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

Mohammad R. Mohammadizadeh* **and Neda Firoozi**

Department of Chemistry, Faculty of Sciences, Persian Gulf University, Bushehr 75169, Iran
**E-mail: mrmohamadizadeh@pgu.ac.ir*
Received April 27, 2009, Accepted June 23, 2009

Key Words: Multicomponent reaction, Ninhydrin, Phenylenediamines, Proline, Spiro[indeno[1,2-b]quinoxaline-11,3'-pyrrolizidine]

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.[1] 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-heterocycle, thus providing a rather rigid ring template those results in a better diastereofacial approach between dipolar and dipolarophile.[2] 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.[3]

In recent years, multicomponent reactions (MCRs) have been extensively studied due to their efficiency, atom economy and convenience in construction of multiple new bonds in one pot processes, which played as powerful roles in approach to complex structures and promoted the "green chemistry".[4] In continuing our interest in synthesis of nitrogen containing heterocycles[5] and as a part of our ongoing programs on ninhydrin-based multi-component reactions,[6] 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] **5** *via* the four-component condensation of ninhydrin **1**, phenylenediamine **2**, proline **3**, and chalcone **4** in ethanol in very good yields (Scheme 1).

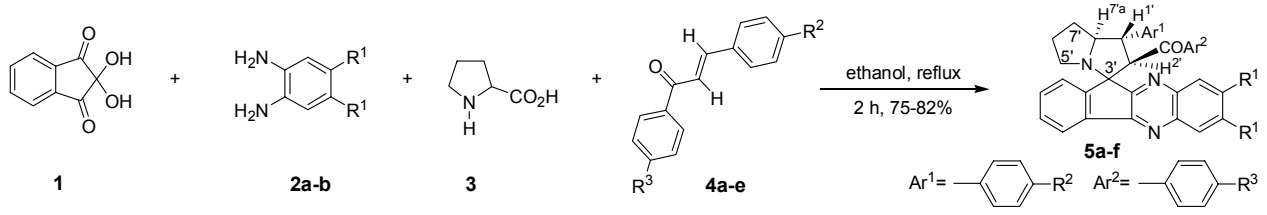
The one-pot four-component reaction proceeds fast and very cleanly at reflux temperature and no undesirable side reactions were observed. The results are shown in Table 1. The isolated spiro[indeno[1,2-b]quinoxaline-11,3'-pyrrolizine]-2'-carboxylates **5** were characterized on the basis of IR, ^{1}H and ^{13}C NMR spectroscopy and elemental analysis. The IR spectrum of **5a** shows absorption at 1695 cm^{-1} indicating the presence of carbonyl functionality. The ^{1}H NMR spectrum of **5a** exhibited characteristic multiplets of pyrrolizidine ring at δ 1.92 - 2.72. Additionally, ^{1}H NMR spectra of **5a** shown characteristic triplet at δ 4.24, doublet of triplet at δ 4.51 and doublets at δ 5.47 for protons $H^{1'}$, $H^{7'a}$ and $H^{2'}$ respectively. It is noticible, if the signal at 4.24 was irradiated, peaks of $H^{7'a}$ and $H^{2'}$ change to triplet and singlet, respectively. In the ^{13}C NMR spectrum of **5a**, the spiro carbon and ester's carbonyl are resonated at δ 75.8 and 198.2 respectively and the signals for all other 27 carbons are located at appropriate chemical shifts in agreement with the proposed structure.

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,[7] mechanistically, it is

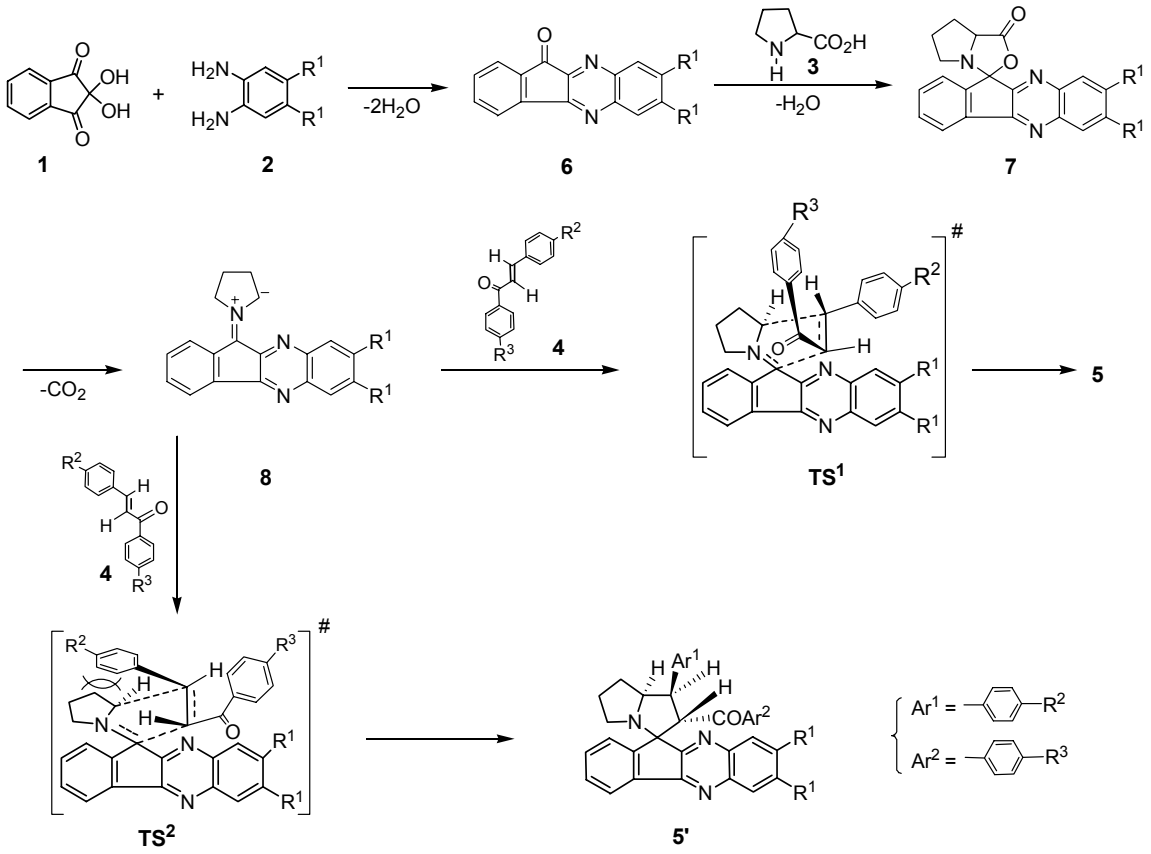
Table 1. One-pot synthesis of spiro[indeno[1,2-b]quinoxaline-11,3'-pyrrolizidine **5a-f**

5[a,b]	R^1	R^2	R^3	Yield[c]
a	H	H	H	75
b	Me	H	H	80
c	Me	Me	H	77
d	H	F	H	75
e	Me	H	F	80
f	Me	F	F	82

[a]Ninhydrin:diamine:proline:chalcone (1 mmol:1 mmol:1 mmol:1 mmol); [b]The structure of products **5a-f** were fully characterized by nmr and mass spectroscopy; [c]All referred to isolated pure products.



Scheme 1. One-pot four-component stereoslective synthesis of spiro[indeno[1,2-b]quinoxaline-11,3'-pyrrolizidine]



Scheme 2. The proposed mechanism for the one-pot four-component stereoslective preparation of spiro[indeno[1,2-b]quinoxaline-11,3'-pyrrolizidine]

reasonable to assume that initial condensation of the phenylenediamine **2** and the ninhydrin **1** gives indenoquinoxline-11-one intermediate **6**, which condensed with proline **3** to produce 1,3-dipolar azomethine ylides **8**.[8] The formed 1,3-dipolar species **8** subsequently undergoes cycloaddition reaction with chalcone **4**, to produce stereoselectively the new adduct **5** (Scheme 2).

According to the presence of carbonyl group as a spacer, R^3 substituted phenyl ring can get sufficiently away from the indenoquinoxaline structure, therefore TS^1 has lower strike hindrance compared to TS^2, in which the R^2 substituted phenyl ring is substantially close to proline moiety. Consequently, the reaction proceeds *via* TS^1. In practice, almost stereoisomer **5** was obtained, without obtaining any stereoisomer **5′**.

High diastereomeric excess of reaction was deduced on the basis of ^{1}H NMR spectra through which no other diastereomers 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 fixed configuration of dipole **8** and the structure of transition state 1 (TS^1), that has been mentioned by Grigg and his co-workers later, in their extensive studies.[9] Stereochemical assignments of the cycloadducts **5a** are made on the basis of N.O.E. difference spectroscopy and comparison with previously reported relative systems.[7] The possibility of the formation of other isomer, *via* TS^2, was ruled out by ^{1}H NOESY studies. For example irradiation of $H^{1'}$ at $\delta = 4.24$ caused no considerable enhancement of $H^{2'}$ and $H^{7'a}$ at $\delta = 4.51$ and 5.47, respectively, supporting the mutual *trans* arrangement of $H^{7'a}$ and $H^{1'}$.

However, the products can be achieved by a two-step procedure: first, the indenoquinoxaline **6** was 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 chalcone **4**. Using this two step procedure the overall yield for preparation of 2'-benzoyl-1',2',5',6',7',7'a-hexahydro-1'-phenylspiro[indeno[1,2-b]quinoxaline-11,3'-pyrrolizine] **5a** is about 67%, which much less than the one-pot four-component procedure. Moreover, many times and solvents were saved using the one-pot four-component procedure.

In summary, our study introduced a new interesting ninhydrin based one-pot four-component reaction which provides a simple and direct entry into a number of some new spiro [indeno[1,2-b]quinoxaline-11,3'-pyrrolizidine] derivatives that may be of value in biological interest.

Experimental Section

Synthesis of 2'-benzoyl-1',2',5',6',7',7'a-hexahydro-1'-phenylspiro[indeno[1,2-b]quinoxaline-11,3'-pyrrolizine] (5a) as a typical procedure. Proline **3** (0.115 g, 1 mmol) and chalcone **4a** (0.21 g, 1 mmol) were added to a solution of ninhydrin **1** (0.178 g, 1 mmol) and 1,2-phenylenediamine **2a** (0.108 g, 1

mmol) in ethanol (5 mL) and the mixture was refluxed for 2 h. 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 0 °C, the resulting solid was filtered off and washed with 3 ml cooled ethanol (70%) to give pure **5a** in 85% yield. Cream solid; mp 167-169 °C; IR (KBr): $\overline{V}$ 1695 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 1.92-2.21 (m, 4H, pyrrolizine), 2.56 (m, 1H, pyrrolizine), 2.72 (m, 1H, pyrrolizine), 4.24 (t, *J* = 10 Hz, 1H, $H^{1'}$), 4.51 (dt, *J* = 9.6, 6.7 Hz, 1H, $H^{7'a}$), 5.47 (d, *J* = 10 Hz, $H^{2'}$), 6.60-8.42 (m, 18H, arom). ^{13}C NMR (125 MHz, $CDCl_3$): δ 28.4, 31.9, 48.3, 52.9, 66.5, 73.1, 75.8, 122.5, 127.3, 127.6, 127.9, 128.4, 128.6, 129.1, 129.2, 129.3, 130.0, 130.2, 131.3, 132.5, 137.3, 138.0, 140.9, 142.7, 143.1, 144.0, 153.1, 164.9, 198.2. MS: (*m/z*) 493 (M^+), 285, 256, 218. *Anal*. Calcd. for $C_{34}H_{27}N_3O$: C, 82.73; H, 5.51; N, 8.51. Found: C, 82.80; H, 5.42; N, 8.41. NOE (%): irradiation of $H^{1'}$ caused no considerable enhancement of $H^{2'}$ and $H^{7'a}$. More purified products can be achieved by column chromatography on silica gel.

Selected physical and spectroscopic data for isolated products. 2'-Benzoyl-7,8-dimethyl-1',2',5',6',7',7'a-hexahydro-1'-phenylspiro[indeno[1,2-b]quinoxaline-11,3'-pyrrolizine] (5b). Light yellow solid; mp 202-203 °C (dec.); IR (KBr): $\overline{V}$ 1697 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 1.82-2.17 (m, 4H, pyrrolizine), 2.48 (m, 1H, pyrrolizine), 2.52 (s, 3H, CH_3), 2.57 (s, 3H, CH_3), 2.67 (m, 1H, pyrrolizine), 4.18 (t, *J* = 10.2 Hz, 1H, $H^{1'}$), 4.50 (dt, *J* = 9.4, 6.7 Hz, 1H, $H^{7'a}$), 5.40 (d, *J* = 11.4 Hz, $H^{2'}$), 6.56-8.15 (m, 16H, arom). ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.3, 20.4, 27.8, 31.4, 48.0, 52.5, 65.9, 72.6, 75.2, 121.8, 126.9, 127.2, 127.5, 127.8, 128.2, 128.3, 128.7, 129.1, 129.5, 130.4, 132.1, 136.8, 138.0, 139.2, 139.9, 140.5, 141.1, 141.5, 143.3, 151.7, 197.8. MS: (*m/z*) 521 (M^+), 256, 83. *Anal*. Calcd. for $C_{36}H_{31}N_3O$: C, 82.89; H, 5.99; N, 8.06. Found: C, 82.96; H, 6.09; N, 8.18. NOE (%): irradiation of $H^{1'}$ caused enhancement of $H^{2'}$ (0.5%) and $H^{7'a}$ (0.6%).

2'-Benzoyl-7,8-dimethyl-1',2',5',6',7',7'a-hexahydro-1'-(4-methylphenyl)spiro[indeno[1,2-b]quinoxaline-11,3'-pyrrolizine] (5c). Cream solid; mp 193-195 °C; IR (KBr): $\overline{V}$ 1695 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 1.89-2.19 (m, 4H, pyrrolizine), 2.36 (s, 3H, CH_3), 2.52 (m, 1H, pyrrolizine), 2.55 (s, 3H, CH_3), 2.61 (s, 3H, CH_3), 2.68 (m, 1H, pyrrolizine), 4.19 (t, *J* = 6.6 Hz, 1H, $H^{1'}$), 4.53 (ddd, *J* = 16.5, 6.6, 6.6, 1H, $H^{7'a}$), 5.42 (d, *J* = 11.5 Hz, $H^{2'}$), 6.61-8.17 (m, 15H, arom). ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.7, 20.8, 21.5, 28.3, 31.8, 48.3, 52.6, 66.4, 73.0, 75.7, 122.1, 127.6, 127.9, 128.3, 128.5, 128.6, 129.5, 129.7, 129.8, 130.8, 132.4, 136.8, 137.3, 137.9, 138.3, 139.5, 140.2, 141.5, 143.8, 152.2, 163.9, 198.3. MS: (*m/z*) 535 (M^+), 284, 246. *Anal*. Calcd. for $C_{37}H_{33}N_3O$: C, 82.96; H, 6.21; N, 7.84. Found: C, 83.06; H, 6.10; N, 7.99. NOE (%): irradiation of $H^{1'}$ caused no considerable enhancement of $H^{2'}$ and $H^{7'a}$.

2'-Benzoyl-1'-(4-fluorophenyl)-1',2',5',6',7',7'a-hexahydrospiro[indeno[1,2-b]quinoxaline-11,3'-pyrrolizine] (5d). Cream solid; mp 218-219 °C; IR (KBr): $\overline{V}$ 1692 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 1.89-2.19 (m, 4H, pyrrolizine), 2.36 (s, 3H, CH_3), 2.52 (m, 1H, pyrrolizine), 2.55 (s, 3H, CH_3), 2.61 (s, 3H, CH_3), 2.68 (m, 1H, pyrrolizine), 4.19 (t, *J* = 6.6 Hz, 1H, $H^{1'}$), 4.53 (ddd, *J* = 16.5, 6.6, 6.6 Hz, 1H, $H^{7'a}$), 5.42 (d, *J* = 11.5 Hz, $H^{2'}$), 6.61-8.17 (m, 15H, arom). ^{13}C NMR (125 MHz, $CDCl_3$): δ 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*) 511 (M^+), 285, 218; *Anal*. Calcd. for $C_{34}H_{26}FN_3O$: C, 79.82; H, 5.12; N, 8.21. Found: C, 79.69; H, 5.25; N, 8.29. NOE (%): irradiation of $H^{1'}$ caused enhancement of $H^{2'}$ (1.5%) and $H^{7'a}$ (1.2%).

7,8-Dimethyl-2'-(4-fluorobenzoyl)-1',2',5',6',7',7'a-hexahydro-1'-phenylspiro[indeno[1,2-b]quinoxaline-11,3'-pyrrolizine] (5e). Light yellow solid; mp 164-165 °C (dec.); IR (KBr): $\overline{V}$ 1698 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 1.90, 2.01, 2.16 (m, 4H, pyrrolizine), 2.53 (s, 3H, CH_3), 2.54 (m, 1H, pyrrolizine), 2.57 (s, 3H, CH_3), 2.65 (m, 1H, pyrrolizine), 4.19 (m, 1H, $H^{1'}$), 4.51 (m, 1H, $H^{7'a}$), 5.36 (d, *J* = 9 Hz, $H^{2'}$), 6.27-8.13 (m, 15H, arom). ^{13}C NMR (125 MHz, $CDCl_3$): δ 19.8,19.9, 27.4, 30.8, 47.4, 52.0, 65.4, 72.1, 74.7, 121.3, 126.5, 127.4, 127.7, 128.2, 128.5, 129.0, 129.6, 129.7, 130.0, 132.7, 134.3, 136.7, 136.8, 137.4, 137.8, 138.9, 139.4, 140.5, 141.0, 145.5, 154.4, 163.5, 195.6. MS: (*m/z*) 511 (M^+), 285 (100), 256 (70), 83 (90). *Anal*. Calcd. for $C_{36}H_{30}FN_3O$: C, 80.12; H, 5.60; N, 7.79; Found: C, 80.22; H, 5.52, N, 7.70. NOE (%): irradiation of $H^{1'}$ caused enhancement of $H^{2'}$ (1.2%) and $H^{7'a}$ (1.1%).

7,8-Dimethyl-2'-(4-fluorobenzoyl)-1'-(4-fluorophenyl)-1',2',5',6',7',7'a-hexahydrospiro[indeno[1,2-b]quinoxaline-11,3'-pyrrolizine] (5f). Light yellow solid; mp 167-169 °C (dec.); IR (KBr): $\overline{V}$ 1746 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 1.48-2.15 (m, 4H, pyrrolizine), 2.53 (s, 3H, CH_3), 2.54 (m, 1H, pyrrolizine), 2.58 (s, 3H, CH_3), 2.65 (m, 1H, pyrrolizine), 4.17 (t, *J* = 9.7 Hz, 1H, $H^{1'}$), 4.48 (m, 1H, $H^{7'a}$), 5.36 (d, *J* = 10.2 Hz, $H^{2'}$), 6.27-8.13 (m, 14H, arom). ^{13}C NMR (125 MHz, $CDCl_3$): δ 17.9, 19.8, 27.3, 30.7, 47.3, 51.3, 65.5, 72.0, 74.6, 113.8, 114.1, 114.9, 115.2, 121.4, 127.3, 127.8, 128.4, 129.1, 129.2, 129.5, 129.6, 130.0, 132.6, 135.5, 137.4, 139.0, 139.7, 140.5, 141.0, 159.7, 163.0, 195.6. MS: (*m/z*) 557 (M^+). *Anal*. Calcd. for $C_{36}H_{29}F_2N_3O$: C, 77.54; H, 5.24; N, 7.54. Found: C, 77.55; H, 5.32; N, 7.66. NOE (%): irradiation of $H^{1'}$ caused no considerable enhancement of $H^{2'}$ and $H^{7'a}$.

Acknowledgments. We gratefully acknowledge the financial support from the Research Council of Persian Gulf University.

References

1. (a) Tries, S.; Laufer, S. *Inflammopharmacology* **2001**, *9*, 113; (b) Argyropoulos, N. G.; Sarli, V. C.; Gdaniec, M. *Eur. J. Org. Chem*. **2006**, *71*, 3738; (c) Borsini, E.; Broggini, G.; Contini, A.; Zecchi, G. *Eur. J. Org. Chem*. **2008**, *73*, 2808, and references cited there in.
2. (a) Sardina, F. J.; Rapoport, H. *Chem. Rev*. **1996**, *96*, 1825; (b) *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, 1984; Vols. 1 and 2; (c) Tsuge, O.; Kanemasa, S. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Ed.; Academic Press: San Diego, 1989; Vol. 45, p 231.
3. (a) Gothelf, K. V.; Jørgensen, K. A. *Chem. Rev*. **1998**, *98*, 863; (b) Najera, C.; Sansano, G. M. *Curr. Org. Chem*. **2003**, *7*, 1105.
4. (a) Zhu, J.; Bienayme, H. *Multi-component Reactions*; VCH: Weinhein, Germany, 2005; (b) Domling, A. *Chem. Rev*. **2006**, *106*, 17.
5. (a) Azizian, J.; Mohammadizadeh, M. R.; Zomorodbakhsh, S.; Mohammad, A. A.; Karimi, A. R. Arkivoc **2007**, *XV*, 25; (b) Azizian, J.; Mohammadizadeh, M. R.; Mohammad, A. A.;

Karimi, A. R. *Heteroatom Chem.* **2005**, *16*, 259; (c) Azizian, J.; Mohammadizadeh, M. R.; Mohammad, A. A.; Karimi, A. R. *J. Org. Chem.* **2005**, *70*, 350; (d) Azizian, J.; Karimi, A. R.; Kazemizadeh, Z.; Mohammad, A. A.; Mohammadizadeh, M. R. *Synthesis* **2005**, 1095; (e) Azizian, J.; Karimi, A. R.; Kazemizadeh, Z.; Mohammad, A. A.; Mohammadizadeh, M. R. *J. Org. Chem*. **2005**, *70*, 1471.

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