HETEROCYCLES, Vol. 85, No. 7, 2012, pp. 1727 - 1733. © 2012 The Japan Institute of Heterocyclic Chemistry
Received, 24th May, 2012, Accepted, 29th May, 2012, Published online, 6th June, 2012
DOI: 10.3987/COM-12-12516

DOUBLE INTRAMOLECULAR 1,3-DIPOLAR CYCLOADDITION OF DIAZIDO-TERMINAL DIALKYNE: SYNTHESIS OF A NEW BIS(1,2,3-TRIAZOLO-1,4-OXAZINE)

Nejib Husein Mekni[1, 2]* and Ahmed Baklouti[1]

[1] Organic Structural Chemistry Laboratory, Synthesis and Physico-Chemical Studies, Chemistry Department, Faculty of Sciences of Tunis, Almanar, 2092 Tunis, Tunisia

[2] Chemistry Department, Faculty of Science of Al Ula, Taibah University, Kingdom of Saudi Arabia. e-mail : n.mekni@gmail.com

Abstract – A new bis(1,2,3-triazolo-1,4-oxazine) fused heterocyclic compound was synthesized from terminal *meso*-1,2,3,4-diepoxybutane via azide ring opening reaction, followed by propargylation and double 1,3-dipolar intramolecular cycloaddition. No effect on the reaction outcome was observed when Cu(I) was used as catalyst. In both cases catalyzed and uncatalyzed reactions, only the *exo*-tetracyclic two to two fused isomer was obtained.

1,2,3-Triazoles and oxazines, are heterocycles which constitute a large number of synthetic compounds.[1] Applications of these heterocycles in various areas have been reported.[2,3] For example, they are used as an anti-HIV,[4] anti-allergic,[5] antibacterial,[6] fungicides,[7] herbicides,[8] paints,[9] corrosion inhibitors,[10] pesticides[11] and agrochemical agents.[3,12] For oxazines and their derivatives, a particular interest has emerged since the discovery of Efavirenz (trifluoromethyl-1,3-oxazin-2-one) inhibitor non-nucleoside reverse transcriptase used as a selective anti-HIV drug.[13]

On the other hand, the 1,3-dipolar azide-alkyne cycloaddition is a well known reaction[14] which has been recently applied in the "Click Chemistry".[15] A remarkable development is potentiated by the use of catalytic metals such as (Cu^{+})[16] and (Ru^{2+}).[17] The majority of azide/alkyne reaction studies deal with intermolecular cycloadducts.[18] However those related to the intramolecular processes remain limited.[19,20] Furthermore, previous studies have focused on the synthesis of target and specific molecules rather than on a general systematic investigation of its potential application in organic synthesis.[19,21]

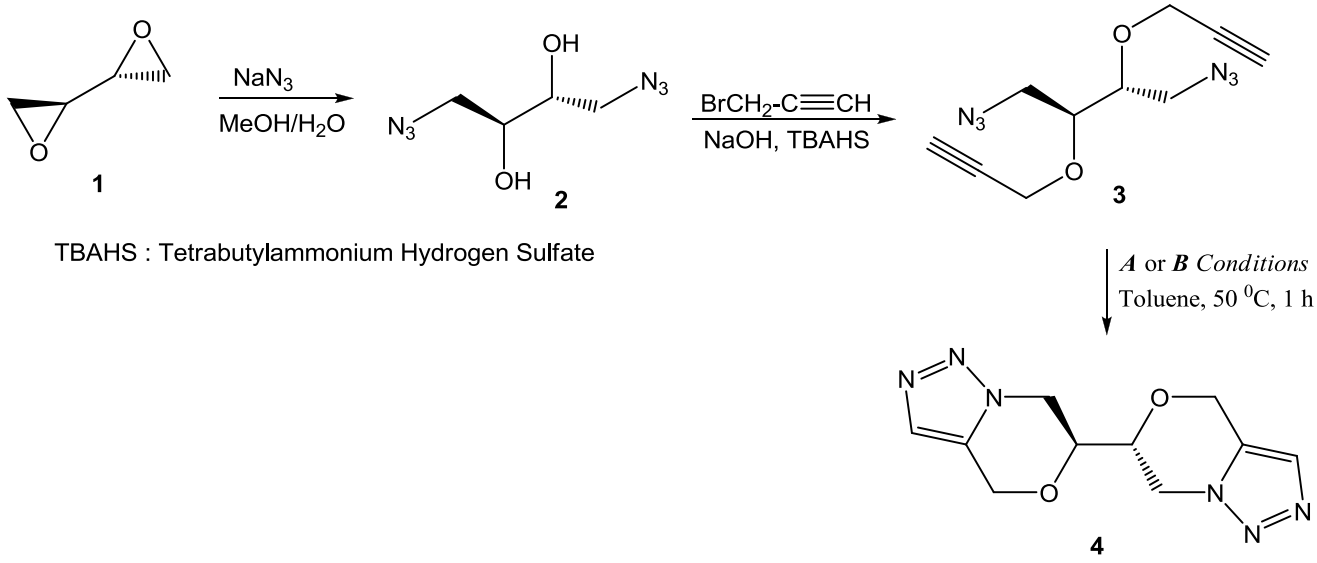
In the present work, we describe the synthesis of one compound having four hetrerocycles, two to two fused, in three steps[22] starting from diepoxybutane.[23,24]

The preparation of the *meso*-diazido-dialkyne ether **2** was carried out through opening of the *meso*-diepoxybutane rings **1** by azide ion followed by reaction of propargyl bromide (Scheme 1). The *meso*-diazido-dialkyne ether **3** was obtained in satisfactory yields (81%).

The *meso*-diazido-dialkyne **3** is unstable and decomposes on contact with air. Therefore, the mixture obtained from the propargylation reaction was diluted in situ in dry toluene and used in situ without purification in the next step.

The uncatalyzed dipolar [3+2] double intramolecular cycloaddition reaction of product **3** proceeds spontaneously at room temperature, producing exclusively the *exo*-tetraheterocyclic compound **4**. To reduce the reaction time, the mixture was heated at 50 °C in toluene (***A*** *Condition*[25]). In an attempt to direct the reaction towards the formation of another polyheterocyclic compound, the reaction was performed in the presence of a catalytic amount of CuCl (5%) (***B*** *Condition*[26]).

Either carried out according to ***A*** (79%) or ***B*** (75%) conditions, the double intramolecular cycloaddition reaction of diazido-dialkyne ether **3** leads always to the formation of the same isomer **4** (Scheme 1).



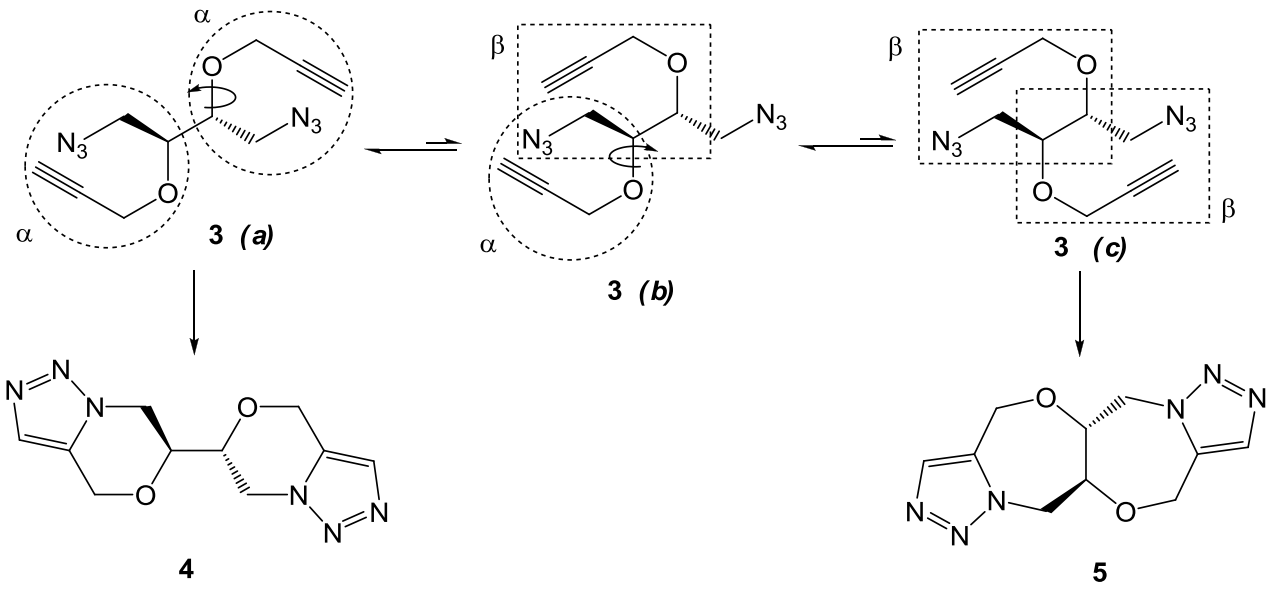
Scheme 1. Synthesis of the *meso*-bis(1,2,3-triazolo-1,4-oxazine)

It is worth to note that several conformers are possible for compound **3**, due to the free rotation around the CH-CH central bond. Because of the free rotation around the two CH-O bonds, the stable conformation can exist in three geometric forms (***a***), (***b***) and (***c***). From these forms, two *exo*-cyclic isomers may be formed **4** and **5** (Scheme 2).

The (***a***) form has both azide and alkyne dipoles one in face to the other with a favorable orbital overlap flatness which explain the exclusive formation of the *exo*-tetracyclic isomer **4**.

For the (***b***) form, the α part of favorable flatness cyclizes easily (Scheme 2). So in the β side, the propargylic group must rotate around C-O to cyclize with the second azide group and would lead once

again to the isomer **4**. The (***c***) form does not afford a favorable orbital overlap which can explain the absence of the *exo*-cyclic isomer **5**. Therefore, (***c***) turns into (***b***) and/or (***a***) to give also compound **4**.



Scheme 2. Explication of the formation of the tetracyclic isomer **4**

The ^{1}H and ^{13}C NMR spectral data confirm the symmetrical structure proposed. In particular the ^{1}H NMR spectrum shows an *AB* system corresponding to the allylic protons O-CH_2-C=C, appearing into 5.0 ppm ($^{2}J_{AB}$ = 15 Hz). Moreover, the -CH_2-N protons show another *AB* system ($^{2}J_{AB}$ ~ 12 Hz) which is partially coupled with the proton of the asymmetric carbon.

ANTIBACTERIAL TEST

The preliminary antibacterial activity study of compound **4** was followed by the disk diffusion method against five bacteria (Gram+ and Gram-) of widely encountered references in many human diseases.[27] The results are given in Table 1.

As can be seen from Table 1, it appears that compound **4** has no activity against Escherichia coli (DH5α), Pseudomonas aeruginosa (PAO1), Salmonella typhi (ATCC 25922) and Staphylococcus aureus (ATCC 6538). However, it presents a moderate activity against Enterococcus feacium strain ATCC (19,436) for which inhibition diameter is 11 mm. This value is the average of three experimental tries (10 mm, 11 mm and 12 mm).

Table 1. The five bacteria test results of compound **4**

Strain	*E. Coli*	*P. aeruginosa*	*S. typhi*	*S. aureu*	*E. feacium*
Solution	-	-	-	-	11 mm
Gentamicin (10UI)	20 mm	20 mm	25 mm	30 mm	25 mm

The *exo*-tetraheterocyclic isomer **4** was obtained exclusively from simple *meso*-diepoxybutane, via mild reaction series in which the latter is a double intramolecular cycloaddition.

In addition, the *exo*-cyclic 1,2,3-triazolo-1,4-oxazine **4**, is an aromatic heteropolycyclic compound combining four fused two to two heterocycles that are well known for their wide area of applications. The title compound may present a priori interesting applications[28,29] with preliminary antibacterial tests showing a moderate activity towards the Enterococcus feacium bacteria.

EXPERIMENTAL

IR spectra were realized on Perkin Elmer Paragon 1000 PC spectrometer. The NMR ^{1}H and ^{13}C spectra were realized on a Bruker AC 300 spectrometer respectively at 300 and 75 MHz. The TMS was used as a standard reference for ^{1}H and ^{13}C NMR spectra. HRMS spectra was realized on a MAT 95 SBE spectrometer in C. I. mode. The silica gel is of the Merck 7734 type, *meso*-diepoxybutane, sodium azide, propargyl bromide, CH_2Cl_2, toluene and Na_2SO_4 are Fluka commercial products.

Preparation of azido-alcohol **2**: A solution of (3.44 g, 40 mmol) of *meso*-diepoxybutane **1**, 10 g of sodium azide, 2.5 g of ammonium chloride in 25 mL of water and 100 mL of MeOH was stirred for 16 h at 80 °C, then filtered and the MeOH was evaporated. The mixture was extracted with Et_2O (3 x 100 mL), washed with water and dried on Na_2SO_4. Et_2O was evaporated, the obtained crude product was purified on silica gel chromatographic column, using Et_2O as eluant to obtain pure compound **2** as yellowish viscous liquid.

Synthesis of diazido-dialkynes **3**: To a mixture of sodium hydroxide (4.80 g, 120 mmol), water (0.4 mL), tetrabutylammonium hydrogen sulfate TBAHS (0.2 g) and 120 mmol of propargyl bromide, vigorously stirred and cooled at 0 °C, (30 mmol, 5.16 g) of azido-alcohol **2** was added slowly. The mixture was stirred for 45 min at 0 °C, then 20 mL of CH_2Cl_2 was added. The mixture was filtered and the salt washed with CH_2Cl_2 (3 x 20 mL). After draying on Na_2SO_4, the mixture was filtered, then 50 mL of dry toluene was added. The CH_2Cl_2 and the excess of propargyl bromide were evaporated under vacuum. The crude product was conserved in toluene and used in the next step without purification.

Synthesis of bis(1,2,3-triazolo-1,4-oxazine) **4***:* The crud product of **3** conserved in dry toluene was heated for 2 h at 50 °C (***A***: without Cu^{+}; ***B*** in the presence of: 5% of CuCl, 0.3 g). Toluene was evaporated and the obtained solid was purified by recrystallization in MeOH to give isomer **4** as a "color" solid (***A***: 79%, 5.88 g; ***B***: 75%, 5.58 g).

6,6'7,7'-Tetrahydro-4H,4'H-6,6'-bi[1,2,3]triazolo[5,1-c][1,4]oxazine **(4)*:*** mp 221 °C *IR* (KBr): $\nu_{C=C}$ = 1453, $\nu_{N=N}$ = 1495 cm^{-1}*;* ^{1}H *NMR* (DMSO): δ 4.63-4.38 (m, 4H, 2CH-CH_2-N, $^{2}J_{AB}$ = 12 Hz), 4.30 (m, 2H, 2C*H*), 5.13-4.86 (d. d. 4H, 2O-CH_2-C=, $^{2}J_{AB}$ = 15 Hz), 7.58 (s, 2H, C=C*H*); ^{13}C *NMR* (DMSO): δ 51.80

(2CH_2), 67.20 (2CH_2), 75.70 (2CH), 128.60 (2C=), 128.90 (2CH=); *HRMS Calculated:* 248,10233, *Found:* 248,10303, *Δ(umm):* +0.7; Anal. Cacd for $C_{10}H_{12}N_6O_2$: C 48.37%, H 4.87%, N 33.86%. Found: C 48.31%, H 4.89%, N 33.78%.

Microorganisms

Antibacterial activity was tested using the disc diffusion method.[24] A loop of bacteria from the agar slant stock was cultured in nutrient broth overnight and the inoculates grown were diluted to approximately 2 x 10^6 CFU/mL in molten nutrient agar. The concentration of the suspension used for inoculation was standardized by adjusting the optical density to 0.5 at 570 nm wavelength (spectrophotometer UV/visible). Sterile filter paper discs (6 mm in diameter) impregnated with the solution were placed on the cultured plates and incubated at 37 °C. The solvent (DMSO) without extracts served as negative control. Standard antibiotic of Gentamicin (10UI) was used as positive controls. After 24 h of incubation, the diameter in mm of the inhibitory or clear zones around the disks was recorded. Each test was repeated three times and the average was reported.

ACNKNOWLEDGEMENTS

The authors wish to thank the Tunisian Ministry of High Education and Scientific Research and Technology for financial support (LR99ES14) of this research, Dr. Feten MEDINI for Antibacterial Tests and Dr. M. A. K. Sanhoury, MRSC from the Department of Chemistry, Faculty of Science of Tunis for technical assistance.

REFERENCES

1. M. Meldal and C. W. Tornoe, *Chem. Rev.*, 2008, **108**, 2952 and references therein; N. Benaamane, B. Nedjar-Kollim, Y. Bentarzi, L. Hammal, A. Geronikaki, P. Eleftherio, and A. Lagunin, *Bioorg. Med. Chem.*, 2008, **16**, 3059; R. K. O'Reilly, M. J. Joralemon, K. L. Wooley, and C. J. Hawker, *Chem. Mater.*, 2005, **17**, 5976.
2. T. L. Gilchrist, Heterocyclic Chemistry; 3rd Ed. Addison Wesley Longman: Beijing 1997; pp. 304-319; The Structure Reactions, Synthesis and Use of Hetercyclic Compounds; ed. by A. R. Katritzky, C. W. Rees, and E. F. V. Scriven; Elsevier Science: New York, 1996; Vol. 4, pp. 1-126; H. Li and C. T. Walsh, *J. Am. Chem. Soc.*, 2004, **126**, 13998.
3. W. Q. Fan and A. R. Katrisky, in 'Comprehensive Heterocyclic Chemistry II', ed. by A. R. Katrisky, C. W. Rees, and C. W. V. Scriven, Vol. 4. Elsevier Sciences, Oxford, 1996, pp. 1-126; P. Wu, A. K. Feldmann, A. K. Nugent, C. J. Hawker, A. Scheel, B. Voit, J. Pyun, J. M. J. Frechet, K. B. Sharpless, and V. V. Fokin, *Angew Chem. Int. Ed.*, 2004, **43**, 3928; B. Helms, J. L. Mynar, C. J. Hawker, and J.

M. J. Frechet, *J. Am. Chem. Soc.*, 2004, **126**, 15020; C. J. Hawker and K. L. Wooley, *Science*, 2005, **309**, 1200; A. Devadoss and C. E. D. Chidsey, *J. Am. Chem. Soc.*, 2007, **129**, 5370.

4. R. Alvarez, S. Velazquez, A. San-Felix, S. Aquaro, E. De Clercq, C.-F. Perno, A. Karlsson, J. Balzarini, and M. J. Camarasa, *J. Med. Chem.*, 1994, **37**, 4185; P. B. Bhuyan, H. N. Borah, and J. S. Sandhu, *J. Chem. Soc., Perkin Trans. 1*, 1999, 8083.
5. D. R. Buckle, C. J. M. Rockell, H. Smith, and B. A. Spicer, *J. Med. Chem.*, 1986, **29**, 2262.
6. M. J. Genin, D. A. Allwine, D. J. Anderson, M. R. Barbachyn, D. E Emmert, S. A. Garmon, D. R. Graber, K. C. Grega, J. B. Hester, D. K. Hutchinson, J. Morris, R. J. Reischer, C. W. Ford, G. E. Zurenko, J. C. Hamel, R. D. Schaadt, D. Stper, and B. H. Yagi, *J. Med. Chem.*, 2000, **43**, 953.
7. H. Wamhoff, In Comprehensive Heterocyclic Chemistry, ed. by A. R. Katritzky and C. W. Rees, Pergamon: Oxford, 1984; Vol. 5, pp. 669-732.
8. J. Yang, D. Hoffmeister, L. Liu, X. Fu, and J. S. Thorson, *Bioorg. Med. Chem.*, 2004, **12**, 1577; H. Lin and C. T. Walsh, *J. Am. Chem. Soc.*, 2004, **126**, 13998.
9. J. Rody and M. Slongo, Eur. Pat. 80 810 394 (1981) (*Chem. Abstr.*, 1981, **95**, 187267).
10. A. M. S. Abdennabi, A. I. Abdulhadi, S. T. Abu-Orabi, and H. Saricimen, *Corrosion Sci.*, 1996, **38**, 1791; K. K. Nippon. Kogyo, Jpn. Pat. 5610882 (1981) (*Chem. Abstr.*, 1981, **96**, 56298).
11. I. K. Boddy, G. G. Briggs, R. P. Harrison, T. H. Jones, M. J. O'Mahony, I. D. Marlow, B. G. Robers, R. J. Willis, R. Bardsley, and J. Reid, *Pestic. Sci.*, 1996, **48**, 189.
12. Y. Yanase, Y. Yoshikawa, H. Kawashima, A. Takashi, and T. Akase, Jpn. Kokai Tokkyo Koho JP 2001072507 (*Chem. Abstr.*, 2001, **134**, 233062); Y. Yanase, Y. Yoshikawa and A. Takashi, Jpn. Kokai Tokkyo Koho JP 2001072512 (*Chem. Abstr.*, 2001, **134**, 233064).
13. M. E. Pierce, R. L. Parsons, L. A. Radesca, Y. S. Lo, S. Silvermon, J. R. Moore, Q. Islam, A. Chaodhury, J. M. D. Fortunak, D. Nguyen, C. Luo, S. F. Morgan, W. P. Davis, P. N. Confalone, C. Chen, R. D. Tillyer, L. Frey, L. Tan, F. Xu, D. Zhao, A. S. Thompson, E. G. Corley, E. J. J. Grabowski, R. Reamer, and P. J. Reider, *J. Org. Chem.*, 1998, **63**, 8536.
14. T. Pirali, G. C. Tron, and J. Zhu, *Org. Lett.*, 2006, **8**, 4145 and references therein.
15. A. Bolognese, G. Correale, M. Manfra, A. Lavecchia, O. Mazzoni, E. Novellino, V. Barone, P. La Colla, and R. Loddo, *J. Med. Chem.*, 2002, **45**, 5217.
16. M. Meldal and C. W. Tomøe, *Chem. Rev.*, 2008, **108**, 2952; R. L. Jarvest, S. C. Connor, J. G. Gorniak, L. J. Jennings, H. T. Serafinowska, and A. West, *Bioorg. Med. Chem. Lett.*, 1997, **7**, 1733; N. A. Abood, L. A. Schretzman, D. L. Flynn, K. A. Houseman, A. J. Wittwer, V. M. Dilworth, P. J. Hippenmeyer, and B. C. Holwerda, *Bioorg. Med. Chem. Lett.*, 1997, **7**, 2105.
17. L. Zhang, X. Chen, P. Xue, H. H. Y. Sun, I. D. Williams, K. B. Sharpless, V. V. Fokin, and G. Gia, *J. Am. Chem. Soc.*, 2005, **127**, 15998; M. M. Majireck and S. M. Weinreb, *J. Org. Chem.*, 2006, **71**,

8680; B. C. Boren, S. Narayan, L. K. Rasmussen, L. Zhang, H. Zhao, Z. Lin, G. Jia, and V. V. Fokin, *J. Am. Chem. Soc.*, 2008, **130**, 8923.

18. M. Meldal and C. W. Tornoe, *Chem. Rev.*, 2008, **108**, 2952; J. E. Moses and A. D. Moorhouse, *Chem. Soc. Rev.*, 2007, **36**, 1249; Y. L. Angell and K. Burgess, *Chem. Soc. Rev.*, 2007, **36**, 1674; Y. L. Angell and K. Burgess, *QSAR Comb. Sci.*, 2007, **26**, 11; W. Peng and V. V. Fokin, *Aldrichimica Acta*, 2007, **40**, 7.
19. A. I. Oliva, U. Christmann, D. Font, F. Cuevas, P. Ballester, H. Buschmann, A. Torrens, S. Yenes, and M. A. Pericas, *Org. Lett.*, 2008, **10**, 1617; S. Cantel, A. L. C. Isaad, M. Scrima, J. J. Levy, R. D. DiMarchi, P. Rovero, J. A. Halperin, A. M. D'Ursi, A. M. Papini, and M. Chorev, *J. Org. Chem.*, 2008, **73**, 5663.
20. In a recent SciFinder search of the key phrase "azide-alkyne cycloaddition", more than 95% of the 'hits' obtained were found to involve intermolecular version of the cycloaddition.
21. S. Punna, J. Kuzelka, Q. Wang, and M. G. Finn, *Angew. Chem. Int. Ed.*, 2005, **44**, 2215; R. L. Weller, and S. R. Rajski, *Org. Lett.*, 2005, **7**, 2141; R. Li, D. J. Jansen, and A. Datta, *Org. Biomol. Chem.*, 2009, **7**, 1921.
22. N. H. Mekni and A. Baklouti, *The all results Journals: Chem.,* 2012, **3**, 1; R. Li, D. J. Jansen and A. Datta, *Org. Biomol. Chem.*, 2009, **7**, 1921; A. I. Oliva, U. Christmann, D. Font, F. Cuevas, P. Ballester, H. Buschmann, A. Torrens, S. Yenes, and M. A. Pericas, *Org. Lett.*, 2008, **10**, 1617.
23. A. Fasi, I. Palinko, and I. Kiricsi, *Cat. Lett.*, 2005, **101**, 105; J. Branalt and I. Kvarnström, *J. Org. Chem.*, 1996, **61**, 3611; P. March, M. Figueredo, J. Font, and J. Medrano, *Tetrahedron*, 1999, **55**, 7907; M. A. Robbins, P. N. Devine, and T. Oh, *Org. Syn.*, 1999, **76**, 101; J. Branalt, I. Kvarnstrom, B. Classon, and B. Samuelson, *J. Org. Chem.*, 1996, **61**, 3611.
24. P. M. Vacek, R. J. Albertini, R. J. Sram, P. Upton, and J. A. Swenberg, *Chem.-Biol. Int.*, 2010, **188**, 668; J. A. Swenberg, N. K. Bordeerat, G. Boysen, S. Carro, N. I. Georgieva, J. Nakamura, J. M. Troutman, P. B. Upton, R. J. Albertini, P. M. Vacek, V. E. Walker, R. J. Sram, M. Goggin, and N. Tretyakova, *Chem. Biol. Int.*, 2011, **192**, 150.
25. H. C. Kolb and K. B. Sharpless, *Drug Discovery Today,* 2004, **8**, 1128.
26. A. Krasinski, V. V. Fokin, and K. B. Sharpless, *Org. Lett.*, 2004, **6**, 1237.
27. H. Najjaa, M. Neffati, S. Zouari, and E. Ammar, *C. R. Chimie*, 2007, 1.
28. N. Benaamane, B. Nedjar-Kollim, Y. Bentarzi, L. Hammal, A. Geronikaki, P. Eleftheriou, and A. Lagunin, *Bioorg. Med. Chem.*, 2008, **16**, 3059.
29. T. L. Gilchrist, Heterocyclic Chemistry; 3rd Ed. Addison Wesley Longman: Beijing, 1997, 304-319; J. Yang, D. Hoffmeister, L. Liu, X. Fu, and J. S. Thorson, *Bioorg. Med. Chem.*, 2004, **12**, 1577; H. Lin and C. T. Walsh, *J. Am. Chem. Soc.*, 2004, **126**, 13998.