Cyclic oxyphosphoranes in synthesis. A novel synthesis of oxathiaphospholenes, fused pyrimidines, and aminooxyphosphoranes

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Dedicated to Professor Richard Neidlein on the occasion of his 73rd birthday

Abstract

Trialkyl phosphites induced the condensation of one molecule of 3,5-di-*tert*-butyl-1,2-benzoquinone (**1**) with two molecules of methyl-, ethyl-, phenyl- and hexyl iso thiocyanates (**6a-6d**) leading to the formation of quinazoline-2,4-dithione derivatives (**12a, 12b, 14,** and **15**) and trialkyl phosphates. Three steps were involved, and the intermediates could, but need not, be isolated. In the second step, the intermediates, new six-membered phosphorus heterocycles **8a-8d** were isolated and identified. In contrast, condensation of 4,6-di-*tert*-butylbenzo-2-methoxy-2-oxo-1,3,2-dioxaphosphole (**19**) with one molecule of **6a-6d** afforded the corresponding aminooxyphosphoranes **22a-22d**. Allyl iso thiocyanate (**16**), on the other hand, reacted with 2,2,2-trialkoxy-1,3,2-dioxaphospholenes **3a** and **3b** to give the phosphates **18a** and **18b** whereas with **19** spirocyclic oxaphosphole **24** was isolated.

Keywords: 3,5-Di-*tert*-butyl-1,2-benzoquinone, cyclic pentaoxyphosphoranes, iso thiocyanates, six-membered phosphorus heterocycles, spirocyclic oxaphosphole

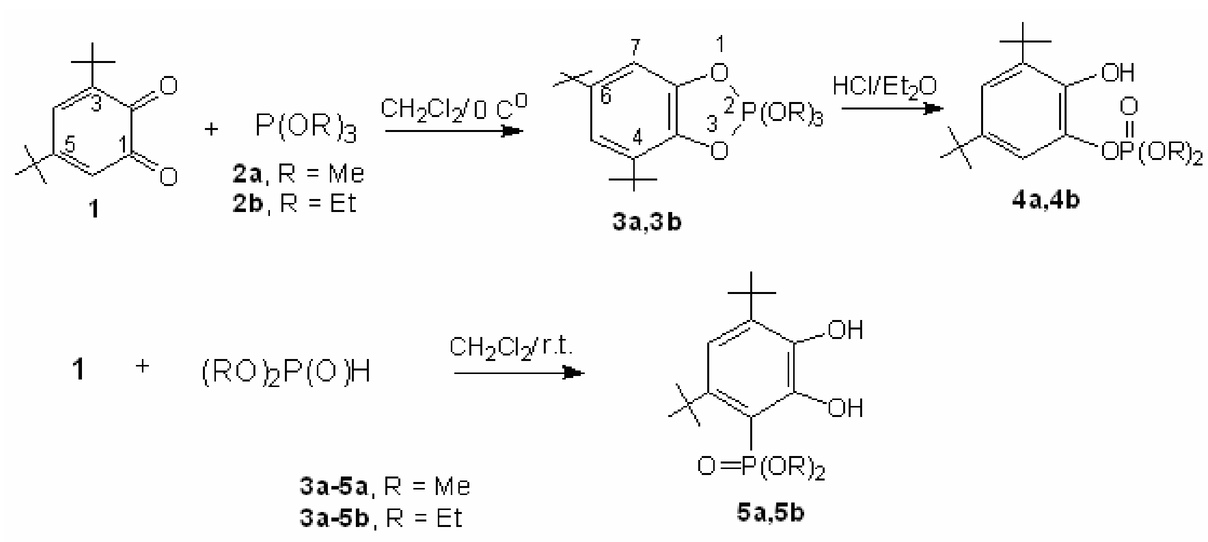
Introduction

Cyclic pentacoordinate phosphoranes are compounds possessing a phosphorus atom to which five ligands are covalently bonded. They are useful models for intermediates in phosphate ester hydrolysis.[1] The inclusion of five-membered cyclic substituents in phosphoranes has aided the interpretation of the great acceleration in hydrolysis of similarly constructed cyclic phosphole esters, which is of importance in biological mechanisms. The latter interpretation has been summarized in Westheimer model.[1b]

Although there exists a wealth of studies on the synthesis, structure[1,2], and synthetic potential[3,4] of phosphoranes containing five-membered rings, little is known about the six-membered rings.[5] The latter, which, are present in trigonal bipyramidal arrangements are expected to exert less ring strain than the five-membered rings.[5]

In the present work, it is intended to investigate the electrophilic addition reactions of some isothiocyanates **6a-6d** and **16** to 2,2,2-trialkoxy 4,6-di-*tert*-butylbenzo-1,3,2-dioxaphospholenes **3a** and **3b**, attempting not only to study the regioselectivity of the reactions but also to isolate oxathiaphosphoranes containing six-membered rings and biologically active pyrimidine derivatives. Pyrimidines were originally synthesized as compounds bearing structure kinship to many potent chemotherapeutic agents.[6] Condensation of the relevant cyclic enediol methylphosphate **19** with **6a-6d** and **16** was also studied. The result is the formation of aminooxyphosphoranes **22a-22d** and cyclic spiro oxaphospholes **24**, respectively.

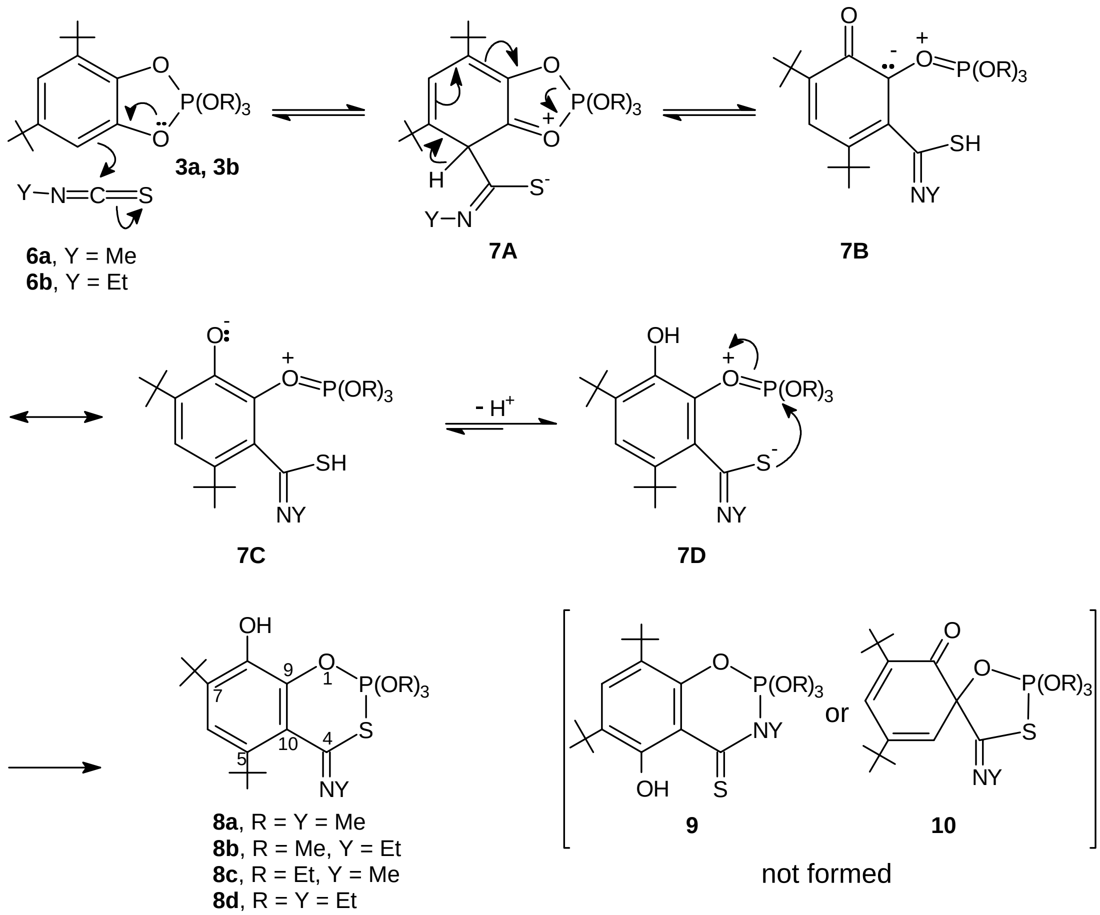
In one of our previous studies[7, 8] on the reactivity of *P(III)* and *P(V)* reagents toward 3,5-di-*tert*-butylbenzoquinones, we reported[7] that *o*-quinone **1** reacted with trialkyl phosphites **2a** and **2b** to give pentaoxyphosphoranes **3a** and **3b,** as presumably observed with *o*-quinones, whereas when reacting with dialkyl phosphonates an anomalous behavior was shown, whereupon a ring attack occurred to give phosphonate adducts **5a** and **5b.** It has been also pointed out that when **3a** and **3b** were treated with dry HCl gas in ether, *o*-quinol monophosphates **4a** and **4b** were produced (Scheme 1). The latter observation was attributed to the substitution pattern in **1**, which would obstruct (for steric reasons[9]) a nucleophilic approach by the phosphorus moiety to C-2(O); i.e. the effect of the neighboring *t-Bu* moiety on the C-2(O) group would be quite unfavorable.



Scheme 1

Results and Discussion

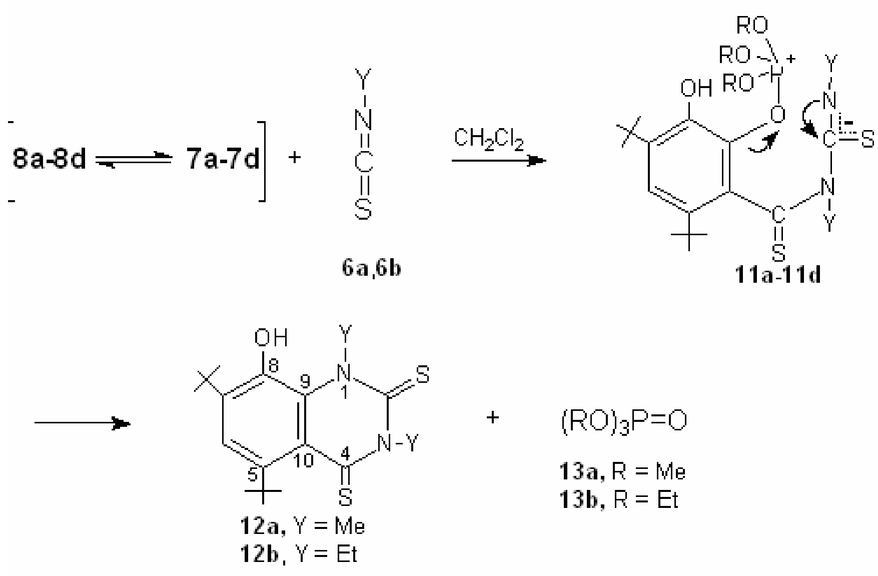
The 2,2,2-trialkoxy-1,3,2-dioxaphospholenes (*DOP*) **3a** and **3b,** prepared from *o*-quinone **1** and trialkyl phosphites **2a** and **2b**,[7] reacted smoothly with methyl- **6a** and ethyl isothiocyanates (**6b**) in methylene chloride at 25 ^{o}C and yielded, in each case, only one regioisomer of structure **8**. Oxathiaphospholenes **8a-8d** are quite stable and will remain intact for months if stored frozen under argon. The assigned structure was determined to be **8** rather than **9** or **10** based on the following: (a) Compatible elementary analyses and molecular weight determinations (MS) were gained for all adducts. (b) Compounds **8a-8d** had ^{31}P NMR ($CDCl_3$) chemical shifts around δp -66 ppm *vs*. H_3PO_4, which are within the range expected for oxathiaphosphoranes, and can readily eliminate a structure like **9**, which would predict a chemical shift in the range δp –30 to - 40 ppm in their ^{31}P NMR spectra. (c) The IR (KBr) spectrum of **8a**, taken as an example, revealed the presence of absorption bands at 3450 (OH), 1672 (= NMe), and at 1030 cm^{-1} (P-O-Me). (d) The ^{1}H NMR ($CDCl_3$) spectrum of **8a** had two 9^{1}H singlets at δ 1.25 and 1.34 that correspond to the protons of the *tert*-butyl groups. The 3^{1}H singlet at 3.18 was assigned to N-CH_3. The 9^{1}H of the three-methoxy groups attached to the phosphorus atom gave rise to one doublet ($^{3}J_{PH}$ = 12.5 Hz) at δ 3.69 ppm. Moreover, the two doublets (2 x 1H, J_{HH} = 4 Hz)) at δ_H 6.23 and 6.99 assignable to protons on C-7 and C-5 in the ^{1}H NMR spectrum of **3a**[7] were absent in the PMR spectrum of the adduct **8a**. Instead, a singlet at δ_H 6.98 accounted for the proton on C-6 in PMR of **8a**, while the broad signal present around δ 8.76 ppm was assigned for the phenolic O*H* group. Furthermore, the distinguishing features of ^{13}C NMR of **8a-8d** were the presence of signals around δ 180 (*C*-4), 148 (*C*-8), and 117 (*C*-6) ppm. The recorded data of the exocyclic =NCH_3, and the lack of a signal due to the second proton of the aryl moiety in the ^{1}H and ^{13}C NMR spectra of the adducts; as well as the absence of thioamidecarbonyl- or carbonyl group bands in their IR and ^{13}C NMR spectra confirm the assigned structure **8** and rule out other alternative structures like **9** and **10**.



Scheme 2

The more plausible depiction *suggested by the editor*, of the electrophilic aromatic substitution of an iso thiocyanates is outlined in Scheme 2. Accordingly, the formation of **8a-8d** involves the initial electrophilic aromatic substitution in which the highly activated aromatic ring (contains two OR groups, *cf* Scheme 1-ii)[7, 9] suffers an electrophilic attack by the weak electrophile **6** to give the zwitterionic intermediate **7A**. Rearrangement of **7A** to **7D** via the intermediates **7B** and **7C**, and subsequent aromatization with concomitant proton-shift then leads directly to **8**. The ring attack of iso thiocyanates to dioxaphospholenes has been previously reported by Neidlein and Mosebach[10a] for the reaction of 2,2,2-trimethoxy cyclohexane-1,3,2-dioxaphospholene. Furthermore, the formation of the six-membered phosphorus heterocycles **8** instead of the aminotetraoxyphosphoranes **9** is consistent with the reports[4,11] on the relative stabilities of these ring systems. It is pointed out that the alternate cyclization of **7** to **9** would give a phosphorane with one *N* and four *O* attached to phosphorus. Due to the larger steric requirements associated with the azaphosphorane *vs*. oxathiaphosphorane, the former are favored over the latter, i. e. **8** should be formed. However, the formation of **8** in one concerted step that requires little or no charge separation, i.e. without the transient state such as **7**, was also reported.[11a,b] Furthermore, a structural isomer of the spiro-1,3,2-oxathiaphospholene **10,** which would arose[4] by the nucleophilic addition of a carbon atom of the phospholene **3** to the carbon of iso thiocyanate, could not be isolated. The loss of aromaticity is most likely the reason **10** is not formed.

The phospholenes **8a-8d** were further allowed to react with a second molecule of alkyl isothiocyanates **6a** and **6b** in methylene chloride. The reaction had a 1:1 stoichiometry and produced trialkyl phosphates **13a** and **13b** together with 5,7-di-*tert*-butyl-8-hydroxy-1,3-dialkylquinazoline-2,4(1H,3H)-dithiones **12a** and **12b** in good yields. The rates of the reactions of alkyl iso thiocyanates with the phospholenes **3** and with the phospholenes **8** were very similar. Therefore, the best procedure to make **8** involved slow addition of **6a** (and **6b**) to **3a** (or **3b**) in CH_2Cl_2 at $-5 \rightarrow 0$ ^oC. On the other hand, compounds **12a** and **12b** were isolated in ~80% yields when 2.2 mol of iso thiocyanates **6a** (or **6b**) and 1mol of the phospholenes **3a** (or **3b**) were allowed to react in boiling CH_2Cl_2 solution. Small amounts of a second substance **8** could not be detected in this reaction.

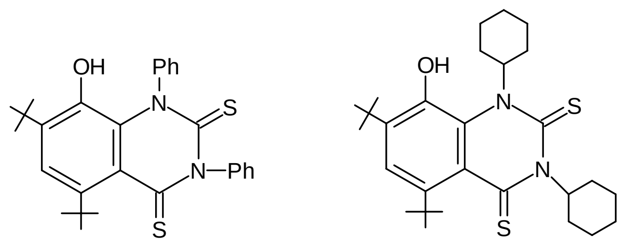


Scheme 3

It was possible to condense *o*-quinone **1** with two moles of **6a** (or **6b**) and one mole of trialkyl phosphites **2a** (or **2b**) *in situ,* without isolation of intermediates: i. e. **1** + **6a (**or **6b)** + **2a** (or **2b**) → **12a** (or **12b**) + **13a** (or **13b**). Obviously, the key intermediate in the DOP – isothiocyanate condensation is the iminophospholene, which can generate a dipolar ambident anion **7** by rupture of P-O bond. The dipolar anion **7** reacts with a second isothiocyanate molecule by virtue of the nucleophilicity of nitrogen; the resulting 1:2 intermediate cyclizes to the pyrimidine. The driving force for the ring closure is, however, the formation of P=O bond resulting in the elimination of a phosphate. The chemical structure **12** was in accord with the elemental analyses, molecular weight determinations (MS), and the spectroscopic data.

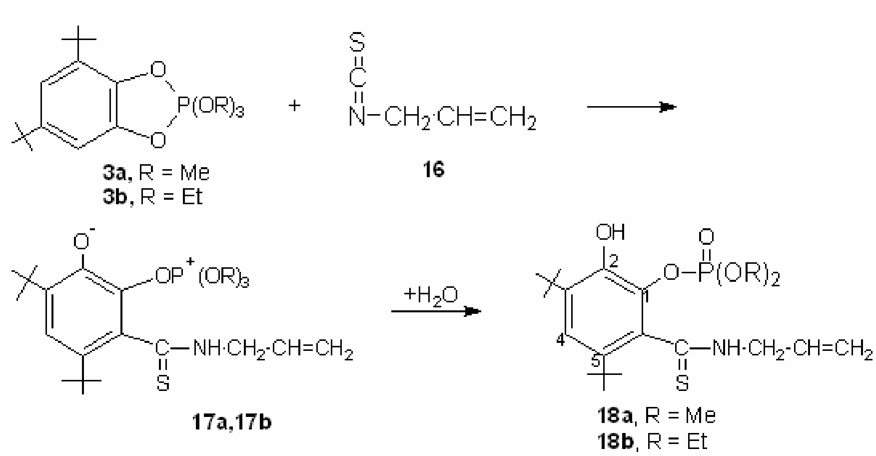
Compounds **12a** and **12b** had infrared bands at υ ≈ 3450, 1185 and 1190 cm^{-1} attributed to the phenolic OH and the two-thione groups. The ^1H NMR spectrum of **12a** had the expected 18^1H *tert*-butyl singlets at δ1.23 and 1.46 along with two 3^1H signals at δ 3.21 and 3.26 ppm due to the two N-*Me* groups. Carbon atoms of the N-*Me* groups in the ^{13}C NMR spectrum of **12a** appeared at δ 39.7 and 42.5 ppm.

When phenyl- **6c** and cyclohexyl isothiocyanates **6d** were caused to react with equivocal amount of phospholenes **3a** (or **3b**), the starting *P(V)* **3** was not totally consumed until the second equivalent of isothiocyanate was added. The pyrimidinedithiones: **14** (80% yield) and **15** (82% yield) were the reaction products whereas thiaphospholene analogs of **8** could not be isolated from these latter reactions. Obviously, the formation of **14** and **15** involved the transformation of the initially formed **7** to **8** analogs. However, these very sterically hindered molecules apparently underwent a fast follow up reaction with **6c** (or **6d** to form **14** (or **15**). Since the latter reaction is faster than the initial reaction of **3** with **6c** (or **6d**), **7** (or **8**) are not fully consumed.



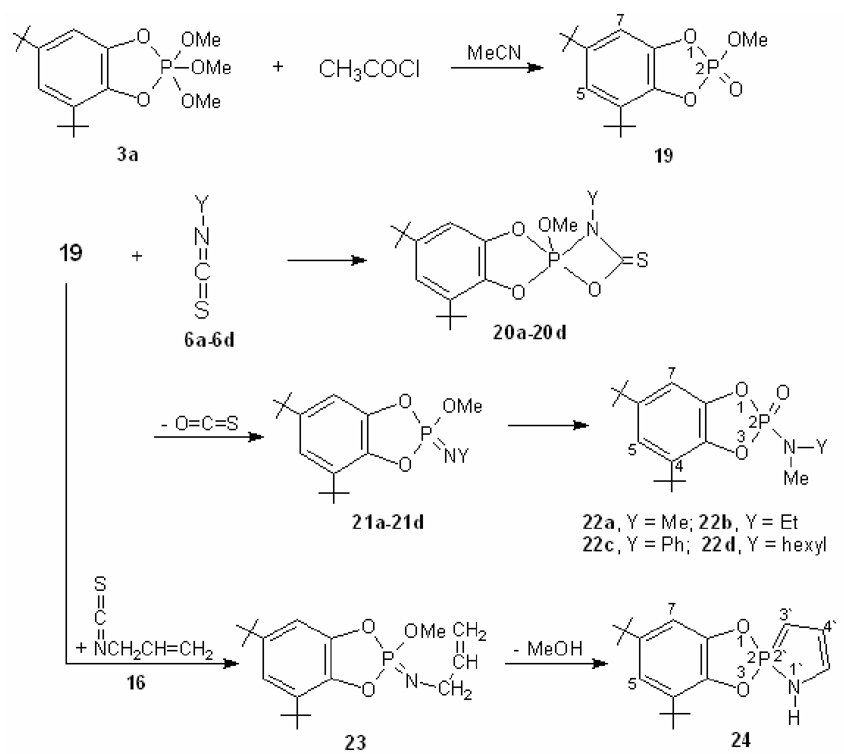
14 **15**

In contrast to the findings obtained from the reactions of **3a** and **3b** with **6a-6d,** protonation of the iso thiocyanate occurred when **3a** and **3b** were allowed to react with allyl isothiocyanate **16** and gave 1:1 adducts formulated as thiocarbamyl phosphates **18a** and **18b**. A possible mechanism for this reaction is illustrated in Scheme 4. At the stage of the formation of the dipolar ion **17**, the proton can shift from C-6 to nitrogen instead of C-2 (O) (*cf*. Scheme 2) with considerable resonance stabilization to give **17**. Dealkylation of **17** with adventitious moisture yielded the final products **18a** (or **18b**). Compounds **18a** (or **18b**) was isolated as a sole reaction product whether one or two moles of **16** were used in the above reaction. Furthermore, no reaction was observed when **18** was caused to react with a second mole of **16**.



Next, the cyclic enediol phosphate-iso thiocyanate condensation was investigated. The required phosphate **19** was readily obtained in 74% yield by *O*-acylation of the oxaphospholene **3a**, using freshly distilled acetyl chloride as an acylating agent and acetonitrile as a solvent. The ester **19** reacted with isothiocyanates **6a-6d** and gave the corresponding aminooxyphosphorane derivatives **22a-22d**, according to Scheme 5. Isomerization of **21** to **22** is not surprising as it is known that the iminophosphoranes like **21,** rapidly rearrange and/or dealkylate to the aminooxyphosphoranes.[13] Products **22a-22d** had singlets around δ 19 ppm in their ^{31}P NMR spectra,[14] while their IR spectra revealed a strong absorption band at $\upsilon \approx 1237$ cm^{-1} (P=O). The ^{1}H NMR spectrum of **22a** showed the presence of a doublet ($^{3}J_{PH}$ = 10.8 Hz, 6H, N(CH_3)$_2$) at δ 3.18, whereas the aromatic protons gave two doublets (each with J_{HH} = 4.0 Hz) at 6.23 (7-C-*H*) and 6.99 (5-C*H*). Its ^{13}C NMR spectrum displayed carbon resonance of dimethylamine at δ 36.3 ppm.

On the other hand, bicyclic spiro-oxaphosphole **24** was obtained when the ester **19** was caused to react with allyl iso thiocyanate (**16**) (Scheme 5). The ^{1}H NMR spectrum of **24** showed the characteristic resonances for the pyrrole ring system at δ 6.25 (m, 1H, 3\`-C*H*), 6.86 (d, 2H, $J_{HH}$= 3.5 Hz, 4\`-, 5\`-C-*H*) along with resonance corresponding to N*H* at $\delta$ 8.92 ppm. The C-5\` and C-4\` atoms in the $^{13}$C NMR spectrum of **24** appeared at $\delta$ 141.8 and 125.3, while C-3\` appeared at δ_C 205.6 (d, $^{1}J_{PC}$ = 57.8 Hz) ppm; its ^{31}P NMR spectrum exhibited a signal at δ = 11.78 ppm. We presumed that the iminooxyphosphorane **23**, initially formed, underwent ring closure with elimination of methyl alcohol molecule (Scheme 5). Relevant spiro phospholes were intensively studied in the literature.[9b, 15]



Scheme 5

Conclusions

A comparison of the behavior of 1,3,2-dioxaphospholenes **3a, 3b** and the enediol cyclophosphole **19** toward iso thiocyanates **6a-6d** is instructive. The key intermediate in the dioxyphosphorane-iso thiocyanates condensation is the iminothiaphospholenes **8a-8d**, which is derived from the ring attack. These intermediates were, in turn capable of nucleophilic addition by nitrogen to iso thiocyanates yielding the 1:2 adducts **12a, 12b, 14** and **15**. In the second step, the driving force is the ejection of trialkyl phosphate. On the other hand, nucleophilic addition of phosphoryl group in the phosphole **19** to the isothiocyanates was observed in the second reaction and afforded aminooxyphosphoranes **22a-22d**. Finally, although the first step in the two reactions of allyl isothiocyanate **16** with either **3a, 3b** or **19** is the same as other iso thiocyanates, the consequences of the initial step varied markedly and yielded the phosphates **18a**, **18b** or spiro compound **24**, respectively.

Finally, it is note worthy that the two novel systems studied: 1,3-substituted quinazoline-2,4 (1H, 3H)-dithiones **12a**, **12b**, **14** and **15** and spiro[benzo-1,2-dioxaphosphole-2,2'-pyrrole] **24** have not been described in the literature (Beilstein research) and that the described method in this work is a reasonable way of making them.

Experimental Section

General Procedures. Melting points are uncorrected. Infrared spectra were measured with a Perkin-Elmer IR-spectrometer model 597 using KBr discs. The ^{1}H and ^{13}C NMR spectra were recorded with a Bruker Model WH-300 MHz spectrometer, using TMS as an internal reference. Chemical shifts are given in the δ-scale (ppm), coupling constants *J* in Hz. The ^{31}P NMR spectra were run on a Varian CFT-20 relative to external H_3PO_4. Mass spectra were performed at 70 eV on a Schimatzu GCS-QPEX spectrometer provided with a data system. The appropriate precautions in handling moisture-sensitive compounds were observed. Light petroleum refers to the fraction 40-60 ^{o}C. *o*-Quinone **1** and iso thiocyanates **6a-6d** and **16** are available from Aldrich Company.

Preparation of oxathiaphospholenes 8a-8d. Reaction of 2,2,2-trialkoxy 4,6-di-tert-butylbenzo-1,3,2-dioxaphospholenes (3a and 3b) with 1 molar equiv of methyl- 6a and ethyl iso thiocyanates (6b). General procedure

Oxaphospholene (1.45 mmol) **3a** or **3b**[7] was transferred via cannule into a flame-dried flask under Ar and dissolved in 5 mL of freshly distilled CH_2Cl_2. To the flask, 1.46 mmol of freshly distilled **6a** or **6b** in 20 mL CH_2Cl_2 was added dropwise over 3 h period at 0 ^{o}C. The reaction was allowed to stir at r.t. for an additional 12 h. During this time, the reaction turned slightly yellow, and the solvent was evaporated. The viscous, non-crystalline residue was triturated with light petroleum and crystallized from the proper solvent to give oxathiaphospholenes **8a-8d**. Percentage yields; physical and spectral data of compounds **8a-8d** are listed in Tables 1, 2, and 3.

Preparation of Dialkylquinazoline-2,4-dithiones 12a and 12b. Method 1. Reaction of 2,2,2-trialkoxy 5,7-di-tert-butyl-8-hydroxybenzo[1,2-d]-4-alkylimino-1,3,2-oxathiaphospholenes 8a-8d with alkyl iso thiocyanates 6a and 6b. Compounds **8a-8d** ((0.96 mmol) obtained above were converted into the 1,3-dialkyl-5,7-di-*tert*-butyl-8-hydroxy-1,3-dialkylquinazoline-2,4 (1H, 3H)-dithiones (**12a** and **12b**) by treating them with 0.96 mmol of **6a** (or **6b**) in 20 mL CH_2Cl_2 at reflux temperature for 6 h (or at r.t. for 48 h). The removal of the solvent and trialkyl phosphate (δp = -3.96 ppm) left a residue, which was triturated with light petroleum and crystallized from the proper solvent to give **12a** and **12b** in 68 and 72% yields, respectively, based on **3a** (or **3b**). Physical and spectroscopic data of **12a** and **12b** are listed in Tables 1, 2, and 3.

Method 2. Reaction of dioxaphospholenes 3a and 3b with 2 molar equiv of 6a and 6b. Optimum conditions for the synthesis of 12a and 12b. A solution of 1.45 mmol of the phospholenes **3a** (or **3b**) in 15 mL CH_2Cl_2 was added dropwise, at r.t. to a solution of 3.9 mmol of alkyl isothiocyanates **6a** (and **6b**) in 15 mL CH_2Cl_2. The solution was stirred for 4 h at r.t., followed by 6 h at reflux temperature. The product mixture was evaporated to remove first the solvent at r.t., and then trialkyl phosphate (0.1 mm, bath at 80 ^oC). The residue was crystallized from the appropriate solvent to give **12a** (82% yield) and **12b** (87% yield).

Method 3. Direct synthesis of 12a and 12b from o-quinone 1, isothiocyanates 6a, 6b, and phosphites 2a, (or 2b) without isolation of intermediates. *o*-Quinone **1** (2.27 mmol) and 4.54 mmol of **6a** (or **6b**) were dissolved in 20 mL of CH_2Cl_2. The solution was cooled to 0 ^oC and was treated with 2.27 mmol of trimethyl- **2a** or triethyl phosphite **2b**. The solution was stirred 1 h at 0 ^oC, and then kept at r.t. for 2 h followed by heating at the reflux temperature for 6 h. The reaction mixture was worked up as described above and gave **12a** (52% yield) or **12b** (58% yield).

Reaction of dioxaphospholenes 3a and 3b with phenyl-6c and hexyl isothiocyanates (6d) When a mixture of equimolar amounts of **3a** (or **3b**) and the appropriate iso thiocyanate **6c (**or **6d**) in CH_2Cl_2 whereby the procedure and the workup were the same with **6a** (or **6b**) (*General Procedure*). The product was **14** (or **15**) in ~ 30% yields along with unchanged **3a** (or **3b**). There was no experimental indication of the presence of the oxathiaphospholene analogs. The reaction was repeated using one mole equiv of **3a** (or **3b**) and two equivs of **6c** (or **6d**) in boiling CH_2Cl_2 for 8 h; and then the mixture was freed from the solvent and trialkyl phosphate. The residue was crystallized from the appropriate solvent to give **14** (or **15**). Yields, physical and spectral data were listed in Tables 1, 2, and 3.

Compounds **14** and **15** could also be obtained in ≈ 55% yields, according to method 3.

Reaction of dioxaphospholenes 3a and 3b with allyl iso thiocyanate (16). A solution of 1.45 mmol of the phospholene **3a** (or **3b**) in 15 mL CH_2CL_2 was added dropwise at 0 ^oC to a solution of 145 mg (1.46 mmol) of ally iso thiocyanate (**16**) in 15 mL of CH_2Cl_2. The reaction was mildly exothermic and the solution was stirred for 10 h at 20 ^oC, and then the volatile materials were removed by distillation at 20 °C/3 mm. The phosphate products **18a** (or **18b**) was purified by triturating with cold ether, followed by crystallization from acetone. Data were listed in Tables 1, 2, and 3.

The reaction of **3a** (or **3b**) with 2 molar equiv. of **16** gave the same phosphates **18a** and **18b** plus unchanged **3a** (or **3b**). No reaction was occurred when **18a** or **18b** were allowed to react with a second molecule **16**.

Preparation of 4,6-di-*tert*-butylbenzo-2-methoxy-2-oxo-1,3,2-dioxaphosphole (19). 5 g (0.023 mol) of *o*-quinone **1** in 20 mL CH_2CL_2 was added dropwise with stirring over 1 h to 2.9 mL (0.023 mol) of freshly distilled trimethyl phosphite in 5 mL CH_2CL_2 with the temperature kept at 0-5 °C. After 3 h at 25 °C, the reaction mixture was freed from CH_2CL_2, and 25 mL of acetonitrile was added to the residue followed by 1.8 g (0.023 mol) of freshly distilled acetyl chloride over 2 h. The reaction was exothermic and the addition was carried out at a rate, which kept the solution at ~ 40 °C. After further 2 h at 25 °C, the solution was evaporated and the residue was triturated with cold ether and purified by crystallization from cyclohexane to give 4.7 g (70% yield) of the phosphole **19**, as colorless crystals, m.p. 140-142 °C; Anal. Calcd. For $C_{15}H_{23}O_4P$ (298.32): C, 60.39; H, 7.77; P, 10.38. Found: C, 60.44; H, 7.73; P, 10.41%; IR (KBr) 1256 (P=O), 1050 (P-O-C); ^{1}H NMR ($CDCl_3$): δ_H 1.28, 1.30 (2s, 2 x 9H, C(CH_3)$_3$), 4.04 (d, J_{PH} = 12.3 Hz, OCH_3, 6.23 (d, J_{HH} = 4.2 Hz, 1H, 4-C-*H*), 6.93 (d, J_{HH} = 4.2 Hz, 1H, 6- C-*H*); ^{13}C NMR: δc 29.9, 30.1 [2 x C(*C*H_3)], 35.3 (2 x *C*(CH_3), 54.8 (P-O-*C*H_3), 114.2 (7-*C*), 118.6 (5-*C*), 136.1, 142.1 (4, 6-*C*), 145.4 (8-*C*), 137.6 (9-*C*); ^{31}P NMR: δp = + 4 ppm; MS: *m/z* (%) 298 [M^+] (33), 283 (100).

Reaction of the phosphoryl ester 9 with isothiocyanates 6a-d and 16. General procedure solution of 0.5 g (1.68 mmol) of the ester **19** in 15 mL CH_2Cl_2 at 0 °C was added dropwise in 30 min to a stirred solution of 1.68 mmol of methyl-**6a**, ethyl-**6b,** phenyl-**6c**, hexyl-**6d** or allyl iso thiocyanate (**16**) in 15 mL CH_2Cl_2. The solution was stirred for 1 h at 0 °C and 24 h at 25 °C. The solvent was evaporated at 30 °C and 20 mm, and the residue was stirred with cold ether and filtered. The products, aminooxyphosphoranes **22a-22d** and 4,6-di-*tert*-butyl spiro[benzo-1,2-dioxaphosphole-2,2'-pyrrole] (**24**) were purified and identified as in Tables 1, 2, and 3.

Table 1. Physical Properties, and Analytical Data of the Products **8a-8d, 12a, 12b, 14, 15, 18a, 18b, 22a-22d**, and **24**

Product/ color	R and / or Y	Mp (°C) / solvent	Yield (%)	Mol. formula (Mol. Wt.)	Analysis (Calcd./found) C	H	N	P	S
8a/ pale yellow	R = Me, Y = Me	85-87 (pentane)	66[a]	$C_{19}H_{32}NO_5PS$ (417.5)	54.66 54.52	7.73 7.82	3.35 3.37	7.42 7.36	7.66 7.75
8b / pale yellow	R = Me, Y = Et	70-72 (pentane)	68[a]	$C_{20}H_{34}NO_5PS$ (431.53)	55.67 55.61	7.94 7.88	3.25 3.29	7.18 7.24	7.43 7.51
8c / pale yellow	R = Et, Y = Me	82-84 (pentane)	72[a]	$C_{22}H_{38}NO_5PS$ (459.58)	57.49 57.43	8.33 8.43	3.05 3.16	6.74 6.59	6.98 7.03
8d / pale yellow	R = Et, Y = Et	72-74 (pentane)	76[a]	$C_{23}H_{40}NO_5PS$ (473.61)	58.33 58.45	8.51 8.55	2.96 2.84	6.54 6.60	6.77 6.79
12a / orange	Y = Me	185-187 (MeCN)	82[b]	$C_{18}H_{26}N_2OS_2$ (350.54)	61.67 61.73	7.48 7.42	7.99 7.97	– –	18.30 18.37
12b / orange	Y = Et	166-168 (MeCN)	87[b]	$C_{20}H_{30}N_2OS_2$ (378.6)	63.45 63.49	7.99 8.03	7.40 7.37	– –	16.94 16.99
14 / orange	Y = Ph	232-234 (EtOH)	80[b]	$C_{28}H_{30}N_2OS_2$ (474.68)	70.85 70.89	6.37 6.33	5.90 5.84	– –	13.51 13.59
15 / yellow	Y= hexyl	218-220 (EtOH)	82[b]	$C_{28}H_{42}N_2OS_2$ (486.78)	69.09 68.98	8.70 8.73	5.75 5.82	– –	13.17 13.23
18a / yellow	R = Me	146-148 (cyc.hexane)	72[a]	$C_{20}H_{32}NO_5PS$ (429.46)	55.93 55.99	7.51 7.46	3.26 3.34	7.21 7.28	7.45 7.32
18b / yellow	R = Et	133-135 (cyc hexane)	76[a]	$C_{22}H_{36}NO_5PS$ (457.51)	57.75 57.83	7.93 7.96	3.06 3.11	6.76 6.70	6.99 6.92
22a / colorless	Y = Me	163-165 (acetone)	58[c]	$C_{16}H_{23}NO_3P$ (311.36)	61.72 61.78	8.42 8.36	4.50 4.46	9.95 9.97	– –
22b / colorless	Y = Et	148-150 (acetone)	70[c]	$C_{17}H_{28}NO_3P$ (325.38)	62.75 62.67	8.67 8.69	4.30 4.35	9.52 9.48	– –
22c / colorless	Y = Ph	182-184 (acetone)	78[c]	$C_{21}H_{28}NO_3P$ (373.43)	67.54 67.46	7.56 7.53	3.75 3.83	8.29 8.34	– –
22d / colorless	Y= hexyl	170-172 (acetone)	68[c]	$C_{21}H_{34}NO_3P$ (379.48)	66.47 66.50	9.03 9.11	3.69 3.75	8.16 8.24	– –
24 / colorless	–	133-135 (benzene)	62[c]	$C_{17}H_{24}NO_3P$ (305.56)	66.86 66.69	7.92 7.90	4.59 4.52	10.14 10.21	– –

(a) Yield is based on the *o*-quinone **1**, (b) Yield is based on the substrate **1** from method **2**, (c) Yield is based on the ester **19**.

Table 2. IR, ^{1}H-, ^{31}P NMR and MS Data[a] for Compounds **8a-8d, 12a, 12b, 14, 15, 18a, 18b, 22a-22d**, and **24**

Product	IR (KBr) (cm^{-1}) / υ_{max}	^{1}H NMR,[b] & ^{31}P NMR, δ (ppm)	MS: m/z (%) = [M^+] and relevant fragments
8a[c]	3450 (OH), 1672 (C=NMe), 1030 (P-O-C)	3.18 (s, 3H, NCH_3), 3.69 (d, $^3J_{PH}$ = 12.5 Hz, 9H, OCH_3), 6.98 (s, 1H, 6-C*H*), 8.76 (s br, 1H, O*H*). δp = - 66.2	417 (16) [M^+], 416 (15), 401 (18), 399 (22), 387 (33), 371 (100), 328 (17), 284 (8), 262 (50), 259 (18).
8b[c]	3494 (OH), 1670 (C=NMe), 1055 (P-O-C)	1.06 (t, J_{HH} = 6.5 Hz, 3H, NC.CH_3), 3.43 (q, J_{HH} = 6.5 Hz, 2H, NCH_2), 3.72 (d, $^3J_{PH}$ = 12.5 Hz, 9H, OCH_3), 6.98 (s, 1H, 6- C*H*), 8.49 (s br, 1H, O*H*). δp = - 63.88	431 (11) [M^+], 430 (13), 401 (17), 399 (20), 387 (100), 371 (100), 328 (14) 284 (16), 262 (51), 259 (21).
8c[c]	3460 (OH), 1665 (C=NEt), 1020 (P-O-C)	1.15 (dt, J_{HH} = 6.6 Hz, J_{PH} = 4.5 Hz, 9H, OC.CH_3), 3.16 (s, 3H, NCH_3), 4.14 (dq, J_{HH} = 6.6 Hz, J_{PH} = 6.0 Hz, 6H, OCH_2), 7.05 (s, 1H, 6-C-*H*), 8.55 (br, 1H, O*H*). δp = - 66.2	459 (8) [M^+], 458 (16), 443 (10), 429 (23), 384 (32), 371 (100), 262 (62), 259 (23), 244 (29).
8d[c]	3450 (OH), 1668 (C=NEt), 1031 (P-O-C)	1.12 -1.33 (2t (m), 12 H, 3 x OC.CH_3 & NC.CH_3), 3.52 (q, J_{HH} = 6.5 Hz, 2H, NCH_2), 4.16 (dq, J_{PH} = 12.2 Hz, 6H, 3 x OCH_2), 6.98 (s, 1H, 6-C*H*), 8.87 (s br, 1H, O*H*) δp = - 68.6	473 (14) [M^+], 472 (10), 443 (18), 429 (29), 384 (35), 371 (100), 284 (22), 262 (57), 259 (29).
12a[d]	3450 (OH), 1197, 1185 (2 x C=S).	3.21, 3.26 (2s, 2 x 3H, 2 x NCH_3), 7.06 (s, 1H, 6-C-*H*), 8.64 (s br, 1H, O*H*).	350 (16) [M^+], 349 (21), 334 (31), 319 (100), 263 (21), 207 (15).
12b[d]	3455 (OH), 1190, 1185 (2 x C=S).	1.26 -1.38 (2t (m), 2 x 3H, 2 x NC.CH_3), 3.75, 4.01 (2q, 4H, 2 x NCH_2), 7.04 (s, 6-C*H*), 8.49 (s br, 1H, O*H*).	378 (26) [M^+], 377 (29), 348 (34), 319 (100), 263 (11), 207 (16).
14[d]	3450 (OH), 1192, 1183 (2 x C=S).	6.89 (s, 1H, 6-C-*H*), 7.25 (m, 6H, Ph-*H*), 7.42 (m, 4H, Ph-*H*), 8.68 (s br, 1H, O*H*)	474 (31) [M^+], 473 (22), 396 (14), 319 (100), 263 (21), 207 (35), 77 (72).
15[d]	3430 (OH), 1190, 1187 (2 x C=S).	1.41 (s, 20H, cyclohexyl-*H*), 5.22 (s br, 2H, cyclohexyl -*H*), 7.01 (s, 1H, 6-C-*H*), 8.68 (s, br, 1H, O*H*).	486 (24) [M^+], 485 (20), 401 (42), 319 (100), 263 (50), 207 (19), 83 (66).

Table 2. Continued

18a[c]	3426, 3238 (OH & NH), 1592 (=CH_2), 1220 (P=O), 2215 (C=S), 1031(POC).	2.98 (m, 2H, NHC*H₂*), 3.45 (d, J_{HP} = 12.8 Hz, 6H, OCH_3), 4.25 (d, J_{HH} = 7.8 Hz, 2H, CH=CH_2), 5.4 (br, 1H, N*H*), 6.75-7.12 (m, 2H,CH_2=C*H* & 4-C-*H*), 8.24 (s br, 1H, O*H*). δp = - 4.02	413 (55), [M^+], 412 (23), 411 (36), 396 (13), 381 (31), 370 (18), 340 (100), 264 (8), 255 (42).
18b[d]	3430, 3230 (OH & NH), 1598 (=CH_2), 1219 (P=O, bonded), 2205 (C=S, 1025 (P-O-C)	0.95 (dt, J_{HH} = 7.4 Hz, J_{PH} = 4.8 Hz, 6H, OC.CH_3), 2.99 (m, 2H, N-CH_2), 3.6 (q, J_{PH} = 12.6 Hz, 4H, OCH_2), 4.24 (d, J_{HH} = 7.8 Hz, 2H, CH=CH_2, 5.44 (br, 1H, NH), 6.74-7.13 (m, 2H, CH_2=C*H* & 4-C-*H*), 8.34 (br, 1H, O*H*). δp = - 3.96.	441 (61) [M^+], 440 (26), 439 (41), 410 (18), 398 (33), 385 (24), 381 (18), 340 (100), 264 (13).
22a[c]	1243 (P=O).	3.18 (d, $^3J_{PH}$ = 10.8 Hz, 6H, N (CH_3)$_2$), 6.23 (d, J_{HH} = 4 Hz, 1H, 7- C-*H*), 6.99 (d, J_{HH} = 4 Hz, 1H, 5- C-*H*). δp = 19.3.[14]	311 (14), [M^+], 267 (35), 220 (100).
22b[c]	1238 (P=O).	1.42 (dt, J_{PH} = 8.4 Hz, 3H, NC.CH_3), 2.95 (dt, J_{PH} = 6.4 Hz, 3H, N-CH_3), 3.51 (q, J_{PH} = 8.4 Hz, 2H, NCH_2), 6.23 (d, J_{HH} = 4 Hz, 1H, 7-C-*H*), 6.98 (d, J_{HH} = 4 Hz, 1H, 5- C-*H*). δp = 17.6.	325 (19), 267 (43), 220 (100).
22c[c]	1235 (P=O).	2.98 (d, J_{PH} = 9.7 Hz, 3H, NCH_3), 6.23 (d, J_{HH} = 4 Hz, 1H, 7- C-*H*), 6.99 (d, J_{HH} = 4 Hz, 1H, 5- C-*H*), 7.27 (m, 3H, Ph-*H*), 7.48 (m, 2H, Ph-*H*) δp = 20.3.	373 (13) [M^+], 358 (31), 281 (25), 267 (39), 220 (100), 83 (40).
22d[c]	1235 (P=O).	1.52 (s, 10H, cyclohexyl-*H*), 2.98 (d, J_{PH} = 8.5 Hz, 3H, N-CH_3), 5.02 (s br, 1H, cyclohexyl-*H*), 6.24 (d, J_{HH} = 4 Hz, 1H, 7- C-*H*), 6.98 (d, J_{HH} = 4 Hz, 1H, 5- C-*H*). δp = 18.78.	379 (13) [M^+], 364 (28), 287 (17), 267 (36), 220 (100), 63 (51).
24[c]	3235 (NH).	6.23 (d, J_{HH} = 3.8 Hz, 1H, 7- C-*H*), 6.25 (m, 1H, 3`- C-*H*), 6.86 (d, $J_{HH}$ = 3.5 Hz, 2H, 4`&5`- C-*H*), 6.99 (d, J_{HH} = 3.8 Hz, 1H, 5- C-*H*), 8.92 (br, 1H, N*H*). δp = 11.78.	305 (36) [M^+], 304 (63), 220 (100), 85 (72).

(a) See experimental section for further details. (b) ^{1}H NMR spectra of all listed products showed *tert-Bu* signals as two singlets at δ ~1.24 and ~ 1.36 ppm. (c) The solvent (NMR) is $CDCl_3$. (d) The solvent (NMR) is d_6-DMSO.

Table 3. ^{13}C NMR Data[a] for Compounds **8a-8d, 12a, 12b, 14, 15, 18a, 18b, 22a-22d**, and **24**

Product	^{13}C NMR, δ ppm
8a[b]	41.5 (N.*C*H$_3$), 52.4 (O*C*H$_3$), 109.2 (*C*-10), 117.8 (*C*-6), 133.3 (*C*-5), 136.4 (*C*-9), 139.8 (*C*-7), 147.2 (*C*-8), 187.6 (*C*-4).
8b[b]	16.8 (NC.*C*H$_3$), 46.7 (N.*C*H$_2$), 53.7 (O*C*H$_3$), 110.2 (*C*-10), 116.4 (*C*-6), 133.3 (*C*-5), 136.2 (*C*-9), 138.9 (*C*-7), 146.6 (*C*-8), 170.8 (*C*-4).
8c[b]	19.2 (d, O.C.*C*H$_3$), 41.5 (N.*C*H$_3$), 58.8 (O*C*H$_2$), 109.2 (*C*-10), 117.0 (*C*-6), 133.5 (*C*-5), 135.8 (*C*-9), 139.7 (*C*-7), 148.2 (*C*-8), 187.5 (*C*-4).
8d[b]	16.8 (N.C.*C*H$_3$), 19.8 (O.C.*C*H$_3$), 49.4 (N.*C*H$_2$), 60.1 (d, O*C*H$_2$), 110.2 (*C*-10), 116.8 (*C*-6), 133.4 (*C*-5), 135.1 (*C*-9), 138.3 (*C*-7), 149.1 (*C*-8), 169.8 (*C*-4).
12a[c]	39.7, 42.5 (2 x N*C*H$_3$), 116.6 (*C*-6), 124.5 (*C*-10), 138.6 (*C*-7), 142.1 (*C*-5), 146.2 (*C*-8), 173.5, 176.1 [*C*-2 (S)], *C*-4 (S)].
12b[c]	12.6, 13.4 (2 x NC.*C*H$_3$), 45.6, 48.3 (2 x N*C*H$_2$), 116.6 (*C*-6), 125.3 (*C*-10), 136.2 (*C*-7), 142.2 (*C*-5), 147.4 (*C*-8), 173.9, 174.2 [*C*-2(S), *C*-4 (S)].
14[c]	116.7 (*C*-6), 117.2, 120.6, 114.2, 125.4, 127.4, 130.1, 137.6, 138.1, 143.4 (*C*-Ph), 146 (*C*-8), 163.4, 164.6 [*C*-2 (S), *C*-4 (S)].
15[c]	25.6, (*C*, hexyl), 32.8 (*C*-hexyl), 60.5, 61.6 (*C*-hexyl), 116.7 (*C*-6), 123.5 (*C*-10), 135.6 (*C*-7), 137.7 (*C*-9), 141.0 (*C*-5), 147.0 (*C*-8), 179.6, 180.8 [*C*-2(S), *C*-4(S)].
18a[b]	53.3 (NH*C*H$_2$), 55.9 (O*C*H$_3$), 113.7 (CH=*C*H$_2$), 118.3 (*C*-4), 128.2 (*C*-6), 136.2 (*C*-3), 137.7 (*C*-1), 138.1 (*C*H=CH$_2$), 141.6 (*C*-5), 148.2 (*C*-2), 208.3 (*C*=S).
18b[c]	16.7 (OC.*CH$_3$*), 53.6 (NH*C*H$_2$), 64.2 (O*CH$_2$*), 113.5 (CH=*C*H$_2$), 118.4 (*C*-4), 128.5 (*C*-6), 136.2 (*C*-3), 136.8 (*C*-1), 138.6 (*C*H=CH$_2$), 141.4 (*C*-5), 145.8 (*C*-2), 211.3 (*C*=S).
22a[b]	36.3 [N(*C*H$_3$)$_2$], 115.4 (*C*-7), 118.4 (*C*-5), 136.8 (*C*-4), 139.8 (*C*-9), 141.9 (*C*-6), 147.6 (*C*-8).
22b[b]	13.1 (NC.*CH$_3$*), 36.5 (N*CH$_3$*), 39.2 (N*C*H$_2$), 115.2 (*C*-7), 118.4 (*C*-5), 136.7 (*C*-4), 139.4 (*C*-9), 142.2 (*C*-6), 147.5 (*C*-8).
22c[b]	37.3 (N*CH$_3$*), 115.4 (*C*-7), 118.4 (*C*-5), 124.2, 125.5, 129.2, 143.6 (*C*-Ph), 136.9 (*C*-4), 139.4 (*C*-9), 142.1 (*C*-6), 147.5 (*C*-8).
22d[b]	26.1 (*C*-hexyl), 32.4 (*C*-hexyl), 37.6 (N*CH$_3$*), 51.3 (*C*-hexyl), 115.1 (*C*-7), 118.3 (*C*-5), 136.9 (*C*-4), 139.4 (*C*-9), 140.8 (*C*-6), 146.4 (*C*-8).
24[b]	117.2, 117.9 (*C*-5, *C*-7), 125.3 (*C*-4\`), 135.3 (*C*-4), 139.7 (*C*-6), 141.8 (*C*-5\`), 142.3 (*C*-9), 149.6 (*C*-8), 205.6 (d, $^{1}J_{CP}$ = 57.8 Hz, *C*-3\`).

(a) ^{13}C NMR spectra of all listed compounds showed signals at δ ≈29, 31 [2 x C(*C*H$_3$)$_3$] and 32, 34 (*C*Me$_3$), (b) the solvent (NMR) is $CDCl_3$, (c) the solvent (NMR) is d_6-DMSO.

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