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SYNTHESIS AND CHARACTERIZATION OF NEW PHENOTHIAZINYL-DIPHENYL-PHOSPHINES

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ABSTRACT. New phenothiazinyl-diphenyl-phosphine derivatives were prepared based on a synthetic strategy which imply two reaction steps: a lithiation of phenothiazine derivative followed by the reaction of the C-lithiated intermediate with 1 equivalent of chlorodiphenylphosphine. Sulfonation with chlorosulfonic acid or sulfuric acid gave water soluble phenothiazinyl-phosphine ligands. Structural characterization of the new compounds is based on high resolution ^{1}H-, ^{13}C-, ^{31}P-NMR spectroscopy, FT-IR spectroscopy and mass spectrometry.

Keywords: *Phenothiazine, triphenylphosphine (TPP), arylsulfonic acid*

INTRODUCTION

Organometallic catalysis proved to be a powerful tool for increasing the stereoselective conversion of many organic substrates during important synthetic reactions. Triphenylphosphine ligands appear as parts of consecrated organometallic catalysts highly efficient in different synthetic reactions such as: carbon-carbon coupling (Heck, Suzuki), hydrogenation, hydroformylation. A green chemistry survey recognizes the use of amphiphilic triphenylphosphine ligands in aqueous-phase organometallic catalysis or biphasic catalysis, as promising developments towards more environmentally friendly chemical processes.

Amphiphilic triphenylphosphine ligands may posses in the same molecular structure both functions of a ligand and a surfactant, thus enabling the catalytic effect, as well as the easy recovery of a water soluble catalyst from the organic reaction mass. Sulfonated triarylphosphines obtained by the direct sulfonation of the aromatic rings, are frequently used as such amphiphilic ligands for aqueous and aqueous-organic two-phase catalysis.

Trisulfonated triphenylphosphine (TPPTS) was employed as a ligand in Rh complexes used in hydroformylation of olefins and hydrosoluble substrates [1] Sulfonation of Wilkinson's catalyst (tris(triphenylphosphine)rhodium

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chloride), was performed by a two-step method in which the synthesis of triphenylphosphine monosulfonate was followed by the formation of a complex with rhodium chloride, or, by the direct sulfonation of tris(triphenylphosphine) rhodium chloride with 20% sulfuric acid at 45°C for 8h, in sealed reaction flask and generated the trisulfonated triphenylphosphine (TPPTS) rhodium catalyst [2].

Due to the fact that the hydrophilic character of the sulfonated triarylphosphine ligand may be correlated with the number of sulfonic groups introduced in its molecular structure, different attempts to design new triarylphosphine substrates for selective sulfonation were described in the literature.

Trisulfonated triphenylphosphine (TPPTS) was prepared by the direct sulfonation of triphenylphosphine [3]. The reaction requires fuming sulfuric acid and relatively long reaction time, conditions which favors different degrees of sulfonation of the substrate and formation of phosphine oxide derivatives as well. Selective preparation of disulfonated triphenylphosphine (TPPDS), is based on careful control of reaction conditions and work-up procedure which provides TPPDS·2H2O in 60% yield [4]. In order to avoid oversulfonation in the preparation of monosulfonated triphenylphosphine (TPPMS), the reaction needs to be interrupted at moderate conversions, thus generating low yields (29%) of TPPMS [5].

By introducing activating groups into the appropriate positions of certain phenyl-rings, the corresponding sulfonated triphenylphosphine were obtained selectively. Methyl or methoxy activating groups have been introduced into the *ortho*- and *para*-positions of the phenyl rings and the selective substitution occurred in relatively mild conditions and short reaction times without secondary oxidation reactions [6].

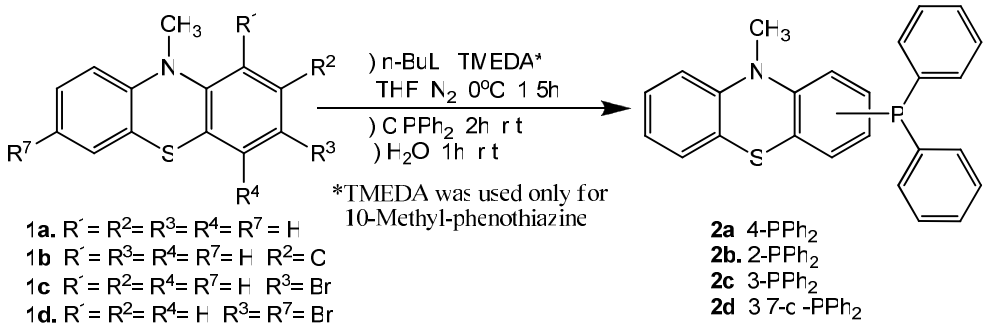
Sulfonation of dibenzofurane-aryl-phosphines occurred under mild reaction conditions, with complete selectivity and high yields, due to the presence of the π electron- rich aromatic ring [7].

Taking into consideration the facts described above, here we wish to report the preparation of some new phenothiazine containing triphenyl-phosphine analogues, which were transformed in water soluble sulfonates.

RESULTS AND DISCUSSION

N-alkyl-phenothiazine derivatives, are activated substrates for regioselective preparation of C-substituted phenothiazine derivatives by using direct aromatic electrophilic substitution, as well as organometallic intermediates. Halogenated N-alkyl-phenothiazine derivatives are also easily available substrates by direct halogenation of N-alkyl-phenothiazine or ring closure reactions of halogenated diphenylamines or diphenylthioethers [8]. The characteristic reactivity of the phenothiazine derivatives enabled us to develop a synthetic strategy for the preparation of phenothiazine containing arylphosphines based on

two reaction steps: i) lithiation of phenothiazine derivative followed by ii) reaction of the C-lithiated intermediate with one equivalent of chlorodiphenylphosphine. Scheme 1 shows the transformation of 10-methyl-10*H*phenothiazine derivatives **1a-d** in to the corresponding phenothiazinyl-diphenylphosphines **2a-d.**



Scheme 1

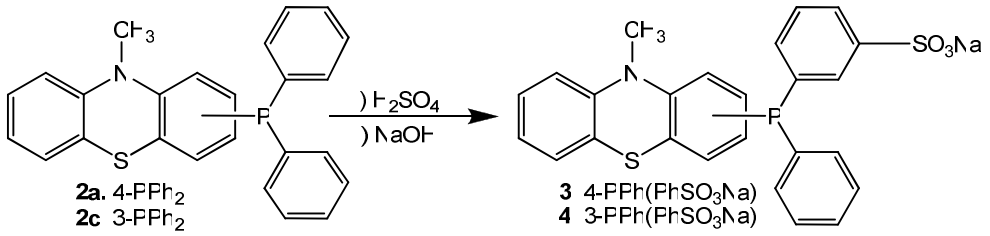
When 10-methyl-10*H*phenothiazine **1a** was treated with *n*-buthyl-lithium a dark red slurry was obtained, which was then treated with one equivalent of chlorodiphenylphosphine and gave 4-(diphenylphosphino)-10-methyl-10*H*phenothiazine **2a** in 32% yields. Lithium-Halogen exchange reactions were performed starting with 2-chloro-10-methyl-10*H*phenothiazine **1b** and 3-bromo-10-methyl-10*H*phenothiazine **1c** respectively and thus 2-(diphenylphosphino)-10-methyl-10*H*phenothiazine **2b** was obtained in 58% yields, while 3-(diphenylphosphino)-10-methyl-10*H*phenothiazine **2c** was obtained in 52% yields after purification by column chromatography. 3,7-dibromo-10-methyl-10*H*phenothiazine **1d** was also subjected to the same reactions pattern and 3,7-bis(diphenylphosphino)-10-methyl-10*H*-phenothiazine **2d** was obtained in 48% yield.

In the mass spectrometric analysis, the new 2-, 3- and 4-diphenylphosphino-10-methyl-10*H***-**phenothiazine **2a-c** generate the molecular ion observable at the same value (m/z=397 *a.m.u*.) in high abundance. The characteristic substitution was confirmed in each case by the coupling pattern between the protons attached to the substituted phenothiazine ring, which show the signals of the protons situated in position *ortho* to the phosphorus substituent as the most shielded signals in the aromatic region (δ=6.4-6.7 ppm). Even though the reactions were carried out under inert atmosphere in order to prevent the oxidation processes, small amounts of phosphinoxide analogues of **2a-b** were identified by mass spectrometry ($M^{+\cdot}$ m/z=413 *a.m.u.*).

The sulfonation of 10*H*phenothiazine ring by direct electrophilic aromatic substitution appears to be difficult because of easy polysubstitution and facile oxidation of the sulfur atom. Literature data indicate the fail in the sulfonation of phenothiazine with chorosulfonic acid [9**].** Sulfonation of N-alkyl-phenothiazine

derivatives was reported to take place in position 3 (*para* to the nitrogen atom) [10]), while sulfonation of N-acyl-phenothiazine derivatives appears with regioselectivity for position 2 (*para* to the sulfur atom in the heterocycle) [11]. We tested the reactivity of 3,7-dibromo-10-methyl-phenothiazine in the reaction with chlorosulfonic acid and we observed the formation of a water soluble adduct, but according to the coupling pattern in the recorded proton NMR spectrum, no supplementary C-substitution occurred in the aromatic rings.

The new phenothiazinyl-diphenylphosphines **2a,c** were treated with concentrated sulfuric acid and mono-sulfonation product **3** was obtained in high yields, while **4** was obtained only in small amounts (scheme 2).



Scheme 2

Assignment of the recorded proton NMR spectra of sulfonates **3, 4** indicate that the sulfonation by a direct electrophilic aromatic substitution appeared in the *meta* position of the phenyl ring, in accordance with the directing effect of the phosphorus, which appears protonated in the strong acidic reaction medium. We can suppose that the formation of adducts with sulfuric acid considerably lowered the reactivity of the phenothiazine unit in the substrate, thus preventing the electrophilic substitution of the heterocycle. The sulfonic acids intermediates were transformed without isolation into water soluble sodium salts upon treatment with NaOH. Low amounts of phosphinoxide analogue was formed, a fact which was clearly observed in the ^{31}P-NMR spectrum of **3**, where two signals situated at δ=-13.3 ppm and 30.6 ppm appear in 1:6 ratio.

CONCLUSIONS

New phenothiazine containing triphenylphosphine analogues, were conveniently prepared in two reaction steps involving the lithiation of a N-alyl-phenothiazine derivative, followed by the reaction of the C-lithiated intermediate with one equivalent of chlorodiphenylphosphine. Upon treatment of the new compounds with sufuric acid, sulfonation occurred in the *meta* position of the phenyl ring. Sulfonic acid derivatives were transformed without isolation into their water soluble sodium salts.

EXPERIMENTAL SECTION

All chemicals and solvents were dried and purified by usual methods. Compounds **1a-d** were prepared according to described procedures [12-14].

All reactions as well as column chromatography were followed by TLC analysis using Merck pre-coated silica gel 60 F_{254} aluminium sheets. Column chromatography was performed using Merck silica gel 60 (63- 200 mesh). Melting points were determined with an Electrothermal IA 9200 digital melting point apparatus and are uncorrected. The mass spectra were obtained 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 r.t., on Bruker Avance 300 MHz. The spectral data are listed below.

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

To a stirred solution of 10-methyl-10*H*-phenothiazine (**1a**) (2.0 g, 9.4 mmol) in dry THF (40 cm^3) was added TMEDA (3.0 mL, 20 mmol), followed by dropwised *n*-BuLi (20 mmol, 12.5 cm^3 of a 1.6 M solution in hexane) at 0 ºC under N_2. The mixture was stirred at 0 ºC for 1.5 h and Ph_2PCl (4.41 g, 20 mmol) was then added. After 3 h stirring at r.t., the reaction mixture was treated with 5 mL of H_2O. The organic phase was separated and the aqueous phase was extracted with EtOAc (3x25 mL). The combined organic phase was dried over Na_2SO_4. After removal of the solvent *in vacuo*, the residue was separated by column chromatography on silica gel with toluene/Et_3N (100:1) as eluent and then recrystallized from Et_2O to give white crystals m.p.: 189-191 ºC (1.2 g, 32%). **IR** (ATR) ν [cm^{-1}]: 693, 723, 744, 780, 880, 1140, 1254, 1327, 1404, 1439, 1476, 1553, 1587, 2811, 2882, 2957, 3055. **^{31}P NMR** (121.5 MHz, $CDCl_3$) δ (ppm): -13.40. **^{1}H NMR** (300 MHz, $CDCl_3$) δ (ppm): 3.42 (s, 3H, *N*-CH_3), 6.45 (dd, 1H, $^3J_{HH}$= 7.5 Hz, $^3J_{PH}$=3.6 Hz, H_3), 6.84 (d, 2H, $^3J_{HH}$= 8.1 Hz, H1,9), 6.93 (t, 1H, $^3J_{HH}$= 7.5 Hz, H2), 7.10 (t, 1H, $^3J_{HH}$= 7.8 Hz, H7), 7.16 (d, 1H, $^3J_{HH}$= 7.8 Hz, H6); 7.20 (1H, t, $^3J_{HH}$= 8.1 Hz, H8), 7.31-7.41 (10H, m, H_{Ph}). **^{13}C NMR** (75 MHz, $CDCl_3$): 35.7, 113.9, 114.1, 114.4, 122.5, 123.5, 127.2, 127.5, 128.3, 128.6, 128.9, 134.0, 134.2, 135.8, 135.9, 136.1, 146.1 **MS** (EI^+) m/z: 397 (M^+, 100%), 382, 286, 273, 242, 212, 183, 77. The phosphine oxide was also detected MS (EI^+) m/z: 413 (M^+), 398, 336, 201.

2-(diphenylphosphino)-10-methyl-10*H*-phenothiazine (2b)

To a stirred solution of 2-cloro-10-methyl-10*H*-phenothiazine (**1b**) (2.47 g, 10 mmol) in dry THF (40 cm^3) *n*-BuLi (20 mmol, 12.5 cm^3 of a 1.6 M solution in hexane) was added drop wise at 0 ºC under N_2 and the stirring was continued for 1 h. To the resulting yellow-red solution, Ph_2PCl (20 mmol, 4.41 g) was slowly added and the mixture was allowed to warm to r.t. and stirred overnight. The reaction mixture was treated with 10 cm^3 H_2O. The organic phase was separated and the aqueous phase was extracted with EtOAc (3x25 cm^3). The combined organic phase was dried over Na_2SO_4. After removal of the

solvent *in vacuo*, the residue was separated by column chromatography on silica gel with toluene/Et_3N (100:1) as eluent to give a yellow liquid (2.3 g, 58%). **^{31}P NMR** (121.5 MHz, $CDCl_3$) δ (ppm): - 16.02. **^{1}H NMR** (300 MHz, $CDCl_3$) δ (ppm): 3.42 (s, 3H, *N*-CH_3), 6.69 (s, 1H, $^4J_{HH}$= 1.5 Hz, H1), 6.82 (dd, 1H, $^3J_{HH}$= 7.8 Hz, $^4J_{HH}$= 1.5 Hz, H3), 6.86 (d, 1H, $^3J_{HH}$= 8.1 Hz, H9), 6.97 (m, 2H, $^4J_{HH}$= 1.2 Hz, H6,8), 7.10 (d, 1H, $^3J_{HH}$= 7.8 Hz, H4); 7.20 (4H, d, $^3J_{HH}$= 6.3 Hz, H_{Ph}) 7.22 (1H, t, $^3J_{HH}$= 8.1 Hz, H7), 7.37-7.41 (6H, m, H_{Ph}). **^{13}C NMR** (75 MHz, $CDCl_3$) δ (ppm): 35.7, 114.1, 114.5, 122.4, 122.5, 123.7, 126.9, 127.2, 127.3, 127.5, 128.3, 128.5, 129.1, 132.6, 132.9, 145.8, 146.0. **MS** (EI^+) m/z: 397 (M^+, 100%), 382.

3-(diphenylphosphino)-10-methyl-10*H*-phenothiazine (2c)

To a stirred solution of 3-bromo-10-methyl-10*H*-phenothiazine (**1c**) (10 mmol, 2.92 g) in dry THF (120 cm^3) *s*-BuLi (20.3 mmol, 15.6 cm^3 of a 1.3 M solution in cyclohexane) was added drop wise at -78 ºC under N_2 and the stirring was continued for 0.5 h.To the resulting yellow solution, Ph_2PCl (20.3 mmol, 4.48 g) was slowly added and the mixture was stirred for an additional 1h at -78 ºC and than allowed to warm to r.t. overnight. The reaction mixture was treated with HCl solution (30 ml, 5%) and stirred at 0 ºC for 0.5 h. The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (3x25 cm^3). The combined organic phase was dried over Na_2SO_4. After removal of the solvent *in vacuo*, the residue was separated by column chromatography on silicagel with hexane/Et_2O (19:1) as eluent to give yellow-white crystals (2.07 g, 52%) m.p.: 112.5 ºC.

IR (ATR) v [cm^{-1}]: 696, 748, 796, 818, 970, 1067, 1096, 1141, 1207, 1261, 1331, 1395, 1432, 1459, 1541, 1567, 2878, 2970, 3010, 3052. **^{31}P NMR** (121.5 MHz, $CDCl_3$) δ (ppm): - 6.92. **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): 3.42 (s, 3H, *N*-CH_3), 6.78 (d, 1H, $^3J_{HH}$= 8.0 Hz, H_9), 6.80 (d, 1H, $^3J_{HH}$= 8.4 Hz, H1), 6.92 (t, 1H, $^3J_{HH}$= 7.6 Hz, H7), 7.06 (dd, 1H, $^3J_{HH}$= Hz, $^3J_{HH}$= Hz, H6), 7.10 (dd, 1H, $^3J_{HH}$= 1.2 Hz, H2); 7.14 (1H, s, H4), 7.17 (td, 1H, $^3J_{HH}$= 8.0 Hz, H8), 7.26-7.33 (10H, m, H_{Ph}). **^{13}C NMR** (75 MHz, $CDCl_3$) δ (ppm): 35.4, 114.2, 122.8, 123.1, 123.9, 127.3, 127.6, 128.7, 130.1, 132.2, 132.4, 133.6, 133.7, 133.9, 137.3, 145.4, 146.6. Anal. Calcd.For $C_{25}H_{20}NPS$ (%): C, 75.54; H, 5.07; N, 3.52; S, 8.07. Found (%): C, 75.47; H, 5.04; N, 3.25; S, 8.07. **MS** (EI^+) m/z: 397 (M^+, 100%), 382, 320, 304, 289, 274, 212. The phosphine oxide was also detected MS (EI^+) m/z: 413 (M^+), 336, 201,183.

3,7-bis(diphenylphosphino)-10-methyl-10H-phenothiazine (2d)

To a stirred solution of 3,7-dibromo-10-methyl-10*H*-phenothiazine (**1d**) (1.86 g, 5 mmol) in dry Et_2O (120 cm^3) *n*-BuLi (20.4 mmol, 12.8 cm^3 of a 1.6 M solution in hexane) was added drop wise at 0 ºC under N_2 and the stirring was continued for 1 h. To the resulting yellow solution, Ph_2PCl (20.4 mmol, 4.5 g) was slowly added and the mixture was stirred for an additional 1 h at 0 ºC and than allowed to warm to r.t. overnight. The reaction mixture was treated with H_2O (5 cm^3). The organic phase was separated and the aqueous

phase was extracted with EtOAc (3x25 cm^3). The combined organic phase was dried over Na_2SO_4. After removal of the solvent *in vacuo*, the residue was separated by column chromatography on silicagel with hexane/Et_2O (19:1) as eluent to give yellow crystals (1.3 g, 48%) m.p.: 140 ºC. **^{31}P NMR** (121.5 MHz, $CDCl_3$) δ (ppm): - 6.92. **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): 3.39 (s, 3H, *N*-CH_3), 7.07 (2H, dd, H2), 7.33 (2H, d, H1), 7.50 (2H, s, H4). **^{13}C NMR** (75 MHz, $CDCl_3$) δ (ppm): 35.4, 113.7, 114.95, 114.96, 116.3, 125.9, 128.3, 129.9, 130.0, 130.1, 132.2, 145.2. **MS** (EI^+) m/z: 581 (M^+, 100%), 566, 536, 506, 480, 424, 409, 381, 318.

General procedure for sulfonation of phosphine derivatives 2a and 2c.

Diphenylphosphino-10-methyl-10*H*-phenothiazine (0.2 g, 0.5 mol) was stirred with sulfuric acid (1 cm^3) at rt. The solid slowly dissolved to give a red solution. After being stirred for 20 h the mixture was cooled to 0 °C and degassed water (8 mL) was added slowly. The mixture decolourised and a white precipitate was formed. The mixture was neutralised with 0.5 M aq NaOH to pH 7 and concentrated. The resulting white solid was extracted with ethyl acetate or methanol to give the product after evaporation of the solvent.

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

The product was isolated after extraction with ethyl acetate and evaporation of the solvent as a green-white solid (0.2 g, 80%) m.p. 199 °C decomposition. **IR** (ATR) v [cm^{-1}]: 692, 722, 744, 780, 1050, 1117, 1140, 1256, 1327, 1404, 1439, 1553, 1588, 2815, 2857, 2954, 3055. **^{31}P NMR** (121.5 MHz, $CDCl_3$) δ (ppm): - 13.38, oxidized product was also detected at 30.59. **^{1}H NMR** (300 MHz, $CDCl_3$) δ (ppm): 3.40 (s, 3H, *N*-CH_3), 6.47 (ddd, 1H, $^3J_{HH}$= 7.5 Hz, $^3J_{PH}$= 3.3 Hz, $^4J_{HH}$= 0.9 Hz, H_3), 6.83 (d, 1H, $^3J_{HH}$= 8.1 Hz, H9), 6.84 (d, 1H, $^3J_{HH}$= 7.5 Hz, H1), 6.93 (td, 1H, $^4J_{HH}$= 0.9 Hz, H2), 7.10 (t, 1H, $^3J_{HH}$= 7.8 Hz, H7), 7.14-7.20 (m, 2H, H6,8); 7.37-7.41 (9H, m, H_{Ph}). **^{13}C NMR** (75 MHz, $CDCl_3$): 35.7, 114.0, 114.1, 114.4, 122.6, 123.5, 126.8, 127.0, 127.2, 127.6, 128.5, 128.8, 129.0, 129.3, 132.0, 132.1, 134.0, 134.2, 135.8, 135.9, 136.0, 136.1, 146.1. **MS** (EI^+) was not successful for the sodium salt due to low volatility of the compound and there were detected decomposition products with m/z: 490, 413, 397, 382, 286, 273, 242, 212, 183, 77.

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

Sulfonation was performed according the general procedure presented above. The starting material **2c** and the corresponding phosphine oxide were recovered by extraction with ethyl acetate. Extraction with methanol gave only traces of sulfonated product.

IR (ATR) v [cm^{-1}]: 640, 695, 746, 814, 873, 1045, 1102, 1120, 1162, 1194, 1260, 1332, 1374, 1436, 1459, 1566, 1592, 2879, 2963, 3054.

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