Photolysis of Diacyl Peroxides: A Radical-Based Approach for the Synthesis of Functionalized Amino Acids

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ABSTRACT



Photolysis of the amino acid derived symmetrical and unsymmetrical diacyl peroxides at 254 nm at low temperature (-78 to -196 °C) generates various bis(amino acids) in a concise manner and with orthogonal protection. The methodology was applied to the synthesis of (4*R*)-5-propyl-L-leucine (PrLeu), a component of HUN-7293.

Thermal or photochemical decompositions of diacyl peroxides are well-studied reactions that in principle provide an extremely useful method of carbon–carbon bond formation starting from two carboxylic acids (Figure 1).¹ In practice,



Figure 1. Decomposition of diacyl peroxides with radical coupling.

the approach is not often used because of the perception that all diacyl peroxides are explosive² and the recurring observation that extensive side reactions (e.g., hydrogen abstraction) and crossover radical coupling products occur. However, in 1985 Schäfer and co-workers reported the low temperature (-78 °C) photolysis of aliphatic diacyl peroxides for the efficient synthesis of long chain aliphatic hydrocarbons.³ The potential of this chemistry remains relatively unexplored, especially for synthesis of chiral molecules bearing multiple heteroatoms and functional groups.^{3c} Our interest in diaminopimelic acid (DAP) derivatives as antimicrobial enzyme inhibitors⁴ and also in cross-linking of linear peptides to replace cysteine disulfides with diaminosuberic acid moieties⁵ led us to examine low-temperature photolysis of peroxides derived from protected glutamic and/or aspartic acids. We

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⁽²⁾ Warning: Although larger diacyl peroxides cannot be detonated, small diacyl peroxides with \leq 7 carbons on each side (e.g., diacetyl peroxide) can be explosive and hazardous. As scrambling of acyl groups can occur during preparation, coupling of small acyl groups (e.g., acetyl) should be avoided. For example of scrambling, see: Staab, H. A.; Rohr, W.; Graf, F. *Chem. Ber.* **1965**, *98*, 1128–1133.

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^{*a*}isolated yield; ^{*b*}yield over three steps; ^{*c*}yield based on recovered diacyl peroxide.

Figure 2. Synthesis and photolysis of amino acid derived diacyl peroxides.

now report that this offers facile access to complex amino acids⁶ with surprising stereocontrol at the intermediate radical center.

Both symmetrical and unsymmetrical diacyl peroxides of amino acids served as starting materials for this study. The symmetrical diacyl peroxides of the suitably protected aspartic or glutamic acids **1** can be synthesized by activation of the carboxyl group with DCC and coupling with 0.5 equiv of urea-hydrogen peroxide (UHP)⁷ (Figure 2). The unsymmetrical diacyl peroxides **4** ($n \neq m$) are available by DCC-

mediated coupling of protected amino acids with 2-methoxyprop-2-yl hydroperoxide,⁸ acidic deprotection of the resultant peresters **2**, and acylation of the corresponding peracids **3** with another protected amino acid (DCC/MeCN). The diacyl peroxides **4** are stable to shock and can be stored for several weeks at -20 °C without decomposition (especially as solutions in ethyl acetate).

To avoid generation of complex mixtures and crossover products, the photolysis reactions on the peroxides are best done on neat substrates (solids as well as oils, no solvent)³ at either -78 °C (Ar atmosphere) or -196 °C (N₂ atmosphere) with a 254-nm UV lamp (typical reaction times are 2-5 days).⁹ In this fashion, cage recombination of the resulting alkyl radicals is enhanced as movement of the reactive partners is relatively constrained.³ Higher temperatures or frozen solutions (e.g., dioxane, alcohols, water) afford numerous side products and low yields. Thus, photolysis of the symmetrical diacyl peroxides (+)-4a and (+)-4b generates enantiomerically pure derivatives of diaminoadipate (+)-5a and diaminosuberate (+)-5b, respectively. Photolysis of unsymmetrical diacyl peroxides (+)-4c and (+)-4d produces optically pure diaminopimelate derivatives, (+)-5c and (+)-5d, which are orthogonally protected, with no detectable crossover products (i.e. diaminoadipates or diaminosuberates).

Some starting material is generally recovered even after prolonged (2-5 days) irradiation, possibly because of photoprotection of lower substrate layers by strata above them. Although optimal ratios of surface area to layer thickness may be substrate-dependent and have not yet been determined, photolyses on ca. 0.5 mmol are readily accomplished using a 100-mL beaker as the reaction vessel. In this regard, benzyl and Cbz protecting groups are compatible with the photolysis method, but Fmoc moieties hinder facile cleavage of the diacyl peroxide, as does an aromatic acyl group directly attached to the peroxide oxygen. An alternative approach to symmetrical amino acids is Kolbe electrolysis¹⁰ of suitably protected aspartic or glutamic acids having a free distal carboxyl.¹¹ However, coupling of two different partners by electrolysis usually generates complex mixtures and very low yields of desired products.¹² The present method offers an attractive alternative.

Stereocontrol in the photolysis step is demonstrated by synthesis of (4R)-5-propyl-L-leucine (PrLeu¹³ derivative 9,

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⁽⁹⁾ All reactions were conducted with a 0.9-A UV lamp. The apparatus is extremely simple. For reactions at -78 or -85 °C, the substrate can be placed on the bottom of an open 500-mL capacity measuring cylinder immersed in a cooling bath, while for reactions at -196 °C, the substrate can be placed on the bottom of an open beaker sunk in a dewar of liquid N₂, with irradiation directly from above.

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Figure 3. Syntheses of (2S,4R)-5-propyl-L-leucine (9) and its isomer 14.

Figure 3), a component of HUN-7293 (a potent inhibitor of vascular cell adhesion molecule 1 (VCAM-1) exhibiting antiinflammatory properties).¹⁴ Conversion of Boc-Glu-OBzl-(OH) (6) into its α -methyl ester and subsequent alkylation with LiHMDS/MeI gives the *anti*-isomer 7 of β -methylglutamate.¹⁵ Hydrogenolysis and treatment with pervaleric acid¹⁶/DCC affords diacyl peroxide (+)-8. Photolysis of neat 8 at -85 °C produces (-)-9 in 53% yield along with its (4*S*)-isomer in 4.3:1 diastereomeric ratio.

The retention of configuration at C4 in the photolysis reaction is confirmed by comparison (¹H NMR in C₆D₆) of (–)-**9** with its *syn*-diastereomer ((4*R*)-5-propyl-D-leucine, the enantiomer of (+)-**14**), synthesized by an approach closely related to that of Boger and co-workers.¹³ The diastereomeric ratio in the photolysis reaction can be improved to 5.1:1 at –196 °C (50% yield of **9**). In contrast, photolysis of neat **8** at 20 °C in open atmosphere gives 30% yield of **9** with a



Figure 4. Syntheses of serine (16a) and homoserine (16b).

1.5:1 diastereomeric ratio. Lower yields in the photolysis reaction are due to the formation of Boc-allylglycine (10) as a byproduct (26–34%). To probe the possible effect of the second chiral center in 9 on the stereochemical outcome of the photolysis reaction, the corresponding *syn*-diastereomer (–)-13 was synthesized starting from pyrrolidin-2-one derivative 11.¹⁷ Photolysis of neat (–)-13 at –196 °C again generates primarily the product showing retention of configuration during coupling, (+)-14 (dr 5:1).

The photolysis is readily extended to amino acid peresters. DCC-mediated coupling of protected aspartic or glutamic acids with *tert*-butyl hydroperoxide provides the corresponding peresters **15a,b** in quantitative yields. Photolysis as before forms the corresponding protected serine ((–)-16a, 54% yield) and homoserine derivatives ((+)-16b, 89% yield). In conclusion, photolysis of glutamate- or aspartate-derived diacyl peroxides or peresters is a concise method for the synthesis of functionalized optically pure amino acids, including orthogonally protected bis(amino acids). These C–C bond-forming reactions are safe, do not require complex apparatus,⁹ and show surprising stereocontrol. Current investigations on the scope and limitations of this method as well as applications to synthesis of cyclic peptides will be reported later.

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Supporting Information Available: Typical experimental procedures and spectroscopic data of diacyl peroxides and photolysis products. This material is available free of charge via the Internet at http://pubs.acs.org.

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