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THE OXAZOLE-TRIAMIDE REARRANGEMENT. APPLICATION TO PEPTIDE SYNTHESIS

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Abstract: The carboxyl group of a N-acylated amino acid may be protected by conversion to an oxazole derivative which, on photooxygenation, regenerates the carboxyl group in activated (triamide) form for peptide synthesis.

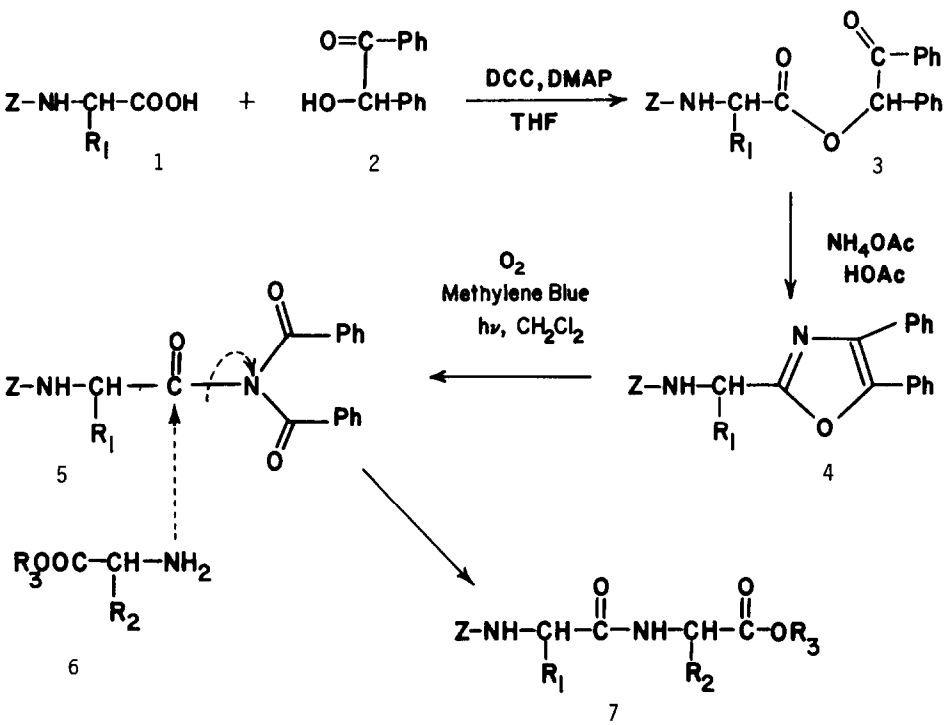
We have recently reported[1,2,3,4] that the dye-sensitized photooxidation of 2-alkyl-4,5-diaryl oxazoles yields triamides which undergo ready intramolecular alcoholysis at the acyl carbonyl group, leading to the synthesis of a series of macrolides. Generation of activated carboxylates by this mild, efficient procedure offers possibilities for acylation reactions applicable to the formation of peptide linkages.

Use of an oxazole as the source of a latent carboxyl group has special advantages, because the heterocyclic system is relatively resistant to many of the operations involved in the introduction or removal of protecting groups during peptide synthesis. Of particular significance is the fact that the carboxyl group is liberated from its protected state (in nearly quantitative yields) in an activated (triamide) form for reaction with nucleophilic species.

We have now developed a procedure for converting N-protected amino acids to dipeptides through the steps of protection (by conversion to the oxazole) and then deprotection-activation (by dye-sensitized photooxidation). As part of the triamide function, the carboxyl group is sufficiently reactive to couple directly with the amino group of an amino acid. As described below, the yields are good, and, for dipeptide synthesis, the method is gentle enough to preserve the optical integrity of chiral reactants. In our further work we are seeking to increase the sensitivity of our analytical method for detecting racemization by use of the Merrifield modification[17] of the Manning and Moore method[18].

The N-carbobenzyloxyamino acid (1) is reacted with (±)-benzoin (2), in THF using N,N'-dicyclohexylcarbodiimide[5] (DCC) and 4-N,N'-dimethylaminopyridine (DMAP) as coupling reagents, to give the benzoin ester (3), which is treated with ammonium acetate in glacial acetic acid to afford the oxazole[6] (4) in yields of 80-85%.

Photooxygenation[3] of the substituted oxazole (4) in dry CH_2Cl_2 using methylene blue as a sensitizer forms the triamide (5) which is reacted directly with an amino acid or ester (6) in DMF to yield the dipeptide (7). The dipeptides prepared by this sequence are listed in Table I. Full details of these procedures are provided in footnotes 15 and 16.



We are exploring further applications of this method in the formation of peptides including solid-phase peptide synthesis.

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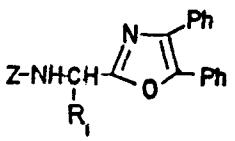
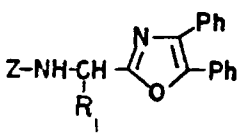
TABLE

Protected Amino Oxazole	Amino Acid or Ester	Dipeptide[c]	m.p., °C	$[\alpha]_D^d$	Yield[e]
 4a, R = CH_2Ph	$H_2N-CH(CH_3)-COOH$ (6a)	Z-Phe-AlaOH (7a)	153-154 152-153[9] ---[b,11]	-10.00±0.01 -10.68±0.01[a] -10.00±0.05[b]	64
	$H_2N-CH(CH_3)-COOC_2H_5$ (6b)	Z-Phe-AlaOEt (7b)	118-119 121.5[b,12]	-22.12±0.01 -19.68[b]	85
	$H_2N-CH(CH_2CH(CH_3)_2)-COOH$ (6c)	Z-Phe-LeuOH (7c)	139-141 140-141[a] 141-142[b,13]	-16.35±0.01 -16.76±0.01[a] -20[b]	64
 4b, R = H	H_2N-CH_2-COOH (6d)	Z-Gly-GlyOH (7d)	176-178 177-178[a] 178[b,14]	--	52
	$H_2N-CH(CH_2Ph)-COOH$ (6e)	Z-Gly-PheOH (7e)	124-125 126.5-127.5[b,15]	39.67±0.01 40.7±1.7[b]	71

a. authentic sample
b. literature value
c. all amino acids have the L-configuration
d. temperature and solvents are the same as those used in references 11-15
e. yields are for pure products isolated after workup and purification by chromatography

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9. We thank Dr. J.S. Fruton for an authentic sample.

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15. 2-[1-[N-[(phenylmethoxy)carbonyl] amino]-2-phenylethyl]-4,5-diphenyloxazole (4a): To a mixture of N-[(phenylmethoxy)carbonyl]-L-phenylalanine (1.50 g, 5 mmol), (±)-benzoin (1.17 g, 5.5 mmol), DCC (1.14 g, 5.5 mmol) and DMAP (0.06 g, 0.5 mmol) in a dry flask, was added dry (freshly distilled) THF (25 mL) with stirring at ambient temperature under N_2 pressure for 6 h. The N,N'-dicyclohexylurea was removed by filtration and the solvent evaporated at reduced pressure. The residue was taken up in CH_2Cl_2 (150 mL) and washed successively with 5% aq HCl (3x75 mL), sat. $NaHCO_3$ (2x75 mL) and sat. NaCl (1x75 mL), and the organic layer dried (anhy. Na_2SO_4), filtered, and solvent removed to give the benzoin ester as a pale yellow solid. To this crude product, dissolved in glacial acetic acid (10mL), was added ammonium acetate (0.96 g, 12.5 mmol), and the stirred reaction heated at 90°C under N_2 pressure for 10 h. The dark brown reaction mixture was cooled, treated with water (100 mL) and the resulting oil extracted with CH_2Cl_2 (4x50 mL). The combined CH_2Cl_2 extracts were washed successively with water (1x100 mL) and sat. NaCl (1x75 mL), dried (anhy. Na_2SO_4), filtered, and the CH_2Cl_2 removed at reduced pressure to give the crude oxazole (4a). Purification was effected by flash chromatography on silica gel (150 g, CH_2Cl_2-EtOAc, 119:1) furnishing 1.88 g (79%) of pure (4a) as a pale yellow viscous oil. ^{1}H NMR ($CDCl_3$) δ7.03-7.65 (m, 20H), 5.65 (d, 1H), 5.32 (m, 1H), 5.09 (s, 2H), 3.28 (d, J=8 Hz, 2H); IR ($CDCl_3$) 3425, 3030, 2940, 1718, 1510 cm^{-1}; mass spectrum, m/z 474 (M).

16. N-[N-[(phenylmethoxy)carbonyl]-L-phenylalanyl]-L-alanine (7a): To a dry photolysis well containing methylene blue (1 mg) was added (syringe) a solution of 2-[1-[N-[(phenylmethoxy) carbonyl] amino]-2-phenylethyl]-4,5-diphenyloxazole (4a) (60 mg, 0.126 mmol) in dry CH_2Cl_2 (25 mL), and dry oxygen bubbled through the closed system during illumination by a tungsten-halogen lamp (650w, 100v) for 0.5 h at cooling water temperature. The reaction mixture was transferred through a needle to a dry flask containing L-alanine (6a) (14 mg, 0.158 mmol, 1.25 eq) and the CH_2Cl_2 removed under reduced pressure. Dry DMF (2 mL) was added to the mixture containing intermediate triamide and L-alanine, and the reaction stirred under N_2 at ambient temp. for 6 h. The DMF was removed in vacuo (0.25 mmHg, 0 C then 25 C), and the residue taken up in ethyl acetate (20 mL). The EtOAc extract was filtered to remove excess L-alanine, and solvent removed to give the crude dipeptide (7a) which was purified by flash chromatography (silica gel 6 g, HOAc-Hexane-EtOAc, 1:50:50) yielding 30 mg (64%) of pure (10) as a white solid. A sample recrystallized from EtOAc-Hexane had a melting point 153-154°C, and $[\alpha]_D^{22}$ -10.00±0.01° (c=1.9, alc.), ^{1}H NMR ($CDCl_3$) δ 7.30, 7.22 (m, 10H), 6.10 (br., 2H), 5.56 (d, br., J 7.5 Hz, 1H), 5.05 (s, 2H), 4.45 (m, 1H), 3.04 (d, J 7 Hz, 2H), 1.29 (d, J 11 Hz, 3H). IR (KBr) 3275, 1695, 1645, 1535 cm^{-1}.

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