

## A Novel, Fast and Efficient One-Pot Four-Component Procedure for Preparation of Some Alkyl Spiro[indeno[1,2-*b*]quinoxaline-11,3'-pyrrolizine]-2'-carboxylates

A. Alizadeh Karsalary<sup>a</sup>, M.R. Mohammadizadeh<sup>b,\*</sup>, A.R. Hasaninejad<sup>b</sup>, A.A. Mohammadi<sup>c</sup> and A.R. Karimi<sup>d</sup>

<sup>a</sup>Department of Chemistry, Islamic Azad University, Savad Kooch Branch, P.O. Box 155, Savad Kooch, Iran

<sup>b</sup>Department of Chemistry, Faculty of Sciences, Persian Gulf University, Bushehr 75169, Iran

<sup>c</sup>Department of Chemistry, Faculty of Sciences, Shahid Beheshti University, P.O. Box 19395-4716, Tehran, Iran

<sup>d</sup>Department of Chemistry, Arak University, Arak 38156, Iran

(Received 5 September 2008, Accepted 24 October 2008)

In this study we report a novel one-pot reaction which stereoselectively affords alkyl spiro[indeno[1,2-*b*]quinoxaline-11,3'-pyrrolizine]-2'-carboxylates *via* the four-component condensation of ninhydrin, phenylenediamines, proline, and acrylic acid derivatives. The reactions were run in ethanol and completed at less than 25 min and the products were obtained in very good yields. The stereochemistry of the products was deduced on the basis of the <sup>1</sup>H NOESY and comparison with the related systems.

**Keywords:** Ninhydrin, Phenylenediamines, Proline, Alkyl acrylates, Alkyl spiro[indeno[1,2-*b*]quinoxaline-11,3'-pyrrolizine]-2'-carboxylates

---

### INTRODUCTION

Multi-component reactions (MCRs) are one-pot processes in which three or more components come together to form a product containing substantial elements of all the reactants [1,2]. They provide an inherently more efficient approach to chemical synthesis than the conventional bimolecular reactions, and considerable current effort is focused on the development of new MCRs [3].

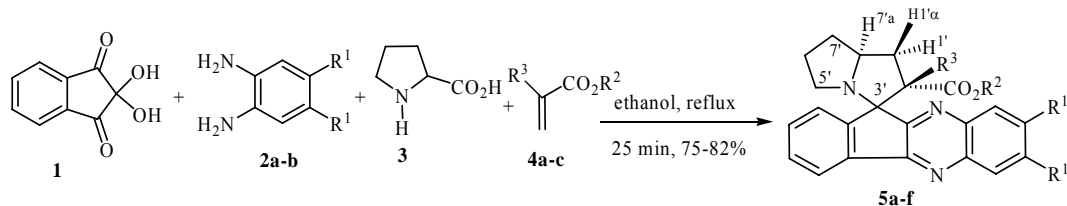
Indenoquinoxaline derivatives are important classes of nitrogen containing heterocycles which constitute useful intermediates in organic synthesis [4]. They have been reported for their applications in dyes and have also been used as building blocks for the synthesis of organic semiconductors. More interestingly, research has revealed that these compounds exhibit diverse medicinal functions such as antimetabolism and antitubercular properties [5].

Pyrrolizine and indolizine skeletons, partially or totally saturated, are present in a large array of alkaloids and related unnatural compounds. Such compounds exhibit potent biological activities, particularly as glycosidase inhibitors. They consequently have a cytostatic effect that has potential applications in antitumour and antiviral chemotherapy. For example, ML3000 ([2,2-dimethyl-6-(4-chlorophenyl)-7-phenyl-2,3-dihydro-1H-pyrrolizine-5-yl]-acetic acid) is a new pyrrolizine compound with a balanced inhibitory effect on COX and 5-LOX in the submicromolar range. ML3000 has demonstrated anti-inflammatory, analgesic, antipyretic, anti-asthmatic, and antiplatelet aggregation activity, plus high gastrointestinal tolerance in animal models. It is currently in Phase III clinical trials for the treatment of osteoarthritis [6].

The cycloaddition of azomethine ylides to alkenes is an important way to synthesize heterocycles containing pyrrolidine substructures with high stereoselectivity. The stereoselectivity of these cycloaddition reactions is greatly enhanced if the azomethine ylide functionality is part of an N-

---

\*Corresponding author. E-mail: mrmohamadizadeh@pgu.ac.ir



Scheme 1

heterocycle, thus providing a rather rigid ring template that results in a better diastereofacial approach between dipolar and dipolarophile [7]. Cyclic azomethine ylides, in which the central nitrogen atom is part of a pyrrolidine ring, are of particular importance, since they can be directly transformed into pyrrolizidine rings through a cycloaddition reaction with alkenes in a highly stereoselective way [8].

To pursue our interest in the synthesis of nitrogen containing heterocycles [9] and as a part of our ongoing studies on ninhydrin-based multi-component reactions [10], and due to the resultant pharmacological interest in pyrrolizidine alkaloids, here we report a novel, one-pot reaction which affords alkyl spiro[indeno[1,2-*b*]quinoxaline-11,3'-pyrrolizidine]-2'-carboxylates **5** *via* the four-component condensation of ninhydrin **1**, phenylenediamine **2**, proline **3**, and acrylic acid derivative **4** in ethanol in very good yields (Scheme 1).

## EXPERIMENTAL

Melting points were measured on the Electrothermal 9100 apparatus and are uncorrected. Infrared spectra were measured on a Shimadzu IR-470 Spectrophotometer. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded in CDCl<sub>3</sub> on a bruker 500 DRX AVNCE at 500 and 125 MHz, respectively. MS spectra were taken by Shimadzu QP 1100EX Mass Spectrometer operating at an ionization potential of 70 eV. CHN Elemental analyses were performed using a Heracus CHN-O-Rapid analyzer. Chemicals were of commercial grade and used without further purification.

### General Procedure for the Four-Component Diastereoselective Synthesis of Spiro Pyrrolizidines

Proline (0.115 g, 1 mmol) and ethyl acrylate (0.11 ml, 1 mmol) were added to a solution of ninhydrin (0.178 g, 1

mmol) and 1,2-phenylenediamine (0.108 g, 1 mmol) in ethanol (5 ml) and the mixture was refluxed for 25 min. Progress of the reaction was monitored by t.l.c using n-hexane/ethyl acetate (10/5) mixture as eluent. The reaction mixture was cooled to room temperature, water was added and the separated solid was filtered off and recrystallized from ethanol to give pure **5b** (80%).

### Selected Physical and Spectroscopic Data of Isolated Products

**Methyl 1',2',5',6',7',7'<sup>1a</sup>-hexahydrospiro[indeno[1,2-*b*]quinoxaline-11,3'-pyrrolizidine]-2'-carboxylate (5a).** Cream solid, m.p.: 108-110 °C; IR (KBr): 1746 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ (ppm) 1.72 (m, 1H, pyrrolizidine protons (pyp)), 2.00 (m, 2H, pyp), 2.22 (m, 1H, pyp), 2.48 (m, 3H, pyp), 2.63 (dt, 12.8, 6.5, Hz, 1H, H<sup>1'α</sup>), 2.98 (s, 3H, O-CH<sub>3</sub>), 4.32 (m, 1H, H<sup>7'a</sup>), 4.37 (dd, J = 12.8, 6.9 Hz, 1H, H<sup>2'</sup>), 7.58, 7.74, 8.14, 8.25, 8.29 (m, 8H, arom); <sup>13</sup>C NMR (CDCl<sub>3</sub>): δ (ppm) 29.4, 33.6, 34.0, 47.6, 51.6, 57.3, 65.3, 75.0, 122.8, 127.0, 129.2, 129.4, 129.8, 130.0, 130.3, 132.0, 138.6, 142.8, 143.3, 145.2, 153.9, 165.0, 171.3; MS m/z (%): 371 (M<sup>+</sup>, 3), 289 (20), 256 (25), 83 (100). Anal. Calcd. For C<sub>23</sub>H<sub>21</sub>N<sub>3</sub>O<sub>2</sub>: C, 74.37; H, 5.70; N, 11.31. Found: C, 74.29; H, 5.78; N, 11.25.

**Ethyl 1',2',5',6',7',7'<sup>1a</sup>-hexahydrospiro[indeno[1,2-*b*]quinoxaline-11,3'-pyrrolizidine]-2'-carboxylate (5b).** Light yellow solid; m.p.: 159-160 °C (dec.); IR (KBr): 1742 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ (ppm) 0.47 (t, J = 7.1 Hz, 3H, O-CH<sub>2</sub>-CH<sub>3</sub>), 1.71 (m, 1H, pyp), 2.00 (m, 2H, pyp), 2.22 (m, 1H, pyp), 2.50 (m, 3H, pyp), 2.62 (dt, 13.0, 6.7, Hz, 1H, H<sup>1'α</sup>), 3.39 (dq, J = 10.7, 7.1 Hz, 1H, O-CH<sub>2</sub>), 3.55 (dq, J = 10.7, 7.1 Hz, 1H, O-CH<sub>2</sub>), 4.32 (m, 1H, H<sup>7'a</sup>), 4.37 (dd, 12.9, 6.9 Hz, 1H, H<sup>2'</sup>), 7.57, 7.76, 8.14, 8.25, 8.30 (m, 8H, arom); <sup>13</sup>C NMR (CDCl<sub>3</sub>): δ (ppm) 13.8, 29.5, 33.0, 34.1, 47.2, 57.3, 60.3, 65.4, 74.5, 122.7, 127.8, 129.7, 129.9, 130.0, 130.5, 130.6, 132.2, 138.5, 142.5, 143.1, 145.4, 154.0, 165.8, 170.4; MS m/z (%):

385 (M<sup>+</sup>, 20), 303 (48), 256 (52), 83 (100). Anal. Calcd. For C<sub>24</sub>H<sub>23</sub>N<sub>3</sub>O<sub>2</sub>: C, 74.78; H, 6.01; N, 10.90. Found: C, 74.70; H, 6.09; N, 11.05.

NOE (%): irradiation of H<sup>1 $\alpha$</sup>  caused enhancement of H<sup>2</sup> (10.4) and H<sup>7 $\alpha$</sup>  (1.9).

**Methyl 7,8-dimethyl-1',2',5',6',7',7'<sup>ia</sup>-hexahydrospiro[indeno[1,2-*b*]quinoxaline-11,3'-pyrrolizine]-2'-carboxylate (5c).** Cream solid, m.p.: 170-172 °C; IR (KBr): 1744 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  (ppm) 1.68, 1.69 (m, 2H, pyp), 1.90, 2.05 (m, 2H, pyp), 2.21 (m, 1H, pyp), 2.34 (m, 2H, pyp), 2.49 (m, 1H, H<sup>1 $\alpha$</sup> ), 2.50 (s, 3H, CH<sub>3</sub>), 2.51 (s, 3H, CH<sub>3</sub>), 2.87 (s, 3H, O-CH<sub>3</sub>), 4.04 (m, 1H, H<sup>7 $\alpha$</sup> ), 4.15 (dd, J = 12.6, 6.6 Hz, 1H, H<sup>2</sup>), 7.57, 7.90, 8.06 (m, 6H, arom); <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  (ppm) 20.5, 20.6, 29.6, 33.0, 34.1, 47.2, 51.7, 57.3, 65.3, 74.4, 122.4, 127.6, 128.8, 129.1, 130.4, 131.7, 138.5, 140.1, 140.5, 141.3, 141.7, 145.0, 152.9, 164.5, 171.0; MS m/z (%): 399 (M<sup>+</sup>, 9), 232 (25), 83 (100). Anal. Calcd. For C<sub>25</sub>H<sub>25</sub>N<sub>3</sub>O<sub>2</sub>: C, 75.16; H, 6.31; N, 10.52. Found: C, 75.24; H, 6.33; N, 10.44.

NOE (%): irradiation of H<sup>1 $\alpha$</sup>  caused enhancement of H<sup>2</sup> (9.3) and H<sup>7 $\alpha$</sup>  (1.4).

**Ethyl 7,8-dimethyl-1',2',5',6',7',7'<sup>ia</sup>-hexahydrospiro[indeno[1,2-*b*]quinoxaline-11,3'-pyrrolizine]-2'-carboxylate (5d).** Cream solid, m.p.: 222-224 °C; IR (KBr): 1746 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  (ppm) 0.31 (t, J = 7.1 Hz, 3H, O-CH<sub>2</sub>-CH<sub>3</sub>), 1.67, 1.79 (m, 2H, pyp), 1.89, 2.05 (m, 2H, pyp), 2.20 (m, 1H, pyp), 2.29, 2.35 (m, 2H, pyp), 2.45 (m, 1H, H<sup>1 $\alpha$</sup> ), 2.46 (s, 3H, CH<sub>3</sub>), 2.47 (s, 3H, CH<sub>3</sub>), 3.26 (dq, J = 10.8, 7.1 Hz, 1H, O-CH<sub>2</sub>), 3.39 (dq, J = 10.8, 7.1 Hz, 1H, O-CH<sub>2</sub>), 4.03 (m, 1H, H<sup>7 $\alpha$</sup> ), 4.14 (dd, 12.8, 6.7 Hz, 1H, H<sup>2</sup>), 7.57, 7.91, 8.06 (m, 6H, arom); <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  (ppm) 13.8, 20.6, 20.7, 29.5, 33.0, 34.1, 47.2, 57.2, 60.2, 65.3, 75.1, 122.4, 127.7, 128.9, 129.2, 130.4, 131.6, 138.8, 140.2, 140.4, 141.2, 141.7, 145.3, 154.1, 165.0, 170.4; MS m/z (%): 413 (M<sup>+</sup>, 20), 331 (87), 285 (50), 246 (25), 83 (100); Anal. Calcd. For C<sub>26</sub>H<sub>27</sub>N<sub>3</sub>O<sub>2</sub>: C, 75.52; H, 6.58; N, 10.16. Found: C, 75.43; H, 6.50; N, 10.24.

**Ethyl 2'-methyl-1',2',5',6',7',7'<sup>ia</sup>-hexahydrospiro[indeno[1,2-*b*]quinoxaline-11,3'-pyrrolizine]-2'-carboxylate (5e).** Light yellow solid, m.p.: 118-120 °C (dec.); IR (KBr): 1744 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  (ppm) 0.61 (t, J = 7.1 Hz, 3H, O-CH<sub>2</sub>-CH<sub>3</sub>), 1.72, (m, 1H, pyp), 1.82 (s, 3H, CH<sub>3</sub>), 2.04, 2.24 (m, 3H, pyp), 2.28, 2.40 (m, 2H, pyp), 2.54 (m, 1H, pyp), 2.87 (dd, J = 12.9, 10.1 Hz, 1H, H<sup>1 $\alpha$</sup> ), 3.43 (m, 2H, O-CH<sub>2</sub>), 4.36 (m, 1H, H<sup>7 $\alpha$</sup> ), 7.53, 7.62, 7.75, 8.17, 8.23, 8.33 (m, 8H, arom);

<sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  (ppm) 13.6, 24.2, 29.7, 33.5, 41.2, 47.3, 60.8, 62.4, 63.5, 77.3, 122.5, 127.1, 129.0, 129.3, 129.7, 129.8, 130.5, 131.2, 139.2, 142.1, 143.0, 147.1, 154.4, 163.5, 174.1; MS m/z (%): 399 (M<sup>+</sup>, 25), 317 (30), 285 (100), 256 (70), 83 (90); Anal. Calcd. For C<sub>25</sub>H<sub>25</sub>N<sub>3</sub>O<sub>2</sub>: C, 75.16; H, 6.31; N, 10.52. Found: C, 75.11; H, 6.24; N, 10.62.

**Ethyl 2',7,8-trimethyl-1',2',5',6',7',7'<sup>ia</sup>-hexahydrospiro[indeno[1,2-*b*]quinoxaline-11,3'-pyrrolizine]-2'-carboxylate (5f).** Light yellow solid, m.p.: 179-180 °C (dec.); IR (KBr): 1746 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  (ppm) 0.59 (t, J = 7.1 Hz, 3H, O-CH<sub>2</sub>-CH<sub>3</sub>), 1.73, (m, 1H, pyp), 1.80 (s, 3H, CH<sub>3</sub>), 2.04, 2.24 (m, 3H, pyp), 2.27, 2.38, (m, 2H, pyp), 2.53 (m, 1H, pyp), 2.54 (s, 3H, CH<sub>3</sub>), 2.55 (s, 3H, CH<sub>3</sub>), 2.86 (dd, J = 12.8, 10.1 Hz, 1H, H<sup>1 $\alpha$</sup> ), 3.43 (m, 2H, O-CH<sub>2</sub>), 4.34 (m, 1H, H<sup>7 $\alpha$</sup> ), 7.50, 7.59, 7.93, 8.10, 8.19 (m, 8H, arom); <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  (ppm) 13.6, 20.6, 20.7, 24.2, 29.7, 33.6, 41.3, 47.3, 60.7, 62.3, 63.4, 77.3, 122.2, 127.0, 128.5, 129.6, 129.8, 130.7, 139.2, 139.4, 140.0, 140.9, 141.7, 146.9, 153.6, 162.4, 174.1; MS m/z (%): 427 (M<sup>+</sup>, 15); 345 (60), 313 (90), 284 (75), 83 (80), 41 (100); Anal. Calcd. For C<sub>27</sub>H<sub>29</sub>N<sub>3</sub>O<sub>2</sub>: C, 75.85; H, 6.84; N, 9.83. Found: C, 75.79; H, 6.89; N, 9.83.

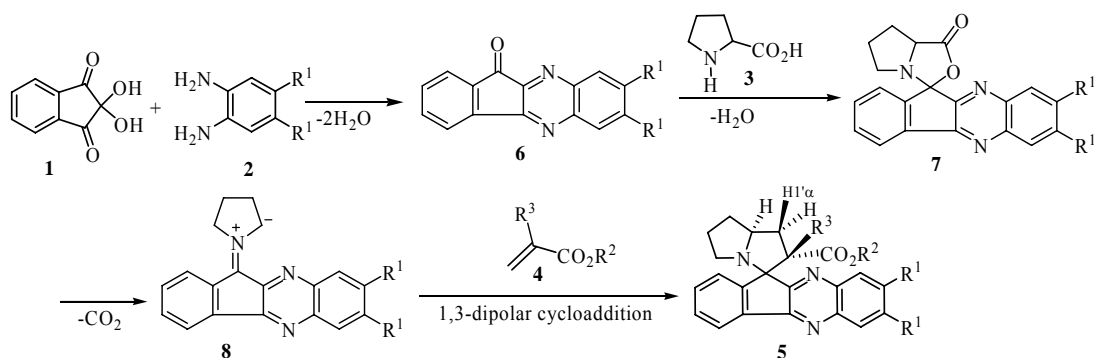
## RESULTS AND DISCUSSION

The one-pot four-component reaction proceeded fast and very cleanly at reflux temperature and no undesirable side reactions were observed. The results are shown in Table 1.

On the other hand, the products could be prepared by a two-step procedure: first, the indenoquinoxaline **6** was

**Table 1.** One-Pot Synthesis of Alkyl Spiro[indeno[1,2-*b*]quinoxaline-11,3'-pyrrolizine]-2'-carboxylate **5a-f**

5	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	Yield
<b>a</b>	H	Me	H	75
<b>b</b>	H	Et	H	80
<b>c</b>	Me	Me	H	77
<b>d</b>	Me	Et	H	75
<b>e</b>	H	Et	Me	80
<b>f</b>	Me	Et	Me	82



Scheme 2

synthesized and purified from the reaction of ninhydrin **1** and aromatic diamine **2**, and then the final product **5** was prepared *via* a three-component reaction between indenoquinoxaline **6**, proline **3** and alkyl acrylate **4**. Using this two-step procedure, the overall yield for the preparation of methyl 1',2',5',6',7',7'-a-hexahydrospiro[indeno[1,2-*b*]quinoxaline-11,3'-pyrrolizine]-2'-carboxylate **5a** was about 60%, which was much less than the one-pot four-component procedure. Moreover, a lot of time was saved using the one-pot four-component procedure.

The isolated spiro[indeno[1,2-*b*]quinoxaline-11,3'-pyrrolizine]-2'-carboxylates **5** were characterized on the basis of IR,  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectroscopy, mass spectrometry and elemental analysis. The mass spectrum of **5b** displayed the molecular ion ( $\text{M}^+$ ) peak at  $m/z$  371, which was in agreement with the estimated product. The IR spectrum of **5b** shows absorption at  $1750\text{ cm}^{-1}$  indicating the presence of ester functionality.

The  $^1\text{H}$  NMR spectrum of **5b** exhibited characteristic triplet of methyl group at  $\delta$  0.47. Because of relatively high steric repulsion between ethyl group and indenoquinoxaline cycles, rotation around O- $\text{CH}_2$  bond was restricted. Consequently, the methylene protons feel different chemical environments and, consequently, becoming diastereotopic and showed two separate doublets of quartets which were located at  $\delta = 3.39$  and  $3.55$ . Additionally,  $^1\text{H}$  NMR spectra of **5b** showed characteristic multiplets with appropriate chemical shifts and coupling constants for the ten protons of the hexahydropyrrolizine ring and the eight protons of the indenoquinoxaline ring. In the  $^{13}\text{C}$  NMR spectrum of **5b**, the spiro carbon and ester carbonyl were resonated at  $\delta$  74.5 and 170.4, respectively and the signals for all other 22 carbons

were located at appropriate chemical shifts in agreement with the proposed structure.

High diastereomeric excess of reaction was deduced on the basis of  $^1\text{H}$  NMR spectra through which no or just traces of *endo*-isomer could be detected. It is noteworthy that adducts **5** have three or four (concerning nitrogen) chiral centers, but their synthesis affords only one diastereomer, due to the dipole configuration **8** and *exo*-transition state structure, that has been mentioned by Grigg and his co-workers lately, in their extensive studies [11]. The stereochemistry of the cycloadducts **5b** was deduced on the basis of the  $^1\text{H}$  NOESY and comparison with related systems [11]. The possibility of the other isomer forming *via* an *endo*-transition state was ruled out by  $^1\text{H}$  NOESY studies. For example, irradiation of the  $\text{H}^{1\alpha}$  at  $\delta = 2.62$  caused a considerable enhancement of the signal located at  $\delta = 4.35$ , which was assigned  $\text{H}^{2'}$ . However, saturation of  $\text{H}^{1\alpha}$  at  $\delta = 2.62$  caused little enhancement of the signal for  $\text{H}^{7a}$  at  $\delta = 4.32$ , which supports the mutual *trans* arrangement of  $\text{H}^{7a}$  and  $\text{H}^{2'}$ .

The formation of the spiro[indeno[1,2-*b*]quinoxaline-11,3'-pyrrolizine] scaffold probably involves a complex multistep sequence of events. On the basis of the well-known chemistry of ninhydrin and indenoquinoxaline [12], mechanistically, it is reasonable to assume that initial condensation of the phenylenediamine **2** and the ninhydrin **1** gives indenoquinoxaline-11-one intermediate **6**, which was condensed with proline **3** to produce 1,3-dipolar azomethine ylides **8** [13]. The resulting 1,3-dipole **8** subsequently undergoes cycloaddition reaction with alkyl acrylates **4** as dipolarophile, to produce, stereoselectively, the new adduct **5** (Scheme 2).

## CONCLUSIONS

In summary, our study introduces a new and interesting ninhydrin based one-pot four-component reaction which provides a simple and direct entry into a number of interesting and novel spiro[indeno[1,2-*b*]quinoxaline-11,3'-pyrrolizine] derivatives that could be of value in biological sense.

## ACKNOWLEDGMENTS

We gratefully acknowledge the financial support from the Research Council of Savad Kooch Branch of Islamic Azad University and the research Council of Persian Gulf University.

## REFERENCES

- [1] For a monograph, see: J. Zhu, H. Bienayme, Multi-component reactions, VCH, Weinheim, Germany, 2005.
- [2] For reviews, see: a) A. Domling, I. Ugi, *Angew. Chem. Int. Ed.* 39 (2000) 3169; b) I. Ugi, S. Heck, *Comb. Chem. High Throughput Screen* 4 (2001) 1; c) L. Weber, *Drug Discovery Today* 7 (2002) 143; d) C. Hulme, V. Gore, *Curr. Med. Chem.* 10 (2003) 51; e) R.V.A Orru, M. de Greef, *Synthesis* (2003) 1471; f) D.J. Ramon, M. Yus, *Angew. Chem. Int. Ed.* 44 (2005) 1602; g) M. Syamala, *Org. Prep. Proced. Int.* 37 (2005) 103; h) A. Domling, *Chem. Rev.* 106 (2006) 17.
- [3] For selected recent examples, see: a) C. Montagne, J.J. Shiers, M. Shipman, *Tetrahedron Lett.* 47 (2006) 9207; b) M.S.A. Dondoni, A. Massi, *Acc. Chem. Res.* 39 (2006) 451; c) P. Toto, J.C. Gesquiere, N. Cousaert, B. Deprez, N. Willand, *Tetrahedron Lett.* 47 (2006) 4973; d) T. Ngouansavanh, J.P. Zhu, *Angew. Chem., Int. Ed.* 45 (2006) 3495; e) J. Pospisil, T. Kumamoto, I.E. Marko, *Angew. Chem., Int. Ed.* 45 (2006) 3357; f) G. Sklute, I.J. Marek, *J. Am. Chem. Soc.* 128 (2006) 4642.
- [4] A. Gazit, H. App, G. Mc Mahon, J. Chen, A. Levitzki, F.D. Bohmer, *J. Med. Chem.* 39 (1996) 2170.
- [5] a) U. Sehlstedt, P. Aich, J. Bergman, E.I. Vallberg, B. Norden, A. Graslund, *J. Mol. Biol.* 278 (1998) 3156; b) R.P. Trillo, *Univ. Microfilms (Ann. Arbor. Mich.)*, L.C. card no. Mic. 59-4672, 106, Dissertation Abstr. 20 (1959) 1597.
- [6] a) S. Tries, S. Laufer, *Inflammopharmacology* 9 (2001) 113; b) N.G. Argyropoulos, V.C. Sarli, M. Gdaniec, *Eur. J. Org. Chem.* (2006) 3738; c) E. Borsini, G. Brogгинi, A. Contini, G. Zecchi, *Eur. J. Org. Chem.* (2008) 2808, and references cited there in; d) H. Farsam, N. Yassa, P. Sarkhail, A. Shafiee, *Planta Med.* 66 (2000) 389; e) N. Yassa, H. Farsam, A. Shafiee, A. Rustaiyan, *Planta Med.* 62 (1996) 583; f) H. Farsam, N. Yassa, A. Shafiee, M. Amanlou, M. Biglar, T. Pourlotfali, *Pharm. Pharmacol. Lett.* 4 (1998) 79; g) N. Yassa, H. Farsam, A. Rustaiyan, A. Shafiee, *J. Sci. I.R. Iran* 10 (1999) 39.
- [7] a) W.J. Lown, in: A. Padwa (Ed.), *1,3-Dipolar Cycloaddition Chemistry*, Vol. 1, Wiley, New York, 1984, p. 653; b) R. Huisgen, A. Padwa (Eds.), *1,3-Dipolar Cycloaddition Chemistry*, Vol. 1, Wiley, New York, 1984, p. 1; c) A. Padwa (Ed.), *1,3-Dipolar Cycloaddition Chemistry*, Vol. 1, Wiley, New York, 1984, p. 227; d) E. Vedejs, in: D.P. Curran (Ed.), *Advances in Cycloadditions*, Vol. 1, JAI Press, Greenwich, CT, 1988, p. 33; e) O. Tsuge, S. Kanemasa, *Adv. Heterocycl. Chem.* 45 (1989) 231; f) A. Padwa, in: B.M. Trost, I. Fleming (Eds.), *Comprehensive Organic Synthesis*, Vol. 4, Pergamon Press, Oxford, 1991, p. 1069; g) P.A. Wade, in: B.M. Trost, I. Fleming (Eds.), *Comprehensive Organic Synthesis*, Vol. 4, Pergamon Press, Oxford, 1991, p. 1111.
- [8] a) K.V. Gothelf, K.A. Jørgensen, *Chem. Rev.* 98 (1998) 863; b) C. Najera, G.M. *Curr. Org. Chem.* 7 (2003) 1105.
- [9] a) J. Azizian, M.R. Mohammadizadeh, S. Zomorodbakhsh, A.A. Mohammad, A.R. Karimi, *Arkivoc* XV (2007) 25; b) J. Azizian, M.R. Mohammadizadeh, S. Zomorodbakhsh, A.A. Mohammad, A.R. Karimi, *Heteroatom Chem.* 16 (2005) 259; c) J. Azizian, M.R. Mohammadizadeh, A.A. Mohammad, A.R. Karimi, *J. Org. Chem.* 70 (2005) 350; d) J. Azizian, A.R. Karimi, Z. Kazemizadeh, A.A. Mohammad, M.R. Mohammadizadeh, *Synthesis* (2005) 1095; e) J. Azizian, A.R. Karimi, Z. Kazemizadeh, A.A. Mohammad, M.R. Mohammadizadeh, *J. Org. Chem.* 70 (2005) 1471.

- [10] a) J. Azizian, M.R. Mohammadizadeh, N. Karimi, Z. Kazemizadeh, A.A. Mohammad, A.R. Karimi, *Heteroatom Chem.* 16 (2005) 549; b) J. Azizian, M.R. Mohammadizadeh, A.A. Mohammad, A.R. Karimi, F. Teimouri, *Heteroatom Chem.* 18 (2007) 16; c) J. Azizian, A.R. Karimi, A.A. Mohammad, M.R. Mohammadizadeh, *Synthesis* (2004) 2263.
- [11] a) P. Allway, R. Grigg, *Tetrahedron Lett.* 32 (1991) 5817; b) T. Coulter, R. Grigg, J.F. Malone, V. Sridharan, *Tetrahedron Lett.* 32 (1991) 5417; c) R. Grigg, J. Idle, M. McMeekin, S. Surendrakumar, D. Vinod, *J. Chem. Soc., Perkin Trans. 1* (1988) 2693; d) R. Grigg, J. Idle, M. McMeekin, S. Surendrakumar, D. Vinod, *J. Chem. Soc., Perkin Trans. 1* (1988) 2703.
- [12] a) M. Friedman, *J. Agric. Food Chem.* 52 (2004) 385; b) J.L. Hallman, R.A. Bartsch, *J. Org. Chem.* 56 (1991) 6243; c) D.J. McCaldin, *Chem. Rev.* 60 (1960) 39; d) R. Shapiro, N. Chatterjie, *J. Org. Chem.* 35 (1970) 447; e) G.H. Posner, *Chem. Rev.* 86 (1986) 831.
- [13] a) G. Brogini, G. Zecchi, *Synthesis* (1999) 905; b) C. Najera, J.M. Sansano, *Angew. Chem. Int. Ed. Engl.* 44 (2005) 6272.