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A new method for the synthesis of carboxamides and peptides using 1,1′-carbonyldioxydi[2(1*H*)-pyridone] (CDOP) in the absence of basic promoters

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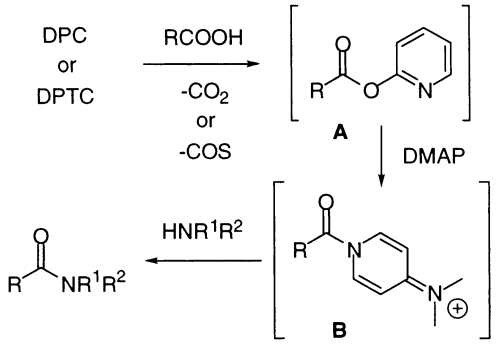
Abstract—Various carboxamides or peptides are synthesized from the corresponding carboxylic acids and amines or α-amino acids using 1,1′-carbonyldioxydi[2(1*H*)-pyridone]. The reaction proceeds in the absence of basic promoters such as triethylamine or 4-(dimethylamino)pyridine, therefore, the undesired racemization does not occur at all in the segment coupling producing Z-Gly-Phe-Val-OMe and Z-Phe-Val-Ala-OMe.

The carboxamide moiety is one of the most important ingredients in natural bioactive compounds such as peptides, β-lactams and macrolactams. A new and useful method for the synthesis of these components under mild reaction conditions is now required.[1] Although many coupling reagents giving carboxamides have been investigated, there remains the severe problem that a frequent racemization occurs in the segment coupling for producing oligopeptides.[2]

Recently, we reported an effective method for the synthesis of carboxamides or dipeptides in high yields from the corresponding carboxylic acids and amines or α-amino acids by dehydration condensation using di(2-pyridyl) carbonate (DPC) or *O*,*O*-di(2-pyridyl) thiocarbonate (DPTC) in the presence of a catalytic amount of 4-(dimethylamino)pyridine (DMAP).[3,4] It was revealed there that 2-pyridyl esters **A**, reactive acylating intermediates, were in situ formed from carboxylic acids upon treatment with DPC or DPTC by the catalysis of DMAP (Scheme 1).

However, these methods were not effective for the preparation of a tripeptide derived from Z-Gly-Phe and Val-OMe since the undesired racemization proceeded to form a mixture of nearly equal amounts of LL- and DL-isomers.[5] In this reaction, the pyridyl ester **A** derived from Z-Gly-Phe would react with DMAP to form the more active pyridinium salt **B** which caused the racemization via the oxazolone intermediate.[2] Therefore, we have to investigate more efficient amidation reagents which promote the segment coupling to produce oligopeptides without the accompanying undesirable racemization.

We would now like to report a novel method for the synthesis of carboxamides using 1,1′-carbonyldioxydi[2(1*H*)-pyridone] (CDOP), a new coupling reagent related to DPC. Since this reaction proceeds in the absence of basic promoters such as DMAP, it is applied to the coupling of α-amino acids in order to produce di- or tripeptides without any loss of the chirality of the acid segments.



Scheme 1. Carboxamide-forming reaction using DPC or DPTC.

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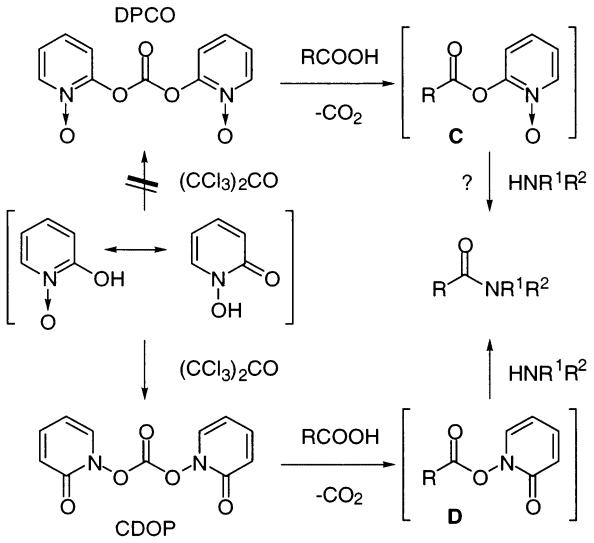


Scheme 2. Attempted synthesis of DPCO and formation of CDOP.

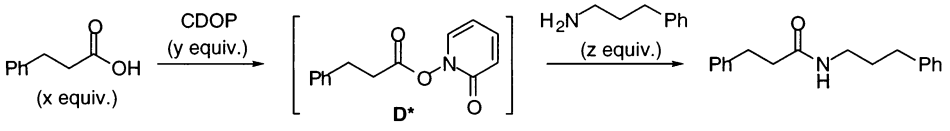
First, we tried to prepare di(2-pyridyl) carbonate *N*,*N*′-dioxide (DPCO) because it might potentially produce very active intermediates, 2-pyridyl ester *N*-oxides **C**, by the reaction with carboxylic acids (Scheme 2). However, the reaction of 2-hydroxypyridine *N*-oxides (6 equiv.) with triphosgene (1 equiv.) in the presence of pyridine (12 equiv.) did not produce the desired DPCO, but CDOP, the corresponding tautomer of DPCO, was unpredictably prepared in high yield, as shown in Scheme 2.[6,7] The structure of CDOP was confirmed by ^{1}H and ^{13}C NMR by comparison of all signals to those of a reference compound.[8] It is also assumed that the 2(1*H*)-oxo-1-pyridyl esters **D** generated from CDOP with carboxylic acids might act as reactive intermediates to form the carboxamides by the reaction with amines. Therefore, we then tried to develop a new coupling reaction using CDOP instead of DPCO according to the general procedure reported in the amidation reactions using DPC and DPTC.[3,4]

A simple amidation reaction was chosen as a model case for the first stage of the present research. 3-Phenylpropylamine (1.0 equiv.) was added to the reaction mixture of CDOP (1.1 equiv.) and 3-phenylpropanoic acid (1.1 equiv.) in dichloromethane at room temperature, and then the corresponding amide was obtained in 88% yield (Table 1, entry 1). The ^{1}H NMR of the reaction mixture in chloroform-*d* showed that 82% 2(1*H*)-oxo-1-pyridyl ester **D*** was generated from CDOP (1.2 equiv.) with 3-phenylpropanoic acid (1.0 equiv.) before adding 3-phenylpropylamine (entry 3).[9] Furthermore, the use of an excess amount of CDOP (1.5 equiv.) increased the ratio of **D*** (94%) in the ^{1}H NMR experiment (entry 4), and it was then revealed that **D*** was completely formed when 1.8 equiv. of CDOP was employed (entry 5). Actually, it was shown that the greater molar amounts of CDOP used, higher yields of the amide were attained by the successive reactions (entries 3–6). In these cases, an equal amount of amine to CDOP has to be used since an excess amount of CDOP would directly react with the amine to form the corresponding carbamate. It was determined that the use of not less than 1.8 equiv. molar amounts of CDOP with an equal amount of 3-phenylpropylamine gave the desired carboxamide in quantitative yields (entries 5 and 6).

The present reaction was performed in several polar and nonpolar solvents such as DMF (41%), THF (74%), Et_2O (46%), toluene (93%) and benzene (94%) at room temperature, and the best yield was observed when the reaction was carried out in CH_2Cl_2 (quant.).

Table 2 shows the yields of a variety of carboxamides including ones derived from bulky substrates. The reactions of benzylamine, diphenylmethylamine, benzyl-

Table 1. Formation of an active 2(1*H*)-oxo-1-pyridyl ester and its reaction with amine



Entry	*x*	*y*	*z*	Yield of **D*** (%)[a]	Yield of amide (%)[b]
1	1.1	1.1	1.0	Nd	88
2	1.2	1.2	1.0	Nd	82
3	1.0	1.2	1.2	82	88
4	1.0	1.5	1.5	94	90
5	1.0	1.8	1.8	Quant.	Quant.
6	1.0	2.0	2.0	Quant.	Quant.

[a] Conversion yield. Determined by ^{1}H NMR.[9]
[b] Isolated yield.

Table 2. Synthesis of carboxamides

Entry	Acid	Amine	Yield (%)[a]
1	$PhCH_2CH_2COOH$	$PhCH_2CH_2CH_2NH_2$	Quant.
2	$PhCH_2CH_2COOH$	$PhCH_2NH_2$	97
3	$PhCH_2CH_2COOH$	Ph_2CHNH_2	Quant.
4	$PhCH_2CH_2COOH$	$PhCH_2NHMe$	97
5	$PhCH_2CH_2COOH$	1-Adamantyl-NH_2	90
6	$PhCH_2CH_2COOH$	Piperidine	91
7	$PhCH_2CH_2COOH$	$PhNH_2$	90
8	PhMeCHCOOH	$PhCH_2CH_2CH_2NH_2$	98
9	PhCOOH	$PhCH_2CH_2CH_2NH_2$	67
10	Me_3CCOOH	$PhCH_2CH_2CH_2NH_2$	83
11	(*E*)-MeCH=CHCOOH	$PhCH_2CH_2CH_2NH_2$	87
12	(*Z*)-MeCH=CMeCOOH	$PhCH_2CH_2CH_2NH_2$	88

[a] Isolated yield.

methylamine, 1-adamantanamine and piperidine with the 2(1*H*)-oxo-1-pyridyl ester **D*** derived from 3-phenylpropanoic acid proceeded to form the corresponding coupling products in quite high yields (entries 2–6). A weak nucleophile such as aniline also reacted with **D*** to form the desired anilide in good yield (entry 7). Other 2(1*H*)-oxo-1-pyridyl esters were generated from several carboxylic acids in situ, and the reaction of the active intermediates **D** with 3-phenylpropylamine gave the corresponding carboxamides in good to excellent yields (entries 8–10). It is known that the reactions of crotonic and angelic acids with nucleophiles promoted by basic catalysts afford the *E*- and Z-mixtures since the double bond easily isomerized under basic conditions.[10] For example, the EDC/DMAP-, 2-fluoro-1-methylpyridinium 4-toluenesulfonate/triethylamine-[11] and DPC/DMAP-promoted amidation of the *E*-crotonic and angelic acids with 3-phenylpropylamine gave mixtures of two isomers (*E*- or Z-*N*-(3-phenylpropyl)crotonamide; $E/Z=96/4$, 93/7 and 93/7, respectively; *N*-(3-phenylpropyl)angelamide or *N*-(3-phenylpropyl)tiglamide; $Z/E=84/16$, 95/5 and 10/90, respectively); however, the CDOP method produced only the corresponding *E*- or *Z*-isomer in high yield (entries 11 and 12) since the present reaction takes place without any basic promoters such as tertiary amines or DMAP.

A typical experimental procedure is described for the synthesis of 3-phenyl-*N*-benzylpropanamide. To a solution of CDOP (54.8 mg, 0.221 mmol) in dichloromethane (0.8 mL) at room temperature under an argon atmosphere was added 3-phenylpropanonic acid (18.4 mg, 0.123 mmol). After the reaction mixture had been stirred for 1 h, complete consumption of the 3-phenylpropanonic acid was monitored by TLC, and then a solution of benzylamine (23.6 mg, 0.221 mmol) in dichloromethane (1.0 mL) was added at room temperature. The reaction mixture was stirred for 30 min and then the solvent was evaporated. The resulting mixture was purified by preparative TLC on silica gel (hexane/ethyl acetate = 1/1) to afford 3-phenyl-*N*-benzylpropanamide (28.4 mg, 97%) as a white solid.

Next, we applied this protocol to the synthesis of the di- and tripeptides. After treatment of several *Z*-amino acids with CDOP to produce the corresponding 2(1*H*)-oxo-1-pyridyl esters **D** in situ, Gly-OEt·HCl was added to the mixture with an equal amount of triethylamine (Table 3, entries 1–6). All reactions proceeded smoothly to afford the desired dipeptides in high yields and the optical purities of the products were not reduced through the successive reactions. Although facile racemization has been observed for the synthesis of peptides from Z-Gly-Phe with several amino acids when using conventional coupling reagents (Anteunis' test),[1f,1h–l,12] the CDOP-mediated amidation proved to be quite effective for the preparation of the LL-type of Z-Gly-Phe-Val-OMe without forming the DL-isomer (entry 7). Furthermore, the reaction of Z-Phe-Val with Ala-OMe·HCl was also examined by employing the present reaction (entries 8).[1g,13] The ^1H NMR and HPLC analyses of the formed crude product showed that the undesired LDL-stereoisomer was not generated in the least, and only the desired LLL-peptide was obtained in high yield. It is noteworthy that these segment couplings were performed without any loss of chirality and the corresponding tripeptides were synthesized in high yields with excellent purities. We further

Table 3. Synthesis of peptides and their LOC

Entry	Acid	Amine	Yield (%)[a]	LOC[b] (%)
1	Z-L-Leu	Gly-OEt·HCl	99	Nd[d]
2	Z-L-ALa	Gly-OEt·HCl	99	Nd[e]
3	Z-L-Phe	Gly-OEt·HCl	90	Nd[f]
4	Z-L-Val	Gly-OEt·HCl	93	Nd[g]
5	Z-L-Met	Gly-OEt·HCl	91	Nd[h]
6	Z-L-Pro	Gly-OEt·HCl	Quant.	Nd[i]
7	Z-Gly-L-Phe	L-Val-OMe·HCl	78	<0.1[c]
8	Z-L-Phe-L-Val	L-Ala-OMe·HCl	89	<0.1[c]
9[j]	Z-Gly-L-Phe	L-Val-OMe·HCl	58	7.6[c]
10[k]	Z-Gly-L-Phe	L-Val-OMe·HCl	56	1.6[c]
11[l]	Z-Gly-L-Phe	L-Val-OMe·HCl	62	3.0[c]
12[m]	Z-Gly-L-Phe	L-Val-OMe·HCl	77	<0.1[c]
13[n]	Z-Gly-L-Phe	L-Val-OMe·HCl	60	<0.1[c]
14[o]	Z-Gly-L-Phe	L-Val-OMe·HCl	46	14.6[c]
15[p]	Z-Gly-L-Phe	L-Val-OMe·HCl	76	96.0[c]

[a] Isolated yield.

[b] LOC = (diastereomeric excess of acid)–(enantiomeric or diastereomeric excess of product).

[c] Enantiomeric or diastereomeric excesses of acids and products were determined by HPLC.[14–16]

[d] $[\alpha]_D^{18}$ −26.3° (*c* 1.94, EtOH); cf. −26.3°.[17]

[e] $[\alpha]_D^{17}$ −22.1° (*c* 1.81, EtOH); cf. −22.2°.[18]

[f] $[\alpha]_D^{18}$ −16.7° (*c* 1.97, EtOH); cf. −16.9°.[19]

[g] $[\alpha]_D^{18}$ −25.6° (*c* 0.973, EtOH); cf. −25.3°.[20]

[h] $[\alpha]_D^{18}$ −19.7° (*c* 3.01, EtOH); cf. −19.8°.[21]

[i] $[\alpha]_D^{16}$ −60.4° (*c* 1.76, AcOEt); cf. −60.4°.[22]

[j] TBTU (1.1 equiv.), NMM (2.0 equiv.), DMF, −18°C.

[k] TBTU (1.1 equiv.), HOBt (1.1 equiv.), NMM (2.0 equiv.), DMF, −18°C.

[l] TBTU (1.1 equiv.), DIEA (2.0 equiv.), DMF, −18°C.

[m] TBTU (1.1 equiv.), HOBt (1.1 equiv.), DIEA (2.0 equiv.), DMF, −18°C.

[n] TBTU (1.1 equiv.), HOAt (1.1 equiv.), DIEA (2.0 equiv.), DMF, −18°C.

[o] DCC (1.1 equiv.), TEA (1.1 equiv.), CH_2Cl_2, −18°C.

[p] DPC (1.1 equiv.), DMAP (0.1 equiv.), CH_2Cl_2, rt, then TEA, −18°C.

examined the Anteunis' test using other effective reagents for the formation of carboxamides, and each LOC (loss of chirality) was found as shown in entries 9–15.

A typical experimental procedure is described for the synthesis of Z-Gly-Phe-Val-OMe. To a solution of CDOP (77.0 mg, 0.310 mmol) in dichloromethane (1.3 mL) at 0°C under an argon atmosphere was added Z-Gly-Phe (61.4 mg, 0.172 mmol) in dichloromethane (0.8 mL). After the reaction mixture had been stirred for 1 h at room temperature, complete consumption of the Z-Gly-Phe was monitored by TLC, and then Val-OMe·HCl (52.0 mg, 0.310 mmol) and a solution of triethylamine (31.4 mg, 0.310 mmol) in dichloromethane (1.2 mL) were successively added at −18°C. The reaction mixture was stirred for 5 min and then iced brine (10 mL) was added. The mixture was extracted with dichloromethane, and the organic layer was washed with 1 M HCl, water and brine, and dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by preparative TLC on silica gel (hexane/ethyl acetate = 1/3) to afford Z-Gly-Phe-Val-OMe (63.2 mg, 78%) as a white solid.

Thus, we developed a new reaction providing amides and peptides in high yields via active intermediates, 2(1*H*)-oxo-1-pyridyl esters **D**, using CDOP. Since this reaction proceeds in the absence of basic promoters such as tertiary amines or substituted pyridines, the undesired racemization was completely prevented in the segment coupling to afford oligopeptides. Further studies of the reaction using CDOP and other applications of the present protocol for the syntheses of useful complex molecules are now in progress.

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5. For example, a mixture of the LL- and DL-isomers (48/52) was obtained in 77% yield when using DPC (1.1 equiv.) with DMAP (0.1 equiv.) for the reaction of Z-Gly-L-Phe (1.1 equiv.) with L-Val-OMe·HCl (1.0 equiv.) and triethylamine (1.0 equiv.).
6. CDOP was synthesized as follows. To a mixture of 2-hydroxypyridine *N*-oxide (1.00 g, 9.00 mmol) and triphosgene (450 mg, 1.51 mmol) in dichloromethane (30 mL) at 0°C under an argon atmosphere was added pyridine (1.5 mL). After the reaction mixture had been stirred for 24 h at room temperature, the solvent was evaporated. The residue was washed with ether three times (each 30 mL) under an argon atmosphere. The crude CDOP was dissolved in THF (50 mL) and the suspension including pyridine·HCl salt was stirred for 2 h at room temperature and then it was allowed to stand for 30 min. After filtration of the mixture under an argon atmosphere and evaporation of the solvent at 45°C, THF (50 mL) was added to the yellow residue, and then the above operation was repeated three times. Dichloromethane (each 3 mL) and ether (each 6 mL) were successively added to the resulted mixture and the yellow solution was separated from white precipitates under an argon atmosphere, and then the above operation was repeated twice. The remaining solvent was removed under reduced pressure at 45°C to produce CDOP (1.02 g, 91%) as a white solid.
7. CDOP: mp 142–144°C (under an argon atmosphere); ^{1}H NMR ($CDCl_3$): δ 7.64 (2H, dd, J = 7.2, 2.2 Hz, H-6), 7.40 (2H, ddd, J = 9.3, 6.9, 2.2 Hz, H-4), 6.73 (2H, dd, J = 9.3, 1.8 Hz, H-3), 6.23 (2H, ddd, J = 7.2, 6.9, 1.8 Hz, H-5); ^{13}C NMR ($CDCl_3$): δ 156.3 (2), 150.2 (C=O), 140.0 (4), 134.5 (6), 122.9 (3), 105.5 (5).
8. 1-Methyl-2-pyridone: ^{1}H NMR ($CDCl_3$): δ 7.35 (2H, dd, J = 8.1, 2.2 Hz, H-6), 7.34 (2H, ddd, J = 9.7, 6.6, 2.2 Hz, H-4), 6.54 (2H, dd, J = 9.7, 1.4 Hz, H-3), 6.17 (2H, ddd, J = 8.1, 6.6, 1.4 Hz, H-5), 3.54 (3H, s, Me); ^{13}C NMR

($CDCl_3$): δ 162.9 (2), 139.7 (6), 138.8 (4), 120.2 (3), 105.8 (5), 37.4 (Me).

9. We compared the integration of the ^1H NMR peaks of H-2 in 3-phenylpropanoic acid with those of H-3 in **D*** for the determination of the conversion yield. 3-Phenylpropanoic acid: ^1H NMR (CD_2Cl_2): δ 7.35–7.23 (5H, m, Ph), 2.98 (2H, t, $J=7.6$ Hz, H-3), 2.71 (2H, t, $J=7.6$ Hz, H-2). 2(1*H*)-Oxo-1-pyridyl 3-phenylpropanoate (**D***): ^1H NMR (CD_2Cl_2): δ 7.81–5.32 (9H, m, Ph, Py), 3.11–3.06 (2H, m, H-3), 2.99–2.93 (2H, m, H-2).
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14. Z-Gly-D/L-Phe; HPLC (CHIRALCEL AS-RH, CH_3CN/H_2O–H_3PO_4 (pH 2) = 40/60, flow rate = 0.35 mL/min, detect 220 nm): $t_R = 12.1$ min (L form), $t_R = 13.8$ min (D form).
15. Z-Gly-D/L-Phe-L-Val-OMe;[1f,1i–l] HPLC (Kromasil KR 100-10 C18 (4.6×25 cm), CH_3CN/H_2O (0.1% TFA) = 48/52, flow rate = 1.5 mL/min, detect 220 nm): $t_R = 9.5$ min (LL form), $t_R = 10.6$ min (DL form).
16. Z-L-Phe-D/L-Val-L-Ala-OMe;[23] HPLC (Cosmosil 5C18 (4.6 I.D.×150 mm), $MeOH/H_2O = 60/40$, flow rate = 1.0 mL/min, detect 254 nm): $t_R = 15.2$ min (LLL form), $t_R = 17.9$ min (LDL form).
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