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PHOSPHORUS IN ORGANIC SYNTHESIS—VII[1]

DIPHENYL PHOSPHORAZIDATE (DPPA). A NEW CONVENIENT REAGENT FOR A MODIFIED CURTIUS REACTION[2]

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Abstract—A simple one-step conversion of carboxylic acids to urethanes was achieved by diphenyl phosphorazidate (DPPA). The reaction procedure is quite simple, occurring by refluxing an equimolecular mixture of a carboxylic acid, DPPA, and triethylamine in the presence of a hydroxyl component. Aromatic, aliphatic, and heterocyclic carboxylic acids underwent rearrangements in satisfactory yields. As this modified Curtius reaction is much simpler and less laborious than the classical Curtius reaction and proceeds under mild conditions, it may have a broad synthetic utility.

Conversion of carboxylic acids or their derivatives to amines through molecular rearrangements is a well-known process as Hofmann, Curtius, Schmidt and Lossen reactions.[3] These reactions respectively have advantages and disadvantages, which have been discussed in detail by Smith.[4]

We have recently reported[5] a preliminary account of a modified Curtius reaction using diethyl phosphorazidate by which benzoic acid was smoothly converted to ethyl carbanilate in EtOH in the presence of triethylamine (TEA). In the light of this preliminary experiment we thought that phosphoryl azides might be a suitable general reagent for the convenient transformation of carboxylic acids into urethanes by a Curtius-type rearrangement. We now wish to describe here the details of the modified Curtius reaction by phosphoryl azides, which is represented by the general equation:

$$RCO_2H \xrightarrow[Et_3N,R''OH]{N_3PO(OR')_2} RNHCO_2R''$$

First we compared diethyl phosphorazidate with diphenyl phosphorazidate (DPPA) which has been proved to be a more convenient reagent for the racemization-free peptide synthesis.[2,5,6] Thus octanoic acid was refluxed with either diethyl phosphorazidate or DPPA in t-BuOH in the presence of TEA. The rearrangement proceeded smoothly in either case to give t-butyl N-heptylcarbamate, the yield of which was better when DPPA was used. This is not unexpected because the phenyl group is more electron-withdrawing and the attack of the carboxylate anion to the P atom of phosphoryl azides, which is an initial stage of the reaction, will be much more favored.[6] Furthermore, the use of one molar equivalent of the base TEA was proved to be sufficient to conduct the modified Curtius reaction, as shown in Table 1.

Using DPPA, variation of OH components in the modified Curtius reaction was made about benzoic acid. The urethanes corresponding to respective OH components were obtained, together with a small amount of N,N'-diphenylurea in some cases. The results are shown in Table 2, which reveals that both alcohols and phenols can be used as OH components.

These successful results encouraged us to investigate extensively the modified Curtius reaction by DPPA on various carboxylic acids containing various functions. t-BuOH and benzyl alcohol were chosen as OH components because the rearranged products t-butyl or benzyl urethanes can be easily converted to amines under mild reaction conditions of either cold acid or catalytic reduction.[7]

A general procedure of the reaction is as follows: an equimolecular mixture of a carboxylic acid, DPPA, and TEA was refluxed in a large excess of t-BuOH or in C_6H_6 with a slight excess of benzyl alcohol for several hours or overnight. The rearrangement products were isolated from the neutral fraction.

The results are summarized in Table 3. The reaction time indicated in Table 3 is not necessarily the required time for completion of the transformation: often the required time might be much shorter. The rearrangement reaction mostly proceeds smoothly. 3-Phenylpropionic acid, *trans*-cinnamic acid, and 3-methoxypropionic acid satisfactorily underwent the rearrangement to give t-butyl urethanes. Adipic acid, a typical dicarboxylic acid,

Table 1.

$$n\text{-}C_7H_{15}CO_2H \xrightarrow[\text{in t-BuOH}]{Et_3N} n\text{-}C_7H_{15}NHCO_2t\text{-}Bu$$

Expt.	Reagent	Reaction time (h)	Yield (%)
(a) (i)	$N_3PO(OEt)_2$	20·5	54
(a) (ii)	$N_3PO(OPh)_2$	12	67
(a) (iii)	$N_3PO(OPh)_2$	18	64[a]

[a]Two equiv. of TEA were used.

Table 2.

$$PhCO_2H \xrightarrow[Et_3N,ROH]{N_3PO(OPh)_2} PhNHCO_2R$$

Expt.	ROH	Solvent	Reaction time (h)	Yield
(b) (i)	EtOH	EtOH	19	62[a]
(b) (ii)	t-BuOH	t-BuOH	5	74
(b) (iii)	PhOH	Dioxane	13	57
(b) (iv)	$PhCH_2OH$	Dioxane	14	61

[a]Diethyl phosphorazidate was used.

afforded a tetramethylenediamine derivative by the use of 2 equiv of DPPA and TEA, respectively. Pyridine-2-carboxylic acid is reported[8] to undergo the ordinary Curtius reaction to give the rearranged product in low yield, and failed to undergo the Schmidt reaction.[9] The modified Curtius reaction of pyridine-2-carboxylic acid, however, afforded a 2-amino-pyridine derivative in good yield. *o*-Nitrobenzoic acid, which was presumed to be unreactive owing to the steric hindrance, afforded the rearranged product with ease as in the case of its *p*-nitro analog. Pivalic acid was also expected to be less reactive, but the benzyl urethane was obtained in good yield. The optical activity of the carboxylic acid is retained in the rearrangement of N-benzyloxycarbonyl-L-serine, affording the optically active oxazolidone derivative whose optical rotation was almost the same as that of the oxazolidone obtained by the ordinary Curtius reaction.[10]

Cyclohexanecarboxylic acid in t-BuOH underwent the modified Curtius reaction to furnish t-butyl N-cyclohexylcarbamate in moderate yield, together with amounts of N-cyclohexylcarbamoyl azide and N,N'-dicyclohexylurea. The relative stability of cyclohexylisocyanate* will inhibit the smooth addition of t-BuOH to the isocyanate, and may facilitate the formation of the carbamoyl azide and the urea, the formation mechanism of which will be described later in this paper. The rearrangement in benzyl alcohol also took a course similar to the above.

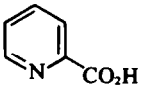
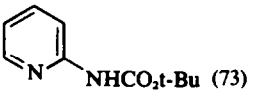
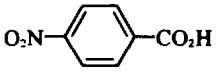
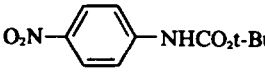
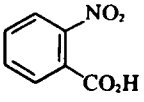
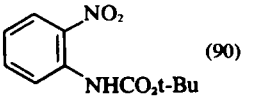
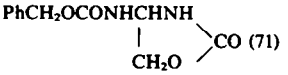
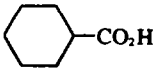
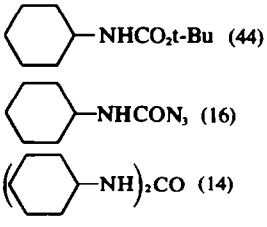
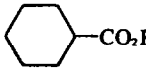
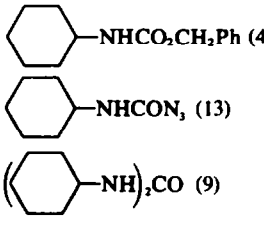
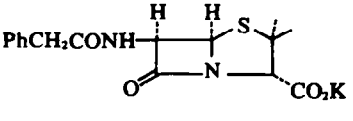
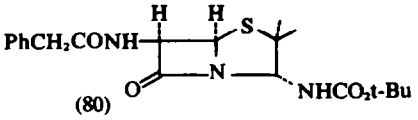
*The presence of a small amount of cyclohexylisocyanate was recognized on the IR spectrum even after the reaction followed by aqueous treatment.

Ketones undergo the Schmidt reaction much easier than carboxylic acids.[9] Thus, levulinic acid, on treatment of an equimolecular amount of hydrazoic acid followed by hydrolysis, yields β-alanine, acetic acid, methylamine, and succinic acid. The DPPA method, however, afforded the t-butyl urethane together with the carbamoyl azide. The total yield of the rearrangement reaction was a little bit lower than the usual case, but it is advantageous that the Curtius-type rearrangement could be carried out without any protection of the CO group. When the ketonic function of levulinic acid was protected as a ketal, the total yield of the modified Curtius reaction increased to 91%. This proves that the DPPA method can be used for the rearrangement of the substrates containing acid-labile groups, which appears to be one of its major virtues.

Another intriguing example of the DPPA method is the Curtius degradation of the important antibiotics penicillins, which provides a simple method for opening the thiazolidine ring of the penam nucleus.[11] The ordinary degradation requires tedius processes[11,12] involving conversion of a penam-3-carboxylic acid to a mixed anhydride, treatment with sodium azide, thermal rearrangement of the resultant acid azide, followed by either acid hydrolysis or urethane formation. Heusler[12] recently reported an application of the method to penicillin G which was converted to the corresponding 2,2,2-trichlorethyl urethane in 74% overall yield. We found penicillin G potassium smoothly underwent the modified Curtius reaction by DPPA in t-BuOH to give the t-butyl urethane in 80% yield in a single operation. The product is assigned the 3α-orientation on the reasonable assumption that the modified Curtius rearrangement will proceed with retention of configuration as the ordinary Curtius rearrangement.[12,13] The DPPA method may simplify the experimental operation, and is potentially useful for compounds having highly reactive functions, such as β-lactams.

The modified Curtius reaction by DPPA is similar to the Schmidt reaction in the sense that carboxylic acids yield amine derivatives in a single operation, but it may belong to the Curtius reaction from the mechanistic point of view. The interaction of a carboxylate anion with DPPA will produce a carboxylic acid azide via a mixed carboxylic phosphoric anhydride.[6] The carboxylic acid azide will thermally undergo the rearrangement according to the same mechanism as that of the ordinary Curtius rearrangement, yielding an isocyanate which will react with an OH component to furnish a urethane as a major product. In some cases, hydrazoic acid formed in the above process will add to the isocyanate to give a carbomoyl azide. Urea and ester derivatives will be formed, though in rare cases, by the addition of the starting carboxylic acid to the isocyanate, followed by a well-known

Table 3. A modified Curtius reaction by DPPA

Expt.	RCO_2H	R'OH	Reaction time (h)	Product (yield, %)
(c)	$PhCH_2CO_2H$	EtOH	20	$PhCH_2NHCO_2Et$ (51)[a]
(d)	$Ph(CH_2)_2CO_2H$	t-BuOH	25	$Ph(CH_2)_2NHCO_2t$-Bu (61) $Ph(CH_2)_2NHCON_3$ (3)
(e)	$PhCH{=}CHCO_2H$	t-BuOH	5	$PhCH{=}CHNHCO_2t$-Bu (70)
(f)	$CH_3O(CH_2)_2CO_2H$	t-BuOH	15	$CH_3O(CH_2)_2NHCO_2t$-Bu (75)
(g)	$HO_2C(CH_2)_4CO_2H$	t-BuOH	21	t-$BuO_2C\ NH(CH_2)_4NHCO_2t$-Bu (53)
(h)		t-BuOH	23	 (73)
(i)		t-BuOH	20	 (84)
(j)		t-BuOH	15	 (90)
(k)		—[b]	21	 (71)
(l)	$(CH_3)_3CCO_2H$	$PhCH_2OH$	0·5, 37[c]	$(CH_3)_3CNHCO_2CH_2Ph$ (63)
(m) (i)		t-BuOH	21·5	
(m)(ii)		$PhCH_2OH$	0·5, 17[c]	
(n)	$CH_3CO(CH_2)_2CO_2H$	t-BuOH	17	$CH_3CO(CH_2)_2NHCO_2t$-Bu (27·5) $CH_3CO(CH_2)_2NHCON_3$ (14)
(o)	$CH_3C(CH_2)_2CO_2H$ 	$PhCH_2OH$	0·75, 18[c]	$CH_3C(CH_2)_2NHCO_2CH_2Ph$ (83)  $CH_3C(CH_2)_2NHCON_3$ (8)  $CH_3C(CH_2)_2CO_2CH_2Ph$ (6) 
(p)		t-BuOH	28	 (80)

[a] Diethyl phosphorazidate was used.
[b] Reflux in dioxane.
[c] Reflux first in C_6H_6, followed by reflux again after addition of benzyl alcohol.

transformation when the ordinary Curtius reaction is carried out in carboxylic acid solvent.[4,14]

The modified Curtius reaction is much more convenient and simpler than the ordinary Curtius reaction. The reaction proceeds under more or less neutral and non-oxidizing conditions, and does not require either strong acid in the Schmidt reaction or strong alkali in the Hofmann reaction. Thus the modified Curtius reaction may have a considerable synthetic utility and create added flexibility in synthesis.*

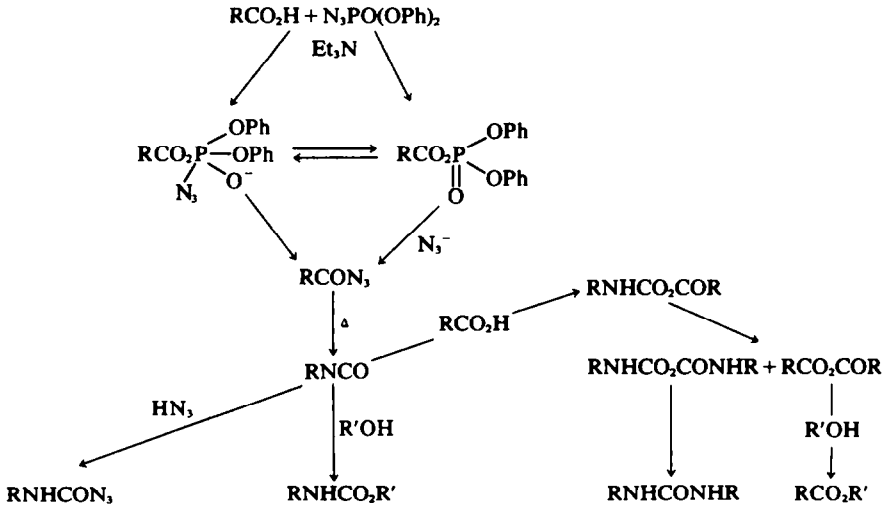


CHART 1.

EXPERIMENTAL

Unless otherwise stated, m.ps were measured on a hot stage apparatus and uncorrected; IR spectra were measured either in Nujol mulls (for crystals) or in liquid films (for oils); NMR spectra (60 or 100 MH_z) were measured in $CDCl_3$, and chemical shifts (δ) are given in ppm relative to internal TMS. Silica gel (Wakogel C-200) was used for column chromatography. The organic solns were dried over Na_2SO_4 before vacuum evaporation.

Starting materials. DPPA was prepared according to our previous report.[5] Commercially available carboxylic acids were purified by recrystallization or distillation before use. 3-Methoxypropionic acid[15] and 4-ethylenedioxypentanoic acid[16] were prepared according to the literatures. Penicillin G potassium was kindly donated by Mr. M. Kuramoto, Toyo Jozo Co. Ltd., to whom the authors', thanks are due.

A modified Curtius reaction of carboxylic acids by DPPA

(a) *Octanoic acid.* (i) A mixture of octanoic acid (1·44 g), diethyl phosphorazidate[17] (1·79 g), and TEA (1·02 g) in t-BuOH (30 ml) was stirred at reflux for 20·5 h. The mixture was evaporated, and the residue was dissolved in C_6H_6 (250 ml). The soln was successively washed with 5% citric acid aq (30 ml), H_2O (15 ml), sat $NaHCO_3$ aq (30 ml), and sat NaCl aq (15 ml). Drying followed by evaporation gave an oily residue, which was distilled at 112° (2 mmHg) to give t-butyl N-heptylcarbamate (1·17 g, 54%) as a colorless oil, IR 3300, 1690, 1530 cm^{-1}; NMR 0·89 (3H, m, Me), 1·30 (10H, m, $-(CH_2)_5-$), 1·40 (9H, s, t-Bu), 3·03 (2H, q, $J = 7$ H_z, CH_2N), 4·80 (1H, s, NH), Mass 215 (M^+). (Found: C, 66·56; H, 12·05. $C_{12}H_{25}O_2N$ requires: C, 66·93; H, 11·70%).

(ii) A mixture of octanoic acid (1·44 g), DPPA (2·75 g), and TEA (1·05 g) in t-BuOH (30 ml) was refluxed with stirring for 12 h. After aqueous work-ups as above, the C_6H_6 soln was evaporated to give an oily residue, from which a colorless solid separated upon standing. The mixture of the oil and the solid was diluted with C_6H_6, and filtered to give colorless crystals (0·045 g, 3·5%), m.p. 90–93°, which was identified to be N,N'-di-heptylurea by IR (3260, 1615, 1580 cm^{-1}) and NMR (0·89 (6H, m, Me), 1·30 (20H, m, $-(CH_2)_5-$), 3·14 (4H, m, CH_2N), 4·56 (2H, s, NH)).

The filtrate was evaporated, and distilled at 100–101° (1·4 mmHg) to give t-butyl N-heptylcarbamate (1·45 g, 67%).

(iii) The reaction was carried out as in (a)(ii) except use of TEA (2·04 g). After reflux for 18 h, work-up as in (a)(ii) gave N,N'-di-heptylurea (0·1 g, 8%) and t-butyl N-heptylcarbamate (1·38 g, 64%).

(b) *Benzoic acid.* (i) Experimental details were described in Ref 5.

(ii) A mixture of benzoic acid (1·22 g), DPPA (2·75 g), and TEA (1·02 g) in t-BuOH (30 ml) was stirred at reflux for 5 h. Work-up as in (a)(i) gave a colorless solid, from which N,N'-diphenylurea (0·06 g, 6%), identical with an authentic specimen of commercial origin, was obtained as a hexane insoluble portion. Recrystallization from hexane gave t-butyl carbanilate (1·42 g, 74%) as colorless needles, m.p. 133–138° (Lit.[18] 136°), identical with an authentic specimen prepared by the action of phenylisocyanate with t-BuOH.[18]

*Application of the modified Curtius reaction to the synthesis of α-amino acids was communicated: S. Yamada, K. Ninomiya, and T. Shioiri, *Tetrahedron Letters* 2343 (1973).

(iii) A mixture of benzoic acid (1·22 g), DPPA (2·75 g), phenol (1·1 g), and TEA (1·02 g) in dioxane (30 ml) was stirred at reflux for 13 h. The mixture was evaporated, and the residue was dissolved in C_6H_6. The C_6H_6 soln was washed with 5% HCl, H_2O, sat $NaHCO_3$ aq, and sat NaCl aq. Drying followed by evaporation gave slightly yellow crystals which were recrystallized from C_6H_6–hexane to furnish phenyl carbanilate (1·22 g, 57%) as colorless needles, m.p. 127–128·5° (Lit.[19] 126°). IR 3240, 1710, 1598, 1530, 760, 690 cm^{-1}.

(iv) A mixture of benzoic acid (1·22 g), DPPA (2·75 g), benzyl alcohol (1·09 g), and TEA (1·02 g) in dioxane (30 ml) was stirred at reflux for 14 h. Work-up was carried out as in (b)(iii), and during the washing with sat $NaHCO_3$ aq a white solid was precipitated, which was identified to be N,N'-diphenylurea (0·12 g, 11%).

The crude product after aqueous work-ups was purified by silica gel column chromatography (C_6H_6 – $CHCl_3$ – Me_2CO, 200:60:1) followed by recrystallization from C_6H_6–Et_2O–hexane to furnish benzyl carbanilate (1·38 g, 61%) as colorless needles, m.p. 77–78° (Lit.[20] 75·5–76°). IR 3200, 1685, 1598, 1545, 762, 735, 690 cm^{-1}, NMR 5·18 (2H, s, CH_2), 6·76 (1H, s, NH), 7·3 (10H, m, $2 \times C_6H_5$).

(c) *Phenylacetic acid.* A mixture of phenylacetic acid (0·27 g), diethyl phosphorazidate[17] (0·36 g), and TEA (0·20 g) in EtOH (10 ml) was stirred at reflux for 20 h. Work-up as in (b)(iii) gave a crude colorless oil, which was purified by preparative layer chromatography (silica G. F. plates, Et_2O–hexane, 1:1) to afford ethyl N-benzylcarbamate (0·18 g, 51%) as colorless crystals, m.p. 45° (Lit.[20] 48–49°), identified with an authentic specimen prepared by the action of benzylamine with ethyl-chloroformate.[21]

(d) *3-Phenylpropionic acid.* A mixture of 3-phenylpropionic acid (1·52 g), DPPA (2·75 g), and TEA (1·05 g) in t-BuOH (30 ml) was stirred at reflux for 25 h. Work-up as in (a)(i) gave a slightly yellow viscous oil, which was subjected to column chromatography (hexane–$CHCl_3$–AcOEt, 20:4:1) to give t-butyl N-(2-phenylethyl) carbamate (1·35 g, 61%) as colorless crystals (hexane), m.p. 56–57°, IR 3340, 1680, 1520, 740, 690 cm^{-1}, NMR 1·42 (9H, s, t-Bu), 2·76 (2H, t, J = 7 H_z, $CH_2C_6H_5$), 3·34 (2H, q, J = 7 H_z, CH_2N), 4·63 (1H, s, NH), 7·20 (5H, m, C_6H_5). (Found: C, 70·71; H, 8·67; N, 6·34. $C_{13}H_{19}O_2N$ requires: C, 70·56; H, 8·65; N, 6·33%).

A further elution of the column gave N-(2-phenylethyl)-carbamoyl azide (0·05 g, 3%) as colorless crystals (hexane), m.p. 85·5–87°, IR 3250, 2140, 2100, 1695, 1540 cm^{-1}, NMR 2·80 (2H, t, J = 7 H_z, $CH_2C_6H_5$), 3·48 (2H, q, J = 7 H_z, CH_2N), 5·24 (1H, s, NH), 7·21 (5H, s, C_6H_5). (Found: C, 56·87; H, 5·39; N, 29·29. $C_9H_{10}ON_4$ requires: C, 56·83; H, 5·30; N, 29·46%).

(e) trans-*Cinnamic acid.* A mixture of *trans*-cinnamic acid (1·48 g), DPPA (2·75 g), and TEA (1·05 g) in t-BuOH (30 ml) was stirred at reflux for 5 h. The mixture was worked up as in (a)(i) to give a yellow solid, which was purified by column chromatography (C_6H_6–$CHCl_3$) to give t-butyl N-styrylcarbamate (1·54 g, 70%) as colorless needles (AcOEt–C_6H_6), m.p. 139–141°, IR 3260, 1685, 1655, 1515, 950, 753, 685 cm^{-1}. (Found: C, 71·30; H, 7·83; N, 6·43. $C_{13}H_{17}O_2N$ requires: C, 71·20; H, 7·82; N, 6·39%). The product will be a mixture of geometrical (*cis* and *trans*) and position isomers (aldimines) at least in $CDCl_3$ soln because it shows a complex pattern on its NMR spectrum (e.g., t-Bu and phenyl protons, multiplets). The validity of the structure was further confirmed by comparisons with an authentic specimen prepared by the thermal treatment of *trans*-cinnamyl chloride with sodium azide in dioxane, distillation of the product at 126° (18 mmHg) (b.p. of trans-styryl isocyanate: 44–45° (0·10 mmHg)[22], 107° (12 mmHg)[23]), followed by refluxing the isocyanate in t-BuOH.

(f) *3-Methoxypropionic acid.* A mixture of 3-methoxypropionic acid (1·04 g), DDPA (2·75 g), and TEA (1·08 g) in t-BuOH (30 ml) was stirred at reflux for 15 h and worked up as in (a)(i). Purification of the crude product by column chromatography (hexane–Et_2O) gave t-butyl N-(2-methoxyethyl)carbamate (1·30 g, 75%) as a colorless oil, b.p. 63–64° (0·6 mmHg), IR 3340, 1720, 1530 cm^{-1}, NMR 1·40 (9H, s, t-Bu), 3·30 (7H, m, Me and $-(CH_2)_2-$), 5·23 (1H, s, NH), Mass 175 (M^+).

(g) *Adipic acid.* A mixture of adipic acid (0·73 g), DPPA (2·75 g), and TEA (1·04 g) in t-BuOH (30 ml) was refluxed for 21 h. The mixture was treated as in (a)(i) to give a colorless powder, which was purified by column chromatography (hexane–$CHCl_3$–AcOEt) to furnish di-t-butyl tetramethylenedicarbamate (0·76 g, 53%) as colorless crystals (C_6H_6), m.p. 137–139·5° (Lit.[24] 135–137°), IR 3300, 1685, 1530 cm^{-1}, NMR 1·43 (18H, s, $2 \times$ t-Bu), 1·48 (4H, m, $-(CH_2)_2-$), 3·10 (4H, m, $2 \times CH_2N$), 4·80 (2H, s, $2 \times$ NH). (Found: C, 58·36; H, 9·48; N, 10·01. $C_{12}H_{24}O_4N_2$ requires: C, 58·31; H, 9·71; N, 9·79%).

(h) *Pyridine-2-carboxylic acid.* A mixture of pyridine-2-carboxylic acid (1·23 g), DPPA (2·75 g), and TEA (1·05 g) in t-BuOH (30 ml) was stirred at reflux for 23 h, and worked up as in (a)(i) to give a yellow solid, which was recrystallized from AcOEt–EtOH–hexane to give a high melting compound (0·025 g, m.p. > 300°). The mother liquor was chromatographed (hexane–$CHCl_3$–AcOEt, 20:4:1) to give t-butyl N-(2-pyridyl)carbamate (1·42 g, 73%) as colorless prisms (hexane), m.p. 96·5–97·5°, IR 3150, 1720, 1590, 1530, 775 cm^{-1}, NMR 1·54 (9H, s, t-Bu), 6·90 (1H, t, J = 6·5 H_z, 5–H), 7·62 (1H, pair of triplets, J = 2 and 7 H_z, 4-H), 7·98 (1H, d, J = 7 H_z, 3-H), 8·32 (1H, d, J = 7 H_z, 6-H), 9·8 (1H, s, NH). (Found: C, 61·71; H, 7·16; N, 14·42. $C_{10}H_{14}O_2N_2$ requires; C, 61·83; H, 7·27; N, 14·42%).

(i) p-*Nitrobenzoic acid.* A mixture of *p*-nitrobenzoic acid (1·67 g), DPPA (3·3 g), and TEA (1·06 g) in t-BuOH (30 ml) was stirred at reflux for 20 h. Work-up as in (a)(i) followed by chromatography (C_6H_6–hexane–AcOEt, 4:5:1) afforded t-butyl *p*-nitrocarbanilate (2·01 g, 84%) as yellow crystals (C_6H_6–hexane), m.p. 112–114°, IR 3280, 1690, 1612, 1550, 1530, 1350, 750, 690 cm^{-1}, NMR 1·52 (9H, s, t-Bu), 7·12 (1H, s, NH), 7·52 (2H, d, J = 9 H_z, $2 \times$ ortho-H), 8·16 (2H, d, J = 9 H_z, $2 \times$ meta-H). (Found: C, 55·41; H, 5·89; N, 11·78. $C_{11}H_{14}O_4N_2$ requires: C, 55·45; H, 5·92; N, 11·76%).

(j) o-*Nitrobenzoic acid.* A mixture of *o*-nitrobenzoic acid (1·67 g), DPPA (2·90 g), and TEA (1·08 g) in t-BuOH (30 ml) was stirred at reflux for 15 h, and worked up as in (a)(i). The crude product was purified by column chromatography (hexane–Et_2O, 20:3) to give t-butyl *o*-nitrocarbanilate (2·14 g, 90%) as yellow crystals (Et_2O–hexane), m.p. 91–91·5°, IR 3360, 1730, 1613, 1590, 1520, 1500, 1350, 755, 670 cm^{-1}, NMR 1·52 (9H, s, t-Bu), 7·04 (1H, t, J = 8 H_z, para-H), 7·57 (1H, t, J = 8 H_z, ), 8·14 (1H, d, J = 8 H_z, ortho-H), 8·52; (1H, d, J = 8, ), 9·61 (1H, s, NH). (Found: C, 55·41; H, 5·85; N, 11·73. $C_{11}H_{14}O_4N_2$ requires: C, 55·45; H, 5·92; N, 11·76%).

(k) *N-Benzyloxycarbonyl-L-serine.* A mixture of N-benzyloxycarbonyl-L-serine (1·20 g), DPPA (1·38 g), and TEA (0·53 g) in dioxane (50 ml) was stirred at reflux for 21 h. After evaporation of the solvent, the residue was dissolved in AcOEt–C_6H_6 and washed as in (b)(iii). Drying the extracts followed by evaporation afforded a pale yellow solid, which was recrystallized from EtOH–C_6H_6 to give 4-benzyloxycarbonylamino-oxazolidone-2 (0·84 g, 71%) as colorless crystals, m.p. 174–175° (Lit.[10] 169–171°), $[\alpha]_D^{25} - 46·7°$ (c = 0·6, AcOEt) (Lit.[10] − 50°), IR 3300, 1760, 1725, 1690, 1530 cm^{-1}. (Found: C, 56·01; H, 5·16; N, 11·79. $C_{11}H_{12}O_4N_2$ requires: C, 55·93; H, 5·12; N, 11·86%).

(l) *Pivalic acid.* A mixture of pivalic acid (1·02 g), DPPA (2·90 g) and TEA (1·1 g) in C_6H_6 (30 ml) was stirred at room temp for 0·75 h, and then refluxed for 0·5 h. Benzyl alcohol (2·2 g) was added to the mixture, which was refluxed for 37 h. The mixture was worked up as in (b)(iii) to give the crude product which was purified by column chromatography (hexane–Et_2O, 2:1) to give benzyl N-t-butylcarbamate (1·31 g 63%) as a colorless oil, b.p. 93° (0·2 mmHg), IR 3340, 1710, 1520 cm^{-1}, NMR 1·26 (9H, s, t-Bu), 4·89 (2H, s, CH_2), 4·93 (1H, s, NH) 7·17 (5H, s, C_6H_5). (Found: C, 69·70; H, 8·34; N, 6·97. $C_{12}H_{17}O_2N$ requires: C, 69·54; H, 8·27; N, 6·76%).

(m) *Cyclohexanecarboxylic acid.* (i) A mixture of cyclohexanecarboxylic acid (1·28 g), DPPA (2·75 g), and TEA (1·05 g) in t-BuOH (30 ml) was stirred at reflux for 21·5 h. After work-up as in (a)(i), the crude yellow viscous residue was tritulated with hexane to give N,N'-dicyclohexylurea (0·04 g, 4%) as colorless crystals, m.p. 232°, identical with an authentic specimen. The filtrate was chromatographed on silica gel with hexane–$CHCl_3$–AcOEt (20:2:1) to give t-butyl N-cyclohexylcarbamate (0·88 g, 44%) as colorless crystals (hexane), m.p. 80·5–81°, (Lit.[25] 78°), IR 3300, 1680, 1525 cm^{-1}, NMR 1·2 (10H, m, $5CH_2$ of cyclohexane), 1·44 (9H, s, t-Bu), 3·36 (1H, m, CHN), 4·48 (1H, s, NH). (Found: C, 66·31; H, 10·89; N, 6·84. $C_{11}H_{21}O_2N$ requires: C, 66·29; H, 10·62; N, 7·03%).

Further elution of the column afforded N-cyclohexylcarbamoyl azide (0·26 g, 16%) as colorless crystals (hexane), m.p. 102–103°, IR 3240, 2110, 1710, 1680, 1545 cm^{-1}, NMR 1·2 (10H, m, $5CH_2$ of cyclohexane), 3·6 (1H, m, CH-N), 5·32 (1H, s, NH). (Found: C, 49·98; H, 7·14; N, 33·23. $C_7H_{12}ON_4$ requires: C, 49·98; H, 7·19; N, 33·31%). The structure of the carbamoyl azide was further confirmed through its conversion to N,N'-dicyclohexylurea by the action of cyclohexylamine in C_6H_6.

(ii) A mixture of cyclohexanecarboxylic acid (1·28 g), DPPA (3·3 g), and TEA (1·12 g) in C_6H_6 (30 ml) was stirred at room temp for 0·5 h, and then refluxed for 0·5 h. Benzyl alcohol (1·30 g) was added to the mixture, which was refluxed for 17 h. Work-up as in (m)(i) gave N,N'-dicyclohexylurea (0·10 g, 9%), benzyl N-cyclohexylcarbamate (1·04 g, 45%) as colorless crystals (hexane), m.p. 93–94°, IR 3340, 1695, 1550, 760, 720, 695 cm^{-1}, NMR 0·9–2·0 (10H, m, $5CH_2$ of cyclohexane), 3·43 (1H, m, CH), 4·97 (1H, s, NH), 4·99 (2H, s, CH_2), 720 (5H, s, C_6H_5), (Found: C, 71·92; H, 8·31; N, 6·02. $C_{14}H_{19}O_2N$ requires: C, 72·07; H, 8·21; N, 6·00%), and N-cyclohexylcarbamoyl azide (0·22 g, 13%).

(n) *Levulinic acid.* A mixture of levulinic acid (2·32 g), DPPA (5·5 g), and TEA (2·2 g) in t-BuOH (60 ml) was stirred at reflux for 17 h, and worked-up as in (a)(i) to give an orange oil, which was chromatographed on silica gel (hexane–$CHCl_3$–AcOEt, 4:1:1) to give t-butyl N-(3-keto-butyl)-carbamate (1·03 g. 27·5%) as a colorless oil, b.p. 113–115° (5 mmHg), IR 3320, 1715, 1690, 1520 cm^{-1}, NMR 1·42 (9H, s, t-Bu), 2·13 (3H, s, Ac), 2·66 (2H, t, J = 6 H_z, $COCH_2$), 3·32 (2H, q, J = 6 H_z, CH_2N), 5·16 (1H, s, NH). (Found: C, 57·69; H, 8·96; N, 7·34. $C_9H_{17}O_3N$ requires: C, 57·73; H, 9·15, N, 7·48%).

Further elution of the column furnished N-(3-keto-butyl)carbamoyl azide (0·45 g, 14%) as colorless crystals (Et_2O-pet. ether), m.p. 29·5°, IR 3250, 2120, 1720, 1685, 1560 cm^{-1}, NMR 2·17 (3H, s, Ac), 2·72 (2H, t, J = 6H_z, $COCH_2$), 3·43 (2H, q, J = 6 H_z, CH_2N), 6·22 (1H, s, NH).

(o) *4-Ethylenedioxypentanoic acid.* A mixture of 4-ethylenedioxypentanoic acid (0·80 g), DPPA (1·45 g), and TEA (0·55 g) in C_6H_6 (20 ml) was stirred at reflux for 0·75 h. Benzyl alcohol (1·1 g) was added to the mixture, which was refluxed for 18 h. The mixture was worked up as in (a)(i), and fractionated by column chromatography (hexane–Et_2O, 3:1). The first fraction to be eluted was benzyl 4-ethylenedioxypentanoate (0·075 g, 6%) as a colorless oil, IR 1740, 750, 700 cm^{-1}, NMR 1·26 (3H, s, Me), 2·00 and 2·29 (4H, A_2B_2 multiplets, $-(CH_2)_2-$), 3·82 (4H, s, $-O(CH_2)_2O-$), 5·02 (2H, s, CH_2 of ester), 7·28 (5H, s, C_6H_5).

The second fraction to be isolated was N-(3-ethylenedioxybutyl)carbamoyl azide (0·08 g, 8%) as a colorless oil, IR 3320, 2140, 1710, 1520 cm^{-1}, NMR 1·23 (3H, s, Me), 1·80 (2H, t, J = 6 H_z, CH_2–C), 3·42 (2H, q, J = 6 H_z, CH_2N), 3·86 (4H, s, $-O(CH_2)_2O-$), 6·03 (1H, s, NH).

The third fraction to be eluted was benzyl N-(3-ethylenedioxybutyl)carbamate (1·10 g, 83%) as a colorless oil, IR 3320, 1710, 1520 cm^{-1}, NMR 1·23 (3H, s, Me), 1·78 (2H, t, J = 6 H_z, CH_2–C), 3·22 (2H, q, J = 6 H_z, CH_2N), 3·84 (4H, s, $-O(CH_2)_2O$), 4·99 (2H, s, CH_2 of ester), 5·38 (1H, s, NH), 7·22 (5H, s, C_6H_5). (Found: C, 63·06; H, 7·35; N, 5·19. $C_{14}H_{19}O_4N$ requires: C, 63·38; H, 7·22; N, 5·28%).

(p) *Penicillin G potassium.* A suspension of penicillin G potassium (1·12 g) and DPPA (0·85 g) in t-BuOH (60 ml) was stirred at 70° (external temp) for 28 h. $CHCl_3$ (50 ml) was added to the mixture, which was then filtered. The filtrate was evaporated, and the residue was purified by column chromatography (C_6H_6–AcOEt–$CHCl_3$, 4:3:1) to give t-butyl N-(2,2-dimethyl-6-phenylacetamido-3-penamyl)carbamate (0·97 g, 80%) as colorless needles ($CHCl_3$-hexane), m.p. 203–207° (dec), $[\alpha]_D^{20} + 203°$ (c = 0·7, EtOH), IR 3320, 3250, 1800, 1695, 1660, 1550, 1530, 760, 730, 700 cm^{-1}, NMR 1·29 (3H, s, Me), 1·40 (3H, s, Me), 1·45 (9H, s, t-Bu), 3·61 (2H, s, CH_2), 5·16–5·34 (3H, m, 3-H, 5-H, 6-H), 5·49 (1H, d, J = 4 H_z, NH of urethane), 6·26 (1H, d, J = 9 H_z, NH of amide), 7·25 (5H, s, C_6H_5). (Found: C, 58·87; H, 6·74; N, 10·17. $C_{20}H_{27}O_4N_3S$ requires: C, 59·24; H, 6·71; N, 10·37%).

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