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Research Article

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A green alternative approach for synthesis of 2-substituted-*1H*-Perimidine catalysed by NBS in Ultra Sonication method

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ABSTRACT

An expeditious and greener one-pot procedure was developed for the synthesis of 2-substituted-1H-perimidine derivatives. In the presence of catalytic amount of NBS, aldehydes and 1,8-diaminonaphthalene were converted into the corresponding 2-substituted-1H-perimidine derivatives in moderate to high yields under sonication. Highly efficient and simple methods have been described in this manuscript for the synthesis with competent yields. Present synthesis complies with principle of Green chemistry. As part of current studies, we here in report economical practical techniques like ultrasonic wave organic synthesis and by application of green solvents. On completion of reaction the products were characterized by IR, NMR and Mass Spectra. These methods are more convenient and reactions can be carried out in higher yield (94-97%), shorter reaction time (08mins-20mins) and milder conditions, without generation of pollution and safer to analyst.

Keywords: Ultrasonic irradiation, Green chemistry, N-Bromosuccinamide (NBS), perimidine, Ecofriendly, Efficient.

INTRODUCTION

Nitrogen-containing heterocycles are ubiquitous to among pharmaceutical compounds [1-3]. Perimidine moiety is an important class of N-containing heterocycles widely used as key building blocks for pharmaceutical agents. There has special interest in the chemistry of perimidines due to a wide range of biological activities exhibited by these compounds[4-8]. Perimidine moiety shows bactericidal, fungicidal [9], analgesic [10] antihypertensive [11] and anti-tumor activity [12]. Among the substituted pyrimidines, thiouracils are well known for anti-inflammatory and virucidal agents [13]. The biological and synthetic significance places this scaffold at a prestigious position in medicinal chemistry research. These heterocyclic systems find wide use in medicine, agriculture and industry. A series of compounds based on perimidine have been synthesized and evaluated for their DNA-binding properties and antitumor activity [14].

Perimidines have also used as intermediates in organic synthesis [15]. A variety methods have been reported for the synthesis of perimidines in literatures [16-24] Several classical synthetic methods have been reported for synthesis of perimidine derivatives. Different catalysts were used like Lewis or mineral acid [25], cerium ammonium nitrate (CAN) [26], zeolite [27] some ionic liquids. Many of these methods are associated with some limitations and generally need strong acidic conditions, expensive or non-available reagents, prolonged reaction times and high temperatures. Thus, the introduction of new methods and /or further work on technical improvements to overcome these limitations is still needed.

In such consequence we have developed a new protocol for the preparation of perimidines in aqueous media with short times and high yields. In our present work, we unzip our results for preparation of perimidines in aqueous medium under the aspect of environmentally benign process with high yields which is superior to above methods. In

order to avoid the above disadvantages we used the aqueous medium under ultra sound irradiation in presence of NBS to accomplish good results. NBS is trouble-free for work up process which is simply soluble in water medium.

EXPERIMENTAL SECTION

Melting points were determined in open-end capillaries and are uncorrected. Compounds were checked for their purity by TLC on silica gel G plates and spots were located by iodine vapors. The IR spectra were recorded on Perkin-Elmer spectrum RX IFT-IR System using KBr pellets. Elemental analyses of the newly synthesized compounds were carried out on Perkin Elmer model 2400 C H N analyzer. All the compounds gave satisfactory elemental analysis within ±0.4% of theoretical values. Ultra sonication was performed using BANDELIN SONOREX ® (Germany) 4D ultrasound cleaner with a frequency of 50 KHz and an output power of 480 W. The flask was located at the maximum energy area in the cleaner and addition or removal of water was used to control the temperature of the water bath.

All reactions were carried out under argon in oven-dried glassware with magnetic stirring. Unless otherwise noted, all materials were obtained from commercial suppliers and were used without further purification. All solvents were reagent grade. THF was distilled from sodium benzophenone ketyl and degassed thoroughly with dry argon directly before use. Unless otherwise noted, organic extracts were dried with anhydrous Na_2SO_4, filtered through a fritted glass funnel, and concentrated with a rotary evaporator (20–30 Torr). Flash chromatography was performed with silica gel (200–300 mesh) by using the mobile phase indicated. The NMR spectra were measured with a 400 MHz Bruker Avance spectrometer at 400.1 and 100.6 MHz, for ^1H for ^{13}C, respectively, in $CDCl_3$ solution with tetramethylsilane as internal standard. Chemical shifts are given in ppm (δ) and are referenced to the residual proton resonances of the solvents. Proton and carbon magnetic resonance spectra (^1H NMR and ^{13}C NMR) were recorded using tetramethylsilane (TMS) in the solvent of $CDCl_3$-*d* or DMSO-*d*6 as the internal standard (^1H NMR: TMS at 0.00 ppm, $CDCl_3$ at 7.26 ppm ,DMSO at 2.50 ppm; ^{13}C NMR: $CDCl_3$ at 77.16 ppm, DMSO at 40.00 ppm.

General procedure for synthesis of 2-substituted-1H-perimidines:

Sonication Method

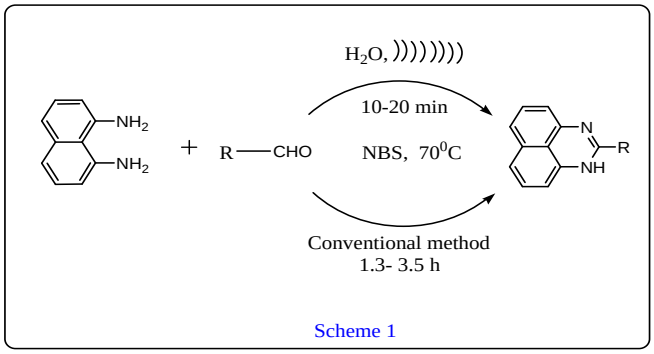
1,8-Napthalene diamine 1 (0.237 g, 0.0015 mol), thiophene-2-carbaldehyde 2 (0.137 mL, 0.0015 mol) were taken in water (10 mL) and irradiated by ultrasound for 3 min at room temparature. After formation of Schiff's base, NBS (0.266 g, 0.0015 mol) is added and raised the temperature to 70^{o}C and irradiated until the completion of starting compounds. The reaction progress was monitored by thin layer chromatography (TLC), ethyl acetate: hexane (3:2). After completion of the reaction, 20% NaOH solution was added and extracted with ethyl acetate. Solvent was removed in a rota-evaporator to afford the title compound, 2-(thiophen-2-yl)-1H-perimidine (3a). The same experimental procedure was adopted for the preparation of the remaining title compounds 3b-j.

Conventional Method

To a stirred solution of 1,8-Napthalene diamine 1 (0.237 g, 0.0015 mol) solution, thiophene-2-carbaldehyde 2 (0.137 mL, 0.0015 mol) was added in water (10 mL) and stirred for 20 min at room temperature to this NBS (0.266 g, 0.0015 mol) is added and raised the temperature to 80^{o}C and refluxed until the completion of starting compounds. The reaction progress was monitored by thin layer chromatography (TLC), ethyl acetate: hexane (3:2). After completion of the reaction, 20% NaOH solution was added and extracted with ethyl acetate. Solvent was removed in a rota- evaporator and was purified by silica gel column chromatography eluting with ethyl acetate: hexane (2:3) mixture to afford the title compound, 2-(thiophen-2-yl)-1H-perimidine (3a). The same experimental procedure was adopted for the preparation of the remaining title compounds 3b-j.

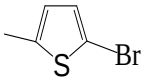
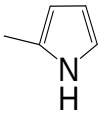
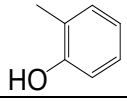
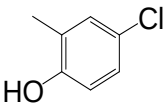
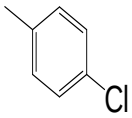
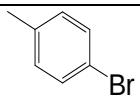
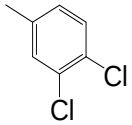
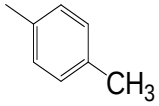
Scheme I:

The synthetic route was depicted in scheme I. The title compounds 3(a-j) were synthesised in single step using sonication and conventional method. the 3(a-j) were obtained in moderate yields (Table-1). The structure were established by spectral (IR, ^1H NMR, ^{13}C NMR and mass) and analytical data.



Scheme 1

Table 1: Synthesis of 2-substituted-1H-perimidines (3a-j)

Entry	-R	Product	Sonication Method	Conventional Method
			Time(min)/ Yield(%)	Time(min)/Yield(%)
1		3a	20/90	2/70
2		3b	15/90	2/75
3		3c	20/92	4/77
4		3d	16/89	2.3/71
5		3e	21/92	3.3/70
6		3f	15/95	4/82
7		3g	14/96	2/78
8		3h	18/94	2.5/73
9		3i	12/93	1.5/80
10		3j	18/88	3.5/73

Spectral data for selected compounds.

2-(thiophen-2-yl)-1H-perimidine (3a) : ^{1}H NMR (400 MHz, DMSO-d6) δ 14.80 (s, br, 1H), 7.97 (dd, J = 8.0 Hz, 1H), 7.45 (d, *J*= 3.7 Hz, 1H), 7.41 (d, J = 7.0 Hz, 1H), 7.26 – 7.11 (m, 3H), 7.13 (d, J = 8.2 Hz, 2H), 6.21 (dd, J = 7.2 Hz, 1H). ^{13}C NMR (126 MHz, DMSO-d6) δ 154.67, 130.7, 126.20, 125.6, 121.4, 118.7, 116.3, 114.9, 112.77.

2-(5-bromothiophen-2-yl)-1H-perimidine (3b): ^{1}H NMR (400 MHz, DMSO-d6) δ 14.80 (s, br, 1H), 7.97 (dd, J = 8.0 Hz, 1H), 7.45 (d, *J*= 3.7 Hz, 1H), 7.41 (d, J = 7.0 Hz, 1H), 7.26 – 7.11 (m, 2H), 7.13 (d, J = 8.2 Hz, 2H), 6.21 (dd, J = 7.2 Hz, 1H). ^{13}C NMR (126 MHz, DMSO-d6) δ 154.67, 131.4, 130.7, 126.20, 125.6, 118.7, 116.3, 114.9, 112.77.

2-(1H-pyrrol-2-yl)-1H-perimidine (3c): ^{1}H NMR (400 MHz, DMSO-d6) δ 14.80 (s, br, 1H), 9.59 (s, br, 1H), 7.97 (dd, J = 8.0 Hz, 1H), 7.41 (d, J = 7.0 Hz, 1H), 7.26 – 7.11 (m, 3H), 7.13 (d, J = 8.2 Hz, 2H), 6.61(m, *J* = 7.2 Hz, 1H), 6.25 (dd, J = 7.2 Hz, 1H). ^{13}C NMR (126 MHz, DMSO-d6) δ 154.67, 135.4, 126.20, 121.4, 118.7, 117.95, 114.9, 112.77, 110.4.

2-(1H-Perimidin-2-yl)Phenol (3d): ^{1}H NMR (400 MHz, DMSO-d6) δ 14.80 (s, br, 1H), 10.72 (s, br, 1H), 7.97 (dd, J = 8.0 Hz, 1H), 7.41 (d, J = 7.0 Hz, 1H), 7.26 – 7.17 (m, 2H), 7.13 (d, J = 8.2 Hz, 2H), 7.01 – 6.87 (m, 2H), 6.70 (dd, J = 7.2 Hz, 2H). ^{13} C NMR (126 MHz, DMSO-d6) δ 161.11, 154.67, 134.77, 133.29, 126.20, 120.98, 117.95, 112.77.

4-chloro-2-(1H-Perimidin-2-yl)Phenol (3e): 92% yield. Dark yellow solid. ^{1}H NMR (400 MHz, DMSO-d6) δ 14.80 (s, br, 1H), 10.72 (s, br, 1H), 7.97 (dd, J = 8.0 Hz, 1H), 7.41 (d, J = 7.0 Hz, 1H), 7.26 – 7.17 (m, 2H), 7.13 (d, J = 8.2 Hz, 2H), 7.01 – 6.87 (m, 2H), 6.70 (dd, J = 7.2 Hz, 1H). ^{13}C NMR (126 MHz, DMSO-d6) δ 153.67, 136.27, 133.29, 133.8, 126.20, 120.98, 117.95, 112.77.

2-phenyl-1H-Perimidine (3f): 95% yield. Dark reddish solid. ^{1}H NMR (400 MHz, DMSO-d6) δ 14.80 (s, br, 1H), 7.97 (dd, J = 8.0 Hz, 1H), 7.41 (d, J = 7.0 Hz, 1H), 7.26 – 7.17 (m, 2H), 7.13 (d, J = 8.2 Hz, 2H), 7.01 – 6.87 (m, 3H), 6.70 (dd, J = 7.2 Hz, 2H). ^{13} C NMR (126 MHz, DMSO-d6) δ 154.67, 135.29, 133.29, 126.20, 120.98, 118.4, 117.95, 112.77.

2-(4-chlorophenyl)-1H-Perimidine (3g): 96% yield. Dark reddish solid. ^{1}H NMR (400 MHz, DMSO-d6) δ 14.80 (s, br, 1H), 7.97 (dd, J = 8.0 Hz, 1H), 7.41 (dd, J = 8.0 Hz, 2H), 7.26 – 7.17 (m, 2H), 7.13 (d, J = 8.2 Hz, 2H), 7.01 – 6.87 (m, 2H), 6.70 (dd, J = 7.2 Hz, 1H). ^{13} C NMR (126 MHz, DMSO-d6) δ 154.67, 134.77, 133.8, 133.29, 126.20, 120.98, 117.95, 112.77.

2-(4-Bromophenyl)-1H-Perimidine (3h): 94% yield. reddish solid. ^{1}H NMR (400 MHz, DMSO-d6) δ 14.80 (s, br, 1H), 7.97 (dd, J = 8.0 Hz, 1H), 7.41 (dd, J = 7.0 Hz, 2H), 7.26 – 7.17 (m, 2H), 7.13 (d, J = 8.2 Hz, 2H), 7.01 – 6.87 (m, 2H), 6.70 (dd, J = 7.2 Hz, 1H). ^{13}C NMR (126 MHz, DMSO-d6) δ 153.67, 136.27, 133.29, 126.20, 123.1, 120.98, 117.95, 112.77.

2-(3,4-dichlorophenyl)-1H-Perimidine (3i): 93% yield. yellow solid. ^{1}H NMR (400 MHz, DMSO-d6) δ 14.80 (s, br, 1H), 7.97 (dd, J = 8.0 Hz, 1H), 7.41 (d, J = 7.0 Hz, 1H), 7.26 – 7.17 (m, 2H), 7.13 (d, J = 8.2 Hz, 2H), 7.01 – 6.87 (m, 2H), 6.70 (dd, J = 7.2 Hz, 1H). ^{13}C NMR (126 MHz, DMSO-d6) δ 153.67, 136.27, 133.29, 131.8, 126.20, 120.98, 117.95, 112.77.

2-(4-Methylphenyl)-1H-Perimidine (3j): 92% yield. White solid. ^{1}H NMR (400 MHz, DMSO-d6) δ 14.80 (s, br, 1H), 7.97 (dd, J = 8.0 Hz, 1H), 7.41 (dd, J = 7.0 Hz, 2H), 7.26 – 7.17 (m, 2H), 7.13 (d, J = 8.2 Hz, 2H), 7.01 – 6.87 (m, 2H), 6.70 (dd, J = 7.2 Hz, 1H), 2.50 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d6) δ 153.67, 136.27, 133.29, 126.20, 120.98, 117.95, 112.77, 21.54.

Biological screening

Antibacterial activity

The antibacterial activity of synthesized compounds was studied by the disc diffusion method against the following pathogenic organisms. The gram-positive bacterial screened were Staphylococcus aureus NCCS 2079 (SA) and Bacillus cereus NCCS 2106 (BC). The gram negative bacterial screened were Escherichia coli NCCS 2065 (EC) and Pseudomonas aeruginosa NCCS 2200 (PA). The synthesized compounds were used at the concentration of 250 µg/ml and 500 µg/ml using DMSO as a solvent. The amoxicillin 10 µg/disc and Streptomycin 30 µg/disc were used as a standard (Himedia laboratories limited, Mumbai).

Disc Diffusion Method

A suspension of Staphylococcus aureus (SA) was added to sterile nutrient agar at 45ºC. The mixture was transferred to sterile petridishes to give a depth of 3 to 4 mm and allowed to solidify. Precautions were observed to reduce uniform layer of medium on the plate. Sterile discs 5mm in diameter (made from Whatman Filter paper) were immersed in the solutions of synthesized compounds (250µg/ml) and maintain an untreated control sample for comparison. Leave the plates to stand for 1hour at room temperature as a period of preincubation diffusion to

minimize the effects of variations in different time. Then the plates were incubated at 37ºC for 24 hours and observed for antibacterial activity. The diameter of the zone of inhibition was measured for each plate in which zone of inhibition was observed. The average zone of inhibition was calculated and compared with that of standard. A similar procedure was adopted for studying the antibacterial activity against other organisms.

Antifungal activity

The antifungal activity of synthesized compounds were studied by disc diffusion method against the organisms of Aspergillus nigeri NCCS 1196 (AN) and Candida albicans NCCS 3471(CA) Compounds were treated at the concentrations of 250 µg/ml using DMSO as a solvent. The standard used was Ketaconazole 50 µg/ml and Griseofulvin 50 µg/ml against both the organisms.

Disc Diffusion Method

A suspension of Aspergills nigeri NCCS 1196 (AN) was added to a sterile sabouraud dextrose agar at 45ºC. The mixture was transferred to sterile petridishes and allowed to solidify. Sterile discs 5 mm in diameter (made from Whatmann Filter paper) immersed in the solutions of synthesized comopounds and control were placed on the surface of agar medium with forceps and pressed gently to ensure even contact. Leave the plates to stand for 1 hour at room temperature as a period of preincubation diffusion to minimize the effects of variation at 37ºC for 13 hours and observed for antibacterial activity. The diameters of the zone of inhibition were measured for the plates in which the zone of inhibition was observed. The average zone of inhibition was calculated with that of standard. The perimidine derivatives containing –Cl (3g) and -Br atom (3h) showed more activity than other substituent's.

Table 2. Antibacterial activity and antifungal activity of synthesized compounds 3(a-h)

Compound No	Zone of inhibition in mm					
	Antibacterial activity			Antifungal activity		
	S.aureus	***E.coli***	***P.aeruginosa***	***C. albicans***	***A. flavus***	***A.fumigatus***
3a	20	17	18	10	9	10
3b	22	20	21	10	9	10
3c	21	18	19	10	9	10
3d	19	17	17	11	10	11
3e	22	20	21	10	8	9
3f	21	19	20	9	7	8
3g	24	22	23	12	10	11
3h	23	21	22	11	9	10
Ampicillin	20	21	22	21	-	-
Flucanazole	22	20	23	22	-	--

RESULTS AND DISCUSSION

In continuation of our work to develop new and eco-friendly synthetic methodologies, we herein report an efficient, green and facile protocol for the synthesis of 2-substituted-1H-perimidines (3a-j) catalyzed by NBS under ultrasound irradiation at 70°C in 13-25 min (Scheme 1) and also conventional method. Among these two methods Sonication was found to be better method giving high yields in less reaction time. Ultra sound will increase the collisions between the molecules and causes to form radicals very fast. So the rate of the reaction was increased. Here the solvent is water which is very effective solvent facilitate access to different reactivity and selectivity patterns and is also gracious to environment.

By using various aldehydes we had found that, aldehydes having electron withdrawing group at ortho and para positions (2g, 2h & 2i) will undergo fast reaction and gives the high yields when compared with the meta position (2e & 2g) and electron donating groups (2d & 2j). Due to the presence of withdrawing group at ortho or para positions of aldehyde, the attraction of radical electron from oxygen and the removal of hydrogen radical were took place easily.

Biological Activity screening:

The results of biological studies of newly synthesized compounds reveal that the compounds possess significant anti-bacterial and anti-fungal activities. The results of these studies are given in Table 2.

CONCLUSION

It can be concluded that the ultrasonication method is an efficient, fast, avoiding the use of harmful solvents, cleaner reactions, easy work up, simple and environment friendly method for the synthesis of 2-substituted-1H-Perimidine. Performing organic reactions in water is safe, nontoxic, environmentally friendly, and cheap. Compared with

traditional methods, the applied methods are more convenient and reactions can be carried out in higher yield, shorter reaction time and milder conditions, without generation of pollution.

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REFERENCES

[1]. Eicher, T.; Hauptmann, S. The Chemistry of Heterocycles, 2nd ed.; Wiley-VCH: Weinheim, **2003**.
[2]. Suresh, M.; Jonnalagadda, S. B.; Rao, C. V. *Oriental. J. Chem*. **2011**, 27, 127.
[3]. Suresh, M.; Lavanya, P.; Rao, C. V. *Arabian. J. Chem*. **2011**. DOI: 10.1016/j.arabjc.2011.02.004.
[4]. N.M. Starshikoy, F.T. Pozharskii, *Chemistry of Heterocyclic Compounds*.,**1975**, 9, 922
[5]. F.T. Pozharskii, V.V. Dalnikovskaya, *Russ. Chem. Rev*., **1981**, 50, 816.
[6]. X. Bu, L.W. Deady, G.J. Finlay, B.C. Baguley, W.A. Denny, *J. Med. Chem*., **2001**, 44, 2004.
[7]. K.Undheim, T. Benneche, Comprehensive Heteocyclic Chemistry, A.R.Katritzky, C.W. Ress, E.F.V. Scriven, Pergamon Oxford, Vol 6, **1996**.
[8]. D.P. Panchasara, S. Pande, *E-J. Chem*., **2009**, 6, 91.
[9].. El-Gazzar, A. R. B. A.; Hafez, H. N. *Acta Chim. Slov*. **2008**, 55, 359.
[10]. Regnier, G.; Canevar, L.; Le, R. J.; Douarec, J. C.; Hal- stop, S.; Daussy, J. *J. Med. Chem.* **1972**, 15, 295.
[11]. Winter, C. A.; Fisley, E. A. R.; Nuss, G. W. *Proc. Soc. Exp. Biol. Med*. **1962**, 111, 544.
[12]. Suguira, K.; Schmid, A. F.; Schmid, M. M.; Brown, F. G. *Cancer Chemother. Rep. Part***. 1973**, 23(1), 231.
[13]. Mojtahedi, M. M.; Saidi, M. R.; Shirzi, J. S.; Bolourtch- ian, M. *Syn. Commun.* **2002**, 32, 851.
[14]. John M. Herbert, Paul D. Woodgate, and William A. Denny**,** *J. Med. Chem*. **1987**, 30, 2081-2086.
[15]. A. Mobinikhaledi, M.A. Amrollahi, N. Foroughifar, H. Fathinejad, *Asian. J. Chem.*, **2005**, 17, 2411 .
[16]. I. Yavari, I. M. Adib, F. Jahani-moghaddam, H.R. Bijanzadeh, *Tetrahedron*., **2002**, 58, 6901.
[17]. Mobinikhaledi, A.; Moghanian, H.; and Sasani, F. *Inter. Journal. Green Nanotechn: Physics and Chemistry*, **2010**, 2, 47.
[18]. J.B. Hendrickson, M.S. Hussoin, *J. Org. Chem*., **1987**, 52, 4137.
[19]. L.W. Deady, T. Rodemann, *J. Heterocyclic. Chem.*, **1998**, 35, 1417.
[20]. U.T. Mueller-Westerhoff, S. Vance, DI. Yoon, *Tetrahedron*, **1991**, 47, 909.
[21]. A. Mobinikhaledi, N. Foroughifar, R. Goli, *Phosphorus, Sulfur& Silicon*., **2005**, 180, 2549.
[22]. A. Mobinikhaledi, N. Foroughifar, N. Basaki, *Turk. J. Chem*. **2009**, 33, 1.
[23]. a) Mobinikhaledi, A.; and J. Stell, P. *Synth.Reac. Inorg. M*., **2009**, 39, 13.
b) Bulg. *Chem. Commun*. **2012**, 44, 122.
[24]. Song-Lin, Z., Jun-Min, Z., *Chinese J. Chem*., **2008**, 26, 185.
[25] Mobinikhaledi, A.; Foroughifar, N.; Goli, R. *Phosphorus,Sulfur Silicon Relat. Elem*. **2005**, 180, 2549–2554.
[26]. A. Shaabani, A. Maleki, *Chem. Pharm. Bull*. **2008**, 56, 79-81.
[27]. A. Mobinikhaledi, N. Foroughifar, N. Basaki, *Turk J Chem*, **2009**, 33, 555–560.