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Retention of Configuration in Photolytic Decarboxylation of Peresters to Form Chiral Acetals and Ethers

M. Daniel Spantulescu, Marc A. Boudreau, and John C. Vederas*

Department of Chemistry, University of Alberta, Edmonton, Alberta, Canada T6G 2G2

john.vederas@ualberta.ca

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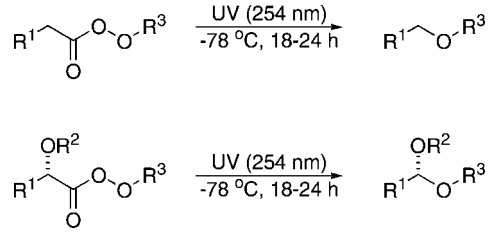
ABSTRACT



Peresters generate ethers in good yields when photolyzed in the absence of solvent using short wavelength UV light. At −78 °C or below, the process proceeds predominantly with retention of configuration at the site adjacent to the carbonyl where the decarboxylation occurs, but increase in temperature results in loss of stereochemical control. Chiral acyclic acetals can be prepared using precursors derived from tartaric or malic acids.

Photolysis of diacyl peroxides derived from glutamic and/or aspartic acids provides a convenient method for generation of unusual chiral α-amino acids (Scheme 1).[1,2] Interestingly, an aspartic peracid derivative used as a precursor in the synthesis of such diacyl peroxides is also useful for chiral epoxidations.[3] During our studies, we observed that photolysis of analogous peresters results in homolytic cleavage of the peroxide bond followed by decarboxylation and radical coupling to give ether derivatives of serine or homoserine.[1a] As coupling of the radicals derived from the diacyl peroxides[1,2] proceeds with excellent retention of configuration at low temperature in the absence of solvent, it seemed that the corresponding reaction of peresters having a stereogenic center adjacent to the carbonyl could allow generation of chiral ethers. In the present study, we investigate the scope of this reaction with derivatives of glutamic acid, malic acid and tartaric acid for preparation of ethers, chiral acyclic acetals and deoxy sugar derivatives. Although excellent stereochemical control of formation of cyclic acetals (e.g., sugars) is often readily achieved with the assistance of stereoelectronic effects, this is more difficult with acyclic systems. Previous syntheses of chiral acyclic acetals have been realized via the Baeyer−Villiger oxidation of optically active α-alkoxy ketones,[4] the enantioselective reduction and acetylation of esters,[5] or the methoxyselenenylation of alkyl vinyl ethers.[6] These methodologies are useful, but employ different starting materials. In addition, they can sometimes necessitate either lengthy syntheses to access the required

(1) (a) Spantulescu, M. D.; Jain, R. P.; Derksen, D. J.; Vederas, J. C. *Org. Lett.* **2003**, *5*, 2963–2965. (b) Jain, R. P.; Vederas, J. C. *Org. Lett.* **2003**, *5*, 4669–4672. (c) Stymiest, J. L.; Mitchell, B. F.; Wong, S.; Vederas, J. C. *J. Org. Chem.* **2005**, *70*, 7799–7809. (d) Martin, N. I.; Woodward, J. J.; Winter, M. B.; Beeson, W. T.; Marletta, M. A. *J. Am. Chem. Soc.* **2007**, *129*, 12563–12570.

(2) For related studies on other peroxides see: (a) Feldhues, M.; Schäfer, H. J. *Tetrahedron* **1985**, *41*, 4213–4235. (b) Feldhues, M.; Schäfer, H. J. *Tetrahedron* **1986**, *42*, 1285–1290. (c) Lomölder, R.; Schäfer, H. J. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1253–1254.

(3) (a) Peris, G.; Jakobsche, C. E.; Miller, S. J. *J. Am. Chem. Soc.* **2007**, *129*, 8710–8711. (b) Jakobsche, C. E.; Peris, G.; Miller, S. J. *Angew. Chem., Int. Ed.* **2008**, *47*, 6707–6711. (c) Berkessel, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 3677–3679.

(4) Matsutani, H.; Ichikawa, S.; Yaruva, J.; Kusumoto, T.; Hiyama, T. *J. Am. Chem. Soc.* **1997**, *119*, 4541–454.

(5) Rychnovsky, S. D.; Bax, B. M. *Tetrahedron Lett.* **2000**, *41*, 3593–3596.

(6) Uchiyama, M.; Satoh, S.; Ohta, A. *Tetrahedron Lett.* **2001**, *42*, 1559–1562.

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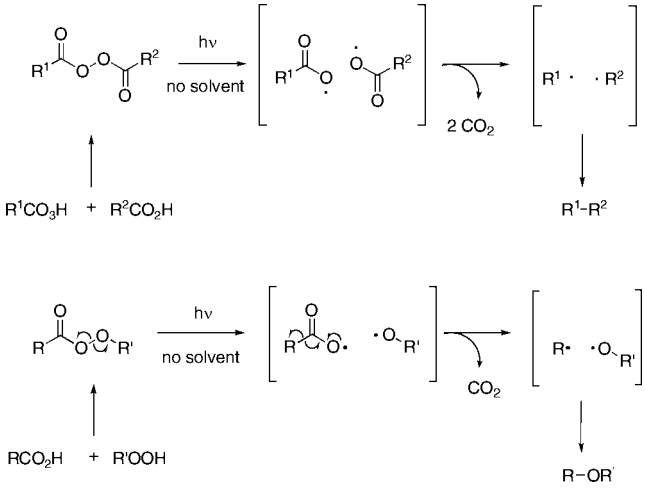
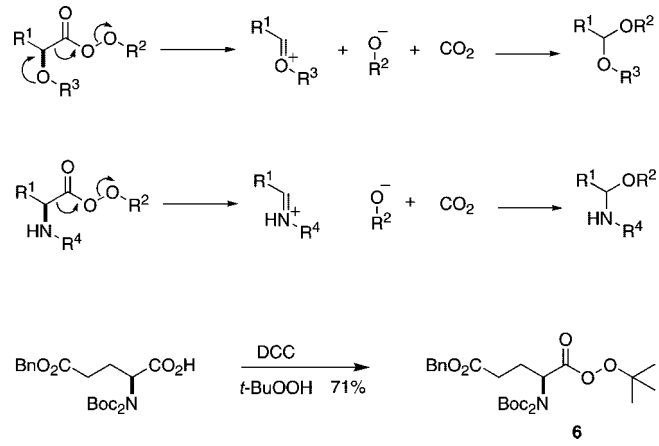
Scheme 1. Preparation and Low Temperature (−78 to −196 °C) Photolysis of Diacyl Peroxides in the Absence of Solvent and Corresponding Formation and Photolysis of Peresters



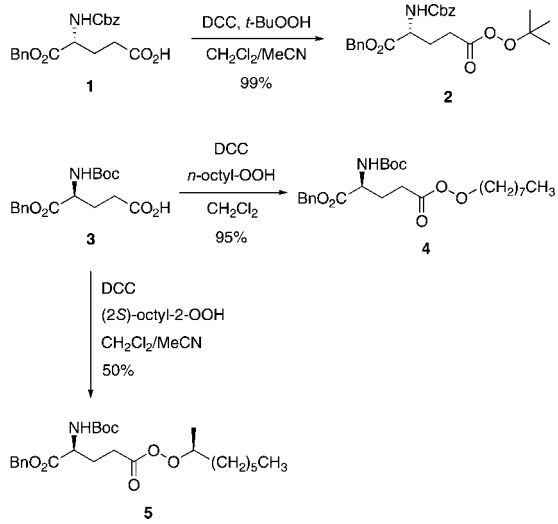
Scheme 3. Proposed Mechanisms of Decomposition of α-Alkoxy (R^3 = Alkyl), α-Hydroxy (R^3 = H) and Mono α-*N*-Acylamino (R^4 = Acyl) Peresters[a]



[a] Peresters such a **6** bearing two acyl substituents on nitrogen are much more stable.

substrates or can suffer from limited scope and modest stereoselectivity.

Scheme 2. Examples of Synthesis of Peresters from Protected Glutamates



Syntheses of functionalized peresters that do not have an oxygen or nitrogen substituent on the α-carbon adjacent to a perester carbonyl usually proceed uneventfully from the corresponding acid and hydroperoxide using a standard ester formation method, such as dicyclohexylcarbodiimide (DCC) and *N*,*N*-dimethylaminopyridine (DMAP) (Scheme 2).[7] Primary and tertiary hydroperoxides typically give better yields of perester (95−99%) than secondary hydroperoxides (50%). In contrast, if a monoacylated nitrogen or nonacylated oxygen (e.g., hydroxy or alkoxy) is present at the α-carbon of the acid, attempted perester formation leads to heterolytic decomposition to an N-acyl iminium ion or oxonium ion, respectively (Scheme 3).[8] These then swiftly react with a nucleophile. Substitution of the nitrogen with an additional acyl group (e.g., phthalimido or succinimido)[8a] does stabilize these systems such that peracids or peresters can be isolated. Hence it is possible to prepare the *t*-butyl perester of a bis-Boc protected α-amino acid such as **6** after a tedious series of protection and deprotection steps. Fortunately, peresters having an acylated oxygen α to the carbonyl are considerably more stable and easier to prepare. Syntheses of such peresters proceeds reasonably from the corresponding acids and hydroperoxides under standard conditions.

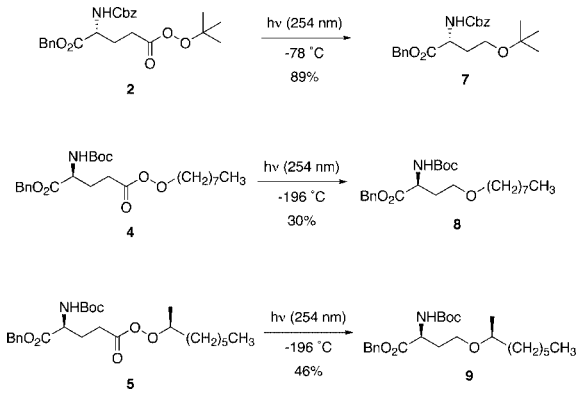
We previously reported preparation of *t*-butyl ethers of protected serine and homoserine (e.g., **7**) by photolysis of the corresponding *t*-butyl peresters of protected aspartate and glutamate (e.g., **2**) (Scheme 4).[1a] To further examine the scope of this reaction, **4** and **5** were photolyzed in the absence of solvent at −196 °C to afford the corresponding homoserine ethers **8** and **9**. The yields are lower upon going from a tertiary to a primary or secondary hydroperoxide. This may be a result of a higher propensity for side reactions to occur with these less-substituted radical intermediates. The results demonstrate that a large variety of chiral α-amino acids with an ether oxygen in the side chain are readily accessible by this method.

To examine the stereochemical outcome of photolyses of *O*-acylated α-hydroxy peresters, commercially available tartaric and malic acid derivatives were converted to corresponding protected *t*-butyl peresters (Scheme 5). Typically, the *R*,*R*-tartaric acid (**10**), its benzoylated derivative **11**, or alternatively, *meso*-tartaric acid (**21**) can be cyclized with

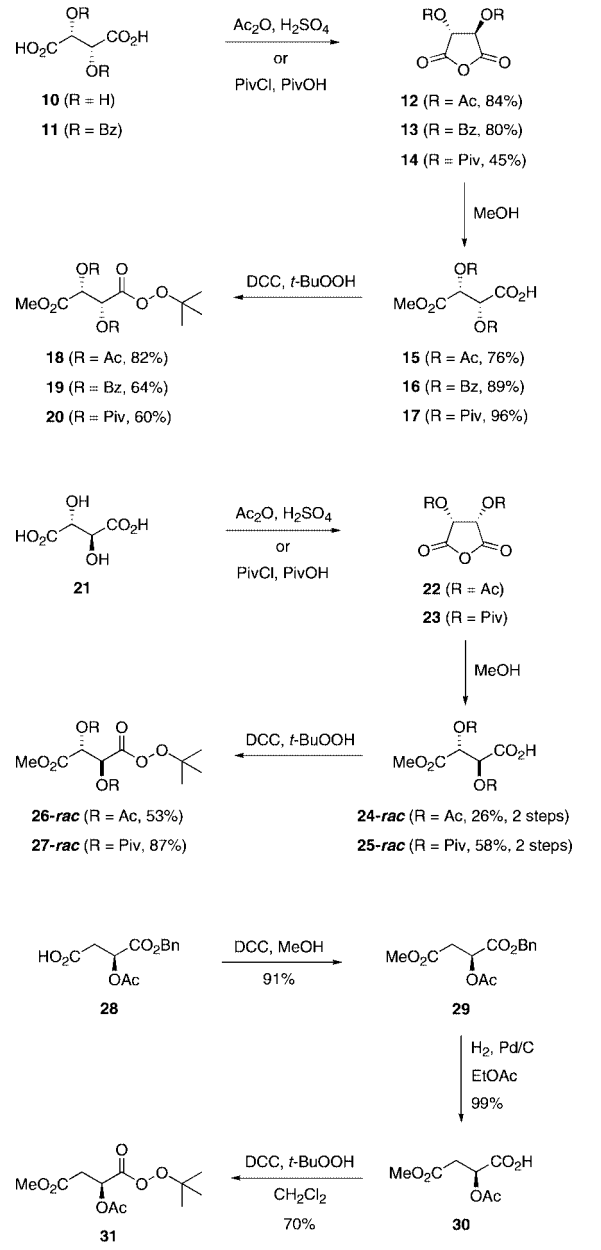
(7) Greene, F. D.; Kazan, J. *J. Org. Chem.* **1963**, *28*, 2168–2171.

(8) (a) Rüchardt, C.; Hamprecht, G. *Chem. Ber.* **1968**, *101*, 3957–3962. (b) Formaggio, F.; Crisma, M.; Scipionato, L.; Antonello, S.; Maran, F.; Toniolo, C. *Org. Lett.* **2004**, *6*, 2753–2756.

Scheme 4. Synthesis of Homoserine Derivatives via Photolysis of Glutamate-Derived Peresters



Scheme 5. Syntheses of *t*-Butyl Peresters Derived from Tartaric and Malic Acids

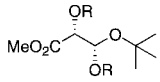
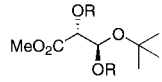
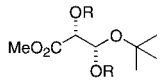
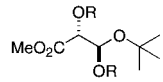
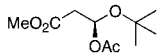
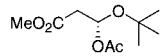


acetic anhydride or pivaloyl chloride to produce the tartaric anhydrides **12**−**14** or **22** and **23**, respectively. Opening of the ring with methanol affords the corresponding acylated monoesters with one free carboxylic acid group **15**−**17** or **24-*rac*** and **25-*rac***. Compounds **15**−**17** are optically pure, but **24** and **25** are produced as racemates because nucleophilic attack proceeds equally well at either the carbonyl adjacent to the *R* center or to the *S* center. Standard esterification with *t*-butyl hydroperoxide and DCC gives reasonable yields of the corresponding peresters **18**−**20** or **26-*rac*** and **27-*rac***. Esterification of benzyl *S*-(*O*-acetyl) malate (**28**) with methanol and DCC to generate diester **29** followed by hydrogenolysis affords **30**, which can be similarly converted to the perester **31**.

Photolysis in the absence of solvent of the peresters (usually not crystalline) at −196 °C, efficiently gives the product acetals in good to excellent yields with nearly full retention of stereochemistry at the α-center (Table 1). Such reaction of diacetoxy tartaric perester **18** gives acetals **32** and **33** in a diastereomeric ratio (d.r.) of 19:1 (Entry 1), as determined from the integration ratio of nonoverlapping signals in the ^{1}H NMR spectrum. Photolysis of its diastereomer **26-*rac*** gives the expected opposite stereochemistry (Entry 4). As observed with diacyl peroxides,[1] retention of stereochemistry presumably arises from homolytic cleavage of the peroxide bond followed by decarboxylation and cage recombination of the radicals. Hence, increasing the size of the protecting groups would be expected to further restrict movement in the viscous solid state, leading to an increase in diastereoselectivity. However, this is not the case, as dibenzoyl tartaric ester **19** gives the corresponding acetals **34** and **35** with the same d.r. as for **18** upon photolysis (Entry 2), and dipivaloyl tartaric peresters **20** and **27-*rac*** result in only a slight increase in the d.r. (Entries 3 and 5, respectively). Apparently, the restriction of movement of the interemediate radicals is not significantly different. However, a major erosion of diastereoselectivity is observed upon increasing the temperature, with a d.r. of approximately 2:1 at room temperature (results not shown). Photolysis of α-acetoxy malic perester **31** gives acetals **42** and **43** with an enantiomeric ratio (e.r.) of 9:1, as determined using a chiral NMR shift reagent. The lower stereoselectivity compared to the tartaric peresters appears to arise because of the absence of the extra substituent β to the perester. Presumably the more compact structure has fewer intermolecular interactions that would further restrict bond rotation and consequent inversion of the intermediate radical.

In summary, this methodology is readily accessible and requires no specialized equipment. As described in Supporting Information, the neat perester precursor can usually be placed in a small polyethylene bag, covered with liquid nitrogen in a dewar and photolyzed with common commercial UV lamps. The approach offers a convenient route to functionalized ethers, for example, α-amino acids bearing an alkoxy group in the side chain. Significantly, it also affords

Table 1. Photolysis of Tartaric and Malic Peresters[a]

entry	substrate	photolysis products		yield	ratio
					
1	**18**	**32** (R = Ac)	**33** (R = Ac)	94%	19:1
2	**19**	**34** (R = Bz)	**35** (R = Bz)	66%	19:1
3	**20**	**36** (R = Piv)	**37** (R = Piv)	85%	39:2
					
4	**26-*rac***	**38-*rac*** (R = Ac)	**39-*rac*** (R = Ac)	91%	1:19
5	**27-*rac***	**40-*rac*** (R = Piv)	**41-*rac*** (R = Piv)	84%	2:39
					
6	**31**	**42**	**43**	66%	9:1

[a] Conditions: neat, −196 °C, 16−24 h

a facile approach to synthesis of chiral *acyclic* acetals with high optical purity. Such compounds, having a stereogenic center at the noncyclic acetal carbon, are often difficult to obtain with high enantiomeric excess.[4−6] Acyclic α-acyloxy ethers, used as mixtures of stereoisomers, are useful intermediates for formation of oxycarbenium ions that can be trapped with a large variety of nucleophiles or utilized in Prins cyclizations.[9] They also offer intriguing potential as enzyme inhibitors or pharmaceutical agents, as some corresponding chiral *O*,*S*-acetals are drug candidates or precursors.[10]

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Supporting Information Available: Experimental details and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) (a) Kopecky, D. J.; Rychnovsky, S. D. *Org. Syn.* **2003**, *80*, 177–183. (b) Jasti, R.; Anderson, C. D.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2005**, *127*, 9939–9945.

(10) (a) Brand, S.; Jones, M. F.; Rayner, C. M. *Tetrahedron Lett.* **1997**, *38*, 3595–3598. (b) Larsen, R. D.; Corley, E. G.; King, A. O.; Carroll, J. D.; Davis, P.; Verhoeven, T. R.; Reider, P. J.; Labelle, M.; Gauthier, J. Y.; Xiang, Y. B.; Zamboni, R. J. *J. Org. Chem.* **1996**, *61*, 3398–3405. (c) Gauthier, J. Y.; Jones, T.; Champion, E.; Charette, L.; Dehaven, R.; Ford-Hutchinson, A. W.; Hoogsteen, K; Lord, A.; Masson, P.; Piechuta, H.; Pong, S. S.; Springer, J. P.; Thbrien, M.; Zamboni, R.; Young, R. N. *J. Med. Chem.* **1990**, *33*, 2841–2845. (d) Gauthier, J. Y.; Martins, E. O.; Young, R. N.; Zamboni, R. J. *SynLett* **2002**, 984–986.