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Mercuration of thiophene-2-carboxylic acid, 2-thienylethanoic acid and 3-(2-thienyl)alanine: preparation and spectral characterization[†]

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Thiophene-2-carboxylic acid, 2-thienylethanoic acid and 3-(2-thienyl)alanine were mercurated with mercury(II) chloride in aqueous media in the presence of sodium acetate trihydrate. Mono- and di-mercurated products were obtained, depending on the reaction conditions. When mercury(II) acetate was used as the mercuration agent a mixture of mono- and di-mercurated products was obtained. The chemical formulae and the structures of the isolated compounds were deduced from elemental chemical analysis and IR spectra. In the case of soluble products the site and degree of mercuration were determined on the basis of ^{1}H and ^{13}C NMR spectra. In monomercurated thiophene-2-carboxylic acid, 2-thienylethanoic acid and 3-(2-thienyl)alanine the H-5 signal was absent, which together with the large downfield shift of the corresponding ^{13}C signal (*ca* 24 and 21 ppm) confirmed that mercuration took place at the C-5. Two- and three-bond ^{199}Hg–^{13}C satellite couplings at C-4 and C-3 as well as four-bond ^{199}Hg–^{1}H coupling at H-4 were also revealed. Copyright © 2000 John Wiley & Sons, Ltd.

Keywords: direct mercuration; 2-thienyl derivatives; IR; NMR

INTRODUCTION

The mercuration of aromatic compounds, in which a carbon–hydrogen bond is replaced by a carbon–mercury bond, is one of the fundamental processes that these compounds undergo.[1] It is well known that benzene, furan, thiophene and other aromatics can also be permercurated upon treatment with mercuric salts at elevated temperatures, as well as that these permercurated compounds can be efficiently transformed into the corresponding persubstituted species upon treatment with electrophiles.[2,3] The mercuration of thiophene has been known for many years. Volhard demonstrated in 1892 that the substitution occurs exclusively α to the sulfur, whereas under more forcing conditions both α-carbons are metallated.[4] The symmetrization reaction is a well-known path to obtain dialkyl- or diaryl-mercurials,[5,6] and the only structurally determined organomercurial of thiophene in the solid state is dithienylmercury,[7] which was prepared by that route. Less is known about the mercuration of 2- and 2,5-substituted thiophene derivatives. ^{1}H and ^{13}C NMR spectroscopy is very useful for determining the site and degree of mercuration in organic and bio-organic molecules. If a C–Hg bond is formed, the ^{199}Hg–^{1}H and ^{199}Hg–^{13}C satellite couplings can be detected.[8,9] In compounds such as mercaptides or thiolates, where the mercury atom is bonded to S and/or O and/or N, satellite couplings to neighbouring C and H atoms are not usually observed.[10–12] On the other hand, the mercury substituent effects on ^{1}H and ^{13}C chemical shifts and ^{13}C–^{1}H and ^{1}H–^{1}H spin–spin couplings always exist if mercury is present in the molecule.

We report here the products of the direct mercuration of thiophene-2-carboxylic, 2-thienylethanoic acid and 3-(2-thienyl)alanine. Mono- and di-mercurated products were obtained, depending on the mercuration agent and the conditions under

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which mercuration was carried out. The ^{1}H and ^{13}C NMR spectra of the soluble mercurated derivatives of substituted thiophenes are described.

EXPERIMENTAL

Materials and measurements

Mercury(II) salts, thiophene-2-carboxylic acid and 2-thienylethanoic acid and 3-(2-thienyl)-DL-alanine (Aldrich) were used as received. The Fourier transform IR spectra of the parent and mercurated molecules were obtained from KBr discs in the region of 4000–450 cm^{-1} with a Perkin-Elmer spectrophotometer model 1600. The ^{1}H and ^{13}C NMR spectra were run on Varian Gemini 300 and Unity Inova 600 spectrometers, operating at 75.46 MHz and 150.9 MHz for the ^{13}C nucleus, respectively. The samples were dissolved in DMSO-d_6 and measured at 293 K in 5-mm NMR tubes. The concentrations of samples were 5 mg ml^{-1} for ^{1}H and 10 mg ml^{-1} for ^{13}C measurements. Chemical shifts (ppm) are referred to tetramethylsilane (TMS). Digital resolution was 0.2 Hz per point in ^{1}H and 0.7 Hz per point in ^{13}C NMR. The ^{1}H, ^{13}C broadband proton-decoupled, ^{13}C gated decoupled, COSY and HETCOR spectra were measured with a Gemini 300 spectrometer, while HMBC spectra were recorded with a Unity Inova 600 spectrometer. The Waltz-16 modulation was used for proton decoupling. The COSY spectra were recorded in the magnitude mode with 1024 points in the F_2 dimension and 256 increments in the F_1 dimension, zero-filled to 1024 points. Increments were measured with 16 scans, 4500 Hz spectral width and a relaxation delay of 1 s. The corresponding digital resolution was 8.9 Hz/point and 17.6 Hz/point in the F_2 and F_1 dimensions, respectively. The HETCOR spectra were recorded with 2048 points in the F_2 dimension and 256 increments in the F_1 dimension. The latter was zero-filled to 512 points. Increments were recorded by 64 scans with a relaxation delay of 0.8 s. Spectral widths were 19000 Hz in the F_2 and 4500 Hz in the F_1 dimensions, giving a digital resolution of 18.6 Hz/point and 17.6 Hz/point, respectively. The HMBC (^{13}C–^{1}H) spectra were recorded with gradient selection and standard settings.

Synthesis

General procedure for mercuration

All the mercuration products were prepared by slow addition of an aqueous solution of the mercurating agent (*ca* 50 ml) to an aqueous solution of 2-substituted thiophene compounds (*ca* 30 ml) in the appropriate stoichiometric ratio if not specified otherwise. If mercury(II) chloride was being used as the mercuration agent, sodium acetate trihydrate was added as a buffer (2 mol sodium salt per mol of the mercury(II) salt). The reaction mixture was left overnight, then the precipitated mercuration product was filtered off, washed with water and dried *in vacuo*.

5-Chloromercurio-thiophene-2-carboxylic acid

From 0.5 g $HgCl_2$ (1.84 mmol), 0.5 g $NaOCOCH_3\cdot 3H_2O$ (3.68 mmol), and 0.24 g thiophene-2-carboxylic acid (1.84 mmol). Analysis: Found: C 16.62, H 1.08, S 8.66, Hg 55.56; Calcd for $C_5H_3ClO_2SHg$: C 16.53, H 0.83, S 8.83, Hg 55.23%. ^{1}H NMR, δ(ppm): 7.85 (d, 1H, $J_{HH} = 3.45$ Hz, H-3), 7.17 (d, 1H, $J_{HH} = 3.42$ Hz, H-4), 12.85 (bs, 1H, COOH). ^{13}C NMR, δ(ppm): 137.94 (C-2), 132.98 (d, $J_{HgC} = 225.4$ Hz, C-3), 135.77 (d, $J_{HgC} = 141.5$ Hz, C-4), 157.28 (C-5), 163.49, (COOH).

4,5-Bis(chloromercurio)thiophene-2-carboxylic acid

From 1.5 g $HgCl_2$ (5.52 mmol), 1.5 g $NaOCOCH_3\cdot 3H_2O$ (11.04 mmol), and 0.35 g thiophene-2-carboxylic acid (2.76 mmol). The reaction mixture was heated for 3 h on a water bath. Analysis: Found: C 9.85, H 0.54, S 5.55, Hg 67.32; Calcd for $C_5H_2Cl_2O_2SHg_2$: C 10.04, H 0.34, S 5.36, Hg 67.06%.

5-Acetoxymercuriothiophene-2-carboxylic acid

From 0.5 g $Hg(OCOCH_3)_2$ (1.57 mmol; with a few drops of 2 M acetic acid) and 0.2 g thiophene-2-carboxylic acid (1.57 mmol). The crude mercurated product was treated with dimethyl sulfoxide (DMSO), and insoluble solid was separated by filtration. Acetone was then added very slowly to the filtrate. The precipitated monomercurated thiophene-2-carboxylic acid left overnight, then filtered off, washed with acetone and dried. Analysis: Found: C 21.88, H, 1.82, S, 8.28, Hg, 51.91; Calcd for $C_7H_6O_4SHg$: C, 21.72, H 1.56, S 8.29, Hg 51.86%.

4,5-Bis(acetoxymercurio)thiophene-2-carboxylic acid

From 0.5 g $Hg(OCOCH_3)_2$ (1.57 mmol; with a few drops of 2 M acetic acid) and 0.1 g thiophene-2-carboxylic acid (0.79 mmol). On mixing the solutions of the reactants the mercurated product was obtained immediately. The mercurated product was then filtered off, washed with water and dried *in vacuo*. Analysis: Found: C 17.01, H 1.21, S 5.02, Hg, 62.24; Calcd for $C_9H_8O_6SHg_2$: C 16.75, H 1.25, S 4.97, Hg 62.16%.

Bis[(5-nitratomercurio)thiophene-2-carboxylato]mercury(II)

From 0.5 g $Hg(NO_3)_2{\cdot}H_2O$ (1.46 mmol; with a few drops of 20% HNO_3) and 0.19 g thiophene-2-carboxylic acid (1.46 mmol). The mercurated product was obtained immediately upon mixing the solutions of the reactants. The reaction mixture was left to stand for a few hours, then filtered off; the precipitate was washed with water and ethanol and dried. Analysis: Found: C 12.27, H 0.54, N 3.01, S 6.64, Hg 61.34; Calcd for $C_{10}H_4N_2O_{10}S_2Hg_3$: C 12.28, H 0.44, N 2.86, S 6.56, Hg 61.53%.

5-Chloromercurio-2-thienylethanoic acid

From 0.5 g $HgCl_2$ (1.84 mmol), 0.5 g $NaOCOCH_3{\cdot}3H_2O$ (3.68 mmol) and 0.26 g 2-thienylethanoic acid (1.84 mmol). Analysis: Found: C 19.29, H 1.75, S 8.79, Hg 53.20; Calcd for $C_6H_5ClO_2SHg$: C 19.10, H 1.34, S 8.50, Hg 53.18%. ^1H NMR, δ(ppm): 7.09 (d, 1H, $J_{HH} = 3.23$ Hz, H-3), 6.95 (d, 1H, $J_{HH} = 3.23$ Hz, H-4), 3.81 (s, 2H, CH_2), 12.49 (bs, 1H, COOH). ^{13}C NMR, δ(ppm): 139.96 (d, $J_{HgC} = 153.0$ Hz, C-2), 126.87 (d, $J_{HgC} = 233.1$ Hz, C-3), 134.29 (d, $J_{HgC} = 140.4$ Hz, C-4), 146.52 (C-5), 35.25 (CH_2), 172.19 (COOH).

4,5-Bis(chloromercurio)-2-thienylethanoic acid

From 1.5 g $HgCl_2$ (5.52 mmol), 3 g $NaOCOCH_3{\cdot}3H_2O$ (22.08 mmol) and 0.39 g 2-thienylethanoic acid (2.76 mmol). The reaction mixture was left to stand for a week and the mercuration product isolated as described in the general procedure. Analysis: Found: C 12.04, H 0.81, S 5.04, Hg 65.66; Calcd for $C_6H_4Cl_2O_2SHg_2$: C 11.77, H 0.66, S 5.23, Hg 65.53%.

4,5-Bis(acetoxymercurio)-2-thienylethanoic acid

From 0.5 g $Hg(OCOCH_3)_2$ (1.57 mmol; with a few drops of 2 M acetic acid) and 0.11 g 2-thienylethanoic acid (0.79 mmol). Immediately after mixing the solutions of the reactants, the mercurated product was obtained. The mercurated product was filtered off, washed with water, and dried *in vacuo*. Analysis: Found: C 18.57, H 1.89, S 4.90, Hg 60.34; Calcd for $C_{10}H_{10}O_6SHg_2$: C 18.21, H 1.53, S 4.86, Hg 60.84%.

5-Trifluoroacetoxymercurio-2-thienylethanoic acid

From 0.5 g $Hg(OCOCF_3)_2$ (1.17 mmol; with a few drops of 2 M acetic acid) and 0.17 g 2-thienylethanoic acid (1.17 mmol). Analysis: Found: C 22.03, H 1.32, S 7.29, Hg 45.92; Calcd for $C_8H_5F_3O_4SHg$: C 22.05, H 1.16, S 7.36, Hg 46.03%.

3-(5-Chloromercurio-2-thienyl)alanine

From 0.5 g $HgCl_2$ (1.84 mmol), 0.5 g $NaOCOCH_3{\cdot}3H_2O$ (3.68 mmol), and 0.35 g 3-(2-thienyl)alanine (1.84 mmol). Analysis: Found: C 20.64, H 2.06, S 7.87, Hg 50.03; Calcd for $C_7H_8ClNO_2SHg$: C, 20.68, H 1.97, S 7.89, Hg 49.37%.

RESULTS AND DISCUSSION

Mercuration reactions

Thiophene-2-carboxylic acid and 2-thienylethanoic acid as well as 3-(2-thienyl)alanine were conveniently mercurated by adaptations of Volhard's original method.[4] The degree of substitution was controlled by the reaction conditions, e.g. stoichiometric ratio, mercurating agent or temperature. The mercurated products of thiophene-2-carboxylic acid and 2-thienylethanoic acid with mercuric chloride in the presence of aqueous sodium acetate were monomercurated acids, irrespectively of the stoichiometric ratio of reactants being used. If the mercuration was carried out at elevated temperatures (e.g. in a water bath) the dimercurated acids were obtained. Mercuric acetate, being a more powerful mercuration agent,[9,13] led to a mixture of mono- and di-mercurials, even at room temperature and irrespectively of the stoichiometric ratio of the reactants. In the case of mercurated thiophene-2-carboxylic acid, monomercurated acid could be separated from dimercurated one by using DMSO as the solvent, due to different solubilities. Unfortunately the mixture of mono and di-mercurated 2-thienylethanoic acid could not be separated in a similar manner, due to their similar solubilities in various solvents. The efficient way to separate them is hydrolysis of the crude mercurated product with dilute hydrochloric acid (0.1 M) and then extraction with DMSO, DMF, γ-picoline, acetonitrile or benzonitrile. Generally, monomercurials are soluble in DMSO or dimethylformamide (DMF), whereas dimercurials are not. In the IR spectra of monochloromercurials the α-CH stretches (*ca* 3097 cm^{-1}), which were present in the spectra of

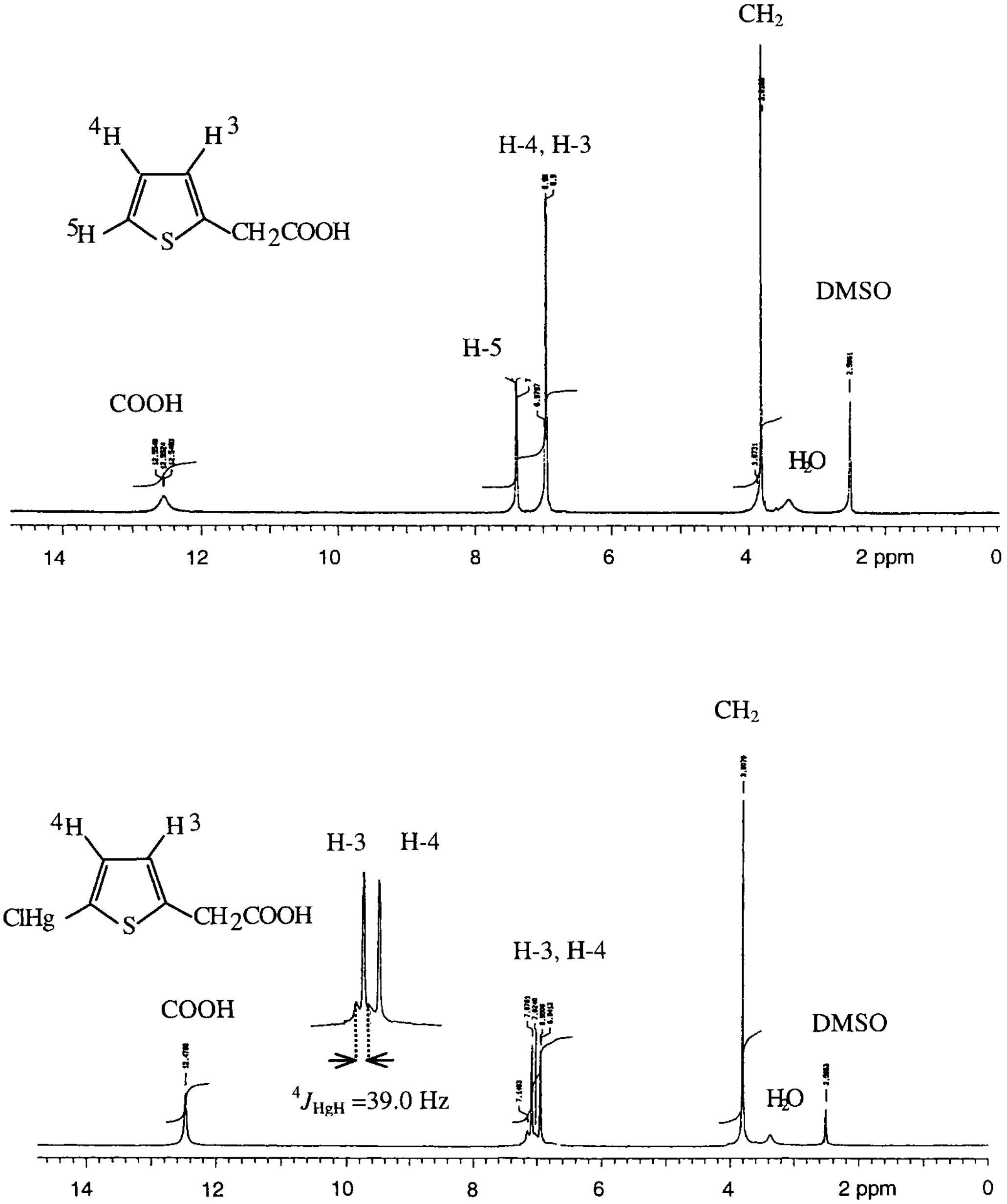

Figure 1 The ^{1}H NMR spectra of TEA (above) and TEA-HgCl (below).

the parent thiophene molecules, are absent and only β-CH stretches (*ca* 3060 cm^{-1}) are visible.

NMR spectra

The absence of the H-5 signal in the ^{1}H NMR spectra of soluble compounds proved that the mercuration took place at C-5. In the spectra of 5-chloromercurio-thiophene-2-carboxylic acid (TCA-HgCl) and 5-chloromercurio-2-thienylethanoic acid (TEA-HgCl) the four-bond ^{199}Hg–^{1}H satellite coupling at H-3 was observed, amounting to 37.9 Hz and 39.0 Hz, respectively. This was confirmed by HMBC measurements. In both molecules the three-bond ^{199}Hg–^{1}H coupling at H-4 was not detected. It is known that Hg–H couplings

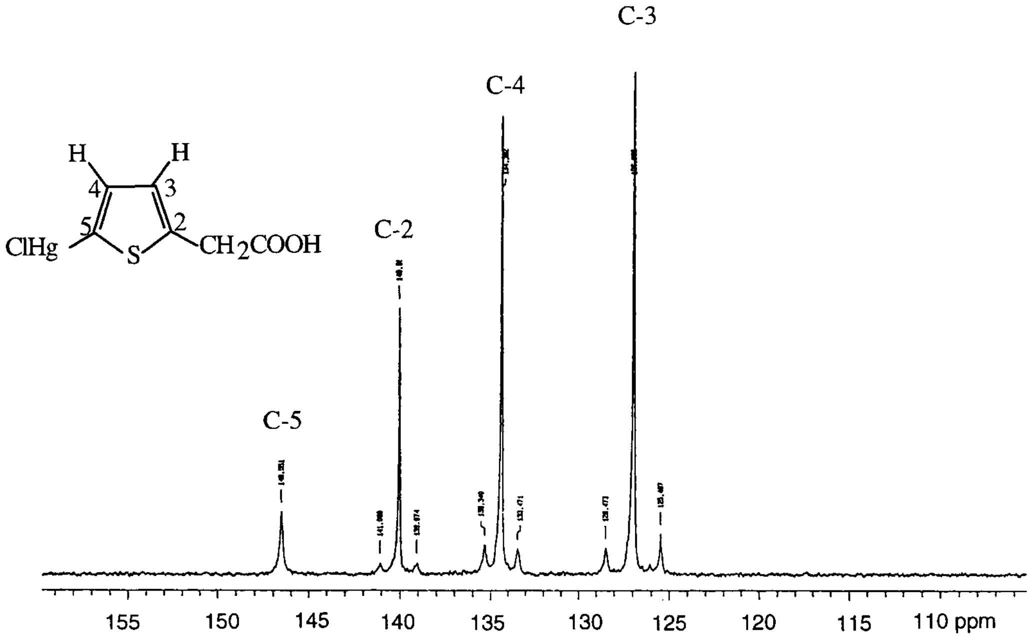

Figure 2 Part of the ^{13}C NMR spectrum of TEA-HgCl, displaying ^{199}Hg–^{13}C satellite couplings.

depend on spatial orientation and hybridization of bonds between coupling nuclei, hence displaying structural and conformational relationships.[14–16] Thus the absence of the three-bond coupling and the existence of the four-bond coupling can be connected with 'W' and *cis*-coupling pathways respectively. The mercuration effect on H-3 and H-4 chemical shifts was found to be negligible here. Figure 1 gives ^{1}H NMR spectra of TEA (above) and TEA-HgCl (below), both measured at 300 MHz, displaying changes upon mercury substitution and the $^{4}J_{\mathrm{HgH}}$. It is noteworthy that in the TCA molecule the proton signal of COOH is somewhat broadened and at a lower field (for 0.23 ppm) than in TCA-HgCl. This is due to the stronger hydrogen bonding in the former than in the latter, which was proved by variable-temperature measurements.

In ^{13}C NMR spectra one can see large downfield shifting of the C-5, which is directly bonded to mercury. This mercury-induced shift is 23.72 ppm in TCA-HgCl and 21.06 ppm in TEA-HgCl. The mercuration site was also proved by the absence of one-bond C–H splitting, amounting to *ca* 185 Hz in parent molecules. A considerable effect of mercuration was found at the C-4 atom too: the deshielding effect amounted to 6.89 and 7.25 ppm in TCA-HgCl and TEA-HgCl, respectively. Several ^{199}Hg–^{13}C satellite couplings were observed in the ^{13}C NMR spectra of the monomercurated compounds investigated here. In Fig. 2 a part of the ^{13}C NMR spectrum of TEA-HgCl is displayed. The low-intensity doublets flanking the C-4, C-3 and C-2 signals are two- and three-bond ^{199}Hg–^{13}C satellite couplings. One can recognize that $^{3}J_{\mathrm{HgC}}$ at C-3 is larger than $^{2}J_{\mathrm{HgC}}$ at C-4, which is related to differences in geometry and hybridization of their coupling pathways.[14] One-bond ^{199}Hg–^{13}C satellite coupling at C-5 was not detected, due to the rather long relaxation time of this quaternary carbon, giving rise to a low-intensity signal. The corresponding doublet of satellites can have only one-tenth of the intensity of the central signal. Variable-temperature measurements and addition of relaxation agent could not reveal this satellite coupling. In molecules where Hg was directly bonded to sulfur, ^{199}Hg–^{13}C and ^{199}Hg–^{1}H satellite couplings were also not detected.[10–12]

In conclusion, one can say that in the case of soluble samples ^{1}H and ^{13}C NMR data revealed the formation of 5-chloromercurio compounds.

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REFERENCES

1. Larock RC. *Organomercury Compounds in Organic Synthesis*. Springer Verlag: Berlin, 1985.
2. Han Y-H, Heeg MJ, Winter CH. *Organometallics* 1994; **13**: 3009.
3. Curtis MD, McClain MD. *Chem. Mater.* 1996; **8**: 936.
4. Volhard J. *Ann. Chem.* 1892; **267**: 172.
5. Makarova LG, Nesmeyanov AN. *Metody Elemento-organitscheskoy Khimii*. Rtut, Izdatelstvo ‘Nauka’: Moscow, 1965.
6. Wardell JL. Mercury. In *Comprehensive Organometallic Chemistry*, Vol. 2, Wilkinson G, Stone FGA, Abel EW. Pergamon: New York, 1982.
7. Grdenić D, Kamenar B, Žeželj V. *Acta Crystallogr.* 1979; **B35**: 1889.
8. Korpar-Čolig B, Popović Z, Matković-Čalogović D, Vikić-Topić D. *Organometallics* 1993; **12**: 4708.
9. Popović Z, Korpar-Čolig B, Matković-Čalogović D, Vikić-Topić D, Sikirica M. *Main Group Chem.* 1996; **1**: 373.
10. Popović Z, Matković-Čalogović D, Hasić J, Vikić-Topić D. *Inorg. Chim. Acta* 1999; **285**: 208.
11. Popović Z, Matković-Čalogović D, Hasić J, Sikirica M, Vikić-Topić D. *Croat. Chem. Acta* 1999; **72**: 279.
12. Popović Z, Matković-Čalogović D, Soldin Ž, Pavlović G, Davidović N, Vikić-Topić D. *Inorg. Chim. Acta* 1999; **294**: 35.
13. Grdenić D, Korpar-Čolig B, Sikirica M. *J. Organomet. Chem.* 1984; **276**: 1.
14. Singh G, Reddy GS. *J. Organomet. Chem.* 1972; **42**: 267.
15. Johnson FA, Perry WD. *Organometallics* 1989; **8**: 2646.
16. Bashall A, McPartin M, Murphy BP, Powell HR, Waikar S. *J. Chem. Soc., Dalton Trans.* 1994; 1383.