Journal of Organometallic Chemistry 695 (2010) 1065–1068

Contents lists available at ScienceDirect

Journal of Organometallic Chemistry

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

Synthesis and characterization of novel quinoline selenium compounds: X-ray structure of 6-methoxy-3H-[1,2]diselenolo[3,4-b]quinoline

K.K. Bhasin [a,*], Ekta Arora [a], Chee-Hun Kwak [b], S.K. Mehta [a]

[a] Department of Chemistry and Centre of Advanced Studies in Chemistry, Panjab University, Chandigarh 160 014, India
[b] Department of Chemistry, Suncheon National University, Suncheon 540-742, South Korea

ARTICLE INFO

Article history:
Received 14 October 2009
Received in revised form 6 January 2010
Accepted 7 January 2010
Available online 14 January 2010

Keywords:
Quinoline
Selenium
Vilsmeier cyclisation
Diselenolo quinoline

ABSTRACT

A series of novel and synthetically important quinoline selenium compounds have been successfully synthesized using an efficient and simple strategy. The method employed leads to the synthesis of both cyclic as well as open chain quinoline selenium compounds. The prepared selenium compounds have been characterized with the help of various spectroscopic techniques *viz*., NMR (^{1}H, ^{13}C), FT-IR, mass spectrometry. The structure of 6-methoxy-3H-[1,2]diselenolo[3,4-b]quinoline has been determined by X-ray crystallography.

1. Introduction

Organic compounds containing selenium are of considerable interest since they exhibit diverse biological activities with numerous therapeutic applications [1,2]. In addition, the presence of a heterocyclic ring as the organic moiety in these compounds alters their properties to a great extent. A pharmacologically active heterocycle is the quinoline ring that occurs in several natural products and displays a broad range of biological activity [3,4] including antitumour, hypoglycemic, antihistamine and anticarcinogenic properties [5], etc. Due to their importance as substructures in a broad range of natural and designed products, significant efforts have been directed into the development of new quinoline based structures [6]. Amongst methodologies reported for the preparation of quinolines, Vilsmeier [7] cyclisation is the most straightforward protocol (Scheme 1). Therefore, for the synthesis of 2-chloro-3-formylquinolines in the present reported work, Vilsmeier reagent was prepared and reacted with the corresponding acetanilides.

Among potentially attractive new starting materials for the preparation of organic selenium compounds are carbonyl compounds, and their reaction with hydrogen selenide and its salts have been explored under a variety of alkaline and acidic conditions to give low yield of diselenides and selenoaldehyde oligomers, respectively [8].

Margolis and Pittman [9] obtained low yields of aliphatic diselenides when the corresponding ketones were treated with excess hydrogen selenide in the presence of strong hydrochloric acid. The synthesis of various diselenides by an amine catalysed reaction of carbonyl compounds with hydrogen selenide has also been reported [10]. In all these methods, long reaction times are required and the products are found to be invariably contaminated with elemental selenium and oligoselenides. The latter are difficult to remove from the desired diselenides and show decomposition with liberation of elemental selenium upon storage and handling.

An alternative method avoiding the use of hydrogen selenide gas involves the reductive selenation of aromatic and heteroaromatic aldehydes (ArCHO) employing $Se/CO/H_2O$ system in DMF [11]. However, this method is less effective in case of aliphatic aldehydes. Consequently, there is a great interest in the synthesis of diselenide derivatives of quinoline by a simple method using reactants containing both carbonyl and halide species.

In continuation of our work on the synthesis of organic selenium compounds [12] and the convenient synthesis of 2-chloro-3-formylquinolines, the present paper deals with the synthesis of quinoline selenium compounds.

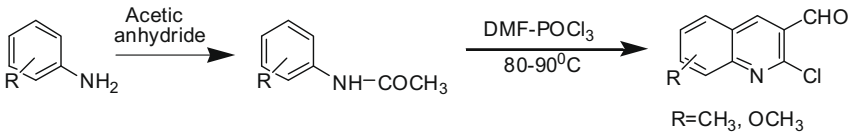
2. Result and discussion

The Vilsmeier cyclisation was performed to prepare the precursors for the synthesis of quinoline selenium compounds (Scheme 1).

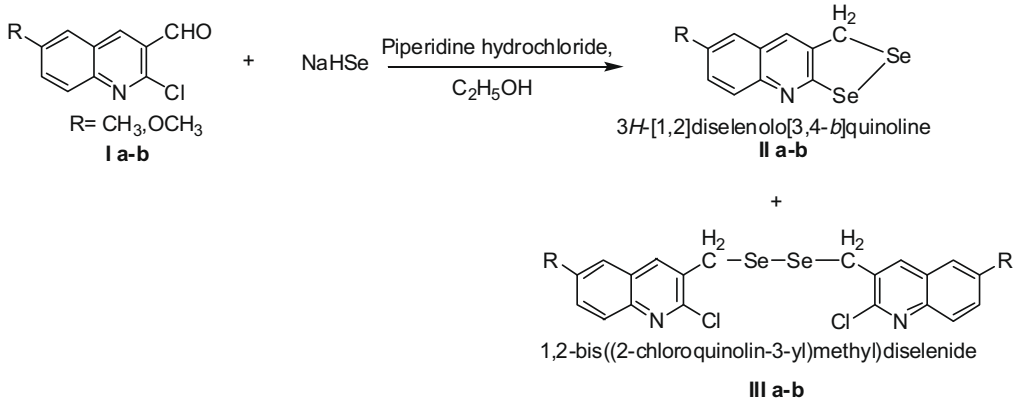
A survey of literature has revealed that compounds containing Se–Se bond, acyclic and cyclic, are potential labilizing agents for lysosomes and mitochondria in vitro [13]. In this paper we wish

* Corresponding author. Tel.: +91 172 2534407; fax: +91 172 254 5074.
E-mail address: kkbhasin1950@yahoo.co.in (K.K. Bhasin).

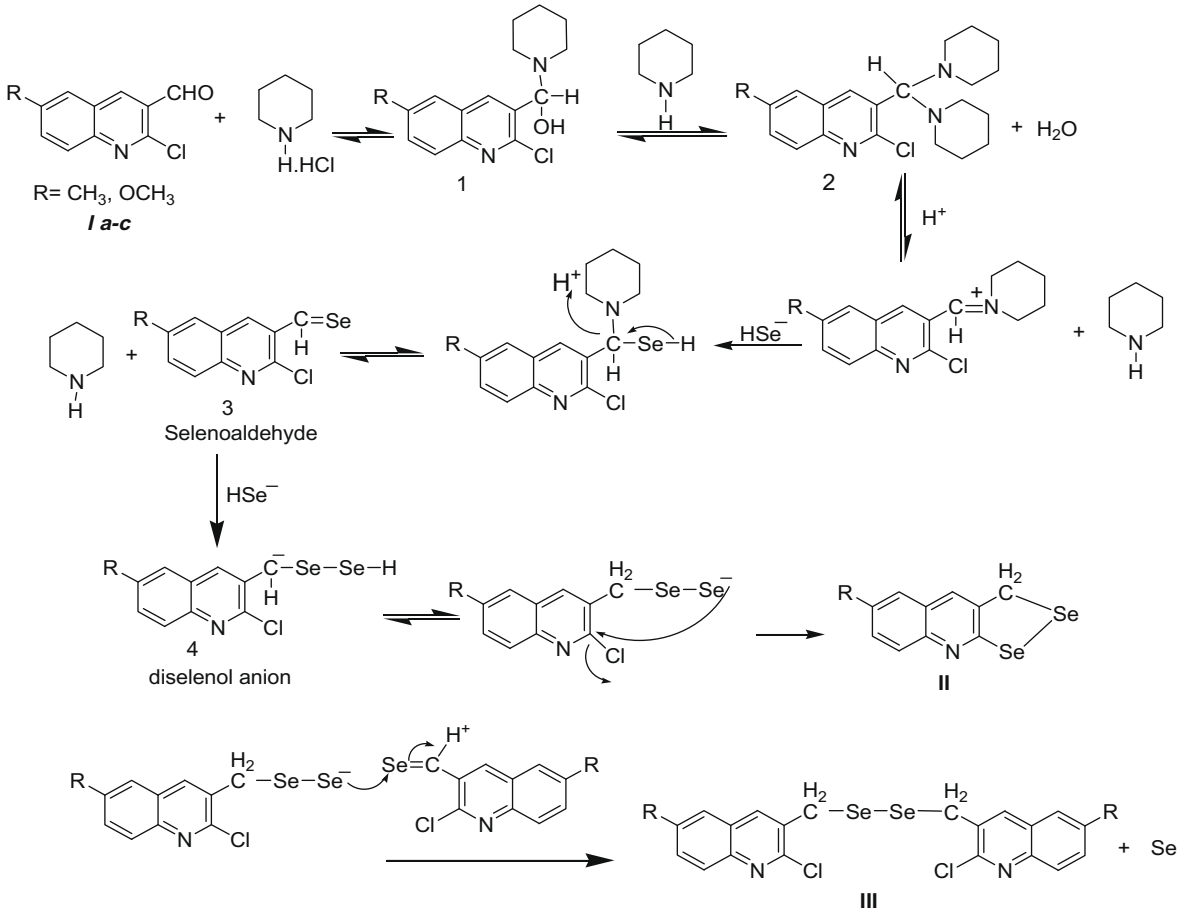
0022-328X/$ - see front matter © 2010 Elsevier B.V. All rights reserved.
doi:10.1016/j.jorganchem.2010.01.012



Scheme 1. Vilsmeier cyclisation.



Scheme 2. Reaction scheme for synthesis of quinoline selenium compounds.



Scheme 3. Mechanistic pathway for diselenolo[3.4-b]quinoline (**II a–b**) and quinolinyl methyl diselenide (**III a–b**).

to report the synthesis and characterization of a few hitherto unknown derivatives of the titled heterocycles and a viable mechanism for the unusual ring closure involved in the reaction.

The present article reveals the synthesis of 3H-[1,2]diselenolo[3,4-b]quinoline (**II a–b**) and 1,2-bis((2-chloroquinolin-3-yl)-methyl)diselenide (**III a–b**) systems (Scheme 2) wherein sodium

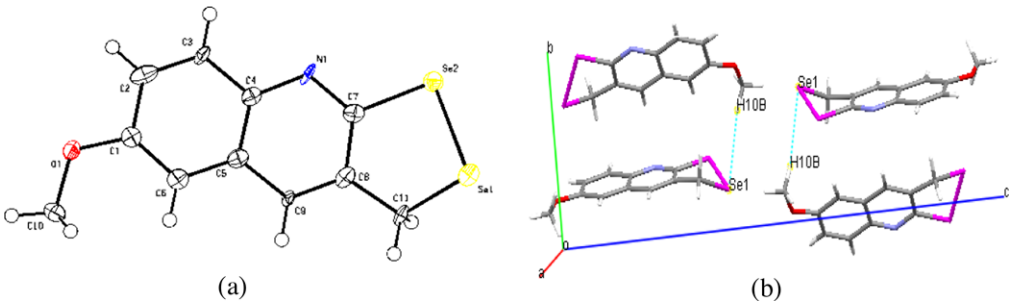


Fig. 1. (a) ORTEP representation and (b) crystal packing of 6-methoxy-3H-[1,2]diselenolo[3,4-b]quinoline (**II b**).

hydrogen selenide (NaHSe) has been used as an nucleophilic reagent for 2-chloro-3-formylquinolines **(I a–b)** in the presence of piperidine hydrochloride.

2.1. Spectroscopic studies

It was observed that the ^{1}H NMR spectra for the diselenolo [3,4-b]quinoline (**II a–b**) display four different sets of protons in aromatic region and one peak in aliphatic region corresponding to the methylene moiety .

Compounds **(III a–b)** whose identity has been tentatively predicted on the basis of NMR studies give rise to four distinct set of signals, three of which correspond to quinolinyl ring protons, whereas the remaining one signal in aliphatic region resonate much upfield (δ 3.60 for **III a** and δ 3.75 for **III b**) as compared to the methylene signal in corresponding cyclised selenium compounds (δ 4.51 for **II a** and δ 4.49 for **II b**). This indicates that the methylene protons are presumably located on a side chain rather than being in a cyclic structure. The two different environments experienced by the selenium atoms in the compounds **II a–b** is also confirmed by the appearance of two signals in ^{77} Se NMR.

In the mass spectrum of 6-methyl-3H-[1,2]diselenolo[3,4-b]quinoline (**II a**), ($[M]^{+}$+1) ion peak appears at *m*/*z* value of 316. 1,2-Bis((2-chloro-6-methoxyquinolin-3-yl)methyl)diselenide **(III b)** display the molecular ion peak at *m*/*z* value of 573. Mass fragments of **II b** and **III a** have also been characterized by mass spectroscopy**.**

A plausible mechanism for the reaction has been demonstrated in Scheme 3. In this sequence, the initial reaction involves the formation of an amine–aldehyde adduct such as hemiaminal or aminal 1 or 2. Nucleophilic displacement by the hydrogen selenide anion on 1 or 2 followed by an intramolecular elimination leads to a short lived selenoaldehyde intermediate 3. In this reaction sequence, two displacement steps, i.e. oxygen by nitrogen, and nitrogen, in turn, by selenium are taking place. Furthermore, it is proposed that the reduction of this selenoaldehyde 3 involves initial selenophilic attack by the hydrogen selenide anion, forming the diselenol anion 4. This diselenol anion then can undergo intramolecular nucleophilic displacement of chloride ion at second position, giving the cyclic diselenide **II a–b** or it can react with selenoaldehyde to give the diselenide **III a–b**.

2.2. X-ray crystallographic studies

Perspective view of the compound **II b** is shown in Fig. 1 and all other relevant details about crystal structure determination and refinement parameters are given in Table 1.

The Se–Se bond length is 2.354 Å. The most predominant short contact is observed between Se (1)···H (10) as depicted by the interatomic distance of 3.010 Å which is less than the sum of the Vander wall radii (3.100 Å). Nonbonding interactions present in the crystal structure are shown in Fig. 1. The crystal packing also shows that the two molecules facing each other have the selenium atoms in the opposite directions.

Table 1
Crystallographic data and measurements of **II b**.

Formula	$C_{11}H_9NOSe_2$
Assymetric unit	$C_{11}H_9NOSe_2$
Formula weight	329.11
T/K	100(1)
Crystal system	Monoclinic
Space group	*P* 21/*n*
a/Å	6.112(4)
b/Å	7.474(5)
c/Å	22.779(6)
β/°	94.345(5)
V/Å ^{3}	1037.6(10)
Z	4
Absorption coefficient/mm^{-1}	7.095
D_{calc}/g cm^{3}	2.107
F(0 0 0)	632.0
2θ/°	57.56
Index ranges	$-8 < h < 6$; $-9 < k < 9$; $-30 < l < 23$
Reflections collected [R_{int}]	6378 [0.0745]
Reflections unique	2552
Parameters	137
GOF	1.144
R_1/wR_2 [$I > 2\sigma(I)$]	0.0716/0.1933
R_1/wR_2 (all data)	0.0933/0.2683
Largest res. peak/e Å^{-3}	0.915

3. Experimental

3.1. General

All the experimental manipulations were carried out in dry and deoxygenated nitrogen atmosphere. Absolute ethanol (Fluka, purity > 99%) was used as the solvent for the reactions. Sodium borohydride (Loba, purity > 99.5%), elemental selenium (Hi-media, purity > 99%) and piperidine hydrochloride (Hi-media, purity > 99%) were newly purchased and stored in dessicator prior to use. 2-Chloro-3-formyl quinolines were prepared by reported methods [14]. All the compounds prepared were fully characterized using elemental analysis on a Perkin–Elmer 2400 CHN analyzer. ^{1}H, ^{13}C NMR spectra were recorded on a Jeol AL 300 MHz spectrometer in $CDCl_3/CCl_4$. Tetramethylsilane (TMS) was used as an internal standard for ^{1}H NMR and ^{13}C NMR. Infrared spectra were obtained between KBr plates using CCl_4 as mulling agent on a Perkin–Elmer model 1430 spectrophotometer. Mass spectrometry was carried out on ES-MS Q-TOF.

3.2. General procedure for the synthesis of quinoline chalcogen compounds (*II a–b*, *III a–b*)

Grey powdered selenium (60 mmol) and sodium borohydride (70.6 mmol) were placed into a 500 mL, three necked flask fitted

with a nitrogen inlet, addition funnel, and reflux condenser. The flask was flushed with nitrogen, immersed in an ice bath, and absolute ethanol (100 mL) was added slowly with stirring. Stirring was continued until all selenium has dissolved and a colorless solution resulted. To this solution was added piperidine hydrochloride (50 mmol) followed by aldehyde (47 mmol). The reaction mixture was heated under reflux for 1 h and cooled to room temperature to give red solution. Addition of sodium borohydride (12 mmol) in small doses resulted in a vigorous reaction. The reaction was monitored by TLC. After completion of reaction, it is diluted with about 250 mL of distilled water and extracted in dichloromethane (3×50 mL). The organic layer was decanted and solvent was evaporated to get the crude product in solid form. The product was subjected to purification on a silica column using hexane and ethyl acetate as eluant (5:1).

*3.2.1. 6-Methyl-3H-[1,2]diselenolo[3,4-b]quinoline (**II a**)*

Red crystalline solid, M.Pt. 122–124 °C, Yield. 57%, Anal. Calcd (%) for $C_{11}H_9NSe_2$, C, 42.19; H, 2.89; N, 4.47. Found: C, 40.31; H, 2.28; N, 4.06%; ^{1}H NMR (300 MHz, $CCl_4/CDCl_3$, δ ppm) 7.71 (d, 1H, *J* 6.0 Hz), 7.64 (s, 1H), 7.37 (d, 1H, *J* 6.0 Hz), 7.34 (s, 1H), 4.51 (s, 2H), 2.47 (s, 3H); ^{13}C NMR (75 MHz, $CCl_4/CDCl_3$, δ ppm) 162.0, 143.7, 134.2, 133.1, 129.9, 128.8, 125.8, 124.3, 122.9, 60.3, 29.2; ^{77}Se NMR (57 MHz, $CCl_4/CDCl_3$, δ ppm) 413.0, 366.9; IR (KBr, ν cm^{-1}): 2925.7, 1723.5, 1559.3, 1259.9, 1107.8, 1009.5, 624.8, 554.8, 483.5; ES-MS: *m/z* (Assignment, R.I.%): 316 ($[C_{11}H_9NSe_2]^{+\cdot}$ + 1, 20).

*3.2.2. 6-Methoxy-3H-[1,2]diselenolo[3,4-b]quinoline (**II b**)*

Red crystalline solid, M.Pt. 118–120 °C, Yield. 59%, Anal. Calcd (%) for $C_{11}H_9NOSe_2$, C, 40.14; H, 2.76; N, 4.25. Found: C, 39.82; H, 2.90; N, 4.30%. ^{1}H NMR (300 MHz, $CCl_4/CDCl_3$, δ ppm) 7.71 (d, 1H, *J* 9.0 Hz), 7.63 (s, 1H), 7.17 (d, 1H, *J* 9.0 Hz), 6.84 (s, 1H), 4.49 (s, 2H), 3.83 (s, 3H); ^{13}C NMR (75 MHz, $CCl_4/CDCl_3$, δ ppm) 133.4, 128.5, 127.4, 119.9, 103.3, 53.3, 29.2; ^{77}Se NMR (57 MHz, $CCl_4/CDCl_3$, δ ppm) 409.8, 369.9; IR (KBr, ν cm^{-1}): 2925.7, 1727.2, 1559.7, 1255.5, 1107.8, 1067.28, 624.8, 529.0, 478.6; ES-MS: *m/z* (Assignment, R.I.%): 301 ($[C_{10}H_6NSe_2]^{+\cdot}$ + 1, 5).

*3.2.3. 1,2-Bis((2-chloro-6-methylquinolin-3-yl)methyl)diselenide (**III a**)*

Yellow crystalline solid, M.Pt. 135–137 °C, Yield. 26%, Anal. Calcd (%) for $C_{22}H_{18}Cl_2N_2Se_2$, C, 49.00; H, 3.64; N, 5.19. Found: C, 48.56; H, 3.12; N, 4.93%; ^{1}H NMR (300 MHz, $CCl_4/CDCl_3$, δ ppm) 8.07 (s, 1H), 7.80 (d, 1H, *J* 8.4 Hz), 7.50 (s, 1H), 7.41 (d, 1H, *J* 8.4 Hz), 3.60 (s, 2H), 2.46 (s, 3H); ^{13}C NMR (75 MHz, $CCl_4/CDCl_3$, δ ppm) 145.4, 137.2, 136.6, 132.0, 130.7, 128.0, 127.5, 126.3, 59.8, 26.2; IR (KBr, ν cm^{-1}): 2925.0, 1718.3, 1550.3, 1248.9, 1102.8, 1002.5, 620.8, 552.2, 478.3. ES-MS: *m/z* (Assignment, R.I.%): 190 ($[C_{11}H_9NCl]^{+\cdot}$, 10).

*3.2.4. 1,2-Bis((2-chloro-6-methoxyquinolin-3-yl)methyl)diselenide (**III b**)*

Yellow crystalline solid, M.Pt. 127–129 °C, Yield. 23%, Anal. Calcd (%) for $C_{22}H_{18}Cl_2N_2O_2Se_2$, C, 46.25; H, 3.17; N, 4.90. Found: C, 45.80; H, 3.02; N, 4.65%; ^{1}H NMR (300 MHz, $CCl_4/CDCl_3$, δ ppm) 7.78 (d, 1H, *J* 9.0 Hz), 7.72 (s, 1H), 7.23 (d, 1H, *J* 9.0 Hz), 6.91 (s, 1H), 3.75 (s, 2H), 3.89 (s, 3H); ^{13}C NMR (75 MHz, $CCl_4/CDCl_3$, δ ppm) 162.1, 142.2, 132.8, 132.4, 127.2, 126.8, 115.2, 102.5, 52.2, 28.1; IR (KBr, ν cm^{-1}): 2925.2, 1732.1, 1552.7, 1252.1, 1108.1, 1058.2, 1002.3, 620.2, 478.6. ES-MS: *m/z* (Assignment, R.I.%): 573 ($[C_{22}H_{18}N_2Se_2Cl_2O_2]^{+\cdot}$, 17), 493 ($[C_{22}H_{18}N_2SeCl_2O_2]^{+\cdot}$, 8), 207 ($[C_{11}H_9NClO]^{+\cdot}$ + 1, 100).

3.2.5. Single crystal X-ray analysis

Diffraction quality red hexagonal crystals of 6-methoxy-3H-[1,2]diselenolo[3,4-b]quinoline (**II b**) were grown in dichloromethane–hexane (3:1) solution of the compound. A selected specimen was diffracted using a Bruker Smart Apex diffractometer using graphite monochromated Mo Kα radiation (0.71069 Å) at 100(1) K. The data integration and reduction were processed with SAINT software. All the non-hydrogen atoms were refined anisotropically. The hydrogen atoms were included in the ideal position with fixed isotropic *U* values and were riding. The empirical absorption corrections for these compounds were performed using SADBAS program. The structure was solved by direct methods and refined on F^2 by full-matrix least-squares using SHELX-97 program package. The compound crystallizes into monoclinic form with *P* 21/*n* space group.

4. Conclusion

In this paper the authors have used a convenient methodology for the synthesis of hitherto unknown quinoline selenium compounds. The diselenolo[3,4-b]quinoline and quinoline methyl diselenide systems can act as suitable candidates for coordination chemistry.

Acknowledgement

The authors are thankful to CSIR for their financial assistance.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jorganchem.2010.01.012.

References

[1] R.J. Shambenger, in: E. Frieden (Ed.), Biochemistry of "Selenium", Plenum Press, 1983.
[2] M. McNaughton, L. Engman, A. Birmingham, G. Powis, I.A. Cotgreave, J. Med. Chem. 47 (2004) 233.
[3] P.M.S. Chauhan, S.K. Srivastava, Curr. Med. Chem. 8 (2001) 1535.
[4] M. Balasubramanian, J.G. Keay, in: A.R.J. Katritzky, C.W. Rees (Eds.), Comprehensive Heterocyclic Chemistry II, vol. 5, Pergamon, New York, NY, 1996, p. 245.
[5] D. Gottlieb, P.D. Shaw (Eds.), Antibiotics II, Biosynthesis, vol. 2, Springer, New York, NY, 1967. p. 105.
[6] M.Z. Hoemann, G. Kumaravel, R.L. Xie, R.F. Rossi, S. Meyer, A. Sidhu, G.D. Cuny, J.R. Hauske, Biorg. Med. Chem. Lett. 10 (2000) 2675.
[7] M.M. Ali, Tasneem, K.C. Ranjanna, P.K. Sai Prakash, Synlett 2 (2001) 251.
[8] W. Lewicki, W.H.H. Gunther, J.Y.C. Chu, J.C.S., Chem. Commun. (1976) 552.
[9] D.S. Margolis, R.W. Pittman, J. Chem. Soc. (1957) 799.
[10] V.C. Cohen, J. Org. Chem. 42 (1977) 2510.
[11] F. Tian, Z. Yu, S. Lu, J. Org. Chem. 69 (2004) 4520.
[12] K.K. Bhasin, E. Arora, K. Kaur, S. Kang, M. Gobel, T.M. Klapoetke, S.K. Mehta, Tetrahedron 65 (2009) 247.
[13] P.V. Caneghem, Biochem. Pharmacol. 23 (1974) 3491.
[14] A. Srivastava, R.M. Singh, Indian J. Chem. (2005) 1868.