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# SYNTHESIS, CHARACTERIZATION AND COMPLEXATION STUDY OF NEW 4-(DIPHENYLPHOSPHINO)-PHENOTHIAZINES

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**ABSTRACT.** The synthesis of new 4-(diphenylphosphino)-phenothiazine derivatives was achieved by a regioselective lithiation of the thio-aryl structural unit of the phenothiazine precursor, followed by *in situ* reaction of the intermediate with chloro-diphenylphosphine. Symmetrical 4,6-*bis*(diphenylphosphino)-phenothiazine was obtained by similar functionalization of the isolated 4-(diphenylphosphino)-phenothiazine. These air stable aryl-phosphines were purified by column chromatography and characterized by MS, FT-IR, $^{1}$H-, $^{13}$C- and $^{31}$P-NMR spectroscopy. Coordination of 10-alkyl-4-(diphenyl-phosphino)-phenothiazines to Pd(II) was confirmed by means of $^{31}$P-NMR spectroscopy which indicated a strong deshielding effect upon P atoms.

***Keywords:*** *Phenothiazine, Heteroaryl-diphenylphosphine, Pd(II) complex, $^{31}$P-NMR*

## INTRODUCTION

Triarylphosphine derivatives attracted considerable interest in the last years, especially due to their reactivity and utilization as ligands for efficient transition metals catalyzed syntheses [1-3]. A wide variety of aryl-diphenyl-phosphines were described in the scientific literature, and their properties such as air stability, redox properties and supramolecular assemblies were thoroughly investigated [4, 5]. The phenothiazine deriva-tives are tricyclic compounds well known for their rich electron structure and redox active character [6, 7]. Moreover, the supramolecular associations of molecules containing folded phenothiazine units may play an important role in the control of conformation, geometry and aggregation of such derivatives. 10-Alkyl-10*H*phenothiazines contain folded structures, characterized by a boat conformation of the central 1,4-thiazine ring; substituents such as methyl,

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ethyl, *iso*-propyl prefer a quasi-equatorial position (when there are no other groups to C(1) or C(9) neighboring positions). As determined by XRD method, the folding angles tend to become smaller when the size of the alkyl substituent becomes larger, since the alkyl chain extends to the convex side of the phenothiazine ring [8-10].

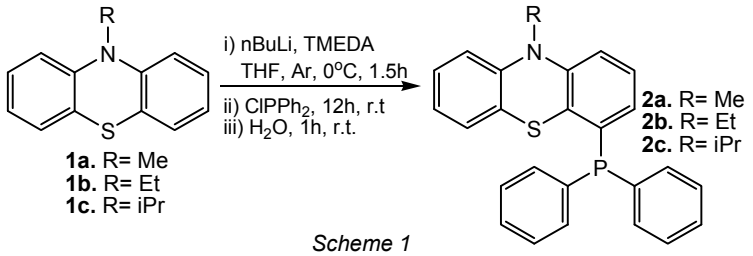
For many palladium catalyzed reactions, an essential step appears to be the reduction of Pd(II) to Pd(0) species right at the beginning of the catalytic cycle [11]. In certain classical phosphine-assisted protocols the oxidation of the phosphine may contribute to the reduction of Pd(II) to Pd(0) but, the resulted phosphine-oxides can no longer participate to the catalytic cycle and thus larger loads of ligand are required. Based on the well recognized low oxidation potential of phenothiazine derivatives, we suggest that in a phenothiazinyl-phosphine ligand, the redox-active phenothiazine unit can overtake the reductive role of the phosphine and under these circumstances, the reduction of Pd(II) to Pd(0) would proceed without the loose of its catalytical activity.

We believe that the structural features of alkyl-phenothiazines may be conveniently exploited in the design of new *tris*-aryl-phosphine type ligands for transition metals complexes with catalytic activity. Continuing our interest in the synthesis and characterization of (diphenylphosphino)-phenothiazine derivatives [12], in this work we add supplementary data regarding the preparation new 10-ethyl- and 10-isopropyl-4-(diphenylphosphino)-phenothiazines and we also describe the formation of complexes between 4-(diphenylphosphino)-phenothiazines and $PdCl_2$.

The applicability of the new 10-alkyl-4-(diphenylphosphino)-phenothiazine palladium complexes in traditional catalytic reactions is to be tested.

## RESULTS AND DISCUTION

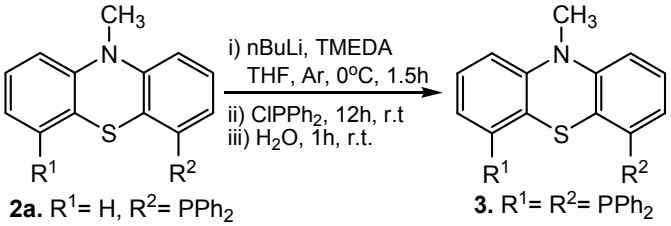
N-alkyl-phenothiazines were often employed as substrates in the preparation of higher substituted-phenothiazine derivatives. The regioselective preparation of 4-substituted-phenothiazines was achieved using a strategy which involved lithiated phenothiazine intermediates, taking benefit of the enhanced reactivity of this electron rich heterocycle coupled with the *orto* directing capacity of the sulphur atom in its arylthio structural unit [13, 14]. We successfully applied this synthetic route for the preparation of 4-(diphenyl-phosphino)-10-methyl-10*H*-phenothiazine, as previously reported [12]. In this work we add supplementary data regarding the preparation of new 10-ethyl- and 10-isopropyl-4-(diphenylphosphino)-phenothiazine **2b,c** as shown in scheme 1. The preparative protocol involved two reaction steps: i) lithiation of alkyl-phenothiazine substrate **1a-c** followed by ii) reaction of the lithiated intermediate with one equivalent of chloro-diphenylphosphine.




*Scheme 1*

GC-MS analysis of the reaction mixtures indicated the formation of 4-(diphenylphosphino)-10-alkyl-10*H*-phenothiazines (**2a** m/z=397, **2b** m/z= 411 and **2c** m/z=425 *a.m.u* respectively), accompanied by small amounts of the corresponding *bis*-(diphenylphosphine)-phenothiazines (M+185), phosphinoxides (M+16) and alkyl-phenothiazines. Moderate yields of 4-(diphenylphosphino)-10-alkyl-10*H*-phenothiazines **2a-c** were isolated by column chromatography.

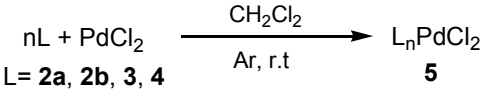
In order to obtain higher amounts of the new 4,6-*bis*(diphenylphosphino)-10-methyl-10H-phenothiazine **3**, **2a** was subjected to lithiation and then, the orange solution thus obtained was further treated with one equiv. of chlorodiphenylphosphine (Scheme 2). The oily product isolated by column chromatography slowly solidified in time.




*Scheme 2*

The structures of the new compounds were unambiguously assigned based on their recorded MS, FT-IR, $^{1}$H-, $^{13}$C- and $^{31}$P-NMR spectra.

The new phenothiazinyl-phosphines **2b** and **3** as well as the previously described **2a** and 4-[(3-sodiumbenzensulfonato)-phenyl-phosphino]-10-methyl-10*H*-phenothiazine **4** [12], were independently used as ligands for complexation of palladium chloride in dichloromethane solution, under inert atmosphere, based on a modified literature procedure [15]. The reaction mixtures were stirred for 12h at room temperature and during this time, the colorless solutions of the reagents slowly turned to orange. Finally, after removing the solvent, the products were thoroughly washed with hexane and diethyl-ether. The insoluble complexes (scheme 3) were examined without other further purification.




*Scheme 3*

$^{31}$P-NMR spectroscopy proved to be an efficient tool for studying the P atom complexes, as well as for the observation of some intermediates in catalytic reactions [16, 17]. The coordination of the phosphorous atom in phosphines produces a strong deshielding effect and consequently the corresponding chemical shift values appear shifted by 50-70 ppm [18]. A similar deshielding effect was detected in the case of each palladium complex **5,** when compared to the parent 4-(diphenylphosphino)-10-alkyl-10*H*-phenothiazine ligand, as it can be seen from the chemical shift values listed in table 1.

**Table 1.** 121.44 MHz $^{31}$P-NMR Chemical shift values (ppm) for 4-(diphenylphosphino)-10-alkyl-10*H*-phenothiazines free ligands and their corresponding palladium complexes.

| $^{31}$P NMR δ(ppm) | **2a** | **2b** | **3** | **4** |
|---|---|---|---|---|
| Free ligand | -13.4 | -13.2 | -16.1 | -13.4[a] |
| Pd complex | 59.7 | 59.6 | 59.7 | 27.3[b] |

[a] recorded in $CDCl_3$
[b] recorded in $d^6$-DMSO

In the $^{31}$P-NMR spectra of ligands **2a**, **2b**, **3** and **4** respectively, an intense signal situated at negative chemical shift values corresponds to a shielded P(III) structure. The compounds separated after the complexation of Pd(II) gave a $^{31}$P-NMR signal considerably shifted downfield, thus supporting the formation of Pd-P bonds. The Pd complex of water soluble ligand **4** was not soluble in $CDCl_3$; its $^{31}$P NMR spectrum was recorded in DMSO-$d_6$ and thus, the intermolecular associations with this polar solvent dramatically modified the observed chemical shift value, but still the shielding effect of complexation remains distinctly observable.

## CONCLUSIONS

The two step reaction strategy involving the lithiation of an alkyl-phenothiazine substrate followed by the reaction of the lithium-organic intermediate with chlorodiphenylphosphine was successfully applied in the preparation of the new 10-ethyl- and 10-isopropyl-4-(diphenylphosphino)-phenothiazine as well as for the preparation of symmetrical 4,6-*bis*(diphenyl-phosphino)-10-methyl-10H-phenothiazine. The phenothiazinyl-diphenyl-phosphines are air stable compounds which can be purified by column chromatography. Coordination of 10-alkyl-4-(diphenylphosphino)-phenothiazines to Pd(II) was confirmed by means of $^{31}$P-NMR spectroscopy which indicated a strong deshielding effect upon P atoms.

## EXPERIMENTAL SECTION

All chemicals and solvents were dried and purified by usual methods. Compounds **1a-c** and **2a** were prepared according to described procedures [12, 19, 20]. All reactions as well as column chromatography were followed by TLC using Merck pre-coated silica gel 60 $F_{254}$ aluminium sheets. Column chromatography was performed using Merck silica gel 60 (63- 200 mesh) and flash chromatography with RediSep$^{TM}$ Silica column with a Teledyne Isco CombiFlash$^{TM}$$R_f$ apparatus. Melting points were determined with an Electro-thermal IA 9200 digital melting point apparatus and are uncorrected. The mass spectra were recorded by a GC-MS (EI, CI) Shimadzu mass spectrometer. IR spectra were recorded on a Bruker Vector 22 FT-IR spectrometer fitted with a Golden Gate ATR accessory. $^{1}$H and $^{13}$C-NMR spectra were recorded in $CDCl_3$ in 5 mm tubes at RT, on Bruker Avance 300 MHz spectrometer, using TMS as internal reference with the deuterium signal of the solvent as the lock. The spectral data are listed in the experimental part.

### General procedure for synthesis of 4-(diphenylphosphino)-10-alkyl-10*H*-phenothiazines

To a stirred solution of 10-alkyl-10*H*-phenothiazine (9.4 mmol) in dry THF (40 cm$^3$) was added TMEDA (3.0 cm$^3$, 20 mmol), followed by dropwise addition of *n*-BuLi (20 mmol, 12.5 cm$^3$ of a 1.6 M solution in hexane) at 0 ºC under Ar. The mixture was stirred at 0 ºC for 1.5 h and $Ph_2PCl$ (4.41 g, 20 mmol) was then added. After 12 h stirring at r.t., the reaction mixture was treated with 10 cm$^3$ of $H_2O$. The organic phase was separated and the aqueous phase was extracted with $Et_2O$ (3x25 cm$^3$). The combined organic phases were dried over $Na_2SO_4$. After removal of the solvent *in vacuo*, the residue was separated by column chromatography on silicagel with heptane/$Et_3N$ (30:1) as eluent and then recrystallized from $Et_2O$.

### 4-(diphenylphosphino)-10-methyl-10*H*-phenothiazine 2a

The product was purified by column chromatography and recrystallized from $Et_2O$ to give white crystals m.p.: 189 ºC (1.5 g, 40%) lit. m.p.= 189-191 ºC [12] MS (EI$^+$) m/z: 397 (M$^+$, 100%), 382, 286, 273, 242, 212, 183, 77.

### 4-(diphenylphosphino)-10-ethyl-10*H*-phenothiazine 2b

Phosphination of 10-ethyl-10H-phenothiazine (**1b**) was carried out according general procedure presented above. The product was purified by column chromatography and recrystallized from $Et_2O$ to give white crystals, m.p.= 151-152ºC (1.26, 33%), IR (ATR) $\nu$ [cm$^{-1}$]: 694, 746, 758, 1136, 1196, 1254, 1281, 1327, 1364, 1409, 1444, 1477, 1557, 1589, 2983, 3011. $^{31}$P NMR (121.5 MHz, $CDCl_3$) $\delta$ (ppm): -13.2. $^{1}$H NMR (300 MHz, $CDCl_3$) $\delta$ (ppm): 1.42 (t, 3H, $^{3}J_{HH}$= 7.2 Hz, $CH_3$), 3.94 (q, 2H, $^{3}J_{HH}$= 7.2 Hz, *N*-$CH_2$), 6.39 (dd, 1H, $^{3}J_{HH}$= 7.2 Hz, $^{3}J_{PH}$=3.3

Hz, H3), 6.86 (d, 2H, $^3J_{HH}$= 7.8 Hz, H1,9), 6.88 (t, 1H, $^3J_{HH}$= 7.2 Hz, $^3J_{HH}$= 7.8 Hz H2), 7.05 (t, 1H, $^3J_{HH}$= 7.7 Hz, $^3J_{HH}$= 8.6 Hz, H7), 7.09 (d, 1H, $^3J_{HH}$= 8.6 Hz, H6); 7.13 (1H, t, $^3J_{HH}$= 7.7 Hz, $^3J_{HH}$= 7.8 Hz, H8), 7.30-7.35 (10H, m, $H_{Ph}$). $^{13}$C NMR (75 MHz, $CDCl_3$): 13.2, 42.1, 115.1, 115.5, 122.5, 124.7, 126.9, 127.4, 128.7, 128.8, 130.0, 134.1, 134.3, 135.6, 136.2, 138.0, 143.5, 145.3 MS (EI$^+$) m/z: 411 ($M^+$, 100%), 396, 382, 272, 183, 77.

**4-(diphenylphosphino)-10-isopropyl-10*H*-phenothiazine 2c**

Phosphination of 10-isopropyl-10H-phenothiazine (**1c**) was carried out according general procedure presented above. The product was purified by column chromatography and recrystallized from $Et_2O$ to give white crystals, m.p.= 146-147 $^o$C (1.1g, 27%), IR (ATR) $\nu$ [cm$^{-1}$]: 687, 726, 916, 1126, 1246, 1290, 1304, 1400, 1446, 1478, 1555, 1589, 2976, 3078. $^{31}$P NMR (121.5 MHz, $CDCl_3$) $\delta$ (ppm): -13.1. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ (ppm): 1.65 (d, 6H, $^3J_{HH}$= 6.8 Hz $CH_3$), 4.32 (h, 1H, $^3J_{HH}$= 6.8 Hz, *N*-CH), 6.43 (dd, 1H, $^3J_{HH}$= 6.5 Hz, $^3J_{PH}$=3.0 Hz, H3), 6.89 (t, 1H, $^3J_{HH}$= 7.8 Hz, H2), 7.05-7.10 (m, 4H, H1,6,7,9), 7.13 (1H, t, H8), 7.33-7.38 (10H, m, $H_{Ph}$). $^{13}$C NMR (75 MHz, $CDCl_3$): 31.6, 53.4, 117.6, 117.9, 122.3, 126.2, 126.7, 127.4, 128.2, 128.3, 128.5, 133.0, 133.6, 133.8, 135.7, 135.9, 144.9, 145.4. MS (EI$^+$) m/z: 425 ($M^+$), 382(100%), 304, 274, 197, 183, 77.

**4,6-bis(diphenylphosphino)-10-methyl-10H-phenothiazine 3**

To a stirred solution of 4-(diphenylphosphino)-10-methyl-10*H*-phenothiazine **2a** (0.4 g, 1 mmol) in dry THF (50 cm$^3$) was added TMEDA (0.3 cm$^3$, 2 mmol), followed by dropwise addition of *n*-BuLi (2 mmol, 1.25 cm$^3$ of a 1.6 M solution in hexane) at 0 ºC under Ar. The mixture was stirred at 0 ºC for 2 h and $Ph_2PCl$ (0.44 g, 2 mmol) was then added. After 12 h stirring at r.t., the reaction mixture was treated with 25 cm$^3$ of $H_2O$. The organic phase was separated and the aqueous phase was extracted with ethyl acetate (3x25 cm$^3$). The combined organic phases were dried over $Na_2SO_4$. After removal of the solvent *in vacuum*, the residue was separated by column chromatography on silica gel with heptane/$Et_3N$ (30:1) as eluent. The resulting colorless oil slowly solidify resulting a white precipitate m.p.= 190-192 $^o$C (0.21 g, 36%). IR (ATR) $\nu$ [cm$^{-1}$]: 686, 727, 772, 1037, 1099, 1192, 1244, 1288, 1331, 1446, 1474, 1555, 1587, 2863, 2965. $^{31}$P NMR (121.5 MHz, $CDCl_3$) $\delta$ (ppm): -16.1. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ (ppm): 3.42 (s, 3H, *N*-$CH_3$), 6.88 (d, 2H, $^3J_{HH}$= 8.3 Hz, H1), 6.92 (dd, 1H, $^3J_{HH}$= 8.3 Hz, $^3J_{PH}$= 2.6 Hz, H3), 7.13 (t, 2H, $^3J_{HH}$= 8.0 Hz, H2), 7.36-7.45 (20H, m, $H_{Ph}$). $^{13}$C NMR (75 MHz, $CDCl_3$): 35.7, 114.2, 122.6, 125.4, 127.3, 128.7, 129.0, 132.7, 136.2, 139.3, 145.9. MS (EI$^+$) m/z: 411 ($M^+$, 100%), 396, 382, 272, 183, 77.

**4-[(3-sodiumbenzensulfonato)-phenyl-phosphino]-10-methyl-10*H*-phenothiazine 4**

Sulfonation of 4-(diphenylphosphino)-10-methyl-10*H*-phenothiazine (0.2 g, 0.5 mmol) was performed according literature procedure [12]. The

product was isolated by extraction with ethyl acetate and evaporation of the solvent as a green-white solid (0.2 g, 80%) m.p. 199 °C decomposition. $^{31}P$ NMR (121.5 MHz, $CDCl_3$) $\delta$ (ppm): -13.4.

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## REFERENCES

1. Y. Guo, H. Fu, H. Chen, X. Li, *Cat. Commun.*, **2008**, 9, 1842.
2. J.R. Briggs, H. Hagen, S. Julka, J.T. Patton, *J. Organomet. Chem.*, **2011**, *696*(8), 1677.
3. P. Pongrácz, Gy. Petöcz, M. Shaw, D. Bradley, G. Williams, L. Kollár, *J. Organomet. Chem.*, **2010**, *695*(22), 2381.
4. H. Shimizu, I. Nagasaki, T. Saito, *Tetrahedron*, **2005**, *61*, 5405.
5. P.W.N.M. van Leeuwen, "Homogeneous Catalysis. Understanding tha Art", Kluwer Academic Publishers, Dodrecht, **2004**, chapter 1.5.
6. J.B. Christensen, M.F. Nielsen, J.A.E.H. Van Haare, M.W.P.L. Baars, R.A.J. Janssen, E.W. Meijer, *Eur. J. Org. Chem.*, **2001**, *11*, 2123.
7. M. Hauck, R. Turdean, K. Memminger, J. Schönhaber, F. Romingers, T.J.J. Müller, *J. Org. Chem.*, **2010**, *75*(24), 8591
8. S.S.C. Chu, D. Van der Helm, *Acta Cryst.*, **1974**, *B30*, 2489.
9. S.S.C. Chu, D. van der Helm, *Acta Cryst.*, **1975**, *B31*, 1179.
10. S.S.C. Chu, D. van der Helm, *Acta Cryst.*, **1976**, *B32*, 1012.
11. S. Aizawa, M. Kondo, R. Miyatake, M. Tamai, *Inorg. Chim. Acta*, **2007**, *360*, 2809.
12. T. Lovasz, E. Gal, L. Gaina, I. Sas, C. Cristea, L. Silaghi-Dumitrescu, *Studia UBB Chemia*, **2010**, *55*(3), 249.
13. S. Ebdrup, *Synthesis*, **1998**, *8*, 1107.
14. S. Ebdrup, *J. Chem. Soc. Perkin Trans I.*, **1998**, 1147.
15. T.R. Krishna, N. Jayaraman, *Tetrahedron*, **2004**, *60*(45), 10325.
16. Gy. Petöcz, Z. Berente, T. Kégl, L. Kollár, *J. Organomet. Chem.*, **2004**, *689*(7), 1188.
17. D.S. Glueck, *Coord. Chem. Rev.*, **2008**, *252*, 2171.
18. V.A. Stepanova, V.V. Dunina, I.P. Smoliakova, *J. Organomet. Chem.*, **2011**, *696*(4), 871.
19. L. Gaina, T. Dallos, C. Cristea, *Studia UBB Chemia*, **2010**, *55*(1), 97
20. H. Gilman, R. D. Nelson, J. F. Champaigne, *J. Am. Chem. Soc.*, **1952**, *74*, 4205.