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The preparation of quinoxaline and 2,3-dihydropyrazine derivatives using selectfluor as an efficient and reusable catalyst

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Abstract

Selectfluor [1-(chloromethyl)-4-flouro-1,4-diazoniabicyclo[2,2,2]octane bis(tetraflouroborate)] has catalyzed the preparation of quinoxaline and 2,3-dihydopyrazine derivatives through one-pot condensation of 1,2-diamines with 1,2-dicarbonyls in solvent and under solvent-free conditions. Short reaction times, high yields of products and the use of a commercially available, stable and reusable catalyst are noteworthy advantages of these methods.

Keywords: Quinoxaline; 2,3-dihydropyrazine; selectfluor; 1,2-diamine; 1,2-dicarbonyl.

Introduction

During recent years, the use of recoverable and reusable catalysts has attracted special attentions due to its economical, environmental and industrial advantages [1]. The development of efficient and reusable catalyst is one of the major challenges in chemistry. Up to now, many different heterogeneous and reusable catalysts have been identified or generated and applied in organic transformations. One useful example is selectfluor [1-(chloromethyl)-4-flouro-1,4- dazoniabicyclo[2,2,2]octane bis(tetraflouroborate)], which is known as a fluorinating agent [2]. Selectfluor is a commercially available, inexpensive, non-toxic, non-volatile and stable reagent. It is not only a good flourinating agent, but also, a highly efficient catalyst that has been recently employed as an efficient Lewis acid in organic transformations [3].

Quinoxalines (benzopyrazines) are an important class of nitrogen containing heterocyclic compounds which have found wide variety of applications in chemistry, biochemistry and pharmacology, so, they have attracted special interest by synthetic chemist for many years. These valuable heterocycles have shown different pharmaceutical activities such as: antibacterial [4-9], antifungal [10-11], anticancer [12-14], antitubercular [15], antimalarial [16,17], antimicrobial [18-19], anti-pain and anti-inflammatory [20-21] properties. Dihydropyrazines are also of importance due to their biological effects such as the introduction of apoptosis [22], mutagenesis [23] and DNA strand-breaking activity [24]. Furthermore, dihydropyrazines are good precursors

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of pyrazines which have been found in various food [25] and are used as flavorants [26].

Numerous methods have been reported for the synthesis of these heterocycles. Conversely, the commonly employed methods involve the condensation of 1,2-diamines with 1,2-dicarbonyls using various catalyst such as O-iodoxybenzoic acid [27], $Yb(OTf)_3$ [28], oxone [29], I_2 [30], heteropoly acid [31], citric acid [32], AcOH [33], oxalic acid [34], $(NH_4)_6Mo_7O_{24}.4H_2O$ [35], etc. However, some of these methods suffer from one or more limitations such as harsh reaction conditions, long reaction times, low yields of products, tedius work-up procedures and the use of expensive, complex and/or toxic reagents. Hence, the development of new catalytic methods for the synthesis of quinoxalines and dihydropyrazines in terms of operational simplicity and economical acceptability of the catalyst are a worthwhile endeavor. Herein, we wish to report highly efficient methods for the synthesis of quinoxalines and dihydropyrazines *via* the condensation of 1,2-diamines and 1,2-dicarbonyls in the presence of selectfluor as a highly efficient catalyst in different reaction conditions.

Experimental

General

All materials were of commercial reagent grade and were prepared from Merck Company. IR spectra were obtained by use of a Shimadzu 435-U-04 spectrophotometer (KBr pellets). ^1H NMR spectra were recorded on a Bruker AVANCE 400 MHz. Melting points were taken on a Bamstead Electrothermal apparatus. Elemental analyses were performed using a Heraeus CHN-O-Rapid analyzer.

General procedure for the synthesis of quinoxaline and 2,3-dihydropyrazine in ethanol

Selectfluor (0.0035 g, 1 mol%) was added to a mixture of 1,2-diamine (1 mmol) and 1,2-dicarbonyl (1 mmol) in EtOH and the mixture was stirred at room temperature. The progress of reaction was followed by TLC (*n*-hexane/ethylacetate, 2:1). After completion of the reaction, the solvent was evaporated and CH_2Cl_2 (20 mL) was added to the reaction mixture. The product was dissolved in CH_2Cl_2 and the catalyst was recovered by simple filtration, washed with CH_2Cl_2 (10 mL) and then dried for reusing. The filtrate was concentrated to afford crude product which purified by column chromatography (Table 1).

General procedure for the synthesis of quinoxaline and 2,3-dihydropyrazine under solvent-free condition

A mixture of 1,2-diamine (1 mmol), 1,2-dicarbonyl (1 mmol) and selectfluor (0.0035 g, 1 mol%) was stirred at 80 °C for appropriate times according to Table 2. After completion of the reaction as indicated by TLC (*n*-hexane/ethyl acetate, 2:1), the mixture was diluted with CH_2Cl_2 (20 mL) and filtered. The solid material was washed with CH_2Cl_2 (10 mL). The solvent of filtrate was evaporated and the crude product was purified by column chromatography (Table 1).

Spectral data of selected compounds

2,3-Diphenylquinoxaline (5d) [31]

mp 124-125 °C; IR (KBr); υ 1540, 1345, 1053 cm^{-1}; ^1H NMR (400 MHz, $CDC1_3$): δ 7.35-7.42 (m, 6H), 7.54-7.59 (m, 4H), 7.78-7.83 (m, 2H), 8.20-8.25 (m, 2H); Anal. Calcd. for $C_{20}H_{14}N_2$: C, 85.11; H, 4.96; N, 9.93; found: C, 85.09; H, 5.05; N, 9.86.

2-Ethyl-3-methyl-quinoxaline (5e) [32]

mp: 52-54 °C; IR (KBr); υ 1585, 1440, 1390 cm^{-1}; ^1H NMR (400 MHz, $CDC1_3$): δ 1.44 (t, J = 7.47 Hz, 3H), 2.8 (s, 3H), 3.05 (q, J = 7.47 Hz, 2H), 7.66-7.72 (m, 2H), 7.98-8.07 (m, 2H); Anal. Calcd. for $C_{11}H_{12}N_2$: C, 76.74; H, 6.98; N, 16.28; found: C, 76.77; H, 6.89; N, 16.34.

8,9-Dihydro-acenaphtho[1,2-b]pyrazine (9) [32]

mp: 124-126 °C; IR (KBr); υ 1620, 1583 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.94 (s, 4H), 7.72 (t, J = 7.47 Hz, 2H), 7.94-8.01 (m, 4H); Anal. Calcd. for $C_{14}H_{10}N_2$: C, 81.55; H, 4.85; N, 13.60; found: C, 81.60; H, 4.83; N, 13.57.

Results and discussion

For optimization of the reaction conditions, the reaction of benzil and 1,2-phenylenediamine was chosen as model reaction. The model reaction was carried out in the presence of different catalytic amounts of selectfluor and in various solvents at room temperature. The best result was obtained in the reaction of 1 mmol 1,2-phenylenediamine with 1 mmol benzil in the presence of 1 mol% selectfluor at room temperature in EtOH, which gives 2,3-diphenylquinoxaline in 91% yield after 5 min (Table 1, Entry 5).

In order to show the efficiency of the catalyst in the current reaction, model reaction was performed in the absence of catalyst, which led to only 40% products after 270 minutes. The result confirms that selectfluor is a good choice for the synthesis of 2,3-diphenylquinoxaline as a Lewis acid catalyst.

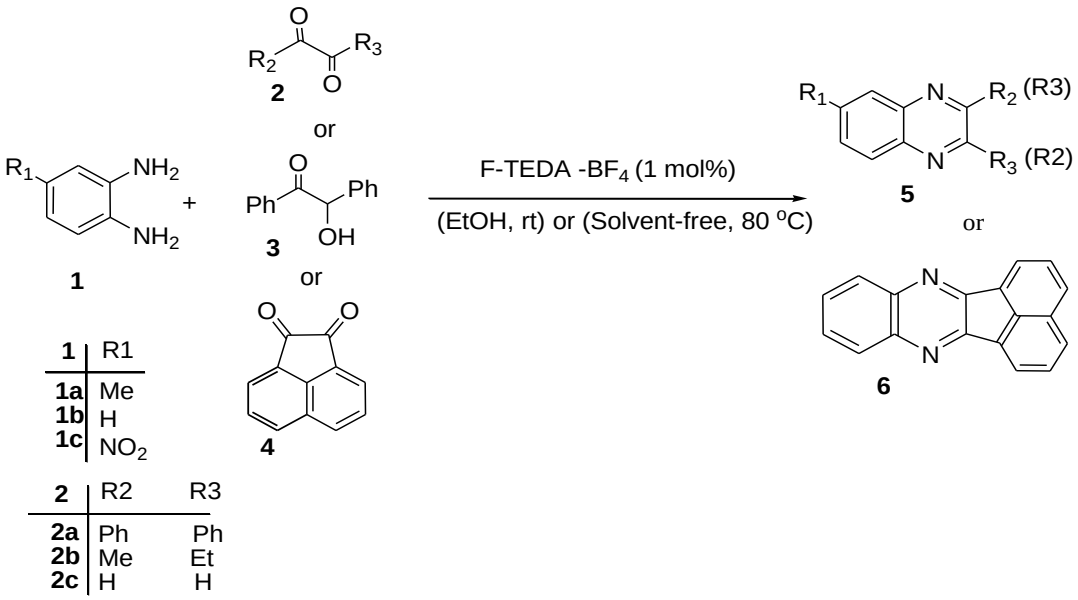
To extend the scope and generality of this method, different 1,2-diamines and 1,2-dicarbonyls were reacted under optimized reaction conditions to afford the corresponding products (Scheme 1, Table 1, Entries 1-12). As shown in Table 1, both aromatic and aliphatic dicarbonyl compounds satisfactorily reacted with 1,2-diamines and generated corresponding quinoxalines in good to excellent yields. In addition, 1,2-diamines with electron-withdrawing group such as NO_2 (Table 1, Entries 9-12), reacted in longer reaction times in comparison with electron-donating substituted diamines (Table 1, Entries 1-4).

Furthermore, the use of asymmetric 1,2-diamines and 1,2-dicarbonyls led to the formation of a 1:1 mixture of two regioisomers (Table 1, Entries 2 and 10). Then, we examined the applicability of this method in the synthesis of 2,3-quinoxaline from α-hydroxycarbonyl. To this aim reactions of benzoin were performed with 1,2-phenylenediamines under optimized reaction conditions and corresponding 2,3-quinoxalines were generated in good yields (Table 1, Entries 13-15). In the next step, we investigated the efficiency of the current method for the synthesis of 2,3-dihydropyrazines from 1,2-ethylendiamine and 1,2-dicarbonyls or α-hydroxycarbonyl compound (Scheme 2). Fortunately, desired products were obtained in very good yields (Table 1, Entries 16-19).

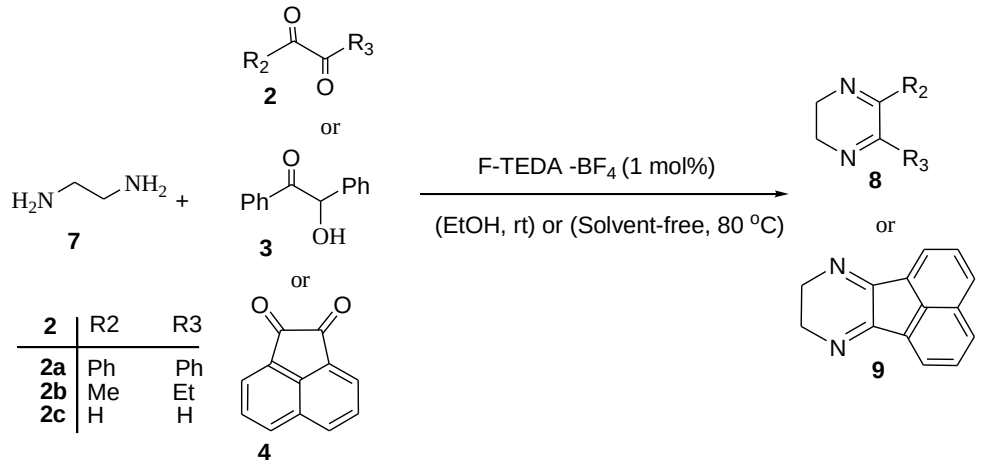
Table 1. Synthesis of quinoxalines and 2,3-dihydropyrazines catalyzed by selectfluor

Entry	Diamine	Dicarbonyl	Product	In EtOH		Solvent-free		Mp ºC (Lit. [ref.])
				Time (min)	Yiled[a] (%)	Time (min)	Yiled[a] (%)	
1	**1a**	**2a**	**5a**	3	99	2	92	112-114 (113-115 [32])
2	**1a**	**2b**	**5b**	2	90	1	91	65-67 (68-70 [32])
3	**1a**	**2c**	**5c**	32	80	14	96	62-63
4	**1a**	**4**	**6a**	2	95	2	94	214-216 (218-220 [32])
5	**1b**	**2a**	**5d**	5	91	3	96	124-125 (125-126 [32])
6	**1b**	**2b**	**5e**	2	96	1	92	52-54 (58-60 [32])
7	**1b**	**2c**	**5f**	45	74	20	98	49-51
8	**1b**	**4**	**6b**	4	94	3	93	238-240 (235-236 [32])
9	**1c**	**2a**	**5g**	40	84	35	82	185 (185-186 [32])
10	**1c**	**2b**	**5h**	24	75	2	80	181-183
11	**1c**	**2c**	**5i**	60	72	69	85	177
12	**1c**	**4**	**6c**	40	80	33	86	> 300 (320 [34])
13	**1a**	**3**	**5a**	34	80	17	88	110-112 (113-115 [32])
14	**1b**	**3**	**5d**	50	81	24	86	124-124 (125-126 [32])
15	**1c**	**3**	**5g**	50	76	60	80	185-187 (185-186 [32])
16	**7**	**2a**	**8a**	40	85	25	94	163 (161-164 [32])
17	**7**	**2b**	**8b**	1	92	1	97	84-86
18	**7**	**4**	**9**	2	92	1	98	124-126 (124-126 [32])
19	**7**	**3**	**8a**	40	88	43	90	160-162 (161-164 [32])

[a]Yields of isolated products



Scheme 1. Synthesis of quinoxalines using selectfluor



Scheme 2. Synthesis of 2,3-dihydropyrazines using selectfluor

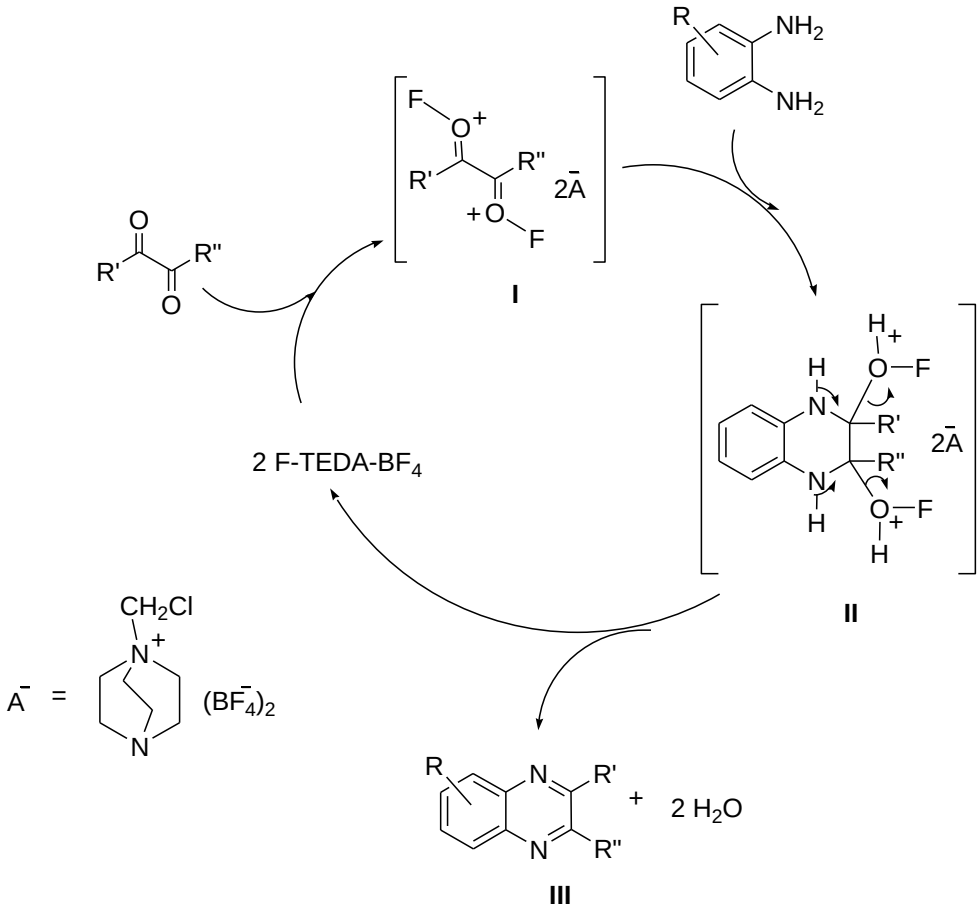
The development of solvent-free organic synthetic methods has become an important research area, because elimination of volatile organic solvents make synthesis simpler, save energy and prevent solvent wastes, hazards and toxicity. These advantages encouraged us to perform the current method under solvent-free condition. Therefore, 1,2-phenylenediamine (1 mmol) reacted with benzil (1 mmol) under optimized reaction conditions (selectfluor (1 mol%), r.t.), but in the absence of solvent. Unfortunately, the reaction didn't perform at room temperature. Hence, the model reaction was carried out at different temperature, and finally, 80 °C was selected as the best temperature for the synthesis of 2,3-diphenylquinoxaline which resulted in 96% yield after 3 min (Table 1, Entry 5).

Next, the generality of this method was investigated by the reaction of a series of aryl-1,2-diamines with 1,2-dicarbonyls or α-hydroxycarbonyl under optimized reaction conditions (Scheme 1) which afford corresponding heterocycles in good to excellent yields in very short times (Table 1, Entries 1-15). Similarly, 2,3-dihydropyrazine derivatives were synthesized from 1,2-ethylenediamine and 1,2-dicarbonyls or α-hydroxycarbonyl compound in high yields (Scheme 2, Table 1, Entries 16-19). Results show that selectfluor is a highly efficient catalyst for the synthesis of both aromatic and non-aromatic six-membered pyrazine and dihydropyrazine rings in different reaction conditions.

The reusability of the catalyst is one of the most important benefits of the catalyst and makes it useful for commercial applications. Thus, the recovery and reusability of selectfluor was investigated in the reaction of benzil and 1,2-phenylenediamine under optimized reaction conditions. The catalyst has been separated and dried as explained in experimental section and reused five times in model reactions (Table 2, Figure 1). The results showed that the catalytic activity of selectfluor was not reduceed significantly.

Although the actual mechanism of reaction is unclear, a reasonable explanation with respect to similar reported methods [27,33] and the high catalytic activity of selectfluor is shown in scheme 3. First, two mols selectfluor releases two flouronium ions, which activate the carbonyl groups to give **I**. Nucleophilic attacking of 1,2-phenylenediamine to the electrophilic centers of **I** yields **II**. Finally, dehydration of compound **II** produces the corresponding heterocycle, and in this step, the flouroniumions are released for the next catalytic cycle.

To show the superiority of the present method over previous ones, we compared our results with some other results reported in the literature. We also calculated the turn over number (TON) values of catalysts in this comparison (Table 3).



Scheme 3. Proposed mechanism for the synthesis of quinoxalines using selectfluor

Table 2. Reusability of the catalyst in the reaction of benzil and 1,2-phenylenediamine

Run no.	1	2	3	4	5
Yield[a] (%)	90	90	88	85	85
Yield[b] (%)	95	94	92	92	90

[a]Isolated yield in EtOH after 5 min
[b]Isolated yield under solvent-free condition after 3 min

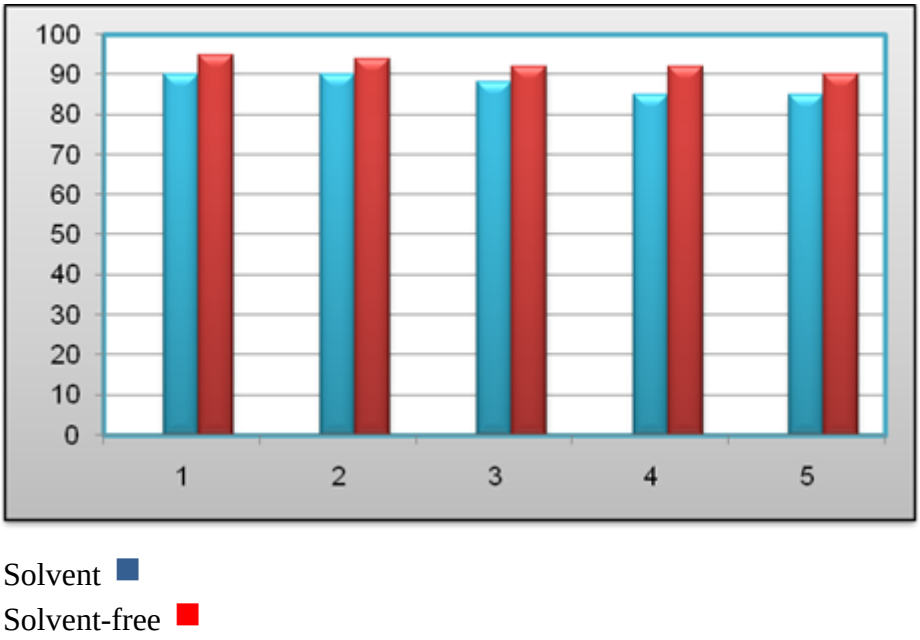


Figure 1. Recyclability of selectfluor in the reaction of benzil with 1,2-phenylenediamine

Table 3. Comparison of the present method with some other procedures for synthesis of 2,3-diphenylquinoxaline from benzil and 1,2-phenylenediamine

Entry	Catalyst (mol%)	Solvent	Time (min)	Yield (%) [Ref.]	TON
1	Selectfluor (1 mol%)	EtOH	5	91	91
2	Selectfluor (1 mol%)	----	3	96	96
3	$ZnCl_2$ (4 mol%)	$EtOH/H_2O$	240	70 [35]	20
4	$Mn(OAc)_2$ (4 mol%)	$EtOH/H_2O$	240	78 [35]	18.25
5	$CoCl_2$ (4 mol%)	$EtOH/H_2O$	240	81 [35]	14.75
6	$(NH_4)_6Mo_7O_{24}.4H_2O$ (2 mol%)	$EtOH/H_2O$	15	95[36]	47.5

Conclusion

In conclusion, we have introduced selectfluor as a highly efficient catalyst for the synthesis of quinoxalines and 2,3-dihydropyrazines from 1,2-dicarbonyls and 1,2-diamines. This catalyst is commercially available, inexpensive, reusable, stable to air and moisture, and relatively non-toxic. Furthermore, very short reaction times, high yields of products, mild reaction conditions, absence of solvent, and easy work-up are other considerable advantages of this procedure.

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References

[1] S. Tamagaki, R.J. Card, Neckers, *J. Am. Chem. Soc.*, **1978**, *100*, 6635-6630.
[2] W. Peng, J.M. Shreeve, *J. Org. Chem.*, **2005**, *70*, 5760-5763.
[3] (a) S. Stavber, M. Zupan, *Acta Chim. Slov.*, **2005**, *52*, 13-26. (b) J.S. Yadav, B.V.S. Reddy, C.S. Reddy, *Tetrahedron Lett.*, **2004**, *45*, 1291-1293. (c) J.S. Yadav, B.V.S. Reddy, V. Sunitha, C.S. Reddy, *Adv. Synth. Catal.*, **2003**, *345*, 1203-1206. (d) J. Liu, C.H. Wong, *Tetrahedron Lett.*, **2002**, *43*, 3915-3917. (e) J. Liu, C.H. Wong, *Tetrahedron Lett.*, **2002**, *43*, 4037-4039. (f) S. Stavber, M. Zupan, *Acta Khim. Slov.*, **2005**, *52*, 13-26.
[4] S. Ganapaty, P. Ramalingam, C.B. Rao, *Indian J. Heterocycl. Chem.*, **2007**, *16*, 283-286.
[5] H.M. Refaat, A.A. Moneer, O.M. Khalil, *Arch. Pharm. Res.*, **2004**, *27*, 1093-1098.
[6] M.M. Badran, K.A.M. Abouzid, M.H.M. Hussein, *Arch. Pharm. Res.*, **2003**, *26*, 107-113.
[7] M. Nasr, A. Nasr, *Arch. Pharm. Med. Chem.*, **2002**, *8*, 389-394.
[8] S.A. El-Hawash, N.S. Habib, N.H. Fanaki, *Pharmazie*, **1999**, *54*, 808-813.
[9] A.A. El-Gendy, S. El-Meligie, A. El-Ansary, A.M. Ahmedy, *Arch. Pharm. Res.*, **1995**, *18*, 44-47.
[10] V.K. Tandon, D.B. Yadav, H.K. Maurya, A.K. Chaturvedi, P.K. Shukla, *Bioorg. Med. Chem.*, **2006**, *14*, 6120-6126.
[11] P. Sanna, A. Carta, M. Loriga, S. Zanetti, L. Sechi, *II Farmaco*, **1999**, *54*, 169-177.
[12] A. Carta, P. Sanna, L. Gherardini, D. Usai, S. Zanetti, *II Farmaco*, **2001**, *56*, 933-938.
[13] P. Sanna, A. Carta, M. Loriga, S. Zanetti, L. Sechi, *II Farmaco*, **1999**, *54*, 161-168.
[14] A. Monge, F.J. Martinez-Crespo, A.L. Cerain, J.A. Palop, S. Narro, V. Senador, A. Marin, Y. Sainz, M. Gonzalez, E. Hamilton, A.J. Barker, *J. Med. Chem.* **1995**, *38*, 4488-4494.
[15] A. Jaso, B. Zarranz, I. Aldana, A. Monge, *Eur. J. Med. Chem.*, **2003**, *38*, 791-800.
[16] J.B. Rangisetty, C.N.V.H.B. Gupta, A.L. Prasad, P. Srinivas, N. Sridhar, P. Parimoo, A. Veeranjaneyulu, *J. Pharm. Pharmacol.*, **2001**, *53*, 1409-1413.
[17] A.F. Crowther, F.H.S. Curd, D.G. Davey, G.J. Stacey, *J. Chem. Soc.*, **1949**, 1260-1271.
[18] M.M. Ali, M.M.F. Ismail, M.S.A. El-Gaby, M.A. Zahran, Y.A. Ammar, *Molecules*, **2000**, *5*, 864-873.
[19] C.A. Obafemi, D.A. Akinpelu, *Phosphorus, Sulfur, Silicon, Relat. Elem.*, **2005**, *180*, 1795-1807.
[20] G.R. Wendt, K.W. Ledig, *U. S. Pat.*, **1969**, 3, 431, 262. (*Chem. Abstr.*, **1969**, *70*, 106, 512).
[21] D.S. Su, M.G. Bock, *U. S. Pat. Appl.*, **2005**, 20050-20591.
[22] T. Ymaguch, H. Nomura, K. Matsunaga, S. Ito, J. Takata, Y. Karube,

Biol. Pharm. Bull., **2003**, *26*, 1523-1527.
[23] S. Takechi, T. Yamaguchi, H. Nomura, T. Minematsu, T. Nakayama, *Mutat. Res.*, **2004**, *560*, 49-55.
[24] N. Kashige, T. Yamaguchi, F. Miake, K. Watanabe, *Biol. Pharm. Bull.*, **2000**, *23*, 1281-1286.
[25] J.A. Maga, C.E. Sizer, *J. Agric. Food Chem.*, **1973**, *21*, 22-30.
[26] T. Akiyama, Y. Enomoyo, T. Shibamoto, *J. Agric. Food Chem.*, **1978**, *26*, 1176-1179.
[27] M.M. Heravi, K. Bakhtiari, M.H. Tehrani, N.M. Javadi, H.A. Oskooie, *Arkivoc*, **2006**, 16-22.
[28] L. Wang, J. Liu, H. Tian, C. Qian, *Synth. Commun.*, **2004**, *34*, 1349-1358.
[29] H.A. Oskooie, M.M. Heravi, K. Bakhtiari, S. Taheri, *Monatsh. Chem.*, **2007**, *138*, 875-877.
[30] A. Shaabani, A.H. Rezayan, M. Behnam, M. Heidary, *Comptes Rendus Chimie*, **2009**, *12*, 1249-1252.
[31] F. Hakimi, Bi Bi F. Mirjalili, *Current Chem. Lett.*, **2013**, *2*, 105-108.
[32] S. Sajjadifar, M.A. Zolfigol, Gh. Chehardoli, S. Miri, P. Moosavi, *Int. J. Chem. Tech. Res.*, **2013**, *5*, 422-429.
[33] M.R. Islami, Z. Hassani *Arkivoc*, **2008**, *xv*, 280-287.
[34] B. Karami, S. Khodabakhshi, *J. Serb. Chem. Soc.*, **2011**, *76*, 1191.
[35] A. Hasaninejad, A. Zare, M.R. Mohammadizadeh, M. Shekouhy, *Arkivoc*, **2008**, *xiii*, 28-35.
[36] A. Hasaninejad, A. Zare, M.R. Mohammadizadeh, Z. Karami, *J. Iran. Chem. Soc.*, **2009**, *6*, 153-158.