Tetrahedron Letters 52 (2011) 5930–5933

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

A two-step synthesis of 1,5-disubstituted tetrazoles containing a siloxy or sulfonamide group

Afshin Sarvary [a], Shabnam Shaabani [a], Ahmad Shaabani [a,*], SeikWeng Ng [b]

[a] Department of Chemistry, Shahid Beheshti University, G. C., PO Box 19396 4716, Tehran, Iran
[b] Department of Chemistry, University of Malaya, 50603 Kuala Lumpur, Malaysia

ARTICLE INFO

Article history:
Received 16 May 2011
Revised 9 August 2011
Accepted 19 August 2011
Available online 7 September 2011

Keywords:
1,5-Disubstituted tetrazole
Ketenimine
Isocyanide
Multicomponent

ABSTRACT

A simple two-step route to the synthesis of 1,5-disubstituted tetrazoles containing a β-siloxy or β-sulfonamide group is presented. The synthesis takes place via an isocyanide-based multicomponent reaction and allows incorporation of a wide variety of substitution patterns starting from commercially available reagents. This is followed by cyclization of the ketenimines with trimethylsilyl azide without using any catalyst or activation.

1,5-Disubstituted tetrazoles are useful heterocycles because of their biological and pharmacological properties. They function as NADPH oxidase inhibitors,[1a] glucokinase activators,[1b] α-methylene tetrazole based peptidomimetic HIV protease inhibitors,[1c] calcitonin gene-related peptide receptor antagonists, and antimigraine agents.[1d] Furthermore, 1,5-disubstituted tetrazoles are useful synthetic intermediates[2a] for the synthesis of energetic salts,[2b] 3,4-dihydropyrimidin-2(1*H*)-ones,[2c] piericidins,[2d] (+)-*trans*-5-allylhexahydroindolizidin-3-ones,[2e] acacetin,[2f] (+)-strictifolione,[2g] vinylsilanes,[2h] and leucascandrolide A.[2i] Moreover, in the design of peptidomimetics, it is often possible to enhance the pharmacological properties of a molecule by replacing amides with amide isosteres. Common replacements which mimic *cis* amides are 1,5-disubstituted tetrazoles.[3]

The synthesis of 1,5-disubstituted tetrazoles has generated significant interest.[4–8] The most direct synthetic routes to 1,5-disubstituted tetrazoles are via intermolecular cycloaddition reactions and conversion of substituted tetrazoles into 1,5-disubstituted tetrazoles.[4] Moreover, isocyanide-based reactions have been used for the preparation of 1,5-disubstituted tetrazoles. The first synthesis of these compounds via isocyanide-based reactions was undertaken by Ugi and Meyr, in which they reported the synthesis of 1,5-disubstituted tetrazoles using a Passerini three-component reaction (P-3CR) of isocyanides, highly reactive carbonyl compounds, and hydrazoic acid (HN_3).[5] Nixey and Hulme developed a $TMSN_3$-modified P-3CR for the synthesis of these compounds.[6] Also, the Ugi four-component reaction (U-4CR) of isocyanides with amines, aldehydes or ketones, and $TMSN_3$ affords 1,5-disubstituted tetrazoles.[7] The corresponding tetrazoles were also obtained via isocyanide-based reactions, according to a sequential one-pot procedure.[8] Therefore, development of a new synthetic approach not requiring any catalyst under mild reaction conditions that could be used to prepare a variety of these templates remains an important task.

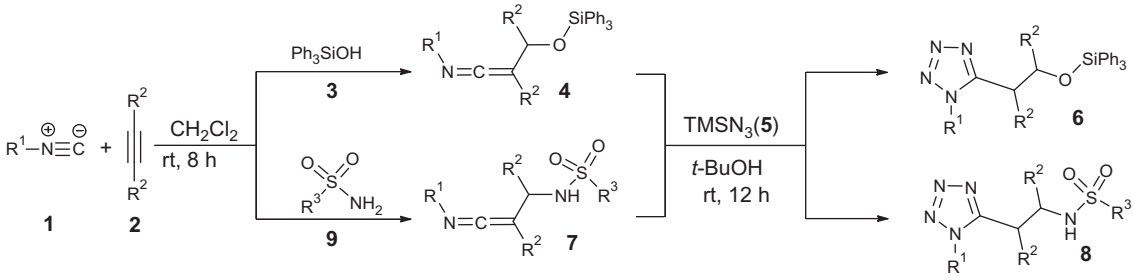
It has been shown that addition of isocyanides to electron-deficient alkynes, such as dimethyl acetylenedicarboxylate (DMAD) generates zwitterionic species. These reactive intermediates can be trapped by a third component, such as CH-acids,[9] NH-acids like amides,[10] OH-acids like oximes[11], and carboxylic acids.[12]

Due to the above-mentioned reasons and as part of our ongoing research on isocyanide-based multicomponent reactions (IMCRs),[13] a simple two-step strategy for the preparation of 1,5-disubstituted tetrazoles containing siloxy **6** or sulfonamide **8** groups via an IMCR, followed by intermolecular cycloaddition reaction of the intermediate ketenimines **4** or **7** with trimethylsilyl azide (without using any catalyst or activation), is reported (Scheme 1). To the best of our knowledge, these ketenimines have not been used previously in intermolecular cycloaddition reactions.

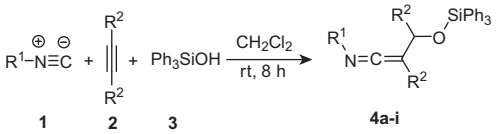
As indicated in Scheme 2, isocyanides **1**, dialkylacetylenedicarboxylates **2,** and triphenylsilanol **3** undergo a smooth 1:1:1 addition reaction to produce, selectively, stable ketenimines **4a–i** containing a siloxy group in high yields in CH_2Cl_2 (Table 1). All of the products are new compounds and their structures were deduced from their IR, mass, ^1H NMR, and ^{13}C NMR spectra. It is important to

* Corresponding author. Tel.: +98 2129902800; fax: +98 2122431663.
E-mail address: a-shaabani@cc.sbu.ac.ir (A. Shaabani).

0040-4039/$ - see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2011.08.114



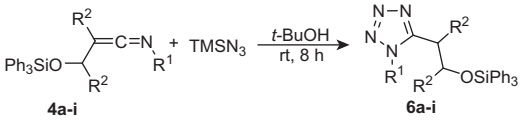
Scheme 1. Synthesis of 1,5-disubstitutedtetrazoles.



Scheme 2.

Table 1
Synthesis of ketenimine derivatives **4a–i**

Entry	R^1	R^2	Product	Yield (%)
1	1,1,3,3-Tetramethylbutyl	CO_2Me	**4a**	92
2	1,1,3,3-Tetramethylbutyl	CO_2Et	**4b**	91
3	1,1,3,3-Tetramethylbutyl	CO_2t-Bu	**4c**	84
4	*t*-Bu	CO_2Me	**4d**	94
5	*t*-Bu	CO_2Et	**4e**	90
6	*t*-Bu	CO_2t-Bu	**4f**	85
7	Cyclohexyl	CO_2Me	**4g**	96
8	Cyclohexyl	CO_2Et	**4h**	93
9	Cyclohexyl	CO_2t-Bu	**4i**	84



Scheme 3.

Table 2
Synthesis of 1,5-disubstituted tetrazoles **6a–i** containing a siloxy group

Entry	R^1	R^2	Product	Yield (%) (*anti*:*syn*)[a]
1	1,1,3,3-Tetramethylbutyl	CO_2Me	**6a**	83 (84:16)
2	1,1,3,3-Tetramethylbutyl	CO_2Et	**6b**	86 (100:Trace)
3	1,1,3,3-Tetramethylbutyl	CO_2t-Bu	**6c**	81 (100:Trace)
4	*t*-Bu	CO_2Me	**6d**	85 (100:Trace)
5	*t*-Bu	CO_2Et	**6e**	85 (77:23)
6	*t*-Bu	CO_2t-Bu	**6f**	79 (66:34)
7	Cyclohexyl	CO_2Me	**6g**	80 (26:74)
8	Cyclohexyl	CO_2Et	**6h**	82 (23:77)
9	Cyclohexyl	CO_2t-Bu	**6i**	78 (12:88)

[A] *Anti*:*syn* ratio determined from the ^{1}H NMR spectra of the crude mixtures.

note that trapping of the initially formed 1:1 intermediate with triphenylsilanol has not been reported until now.

Next, the intermolecular cycloaddition reaction of siloxy ketenimines with trimethylsilyl azide was investigated. In a pilot experiment, a mixture of ketenimine **4a** and trimethylsilyl azide (**5**) was stirred in *tert*-butanol at room temperature for 8 h to give product **6a** in 83% yield.

To explore the scope and limitations of this reaction, the procedure was extended to various siloxy ketenimine derivatives **4b–i**.

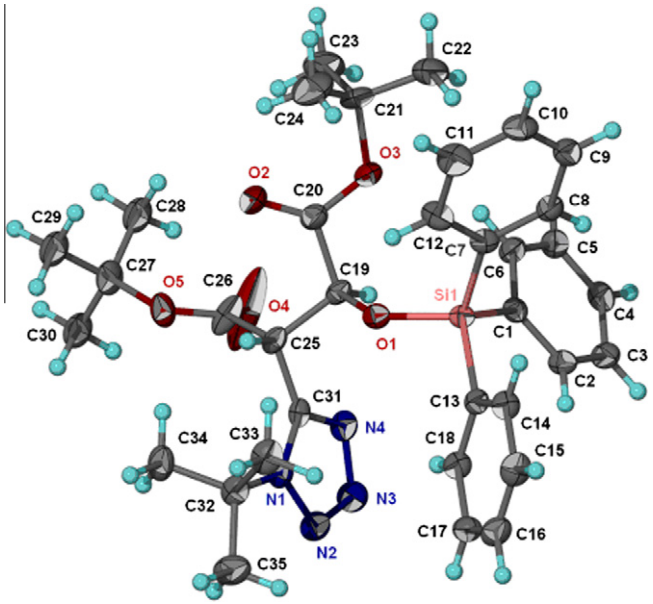
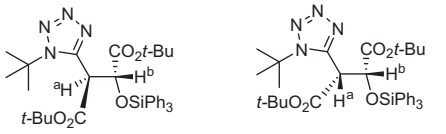
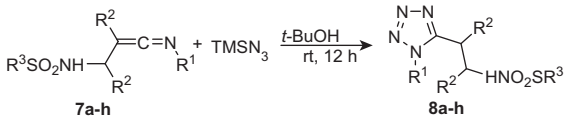


Figure 1. ORTEP representation of **6f** (CCDC 817391).



(2*R*,3*S*)- or (2*S*,3*R*)-**6f** (2*R*,3*R*)-, or (2*S*,3*S*)-**6f'**

Figure 2. NOE studies of compounds **6f** and **6f'**.



Scheme 4.

As indicated in Scheme 3, the reactions proceeded very efficiently, and led to the formation of the corresponding siloxy 1,5-disubstituted tetrazoles **6b–i** in good yields (Table 2). Because of the diversity of substitution patterns possible, this reaction can be used to create combinatorial libraries.

The structures of products **6a–i** were deduced from their IR, mass, ^{1}H NMR, and ^{13}C NMR spectra. The mass spectra of these compounds displayed molecular ion peaks at the appropriate *m*/*z* values. The structure of compound **6f** was confirmed unambiguously by single-crystal X-ray analysis (Fig. 1).

Table 3
Synthesis of 1,5-disubstituted tetrazoles **8a–h** containing a sulfonamide group

Entry	R^1	R^2	R^3	Product	Yield (%) (*anti*:*syn*)[a]
1	Cyclohexyl	CO_2Me	Ph	**8a**	71 (83:17)
2	Cyclohexyl	CO_2Me	4-MeC_6H_4	**8b**	68 (77:23)
3	Cyclohexyl	CO_2Et	4-MeC_6H_4	**8c**	70 (85:15)
4	Cyclohexyl	CO_2t-Bu	Ph	**8d**	73 (66:34)
5	Cyclohexyl	CO_2t-Bu	4-MeC_6H_4	**8e**	67 (75:25)
6	1,1,3,3-Tetramethylbutyl	CO_2Me	Ph	**8f**	78 (67:33)
7	1,1,3,3-Tetramethylbutyl	CO_2Et	Ph	**8g**	74 (74:26)
8	*t*-Bu	CO_2Et	Ph	**8h**	73 (70:30)

[A] *Anti*:*syn* ratio determined from the ^1H NMR spectra of the crude mixtures.

Compounds **6** have two stereogenic centers, and as indicated in Figure 2, two pairs of diastereoisomers are expected. The ^1H NMR and ^{13}C NMR spectra of the crude reaction mixtures obtained for the products (except **6b–d**) were consistent with two diastereoisomers. On the basis of ^1H homonuclear *J* couplings ($^3J_{HH}$) and NOE measurements, the *R*,*S* or *S*,*R* diastereoisomer (*anti* arrangement) was the major diastereoisomer. For example, the $^3J_{HH}$ values of the vicinal methine protons (H^a and H^b) in diastereoisomers **6f** and **6f′** were 10.0 and 7.6 Hz, respectively. Also NOE studies on diastereoisomer **6f′**, showed that H^a exhibited an NOE (3.7%) after the irradiation of H^b. The same trend was not observed for diastereoisomer **6f**. These results indicate that the major diastereoisomer has an *anti* arrangement (*R*,*S* or *S*,*R*) and that the minor diastereoisomer has a *syn* arrangement (*R*,*R* or *S*,*S*) (Fig. 2).

N-Arylsulfonamides constitute an important class of therapeutic agents in medicinal chemistry and more than 30 drugs containing this moiety are known.[14] In this respect, the synthesis of tetrazoles containing a sulfonamide group is relevant. Therefore, the versatility of this intermolecular cycloaddition reaction with respect to ketenimines **7a–h** was studied.[10a] As shown in Scheme 4, reaction of ketenimine derivatives **7a–h** containing a sulfonamide group with trimethylsilyl azide (**5**) in *tert*-butanol led to the formation of a new class of 1,5-disubstituted tetrazole derivatives **8a–h** in high yields after 12 h at room temperature. Representative products of this reaction are shown in Table 3. The ^1H NMR and ^{13}C NMR spectra of the crude reaction mixtures showed the presence of two pairs of diastereoisomers.

In summary, we have demonstrated an efficient and simple route for the preparation of 1,5-disubstituted tetrazole derivatives containing siloxy and sulfonamide groups from readily available substrates in fairly good yields. The advantages of the present procedure are as follows: the reaction is performed by simple mixing of the starting materials, requires neutral reaction conditions, and displays good functional group tolerance. To the best of our knowledge, this reaction is the first example of the conversion of siloxy- or sulfonamide-ketenimines into the corresponding 1,5-disubstituted tetrazoles.

Synthesis of dimethyl 2-[(2,4,4-trimethylpentan-2-ylimino)methylene]-3-(triphenylsilyloxy)succinate (4a)

Typical procedure: To a magnetically stirred solution of triphenylsilanol (0.28 g, 1.0 mmol) and dimethyl acetylenedicarboxylate (0.14 g, 1.0 mmol) in CH_2Cl_2 (10 mL) was added, 1,1,3,3-tetramethylbutyl isocyanide (0.14 g, 1.0 mmol). The mixture was stirred for 8 h at room temperature. The solvent was removed under vacuum and the product was obtained as a yellow oil (no further purification was required) yield 0.51 g (92%); IR (KBr) ν_{max} = 2945, 2062, 1752, 1700, 1433 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 1.14 (9H, s, $(CH_3)_3$), 1.56 (6H, s, $(CH_3)_2$), 1.71 (2H, brs, CH_2), 3.56 (3H, s, OCH_3), 3.65 (3H, s, OCH_3), 5.39 (1H, s, CH–OSi), 7.32–7.82 (15H, m, H–Ar) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 31.2, 31.4, 31.5, 31.8, 51.4, 51.9, 54.7, 65.3, 66.2, 69.4, 127.9, 130.2, 135.1, 135.7, 164.7, 169.0, 171.8 ppm. Anal. Calcd for $C_{33}H_{39}NO_5Si$: C, 71.06; H, 7.05; N, 2.51. Found: C, 72.32; H, 6.80; N, 2.66.

Synthesis of dimethyl 2-[1-(2,4,4-trimethylpentan-2-yl)-1*H*-tetrazol-5-yl]-3-(triphenylsilyloxy)succinate (6a)

Typical procedure: To a magnetically stirred solution of ketenimine **4a** (0.56 g, 1 mmol) in *t*-BuOH (5 mL) was added trimethylsilyl azide (0.12 g, 1 mmol) and the reaction mixture was stirred for 12 h at room temperature. After completion of the reaction as indicated by TLC, the mixture was purified by silica gel column chromatography using *n*-hexane: AcOEt (3:1) to afford the product as a yellow oil, yield 0.5 g (83%); IR (KBr) ν_{max} = 2936, 2863, 1734, 1593, 1436 cm^{-1}; MS, *m*/*z* (%): 685 (M^+−77, 5), 457 (2), 429 (2), 411 (100), 351 (25), 277 (25), 213 (50), 97 (20), 57 (70); ^1H NMR (300 MHz, $CDCl_3$): δ = 0.77–2.19 [34H, m, $(CH_3)_3$, $(CH_3)_2$ and CH_2(*R*,*S* and *R*,*R*)], 3.22 [3H, s, OCH_3(*R*,*R*)], 3.32 [3H, s, OCH_3(*R*,*S*)], 3.48 [3H, s, OCH_3(*R*,*R*)], 3.65 [3H, s, OCH_3(*R*,*S*)], 4.90 [1H, d, $^3J_{HH}$ = 9.2 Hz, CH(*R*,*R*)], 5.12 [1H, d, $^3J_{HH}$ = 11.4 Hz, CH(*R*,*S*)], 5.18 [1H, d, $^3J_{HH}$ = 11.4 Hz, CH(*R*,*S*)], 5.49 [1H, d, $^3J_{HH}$ = 9.2 Hz, CH(*R*,*R*)], 7.25–7.67 [30H, m, H–A*R*(*R*,*S* and *R*,*R*)] ppm; ^{13}C NMR (75 MHz, $CDCl_3$) *R*,*S*: δ = 29.7, 30.9, 31.6, 46.2, 52.8, 54.5, 61.1, 65.9, 73.2, 127.8, 130.3, 132.3, 135.5, 150.4, 167.2, 170.7 ppm. Anal. Calcd for $C_{33}H_{40}N_4O_5Si$: C, 65.97; H, 6.71; N, 9.33. Found: C, 66.29; H, 6.35; N, 9.74.

Acknowledgment

We gratefully acknowledge financial support from the Research Council of Shahid Beheshti University.

Supplementary data

Supplementary data (experimental procedure and spectral data) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.08.114.

References and notes

1. (a) Seki, M.; Tarao, Y.; Yamada, K.; Nakao, A.; Usui, Y.; Komatsu, Y. PCT Int. Appl. WO 2005-JP2974, 2005; *Chem. Abstr.* **2005**, *143*, 266938.; (b) Nonoshita, K.; Ogino, Y.; Ishikawa, M.; Sakai, F.; Nakashima, H.; Nagae, Y.; Tsukahara, D.; Arakawa, K.; Nishimura, T.; Eiki, J. PCT Int. Appl. WO 2004-JP19843, 2005; *Chem. Abstr.* **2005**, *143*, 153371.; (c) May, B. C. H.; Abell, A. D. *J. Chem. Soc., Perkin. Trans. 1* **2002**, 172–178; (d) Luo, G.; Chen, L.; Degnan, A. P.; Dubowchik, G. M.; Macor, J. E.;Tora, G. O.; Chaturvedula, P. V. PCT Int. Appl. WO 2004-US40721, 2005; *Chem. Abstr.* **2005**, *143*, 78091.
2. (a) Brigas, A. F. In *Science of Synthesis*; Storr, R. C., Gilchrist, T. L., Eds.; Thieme: Stuttgart, 2004; Vol. 13, p 861; (b) Liotta, C. L.; Pollet, P.; Belcher, M. A.; Aronson, J. B.; Samanta, S.; Griffith, K. N. US 2005, 269, 001, 2005; *Chem. Abstr.* **2004**, *144*, 37926.; (c) Frija, L. M. T.; Khmelinskii, I. V.; Cristiano, M. L. S. *Tetrahedron Lett.* **2005**, *46*, 6757–6760; (d) Schnermann, M. J.; Boger, D. L. *J. Am. Chem. Soc.* **2005**, *127*, 15704–17705; (e) Potts, D.; Stevenson, P. J.; Thompson, N. *Tetrahedron Lett.* **2000**, *41*, 275–278; (f) Quintin, J.; Lewin, G. *J. Nat. Prod.* **2004**, *67*, 1624–1627; (g) Enders, D.; Lenzen, A.; Muller, M. *Synthesis* **2004**, 1486–

1496; (h) Jankowski, P.; Plesniak, K.; Wicha, J. *Org. Lett.* **2003**, *5*, 2789–2792; (i) Fettes, A.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2002**, *41*, 4098–4101.
3. (a) Zabrocki, J.; Smith, G. D.; Dunbar, J. B.; Iijima, H.; Marshall, G. R. *J. Am. Chem. Soc.* **1988**, *110*, 5875–5880; (b) Yu, K. L.; Johnson, R. L. *J. Org. Chem.* **1987**, *52*, 2051–2059.
4. Katritzky, A. R.; Cai, C.; Meher, N. K. *Synthesis* **2007**, 1204–1208. References cited therein.
5. Ugi, I.; Meyr, R. *Chem. Ber.* **1961**, *94*, 2229–2233.
6. Nixey, T.; Hulme, C. *Tetrahedron Lett.* **2002**, *43*, 6833–6835.
7. (a) Borisov, R. S.; Polyakov, A. I.; Medvedeva, L. A.; Khrustalev, V. N.; Guranova, N. I.; Voskressensky, L. G. *Org. Lett.* **2010**, *12*, 3894–3897; (b) Nayak, M.; Batra, S. *Tetrahedron Lett.* **2010**, *51*, 510–516; (c) Giustiniano, M.; Pirali, T.; Massarotti, A.; Biletta, B.; Novellino, E.; Campiglia, P.; Sorba, G.; Tron, G. C. *Synthesis* **2010**, 4107–4118; (d) Marcos, C. F.; Marcaccini, S.; Menchi, G.; Pepinob, R.; Torroba, T. *Tetrahedron Lett.* **2008**, *49*, 149–152; (e) Marcaccini, S.; Torroba, T. *Nature Protocols* **2007**, *2*, 632–639; (f) Nixey, T.; Kelly, M.; Semin, D.; Hulme, C. *Tetrahedron Lett.* **2002**, *43*, 3681–3684; (g) Nixey, T.; Kelly, M.; Hulme, C. *Tetrahedron Lett.* **2000**, *41*, 8729–8733.
8. (a) El Kaim, L.; Grimaud, L.; Patil, P. *Org. Lett.* **2011**, *13*, 1261–1263; (b) Coffinier, D.; El Kaim, L.; Grimaud, L. *Org. Lett.* **2009**, *11*, 1825–1827; (c) Kiselyov, A. S. *Tetrahedron Lett.* **2005**, *46*, 4851–4854.
9. (a) Esmaeili, A.; Hosseinabadi, R.; Habibi, A. *Synlett* **2010**, 477–1480; (b) Shaabani, A.; Sarvary, A.; Rezayan, A. H.; Keshipour, S. *Tetrahedron* **2009**, *65*, 3492–3495; (c) Shaabani, A.; Ghadari, R.; Sarvary, A.; Rezayan, A. H. *J. Org. Chem.* **2009**, *74*, 4372–4374.
10. (a) Shaabani, A.; Sarvary, A.; Ghasemi, S.; Rezayan, A. H.; Ghadari, R.; Ng, S. W. *Green Chem.* **2011**, *13*, 582–585; (b) Adib, M.; Sayahi, M. H.; Nosrati, M.; Zhu, L. G. *Tetrahedron Lett.* **2007**, *48*, 4195–4198; (c) Yavari, I.; Alizadeh, A.; Anary-Abbasinejad, M.; Bijanzadeh, H. R. *Tetrahedron* **2003**, *59*, 6083–6086.
11. Alizadeh, A.; Rostamnia, S. *Synthesis* **2008**, 57–60.
12. Alizadeh, A.; Oskueyan, Q.; Rostamnia, S.; Ghanbari-Niaki, A.; Mohebbi, A. R. *Synthesis* **2008**, 2929–2932.
13. Shaabani, A.; Maleki, A.; Rezayan, A. H.; Sarvary, A. *Mol. Divers.* **2011**, *15*, 41–68.
14. (a) Casini, A.; Scozzafava, A.; Supuran, C. T. *Expert Opin. Ther. Pat.* **2002**, *12*, 1307–1327; (b) Scozzafava, A.; Owa, T.; Mastrolorenzo, A.; Supuran, C. T. *Curr. Med. Chem.* **2003**, *10*, 925–953; (c) Nelson, D. W.; Gregg, R. J.; Kort, M. E.; Perez-Medrano, A.; Voight, E. A.; Wang, Y.; Grayson, G.; Namovic, M. T.; Donnelly-Roberts, D. L.; Niforatos, W.; Honore, P.; Jarvis, M. F.; Faltynek, C. R.; Carroll, W. A. *J. Med. Chem.* **2006**, *49*, 3659–3666.