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Journal of Organometallic Chemistry 692 (2007) 3685–3690
Journal of Organometallic Chemistry
www.elsevier.com/locate/jorganchem

Distinct chemoselectivity in the reaction of *N*-(thio)phosphoryl imines with diethylzinc

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Received 12 February 2007; received in revised form 23 March 2007; accepted 1 May 2007
Available online 6 May 2007

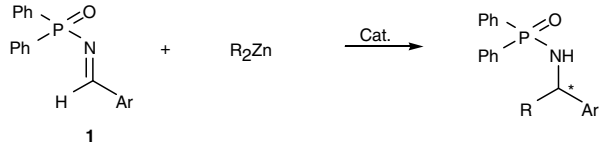
Abstract

This report describes the reaction of *N*-(thio)phosphoryl imines with diethylzinc under different conditions. An interesting and distinct chemoselectivity between hydrogen-addition and ethyl-addition to imine double bond is disclosed: in weakly polar solvent, e.g. toluene, *N*-(thio)phosphoryl imines were exclusively reduced in excellent yields via a β-H transfer from diethylzinc to imine double bond; in polar solvents like THF, the reduction product was competitively formed as a major product together with the minor product resulting from ethyl-addition to imine double bond; in sharp contrast, in the presence of strong coordinative additive *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA), the ethylation product was formed exclusively from the reaction of *N*-(thio)phosphoryl imine with diethylzinc. These results are discussed and explained in terms of the coordination interactions between the imine, solvent, and additive with diethylzinc.

Keywords: (Thio)phosphorylimine; (Thio)phosphinoylimine; Phosphonylimine; Diethylzinc; Reduction; Alkylation

1. Introduction

Asymmetric addition of imines is a convenient and practical method for the preparation of synthetic valuable nitrogen-containing compounds, such as chiral amines, 1,2-diamines, and α- or β-amino acids. Recently, significant progress has been witnessed in this area [1]. Imines with electron-withdrawing groups, e.g. acyl, sulfonyl, aryl and phosphoryl group, on the nitrogen have been intensively investigated due to their enhanced reactivity. For example, diphenylphosphinoylimines **1** have been successfully employed as the substrates in many asymmetric reactions [2], such as hydrogenation, alkylation, Mannich reaction, aza-Henry reaction and Strecker reaction. The asymmetric alkylation of **1** with diethylzinc could also be run smoothly in the presence of chiral copper catalysts [3] or chiral 1,2-aminoalcohols [4].



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We have noted that the *N*-phosphoryl group in phosphorylimines is an excellent imine auxiliary, because of its activation of the C=N bond for nucleophilic addition and its ease of deprotection from the final product under mild acidic conditions. Also, introducing different substituents to phosphorus center could easily modulate its electronic properties. Therefore, we followed this successful strategy to extend diphenylphosphinoylimines **1** to cheaper and readily available *O*,*O*-diethyl phosphorylimine **2** and its thio analogues **3**. Herein, we report an interesting and distinct chemoselectivity between hydrogen-addition and ethyl-addition to imine double bond in the reaction of *N*-(thio)phosphoryl imines and diethylzinc.

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doi:10.1016/j.jorganchem.2007.05.001

2. Results and discussion

It was surprising that the reaction of **2** or **3** with diethylzinc in toluene exclusively afforded the corresponding reduction product rather than the ethylation product. At the same time, the by-product ethylene was detected and confirmed in the reaction. This result revealed that modulating of the substituents on the phosphorus atom in *N*-phosphoryl imine might cause the total reversion of the chemoselectivity in this reaction. Thus, different types of *N*-(thio)phosphoryl imines were further synthesized, and their reactions with diethylzinc in toluene were extensively investigated with the results listed in Table 1.

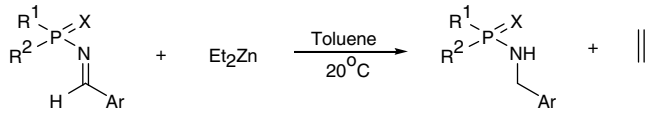
As shown in Table 1, the reduction products were readily obtained in high yields for those substrates containing alkoxy or aryloxy group on phosphorus atom (imines **2**, **3**, **4**, and **6**). However, no reaction occurred when diphenyl-(thio)phosphinoylimine **1**(**7**) and bis(diethylamino)phosphorylimine **5** were employed as the substrate, respectively. The variation of P=O double bond to P=S double bond did not exhibit any considerable influence on the reaction direction, except that better yield was observed for thiophosphorylimine **3a** versus its oxygen analogue **2**. The starting material, *O*,*O*-diethyl phosphorochloridothioate, for the preparation of thiophosphorylimine **3a** is available from the industrial source. Also, the existence of P=S double bond made the thiophosphorylimine or its related intermediate more stable against hydrolysis and heating. This property of P=S double bond resulted in the ease of purification and high yields in the preparation of thiophosphorylimine. Thus, we chose *N*-thiophosphorylimine **3** as the substrate to explore its reaction with diethylzinc. For all selected substrates **3**, the reduction products were obtained in high yields from the reactions with diethylzinc in nonpolar solvent toluene (entries 3–8, Table 1). The aryl group at the carbon atom of imine double bond in **3** did not show much influence on the reaction.

The influence of solvents on the reaction was also investigated employing imine **3a** as the substrate. The results (Table 2) showed that the polarity of solvent had a moderate influence on the reaction, although the conversion of the reaction was nearly 100% in all tested solvents. In non-polar solvent toluene, the reduction product **9a** exclusively formed. However, in polar solvent like THF, chloroform, and ether, the reduction reaction took place competitively with the ethylation reaction, although the reduction product **9a** was still obtained as the major with the minor ethylation product **12a**.

With these findings in hand, we supposed that the chemoselectivity might be adjusted between the hydrogen-reduction and ethylation of the imine double bond in the reaction of imine **3** with diethylzinc by introducing appropriate additives to the reaction system. Thus, the reaction of imine **3** and diethylzinc was surveyed in the presence of different types of additives. The results were listed in Table 3.

Introduction of coordinative additives proved to be a successful strategy to promote the selectivity (stereo- or chemo-) for the reaction of diphenylphosphinoylimine **1** with diethylzinc. For example, many chiral 1,2-aminoalcohols can catalyze or promote the ethylation reaction between diphenylphosphinoylimine **1** and diethylzinc [4]. Thus, the reaction was first carried out in the presence of chiral aminoalcohols **13** or **14**. Almost quantitative reduction product **9a** was isolated in cases of all specified molar ratios of diethylzinc to chiral aminoalcohol used (entries 1–3, Table 3). Beresford has reported that cinchonidine could promote the addition of diethylzinc to diph-

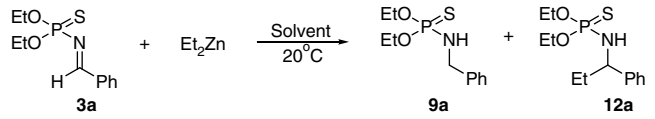
Table 1
Reactions of different phosphoryl imines with diethylzinc in toluene[a]



Entry	Imine	R^1	R^2	X	Ar	Time (h)	Yield (%) of products[b]
1	**1**	Ph	Ph	O	Ph	48	NR[c]
2	**2**	EtO	EtO	O	Ph	1	83 (**8**)
3	**3a**	EtO	EtO	S	Ph	1	90 (**9a**)
4	**3b**	EtO	EtO	S	4-$MeOC_6H_4$	0.5	>99 (**9b**)
5	**3c**	EtO	EtO	S	2-ClC_6H_4	2	90 (**9c**)
6	**3d**	EtO	EtO	S	4-BrC_6H_4	24	77 (**9d**)
7	**3e**	EtO	EtO	S	3-FC_6H_4	12	86 (**9e**)
8	**3f**	EtO	EtO	S	3-$F_3CC_6H_4$	12	79 (**9f**)
9	**4**	PhO	PhO	S	Ph	12	83 (**10**)
10	**5**	Et_2N	Et_2N	O	Ph	48	NR[b]
11	**6**	EtO	Ph	S	Ph	6	83 (**11**)
12	**7**	Ph	Ph	S	Ph	48	NR[b]

[a] All the reactions were carried out with a 1:4 molar ratio of imine substrate to diethylzinc.
[b] Isolated yield.
[c] NR means no reaction.

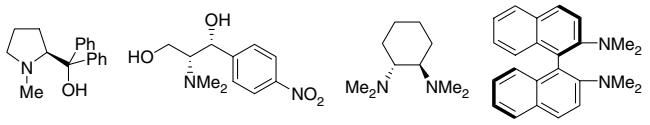
Table 2
Reaction of imine **3a** with diethylzinc in different solvents[a]



Solvent	Toluene	THF	CH_2Cl_2	$CHCl_3$	Et_2O	1,4-Dioxane
Conversion (%)[b]	>99	>99	>99	>99	>99	>99
9a:**12**[a]	100:0	93:7	88:12	72:28 (70:30)[c]	88:12	83:17

[a] All the reactions were carried out in 1 mmol scale with a 1:4 molar ratio of imine substrate to diethylzinc.
[b] Ratio determined by the ^{31}P NMR spectra of the reaction mixture.
[c] Data in the parenthesis determined by GC–MS analysis.

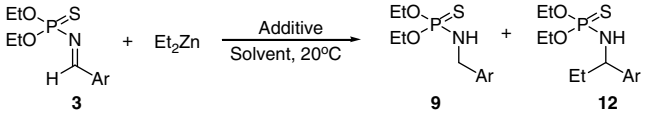
enylphosphinoylimine **1**. The corresponding ethylated products were obtained in good yields (56–77%) with moderate to excellent enantioselectivity (56–93%) [4a,4d]. However, under the similar conditions, the reaction of imine **3a** with diethylzinc exclusively gave the reduction product rather than the ethylation product **12** (entry 4). Further increase of the molar ratio of cinchonidine to diethylzinc to 3:3 made the reaction sluggish, and resulted in the formation of a mixture of ethylation and reduction product (entry 5). Contrarily, it was quite surprising that the use of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) as the additive led to the total reversion of the reaction orientation. The corresponding ethylation products were obtained as the dominant products (entries 6–11). The aryl group in the substrate imine **3** has a margin influence on this addition reaction. Imines substituted with electron-withdrawing group (entries 8 and 9) exhibited higher reactivity than those containing electron-donating group (entries 10 and 11). Based on this result, chiral analogue of TMEDA, cyclohexanediamine **15**, was synthesized and employed as the additive in this reaction. The ethylation product was attained exclusively with the enantioselectivity of 28% ee (entry 12). However, under the otherwise same conditions the non-vicinal aromatic diamine **16** could not promote the alkylation reaction. The reduction product was still preferentially formed (entry 13).



13 14 15 16

Thus far, the exact mechanism of the reaction between *N*-(thio)phosphoryl imine and diethylzinc remains unclear. In terms of the coordination interactions among the imine, diethylzinc, and additive, we herein try to propose a rational mechanism to interpret above results. Since imine **3** has both imine and ethoxy groups, and both N and O atoms are σ-electron donors, it could first coordinate with diethylzinc as a N,O-bidentate ligand. In non-polar solvent like toluene, this coordination binding firmly holds the imine and zinc species together, so that the β-hydrogen of ethyl

Table 3
Reaction of imine **3** with diethylzinc in the presence of different additives[a]



Entry	Additive	Ar	**3**:Et_2Zn:additive	Time (h)	Conversion/%[b] (Yield/%[c])	**9**:**12**[c]
1	**13**	Ph	1:4:1	24	>99	100:0
2	**13**	Ph	1:3:3	36	>99	98:2
3	**14**	Ph	1:3:3	48	>99	100:0
4	Cinchonidine	Ph	1:4:1	24	>99 (90)	100:0
5	Cinchonidine	Ph	1:3:3	36	49	38:62
6	TMEDA	Ph	1:1.6:1.6	48	>99 (82)	4:96 (**12a**)
7	TMEDA	Ph	1:1.6:1.6	48	>99 (86)	7:93 (**12a**)
8	TMEDA	2-ClC_6H_4	1:1.6:1.6	36	>99 (80)	0:100 (**12b**)
9	TMEDA	3-FC_6H_4	1:1.6:1.6	36	>99 (81)	0:100 (**12c**)
10	TMEDA	4-MeC_6H_4	1:1.6:1.6	72	92 (75)	2:98 (**12d**)
11	TMEDA	3-$MeOC_6H_4$	1:1.6:1.6	72	90 (72)	4:96 (**12e**)
12[d]	**15**	Ph	1:3:3	48	>99 (93)	0:100 (**12a**)
13	**16**	Ph	1:3:3	48	>99	91:9

[a] All the reactions were conducted in toluene except for entry 7 which was carried out in THF.
[b] Determined by ^{31}P NMR spectra.
[c] Isolated yield.
[d] The addition product was obtained with 28% ee. Determined by HPLC analysis on an OD-H column, hexane: 2-propanol = 90:10, flow rate 1.0 mL/min, retention time $t_1 = 6.97$ min (major), $t_2 = 33.10$ min (minor).

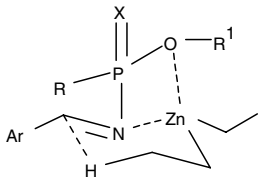


Fig. 1. Transition state for the β-hydrogen transfer process.

group could be easily transferred onto the imine carbon through a chair-like six-membered ring transition state, affording the exclusive hydrogen-reduction product together with the release of ethylene (Fig. 1). When the reaction is carried out in polar solvent, the coordination or solvation of the solvent with diethylzinc weakens the coordination interaction between diethylzinc and imine. Thus the ethylated product could be competitively formed (see Table 2). When TMEDA, which has proven to be a strong coordinating ligand to Zn^{2+} ion [5], is employed, then diethylzinc would preferentially coordinate with such an additive, and its interaction with the imine would be replaced or destroyed. The separation of the imine with diethylzinc would hinder the β-hydrogen transfer through a chair-like six-membered ring transition state (Fig. 1), but favors the nucleophilic attack of diethylzinc as an ethylating agent at the imine double bond. As the result, the ethylated product was formed dominantly in the presence of TMEDA (see Table 3). The fact that the ethylated product was obtained exclusively with an enantioselectivity of 28% ee in the presence of chiral TMEDA analogue **15** does provide a solid support for the coordination interaction between the additive and diethylzinc.

In conclusion, we demonstrate a quite distinct chemoselectivity in the reaction of *O*,*O*-diethyl thiophosphorylimine with diethylzinc. Under different conditions, the hydrogen reduction product or ethylation product could be selectively and exclusively obtained. The determining factor for this chemoselectivity presumably originates from the coordination interactions between the imine, solvent, and additive with diethylzinc. These findings provide some helpful insights for the reactions of imines with diethylzinc. Further investigation on the asymmetric ethylation of *O*,*O*-diethyl thiophosphorylimines with diethylzinc under the promotion of strongly coordinative chiral additives is ongoing in our laboratory.

3. Experimental

3.1. General methods

^1H and ^{31}P NMR spectra were recorded in $CDCl_3$ on a Varian 400 instrumental using TMS as an internal standard for ^1H NMR and 85% H_3PO_4 as an external standard for ^{31}P NMR. Enantiomeric excesses were determined on a HP-1100 instrument (OD-H column; mobile phase: hexane/*i*-PrOH). Elemental analyses were conducted on a Yanaco CHN Corder MT-3 automatic analyzer. Melting points were determined on a T-4 melting point apparatus. All temperatures and pressures were uncorrected. All of the solvent was dried according to the standard method and used after fresh distillation. *N*-(Thio)phosphoryl imines were prepared according to the literature method [6].

3.2. Reaction of N-(thio)phosphoryl imines with diethylzinc (general procedure)

To a solution of *N*-(thio)phosphoryl imine (1 mmol) in toluene (3 mL) was added diethylzinc (4 mL, 1 M solution in *n*-hexane) under an argon atmosphere. The resulting mixture was then stirred at 20 °C until the disappearance of *N*-(thio)phosphoryl imine (monitored by ^{31}P NMR). The reaction was quenched with the addition of saturated aqueous ammonium chloride and stirred for 0.5 h. After phase separation, the aqueous layer was extracted with ethyl acetate (3×5 mL). The combined organic phase was dried over anhydrous sodium sulfate. After removal of solvent the crude product was purified by column chromatography on silica gel (200–300 meshes, gradient eluted with petroleum ether and ethyl acetate).

For **8**: Colourless oil, 83% yield, ^{31}P NMR (δ, $CDCl_3$): 9.58; ^1H NMR (δ, $CDCl_3$): 1.31 (t, 6H, $J_{H-H} = 7.2$ Hz, $2CH_3$), 2.98 (br., 1H, NH), 3.99–4.11 (m, 6H, $3CH_2$), 7.24–7.36 (m, 5H arom). Anal. Calc. for $C_{11}H_{18}NO_3P$: C, 54.31; H, 7.46; N, 5.76. Found: C, 54.19; H, 7.38; N, 5.62%.

For **9a**: Pale yellow oil, 90% yield, ^{31}P NMR (δ, $CDCl_3$): 72.20; ^1H NMR (δ, $CDCl_3$): 1.30 (t, 6H, $J_{H-H} = 7.2$ Hz, $2CH_3$), 3.31 (br., 1H, NH), 3.96–4.14 (m, 6H, $3CH_2$), 7.25–7.35 (m, 5H arom). Anal. Calc. for $C_{11}H_{18}NO_2PS$: C, 50.95; H, 7.00; N, 5.40. Found: C, 50.93; H, 6.89; N, 5.34%.

For **9b**: Pale yellow oil, >99% yield, ^{31}P NMR (δ, $CDCl_3$): 72.35; ^1H NMR (δ, $CDCl_3$): 1.19 (t, 6H, $J_{H-H} = 7.2$ Hz, $2CH_3$), 3.63 (br., 1H, NH), 3.75 (s, 3H, OCH_3), 3.79–3.85 (m, 2H, CH_2), 3.93–4.02 (m, 4H, CH_2), 6.77–6.84 (m, 2H arom), 7.15–7.20 (m, 2H arom). Anal. Calc. for $C_{12}H_{20}NO_3PS$: C, 49.81; H, 6.97; N, 4.84. Found: C, 49.67; H, 6.86; N, 4.79%.

For **9c**: Pale yellow oil, 90% yield, ^{31}P NMR (δ, $CDCl_3$): 72.39; ^1H NMR (δ, $CDCl_3$): 1.24 (t, 3H, $J_{H-H} = 7.2$ Hz, CH_3), 1.25 (t, 3H, $J_{H-H} = 7.2$ Hz, CH_3), 3.53 (br., 1H, NH), 3.90–3.95 (m, 2H, CH_2), 4.01–4.07 (m, 2H, CH_2), 4.18–4.22 (m, 2H, CH_2), 7.20–7.25 (m, 2H arom), 7.32–7.34 (m, 1H arom), 7.40–7.42 (m, 1H arom). Anal. Calc. for $C_{11}H_{17}ClNO_2PS$: C, 44.97; H, 5.83; N, 4.77. Found: C, 44.85; H, 5.66; N, 4.38%.

For **9d**: Pale yellow oil, 77% yield, ^{31}P NMR (δ, $CDCl_3$): 72.40; ^1H NMR (δ, $CDCl_3$): 1.28 (t, 6H, $J_{H-H} = 7.2$ Hz, $2CH_3$), 3.33 (br., 1H, NH), 3.94–4.12 (m, 6H, $3CH_2$), 7.17–7.19 (d, 2H arom, $J_{H-H} = 8.0$ Hz), 7.42–7.44 (d, 2H arom, $J_{H-H} = 8.0$ Hz). Anal. Calc. for $C_{11}H_{17}BrNO_2PS$: C, 39.06; H, 5.07; N, 4.14. Found: C, 38.96; H, 5.05; N, 4.14%.

For **9e**: Pale yellow oil, 86% yield, ^{31}P NMR (δ, $CDCl_3$): 72.42; ^1H NMR (δ, $CDCl_3$): 1.30 (t, 6H, $J_{H-H} = 7.2$ Hz,

$2CH_3$), 3.29 (br., 1H, NH), 3.99–4.16 (m, 6H, $3CH_2$), 6.93–7.09 (m, 3H arom), 7.26–7.32 (m, 1H arom). Anal. Calc. for $C_{11}H_{17}FNO_2PS$: C, 47.64; H, 6.18; N, 5.05. Found: C, 47.53; H, 6.24; N, 4.96%.

For **9f**: Pale yellow oil, 79% yield, ^{31}P NMR (δ, $CDCl_3$): 72.42; ^1H NMR (δ, $CDCl_3$): 1.26 (t, 6H, $J_{H-H} = 7.2$ Hz, $2CH_3$), 3.52 (t, 1H, $J_{H-H} = 6.8$ Hz, NH), 3.93–4.09 (m, 4H, $2CH_2$) 4.19 (dd, 2H, $J_{H-H} = 7.2$ Hz, $J_{P-H} = 12.0$ Hz, CH_2), 7.42–7.44 (t, 1H arom, $J_{H-H} = 7.6$ Hz), 7.49–7.51 (d, 2H arom, $J_{H-H} = 7.6$ Hz), 7.58 (s, 1H arom). Anal. Calc. for $C_{12}H_{17}F_3NO_2PS$: C, 44.03; H, 5.24; N, 4.28. Found: C, 44.06; H, 4.81; N, 4.31%.

For **10**: Pale yellow oil, 80% yield, ^{31}P NMR (δ, $CDCl_3$): 63.96; ^1H NMR (δ, $CDCl_3$): 3.68 (br., 1H, NH), 4.11 (d, 2H, $J_{H-H} = 9.2$ Hz, CH_2), 7.16–7.36 (m, 15H arom). Anal. Calc. for $C_{19}H_{18}NO_2PS$: C, 64.21; H, 5.11; N, 3.94. Found: C, 64.03; H, 5.14; N, 3.74%.

For **11**: Pale yellow oil, 83% yield, ^{31}P NMR (δ, $CDCl_3$): 70.88; ^1H NMR (δ, $CDCl_3$): 1.34 (t, 3H, $J_{H-H} = 7.2$ Hz, CH_3), 3.39 (br., 1H, NH), 3.99–4.07 (m, 3H, CH_2, *H*-CH), 4.17–4.25 (m, 1H, H-C*H*–), 7.21–7.31 (m, 5H arom), 7.43–7.51 (m, 3H arom), 7.87–7.92 (m, 2H arom). Anal. Calc. for $C_{15}H_{18}NOPS$: C, 61.83; H, 6.23; N, 4.81. Found: C, 61.81; H, 6.28; N, 4.79%.

3.3. Reaction of *O,O*-diethyl thiophosphorylimine **3** with diethylzinc in the presence of additives (general procedure)

To a solution of additive (3.2–6.0 mmol, as depicted in Table 3) in solvent (10 mL) was added diethylzinc (3.2–8.0 mmol, as depicted in Table 3, 1 M solution in *n*-hexane) under an argon atmosphere and the resulting mixture was stirred for 15 min. Then *O*,*O*-diethyl thiophosphorylimine **3** (2 mmol) was added and the reaction mixture was stirred at 20 °C for 24–72 h. The reaction was quenched with the addition of saturated ammonium chloride solution. After phase separation, the aqueous layer was extracted with ethyl acetate (3×5 mL). The combined organic phase was dried over anhydrous sodium sulfate. After removal of solvent the crude product was used directly to determine the conversion and the ratio of the reducing product to the ethylation product through ^{31}P NMR analysis. In some cases, the crude product was further purified by column chromatography on silica gel (200–300 meshes, gradient eluted with petroleum ether and ethyl acetate).

For **12a**: Pale yellow oil, 83% yield, ^{31}P NMR (δ, $CDCl_3$): 70.89; ^1H NMR (δ, $CDCl_3$): 0.85 (t, 3H, $J_{H-H} = 7.2$ Hz, CH_3), 0.99 (t, 3H, $J_{H-H} = 7.2$ Hz, CH_3), 1.30 (t, 3H, $J_{H-H} = 7.2$ Hz, CH_3), 1.70–1.80 (m, 2H, CH_2), 3.35–3.54 (m, 2H, CH, NH), 3.83–4.16 (m, 4H, $2CH_2$), 7.23–7.33 (m, 5H arom). Anal. Calc. for $C_{13}H_{22}NO_2PS$: C, 54.33; H, 7.72; N, 4.87. Found: C, 54.69; H, 7.51; N, 4.86%.

For **12b**: White solid, m.p. 43–45 °C, 80% yield, ^{31}P NMR (δ, $CDCl_3$): 70.48; ^1H NMR (δ, $CDCl_3$): 0.91 (t, 3H, $J_{H-H} = 7.2$ Hz, CH_3), 0.96 (t, 3H, $J_{H-H} = 7.2$ Hz, CH_3), 1.31 (t, 3H, $J_{H-H} = 6.8$ Hz, CH_3), 1.69–1.79 (m, 2H, CH_2), 3.47–3.54 (m, 1H, one proton of CH_2), 3.59 (br. 1H, NH), 3.84–4.09 (m, 3H, CH_2 and one proton of CH_2), 4.61–4.63 (m, 1H, CH), 7.17–7.33 (m, 4H arom). Anal. Calc. for $C_{13}H_{21}ClNO_2PS$: C, 48.52; H, 6.58; N, 4.35. Found: C, 48.69; H, 6.45; N, 4.73%.

For **12c**: Pale yellow oil, 81% yield, ^{31}P NMR (δ, $CDCl_3$): 70.43; ^1H NMR (δ, $CDCl_3$): 0.87 (t, 3H, $J_{H-H} = 7.2$ Hz, CH_3), 1.03 (t, 3H, $J_{H-H} = 7.2$ Hz, CH_3), 1.30 (t, 3H, $J_{H-H} = 6.8$ Hz, CH_3), 1.68–1.80 (m, 2H, CH_2), 3.38 (br., 1H, NH), 3.53–3.63 (m, 1H, CH), 3.89–4.18 (m, 4H, $2CH_2$), 6.92–7.31 (m, 4H arom). Anal. Calc. for $C_{13}H_{21}FNO_2PS$: C, 51.13; H, 6.93; N, 4.59. Found: C, 51.32; H, 6.74; N, 4. 68%.

For **12d**: Pale yellow oil, 75% yield, ^{31}P NMR (δ, $CDCl_3$): 71.08; ^1H NMR (δ, $CDCl_3$): 0.85 (t, 3H, $J_{H-H} = 7.2$ Hz, CH_3), 1.01 (t, 3H, $J_{H-H} = 7.2$ Hz, CH_3), 1.30 (t, 3H, $J_{H-H} = 7.2$ Hz, CH_3), 1.66–1.78 (m, 2H, CH_2), 2.32 (s, 3H, CH_3), 3.48 (br., 1H, NH), 3.43–3.52 (m, 1H, CH), 3.91–4.22 (m, 4H, $2CH_2$), 7.32 (d, 2H arom, $J_{H-H} = 8.0$ Hz), 7.96 (d, 2H arom, $J_{H-H} = 8.0$ Hz). Anal. Calc. for $C_{14}H_{24}NO_2PS$: C, 55.79; H, 8.03; N, 4.65. Found: C, 55.58; H, 7.87; N, 4.81%.

For **12e**: Pale yellow oil, 72% yield, ^{31}P NMR (δ, $CDCl_3$): 71.11; ^1H NMR (δ, $CDCl_3$): 0.86 (t, 3H, $J_{H-H} = 7.2$ Hz, CH_3), 0.99 (t, 3H, $J_{H-H} = 7.2$ Hz, CH_3), 1.29 (t, 3H, $J_{H-H} = 6.8$ Hz, CH_3), 1.69–1.78 (m, 2H, CH_2), 3.41 (br., 1H, NH), 3.45–3.61 (m, 1H, CH), 3.80 (s, 3H, OCH_3), 3.89–4.17 (m, 4H, $2CH_2$), 6.79–7.25 (m, 4H arom). Anal. Calc. for $C_{14}H_{24}NO_3PS$: C, 52.98; H, 7.62; N, 4.41. Found: C, 53.02; H, 7.43; N, 4.36%.

Acknowledgments

We are grateful to the National Natural Science Foundation of China (No. 20472033) and Key Science and Technology projects of Ministry of Education of China for generous financial support for our programs. We thank professor Zhengjie He for helpful discussion.

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