[Chem. Pharm. Bull. 22(3) 634—637 (1974)]

UDC 547.559.04.09 : 542.958.2

Phosphorus in Organic Synthesis. I. A New Method for the Preparation of Amides, Carbamates, Esters, and Carbonates by the Reaction of Alkylidenephosphoranes with Nitrosonium Ion[1]

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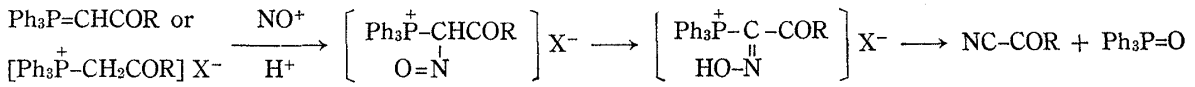
(Received June 30, 1973)

Some amides and carbamates, or some esters and carbonates were synthesized by the reaction of phosphoranes $Ph_3P{=}CHCOR$ (R=Me, Ph, OMe, OEt) with nitrosonium ion in the presence of some amines or alcohols.

Stable alkylidenephosphoranes[3,4] of the general structure $Ph_3P{=}CHCOR$ and phosphonuim salts[3,5] of the structure $[Ph_3P^+\text{-}CH_2COR]X^-$ are known to react with nitrosonium ion to produce acyl cyanides and triphenylphosphine oxide (Chart 1). These acyl cyanides are comparatively stable, but it was thought they might react readily with nucleophiles such as amines and alcohols.[6]



R=C_6H_5, $C_6H_5CH{=}CH$, *p*-Br-C_6H_4, *etc.* X=Cl, Br Ph=phenyl

Chart 1

In the same manner, methyl cyanoformate is obtained by the reaction of carbomethoxymethylenetriphenylphosphorane with nitrosonium ion,[4] and this ester may also be expected to react with nucleophiles.

With this in mind, we undertook the synthesis of some amides and carbamates from amino acid esters by the following typical procedure: Acetic acid was added in portions to a mixture of a phosphorane, sodium nitrite, and DL-phenylalanine ethyl ester in tetrahydrofuran

Table I. Preparation of Amides and Carbamates

$Ph_3P{=}CHCOR + PhCH_2\underset{\underset{NH_2}{|}}{C}HCOOEt \longrightarrow PhCH_2\underset{\underset{NHCOR}{|}}{C}HCOOEt$

R	Yield (%)
Me	49.4
OEt	41.2
OMe	38.1

Ph=phenyl

1) Presented in part at the 92nd Annual Meeting of Pharmaceutical Society of Japan, Osaka, April 5, 1972.
2) Location: *7-3-1, Hongo, Bunkyo-ku, Tokyo, 113, Japan.*
3) E. Zbiral and L. Fenz, *Monatsh. Chem.*, **96**, 1983 (1965).
4) C. Eguchi, K. Akiba, and N. Inamoto, *Bull. Chem. Soc. Japan*, **43**, 438 (1970).
5) M.I. Shevchuk, E.M. Volynskaya, and A.V. Dombrovskii, *Zh. Obsch. Khim.*, **41**, 1999 (1971).
6) J. Thesing and D. Witzel, *Angew. Chem.*, **68**, 425 (1956); D.S. Jones, G.W. Kenner, and R.C. Sheppard, *J. Chem. Soc.*, **1965**, 4393; E.J. Corey, N.W. Gilman, and B.E. Ganem, *J. Am. Chem. Soc.*, **90**, 5616 (1968); N.W. Gilman, *Chem. Comm.*, **1971**, 733; A. Holý and M. Souček, *Tetrahedron Letters*, **1971**, 185.

or dioxane. After the reaction was completed, the solvent was evaporated and the product was isolated from the neutral fraction of the residue. All products were identified through infrared and nuclear magnetic resonance spectra or by comparison with authentic samples. Results are shown in Table I.

The yields of amides and carbamates were depressed by the competitive deamination of the amines with nitrosonium ion. In fact, the gas chromatography of the crude reaction products revealed the presence of deamination products, *i.e.* ethyl 2-acetoxy-3-phenylpropionate, ethyl 3-acetoxy-2-phenylpropionate, ethyl 3-acetoxy-3-phenylpropionate, ethyl *cis*- and *trans*-cinnamates which were characterized in our previous papers.[7]

We also examined the preparation of esters and carbonates using alcohols as nucleophiles in this novel reaction. The experimental procedure used was analogous to that described above. Results are summarized in Table II.

Table II. Preparation of Esters and Carbonates

$Ph_3P{=}CHCOR + R'OH \longrightarrow RCOOR'$

R	R′	Yield (%)
Me	$PhCH_2$	88.9
Ph	*n*-Bu	90.0
Ph	iso-Pro	54.9
Ph	*tert*-Bu	8.4
OEt	$PhCH_2$	75.9
OMe	$PhCH_2$	64.3

Ph=phenyl

This procedure appears to be a good preparative method for esters of primary alcohols under very mild conditions. The yields of iso-propyl and *tert*-butyl esters are lower, possibly due to steric factors. Carbonates were also successfully prepared in good yields by this new method.

Experimental

Materials——All phosphoranes, acetylmethylenetriphenylphosphorane,[8] benzoylmethylenetriphenylphosphorane,[8] carbethoxymethylenetriphenylphosphorane,[9] and carbomethoxymethylenetriphenylphosphorane[9] were prepared from triphenylphosphine and organic halides according to the literature.

N-Acetyl-DL-phenylalanine Ethyl Ester——Acetylmethylenetriphenylphosphorane (1.59 g, 5 mmoles), DL-phenylalanine ethyl ester (1.93 g, 10 mmoles), and sodium nitrite (3.45 g, 5 mmoles) were dissolved in dry tetrahydrofuran (50 ml). Acetic acid (4 ml) was added dropwise to this mixture. The resulting solution was stirred at room temperature overnight. The solvent was evaporated and water (40 ml) was added to the residue, and the aqueous solution was extracted with three 30 ml portions of ethyl acetate. The organic layer was washed with sat. NaCl solution and dried over anhyd. $MgSO_4$. Evaporation of the solvent gave a yellow oil which was chromatographed in benzene on silica gel (200 g).

N-Acetyl-DL-phenylalanine ethyl ester was obtained as a colorless solid in 49.4% yield (0.58 g), mp 64.5—65° (Lit.[10] 69—70°). IR ν_{max}^{Nujol} cm^{-1}: 3270, 1735, 1641, 1020, 740. NMR (τ, $CDCl_3$): 8.87 (3H, t, $-CH_2-C\underline{H}_3$), 8.10 (3H, s, $COCH_3$), 6.98 (2H, q, $-C\underline{H}_2-CH_3$), 5.21 (1H, q, $-\underline{C}H-$), 2.83 (5H, s, C_6H_5-), 2.72 (1H, broad, >NH).

The infrared (IR) and nuclear magnetic resonance (NMR) spectra were identical with those of the authentic sample.[11]

7) S. Yamada, T. Kitagawa, and K. Achiwa, *Tetrahedron Letters*, **1967**, 3007; K. Koga, C.C. Wu, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **20**, 1272 (1972).
8) F. Ramirez and S. Dershowitz, *J. Org. Chem.*, **22**, 41 (1957).
9) O. Isler, H. Gutmann, M. Montavon, R. Ruegg, G. Ryser, and P. Zeller, *Helv. Chim. Acta*, **40**, 1242 (1957).
10) L. Berlinguet, *Can. J. Chem.*, **32**, 31 (1954).
11) Kindly donated by Dr. C.C. Wu.

N-Carbethoxy-DL-phenylalanine Ethyl Ester——Carbethoxymethylenetriphenylphosphorane (1.39 g, 4 mmoles), DL-phenylalanine ethyl ester (0.77 g, 4 mmoles), and sodium nitrite (0.30 g, 4.4 mmoles) were dissolved in dry tetrahydrofuran (40 ml). Acetic acid (6 ml) was added dropwise to the mixture. The resulting solution was stirred at room temperature overnight. The solvent was evaporated, and water (40 ml) was added to the residue, and the aqueous solution was extracted with three 30 ml portions of ethyl acetate. The organic layer was washed with sat. NaCl solution and dried over anhyd. $MgSO_4$. Evaporation of the solvent gave a brown oil which was chromatographed in benzene on silica gel (180 g). N-Carbethoxy-DL-phenylalanine ethyl ester was obtained as a colorless oil in 41.2% yield (0.35 g). IR ν_{max}^{film} cm^{-1}: 3280, 2930, 1720, 1520, 1200, 1028, 698. NMR (τ, $CDCl_3$): 8.80 (6H, t, two $-CH_3-C\underline{H}_3$), 6.94 (2H, d, $C_6H_5-C\underline{H}_2-$), 5.90 (4H, two quartets, two $-C\underline{H}_2CH_3$), 5.40 (1H, q, $-CH-$), 4.51 (1H, d, >NH), 2.83 (5H, s, C_6H_5-).

N-Carbomethoxy-DL-phenylalanine Ethyl Ester——Carbomethoxymethylenetriphenylphosphorane (3.01 g, 9 mmoles), DL-phenylalanine ethyl ester (1.74 g, 9 mmoles), and sodium nitrite (0.75 g, 10.8 mmoles) were dissolved in dioxane (100 ml). Acetic acid (25 ml) was added dropwise to the mixture. The resulting solution was stirred at room temperature overnight. The solvent was evaporated, and water (50 ml) was added to the residue, and the aqueous solution was extracted with three 50 ml portions of ethyl acetate. The organic layer was washed with sat. NaCl solution and dried over anhyd. $MgSO_4$. Evaporation of the solvent gave a yellow oil which was chromatographed in benzene on silica gel (200 g). M-Carbomethoxy-DL-phenylalanine ethyl ester was obtained as a colorless solid in 38.1% yield (0.86 g), mp 51.0—51.5° (Lit.[12] 52°). IR ν_{max}^{Nujol} cm^{-1}: 3300, 1715, 1520, 1225, 1050, 700. NMR (τ, $CDCl_3$): 8.85 (3H, t, $-CH_2-C\underline{H}_3$), 6.95 (2H, d, $C_6H_5-C\underline{H}_2-$), 6.45 (3H, s, $COOCH_3$), 5.92 (2H, q, $-C\underline{H}_2-CH_3$), 5.43 (1H, q, $-CH-$), 4.18 (1H, d, >NH), 2.85 (5H, s, C_6H_5-).

The melting point, IR and NMR spectra were identical with those of the authentic sample prepared by the action of methyl chloroformate on DL-phenylalanine ethyl ester in the presence of sodium hydroxide.

Benzyl Acetate——Acetylmethylenetriphenylphosphorane (0.96 g, 3 mmoles), benzyl alcohol (3.24 g, 30 mmoles), and sodium nitrite (0.25 g, 3.6 mmoles) were dissolved in dry tetrahydrofuran (40 ml). Acetic acid (2.5 ml) was added dropwise to this mixture. The resulting solution was stirred at room temperature for 1 hr. The solvent was evaporated, and water (30 ml) was added to the residue, and the aqueous solution was extracted with three 40 ml portions of benzene. The organic layer was washed with sat. NaCl solution and dried over anhyd. $MgSO_4$. Evaporation of the solvent gave a colorless oil which was chromatographed in benzene on silica gel (120 g). Benzyl acetate was obtained as a colorless oil in 88.9% yield (0.40 g). IR ν_{max}^{film} cm^{-1}: 2960, 1735, 1230, 1025, 755, 700. NMR (τ, $CDCl_3$): 8.07 (3H, s, $-CH_3$), 4.99 (2H, s, $-CH_2$), 2.79 (5H, s, $-C_6H_5$).

The IR and NMR spectra were identical with those of the authentic sample prepared by the action of acetic acid on benzyl alcohol under reflux.

***n*-Butyl Benzoate**——Benzoylmethylenetriphenylphosphorane (1.14 g, 3 mmoles) and sodium nitrite (0.42 g, 6 mmoles) were dissolved in *n*-butyl alcohol (20 ml). Acetic acid (6 ml) was added dropwise to this mixture. The resulting solution was stirred at room temperature for 1 hr. The solvent was evaporated and water (20 ml) was added to the residue, and the aqueous solution was extracted with three 20 ml portions of ethyl acetate. The organic layer was washed with sat. NaCl solution and dried over anhyd. $MgSO_4$. Evaporation of the solvent gave a yellow oil which was chromatographed in benzene on silica gel (120 g). *n*-Butyl benzoate was obtained as a colorless oil in 90.0% yield (0.48 g). IR ν_{max}^{film} cm^{-1}: 2950, 1720, 1447, 1272, 1112, 710. NMR (τ, $CDCl_3$): 9.05 (3H, t, $-CH_3$), 8.0—9.0 (4H, m, $-C\underline{H}_2-C\underline{H}_2-CH_3$), 5.72 (2H, t, $-O-CH_2-$), 1.8—3.0 (5H, m, $-C_6H_5$).

The IR and NMR spectra were identical with those of the authentic sample prepared by the action of *n*-butyl alcohol on benzoyl chloride in the presence of triethylamine, bp_{20} 129—134° (Lit.[13] bp_{21} 129°).

iso-Propyl Benzoate——Benzoylmethylenetriphenylphosphorane (0.76 g, 2 mmoles), iso-propyl alcohol (4 ml), and sodium nitrite (0.15 g, 2.2 mmoles) were dissolved in dry tetrahydrofuran (20 ml). Acetic acid (3 ml) was added dropwise to this mixture. The resulting solution was stirred at room temperature overnight. The solvent was evaporated, and water (20 ml) was added to the residue, and the aqueous solution was extracted with three 20 ml portions of ethyl acetate. The organic layer was washed with sat. NaCl solution and dried over anhyd. $MgSO_4$. Evaporation of the solvent gave an orange oil which was chromatographed in benzene on silica gel (150 g). iso-Propyl benzoate was obtained as a colorless oil in 54.9% yield (0.18 g). IR ν_{max}^{film} cm^{-1}: 2950, 1713, 1275, 1100, 705. NMR (τ, $CDCl_3$): 8.68 (6H, d, two $-CH_3$), 4.82 (1H, q, $-CH-$), 1.9—2.9 (5H, m, C_6H_5-).

***tert*-Butyl Benzoate**——Benzoylmethylenetriphenylphosphorane (0.76 g, 2 mmoles), *tert*-butyl alcohol (4 ml), and sodium nitrite (0.15 g, 2.2 mmoles) were dissolved in dry tetrahydrofuran (25 ml). Acetic acid (5 ml) was added dropwise to this mixture. The resulting solution was stirred at room temperature for 5 hr. The solvent was evaporated, and water (20 ml) was added to the residue, and the aqueous solution was extracted with three 20 ml portions of ethyl acetate. The organic layer was washed with sat. NaCl solution

12) K. Schlögel and G. Korger, *Monatsh. Chem.*, **82**, 799 (1951).
13) Beilstein's "Handbuch der Organischen Chemie," 9, E III 393.

and dried over anhyd. $MgSO_4$. Evaporation of the solvent gave a pale brown oil which was chromatographed in benzene on silica gel (80 g). *tert*-Butyl benzoate was obtained as a colorless oil in 8.4% yield (0.03 g). IR ν_{max}^{film} cm^{-1}: 2950, 1720, 1285, 1110, 705. NMR (τ, $CDCl_3$): 8.42 (9H, s, three CH_3), 1.9—2.7 (5H, m, C_6H_5–).

The IR and NMR spectra were identical with those of the authentic sample prepared by the action of *tert*-butyl alcohol on benzoyl chloride in the presence of pyridine according to the literature.[14]

Benzyl Ethyl Carbonate——Carbethoxymethylenetriphenylphosphorane (1.04 g, 3 mmoles), benzyl alcohol (0.65 g, 6 mmoles), and sodium nitrite (0.42 g, 6 mmoles) were dissolved in dry tetrahydrofuran (30 ml). Acetic acid (6 ml) was added dropwise to this mixture. The resulting solution was stirred at room temperature overnight. The solvent was evaporated, and water (30 ml) was added to the residue, and the aqueous solution was extracted with 40 ml portions of ethyl acetate. The organic layer was washed with sat. NaCl solution and dried over anhyd. $MgSO_4$. Evaporation of the solvent gave a pale yellow oil which was chromatographed in benzene on silica gel (70 g). Benzyl ethyl carbonate was obtained as a colorless oil in 75.9% yield (0.41 g). IR ν_{max}^{film} cm^{-1}: 2970, 1745, 1260, 1003, 690. NMR (τ, $CDCl_3$): 8.82 (3H, t, $-CH_2-\underline{CH_3}$), 5.91 (2H, q, $-\underline{CH_2}-CH_3$), 4.96 (2H, s, $C_6H_5-\underline{CH_2}-$), 2.76 (5H, s, $-\underline{C_6H_5}$).

The IR and NMR spectra were identical with those of the authentic sample prepared by the action of ethyl chloroformate on benzyl alcohol in pyridine, bp_{23} 136—138° (Lit.[15] bp_{20} 122—124°).

Benzyl Methyl Carbonate——Carbomethoxymethylenetriphenylphosphorane (1.00 g, 3 mmoles), benzyl alcohol (0.54 g, 5 mmoles), and sodium nitrite (0.35 g, 5 mmoles) were dissolved in dry tetrahydrofuran (40 ml). Acetic acid (6 ml) was added dropwise to this mixture. The resulting solution was stirred at room temperature for 8 hr. The solvent was evaporated, and water (50 ml) was added to the residue, and the aqueous solution was extracted with 50 ml portions of ethyl acetate. The organic layer was washed with sat. NaCl solution and dried over anhyd. $MgSO_4$. Evaporation of the solvent gave a pale yellow oil which was chromatographed in benzene on silica gel (140 g). Benzyl methyl carbonate was obtained as a colorless oil in 64.3% yield (0.32 g). IR ν_{max}^{film} cm^{-1}: 2990, 1745, 1268, 945, 692. NMR (τ, $CDCl_3$): 6.32 (3H, s, $-CH_3$), 4.94 (2H, s, $-CH_2-$), 2.70 (5H, s, C_6H_5-).

14) J.F. Norris and G.W. Rigby, *J. Am. Chem. Soc.*, **54**, 2088 (1932).
15) Beilstein's "Handbuch der Organischen Chemie," 6, E II 419.