J. Iran. Chem. Soc., Vol. 5, Suppl., October 2008, pp. S91-S96.

JOURNAL OF THE
Iranian
Chemical Society

The First Report on the Synthesis of New Hantzsch *N*-Ethyldimetyl Acetal-1,4-dihydropyridines with Aldehyde Synthon under Microwave Irradiation

M.A. Zolfigol* and M. Mokhlesi
Faculty of Chemistry, Bu-Ali Sina University, Hamedan, Iran

(Received 14 December 2007, Accepted 15 February 2008)

This paper is dedicated to Professor Habib Firouzabadi for his great achievements on the occasion of his 65th birthday and his retirement.

A mixture of ethyl acethylenecarboxylate, various aryl aldehydes and aminoacetaldehyde dimethyl acetal in the presence of silica gel were converted to *N*-ethyldimethyl acetal-1,4-dihydropyridines using microwave irradiation with good yields.

Keywords: *N*-ethyldimethyl acetal-1, 4-Dihydropyridines 1,4-Dihydropyridines, Aminoacetaldehyde dimethyl acetal, Ethyl acethylenecarboxylate, Solvent-free, Microwave irradiation.

INTRODUCTION

Hantzsch 1,4-dihydropyridines, a class of model compounds of NADH coenzyme, have been extensively studied in view of the biological pertinence of these compounds to NADH redox process [1]. Recently, due to the vast medicinal utility of 1,4-dihydropyridine derivatives various methods to prepare these compounds have been reported [2]. They process neuroprotective, platet anti-aggregration and antidiabetic activities [3]. Some representatives like nifedipine, niguldipine, nicardipine or amlodipine are widely used for treatment of hypertension [4]. Hantzsch 1,4-dihydropyridines are easily prepared from hantzsch reaction or its modifications [5-8]. In recent years it was found that drugs such as nifedipine and niguldipine undergo redox processes due to the catalysis of cytochrome P-450 in the liver during their metabolism [9]. Also 1,4-dihydropyridines are well-known compounds as a consequence of their pharmacological profile as the most important calcium channel modulators [10-19]. For example, amlodepine besylate, nifedepine and related dihydropyridines are Ca^{2+} channel blockers, and are rapidly emerging as one of the most important classes of drugs for the treatment of cardiovascular diseases including hypertension. Additionally, dihydropyridines are often produced in a synthetic sequence, and have to be oxidized to pyridines [20]. The classical method for the synthesis of 1,4-dihydropyridines is an one-pot condensation of an aldehyde with 1,3-dicarbonyl compounds, and ammonia either in acetic acid or refluxing in alcohol [21]. For the preparation of 2,6-unsubstituted 1,4-dihydropyridines propiolates are used instead of 1,3-dicarbonyl compounds [22, 23]. Preparation of new 1,4-dihydropyridines with especial properties is an active and attractive ongoing interdisciplinary research area. According to the our previously reported results [24], and an excellent

*Corresponding author.
E-mail: zolfi@basu.ac.ir & mzolfigol@yahoo.com

reported procedure by balalaie *et al*[22], we decided to synthesis a new set of 1,4-dihydropyridines which are susceptible for the conversion into the corresponding aldehyde synthons. Herein, we wish to report the of synthesis of a various *N*-ethyldimethyl acetal-1,4-dihydropyridines under microwave irradiation with good yields.

EXPERIMENTAL

General procedure for the synthesis of diethyl-*N*-ethyldimethyl acetal-4-(3-chlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylate: A typical procedure.

3-Chlorobenzaldehyde **2f** (0.154 g, 1 mmol),ethyl acetylenecarboxylate **1** (0.294 g, 3 mmol), aminoacetaldehyde dimethyl acetal **3** (0.210 g, 2 mmol) and silica gel (1g, mesh 40) were mixed thoroughly in a mortar. Then the reaction mixture transferred to a beaker and irradiated with microwave for 15 min. The progress of reaction monitored by TLC. The Reaction mixture was extracted with methanol (3 x 30 mL) and filtred off. Solvent was removed under reduced pressure and gave **4f** 0.335 g (79%). The crude product of **4f** was recrystallized in petroleum ether:diethyl ether (2:1) and gave a yellow crystals, mp. 98-100 °C, FT-IR (KBr)) υ=: 2983, 1696, 1684, 1574, 1198, 1074, 766, ^{1}H-NMR (90 MHz, $CDCl_3$):δ_{ppm}: 1.186(t, 6H), 3.468 (d, 8H), 4.038 (q, 4H), 4.462 (t, 1H) 4.831(s , 1H), 7.195 (t, 6H), ^{13}C-NMR(22.5 MHz, $CDCl_3$), δ_{ppm}: 14.09, 37.04, 55.10, 56.36, 59.94, 103.28, 108.06, 126.49, 128.38, 128.89, 133.78, 138.31, 148.74, 166.58, MS (EI, 70Ev) m⁄z: 423

Spectral and microanalysis data of Hantzsch *N*-Ethyldimetyl acetal-1,4-dihydropyridines (4):

4a: mp. 88-90 °C, FT-IR (KBr, cm^{-1}) 1696, 1661, 1369, 1214, 1179, 1069; ^{1}H-NMR

(90MHz, $CDCl_3$) δ_{ppm}: 1.14 (t, 6H), 3.37 (s, 8H), 3.96 (q, 4H), 4.39 (t, 1H), 4.81 (s,1H), 7.16 (m, 7H), ^{13}C-NMR (22.5 MHz, $CDCl_3$) δ_{ppm}: 14.26, 37.26, 55.10, 56.47, 60.02, 103.49, 108.95, 126.37, 127.93, 128.32, 138.05, 146.82, 167.01, Accurate MS (EI, 70Ev) m⁄z: Calc: 390.1917, found: 390.1899, Elemental Anal. Calcd. (CHN) For $C_{20}H_{27}NO_6$: C 65.1, H 4.46, N 3.61, Found:C 64.5, H 7, N 3.7.

4h: mp. 117-119 °C, IR (KBr, cm^{-1}) 1698, 1585, 1352, 1197, 1069; ^{1}H NMR (90 MHz, $CDCl_3$) δ_{ppm}: 1.1486 (t, 6H), 3.48 (s, 8H), 4.03 (q, 4H), 4.49 (t, 1H), 4.98 (s, 1H), 7.26 (s, 2H), 7.55, 8.06 (d, 4H), ^{13}C NMR (22.5 MHz, $CDCl_3$), δ : 14.16, 37.59, 55.05, 56.25, 60.14, 103.23, 107.67, 123.22, 129.16, 138.75, 146.61, 153.87, 166.35, Accurate MS (EI, 70Ev) m⁄z: Calc: 435.1767, Found: 435.1754, Elemental Anal. Calcd. (CHN) For $C_{21}H_{25}N_2O_8$: C 58.61, H 5.99, N 6.45, Found: C 57.9, H 5.9, N 6.45.

4-d: mp .89-92 °C, IR (KBr, cm^{-1}) 1697, 1576, 1422, 1304, 1198, 1073; ^{1}H NMR (90 MHz, $CDCl_3$), δ_{ppm}: 1.16 (t, 6H), 3.45 (s, 8H), 4.02 (q, 4H), 4.46 (t, 1H), 4.80 (s, 1H), 7.18 (m, 6H), ^{13}C NMR (22.5 MHz, $CDCl_3$) δ_{ppm}: 60.08, 103.40, 108.22, 122.25, 127.10, 129.36, 131.41, 138.38, 149.10, 166.70, Accurate MS (EI, 70Ev) m⁄z: Calc: 468.0896, found: 468.0917, Elemental Anal Cala (CHN) For $C_{20}H_{26}NOBr$: C 54.19, H 5.16, N 3.01, Found: C 53.4, H 5.5, N 2.8.

4-c: mp. 107-109 °C, IR (KBr, cm^{-1}) 1698, 1582, 1420, 1306, 1197; ^{1}H-NMR (90 MHz, $CDCl_3$) δ_{ppm}: 1.19 (t, 6H), δ 3.49 (s, 8H), 4.12 (q, 4H), 4.51 (t , 1H), 5.31(s, 1H),7.2 (m, 7H), ^{13}C NMR (22.5 MHz, $CDCl_3$) δ_{ppm}: 14.26, 36.91, 55.01, 56.23, 60.09, 103.303, 109.14, 123.18, 131.61, 132.46, 138.59, 146.71, 167.02, Accurate MS (EI, 70Ev) m⁄z: Calc: 468.1022, Found: 468.1004.

4-e: mp. 115-117 °C, IR (KBr, cm^{-1}) 1692, 1552, 1410, 1325, 1153, 1094, ^{1}H NMR
(90 MHz, $CDCl_3$), δ_{ppm}: 1.19 (t, 6H), 3.64 (s, 8H), 4.04 (q, 4H), 4.46 (t, 1H), 4.82 (s,1H), 7.31 (m, 7H), ^{13}C NMR (22.5 MHz, $CDCl_3$), δ_{ppm}: 14.18, 36.80, 54.97, 56.23, 59.99, 103.24, 108.30, 120.15, 130.04, 130.91, 138.18, 145.87, 166.66, Accurate MS (EI, 70Ev) m⁄z: Calc: 468.0896, Found: 468.0899

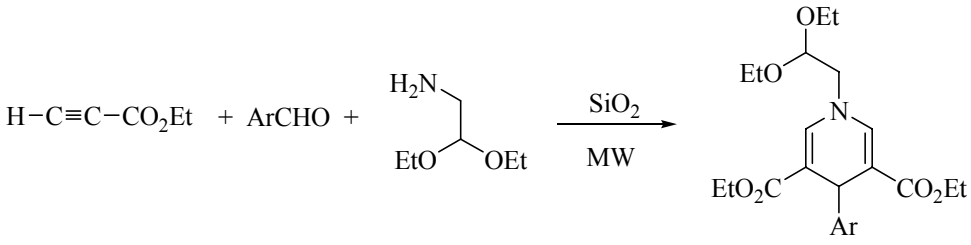
4-g: mp. 124-126 °C, FT-IR (KBr, cm^{-1}) 1696, 1574, 1369, 1423, 1304, 1198, 1074; ^{1}H-NMR (90 MHz, $CDCl_3$), δ_{ppm}: 1.19 (t, 6H), 3.46 (s, 8H), 4.03 (q, 4H), 4.46 (t, 1H), 4.83 (s, 1H), 7.23 (m, 7H), ^{13}C NMR ($CDCl_3$, 22.5 MHz), δ_{ppm}: 14.24, 36.78, 55.06, 56.36, 60.09, 103.35, 108.55, 128.06, 129.71, 132.1, 138.21, 148.74, 166.81, Accurate MS (EI, 70Ev) m⁄z: Calc: 424.1527, Found: 424.1519

4-b: mp. 92-94 °C, IR (KBr, cm^{-1}) 1698, 1585, 1352, 1197, 1060, ^{1}H NMR (90 MHz, $CDCl_3$), δ_{ppm}: 1.16 (t, 6H), 2.24 (s, 3H), 3.42 (s, 8H), 4.01 (q, 4H),4.43 (t, 1H) 4.80 (s, 1H), 7.17 (m, 7H) ^{13}C NMR (22.5 MHz, $CDCl_3$), δ_{ppm}: 14.14, 20.93, 36.61, 54.93, 56.31, 59.84, 103.38, 108.89, 128.05, 128.55, 137.87, 143.94, 166.92 Accurate MS (EI, 70Ev) m⁄z: Calc: 404.2037, Found: 404.2056

RESULTS AND DISCUSSION

A good range of *N*-ethyldimethyl acetal-1,4-dihydropyridines **4** were synthesised from a combination of ethyl acethylenecarboxylate **1**, aldehyde **2**, and aminoacetaldehyde dimethyl acetal **3** in the presence of silica gel under microwave irradiation (Scheme 1, Table 1). The reaction was completed after 4-18 min and the reaction mixture extracted with methanol. Removing of methanol under reduced pressure gives the crude products of **4** with good to excellent yields. The crude products were recrystallized in a suitable solvent(s) and a highly pure crystals of *N*-ethyldimethyl acetal-1,4-dihydropyridines **4** was obtained.

The rapid assembly of molecular diversity is an important goal of synthetic organic chemistry and one of the key paradigms of modern drug discovery. Another approach to address this challenge involves the development of multicomponent reactions (MCRs), in which more than two reactants are combined together in a reaction vessel so that to



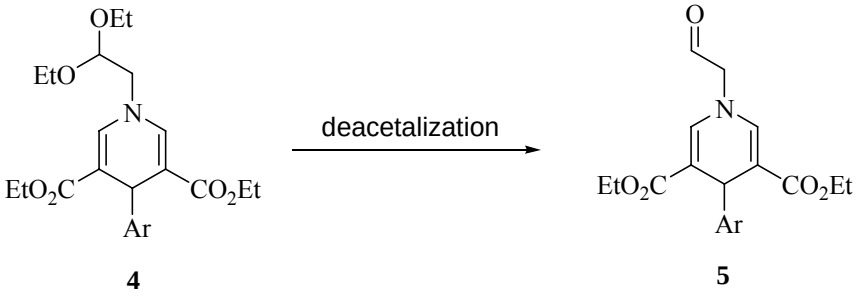
1 **2** **3** **4**

Scheme 1

Table 1. Synthesis *N*-ethyldimethyl acetal-1,4-dihydropyridines under microwave irradiation.

Product	Ar	Reactants (mmol)[a]			Time	Yields [b]	Mp
4	**2**	**1**	**2**	**3**	(min)	(%)	(^{o}C)
4a	C_6H_5	2	1	1	4	85	88-90[c]
4b	4-$CH_3C_6H_4$	2	1	1	3 x 3	75	91-93[d]
4c	2-BrC_6H_4	3	1	2	3 x 3	85	100-103[c]
4d	3-BrC_6H_4	3	1	2	5 x 3	75	87-90[c]
4e	4-BrC_6H_4	3	1	2	3 x 3	90	114-116[d]
4f	3-ClC_6H_4	3	1	2	5 x 3	79	98-100[c]
4g	4-ClC_6H_4	3	1	2	5 x 3	87	122-125[d]
4h	4-$NO_2C_6H_4$	4	1	3	6 x 3	80	118-119[d]

[a] Ethyl acethylenecarboxylate **1**: aldehydes **2**: aminoacetaldehyde dimethyl acetal **3**. [b] Crude isolated yields. [c] Recrystallized in petroleum ether:diethyl ether (2:1). [d] Recrystallized in methanol and the obtaining crystals has been also washed with diethyl ethers.



4 **5**

Scheme 2

generate a product containing of most of the atoms in the starting materials. In addition to the intrinsic atom economy, simpler procedures and equipment, time and energy saving, as well as environmental friendliness have all led to a serious effort to design and implement MCRs in both academia and industry [2b]. On the basis of the above mentioned facts *N*-ethyldimethyl acetal-1,4-dihydropyridines **4** has an excellent aldehyde synthon with 1,4-dihydropyridine moiety **5** (Scheme 2) which may be applicable as a precursor for the synthesis of various complex molecules via MCRs (Figure 1) [24c]. We sure that conversion of acetal will be occurred by choosing a suitable conditions.[23] Therefore deacetalization of **4** should be produced **5** and may be used for the molecular diversity and designing of complex molecules with mono or multi 1,4-dihydropyridine moieties in future [24c].

In conclusion, synthesis of new derivatives of 1,4-dihydropyridines with a synthon ability, efficient work-up, and high yield makes this method an attractive methodology [25]. We believe that the present methodology addresses the current devise toward green chemistry due to high yields and atomic economy, fewer reagents. Meanwhile, the new 1,4-dihydropyridine derivatives that reported in this communication has aldehyde synthon with 1,4-dihydropyridine moiety, which are excellent precursors for the synthesis of new molecules containing of mono or multi 1,4-dihydropyridine moieties in future.

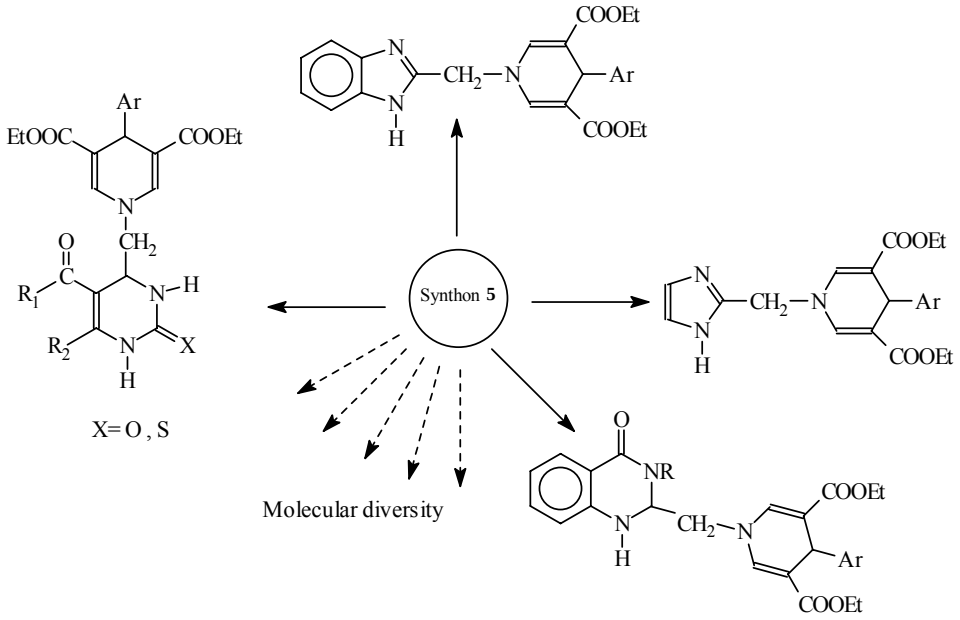


Fig 1. Suggested molecular design by using the new 1,4-dihydropyridine derivatives that reported in this article as suitable precursor of aldehyde synthons.

ACKNOWLEDGEMENT

Financial support for this work by the Management and Programming Organization of I.R. Iran (Special financial support due to selection by ESI as one of the top 1% international researchers on the basis of citation) and Center of Excellence in Development of Chemical Methods (CEDCM), Bu-Ali Sina University, Hamedan, Iran, is gratefully acknowledged.

REFERENCES

[1] G.V.M. Sharma, K.L. Reddy, P.S. Lakshmi and P.R Krishna. Synthesis (2006) 55.

[2] a) R. Miri, K, Javidnia, H. Sarkarzadeh and B. Hemmateenejad, Bioorg. Med. Chem. 14 (2006) 4842; b) N.M. Evdokimov, L.V. Magedov, A.S. Kireev and A. Kornienko, Org. Lett. 8 (2006) 899; c) J. Brackow, K.T. Wanner. Tetrahedron 62 (2006) 2395; d) Q. Liu, B. Han, Z. Liu, R. Mu, W. Zhang, Z.L. Liu and W. Yu. Synlett (2005) 2333; e) A.K. Kapoor, S. Koul, T.K. Rezdan and K.K. Kapoor. Can. J. Chem**.** 84 (2006) 1064; f) G-W. Wang, Xia. Miao, B. X-L.Wu. Bull. Chem. Soc. Jpn. 79 (2006) 454; g)V. Sivamurugan, A. Vinu, M. Palanichamy, V. Murugesan. Heteroatom Chem. 17 (2006) 267; h) H.R. Memarian, M.A. Abdoli-Senejani and D. Döpp. Verlag der Zeitschrift Für Naturforschung (2006) 50; i) E. Rajanarendar, P. Ramesh, M. Srinivas, K. Ramu and G. Mohan. Synthetic Commun. 36 (2006) 665; j) J-C. Legeay, J.J.V. Eynde and J.P. Bazureau. Tetrahedron 61 (2005) 12386; k) M. Maheswara, V. Siddaiah and Y.K. Rao. J. Mil. Catal. A: Chemical, 260 (2006) 179; l) A. Shaabani, A.H. Rezayan & A. Rahmati. Monatsh. Cheim. 137 (2006) 77; m) A. Davood, N. Mansouri, A.R. Dehpour, H. Shafaroudi, E. Ali-Pour and A. Shafiee. Arch. Pharm. Chem. Life. Sci. 339 (2006) 299; n) P. Jin, G. Narang, D.P. Jindal, R. Bansal, C. Calle, R. Carron, K. Pemberton and A.L. Harvey. Pharmazie 61 (2006) 400; o) J. Azizian, J. Hatamjafari and A.R. Karimi. J. Heterocycl. Chem. , 43 (2006) 1349

[3] N. Tewari, N. Dwivedi and R.P. Tripathi. Tetrahedron Lett. 45 (2004) 9011.

[4] X. Cai., H. Yang & G. Zhang. Can. J. Chem 83 (2005)273.

[5] M. Litvic, I. Cepanec, M. Filipan, K. Kos, A. Bartolincic, V. Druskovic, M.M. Tibi and V. Inkovic. Hetrocycles. 65 (2005) 23.

[6] Z.Liu, B. Han, Q. Liu, W. Zhang, L. Yang, Z.L Liu and W. Yu. Synlett (2005) 1579.

[7] M.A. Chari, K. Syamasundar. Catal. Commun. 6 (2005) 624.

[8] S.J. Ji, Z.Q. Jiang, J. Lu and T.P. Loh. Synlett (2004) 831.

[9] G. Sabitha, G.S.K.K. Reddy, C.S. Reddy and J.S. Yadav. Tetrahedron Lett. 44 (2003) 4129.

[10] J.J. Xia, G.W. Wang, Synthesis (2005) 2379.

[11] S. Tu, C. Miao, F. Fang, F. Youjian, T. Li, Q. Zhuang, X. Zhang, S. Zhu and D. Shi. Bioorg. Med. Chem. Lett. 14 (2004) 1533.

[12] L. Navidpour, H. Shafaroodi, R. Miri, A.R. Dehpour and A. Shafiee. Il Farmaco 59 (2004) 261.

[13] S. Visentin, B. Rolando, A.D. Stilo, R. Fruttero, M. Novara, E. Carbone, C. Roussel, N .Vanthuyne and A. Gasco. J. Med. Chem. 47 (2004) 2688.

[14] J.L Harper, C.S. Camerini-Otero, A.H Li, S.A. Kim, K.A. Jacobson and J.W. Daly. Biochem. Pharmacol. 65 (2003) 329.

[15] G.W. Zamponi, S.C. Stotz, R.J. Staples, T.M. Andro, K. Nelson, V. Hulubei, A. Blumenfeld and N.R. Natale. J. Med. Chem 46 (2003) 87.

[16] D. Mauzeral, F.H. Westheimer. J. Am. Chem. Soc. 77 (1955) 2261.

[17] M. Kawase, A. Shah, H. Gaveriya, N. Motohashi, H. Sakagami, A. Varga and J. Molnar. Bioorg. Med. Chem. 10 (2002) 1051

[18] M. Suarez, Y. Verdecia, B.I. llescas, R. Martinez-Alvarez, A. Avarez, E. Ochoa, Seoane, C. Carlos, N. Kayali and N. Martin. Tetrahedron 59 (2003) 9179.

[19] A. Zarghi, H. Sadeghi, A. Fassihi, M. Faizi and A. Shafiee. Il Farmaco 58 (2003) 1077.

[20] a) P. Salehi, M.A. Zolfigol, F. Shirini and M. Baghbanzadeh. Curr. Org. Chem. 10 (2006) 2171; b) M.A. Zolfigol, M. Bagherzadeh, K. Niknam, F. Shirini, I. Mohammadpoor-Baltork, A.G. Choghamarani and M. Baghbanzadeh, J. Iran. Chem. Soc. 3 (2006) 73; c) M.A. Zolfigol, A. Ghorbani Choghamarani, M. Shahamirian, M. Safaiee, I. Mohammadpoor-Baltork, S. Mallakpour and M. Abdollahi-Alibeik, Tetrahedron Lett. 46 (2005) 5581. and references cited therein.

[21] I. Loev, K.M. Snader. J. Org. Chem. 30 (1965) 1914.
[22] S. Balalaie, E. Kowsari. Monatsheft Chem. 132 (2001) 1551.
[23] J.W. Fischer, R.A Hollins, H.C.K. Lowe-Ma, R.A. Nissan & R.D. Chapman. J. Org. Chem. 61 (1996) 9340.
[24] a) M.A. Zolfigol, M. Safaiee. Synlett (2004) 827; b) M.A. Zolfigol, P. Salehi and M. Safaiee, Lett. Org. Chem. 3 (2006) 153; c) M.A. Zolfigol, P. Salehi, A. Khorramabadi-Zad and M. Shayegh. J. Mol. Catal. A: Chem. 261 (2007) 88.
[25] See reviews: b) E. Kolvari, A. Ghorbani-Chghamarani, P. Salehi, F. Shirini and M.A. Zolfigol, J. Iran. Chem. Soc. 4 (2007) 126; c) F. Shirini, M.A. Zolfigol, P. Salehi and M. Abedini, Curr. Org. Chem. 12 (2008), 183.