 3344, 3072, 2934, 2196, 1721, 1674, 1577, 1386, 1065 cm^{-1}; ^1H NMR: δ 7.90 (dd, 1H, J_1 = 8.2, J_2 =1.8 Hz), 7.815-7.75 (m, 2H), 7.70 (s, 2H), 7.62 (t, 1H, J = 2.4 Hz), 7.57-7.52 (m, 3H), 7.32 (dd, 1H, J_1 = 7.8, J_2 = 2.1 Hz), 5.40 (s, 1H), 3.87 (s, 3H); ^{13}C NMR: δ 197.7, 160.0, 159.6, 159.4, 154.7, 152.1, 136.6, 133.3, 130.0, 125.0, 122.1, 121.6, 120.2, 118.5, 116.8, 113.5, 112.6, 101.9, 55.3, 52.0, 37.4. Anal. Calcd for $C_{21}H_{14}N_2O_5$: C, 67.38; H, 3.77; N, 7.48. Found: C, 67.48; H, 3.70; N, 7.56.

2-Amino-4-(4-methoxybenzoyl)-3-cyano-4*H*,5*H*-pyrano[3,2-*c*]chromen-5-one (4h): mp 266-268 ºC; IR 3426, 3320, 2926, 2200, 1714, 1673, 1597, 1383, 1062 cm^{-1}; ^1H NMR: δ 8.15 (d, 2H, J = 9.0 Hz), 7.89 (dd, 1H, J_1 = 8.2, J_2 = 1.4 Hz), 7.80-7.74 (m, 1H), 7.65 (s, 2H), 7.57-7.52 (m, 2H), 7.14 (d, 2H, J = 9.0 Hz), 5.36 (s, 1H), 3.90 (s, 3H); ^{13}C NMR: δ 196.2, 163.9, 160.0, 159.5, 154.6, 152.0, 133.2, 131.6, 128.1, 124.9, 122.1, 118.6, 116.7, 114.1, 112.6, 102.1, 55.6, 52.2, 36.7. Anal. Calcd for $C_{21}H_{14}N_2O_5$: C, 67.38; H, 3.77; N, 7.48. Found: C, 67.40; H, 3.73; N, 7.40.

2-Amino-4-(1-naphthoyl)-3-cyano-4*H*,5*H*-pyrano[3,2-*c*]chromen-5-one (4i): mp 271-273 ºC; IR 3477, 3327, 3050, 2923, 2191, 1727.91, 1674.87, 1573.63, 1381.75, 1177 cm^{-1}; ^1H NMR: δ 8.37 (m, 2H), 8.24 (d, 1H, J = 8.4 Hz), 8.09-8.05 (m, 1H), 7.92 (dd, 1H, J = 8.2, J_2 = 1.8 Hz), 7.83-7.70 (m, 4H), 7.66-7.54 (m, 4H), 5.43 (s, 1H); ^{13}C NMR: δ 200.3, 160.2, 159.6, 154.6, 152.2, 134.2, 133.4, 133.3, 133.2, 129.8, 129.0, 128.5, 128.0, 126.5, 125.1, 125.0, 124.7, 122.2, 118.3, 116.8, 112.6, 101.7, 51.4, 38.6. Anal. Calcd for $C_{24}H_{14}N_2O_4$: C, 73.09; H, 3.58; N, 7.10. Found: C, 73.13; H, 3.55; N, 7.01.

2-Amino-4-(2-naphthoyl)-3-cyano-4*H*,5*H*-pyrano[3,2-*c*]chromen-5-one (4j): mp 278-280 ºC; IR 3428, 3321, 2938, 2199, 1714, 1674, 1631, 1597, 1569, 1382, 1172 cm^{-1}; ^1H NMR: δ 8.44 (s, 1H), 7.98-7.95 (m, 2H), 7.84-7.82 (d, 1H, J = 8.4 Hz), 7.76-7.72 (m, 1H), 7.62-7.52 (m, 3H), 7.49-7.42 (m, 2H), 7.39 (s, 2H), 7.33 (d, 1H, J =7.2 Hz), 5.47 (s, 1H); ^{13}C NMR: δ 199.6, 159.5, 157.8, 153.8, 152.0, 133.2, 132.9, 130.9, 128.4, 127.4, 126.1, 126.1, 126.0, 125.8, 125.7, 124.7, 123.4, 122.4, 119.1, 116.6, 112.9, 104.6, 53.6, 37.2. Anal. Calcd for $C_{24}H_{14}N_2O_4$: C, 73.09; H, 3.58; N, 7.10. Found: C, 73.17; H, 3.60; N, 7.04.

ACKNOWLEDGEMENTS

We gratefully acknowledge the Yasouj University Research Council for their support. We are also grateful to the Iranian Nanotechnology Initiative Council for financial support.

REFERENCES

1. A. Khojastehnezhad, M. Rahimizadeh, H. Eshghi, F. Moeinpour, and M. Bakavoli, *Chin. J. Catal.*, 2014, **35**, 376.
2. Y. Gu, *Green Chem.*, 2012, **14**. 2091.
3. K. Wilson and J. H. Clark, *Pure Appl. Chem.*, 2000, **72**, 1313.
4. L. Cai, Z. Hu, P. Branton, and W. Li, *Chin. J. Catal.*, 2014, **35**, 159.
5. A. Clark, *Ind. Eng. Chem.*, 1953, **45**, 1476.
6. V. Kumar, H. S. B. Naik, D. Girija, and B. V. Kumar, *J. Chem. Sci.*, 2011, **123**, 615.
7. I. Yavari and S. Beheshti, *J. Iran. Chem. Soc.*, 2011, **8**, 1030.
8. M. Hosseini-Sarvari, and M. Tavakolian, *Appl. Catal. A: General.*, 2012, **441-442**, 65.
9. B. Karami, S. Khodabakhshi, and K. Eskandari, *Tetrahedron Lett.*, 2012, **53**, 1445.
10. Y. Liu, J. Zhu, J. Qian, B. Jiang, and Z. Xu, *J. Org. Chem.*, 2011, **76**, 9096.
11. S. Khodabakhshi, B. Karami, and K. Eskandari, *C. R. Chimie*, 2014, **17**, 35.
12. M. V. Dmitrieva, P. S. Silaicheva, and A. N. Maslivetsa, *Russ. J. Org. Chem.*, 2011, **47**, 1263.
13. A. R. Karimi and F. Sedaghatpour, *Synthesis*, 2010, 1731.
14. B. Karami, S. Khodabakhshi, and K. Eskandari, *Lett. Org. Chem.*, 2013, **10**, 105.
15. G. M. Ziarani and P. Hajiabbasi, *Heterocycles*, 2013, **87**, 1415.
16. S. Khodabakhshi and B. Karami, *Catal. Sci. Technol.*, 2012, **2**, 1940.
17. B. Karami, V. Ghashghaee, and S. Khodabakhshi, *Catal. Commun.*, 2012, **20**, 71.
18. V. Kamaei, B. Karami, and S. Khodabakhshi, *Polycyclic Aromat. Compds.*, 2014, **34**, 1.
19. B. Karami, S. Nikoseresht, and S. Khodabakhshi. *Chin. J. Catal.*, 2012, **33**, 298.
20. B. Karami, K. Eskandari, S. Khodabakhshi, S. J. Hoseini, and F. Hashemian, *RSC Adv.*, 2013, **3**, 23335.
21. N. N. Kolos, L. L. Gozalishvili, and F. G. Yaremenko, *Russ. Chem. Bull.*, 2007, **56**, 2277.
22. B. Karami, S. Khodabakhshi, and N. Nikrooz, *Polycyclic Aromat. Compds.*, 2011, **31**, 97.