Communications to the Editor

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AN EFFICIENT TRANSFORMATION OF N-ACYL-α-AMINO ACIDS INTO DIACYLAMINES VIA 2,4-DISUBSTITUTED OXAZOL-5(4H)-ONES[1)]

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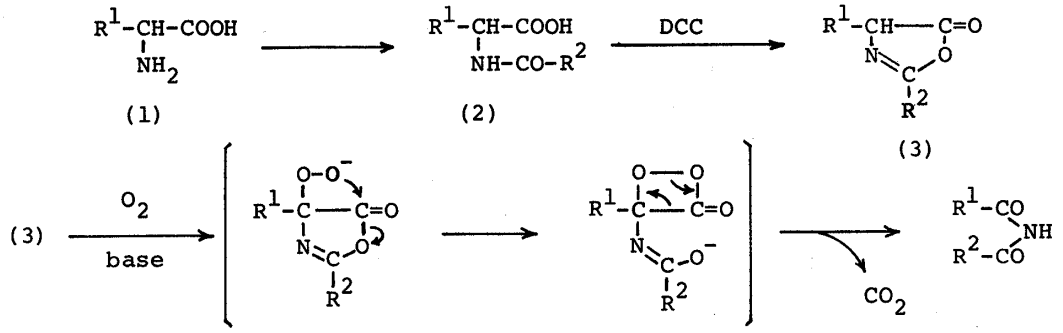
Base-catalyzed oxygenative decarboxylation of a variety of 2,4-disubstituted oxazol-5(4H)-ones in benzene with triethylamine or in dimethyl sulfoxide with potassium tert-butoxide gives diacylamines.

KEYWORDS —— base-catalyzed autooxidation; selective oxygenation; decarboxylation; oxazol-5(4H)-one; N-acyl-α-amino acid; diacylamine

The chemistry of oxazol-5(4H)-ones has been fairly well studied because their formation is often responsible for the racemization observed in peptide syntheses.[2)] Concerning oxidation of the ring system, however, only very few reports are available in the literature.[3-7)] We recently reported that ethyl N-benzoyl-α-phenylglycinates underwent oxygenative deethoxycarbonylation in the presence of strong bases to give dibenzoylamines.[8)] This method, however, could not be applied to the conversion of various carboxamidoacids derived from α-amino acids to diacylamines. We have found that such a conversion of α-amino acids can be realized in good yields by use of a variety of 2,4-disubstituted oxazol-5(4H)-ones (3), synthesized from α-amino acids by an acylation-dehydration sequence, and the preliminary results are reported herein (Chart 1 and Table 1).

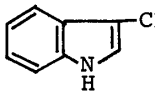
DL-N-Acyl-α-amino acids (2) (1 mmol) derived from the corresponding α-amino acids (1) were converted to 2,4-disubstituted oxazol-5(4H)-ones (3) by treatment with N,N'-dicyclohexylcarbodiimide (1.2 mmol) in tetrahydrofuran at 0-10 °C for 24 h. After the removal of the dicyclohexylurea precipitated, (3a)-(3j) were recrystallized from benzene-n-hexane in good yields. They were characterized by means of elemental analyses and IR spectral data.[18)] The isolation of (3), however, is essentially unnecessary for the subsequent oxygenation.



(1) (2) (3)

(3a) R^1=Pr^i, R^2=Ph (3b) R^1=Et, R^2=Ph (3c) R^1=Ph-CH_2-, R^2=Ph

(3d) R^1=Ph, R^2=Et (3e) R^1=Ph, R^2=Pr^i (3f) R^1=Ph, R^2=Pr^n

(3g) R^1=  , R^2=Ph

(3h) R^1=  , R^2=Ph

(3i) R^1=(p)-PhCOO-Ph-CH_2-, R^2=Ph

(3j) R^1=CH_3-S-$(CH_2)_2$-, R^2=Ph

(3k) R^1=Ph, R^2=(p)-NO_2-Ph-

Chart 1

Table 1. Base-Catalyzed Oxygenative Decarboxylation of Compound (3) to Diacylamines (4)

			Reaction condition		Products (4)[a]	
Compounds[a]	mp/°C	Yield/%[b]	Method	Time/h	Yield/%[b]	mp/°C
(3a)	71-71.5	86	A	2	90	156
(3b)	54-55.5	89	A	2	76	97-98.5
(3c)	70-70.5	83	A	2	86	126-128
(3d)	52.5-54	93	A	2	12	98
			B	9	84	
(3e)	24	80	A	2	33	154
			B	11	93	
(3f)	46-48	90	A	2	16	118-119
(3g)	142	81	A	2	8	
			B	16	76	173.5
			C	0.5	78	
(3h)	141-142.5	87	B	1	78	192
(3i)	98-99	78	B	1	83	78
(3j)	35.5-37	54	B	1	72	94-96

a) (3a)[9] was derived from L-valine, $[\alpha]_D^{25}$ = +4.9, the optical purity is undetermined. Compounds (3b),[10] (3c),[11] (3e),[12] (3i),[13] (3j),[17] and (4a)-(4e)[14-16] are known. The analytical and spectral data of other new compounds were in good agreement with the structures.[18] b) Isolated yields.

When molecular oxygen was bubbled through a mixture of 2-phenyl-4-alkyloxazol-5(4H)-ones (1 mmol), (3a)-(3c), and potassium tert-butoxide (3 mmol) in dimethyl sulfoxide (25 ml) at 0°C (Method A), the corresponding diacylamines (4) were obtained in good yields within 2 h. After neutralization of the reaction mixture with an aqueous HCl solution, (4) was extracted with ethyl acetate and then recrystallized from benzene. On the other hand, the same reactions of 2-alkyl-4-phenyloxazol-5(4H)-ones, (3d)-(3f), were complicated by a side reaction and gave the corresponding (4) in only low yields. Their oxygenative decarboxylations, however, could be achieved in satisfactory yields when the reactions were carried out in benzene (25 ml) with excess triethylamine (~10 mmol) at ambient temperature (Method B). The reactions were certainly slow compared to the reactions carried out by Method A, but the side reaction was minimized. The diacylamines were easily separated by passing the reaction mixture through a short silica-gel column eluting with benzene and then they were recrystallized from benzene. Evolution of carbon dioxide was checked by trapping it in an aqueous $Ba(OH)_2$ solution. No serious side reaction is observed even in the case of oxazol-5(4H)-ones with a singlet-oxygen-labile functional group at the C-4 position such as (3g)-(3j). Nor is protection of the NH group required in (3g) and (3h). The method, therefore, is valuable for selective oxygenative decarboxylation of oxygen-labile α-amino acids. With increased oxygen pressure ($4kg/cm^2$), the reaction time can be shortened and the yield of (4) is slightly increased (Method C).

These oxygenative decarboxylations also proceed in the dark. 9,10-Diphenylanthracene, a compound which was added as a singlet-oxygen trap, had no effect on the yield of (4) and was recovered unchanged (97.5%). The present oxygenation is, therefore, a base-catalyzed autooxidation, and should be distinguished from the singlet-oxygen-promoted oxygenation of some oxazol-5(4H)-ones reported by Chuaqui et al.[7)]

An attempt to trap a peroxidic intermediate was unsuccessful but chemiluminescence (CL) observed during the oxygenative decarboxylation of 2-(p-nitrophenyl)-4-phenyloxazol-5(4H)-ones (3k) suggests that a dioxetanone-mechanism shown in Chart 1 is actually operating to yield the corresponding diacylamine. The pathway, however, will not be necessarily predominant, because the intensity of the CL of (3k) is weaker than that of the closely related compound, ethyl N-(p-nitrobenzoyl)-phenylglycinate (about 19% in relative intensity), which would provide only 1,2-dioxetanone and/or 4-hydroperoxide as a peroxidic intermediate in the oxygenation.

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18) All oxazolones have characteristic IR absorptions due to the C=O and C=N bonds at 1800-1840 and 1630-1650 cm^{-1}, respectively. For example, (3g): Anal. Calcd for $C_{18}H_{14}N_2O_2$:C, 74.47; H, 4.86; N, 9.65. Found: C, 74.63; H, 4.90; N,9.62%. ν_{max} (nujol) 3210 (NH), 1808 (C=O in five-membered ring), 1654 cm^{-1} (C=N in five-membered ring). δ_H ($CDCl_3$) 4.74 ppm (t, 1H, J=6.0 Hz). (4g): Anal. Calcd for $C_{17}H_{14}N_2O_2$: C, 73.36; H, 5.07; N, 10.07. Found: C, 73.54; H, 4.85; N, 10.24%. ν_{max} (nujol) 3405 and 3310 (NH), 1730 and 1640 cm^{-1} (C=O).

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