Iranian Journal of Organic Chemistry Vol. 12, No.3 (2020) 2935-2939

Green synthesis of isoquinoline derivatives using mlticomponent reaction of phthalaldehyde

Samanehsadat Sharifi[*a] and Maryam Kohi[b]

[a]*Department of Chemistry,Faculty of Sciences, University of Sistan and Baluchestan, sistan and Balouchestan, Iran*
[b] *Department of Chemistry, Tarbiat Modares University, Tehran. Iran*

Received: May 2020; Revised: July 2020; Accepted: July 2020

Abstract: In this work, The 1,3-dipolar intermediates generated by addition of isoquinoline that is produced from the reaction of phthalaldehyde and ammonium acetate to dialkyl acetylenedicaboxylates are trapped by N-alkylisatins to produce spiro compounds in excellent yields.

Keywords: Spiro compounds;; Acetylenedicarboxylates; *N*-Alkylisatins; *N*-Heterocycles.

Introduction

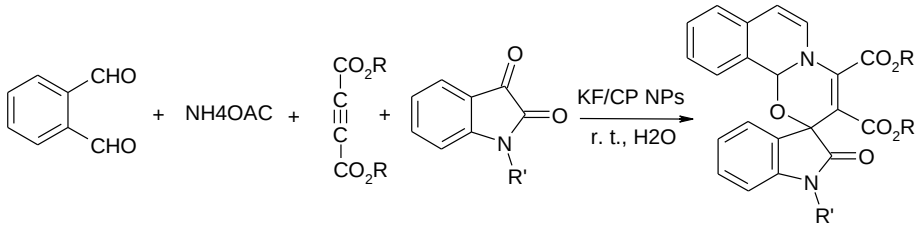
Spiro compounds having cyclic structures fused at a central carbon are of interest due to their interesting conformational features and their structural implications on biological systems [1]. The asymmetric characteristic of the molecule due to the chiral spiro carbon is one of the important criteria of the biological activities. The presence of the sterically constrained spiro structure in various natural products also adds to the interest in the investigations of spiro compounds [2]. The basic principles of dipolar cycloaddition reactions were provided by the work of *Huisgen* and co-workers [3]. An interesting example of this type is the dipole generated from isoquinoline and dimethyl acetylenedicarboxylate (*DMAD*), whose existence was established by *Huisgen* [4]. As part of our current studies on the development of new routes towards heterocyclic systems [5], we describe an efficient synthesis of spiro compounds **5**. Isoqunoline derivatives are as a main group of heterocycle compounds because of their existence in nature [12-13] and their pharmacological activities including antifungal [14] antibacterial [15], antitumor [16], anti-inflammatory [17] anticonvulsant [18], analgesic [19] and antitubercular [20] activities. Employing suitable catalyst increases the way to green chemistry. In the presence of nanocatalyst, some organic reactions have excellent yields and selectivity of product than to usual sized. Among heterogeneous catalysts, zeolites have been reported as a new class of promising support and catalysts for the development of environmentally friendly acidic catalysts. Due to its higher thermal and hydrothermal stability, zeolite has recently been garnering interest as a novel support. Recently, using potassium fluoride supported on zeolites such as clinoptilolite (CP) as new natural and cheap zeolite is very interesting. In this research investigation of antioxidant ability for some of the synthesized compounds is performed. Frequently compounds with antioxidant ability, eliminate the negative property of free radicals and utilize as transitional metals chelators. This result is due to their reducing properties and chemical structure. Also, these compounds could be avoid or decrease many sicknesses such as cardiovascular, inflammatory bowel syndrome, cancer,

*Corresponding author: Tel: 0098-8633677201-9; Fax: 0098-8633677203, E-mail: samanehsharifi1020@gmail.com

ageing, and alzheimer. Herein, in continuation of our studies for discovering new procedure for synthesis of important organic compounds with biological activity, in this research we carry out the synthesis of new derivatives of spiro compounds *via* the reaction of phthalaldehyde **1**, ammonium acetate **2**, activated acetylenic compounds **3** and isatin **4** in good yields (Scheme **1**).

As part of our current studies on the development of new routes in heterocyclic systems, in this letter we describe a simple synthesis of functionalized isoquinolines. The reaction of phthalaldehyde **1**, ammonium acetate **2**, activated acetylenic compounds **3** and isatin **4** in the presence of KF/CP as catalyst in good yields (Scheme **1**).

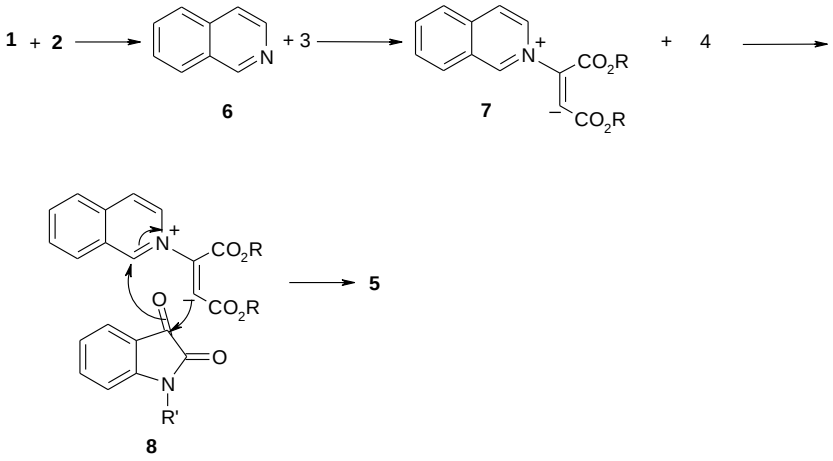
Results and discussion



1 2 3 4 5

	R	R'
a	Me	Me
b	Et	Me
c	Me	Bn
d	Et	Bn
e	Me	Et
f	Et	Et

Scheme 1: Synthesis of spiro compounds **5**



Scheme 2: Proposed mechanism for the formation of **5**.

The structures of compounds **5a**–**5f** were deduced from their elemental analyses and their IR, ^{1}H-NMR, and ^{13}C-NMR spectra. For example, in the ^{1}H-NMR spectrum for the major isomer of **5a**, signals due to the two methoxy groups were visible at δ = 3.29 and 3.98; the corresponding signals for minor isomer of **5a** were observed at δ = 3.25 and 3.96. The ring junction proton of the major isomer of **5a** was discernible as a singlet at δ = 7.08; the corresponding signal for minor isomer of **5a** was seen as a singlet at δ = 6.52. In ^{13}C-NMR spectrum, the signals corresponding to ester and amide carbonyl groups of the major isomer of **5a** were observed at δ = 163.5, 163.9, and 174.5. Those for the minor isomer were visible at δ = 163.6, 163.7, and 174.6. The mass spectrum of **5a** displayed the molecular ion peak at *m*/*z* = 432, which is consistent with the 1:1:1 adduct of isoquinoline, *DMAD* and *N*-methylisatin. Mechanistically, it is conceivable that the reaction involves the initial formation of isoquinoline 6 that is produced from the reaction of phthalaldehyde 1 and ammonium acetate 2. The acetylenic compounds 3 react with isoquinoline 6 and produce intermediate 7 which reacts with the carbonyl group of *N*-alkylisatin to produce **8**. Cyclization of this zwitterionic intermediate leads to the spiro compound **5** (Scheme 2).

Conclusion

In conclusion, we have described a convenient route to spiro compounds from *insitue* produced isoquinoline and react with dialkyl acetylene dicarboxylates in the presence of *N*-alkylisatins. The advantage of the present procedure is that the reaction is performed under neutral conditions by simply mixing the starting materials. The procedure described here provides an acceptable one-pot method for the preparation of spiro heterocyclic compounds.

Experimental

General. Melting points were measured on an *Electrothermal 9100* aparatus. Further purification. IR Spectra: *Shimadzu IR-460* spectrometer. ^{1}H-and ^{13}C-NMR spectra: *Bruker DRX-500 AVANCE* instrument; in $CDCl_3$ at 500.1 and 125.7 MHz, resp; δ in ppm, *j* in Hz. EI-MS (70 eV): *Finnigan-MAT-8430* mass spectrometer, in m/z. Elemental analyses (C, H, N) were performed with a *Heraeus CHN-O-Rapid* analyzer.

General procedure for preparation of compounds 5:

Phthalaldehyde **1** (2 mmol) and ammonium acetate **2** (2 mmol) stirred in water (5 mL) as solvent for 20 min at r.t. in the presence Fe_3O_4 MNPs (10 mol%). In this stage isoquinoline was prepared and for confirmation of it we checked with isoquinoline that are prepared from company by TLC. Then activated acetylenic compounds **3** (2 mmol) was added slowly and mixture was stirred for 15 min. Then isatin **4** was added and mixture was stirred for 2 h in the presence of Fe_3O_4-MNPs (10 mol%) at r.t. for 45 min. After completion of the reaction (2 h; TLC control (hexane–AcOEt, 6:1), the Fe_3O_4 MNPs were separated by external magnet from mixture of reaction. After removing solvent, the residue was purified by column chromatography (4:1 hexane/EtOAc) to afforded pure title compounds.

General Procedure for the Preparation of Compounds 6:

To a stirred solution of isoquinoline **6** that is produce from the reaction of phthalaldehyde 1 (2 mmol) and ammonium acetate 2 (2 mmol). Then dialkyl acetylenedicarboxylate 3 (2 mmol) was added to mixture and after 20 min N-alkylisatin 4 (2 mmol) in 15 mL water was added the N-heterocycle (2 mmol) at room temperature. The reaction mixture was then stirred for 2 h. The solvent was removed under reduced pressure, and the residue was purified by CC (SiO_2; n-hexane/AcOEt 4:1) to afford the pure title compounds.

Dimethyl 1,2-Dihydro-2-oxo-1-methyl-spiro[3H-indole-3,2'-[2H,11bH] [1,3]oxazino[2,3-a] isoquinoline]-3',4'-dicarboxylate (5a):

Yellow crystals. M.p. 210-212°C, Yield 0.84 g, 97%. IR (KBr): ν = 1742, 1721, 1647, 1593, 1566 cm^{-1}; EI-MS: 432 (M^+, 5); 401 (25); 302 (78); 161 (86); 129 (48); 104 (100); 76 (44); 59 (18); NMR data for the major isomer (67%); ^{1}H-NMR: 3.29 (*s*, O*Me*); 3.46 (*s*, *Me*); 3.98 (*s*, O*Me*); 5.83 (*d*, ^{3}J = 7.3, CH); 6.41 (*d*, ^{3}J = 7.2, CH); 6.80 (*d*, ^{3}J = 7.7, CH); 6.96 (*t*, ^{3}J = 7.4, CH); 7.08 (*s*, CH); 7.11 (*t*, ^{3}J = 7.6, CH); 7.16-7.26 (*m*, 4 CH); 7.36 (*d*, ^{3}J = 7.5, CH) ppm; ^{13}C-NMR: 26.3 (N*Me*); 51.7, 53.4 (2 O*Me*); 77.5 (CH); 79.7, 105.8 (2 C); 105.3, 108.3 (2 CH); 122.6, 122.9 (2 C); 123.2, 123.3, 125.2, 126.2, 127.1, 128.3, 129.5, 129.8 (8 CH); 130.2, 145.2, 145.3 (3 C); 163.5, 163.9, 174.5 (3 C=O) ppm.

Diethyl 1,2-Dihydro-2-oxo-1-methyl-spiro[3H-indole-3,2'-[2H,11bH] [1,3]oxazino[2,3-a]isoquinoline]-3',4'-dicarboxylate (5b):

Yellow crystals. M.p. 215-217°, Yield: 0.87 g, 95%. IR (KBr): ν = 1740, 1719, 1650, 1590, 1560 cm^{-1}; EI-MS: 460 (M^+, 12); 415 (48); 370 (78); 331 (96); 161 (48); 129 (56); 76 (44); 45 (100); NMR data for the major isomer (65%); ^{1}H-NMR: δ = 0.91, 1.41 (2 *t*, ^3J = 7.1, 2 *Me*); 3.27 (*s*, N*Me*); 3.87, 4.39 (2 *q*, ^3J = 7.1, 2 OCH_2); 5.80 (*d*, ^3J = 8.7, CH); 6.41 (*d*, ^3J = 7.1, CH); 6.48 (*d*, ^3J = 8.7, CH); 6.81 (*t*, ^3J = 7.4, CH); 7.04 (*s*, CH); 7.10 (*t*, ^3J = 7.6, CH); 7.11-7.26 (*m*, 4 CH); 7.36 (*d*, ^3J = 7.5, CH) ppm; ^{13}C-NMR: δ = 13.6, 14.0 (2 *Me*); 26.3 (N*Me*); 60.4, 62.7 (2 OCH_2); 77.5 (C); 79.6 (CH); 104.9 (C); 105.2, 108.2 (2 CH); 122.6, 123.0 (2 C); 123.2, 123.4, 125.2, 126.2, 127.1, 128.3, 129.5, 129.9 (8 CH); 130.1, 145.3, 145.6 (3 C); 163.1, 163.2, 174.7 (3 C=O) ppm.

Dimethyl 1,2-Dihydro-2-oxo-1-benzyl-spiro[3H-indole-3,2'-[2H,11bH] [1,3]oxazino[2,3-a]isoquinoline]-3',4'-dicarboxylate (5c):

Yellow crystals. M.p. 235-237°C, Yield 0.99 g, 98%. IR (KBr): ν = 1738, 1719, 1647, 1560, 1572 cm^{-1}; EI-MS: 508 (M^+, 10); 477 (65); 446 (25); 417 (86); 129 (48); 91 (100); 76 (44); 31 (100); NMR data for the major isomer (67%); ^{1}H-NMR: 3.33 (*s*, O*Me*); 4.0 (*s*, O*Me*); 5.11 (*AB* system, $^2J_{AB}$ = 15.4, CH_2); 5.82 (*d*, ^3J = 6.2, CH); 6.42 (*d*, ^3J = 6.2, CH); 6.74 (*d*, ^3J = 7.7, CH); 6.80 (*d*, ^3J = 7.6, CH); 6.94 (*t*, ^3J = 7.3, CH); 7.44 (*s*, CH); 7.03-7.44 (*m*, 10 CH) ppm;. ^{13}C-NMR: 44.9 (CH_2); 51.6 (O*Me*); 53.4 (O*Me*); 77.5 (C); 79.5 (CH); 105.2 (C); 109.3 (CH); 123.1 (CH); 123.2 (CH); 123.4 (CH); 125.3 (CH); 126.3 (C); 127.1 (CH); 127.6 (2 CH); 127.7 (CH); 128.1 (CH); 128.7 (C); 128.8 (3 CH); 129.6 (CH); 129.8 (CH); 130.1 (CH); 135.8 (C); 144.3 (C); 145.5 (C); 163.6 (C=O); 163.7 (C=O); 174.7 (C=O) ppm.

Diethyl 1,2-Dihydro-2-oxo-1-benzyl-spiro[3H-indole-3,2'-[2H,11bH] [1,3]oxazino[2,3-a]isoquinoline]-3',4'-dicarboxylate (5d):

Yellow crystals. M.p. 240-242°C, Yield 1.03 g, 96%. IR (KBr): ν = 1742, 1721, 1647, 1593, 1566 cm^{-1}; EI-MS: 536 (M^+, 12); 491 (55); 446 (78); 238 (86); 129 (48); 91 (100); 76 (44); 45 (98); NMR data for the major isomer (60%); ^{1}H-NMR: δ = 0.73, 1.42 (2 *t*, ^3J = 7.1, 2 *Me*); 3.73, 3.98 (2 *q*, ^3J = 7.1, 2 OCH_2); 4.90 (*AB* system, $^2J_{AB}$ = 13.2, CH_2); 5.82 (*d*, ^3J = 7.8, CH); 6.44 (*d*, ^3J = 7.7, CH); 6.78 (*d*, ^3J = 7.8, CH); 7.31 (*s*, CH); 7.02-7.45 (*m*, 12 CH) ppm;. ^{13}C-NMR: δ = 13.5, 13.9 (2 *Me*); 44.5 (CH_2); 60.6, 62.8 (2 OCH_2); 78.2 (C); 80.1 (CH); 104.2 (C); 109.4 (CH); 122.6 (CH); 123.2 (CH); 123.8 (CH); 125.9 (CH); 126.9 (C); 127.5 (CH); 127.7 (2 CH); 127.8 (CH); 128.7 (CH); 128.8 (C); 128.9 (3 CH); 129.8 (CH); 130.1 (CH); 130.2 (CH); 135.7 (C); 143.2 (C); 145.3 (C); 163.0 (C=O); 163.4 (C=O); 173.9 (C=O) ppm.

Dimethyl 1,2-Dihydro-2-oxo-1-ethyl-spiro[3H-indole-3,2'-[2H,11bH] [1,3]oxazino[2,3-a]isoquinoline]-3',4'-dicarboxylate (5e):

Yellow powder. M.p. 223-225°C, Yield 0.84 g, 95%. IR (KBr): ν = 1742, 1721, 1647, 1593, 1566 cm^{-1}; EI-MS: 446 (M^+, 10); 415 (96); 317 (38); 175 (68); 129 (68); 76 (44); 31 (100); NMR data for the major isomer (65%): ^{1}H-NMR: δ = 1.29 (*t*, ^3J = 7.2, *Me*); 3.45 (*s*, O*Me*); 3.67 and 3.95 (*m*, CH_2); 3.98 (*s*, O*Me*); 5.80 (*d*, ^3J = 7.7, CH); 6.39 (*d*, ^3J = 7.7, CH); 6.89 (*d*, ^3J = 7.7, CH); 7.04-7.27 (*m*, 5 CH); 7.29 (*s*. CH); 7.38 (*t*, ^3J = 7.7, CH); 7.44 (*d*, ^3J = 7.6, CH) ppm; ^{13}C-NMR: δ = 12.2 (*Me*); 34.8 (CH_2); 51.7, 53.5 (2 O*Me*); 78.1 (C); 80.2 (CH); 105.0 (C); 105.3, 108.6 (2 CH); 122.5, 123.6 (2 C); 123.8, 124.4, 125.2, 127.0, 127.7, 129.6, 129.9, 130.2 (8 CH); 130.4, 143.1 (2 C); 144.9, 163.6, 163.9 (3 C=O); 173.2 (C=O) ppm.

Diethyl 1,2-Dihydro-2-oxo-1-ethyl-spiro[3H-indole-3,2'-[2H,11bH] [1,3]oxazino[2,3-a]isoquinoline]-3',4'-dicarboxylate (5f):

Yellow crystals. M.p. 102-104°C, Yield 0.87 g, 92%. IR (KBr): ν = 1742, 1721, 1647, 1593, 1566 cm^{-1}; EI-MS: 474 (M^+, 5); 429 (75); 384 (78); 176 (86); 129 (48); 104 (100); 76 (44); 45 (100); NMR data for the major isomer (62%); ^{1}H-NMR: δ = 1.25, 1.33, 1.41 (3 *t*, ^3J = 7.1, 3 *Me*); 3.74 and 3.80 (*m*, CH_2); 3.82 (*q*, ^3J = 7.1, OCH_2); 4.47 (*q*, ^3J = 7.1, OCH_2); 5.79 (*d*, ^3J = 8.2, CH); 6.42 (*d*, ^3J = 7.2, CH); 6.89 (*d*, ^3J = 8.2, CH); 6.97 (*t*, ^3J = 7.4, CH); 7.01 (*s*, CH); 7.08-7.30 (*m*, 5 CH); 7.35 (*s*, CH); 7.46 (*d*, ^3J = 7.5, CH) ppm; ^{13}C-NMR: δ = 12.5, 13.7, 13.9 (3 *Me*); 34.8 (CH_2); 60.3, 62.7 (2 OCH_2); 78.0 (C); 79.4 (CH); 104.7 (C); 104.9 (CH); 108.3 (CH); 122.8 (C); 123.2 (C); 123.6 (CH); 125.1 (CH); 125.9 (CH); 126.2 (CH); 127.1 (CH); 128.1 (CH); 129.5 (CH); 129.9 (CH); 130.1 (C); 145.1 (C); 145.6 (C); 163.1 (C=O); 163.2 (C=O); 174.3 (C=O) ppm.

References

[1] Pradhan, R.; Patra, M.; Behera, A.K.; Mishra, B.K.; Behera, R.K. *Tetrahedron*, **2006**, *62*, 779.
[2] Srivastav, N.; Mittal, A.; Kumar, A. *J. Chem. Soc. Chem. Commun.* **1992**, 493.
[3] (a) Huisgen, R, In *Topics in Heterocyclic Chemistry;* Castle, R. **1969** Ed; John Wiley & Sons: New York, ch 8, p 223; (b) Huisgen, R. Ger Z Chem. **1968**, *8*, 290.
[4] Huisgen, R.; Morikawa, M.; Herbigm K.; Brunn, E. *Chem. Ber*. **1967**, *100*, 1094.
[5] (a) Yavari, I.; Moradi, L. *Helv. Chim. Acta*, **2006**, *89*, 1942; (b) Yavari, I.; Djahaniani, H. *Tetrahedron Lett.* **2006**, *47*, 1477; (c) Yavari, I.; Moradi, L. *Tetrahedron Lett.* **2006**, *47*, 1627; (d) Yavari, I.; Alborzi, A.R.; Mohtat, B. *Dyes Pigments*, **2006**, *68*, 85; (e) Yavari, I.; Djahaniani, H. *Tetrahedron Lett.* **2006**, 47, 7491; (f) Yavari, I.; Djahaniani, H. *Tetrahedron Lett.* **2005**, *46*, 7491; (g) Yavari, I.; Djahaniani, H.; Nasiri, F, *Synthesis*, **2004**, 679; (h) Yavari, I.; Habibi, A. *Synthesis* **2004**, 989; (i) Yavari, I.; Nasiri, F.; Djahaniani, H. *Mol. Divers.* **2004**, 8, 431; (j) Yavari, I.; Alizadeh, A. *Synthesis* **2004**, 237; (k) Yavari, I.; Adib, M.; Esnaashari, M. *Monatsh. Chem.* **2001**, *132*, 1557.
[6] Cobridge DEC, Phosphorus: An Outline of Chemistry, Biochemistry and Uses, 5th edn., Elsevier, Amsterdam, **1995**.
[7] Kolodiazhnyi, O. I. *Russ. Chem. Rev.* **1997**, *66*, 225.
[8] Nair, V.; Rajesh, C.; Vinod, A. U.; Bindu, S.; Sreekanth, A. R.; Mathess, J. S.; Balagopal, L. *Acc. Chem. Res.* **2003**, *36*, 899.
(9) (a) Yavari, I.; Djahaniani, H. *Tetrahedron Lett.* **2006**, *47*, 2953; (b) Yavari, I.; Moradi, L. *Tetrahedron Lett.* **2006**, *47*, 1627; (c) Yavari, I.; Djahaniani, H. *Tetrahedron Lett*. **2005**, *46*, 7491; (d) Yavari, I.; Djahaniani, H.; Nasiri, F. *Synthesis* **2004**, 679; (e) Yavari, I.; Habibi, A. *Synthesis* **2004**, 989; (f) Yavari, I.; Nasiri, F.; Djahaniani, H. *Mol. Divers.* **2004**, *8*, 431; (g) Yavari, I.; Alizadeh, A. *Synthesis* **2004**, 237; (h) Yavari, I.; Adib, M.; Esnaashari, M. *Monatsh. Chem.*, **2001**, *132*, 1557; (i) Yavari, I.; Adib, M. *J. Chem. Res.* (S), **2001**, 543. (j) Yavari, I.; Maghsoodlou, M. T.; Pourmossavi, A. *J. Chem. Res. (S)* **1997**, 212.
[10] Zárate-Zárate, D.; Aguilar, R.; Hernández-Benitez, R. I.; Labarrios EM, Delgado, F.; Tamariz, J. *Tetrahedron* **2015**, *71*, 6961.
[11] Gordon, E. M.; Barrett, R.W.; Dower, W. J.; Fodor, S. P. A.; Gordon, M. A. Gallop *J. Med. Chem.* **1994**, *37*, 1385.
[12] Ardiansah, B. *Asian J. Pharm. Clin. Res.* **2017**, *12*, 45.
[13] Srivastava, M.; Singh, J.; Singh, S. B.; Tiwari, K.; Pathak, K. V.; Singh, J. *Green Chem.* **2012**, *14*, 901.
[14] Pai, G.; Chattopadhyay, A. P. *Tetrahedron Lett.* **2016**, *57*, 3140.
[15] Bekhit, A. A.; Hassan, A. M.; Abd El Razik, H. A.; El-Miligy, M. M.; El-Agroudy, E. J.; Bekhit, Ael-D. *Eur. J. Med. Chem.* **2015**, *94*, 30.
[16] Sony, J. K.; Ganguly, S. *Int. J. Pham Pharm. Sci*. **2016**, *8*, 75.
[17] Surendra, Kumar R.; Arif, I. A.; Ahamed, A.; Idhayadhulla, A. *Saudi J. Biol. Sci*. **2016**, *23*, 614.
[18] Alam, R.; Wahi, D.; Singh, R.; Sinha, D.; Tandon, V.; Grover, A.; Rahisuddin *Bioorg. Chem.* **2016**, 69, 77.
[19] Shamsuzzaman, S.; Siddiqui, T.; Alam, M. G.; Dar, A. M. *J. Saudi Chem. Soc.* **2015**, *19*, 387.
[20] Saisal, M.; Hussain, S.; Haider, A.; Saeed, A.; Larik, F. A. *Chem. Pap.* **2018**, *73*, 1053.