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# A facile synthesis of phenazine and quinoxaline derivatives using magnesium sulfate heptahydrate as a catalyst

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*Abstract*: Convenient and simple procedures for the synthesis of phenazine and quinoxaline derivatives were developed *via* a reaction of *o*-phenylenediamines and 1,2-dicarbonyl compounds. In addition, the synthesis of two new 1,4-benzodiazine derivatives and the catalytic activity of magnesium sulfate heptahydrate ($MgSO_4 \cdot 7H_2O$) in the room temperature condensation of *o*-phenylenediamines and 1,2-dicarbonyl compounds in ethanol as solvent are reported. This method has many appealing attributes, such as excellent yields, short reaction times, and simple work-up procedures.

*Keywords*: phenazine; quinoxaline; magnesium sulfate heptahydrate; catalyst.

## INTRODUCTION

Nitrogen-containing heterocycles, which exhibit extensive biological properties, are abundant in natural compounds.[1] Phenazines and quinoxalines are important classes of benzoheterocycles, which have significance in both chemistry and biology.[2]

Many phenazine compounds, which are produced by bacteria such as *Pseudomonas* spp., *Streptomyces* spp. and *Pantoea agglomerans*, are found in nature These natural phenazine products have been implicated in the virulence and competitive fitness of the producing organisms.[3,4] Quinoxaline and phenazine derivatives constitute the basis of some antitumor agents,[5] bactericides,[6] fungicides,[7] herbicides,[8] and insecticides (*e.g.*, quinalphos).[9] In addition, they are used in dyes,[10] building blocks for the synthesis of organic semiconductors,[11] chemically controllable switches,[12] cavitands,[13] DNA cleaving agents,[14] dehydroannulenes,[15] and electrical-photochemical materials.[16–18]

A number of synthetic strategies have been developed for the preparation of substituted quinoxalines.[19] Many of the existing methods, however, suffer from

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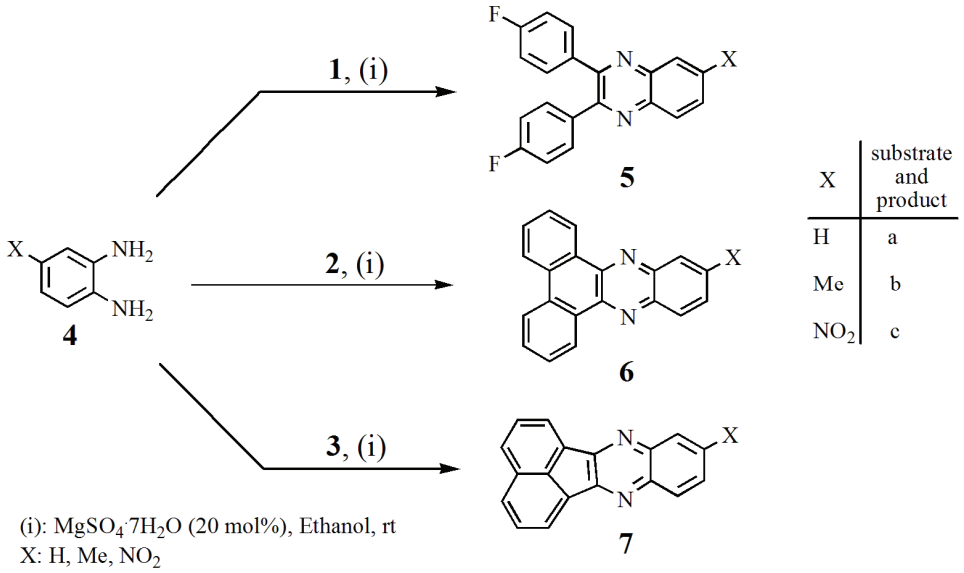
disadvantages such as unsatisfactory product yields, harsh conditions, long reactions times, and critical product isolation procedures.

In recent years, heterogeneous catalysts have gained importance because of enviro-economic reasons. They have successfully been utilized in several organic transformations in order to minimize undesirable wastes which could pollute the environment.

Recently, the use of magnesium sulfate as an efficient and very cheap reagent for the preparation of bis(indolyl)methanes was reported.[20]

## RESULTS AND DISCUSSION

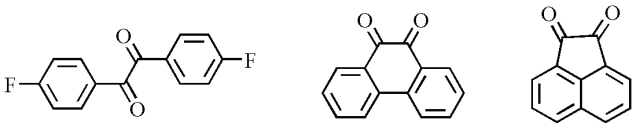
In connection with studies on the synthesis of organic compounds,[21] it was now found that magnesium sulfate heptahydrate ($MgSO_4 \cdot 7H_2O$) can be used as an efficient, safe and very cheap catalyst for the condensation of 1,2-dicarbonyl compounds **1**–**3** and *o*-phenylenediamine (**4**) at room temperature to afford phenazine and quinoxaline derivatives **5**–**9** in excellent yields (Scheme 1).




Scheme 1. The synthesis of quinoxaline and phenazine derivatives using $MgSO_4 \cdot 7H_2O$ as a catalyst.

In this work, 4,4'-difluorobenzil (**1**), 9,10-phenanthrenequinone (**2**) and acenaphthoquinone (**3**) were used as the 1,2-dicarbonyl compounds (Fig. 1).

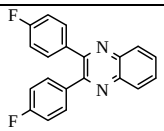
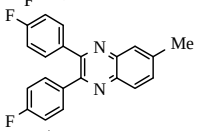
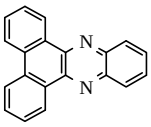
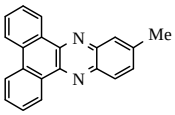
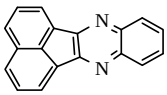
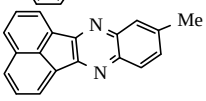
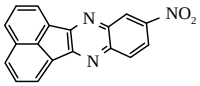
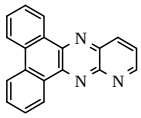
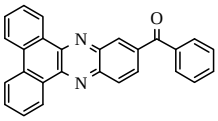
To determine simple and suitable conditions for the preparation of quinoxaline and phenazine derivatives using $MgSO_4 \cdot 7H_2O$ as the Lewis acid catalyst, the treatment of 4,4'-difluoro-benzil (**1**) with *o*-phenylenediamine (**4a**) was chosen as the model reaction (Table I, Entry **5a**).



**1** **2** **3**

Fig. 1. 1,2-Dicarbonyl compounds.

TABLE I. Synthesis of phenazine and quinoxaline derivatives using 20 mol % $MgSO_4 \cdot 7H_2O$

| Entry | Product[a] | Time, min | Yield[b], % | M.p., °C (found (lit.)) |
|---|---|---|---|---|
| **5a** |  | 30 | 95 | 134–136 (135–137)[22] |
| **5b** |  | 35 | 95 | 163–165 (165–167)[22] |
| **6a** |  | 15 | 90 | 224–226 (223–225)[23] |
| **6b** |  | 15 | 92 | 217–219 (208–210)[23] |
| **7a** |  | 20 | 90 | 237–239 (238–240)[23] |
| **7b** |  | 20 | 93 | 230–232 (>300)[23] |
| **7c** |  | 90 | 85 | 320 (>300)[24] |
| **8** |  | 50 | 77 | 225–227 |
| **9** |  | 10 | 98 | 246–248 |

[a]Identified by comparison with authentic samples; [b]refers to isolated yields

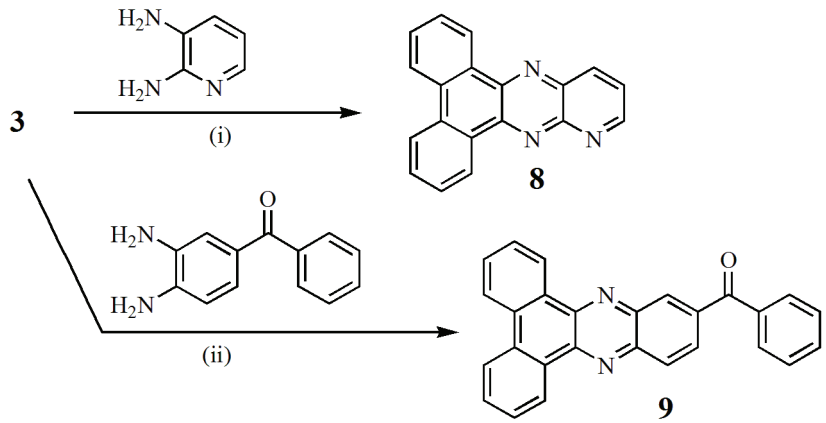
It was observed that the condensation reaction can be efficiently realized in ethanol as solvent by the addition of 20 mol % of the catalyst in a short time span

of 30 min. The use of excess amounts of the catalyst did not have a marked influence on the product yield. The probable reason for this is the coordination of excessive catalyst to the diamine.

In order to prove the general applicability of this method, after optimizing the reaction conditions, different 1,2-dicarbonyl compounds were treated with *o*-phenylenediamines at room temperature in ethanol. The results are presented in Table I.

Although the generally mechanistic details of this reaction are not yet fully understood, a feasible pathway might involve the complexation of magnesium with the dicarbonyl, thereby acting as a Lewis acid, and also playing a complex role in promoting the dehydration steps.

In other variations, with the aim of synthesizing products which have not hitherto been reported, it was found that 1,2-pyridinediamine underwent condensation with compound **2** to produce dibenzo[*f*,*h*]pyrido[2,3-*b*]quinoxaline (**8**) in 77 % yield (Scheme 2); in a similar way, condensation of 3,4-benzophenonediamine with compound **2** produced dibenzo[*a*,*c*]phenazine-11-ylphenylmethanone (**9**) (Scheme 2).




(i): $MgSO_4 \cdot 7H_2O$ , 20 mol % Ethanol, reflux
(ii): $MgSO_4 \cdot 7H_2O$ (20 mol%), Ethanol, rt

Scheme 2. Synthesis of new 1,4-benzodiazines using $MgSO_4 \cdot 7H_2O$ as a catalyst.

All products were characterized by their spectral and physical data, which, when available, were compared with those reported in the literature.[22–25]

*2,3-Bis(4-fluorophenyl)quinoxaline (**5a**)*. Yield: 95 %; m.p. 134–136 °C. IR (KBr, $cm^{-1}$): 3061, 1599, 1555, 1511, 1344, 1225, 839, 786. $^1$H-NMR (400 MHz, $CDC1_3$, $\delta$ / ppm): 7.97 (2H, *dd*, *J* = 6.4 Hz, 3.6 Hz), 7.60 (2H, *dd*, *J* = 6.4 Hz, 3.2 Hz), 7.30–7.33 (4H, *m*), 6.86 (4H, *t*, *J* = 8.8 Hz). $^{13}$C-NMR (100 MHz,

$CDC1_3$, $\delta$ / ppm): 161.99, 152.20, 141.23, 135.02, 131.82, 131.74, 130.23, 129.16, 115.65, 115.43.

*2,3-Bis(4-fluorophenyl)-6-methylquinoxaline (**5b**)*. Yield: 95 %; m.p. 163––165 °C. IR (KBr, $cm^{-1}$): 2925, 2580, 1657, 1597, 1264, 1159, 833, 696. $^1$H--NMR (400 MHz, $CDC1_3$, $\delta$ / ppm): 6.58 (4H, *t*, *J* = 8.8 Hz), 2.43 (3H, *s*), 7.85 (1H, *d*, *J* = 8.8 Hz), 7.73 (1H, *s*), 7.42 (1H, *d*, *J* = 8.8 Hz), 7.30 (4H, *dd*, *J* = 8.0 Hz, 5.2 Hz). $^{13}$C-NMR (100 MHz, $CDC1_3$, $\delta$ / ppm): 161.89, 152.05, 151.29, 141.28, 140.84, 139.69, 135.16, 135.13, 132.59, 131.77, 131.72, 131.69, 128.65, 127.96, 115.59, 115.37, 21.94.

*Dibenzo[*a,c*]phenazine (**6a**)*. Yield: 90 %; m.p. 224–226 °C. IR (KBr, $cm^{-1}$): 3055, 1600, 1490, 1350, 760, 720. $^1$H-NMR (400 MHz, $CDC1_3$, $\delta$ / ppm): 9.18 (2H, *d*, *J* = 7.6 Hz), 8.34 (2H, *d*, *J* = 8.0 Hz), 8.12 (2H, *dd*, *J* = 6.4, 3.6 Hz), 7.51––7.66 (6H, *m*). $^{13}$C-NMR (100 MHz, $CDC1_3$, $\delta$ / ppm): 143.54, 143.28, 133.15, 131.42, 130.88, 130.57, 129.04, 127.38, 124.03.

*11-Methyldibenzo[*a,c*]phenazine (**6b**)*. Yield: 92 %; m.p. 217–219 °C. IR (KBr, $cm^{-1}$): 3055, 2910, 1620, 1500, 1350, 760, 720. $^1$H-NMR (400 MHz, $CDC1_3$, $\delta$ / ppm): 9.14 (2H, *dd*, *J* = 6.0 Hz, 1.6 Hz), 8.32 (2H, *d*, *J* = 8.0 Hz), 7.97 (1H, *d*, *J* = 8.4 Hz), 7.58 (1H, *s*), 7.52–7.53 (5H, *m*), 2.54 (3H, *s*). $^{13}$C-NMR (100 MHz, $CDC1_3$, $\delta$ / ppm): 143.29, 143.27, 142.72, 141.81, 141.41, 133.45, 133.06, 132.87, 131.49, 131.45, 131.20, 131.07, 130.01, 129.10, 128.92, 127.29, 127.15, 123.95, 23.20.

*Acenaphtho[1,2-*b*]quinoxaline (**7a**)*. Yield: 90 %; m.p. 237–239 °C. IR (KBr, $cm^{-1}$): 3050, 1610, 1430, 1300, 830, 760. $^1$H-NMR (400 MHz, $CDC1_3$, $\delta$ / / ppm): 8.21 (2H, *d*, *J* = 6.8 Hz), 8.02 (2H, *dd*, *J* = 6.2 Hz, 3.2 Hz), 7.90 (2H, *d*, *J* = 8.4 Hz), 7.65 (2H, *t*, *J* = 7.0 Hz), 7.57 (2H, *dd*, *J* = 6.4 Hz, 3.6 Hz). $^{13}$C-NMR (100 MHz, $CDC1_3$, $\delta$ / ppm): 155.19, 142.39, 137.60, 132.92, 131.10, 130.47, 130.59, 130.36, 129.78, 122.96.

*9-Methylacenaphtho[1,2-*b*]quinoxaline (**7b**)*. Yield: 93 %; m.p. 230–232 °C. IR (KBr, $cm^{-1}$): 3055, 2910, 1610, 1415, 1300, 810, 790. $^1$H-NMR (400 MHz, $CDC1_3$, $\delta$ / ppm): 8.21 (2H, *t*, *J* = 6.4 Hz), 7.90 (3H, *dd*, *J* = 8.2 Hz, 3.2 Hz), 7.79 (1H, *s*), 7.64 (2H, *t*, *J* = 7.4 Hz), 7.40 (1H, *dd*, *J* = 8.4 Hz, 1.6 Hz), 2.43 (3H, *s*). $^{13}$C-NMR (100 MHz, $CDC1_3$, $\delta$ / ppm): 155.15, 154.44, 142.38, 140.82, 140.71, 137.35, 133.08, 132.44, 131.06, 130.46, 130.31, 130.21, 129.89, 129.72, 122.83, 122.68, 22.94.

*9-Nitroacenaphtho[1,2-*b*]quinoxaline (**7c**)*. Yield: 85 %; m.p. >300 °C. IR (KBr, $cm^{-1}$): 3090, 1580, 1540, 1340, 1060, 680, 720. $^1$H-NMR (400 MHz, $CDC1_3$, $\delta$ / ppm): 8.97 (1H, *d*, *J* = 2.2 Hz), 8.51–8.53 (3H, *m*), 8.40 (3H, *m*), 8.00 (2H, *t*, *J* = 8.0 Hz).

*Dibenzo[*f,h*]pyrido[2,3-*b*]quinoxaline (**8**)*. Yield: 70 %; m.p. 225–227 °C; Anal. Calcd. for $C_{19}H_{11}N_3$: C, 81.12; H, 3.94; N, 14.94 %. Found: C, 81.68, H, 3.953, N, 15.00 %. IR (KBr, $cm^{-1}$): 3056, 1566, 1525, 1384, 1220, 1161, 837.

$^1$H-NMR (400 MHz, $CDC1_3$, $\delta$ / ppm): 9.35 (1H, *d*, *J* = 7.6 Hz), 9.04–9.15 (2H, *m*), 8.48 (1H, *d*, *J* = 8.0 Hz), 8.36 (2H, *d*, *J* = 8.4 Hz), 7.53–7.66 (5H, *m*). $^{13}$C-NMR (100 MHz, $CDC1_3$, $\delta$ / ppm): 155.65, 150.92, 146.09, 144.70, 139.50, 138.45, 133.60, 133.38, 132.30, 131.99, 130.82, 130.60, 129.28, 129.16, 128.46, 127.58, 126.02, 124.12, 123.98. MS (*m*/*z*): 281.03, 280.04, 255.05, 175.99, 140, 86.90.

*Dibenzo[*a,c*]phenazine-11-ylphenylmethanone (**9**)*. Yield: 96 %; m.p. 246––248 °C; Anal. Calcd. for $C_{27}H_{16}N_2O$: C, 84.36; H, 4.20; N, 7.29 %. Found: C, 84.48, H, 4.183, N, 7.375 %. IR (KBr, $cm^{-1}$): 3050, 1650, 1600, 1445, 1320. $^1$H-NMR (400 MHz $CDC1_3$, $\delta$ / ppm): 9.43 (1H, *dd*, *J* = 8.0 Hz, 1.2 Hz), 9.35 (1H, *dd*, *J* = 8.0 Hz, 1.2 Hz), 8.70 (1H, *d*, *J* = 1.6 Hz), 8.58 (2H, *d*, *J* = 8.0 Hz), 8.44 (1H, *d*, *J* = 8.8 Hz), 8.55 (1H, *dd*, *J* = 8.8 Hz, 2.0 Hz), 7.97–7.99 (2H, *m*), 7.68––7.87 (5H, *m*), 7.60 (2H, *t*, *J* = 8.0 Hz). $^{13}$C-NMR (400 MHz, $CDC1_3$, $\delta$ / ppm): 196.00, 184.81, 153.70, 143.74, 143.45, 141.05, 137.92, 137.38, 132.95, 132.84, 132.48, 132.18, 130.99, 130.75, 130.23, 129.94, 129.40, 128.58, 128.12, 126.69, 126.36, 123.01; MS (*m*/*z*): 384.13, 307.06, 279.02, 104.88, 76.91.

## EXPERIMENTAL

### *General*

The commercial starting materials were purchased from Merck, Fluka and Aldrich. The reactions were monitored by TLC (silica-gel 60 $F_{254}$, *n*-hexane:ethyl acetate). The IR spectra were recorded on a FTIR Shimadzu-470 spectrometer and the $^1$H-NMR spectra were obtained on a Bruker-Instrument DPX-400 and 500 MHz Avance 2 model. Mass spectra were recorded on an AMD 604 spectrometer in the EI-mode at 70 eV and FT-mode at 0.005 V. A Vario-El CHN instrument at the Isfahan Industrial University was used for the elemental analyses.

### *General procedure*

A mixture of 1,2-dicarbonyl compound (1 mmol), *o*-phenylenediamine (1.1 mmol) and magnesium sulfate heptahydrate (20 mol %) in ethanol (5 mL) was stirred at room temperature (except for entry **8** when reflux conditions were employed). The progress of the reaction was monitored by TLC. After completion of the reaction, the solid which separated was filtered and then recrystallized from ethanol to afford the pure product.

## CONCLUSIONS

In summary, a new application of magnesium sulfate heptahydrate ($MgSO_4{\cdot}7H_2O$) as an effective, very cheap and non-toxic catalyst for the synthesis of many phenazines and quinoxalines, based on the condensation of 1,2-dicarbonyl compounds with *o*-phenylenediamines under mild reaction conditions, is presented. The most important point in this work is that new derivatives of phenazine and quinoxaline were also synthesized. This method is significant from an environmental viewpoint and economic considerations because it produces little waste.

The availability and stability of the catalyst, the simple work-up procedure and the high yields of products in short reaction times under mild reaction conditions make this method a valid contribution to the existing methodologies.

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И З В О Д

## ЈЕДНОСТАВНА СИНТЕЗА ДЕРИВАТА ФЕНАЗИНА И КИНОКСАЛИНА (НОВИХ 1,4-БЕНЗОДИАЗИНА) ПОМОЋУ МАГНЕЗИЈУМ-СУЛФАТА ХЕПТАХИДРАТА

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Развијен је једноставан поступак за синтезу деривата феназина и хиноксалина, реакцијом *о*-фенилендиамина и 1,2-дикарбонилних једињења. Синтетисана су два нова деривата 1,4-бензодиазина и описана је каталитичка активност магнезијум-сулфата хептахидрата ($MgSO_4 \cdot 7H_2O$) у рекцији кондензације деривата *о*-фенилендиамина и 1,2-дикарбонилних једињења у етанолу на собној температури. Описани поступак има доста погодности, као што је одличан принос, кратко реакционо време и једноставна обрада реакционе смеше.

(Примљено 1. августа, ревидирано 29.новембра 2010)

## REFERENCES

1. a) A. E. A. Porter, in *Comprehensive Heterocyclic Chemistry: the Structure, Reactions, Synthesis and Uses of Heterocyclic Compounds*, A. R. Katritzky, C. W. Rees, Eds., Pergamon Press, Oxford, U.K., 1984, p. 157; b) N. Sato, in *Comprehensive Heterocyclic Chemistry II*, Vol. 6, A. R. Katritzky, C. W. Rees, E. F. V. Scriven, Eds., Pergamon Press, Oxford, UK, 1996, p. 233
2. a) W. Zhu, M. Dai, Y. Xu, X. Qian, *Bioorg. Med. Chem.* **16** (2008) 3255; b) M. M. F. Ismail, Y. A. Ammar, M. K. H. Ibrahim, S. A. Elzahaby, S. S. Mahmoud, *Arzneim.-Forsch.* **55** (2006) 738; c) X. Hui, J. Desrivot, C. Bories, P. M. Loiseau, X. Franck, R. Hocquemiller, B. Figadere, *Bioorg. Med. Chem. Lett.* **16** (2006) 815; d) S. A. Kotharkar, D. B. J. Shinde, *J. Iran. Chem. Soc.* **3** (2006) 267
3. J. M. Turner, A. J. Messenger, *Adv. Microb. Physiol.* **27** (1986) 211
4. M. McDonald, D. V. Mavrodi, *J. Am. Chem. Soc.* **38** (2001) 9459
5. a) S. Nakaike, T. Yamagishi, K. Samata, K. Nishida, K. Inazuki, T. Ichihara, Y. Migita, S. Otomo, H. Aihara, S. Tsukagoshi, *Cancer Chemother. Pharmacol.* **23** (1989) 135; b) P. Corona, A. Carta, M. Loriga, G. Vitale, G. Paglietti, *Eur. J. Med. Chem.* **44** (2009) 1579
6. a) M. L. Edwards, R. E. Bambury, H. K. Kim, *J. Heterocycl. Chem.* **13** (1976) 653; b) J. P. Dirlam, J. E. Presslitz, B. J. Williams, *J. Med. Chem.* **26** (1983) 1122
7. a) M. Patel, V. Hegde, A. C. Horan, V. P. Gullo, D. Loebenberg, J. A. Marquez, G. H. Miller, M. S. Puar, J. A. Waitz, *J. Antibiot. (Tokyo)* **37** (1984) 943; b) G. A. Carter, T. Clark, C. S. James, R. S. T. Loeffler, *Pest. Manag. Sci.* **14** (1983) 135
8. I. Starke, G. Sarodnick, V. V. Ovcharenko, K. Pihlaja, E. Kleinpeter, *Tetrahedron* **60** (2004) 6063
9. a) B. Cross, C. L. Dunn, D. H. Payne, J. D. Tipton, *J. Sci. Food. Agr.* **20** (1969) 340; b) P. Menon, M. Gopal, R. Prasad, *J. Agric. Food. Chem.* **52** (2004) 7370

10. a) A. Katoh, T. Yoshida, J. Ohkanda, *J. Heterocycles* **52** (2000) 911; b) D. M. Geller, *J. Biol. Chem*. **224** (1969) 971
11. S. Dailey, W. J. Feast, R. J. Peace, I. C. Sage, S. Till, E. L. Wood, *J. Mater. Chem*. **11** (2001) 2238
12. M. J. Crossley, L. A. Johnston, *Chem. Commun*. (2002) 1122
13. J. L. Sessler, H. Maeda, T. Mizuno, V. M. Lynch, H. Furuta, *J. Am. Chem. Soc*. **124** (2002) 13474
14. T. Yamaguchi, S. Matsumoto, K. Watanabe, *Tetrahedron Lett.* **39** (1998) 8311
15. O. Sascha, F. Rudiger, *Synlett* (2004) 1509
16. T. Yamamoto, K. Sugiyama, T. Kushida, T. Inoue, T. Kanbara, *J. Am. Chem. Soc*. **118** (1996) 3930
17. I. Nurulla, I. Yamaguchi, T. Yamamoto, *Polym. Bull*. **44** (2000) 231
18. T. Yamamoto, B. L. Lee, H. Kokubo, H. Kishida, K. Hirota, T. Wakabayashi, H. Okamoto, *Macromol. Rapid Commun.* **24** (2003) 440
19. D. J. Brown, in: *Quinoxalines: Supplement II, in The Chemistry of Heterocyclic Compounds*, E. C. Taylor, P. Wipf, Eds., Wiley, New Jersey, USA, 2004
20. A. Hasaninejad, A. Parhami Zare, A. A. Khalafi-Nezhad, A. Nasrolahi Shirazi, A. R. Moosavi Zare, *Pol. J. Chem*. **82** (2008) 565
21. a) B. Karami, J. A. Damavandi, M. Bayat, M. Montazerozohori, *J. Serb. Chem. Soc*. **71** (2006) 27; b) B. Karami, M. Montazerozohori, M. H. Habibi, *Bull. Korean Chem. Soc*. **26** (2005) 1125; c) B. Karami, M. Montazerozohori, G. Karimipour, M. H. Habibi, *Bull. Korean Chem. Soc*. **26** (2005) 1431; d) B. Karami, M. Montazerozohori, M. H. Habibi, M. A. Zolfigol, *Heterocyclic Commun*. **11** (2005) 513; e) B. Karami, M. Montazerozohori, M. H. Habibi, *Phosphorus Sulfur Silicon Relat. Elem*. **181** (2006) 2825; f) M. Montazerozohori, B. Karami, *Helv. Chim. Acta* **89** (2006) 2922; g) M. Montazerozohori, B. Karami, M. Aziz, *Arkivoc* (2007) 99; h) B. Karami, M. Montazerozohori, *Molecules* **11** (2006) 720
22. M. M. Heravi, M. H. Tehrani, K. Bakhtiari, N. M. Javadi, H. A. Oskooie, *Arkivoc* (2006) 16
23. K. Niknam, D. Saberi, M. Mohagheghnejad, *Molecules* **14** (2009) 1915
24. K. Niknam, M. A. Zolfigol, Z. Tavakoli, Z. J. Heydari, *J. Chin. Chem. Soc*. **55** (2008) 1373.