[Chem. Pharm. Bull. 23(8)1738—1740(1975)] UDC 547.747.04 : 547.583.7.04

Phosphorus in Organic Synthesis. X.[1] *tert*-Butyl Carbamate. An Efficient Additive in a Modified Curtius Reaction by Diphenyl Phosphorazidate (DPPA)[2]

KAZUO MURATO, TAKAYUKI SHIOIRI, and SHUN-ICHI YAMADA

Faculty of Pharmaceutical Sciences, University of Tokyo[3]

(Received November 26, 1974)

A modified Curtius reaction of N-benzyloxycarbonyl-L-proline (I) with diphenyl phosphorazidate (DPPA) in the presence of triethylamine in *tert*-butyl alcohol afforded the allophanate (III) as the major product but the expected carbamate (II) as a minor product. Similar result was obtained in the case of the ordinary Curtius reaction of I. However, the use of *tert*-butyl carbamate (X) as an additive changed the reaction course and the desired carbamate (II), though accompanied by racemization, was obtained in good yield.

In earlier papers of the series,[1,4,5,6] we have demonstrated that diphenyl phosphorazidate (DPPA)[4] is a new convenient reagent for a modified Curtius reaction, by which a carboxylic acid is easily converted to a urethane in a single step in the presence of triethylamine and a hydroxyl component.[5] When the method was applied to the synthesis of α-amino acid derivatives, the usual one-step treatment of a malonic acid half ester gave an esterification product, while the two-in-one reaction procedure afforded an expected Curtius rearrangement product.[6] The mechanism of the esterification was also investigated.[1] The present work was undertaken in an effort to apply the modified Curtius reaction by DPPA to N-benzyloxycarbonyl-L-proline (Z-L-Pro-OH, I).

Z-L-Pro-OH (I) in *tert*-butyl alcohol was refluxed with DPPA and triethylamine under the usual modified Curtius reaction by DPPA.[5] Surprisingly, however, the expected *tert*-butyl carbamate (II) could be isolated in poor yield. Instead, the major product was proved to have the elemental composition of $C_{18}H_{25}O_5N_3$ corresponding to that of the carbamate (II) plus HNCO. The infrared spectrum showed two NH absorptions at 3375 and 3320 cm^{-1} as well as two peaks at the CO stretching region. The nuclear magnetic resonance spectrum was quite similar to that of the carbamate (II) except two NH proton signals at δ 8.00 (doublet) and 8.25 ppm (singlet). These data allow its structural assignment as either the allophanate (III) or (IV),[7,8] preferably the former. Conclusive evidence supporting the structure III was obtained by the decoupling technique; double irradiation to the methine proton at 5.66 ppm caused the NH doublet at 8.00 ppm to a singlet, which can be explained only by the structure III. The carbamate (II) and the allophanate (III) were both optically active, and their absolute configurations were assigned (*S*)-form, based on the reasonable assumption

---

[1] Part IX: K. Ninomiya, T. Shioiri, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **22**, 1795 (1974).

[2] Presented in part at the 94th Annual Meeting of Pharmaceutical Society of Japan, Sendai, April, 1974, Abstracts I, p. 119 and II, p. 13.

[3] Location: *7-3-1, Hongo, Bunkyo-ku, Tokyo, 113, Japan.*

[4] Review, T. Shioiri and S. Yamada, *Yuki Gosei Kagaku Kyokai Shi*, **31**, 666 (1973).

[5] T. Shioiri, K. Ninomiya, and S. Yamada, *J. Am. Chem. Soc.*, **94**, 6203 (1972); K. Ninomiya, T. Shioiri, and S. Yamada, *Tetrahedron*, **30**, 2151 (1974).

[6] S. Yamada, K. Ninomiya, and T. Shioiri, *Tetrahedron Letters*, **1973**, 2343; K. Ninomiya, T. Shioiri, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **22**, 1398 (1974).

[7] H.W. Blohm and E.I. Becker, *Chem. Rev.*, **51**, 471 (1952).

[8] Cf. H. Ulrich, B. Tucker, and A.A.R. Sayigh, *J. Org. Chem.*, **32**, 3938 (1967).

NII-Electronic Library Service

that the modified Curtius reaction will proceed with retention of configuration as the ordinary Curtius rearrangement.[9]

In view of this anomalous result, attention was turned to the ordinary Curtius reaction of Z-L-Pro-OH (I). Z-L-Pro-OH (I) was converted to the corresponding acid azide (V) *via* the mixed anhydride according to the method originally developed by Weinstock.[10] Refluxing the azide (V) in *tert*-butyl alcohol again afforded the allophanate (III) as the major product in company with the carbamate (II) as a minor product.

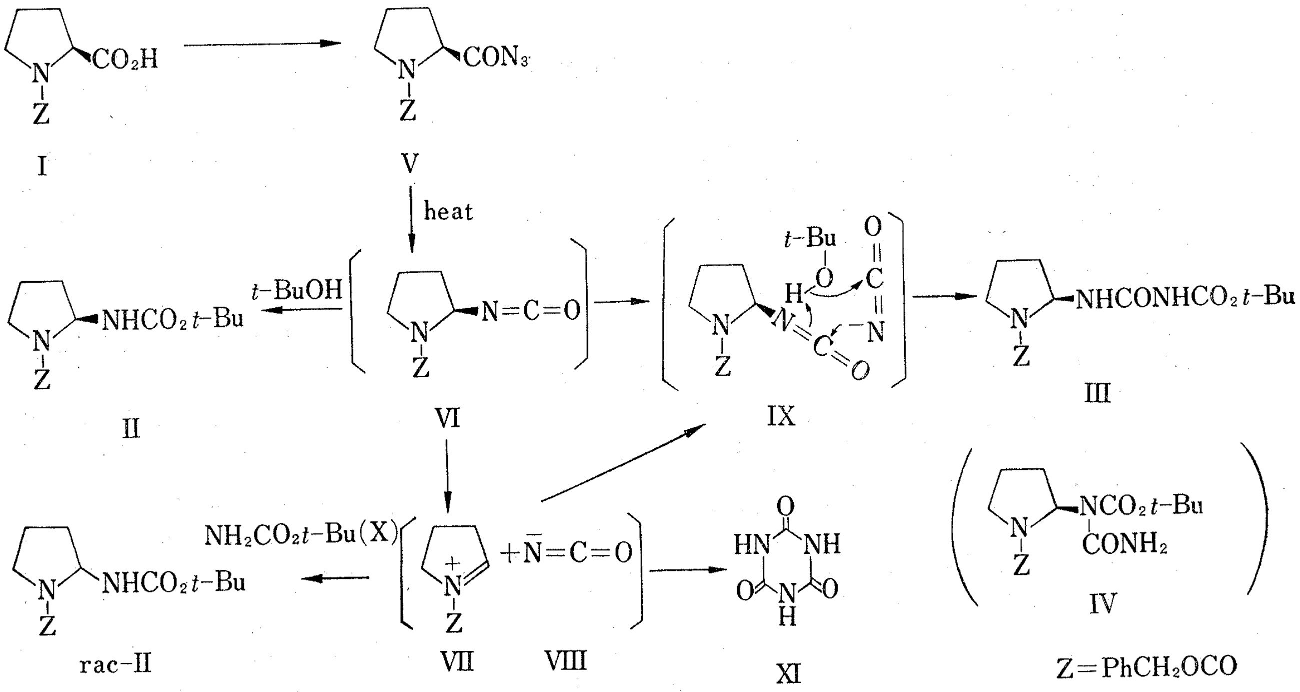

Chart 1

A possible explanation for the reaction course will be as follows. The Curtius rearrangement of Z-L-Pro-OH (I) will give the isocyanate (VI) *via* the acid azide (V) in both Curtius reactions. The isocyanate (VI) will afford the carbamate (II) by the addition of *tert*-butyl alcohol used as a solvent. However, the lone pair electrons on the ring nitrogen of VI, though they are partially delocalized by the benzyloxycarbonyl group, will much facilitate the elimination of the isocyanate group, giving the immonium (VII) and the cyanate ions (VIII). The latter will react with the isocyanate (VI) in the presence of *tert*-butyl alcohol, as represented by the transition state (IX),[11] to furnish the allophanate (III), as shown in Chart 1.

If this is true, the addition of *tert*-butyl carbamate (X) in place of *tert*-butyl alcohol will suppress the formation of the allophanate (III) and increase the yield of the carbamate (II) as a result of the nucleophilic attack[12] of X to the immonium ion (VII), though the resulting carbamate (II) will lose the optical activity. Thus, a mixture of Z-L-Pro-OH (I), DPPA, and triethylamine was refluxed in benzene in the presence of an excess of *tert*-butyl carbamate. Indeed, the desired carbamate (rac-II) was obtained in good yield together with cyanuric acid (XI) which was formed by trimerization of the cyanate ion (VIII).

---

[9] P.A.S. Smith, "Molecular Rearrangements," Vol. I, edited by P. de Mayo, Interscience, New York, **1963**, p. 457; K.K. Lee, S. Terashima, K. Achiwa, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **17**, 2540 (1969).

[10] J. Weinstock, *J. Org. Chem.*, **26**, 3511 (1961); C, Kaiser and J. Weinstock, *Org. Synth.*, **51**, 48 (1971).

[11] *cf.* W.J. Close and M.A. Spielman, *J. Am. Chem. Soc.*, **75**, 4055 (1953).

[12] The nucleophilicity of N-unsubstituted carbamates is well recognized; P. Adams and F.A. Baron, *Chem. Rev.*, **65**, 567 (1965).

As the utility of *tert*-butyl carbamate as an additive for the modified Curtius reaction by DPPA was well evaluated in the case of Z-L-Pro-OH, the generality of the reaction is now under way.

Experimental

Unless otherwise stated, melting points were measured on a hot stage apparatus and uncorrected; infrared (IR) spectra were measured either in nujol mulls (for crystals) or in liquid films (for oils); nuclear magnetic resonance (NMR) spectra (60 or 100 MHz) were measured in deuterochloroform, and chemical shifts (δ) are given in ppm relative to internal tetramethylsilane. Silica gel (Wakogel C-200) was used for column chromatography. The organic solutions were dried over magnesium sulfate before vacuum evaporation. DPPA was prepared according to our previous report.[13]

A Modified Curtius Reaction of N-Benzyloxycarbonyl-L-proline (I)——A mixture of Z-L-Pro-OH (I, 1.30 g, 5.2 mmole), DPPA (1.65 g, 6 mmole), and triethylamine (0.61 g, 6 mmole) in *tert*-butyl alcohol (30 ml) was stirred at reflux for 30 hr. The mixture was evaporated, and the residue was dissolved in ethyl acetate (50 ml). The solution was successively washed with 10% aqueous sodium carbonate (25 × 3 ml), water (25 ml), 5% aqueous citric acid (30 × 2 ml), water (25 ml), and saturated aqueous sodium chloride (25 ml). Drying followed by evaporation gave an oily residue which was fractionated by a silica gel column chromatography using a mixture of methylene chloride and diethyl ether. The first fraction came as a colorless oil (0.34 g) whose structure was not determined; IR $\nu_{\max}$ cm^{-1}: 1720; NMR 1.8, 3.3, 5.1, 7.2.

The second fraction to be eluted was the carbamate (II, 0.085g, 5%) as colorless needles (recrystallized from a mixture of diethyl ether and *n*-hexane), mp 105—106°. IR $\nu_{\max}$ cm^{-1}: 3380, 1730, 1690, 1520, 770, 735. NMR 1.40 (9H, singlet, $C(CH_3)_3$), 1.75—2.0 (4H, multiplet, $2 \times CH_2$), 3.40 (2H, multiplet, CH_2N), 5.10 (3H, multiplet, CO_2CH_2 and CH), 5.37 (1H, broad doublet, NH), 7.25 (5H, singlet, C_6H_5). Mass Spectrum *m/e*: 320 (M$^+$), 264, 219, 203, 185, 129, 91 (base), 85, 68. ORD (c = 1.0, methanol) $[\alpha]^{25}$ (nm): +11 (589), +20 (500), +30 (450), +44 (400), +68 (350), +118 (300), +350 (250). *Anal.* Calcd. for $C_{17}H_{24}O_4N_2$: C, 63.73; H, 7.55; N, 8.74. Found: C, 63.81; H, 7.62; N, 8.58.

The third fraction to be eluted was the allophanate (III, 0.67 g, 35%) as colorless needles (recrystallized from a mixture of diethyl ether and *n*-hexane), mp 130—131°. IR $\nu_{\max}$ cm^{-1}: 3375, 3320, 1720, 1695, 1550, 775, 735. NMR 1.43 (9H, singlet, $C(CH_3)_3$), 1.75—2.1 (4H, multiplet, $2 \times CH_2$), 3.45 (2H, multiplet, CH_2N), 5.11 (2H, singlet, CO_2CH_2), 5.66 (1H, multiplet, CH), 7.26 (5H, singlet, C_6H_5), 8.00 (1H, doublet, $CHN\underline{H}$), 8.25 (1H, singlet, CONHCO). Mass Spectrum *m/e*: 363 (M$^+$), 307, 262, 228, 203, 172, 128, 91 (base), 68. ORD (c = 1.0, methanol) $[\alpha]^{20}$ (nm): −46 (589), −68 (500), −89 (450), −121 (400), −194 (350), −242 (300), −2240 (250). *Anal.* Calcd. for $C_{18}H_{25}O_5N_3$: C, 59.49; H, 6.93; N, 11.56. Found: C, 59.62; H, 6.98; N, 11.54.

The Ordinary Curtius Reaction of N-Benzyloxycarbonyl-L-proline (I)——To a stirred mixture of Z-L-Pro-OH (I, 1.25 g, 5 mmole) and triethylamine (0.56 g, 5.5 mmole) in acetone (8.5 ml) was added ethyl chloroformate (0.60 g, 5.5 mmole) in acetone (1 ml) at −5°—0° during 5 min. After the mixture was stirred for 15 min, sodium azide (0.65 g, 10 mmole) in water (4 ml) was added at −5°—0° during 5 min. The mixture was stirred for 45 min at −5°—0°, poured onto ice-water (100 ml), and extracted with diethyl ether (30 × 4 ml). The ethereal extracts were washed with saturated aqueous sodium chloride, dried, and concentrated to give the azide (V) as a colorless oil, which was dissolved in *tert*-butyl alcohol (30 ml) and refluxed overnight. After evaporation, the residue was fractionated by a column chromatography to give the unknown colorless oil (0.23 g), the carbamate (II, 0.22 g, 14%), and the allophanate (III, 0.60 g, 33%) in the same manner as above.

A Modified Curtius Reaction of N-Benzyloxycarbonyl-L-proline (I) in the Presence of *tert*-Butyl Carbamate (X)——A mixture of Z-L-Pro-OH (I, 249 mg, 1 mmole), DPPA (303 mg, 1.1 mmole), triethylamine (111 mg, 1.1 mmole), and *tert*-butyl carbamate[14] (X, 293 mg, 2.5 mmole) in benzene (9 ml) was stirred at reflux for 37 hr. The colorless crystalline precipitates (15 mg, 12%) were filtered and dried, mp>300°. Mass Spectrum *m/e*: 129 (M$^+$). Its infrared spectrum (3200, 1700) was virtually identical with that of cyanuric acid (XI).

The filtrate was concentrated, and the residue was dissolved in ethyl acetate (25 ml). The solution was successively washed with 10% aqueous sodium carbonate (10 × 3 ml), water (10 ml), 5% aqueous citric acid (10 × 2 ml), water (10 ml), and saturated aqueous sodium chloride (10 ml). Drying and evaporation gave an oily residue which was fractionated by a column chromatography with a mixture of diethyl ether and *n*-hexane. The first fraction to be eluted was *tert*-butyl carbamate (120 mg).

The second fraction to be eluted was the carbamate (rac-II, 210 mg, 66%) as colorless needles (recrystallized from a mixture of diethyl ether and *n*-hexane), mp 105.5—106°. The infrared, nuclear magnetic resonance, and mass spectra were virtually identical with those of the optically active carbamate (II). ORD (c = 1, methanol) $[\alpha]^{20}$ (nm): O (589—250). *Anal.* Calcd. for $C_{17}H_{24}O_4N_2$: C, 63.73; H, 7.55; N, 8.74. Found: C, 63.47; H, 7.56; N, 8.57.

---

13) T. Shioiri and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **22**, 849 (1974).

14) B. Loev and M.F. Kormendy, *J. Org. Chem.*, **28**, 3421 (1963).

NII-Electronic Library Service