Available online at www.sciencedirect.com
SCIENCE DIRECT®
Journal of Organometallic Chemistry 690 (2005) 2186–2190
Journal of Organometallic Chemistry
www.elsevier.com/locate/jorganchem

Synthesis, crystal structure and in vitro antitumor activity of di-*n*-butyltin 4′-(7-oxabicyclo [2,2,1]-5-heptane-2,3-dicarboximide) benzoates

Yizong Zhou [a], Tao Jiang [a,*], Sumei Ren [a], Jingsheng Yu [b], Zhicheng Xia [c]

[a] *Marine Drug and Food Institute, Ocean University of China, Qingdao, Shandong 266003, China*
[b] *The Key Laboratory for Supramolecular Structure and materials of Ministry of Education, Jilin University, Changchun 130023, China*
[c] *Department of Chemistry, McGill University, Montreal, Canada H3A 2K6*

Received 16 September 2004; accepted 31 January 2005
Available online 14 April 2005

Abstract

Dibutyltin(IV) oxide reacts with the cantharidin analogue, 4′-(7-oxabicyclo [2,2,1]-5-heptane-2,3-dicarboximide) benzoic acid, **A**, to give the complexes $[(p\text{-}C_8H_8NO_3\text{–}C_6H_4\text{–}COOBu_2Sn)_2O]_2$ (**1**) and $(p\text{-}C_8H_8NO_3\text{–}C_6H_4\text{–}COO)_2SnBu_2$ (**2**) which had been characterized by IR and ^1H, ^{13}C, ^{119}Sn NMR. Single X-ray crystal structure analysis has been determined for compound (**1**), which was analogue to most other $[(RCOOBu_2Sn)_2O]_2$. The dimer features central of $Bu_4Sn_2O_2$ unit with the two Bu_2Sn groups being linked via bridging oxygen atom. Each tin atom adopts distorted trigonal bipyramidal structures via two carbons from a dibutyl moiety and three oxygen atoms from cantharidin derivative and bridging oxygen atom. In vitro tests show compounds **1** and **2** exhibit high cytotoxicity against P388 and HL-60.

Keywords: Organotin; Cantharidin; Synthesis; Crystal structure; Antitumor activity

1. Introduction

The structural chemistry of organotin carboxylate compounds has attracted considerable attention owing to their antitumor activity [1–3]. Among those compounds dibutyltin derivatives have displayed both higher activity and lower toxicity [4]. So the antitumor activity of many compounds of the type $[(RCOOBu_2Sn)_2O]_2$ and $(RCOO)_2Bu_2Sn$ has been studied [5,6]. This may yield new leads for the development of antitumor drugs that may possess lower toxicity than platinum compounds [7]. Cantharidin is the main effective ingredient of Canthatis vesicatoria, a traditional Chinese medicine for malignancy treatments. Several studies have shown that Cantharidin and its derivatives possess potential antitumor activities for liver, lung, colon and breast cancers [8]. We have recently combined dibutyltin with 5-fluorouracil derivatives to synthesize the complexes of $[(5\text{-flurorouracil})\text{-}1\text{-}(CH_2)_mCOOSnBu_2]O_2$ (m = 1, 2) and the bioassay shows that they exhibit strong antitumor activity against OVCAR-3 and PC-14 cell-line in vitro [9] and acceptable acute toxicity in mice [10].

In order to study organotin complexes as possible candidate for antitumor agent and the structure-activity relationships of these complexes, we successfully prepared the dibutyl organotin(IV) derivatives of Cantharidin analogue, which had been characterized by IR, ^1H, ^{13}C and ^{119}Sn NMR spectra. And crystallographic data is also presented for the compound (**1**).

* Corresponding author. Tel.: +865322032712; fax: +865322033054.
E-mail address: jiangtao@mail.ouc.edu.cn (T. Jiang).

0022-328X/$ - see front matter © 2005 Elsevier B.V. All rights reserved.
doi:10.1016/j.jorganchem.2005.01.062

2. Experimental

2.1. General methods

IR spectra were recorded using KBr pellets for solid samples on a NICOLET NEXUS 470 FT-IR. ^{1}H, ^{13}C NMR spectra were recorded on a Bruker DPX-400 spectrometer operating at 400 and 100.6 MHz, respectively, and with TMS as the internal reference in $CDCl_3$. ^{119}Sn NMR spectra were collected at a spectrometer frequency of 186.4 MHz on a Varian UNITY 500 with a 10 mm broadband probe. All samples were prepared in $CDCl_3$ solution and chemical shift values were referenced externally with Me_4Sn.

Toluene was dried over Na and distilled prior to use under N_2. Dibutyltin oxide was synthesized following the literature methods [11]. The Cantharidin analogue and its carboxylic derivative, 4′-(7-oxabicyclo [2,2,1]-5-heptane-2,3-dicarboximide) benzoic acid, **A**, were synthesized according to the literature methods [12].

The tumor inhibiting effect of compounds **1** and **2** was tested in vitro by using the murine leukemia cell line P388 and human leukemia cell line HL-60 with the method of MTT. The human Lung Epithelial Cell line A-549 with the method of SRB.

2.2. Synthesis of the complexes $[(p\text{-}C_8H_8NO_3\text{–}C_6H_4\text{–}COOBu_2Sn)_2O]_2$ (1) and $(p\text{-}C_8H_8NO_3\text{–}C_6H_4\text{–}COO)_2\text{-}SnBu_2$ (2)

Di-*n*-butyltin oxide (1.24 g, 5 mmol) was dissolved in toluene (40 ml) containing a few of 4 Å molecular sieves and the carboxylic acid, **A**, [(1.44 g, 5 mmol) for compound (**1**) and (2.87 g, 10 mmol) for compound (**2**)] was added. The mixture was stirred under N_2 for 8 h at a temperature of 80 °C. After cooling and filtration, the residue was extracted three times with THF. Concentration of the resulting solution gave colorless solid. The solid obtained was purified by recrystallisation from THF/*n*-hexane.

Compound (**1**): yield 57.8%, m.p.: 248–250 °C. Anal. Calc. for $C_{92}H_{120}N_4O_{22}Sn_4$: Sn, 22.52. Found: 22.32%. IR(cm^{-1}): $\nu(CH_3)$ 3089, 2927, $\nu(CH_2)$ 2957, 2874, ν(C=O) 1770, 1709, ν(Ar) 1607, 1565, 1510, 1463, ν(C–O–C) 1189, ν(Sn–O–Sn) 686, ν(Sn–C) 574, ν(Sn–O) 506.

Compound (**2**): yield 71.6%, m.p. 286–288 °C. Anal. Calc. for $C_{38}H_{42}N_2O_{10}Sn$: 14.94. Found: 14.50%. IR(cm^{-1}): $\nu(CH_3)$ 3104, 2927, $\nu(CH_2)$ 2957, 2874, ν(C=O) 1778, 1705, ν(Ar) 1607, 1566, 1510, 1463, ν(C–O–C) 1188, ν(Sn–C) 575, ν(Sn–O) 505.

2.3. Crystal structure determination of the compound (1)

A single crystal ($0.40 \times 0.36 \times 0.27$ mm) of the compound **1** was mounted in a glass capillary, and data collection was performed on a Rigaku RAXIS-RAPID diffraction by using Mo Kα radiation ($\lambda = 0.71073$ Å) in the θ range from 1.15° to 27.48° at 293 K. The final cycle of full-matrix least-squares refinement was based on 13752 observed reflections. The final agreement factor was $R = 0.0807$ [$I > 2\sigma(I)$]. Crystal data: $C_{92}H_{120}N_4O_{22}Sn_4 \cdot 6C_4H_4O$, $Fw = 2517.11$, Triclinic, $P\bar{1}$, $a = 14.0445(12)$ Å, $b = 14.1483(15)$ Å, $c = 19.051(2)$ Å, $\alpha = 96.418(2)°$, $\beta = 105.204(5)°$, $\gamma = 118.296(2)°$, $V = 3089.8(6)$ Å^3, $Z = 1$, $F(000) = 1292$, $D_c = 1.353$ mg/m^3.

3. Results and discussion

3.1. Synthesis

The carboxylic acid **A** reacts with the di-*n*-butyltin oxide yielding two different compounds depending on molar ratio acid/tin engaged in the reaction: bis[di-*n*-butyl(carboxylato)tin] oxide (**1**) for a 1:1 ratio and di-*n*-butyltin di(carboxylate) (**2**) for a 2:1 ratio. The synthesis route for this compound is shown in Fig. 1.

An X-ray quality crystal of the compound (**1**) was obtained from a 1:1 condensation of dibutyltin(IV) oxide

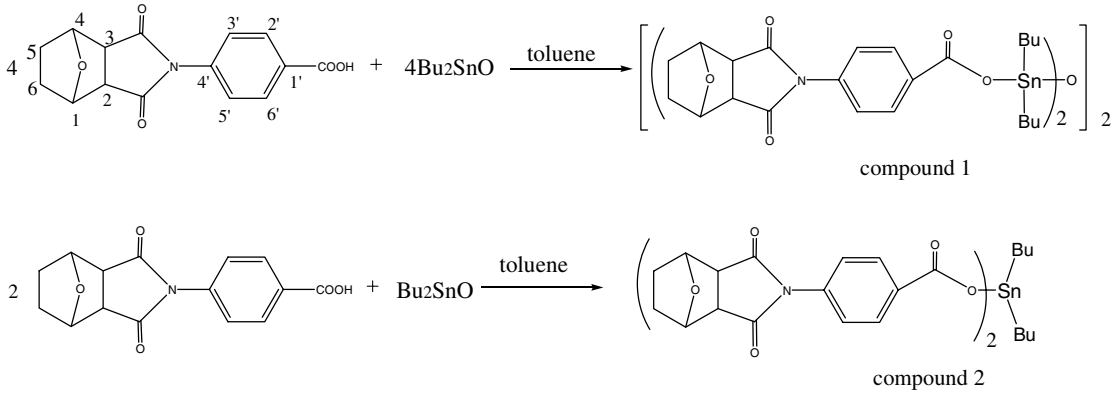

Fig. 1. The synthesis of compounds (**1**) and (**2**).

with **A** and its structure has been determined by spectroscopic and single crystal X-ray diffraction methods.

3.2. Spectroscopic studies

3.2.1. IR spectra

The stretching frequencies of interest are those associated with the acid COO, Sn–C, Sn–O, and Sn–O–Sn groups. The free acid shows a broad band due to O–H absorption of COOH group in the 3500–3050 cm^{-1} region which is absent in the spectrum of the complexes, indicating the deprotonation and coordination of the carboxylate group. A band at 686 cm^{-1} for compound **1** is assigned to ν(Sn–O–Sn), which indicates an Sn–O–Sn bridged structure for compound **1**. The absorption bands at 574 and 506 cm^{-1} for compound **1**, 575 and 505 cm^{-1} for compound **2** are assigned to ν(Sn–C) and ν(Sn–O), respectively [13].

3.2.2. NMR spectra

Compounds **1** and **2** have been characterized by ^{1}H, ^{13}C, ^{119}Sn NMR spectroscopy in $CDCl_3$. The ^{1}H, ^{13}C, ^{119}Sn NMR data are listed in Table 1.

In the ^{1}H NMR spectrum of the ligand a single resonance is observed at 13.15 ppm, which is absent in the complexes indicating the replacement of the carboxylic acid proton by a diorganotin moiety on complex formation. The butyl protons of compound **1** show a multiplet in the region 1.58–1.92 ppm but the butyl protons of compound **2** is better defined. Compound **2** exhibits a single triplet for methylenic protons signifying one tin site, but for compound **1**, a doublet of triplet peaks is observed in the ^{1}H NMR spectrum. It is presumed that two types of tin centres are present due to the inequivalent surroundings. This is confirmed by the crystal structure of compound **1** and the ^{119}Sn NMR spectra.

In ^{13}C NMR spectra for compound **2** only one signal is observed for each methylenic carbon of the butyl group. By contrast two peaks of almost equal height appear for the methyl group around *exo*- and *endo*-cyclic Sn(IV). Butyl groups of compound **1/2**: C_α: 27.7/26.6 ppm, C_β: 27.4/26.2 ppm, C_γ: 26.7/25.5 ppm, and C_δ: 13.6/13.5 ppm. Weak satellites are observed in the DEPT spectra of compound **1**, but the $^{1}J(^{119}Sn–^{13}C_\alpha)$ is not observed, $^{2}J(^{119}Sn–^{13}C_\beta)$ = 41.4 Hz, $^{3}J(^{119}Sn–^{13}C_\gamma)$ = 113.7 Hz. For compound **2** the weak satellites are not very clear, so the coupling constant is not observed.

^{119}Sn NMR spectra of compound **1** display a pair of resonances of equal intensities at −210.9, −215.3 ppm confirming *endo*- and *exo*-cyclic tin atoms which is consistent with the crystal structure, these chemical shifts values are penta-coordinated or weakly hexa-coordinated tin atoms. This shows that the structure of the two types of tin atom in the solid state are still retained in solution. There is only one resonance at −148.4 ppm for compound **2** indicating one type of tin site. The chemical shift is agreement with the penta-coordinated tin atom [14].

Table 1
^{1}H, ^{13}C, and ^{119}Sn NMR data in $CDCl_3$ of compounds **1** and **2**

Atom	Compound **1**		Compound **2**	
	^{1}H	^{13}C	^{1}H	^{13}C
1, 4	5.00 s	79.5	5.02 ψs	79.6
2, 3	3.08 s	50.0	3.07 ψs	50.0
5, 6	1.58–1.66 m	28.6	1.67–1.73 m	28.6
1′		135.0		135.9
2′, 6′	8.12 ψs	130.6	8.23–8.25 d (J = 8.5)	131.3
3′, 5′	7.43 ψs	126.1	7.41–7.44 d (J = 8.5)	126.2
4′		133.3		130.0
Butyl α	1.66–1.92 m	27.7	1.92–1.94 m	26.6
Butyl β	1.66–1.92 m	27.4	1.79–1.83 m	26.2
Butyl γ	1.27–1.45 dq (J = 7.0)	26.7	1.35–1.42 h (J = 7.3)	25.5
Butyl δ	0.79–0.89 dt (J = 7.0)	13.6	0.86–0.90 t (J = 7.3)	13.5
CON		176.0		175.9
COO		171.7		174.7
^{119}Sn	−210.9, −215.3		−148.4	

Abbreviations: s, singlet; ψs, pseudo singlet; d, double; m, complex pattern; t, triplet; h, hexa; dq, double quartet; dt, double triplet.

3.3. Crystal and molecular structure

The molecular structure of compound (**1**), illustrated in Fig. 2 shows that the structure is similar to those of a majority of analogous $[(RCOOBu_2Sn)_2O]_2$ compounds. Its selected interatomic bond distances (Å) and angles (°) are listed in Table 2.

The structure of compound (**1**) is centro-symmetrical about a $Bu_4Sn_2O_2$ core. The two oxygen atoms O(10) and O(10A)are triply bridging, each linking one *exo*-cyclic (Sn(1) or Sn(1A)) and two *endo*-cyclic (Sn(2) and Sn(2A)) $SnBu_2$ groups. The tin atoms are five coordinate. The coordination geometry about each *exo*-cyclic tin atom, Sn(1), is completed by one bridging and one monodentate carboxylate ligand and one bidentate bridging carboxylate ligand. Each *endo*-cyclic tin atom, Sn(2), is completed by two bridging and one bidentate bridging carboxylate ligands. The geometry about the four tin atoms is based on the trigonal bipyramidal structures with the trigonal planes defined by the C(38), C(45), O(10) atoms for Sn(1); C(34), C(42), O(10A) atoms for Sn(2). C(38A), C(45A), O(10A) for Sn(1A), C(34A), C(42A), O(10) for Sn(2A). While the O(5) and O(10), O(9) and O(10), O(5A) and O(11A), O(9A) and O(10A) are in the axial position for Sn(1), Sn(2), Sn(1A), Sn(2A), respectively.

For compound (**1**) the Sn(1)–O(11), Sn(2A)–O(9A) bond distances involving the bridging carboxylate ligand, 2.274(4) and 2.242(3) Å, respectively, differ by

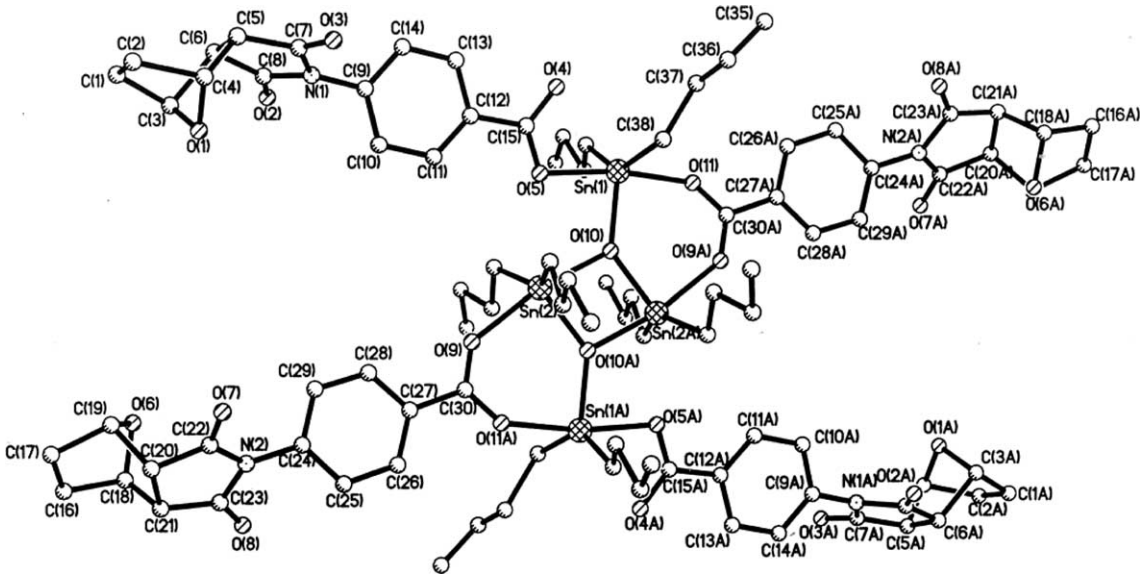

Fig. 2. Molecular structure and atomic numbering system for compound (**1**).

Table 2
Selected bond lengths (Å) and angles (°) for compound (**1**)

Bond lengths			
Sn(1)–O(10)	2.030(3)	Sn(1)–C(38)	2.128(3)
Sn(1)–C(45)	2.099(5)	Sn(1)–O(5)	2.176(3)
Sn(1)–O(11)	2.274(4)	Sn(2)–O(11A)	2.036(3)
Sn(2)–C(42)	2.102(5)	Sn(2)–C(34)	2.125(6)
Sn(2)–O(10)	2.162(3)	Sn(2)–O(9)	2.241(3)
O(10)–Sn(2A)	2.036(3)	O(9)–C(30)	1.205(5)
O(11A)–C(30)	1.241(6)	C(27)–C(30)	1.471(6)
O(4)–C(15)	1.241(6)	O(5)–C(15)	1.273(5)
C(12)–C(15)	1.500(6)		
Bond angles			
O(10)–Sn(1)–C(45)	109.3(3)	O(10)–Sn(1)–C(38)	108.89(19)
C(45)–Sn(1)–C(38)	141.0(4)	O(10)–Sn(1)–O(5)	81.98(11)
C(45)–Sn(1)–O(5)	94.4(3)	C(38)–Sn(1)–O(5)	98.1(2)
O(10)–Sn(1)–O(11)	90.26(12)	C(45)–Sn(1)–O(11)	83.7(3)
C(38)–Sn(1)–O(11)	88.8(2)	O(5)–Sn(1)–O(11)	170.92(14)
O(10A)–Sn(2)–C(42)	111.5(2)	O(10A)–Sn(2)–C(34)	109.56(18)
C(42)–Sn(2)–C(34)	138.7(2)	O(10A)–Sn(2)–O(10)	76.19(11)
C(34)–Sn(2)–O(10)	98.07(2)	O(10A)–Sn(2)–C(9)	91.95(12)
C(42)–Sn(2)–O(9)	86.0(2)	O(10)–Sn(2)–O(9)	167.89(12)
C(34)–Sn(2)–O(9)	88.1(2)	C(42)–Sn(2)–O(10)	95.94(18)
C(30)–O(9)–Sn(2)	138.8(3)	Sn(1)–O(10)–Sn(2A)	135.27(14)
Sn(1)–O(10)–Sn(2)	120.80(12)	Sn(2A)–O(10)–Sn(2)	103.81(11)
C(30A)–O(11)–Sn(1)	137.3(3)	C(41)–C(42)–Sn(2)	115.3(4)
C(33)–C(34)–Sn(2)	120.5(6)	C(37)–C(38)–Sn(1)	108.1(6)
C(44)–C(45)–Sn(1)	145.6(13)	O(9)–C(30)–O(11A)	123.0(4)

only 0.033 Å indicating a nearly symmetrical bridge. This is supported by both distances being longer than the Sn(1)–O(5) distance, 2.176(3) Å, formed by the monodentate carboxylate ligand. The bonding of the bridging ligands is unsymmetrical with a Sn(2)–O(10) bond length of 2.162(3) Å and a Sn(2)–O(10A) bond length of 2.036(3) Å, which forms a parallelogram. The complex also contains two five-member chelate rings, formed via carbonyl oxygen to tin coordination. The structure reported here of the compound (**1**) resembles closely the predominant motif found for compounds of the general formula $\{[R_2Sn(O_2CR')]_2O\}_2$ [15,16].

3.4. Biological activity

Preliminary in vitro tests for tumor-inhibiting activity of compounds **1** and **2** was performed by using the methods of MTT and SRB. The data summarized in Table 3 show that compounds **1** and **2** possess rather high cytotoxicity to tumor cell of P388 and HL-60, but the cytotoxicity to tumor cell of A-549 is lower.

Table 3
Inhibitory effect of the compounds on tumor cells of P388(MTT), HL-60(MTT) and A-549(SRB)

Cell line	Concentration (mol/l)	Inhibitory rate (%)	
		Compound **1**	Compound **2**
P388	10^{-4}	100	100
	10^{-5}	100	100
	10^{-6}	100	100
	10^{-7}	17.2	58.8
	10^{-8}	81.8	0
HL-60	10^{-4}	100	100
	10^{-5}	99.3	98.5
	10^{-6}	96.7	93.5
	10^{-7}	91.8	28.3
	10^{-8}	75.3	25.7
A-549	10^{-4}	100	100
	10^{-5}	73.3	81.9
	10^{-6}	63.2	49.6
	10^{-7}	38.1	27.9
	10^{-8}	18.1	6.8

4. Supplementary material

Crystallographic data for the structure analysis of compound **1** has been deposited with the Cambridge Crystallographic Data Center, CCDC No. 249997. Copies of these information may be obtained free of charge from the Director, CCDC, 12 Union Road Cambridge CB2 1EZ UK (fax: +44 1223 336033; email: deposit@ccdc.cam.ac.ukor www: http://www.ccdc.cam.ac.uk).

Acknowledgement

We thank Dr. Shengbiao Wan, Department of Applied Biology and Chemical Technology, HongKong Polytechnic University, for the ^{1}H, ^{13}C, ^{119}Sn NMR spectra. We also thank the National Nature Science Foundation of China (Grant No. 20371043) and the Sino-French International Research Program (Grant No. PRA B03-04) for financial supported.

References

[1] M. Gielen, Appl. Organometal. Chem. 16 (2002) 481.
[2] L. Pellerito, L. Nagy, Coord. Chem. Rev . 224 (2002) 111.
[3] V.I. Bregadze, S.A. Glazun, P.V. Petrovskii, Z.A. Starikova, A.G. Buyanovskaya, R.U. Takazova, M. Gielen, D. de Vos, M. Kemmer, M. Biesemans, R. Willem, Appl. Organometal. Chem. 18 (2004) 191.
[4] C. Pettina, M. Pellei, F. Marchetti, C. Santina, M. Miliani, Polyhedron 17 (1998) 561.
[5] M. Kemmer, H. Dalil, M. Biesemans, J.C. Martins, B. Mahieu, E. Horn, D. de Vos, E.R.T. Tiekink, R. Willem, M. Gielen, J. Organometal. Chem. 608 (2000) 63.
[6] V.I. Bregadze, S.A. Glazun, P.V. Petrovskii, Z.A. Starikova, V.Y. Rochev, H. Dalil, M. Biesemans, R. Willem, M. Gielen, D. de Vos, Appl. Organometal. Chem. 17 (2003) 453.
[7] M. Gielen, M. Biesemans, J. Inorg. Biochem. 79 (2000) 139.
[8] G.S. Wang, J. Ethnopharmacol. 26 (1989) 147–162.
[9] D.Sh. Zuo, T. Jiang, H.Sh. Gnan, X. Qi, Chin. J. Chem. 19 (2001) 1141.
[10] X. Zh. Cheng, T. Jiang, S.M. Ren, Y.Z. Zhou, X.W. Xue, J. Ocean University of China, 2004, Unpublished results.
[11] C. Hu, S. Wang, S. Zhao, Chin. J. Med. Chem. 4 (1994) 32 (in Chinese).
[12] F.L. Liu, T. Jiang, D.Sh. Zuo, Chin. J. Org. Chem. 22 (10) (2002) 761.
[13] G.K. Sandhu, N. Sharma, E.R.T. Tiekink, J. Organometal. Chem. 403 (1991) 119.
[14] J. HolČeek, M. Nádvorník, K. Handlíř, A. LyČka, J. Organometal. Chem. 315 (1986) 299.
[15] E.R.T. Tiekink, Appl. Organomet. Chem. 5 (1991) 1.
[16] E.R.T. Tiekink, Trends Organomet. Chem. 1 (1994) 71.