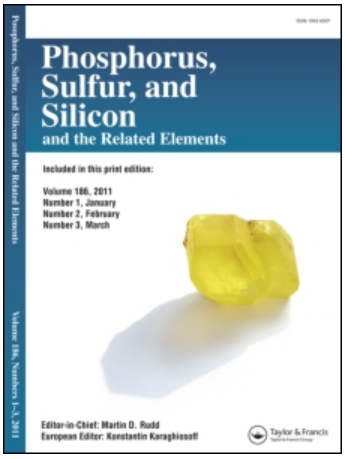

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THIOPHENE-CONTAINING MACROCYCLES DERIVED FROM [2 + 2] CYCLIZATIONS

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Tetra ester macrocycles **7**, **8**, carboxamide macrocycles **9a**, **b** and Schiff base macrocycles **10**, **12a**, **b** containing two or four thiophene moieties are obtained from 2,5-thiophene dicarbonylchloride or various aldehydes and esters derived from thiophene.

Key words: Macrocycle; thiophene.

INTRODUCTION

During the past two decades, numerous publications described the synthesis of various macrocycles containing thiophene subcyclic units.[1] However, few of these reports dealt with compounds derived from the self-assembling of four units: Fenton *et al.* proposed the preparation of Schiff-base macrocycles from thiophene-2,5-dicarboxaldehyde and various primary diamines[2] while Potts *et al.* synthesized macrocyclic tetraesters containing four thiophene subcyclic units.[3]

We herein report the preparation of seven new macrocycles containing thiophene, obtained by four different types of [2 + 2] cyclizations, none of them requiring template reaction or high dilution techniques. In addition, the synthesis of three new thiophene containing precursors suitable for these reactions is described.

RESULTS AND DISCUSSION

Synthesis of precursors. 2,5-thiophene dicarboxylic acid **1** is a well-known precursor for the preparation of numerous difunctional compounds containing the thiophene moieties.[4] For example, 2,5-thiophene dicarbonyl chloride **2**[4,5] obtained by reaction with $SOCl_2$, was already used for the formation of macrocyclic polyetherdiester derivatives.[1c] We also tried to use **2** as starting reagent for macrocycles syntheses,

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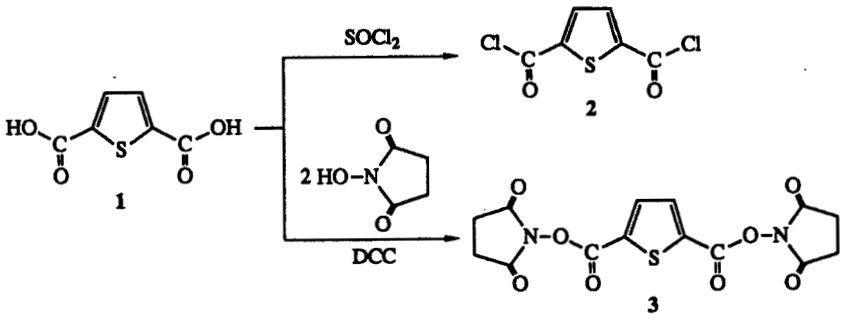
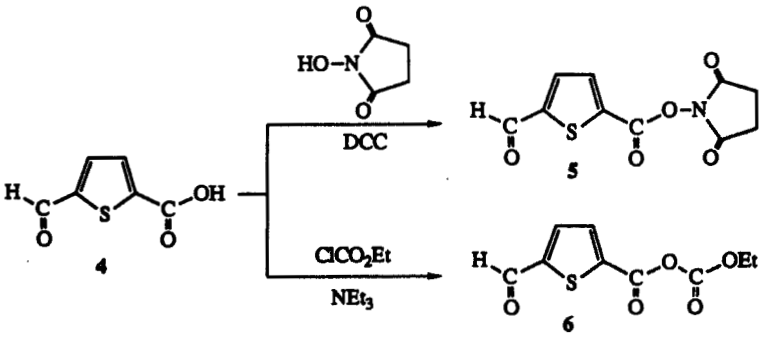
as well as the corresponding methoxy ester.[6] In fact, the later compound was unreactive toward $H_2N(CH_2)_8NH_2$ in refluxing methanol for 10 days, thus we decided to synthesize new activated esters **3**, **5** and **6**.

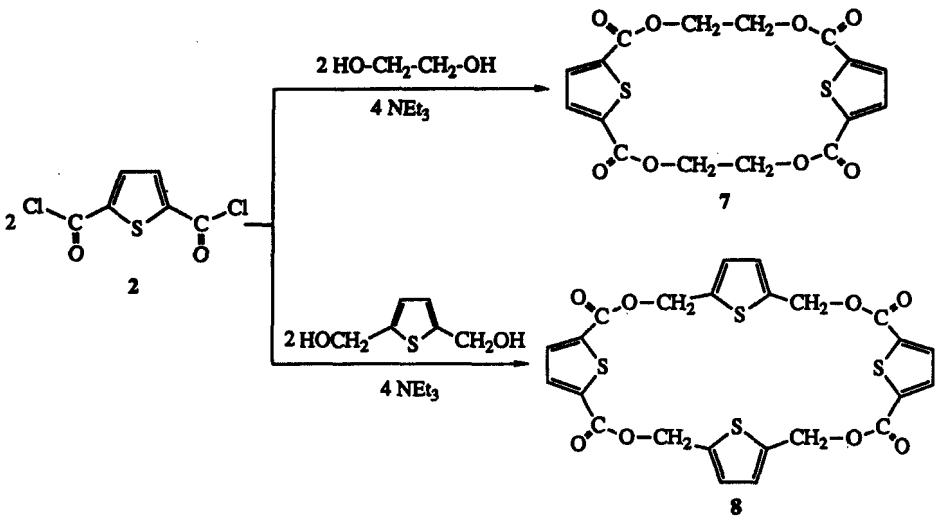
Treatment of two equivalents of N,hydroxysuccinimide with 2,5-thiophene dicarboxylic acid **1** in suspension in dichloromethane, in the presence of two equivalents of 1,3 dicyclohexylcarbodiimide led to the ester **3** after two weeks of stirring.



An analogous reaction applied to a solution of monocarboxylic acid **4** gave monoester **5** after three days. In both cases, the reaction is monitored by ^1H NMR and IR. Another activated ester **6**, was obtained by reacting the same monocarboxylic acid with ethyl chloroformate in the presence of triethylamine.

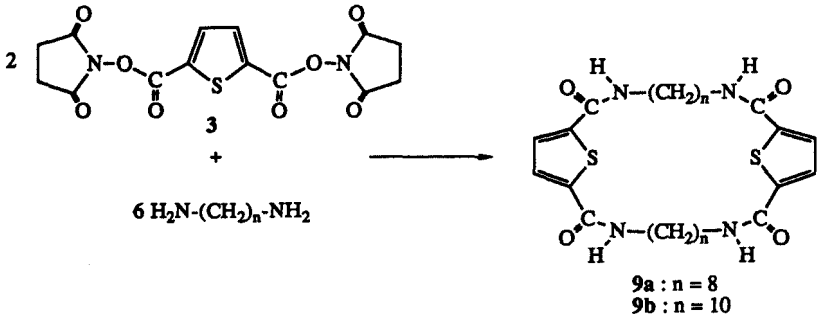


Synthesis of tetraester macrocycles. Reaction of 2,5-dicarbonylchloride **2** with 1,2-ethane diol and triethylamine for three days in chloroform afforded macrocycle **7** in 35% yield after work-up. The structural formulae depicted in the following scheme for macrocycle **7** was deduced from ^1H NMR and IR data, elemental analyses and mass spectrometry. The formation of carboxylic ester functions was shown by the disappearance of the OH signal on ^1H NMR spectra and the disappearance of the $\nu_{CO(Cl)}$ band at 1750 cm^{-1} on behalf of a $\nu_{CO(O)}$ band at 1716 cm^{-1} on IR spectra. The [2 + 2] cyclization was confirmed by mass spectrometry (chemical ionization by NH_3), which exhibited a peak at m/e = 414, corresponding to $[7 + NH_4]^+$.

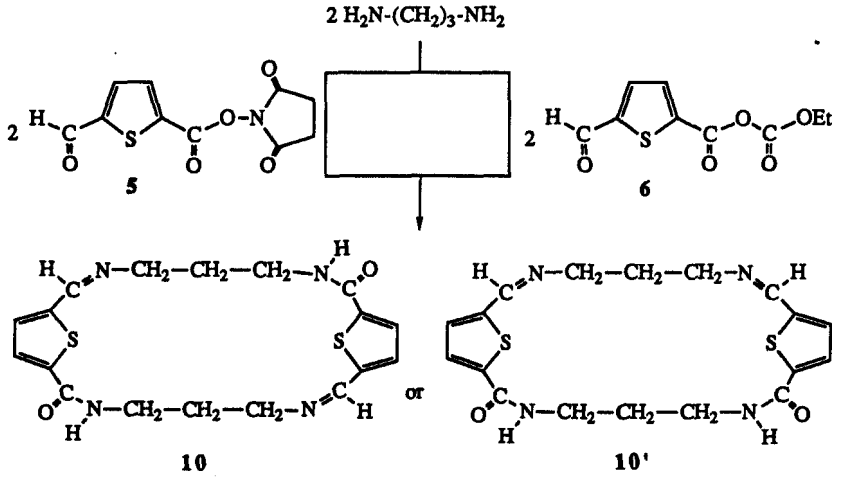


An analogous reaction carried out with 2,5-dihydroxymethylthiophene[7] led to macrocycle **8** incorporating four thiophene subunits in the cycle. ^{1}H NMR spectra exhibited two singlets for thiophene at δ 6.99 and 7.83 ppm, attributed to the $\underline{H}C{\equiv}C{-}CH_2$ and $\underline{H}{-}C{\equiv}C{-}CO_2$ protons, respectively. This attribution was based on the values obtained for the thiophenic protons in 2,5-dihydroxymethyl thiophene (δ 6.74 ppm) and in macrocycle **7** (δ 7.76 ppm).

Synthesis of carboxamide macrocycles. Activated diester **3** reacted for four days with 3 equiv. of 1,8-diaminooctane or 1,10-diaminodecane to afford tetracarboxamide macrocycles **9a** and **9b**, respectively. In this case also we observed a [2 + 2] cyclization leading to 30- and 34-membered rings, as indicated by mass spectrometry.

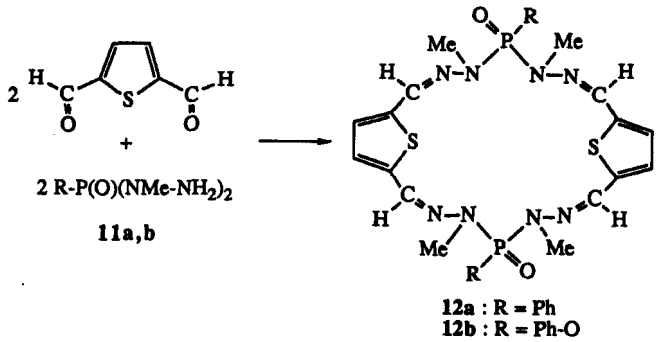


Of interest was the reaction of monoesters **5** or **6** when reacted with 1,3-diamino propane. According to the preceeding reactions, we expected a [2 + 2] cyclization, which could lead to two isomers, namely **10** and **10'**. Mass spectrometry confirmed



the [2 + 2] cyclization and ^{1}H NMR showed unambiguously the formation of only one isomer, **10**: indeed, irradiation of CH_2N signals induced the appearance of only one singlet at δ = 1.93 ppm corresponding to C—CH_2—C. This demonstrated the equivalence of both C—CH_2—C groups as depicted in structure **10**, which possesses a center of symmetry, whereas structure **10'**, which possesses a plane of symmetry would lead to two singlets (one for each C—CH_2—C group) under the same irradiation conditions. Furthermore, ^{13}C NMR spectra show the presence of nine types of carbon atoms, as expected for compound **10**, while compound **10'** would present ten signals.

Synthesis of Schiff base macrocycles. As we have a longstanding interest in the synthesis of phosphorus Schiff base macrocycles[8] obtained from phosphodihydrazides[9] and dialdehydes, we decided to react thiophene 2,5-dicarboxaldehyde[10] with phosphodihydrazides **11a, b**. Cyclization induced the expected upfield shift on ^{31}P NMR spectra. ^{13}C NMR and IR spectra showed the formation of C=N bonds and mass spectrometry confirmed the [2 + 2] cyclization, leading to **12a, b**.



CONCLUSION

The use of 2,5-dicarbonyl chloride **2** and esters **3, 5, 6** allowed the preparation of new 18-, 20-, 24-, 30- and 34-membered rings possessing two thiophene subcyclic

units. Similarly, the addition of phosphodihydrazides **11a, b** to thiophene 2,5-dicarboxaldehyde led to phosphorus macrocycles possessing also two thiophene moieties. All these compounds resulted from [2 + 2] cyclocondensation reactions. Studies of the complexation properties of these new species are underway.

EXPERIMENTAL

Synthesis of diester **3**. A suspension of 2,5-thiophene dicarboxylic acid **1** (1.72 g, 10 mmol) in dichloromethane (50 ml), 1,3-dicyclohexylcarbodiimide (4.13 g, 20 mmol) and N-hydroxysuccinimide (2.30 g, 20 mmol) is left for two weeks upon stirring. The mixture is then filtered and the resulting solution is evaporated to dryness. The powder thus obtained is recrystallized twice in boiling acetonitrile.

3: white powder. 80% yield. m.p. 221°C. ^{1}H NMR ($CDCl_3$): δ = 2.89 (s, 8H, CH_2); 8.25 (s, 2H, CH) ppm. IR(KBr): 1779 and 1736 ($\nu_{C=O}$) cm^{-1}. Anal. Calcd. for $C_{14}H_{10}N_2O_8S$: C, 46.68; H, 3.11; N, 8.01. Found: C, 45.90; H, 2.75; N, 7.64.

Synthesis of monoester **5**. A solution of 5-formylthiophene, 2-carboxylic acid **4** (1.56 g, 10 mmol), 1,3 dicyclohexylcarbodiimide (2.06 g, 10 mmol) and N-hydroxysuccinimide (1.15 g, 10 mmol) in dichloromethane (30 ml) is left for three days upon stirring. The precipitate of dicyclohexylurea is filtered off and the resulting solution, evaporated to dryness, affords a powder which is crystallized in acetonitrile.

5: white powder. 76% yield. ^{1}H NMR($CDCl_3$): δ = 2.88 (s, 4H, CH_2); 7.79 (d, $^3J_{HH}$ = 3.3 Hz, 1H, H—C=C—CHO); 8.02 (d, $^3J_{HH}$ = 3.3 Hz, 1H, H—C=C—CO_2); 10.0 (s, 1H, CHO) ppm. IR (KBr): 1779 and 1735 ($\nu_{C=O}$); 1678 ($\nu_{C=O}$ (CHO)) cm^{-1}.

Synthesis of monoester **6**. A solution of triethylamine (1.51 g, 15 mmol) in ether (30 ml) is added dropwise to a suspension of 5-formyl thiophene, 2-carboxylic acid **4** (1.56 g, 10 mmol) in ether (20 ml) and ethyl chloroformate (1.62 g, 15 mmol). The resulting mixture is stirred for 24 h. Triethylamine hydrochloride is filtered off and the solution is evaporated to dryness. **6** is obtained as an oil.

6: ^{1}H NMR ($CDCl_3$): δ = 1.37 (t, $^3J_{HH}$ = 7.2 Hz, 3H, CH_3); 4.36 (q, $^3J_{HH}$ = 7.2 Hz, 2H, CH_2); 7.72 (d, $^3J_{HH}$ = 3 Hz, 1H, H—C=C); 7.78 (d, $^3J_{HH}$ = 3 Hz, 1H, H—C=C); 9.94 (s, 1H, CHO) ppm. IR (KBr): 1803 ($\nu_{C=O}$[O—C=O(O)]); 1702 ($\nu_{C=O}$[C—C=O(O)]); 1667 ($\nu_{C=O}$[CHO]) cm^{-1}.

Synthesis of macrocycle **7**. A solution of ethylene glycol (0.62 g, 10 mmol) and triethylamine (3.03 g, 30 mmol) in chloroform (30 ml) and a solution of 2,5-thiophene dicarbonyl chloride **2** (2.09 g, 10 mmol) in chloroform (30 ml) are simultaneously added dropwise to 10 ml of chloroform. The resulting mixture is stirred for three days. Triethyl amine hydrochloride is filtered off and the solution is evaporated to dryness. The resulting powder is washed with hot water.

7: white powder. 35% yield. m.p. 140°C. ^{1}H NMR (DMSO-D_6): δ = 4.53 (s, 8H, CH_2); 7.76 (s, 4H, CH) ppm. IR (KBr): 1716 ($\nu_{C=O}$) cm^{-1}. MS: $[M + NH_4]^+$ = 414. Anal. Calcd. for $C_{16}H_{12}O_8S_2$: C, 48.47; H, 3.05. Found: C, 48.01; H, 2.96.

Synthesis of macrocyle **8**. A solution of 2,5-dihydroxymethylthiophene (1.44 g, 10 mmol) and triethylamine (3.03 g, 30 mmol) in chloroform (30 ml) and a solution of 2,5-thiophene dicarbonyl chloride **2** (2.09 g, 10 mmol) in chloroform (30 ml) are simultaneously added dropwise to chloform (10 ml). The resulting mixture is stirred for four days, filtered, then evaporated to dryness. The powder thus obtained is purified by column chromatography on silicagel, with methanol/chloroform (1/9) as eluent.

8: white powder. 41% yield. m.p. 252°C. ^{1}H NMR ($CDCl_3$): δ = 5.43 (s, 8H, CH_2); 6.99 (s, 4H, H—C=C—CH_2); 7.83 (s, 4H, H—C=C—C=O) ppm. IR (KBr): 1716 ($\nu_{C=O}$) cm^{-1}. MS: $[M + H]^+$ = 561 (12.3 %); $[M + NH_4]^+$ = 578 (100%). Anal. Calcd. for $C_{24}H_{16}O_8S_4$: C, 51.41; H, 2.87. Found: C, 51.20; H, 2.95.

Synthesis of macrocycles **9a, b**. A solution of diester **3** (3.66 g, 10 mmol) in dichloromethane (30 ml) and a solution of 1,8-diamino octane (4.33 g, 30 mmol) or 1,10-diamino decane (5.17 g, 30 mmol) in dichloromethane (30 ml) are simultaneously added dropwise to dichloromethane (10 ml). The resulting mixture is stirred for four days. The precipitate (salt) is filtered off and the solution evaporated to dryness.

9a: the resulting powder is washed with hot water, then in refluxing methanol.

9b: the solid obtained after evaporation to dryness is purified by column chromatography on silica gel with methanol/chloroform (1/9) as eluent.

9a: white powder. 28% yield. m.p. > 260°C. ^{1}H NMR (DMSO-D_6): δ = 1.18–1.81 (m, 24H, C—CH_2—C); 3.17 (m, 8H, CH_2NH); 7.67 (s, 4H, CH) ppm. IR (KBr): 3324 (ν_{NH}); 1627 ($\nu_{C=O}$) cm^{-1}. MS: $[M + H]^+$ = 561. Anal. Calcd. for $C_{28}H_{40}N_4O_4S_2$: C, 59.97; H, 7.19; N, 9.99. Found: C, 57.57; H, 7.60; N, 10.34.

9b: white powder. 33% yield. m.p. 169°C. ^{1}H NMR (DMSO-D_6): δ = 1.21–1.95 (m, 32H, C—CH_2—C); 3.42 (m, 8H, CH_2—N); 5.9 (br. s, 4H, NH); 7.61 (s, 4H, CH) ppm. IR (KBr): 3375 (ν_{NH}); 1636 ($\nu_{C=O}$) cm^{-1}. MS: $[M + H]^+$ = 617.

Synthesis of macrocycle **10**. From monoester **5**: a solution of monoester **5** (2.53 g, 10 mmol) in dichloromethane (30 ml) and a solution of 1,3-diaminopropane (1.48 g, 20 mmol) in dichloromethane (30 ml) are simultaneously added dropwise to dichloromethane (10 ml). The resulting mixture is stirred for four days, then evaporated to dryness. The solid thus obtained is purified by column chromatography on silica gel, with methanol/dichloromethane (1/9) as eluent.

From monoester **6**: a solution of monoester **6** (2.28 g, 10 mmol) in dichloromethane (30 ml) and a solution of 1,3-diaminopropane (0.74 g, 10 mmol) in dichloromethane (30 ml) are simultaneously added dropwise to dichloromethane (10 ml). The resulting mixture is stirred for 24 h, then evaporated to dryness and purified as above.

10: white powder. 39% yield. m.p. > 250°C. ^{1}H NMR ($CDCl_3$): δ = 1.93 (m, 4H, C—CH_2—C); 3.75 (m, 8H, CH_2—N); 7.26 (d, $^3J_{HH}$ = 3.8 Hz, 2H, H—C=C—C=N); 7.72 (s, 2H, NH); 7.76 (d, $^3J_{HH}$ = 3.8 Hz, 2H, H—C—C=O); 8.37 (t, $^4J_{HH}$ = 1.4 Hz, 2H, H—C=N) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$): δ = 29.2 (s, C—C—C); 41.9 (s, C—NH); 62.6 (s, C—N=C); 131.9 (s, C=C—C=O); 132.2 (s, C=C—C=N); 139.4 (s, C—C=N); 143.3 (s, C—C=O); 155.6 (s, C=N); 161.1 (s, C=O) ppm. IR(KBr): 1625 ($\nu_{C=O}$ and $\nu_{C=N}$) cm^{-1}. MS: $[M + H]^+$ = 389. Anal. Calcd. for $C_{18}H_{20}N_4O_2S_2$: C, 55.64; H, 5.19; N, 14.42. Found: C, 55.52; H, 5.34; N, 14.54.

Synthesis of macrocycles **12a, b**. A solution of phosphodihydrazide **11a** (2.14 g, 10 mmol) or **11b** (2.30 g, 10 mmol) in chloroform (30 ml) and a solution of 2,5-diformylthiophene (1.40 g, 10 mmol) in chloroform (30 ml) are simultaneously added dropwise to chloroform (10 ml). The resulting mixture is stirred for three days, then evaporated to dryness. Macrocycle **12a** or **12b** is purified by column chromatography on silicagel with methanol/chloroform (1/9) as eluent.

12a: white powder, 53% yield. m.p. 245°C. ^{31}P{^{1}H} NMR ($CDCl_3$): δ = 23.8 (s) ppm. ^{1}H NMR ($CDCl_3$): δ = 2.92 (d, $^3J_{HP}$ = 8.0 Hz, 12H, CH_3); 6.7 (s, 4H, H—C=C); 8.1-7.1 (m, 14H, HC=N, Arom.) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$): δ = 31.3 (d, $^2J_{CP}$ = 7.0 Hz, CH_3); 127.3 (s, C=C—S); 128.0 (d, $^1J_{CP}$ = 166 Hz, C—P); 128.9 (d, J_{CP} = 14 Hz, Arom.); 132.2 (s, Arom.); 133.7 (m, C=N and Arom.); 141.4 (s, C—S) ppm. IR (nujol): 1635 ($\nu_{C=N}$) cm^{-1}. MS: $[M + H]^+$ = 637. Anal. Calcd. for $C_{28}H_{30}N_8O_2P_2S_2$, 0.8 $CH_3CO_2CH_2CH_3$: C, 52.99; H, 5.19; N, 15.85. Found: C, 52.76; H, 4.98; N, 15.79.

12b: white powder. 64% yield. ^{31}P{^{1}H} NMR ($CDCl_3$): δ = 2.03 (s) ppm. ^{1}H NMR ($CDCl_3$): δ = 3.21 (d, $^3J_{HP}$ = 8.0 Hz, 12H, CH_3); 6.96 (s, 4H, H—C=C), 7.20 (m, 10H, Arom.); 7.56 (s, 4H, H—C=N) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$): δ = 32.0 (d, $^2J_{CP}$ = 10.7 Hz, CH_3); 121.3 (d, J_{CP} = 4.7 Hz, Arom.); 124.9 (s, Arom.); 127.7 (s, C=C—S); 129.6 (s, Arom.); 133.1 (d, $^3J_{CP}$ = 14.5 Hz, C=N); 141.1 (s, C—S); 150.9 (d, $^2J_{CP}$ = 7.4 Hz, C—O—P) ppm. IR ($CHCl_3$): 1644 ($\nu_{C=N}$); 1256 ($\nu_{P=O}$) cm^{-1}. MS: $[M + H]^+$ = 669.

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