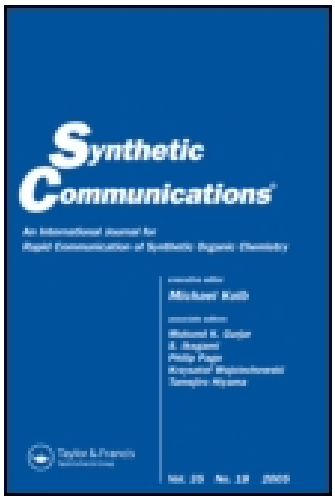

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AN UNUSUAL ADDITION AND RING-CLOSURE REACTION OF 1-(2-BROMOETHYL)-2,3-DIHYDRO- 3-PROPYL-1,3,2-BENZO-DIAZAPHOSPHORIN-4(1H)-ONE 2-OXIDE WITH CARBON DISULFIDE FOR A NEW AND CONVENIENT SYNTHESIS OF THE FUSED PHOSPHORUS HETEROCYCLIC COMPOUND

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AN UNUSUAL ADDITION AND RING-CLOSURE REACTION OF 1-(2-BROMOETHYL)-2,3-DIHYDRO-3-PROPYL-1,3,2-BENZO-DIAZAPHOSPHORIN-4(1*H*)-ONE 2-OXIDE WITH CARBON DISULFIDE FOR A NEW AND CONVENIENT SYNTHESIS OF THE FUSED PHOSPHORUS HETEROCYCLIC COMPOUND

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ABSTRACT

The reaction of 1-(2-bromoethyl)-2,3-dihydro-3-propyl-1,3,2-benzodiazaphosphorin-4(1*H*)-one 2-oxide with carbon disulfide takes an alternative pathway in the use of different bases. The sodium hydride mediated reaction leads to the formation of the tricyclic fused 1,2,3,4,4a,4b,5,6-octahydro-6-oxo-5-propyl-4-thia-3,4b,4a-thiazphosphaphenanthridine 4a-oxide

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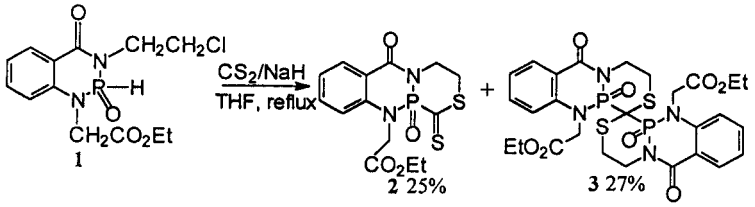
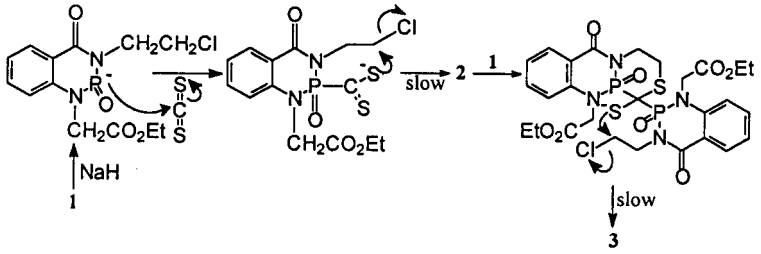
via addition of H-P bond across the double bond of carbon disulfide followed by intramolecular cyclization. In the presence of triethylamine, refluxing a mixture of 1-(2-bromoethyl)-2,3-dihydro-3-propyl-1,3,2-benzodiazaphosphorin-4(1*H*)-one 2-oxide with carbon disulfide in benzene takes an unusual course with formation in excellent yield of the first example of fused phosphorus heterocyclic 4-[1′-(*β*-bromoethyl)-4′-oxo-3′-propyl-1′,2′,3′,4′-tetrahydro-1,3,2-benzodiazaphosphorin-2′-sulfide]-1,2,3,4,4a,4b,5,6-octahydro-6-oxo-5-propyl-3,4b, 4a-thiazphosphaphenanthridine 4a,2′-dioxide, which was confirmed by spectroscopic methods, microanalyses and single crystal X-ray structure determination.

Organophosphorus compounds are ubiquitous in nature and they have broad applications in the fields of agriculture and medicine.[1–4] There has been a considerably growing interest in heterocyclic compounds due to their pharmaceutical importance and extensive application in organic synthesis, and the application of heterocycles is suggested to enhance the biological activity and/or offer other diverse properties.[5–7]Furthermore, a sizeable number of endogenous compounds that play a key role in regulation of various life processes consists of fused heterocycles. As part of ongoing studies in our laboratory to develop novel antitumor and antiviral agents with high activity and low toxicity, in previous work,[8] we have reported that 11-ethoxycarbonylmethyl-6-oxo-3,4,6,11-tetrahydro-1-thio-[1,4,3]thiazaphosphorino-[3,4-*b*][1,3,2]benzodiazaphosphorine 12-oxide **(2)** was designed incorporating the proximate thiono and phosphoryl groups into the benzo-annulated phosphdiamide heterocycle and synthesized by the addition and ring-closure reaction of 3-(2-chloroethyl)-2,3-dihydro-1-ethoxycarbonyl-methyl-1,3,2-benzodiazaphosphorin-4(1*H*)-one 2-oxide **(1)** with carbon disulfide in the presence of sodium hydride, as shown in Scheme 1, which also

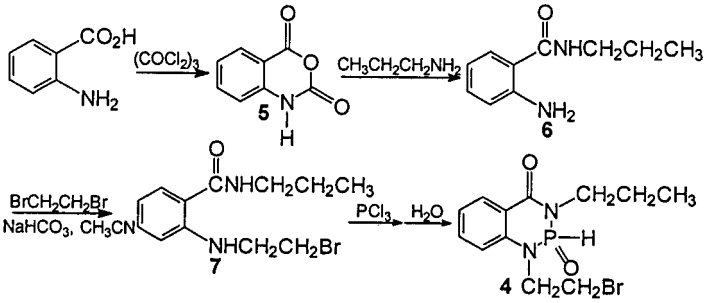


Scheme 1.

afforded 1,1-*bis*spiro{11-ethoxycarbonylmethyl-6-oxo-3,4,6,11-tetrahydro-[1,4,3]thiazaphosphorino[3,4-*b*][1,3,2]benzodiazaphosphorine 12-oxide} **(3)** in a one-pot procedure at the same time, and the mechanism was outlined in Scheme 2.



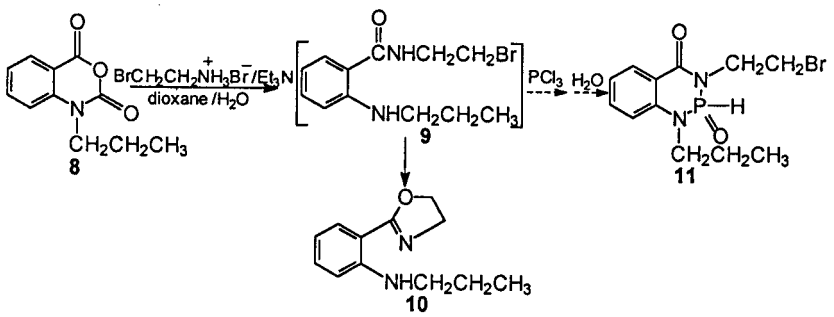
Scheme 2.



Scheme 3.

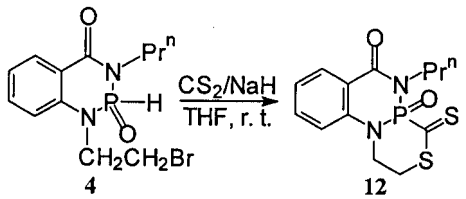
Herein, we wish to report our further investigation on the reaction of 1-(2-bromoethyl)-2,3-dihydro-3-propyl-1,3,2-benzodiazaphosphorin-4(1*H*)-one 2-oxide (**4**) with carbon disulfide. Preparation of **4** was readily accomplished in a four-step sequence outlined in Scheme 3 starting from the cheap and available material of *o*-aminobenzoic acid. In order to protect the amino group and activate the carbonyl group of *o*-aminobenzoic acid, we transformed it into the corresponding cyclic anhydride **5** by the action of triphosgene that is a safe and stable replacement for phosgene. Therefore, the reaction of the cyclic anhydride **5** with propyl amine was carried out under very mild conditions in good yields to provide *N*-propyl anthranilamide **6**. Then, the phosphorus reagent **4** could be obtained by the reaction of *N*-propyl anthranilamide **6** with 1,2-dibromoethane followed by treat-

ment of the intermediate anthranilamide derivative **7** with phosphorus trichloride. We have reported[9] that the reaction of the cyclic anhydride **8** using 2-bromoethylamine (generated from its hydrobromide salt) in place of propyl amine provided oxazoline **10** by cyclization of the expected intermediate anthranilamide derivative **9**. Therefore, as the analog of the phosphorus reagent **1** and **4**, 3-(2-bromoethyl)-2,3-dihydro-1-propyl-1,3,2-benzodiazaphosphorin-4(1*H*)-one 2-oxide (**11**) could not be obtained as shown in Scheme 4.

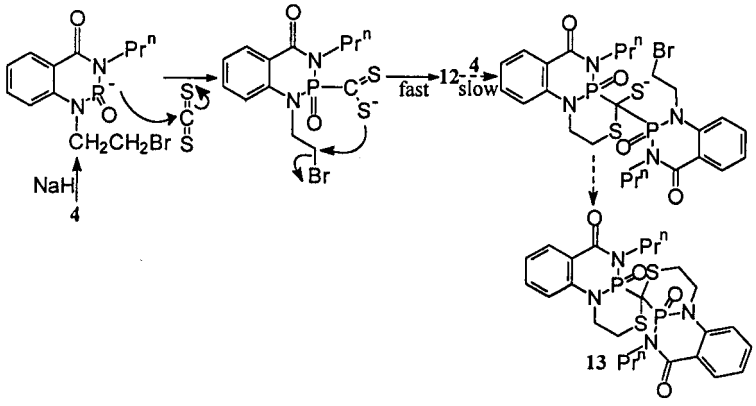


Scheme 4.

As expected, the tricyclic fused compound **12** was only obtained in 67% yield on the treatment of the phosphorus reagent **4** with carbon disulfide in the presence of sodium hydride at room temperature according to Scheme 5. ^{1}H NMR, ^{31}P NMR and elemental analysis data supported the structure of the compound **12**, 1,2,3,4,4a,4b,5,6-octahydro-6-oxo-5-propyl-4-thia-3,4b,4a-thiazphosphaphenanthridine 4a-oxide. The spiro fused heterocyclic compound **13** was not observed in the experiment. We believe the compound **12** is formed by the mechanism outlined in Scheme 6, which involved the nucleophilic addition of the phosphorus reagent **4** con-



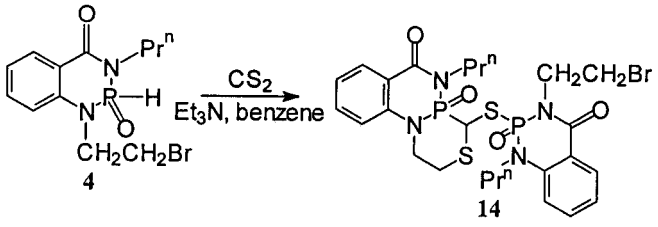
Scheme 5.



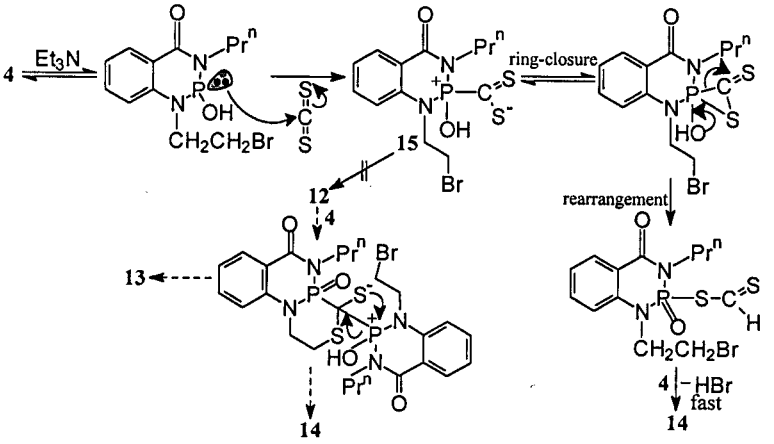
Scheme 6.

taining a P–H bond to the double bond of carbon disulfide followed by the fast intramolecular cyclization in a one-pot procedure.

However, in the presence of triethylamine, refluxing a mixture of **4** with carbon disulfide in benzene gave the first example of fused phosphorus heterocyclic compound **14** in 89% yield, as shown in Scheme 7, which takes an unusual course and provides a novel method for practical synthesis of 4-[1′-(β-bromoethyl)-4′-oxo-3′-propyl-1′,2′,3′,4′-tetrahydro-1,3,2-benzodiazaphosphorin-2′-sulfide]-1,2,3,4,4a,4b,5,6-octahydro-6-oxo-5-propyl-3,4b,4a-thiazphosphaphenanthridine 4a,2′-dioxide. Its structure was determined by X-ray crystallography and is shown in Figure 1.[10] Compounds **12** and **13** were not obtained as the products in this experiment. None of the proposed intermediates in this reaction involved the overall addition of two molecules of **4** to carbon disulfide and loss of the elements HBr were actually observed, but the pathway as outlined in Scheme 8 would appear plausible. It is suggested that the addition of one molecule of **4** to carbon disulfide gives rise to an ionic intermediate **15**, then occurs the ring-closure and rearrange-



Scheme 7.



Scheme 8.

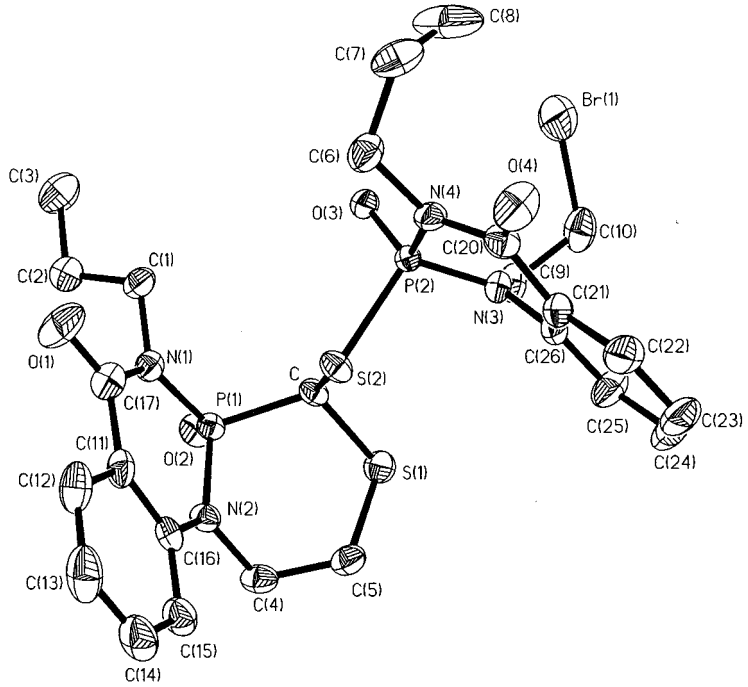


Figure 1. X-ray crystal structure of the fused phosphorus heterocyclic compound **14**.

ment followed by addition with a second molecule of **4** and the fast ring-closure reaction to form **14**.

In conclusion, this study has demonstrated that the unusual addition and ring-closure reaction of 1-(2-bromoethyl)-2,3-dihydro-3-propyl-1,3,2-benzodiazaphosphorin-4(1*H*)-one 2-oxide with carbon disulfide in the presence of triethylamine could be utilized as a template for a new and convenient synthesis of fused phosphorus heterocyclic compounds bearing a (O)P–S–C–P(O) bond structure with special consideration given to the biological activity,[7,11] in which the phosphoryl group is of fundamental significance in many of the most important molecules that control molecular replication, cell biochemistry and metabolic processes in all living species.[12] The synthesis of further examples of this ring system and study of their chemistry is in progress.

EXPERIMENTAL

Melting points were determined with a model YANACO MP-500 apparatus and are uncorrected. The ^{1}H and ^{31}P NMR spectra were recorded on a BRUKER AC-P200 instrument. Tetramethylsilane (TMS) was used as an internal standard for ^{1}H NMR, and 85% phosphoric acid (H_3PO_4) was used as an external standard for ^{31}P NMR spectroscopy. The nuclei that are deshielded relative to their respective standards are assigned a positive chemical shift. Coupling constants, *J*, are given in Hz. Elemental analyses were carried out on a Yana MT-3 instrument. Column chromatography was performed using silica gel H (10–40 μm, Haiyang Chemical Factory of Qingdao).

Preparation of 3,1-Benzoxazine-2,4(1*H*)-dione (5)

To a stirred solution of *o*-aminobenzoic acid (24.69 g, 0.18 mol) in 180 mL of acetonitrile at 50–55°C were added dropwise pyridine (28.48 g, 0.36 mol) and a solution of triphosgene (17.80 g, 0.06 mol) in 100 mL of dichloromethane at the same time. After completion of the addition, the temperature of the reaction mixture was maintained at 50–55°C for an additional 2 h. The solvent was removed under reduced pressure and the residue was added 200 mL of water. The precipitated solid obtained by filtration was washed with water followed by chilled dichloromethane, and dried in a vacuum dryer, yielding 27.72 g (94.4%) of **5**, m.p. 237–240°C. The intermediate **5** thus obtained is pure enough for further

manipulations but can be recrystallized from ethanol/water, m.p. 242°C dec. (Refs. [13,14], m.p. 243°C dec.).

Preparation of *N*-Propyl 2-Aminobenzic Amide (6)

To a stirred suspension of **5** (16.31 g, 0.10 mol) in 150 mL of dioxane, propylamine (8.85 g, 0.15 mol) was added dropwise at 40°C over a period of 30 min. Stirring was continued for an additional 1.5 h at 60–70°C, and then the solvent was removed under reduced pressure to yield 17.20 g (96.5%) of **6**, which was used without further purification. Analytical sample was recrystallized from ether, m.p. 101–102°C. ^{1}H NMR ($CDCl_3$, ppm; *J*, Hz): 0.96 (t, 3H, $NHCH_2CH_2C\mathbf{H}_3$, $^3J_{HH} = 7.4$); 1.60 (m, 2H, $NHCH_2C\mathbf{H}_2CH_3$); 3.33 (m, 2H, $NHC\mathbf{H}_2CH_2CH_3$); 5.42 (br, 2H, $N\mathbf{H}_2$); 6.14 (br, 1H, C(O)N**H**); 6.60–7.34 (m, 4H, $C_6\mathbf{H}_4$). Anal. calcd for $C_{10}H_{14}N_2O$: C, 67.39; H, 7.92; N, 15.72. Found: C, 67.50; H, 7.82; N, 15.69.

Preparation of *N*-Propyl 2-(2-Bromoethyl)aminobenzic Amide (7)

A mixture of **6** (8.91 g, 0.05 mol), 0.1 mol of 1,2-dibromoethane, sodium bicarbonate (8.4 g, 0.1 mol) and 50 mL of acetonitrile was refluxed for 6 h, till the spot of **6** disappeared on silica gel TLC developed with the solvent of ethyl acetate/petroleum ether (1 : 1). The liquid was collected by filtration followed by washing with ethyl acetate, and then the solvent from the filtrate was removed under reduced pressure and the residue was chromatographed on a column of silica gel using a mixture of ethyl acetate/light petroleum (b.p. 60–90°C) to elute the intermediate **7**, 62.8% yield, m.p. 51–53°C. ^{1}H NMR ($CDCl_3$, ppm; *J*, Hz): 0.95 (t, 3H, $NHCH_2CH_2C\mathbf{H}_3$, $^3J_{HH} = 7.4$); 1.61 (m, 2H, $NHCH_2C\mathbf{H}_2CH_3$); 3.35 (m, 2H, $NHC\mathbf{H}_2CH_2CH_3$); 3.58–3.92 (m, 4H, $NHC\mathbf{H}_2C\mathbf{H}_2Br$); 6.24 (br, 1H, C(O)N**H**); 6.62–7.38 (m, 4H, $C_6\mathbf{H}_4$); 7.65 (br, 1H, $N\mathbf{H}CH_2CH_2Br$). Anal. calcd for $C_{12}H_{17}BrN_2O$: C, 50.54; H, 6.01; N, 9.82. Found: C, 50.49; H, 5.86; N, 9.65.

Preparation of 1-(2-Bromoethyl)-2,3-dihydro-3-propyl-1,3,2-benzodiazaphosphorin-4(1*H*)-one 2-Oxide (4)

A mixture of 0.05 mol of **7** and 0.051 mol of phosphorus trichloride in 250 mL of dry benzene was refluxed for 5 h. Ethyl acetate was added to the reaction mixture and it was washed with cold dilute sodium bicarbonate followed by brine, dried over Na_2SO_4. The solvent collected by filtra-

tion followed by washing with ethyl acetate was removed under reduced pressure and the resulting oil was purified by flash chromatography [silica gel 60; ethyl acetate/light petroleum (b.p. 60–90°C), 1 : 1] to give 10.56 g (63.8%) of **4**. M.p. 82–84°C. ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 0.96 (t, 3H, $NCH_2CH_2C\mathbf{H}_3$, $^3J_{HH} = 7.4$ Hz), 1.77 (m, 2H, $NCH_2C\mathbf{H}_2CH_3$), 3.55–4.12 (m, 6H, $PNC\mathbf{H}_2CH_2CH_3 + PNC\mathbf{H}_2C\mathbf{H}_2Br$), 6.90–8.26 (m, 4H, $C_6\mathbf{H}_4$), 7.86 (d, 1H, P(O)**H**, $^1J_{PH} = 645.9$ Hz). ^{31}P NMR ($CDCl_3$, 80.96 MHz) δ: 5.95 (s). Anal. calcd for $C_{12}H_{16}BrN_2O_2P$: C, 43.52; H, 4.87; N, 8.46. Found: C, 43.68; H, 5.05; N, 8.66.

Preparation of 1,2,3,4,4a,4b,5,6-Octahydro-6-oxo-5-propyl-4-thia-3,4b,4a-thiazphosphaphenanthridine 4a-Oxide (12)

To a solution of the compound **4** (3.0 mmol) in 20 mL of anhydrous THF, 3.2 mmol of sodium hydride (80% in mineral oil, pentane washed) was added at −10°C. Stirring the mixture for 0.5 h produced a dense white precipitate. The mixture was treated with carbon disulfide (3.2 mmol) dropwise, stirred 5 h at room temperature, then poured into ice/water (50 mL) and extracted with ethyl acetate (3 × 40 mL). The combined organic extracts were dried (Na_2SO_4) and the solvent was removed under reduced pressure. The resulting residue was chromatographed on a column of silica gel using a mixture of 40% ethyl acetate/petroleum ether (60–90°C) to elute the product in 67% yield. M.p. 207°C (dec.). ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 0.95 (t, 3H, $NCH_2CH_2C\mathbf{H}_3$, $^3J_{HH} = 7.2$ Hz), 1.75 (m, 2H, $NCH_2C\mathbf{H}_2CH_3$), 2.68 (dm, 1H, $1/2 \times SC\mathbf{H}_2CH_2N$, $^2J_{HH} = 15.9$ Hz), 3.52–4.50 (m, 5H, $SCH_2C\mathbf{H}_2N + 1/2 \times SC\mathbf{H}_2CH_2N + NC\mathbf{H}_2CH_2CH_3$), 6.85–8.20 (m, 4H, $C_6\mathbf{H}_4$). ^{31}P NMR ($CDCl_3$, 80.96 MHz) δ: 8.95 (s). Anal. calcd for $C_{13}H_{15}N_2O_2PS_2$: C, 47.84; H, 4.63; N, 8.58. Found: C, 47.72; H, 4.45; N, 8.65.

Preparation of 4-[1′-(β-Bromoethyl)-4′-oxo-3′-propyl-1′,2′,3′,4′-tetrahydro-1,3,2-benzodiazaphosphorin-2′-sulfide]-1,2,3,4,4a,4b,5,6-octahydro-6-oxo-5-propyl-3,4b,4a-thiazphosphaphenanthridine 4a,2′-Dioxide (14)

A mixture of 3.0 mmol of **4**, 3.2 mmol of carbon disulfide and 6.0 mmol of dry triethylamine in 20 mL of anhydrous benzene was heated at reflux till the spot of **4** disappeared on silica gel TLC developed with the solvent of ethyl acetate/petroleum ether (2 : 1), then the produced triethylamine hydrobromide was filtered off. The solvent from the filtrate was removed under reduced pressure and the residue was chromatographed on a column of

silica gel using a mixture of 60% ethyl acetate/petroleum ether (60–90°C) to elute the product in 89% yield. The single crystals suitable X-ray analysis were obtained by recrystallization from mixture solvent of ethyl acetate and 9petroleum ether (90–120°C). M.p. 192°C (dec.). ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 0.96 (m, 6H, $2 \times NCH_2CH_2C\mathbf{H}_3$), 1.74 (m, 4H, $2 \times NCH_2C\mathbf{H}_2CH_3$), 2.47 (dm, 1H, $1/2 \times SC\mathbf{H}_2$ CH_2N, $^2J_{HH} \approx$ 13 Hz), 3.07 (tm, 1H, $1/2 \times SC\mathbf{H}_2CH_2N$, $^2J_{HH} \approx {}^3J_{HH} \approx 13$ Hz), 3.35–4.66 (m, 10H, $2 \times NC\mathbf{H}_2CH_2CH_3 + SCH_2C\mathbf{H}_2N + NC\mathbf{H}_2C\mathbf{H}_2Br$), 4.80 (dd, 1H, C**H**, $^2J_{PH} = 17.7$ Hz, $^3J_{PH} = 14.6$ Hz), 6.84–8.22 (m, 8H, $2 \times C_6\mathbf{H}_4$). ^{31}P NMR ($CDCl_3$, 80.96 MHz) δ: 10.17 (d), 24.45 (d), $^3J_{PP} = 31.6$ Hz. Anal. calcd for $C_{25}H_{31}BrN_4O_4P_2S_2$: C, 45.67; H, 4.75; N, 8.52. Found: C, 45.58; H, 4.72; N, 8.65.

ACKNOWLEDGMENTS

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REFERENCES

1. Fu, H.; Tu, G.Z.; Li, Z.L.; Zhao, Y.F. Synthesis **1998**, 855.
2. Huang, J.M.; Chen, R.Y. Heteroatom Chem. **2000**, *11*, 480.
3. Gorin, B.I.; Ferguson, C.G.; Thatcher, G.R. J. Tetrahedron Lett. **1997**, *38*, 2791.
4. Huang, J.M.; Chen, R.Y. Heteroatom Chem. **2001**, *12*, 97.
5. Meier, C. Angew. Chem. Int. Ed. Engl. **1996**, *35*, 70.
6. Zhou, J.; Qiu, Y.G.; Feng, K.S.; Chen, R.Y. Synthesis **1999**, 40, and references cited therein.
7. Zhou, J.; Chen, R.Y. J. Chem. Soc., Perkin Trans. 1 **1998**, 2917.
8. Chen, R.Y.; Bao, R. Synthesis **1990**, 137.
9. Chen, R.Y.; Bao, R. Synthesis **1989**, 618.
10. *Crystallographic data* for **14**: $C_{25}H_{31}BrN_4O_4P_2S_2$, $M = 657.51$ g mol^{-1}, monoclinic system, space group $P2(1)/c$, $a = 8.632(2)$, $b = 29.008(6)$, $c = 11.634(2)$ Å, $\beta = 90.35°$, $V = 2913.1(10)$ Å^3, $Z = 4$, $D_c = 1.499$ g cm^{-3}, $F(000) = 1352$, crystal dimensions of 0.30 mm × 0.40 mm × 0.40 mm. Data were measured at 293 K on Enraf-Nonius CAD4 diffractometer with graphite crystal monochromated Mo Kα radiation ($\lambda = 0.71073$ Å). The structure of the crystal was solved by the direct methods (SHELXS-86) and anisotropically refined by full-matrix

least-squares on F^2 to final $R = 0.0510$ and $R_w = 0.1423$ with $w = 1/[\sigma^2(F_0^2) + (0.1333P)^2 + 0.0000P]$ where $P = (F_0^2 + 2Fc^2)/3$ using 4991 independent reflections ($2.24^\circ \leq \theta \leq 24.97^\circ$). Corrections for *Lp* factors and empirical absorption type based on PSI-scan technique were applied to the intensity data. Most of the non-hydrogen atoms were located from an E-map. The others were determined with successive difference Fourier syntheses. The hydrogen atoms were added theoretically from a Fourier map and from expected geometry. All calculations were performed on a PDP 11/44 computer using SDP-PLUS program system.

11. Zhou, J.; Chen, R.Y.; Yang, X.F. Heteroatom Chem. **1998**, *9*, 369.
12. Sum, V.; Baird, C.A.; Kee, T.P.; Thornton-Pett, M. J. Chem. Soc., Perkin Trans. 1 **1994**, 3183.
13. Coppola, G.M. Synthesis **1980**, 505.
14. Venuti, M.C. Synthesis **1982**, 266.

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