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Highly Efficient Solid-Phase Oxidative Cleavage of Olefins by OsO_4–$NaIO_4$ in the Intramolecular *N*-Acyliminium Pictet–Spengler Reaction

Thomas E. Nielsen and Morten Meldal*

SPOCC Centre, Carlsberg Laboratory, Gamle Carlsberg Vej 10, DK-2500 Valby, Denmark

mpm@crc.dk

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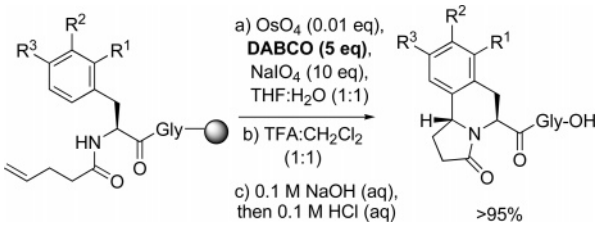
ABSTRACT



In the present investigation, solid-supported peptide olefins were converted quantitatively to aldehydes via the OsO_4–$NaIO_4$-mediated oxidative cleavage reaction. Addition of DABCO was essential to efficiently suppress the formation of hydroxymethyl ketone side products. The generated aldehydes were used in intramolecular *N*-acyliminium Pictet–Spengler reactions to produce highly pure pyrroloisoquinoline derivatives. The methodology was extended to allylglycine derivatives to enable the incorporation of pyrroloisoquinoline scaffolds within peptides.

Many common solution-phase strategies for the generation of aliphatic aldehydes have been applied to solid-phase synthesis,[1] including the conceptually different approaches of oxidation, reduction, and acetal hydrolysis. Not surprisingly, the first approach has turned out to be the most popular, and standard protocols for the oxidation of alcohols to aldehydes have successfully been adapted to solid-phase synthesis, in particular the sulfur trioxide-pyridine/DMSO (Parikh−Doering)[2] but also oxalyl chloride/DMSO (Swern),[3] catalytic TPAP/NMO,[4] and periodinane (Dess−Martin)[5] oxidation methods. Reduction is generally more difficult and most often impractical when carried out on peptide derivatives, although $LiAlH_4$-reduction of solid-supported Weinreb amides has met some success.[6] The application of acetals (or masked aldehydes) has also proven to be highly useful on solid support,[7] e.g., dimethylacetals for the generation of aldehydes undergoing intramolecular condensation reactions[8] and *N*,*N*-acetals for the generation of solid-supported glyoxylic aldehydes.[9]

In previous studies on the chemistry of solid-supported peptide aldehydes, we have reported the use of carboxylic acid building blocks containing the *N*-Boc 1,3-oxazinane

(1) For an overview see: Dörwald, F. Z. *Organic Synthesis on Solid Phase. Supports, Linkers, Reactions*; Wiley-VCH: Weinheim, 2002; Chapter 12.

(2) Selected examples: (a) Chen, C.; Randall, L. A. A.; Miller, R. B.; Jones, A. D.; Kurth, M. J. *J. Am. Chem. Soc.* **1994**, *116*, 2661−2662. (b) Rotella, D. P. *J. Am. Chem. Soc.* **1996**, *118*, 12246−12247. (c) Chen, C.; Randall, L. A. A.; Miller, R. B.; Jones, A. D.; Kurth, M. J. *Tetrahedron* **1997**, *53*, 6595−6609. (d) Page, P.; Bradley, M. *J. Org. Chem.* **1999**, *64*, 794−799. (e) Conde-Frieboes, K.; Schjeltved, R. K.; Breinholt, J. *J. Org. Chem.* **2002**, *67*, 8952−8957.

(3) Marx, M. A.; Grillot, A.-L.; Louer, C. T.; Beaver, K. A.; Bartlett, P. A. *J. Am. Chem. Soc.* **1997**, *119*, 6153−6167.

(4) (a) Yan, B.; Sun, Q.; Wareing, J. R.; Jewell, C. F. *J. Org. Chem.* **1996**, *61*, 8765−8770. (b) Li, W.; Yan, B. *J. Org. Chem.* **1998**, *63*, 4092−4097.

(5) (a) Reggelin, M.; Brenig, V.; Welcker, R. *Tetrahedron Lett.* **1998**, *39*, 4801−4804. (b) Nicolaou, K. C.; Pastor, J.; Winssinger, N.; Murphy, F. *J. Am. Chem. Soc.* **1998**, *120*, 5132−5133. (c) Bang, J. K.; Hasegawa, K.; Kawakami, T.; Aimoto, S.; Akaji, K. *Tetrahedron Lett.* **2004**, *45*, 99−102.

(6) Reggelin, M.; Brenig, V. *Tetrahedron Lett.* **1996**, *37*, 6851−6852.

(7) Veerman, J. J. N.; van Maarseveen, J. H.; Visser, G. M.; Kruse, C. G.; Schoemaker, H. E.; Hiemstra, H.; Rutjes, F. P. J. T. *Eur. J. Org. Chem.* **1998**, 2583−2589.

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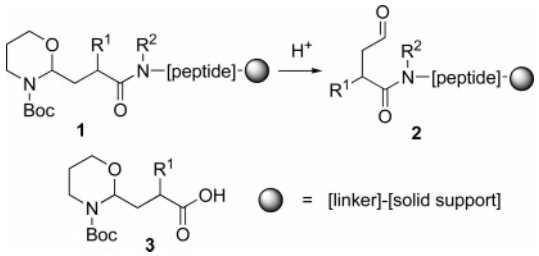
moiety.[10] These may easily be attached to the *N*-terminal of a solid-supported peptide by amide bond formation, and subsequent treatment with aqueous acid converts the oxazinane unit of **1** to the corresponding aldehyde **2** within seconds (Scheme 1). Although it provides a convenient and quantitative access to aldehydes as part of the solid-phase synthesis strategy, this method inherently suffers from lengthy synthetic routes toward the masked aldehyde building blocks **3**.

Scheme 1. Use of *N*-Boc 1,3-Oxazinanes for the Generation of Solid-Supported Peptide Aldehydes

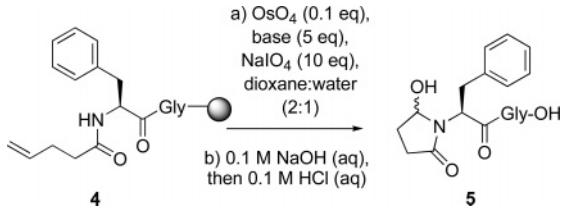


Bearing in mind the feasibility of solid-phase oxidative cleavage of 1,2-diols[11] and amino alcohols[12] with periodate, we expected the classical OsO_4−$NaIO_4$-mediated oxidative cleavage of olefins[13] to be a viable approach toward solid-supported aldehydes.[14,15] The initial test substrate **4** was synthesized by standard peptide synthesis procedures (see Supporting Information) on the PEGA resin, which is very compatible with the aqueous solvent mixtures normally used for the one-pot reaction.

A recent report stated how the addition of pyridine and 2,6-lutidine to OsO_4−$NaIO_4$-mediated oxidative cleavage reactions significantly reduced the formation of hydroxyketone side products.[16] Therefore, pyridine was initially tested with OsO_4−$NaIO_4$ in various solvent mixtures, e.g., organic solvent−H_2O (2:1), comprising organic solvents such as dioxane, acetonitrile, THF, acetone, *t*-BuOH, and DME. In these experiments, substrate **4** was fully converted (complete dihydroxylation); however, the product consisted typically of 5-hydroxylactam **5** (90%) and hydroxymethyl ketone **6** (10%), and it was therefore decided to screen a selection of bases.

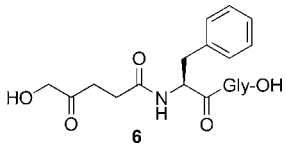
The related pyridine-derived bases (Table 1, entries 2−4) performed almost equally well with purities ranging from 87 to 93%, although clearly better than the more hindered 2,6-di-*tert*-butyl-4-methylpyridine. Most notably, DABCO proved to be superior to all bases with a reaction purity exceeding 95% with *no trace* of the hydroxymethyl ketone side product **6** (Table 1, entry 6). In further rounds of screening, the DABCO reaction conditions were employed in other solvent systems, which may be important for extending the methodology to other resin types.

Table 1. Screening of Bases for Oxidative Cleavage of Phenylalanine Derivative **4** Followed by Amide Backbone Condensation[a]



entry	base	purity of **5** (%)[b,c]
1	no base	84
2	pyridine	87
3	2,6-lutidine	93
4	2,4,6-collidine	89
5	2,6-di-*tert*-butyl-4-methylpyridine	76
6	DABCO	>95

[a] All reactions were run for 20 h at 20 °C. [b] Product **5** was formed as a 1:1 epimeric mixture, and the purity was determined by RP-HPLC. [c] In general, the corresponding hydroxymethyl ketone **6** (or the corresponding 5-hydroxylactam) was found as the only impurity ([M + Na]$^+$ = 359.1, found 359.0).



Although not strictly important for the dihydroxylation step, the addition of water is clearly required for efficient periodate cleavage, i.e., the absence of water resulted in essentially complete dihydroxylation, but only 20% of the diol was cleaved and cyclized to **5**. In summary, mixtures of water with acetonitrile, THF, acetone, and DME (Table 2, entries 4−7) were fully compatible with the DABCO reaction conditions, providing the product **5** quantitatively

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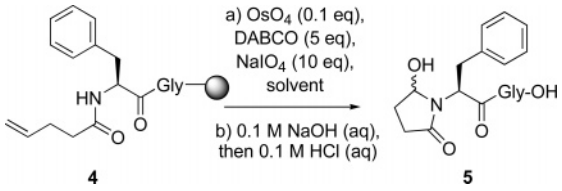
(14) For Os-mediated dihydroxylation on solid support, see: (a) Cernerud, M.; Reina, J. A.; Tegenfeldt, J.; Moberg, C. *Tetrahedron: Asymmetry* **1996**, *7*, 2863−2870. (b) Han, H.; Janda, K. D. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1731−1733. (c) Riedl, R.; Tappe, R.; Berkessel, A. *J. Am. Chem. Soc.* **1998**, *120*, 8994−9000. (d) Bräse, S.; Enders, D.; Köbberling, J.; Avemaria, F. *Angew. Chem., Int. Ed.* **1998**, *37*, 3413−3415. (e) Xia, Y.; Yang, Z.-Y.; Brossi, A.; Lee, K.-H. *Org. Lett.* **1999**, *1*, 2113−2115. (f) Bräse, S.; Dahmen, S.; Pfefferkorn, M. *J. Comb. Chem.* **2000**, *2*, 710−715.

(15) In one report, OsO_4−$NaIO_4$-mediated oxidative cleavage has been carried out on solid support to obtain a glyoxylyl-functionalized resin: Xu, Q.; Lam, K. S. *Tetrahedron Lett.* **2002**, *43*, 4435−4437.

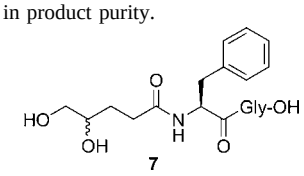
(16) Yu, W.; Mei, Y.; Kang, Y.; Hua, Z.; Jin, Z. *Org. Lett.* **2004**, *6*, 3217−3219.

Table 2. Screening of Solvents for Oxidative Cleavage of Phenylalanine Derivative **4** Followed by Amide Backbone Condensation[a]



entry	solvent	purity of **5** (%)[b]
1	dioxane	34[c]
2	H_2O	87
3	*t*-BuOH−H_2O (2:1)	90
4	CH_3CN−H_2O (2:1)	>95
5	acetone−H_2O (2:1)	>95
6	DME−H_2O (2:1)	>95
7[d]	THF−H_2O (2:1)	>95

[a] All reactions were run for 20 h at 20 °C. [b] Product **5** was formed as a 1:1 epimeric mixture, and the purity was determined by RP-HPLC. [c] Low purity is due to the presence of unconverted diol **7** ($[M + Na]^+ = 361.1$, found 361.1). [d] Amount of OsO_4 could be lowered to 0.005 equiv with no apparent decrease in product purity.

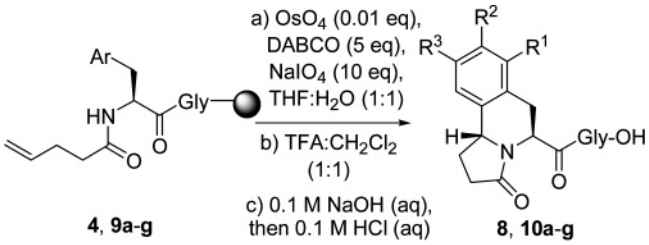


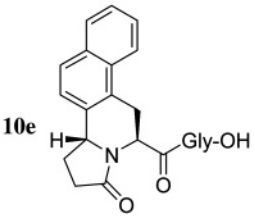
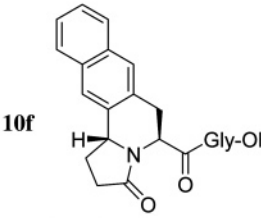
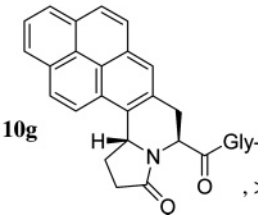
(purity exceeding 95%). It was also demonstrated that the amount of OsO_4 could be lowered to 0.005 equiv with no decrease in product purity (Table 2, entry 7), but no attempts were made to reduce the catalyst loading further. On the other hand, reducing the amount of $NaIO_4$ to 2 equiv resulted in a clean 4:1 mixture of the diol **7** and the hydroxylactam **5**, which justifies the use of a large excess of $NaIO_4$.

The OsO_4−$NaIO_4$−DABCO-mediated oxidative cleavage reaction was utilized to generate solid-supported aldehydes from a series of alkenes (**4**, **9a**−**g**). Subsequent intramolecular *N*-acyliminium Pictet−Spengler cyclizations (Table 3) afforded the expected pyrroloisoquinoline derivatives **8** and **10a**−**g** in excellent purities (>95%) with complete control of diastereoselectivity (>20:1).[17,18]

Oxidative cleavage of olefins by OsO_4−$NaIO_4$ have previously been applied to amino acid derivatives with the purpose of constructing small bicyclic ring-systems.[19] Such motifs can be incorporated in specific peptide sequences to produce conformationally restricted β-turn mimetics,[20] which

Table 3. Oxidative Cleavage of Arylalanine Derivatives Followed by Intramolecular *N*-Acyliminium Pictet−Spengler Reactions[a]



entry	substrate (Ar)	product, purity (%)[b,c]
1	**4** (phenyl)	**8** (R^1=H, R^2=H, R^3=H), >95
2	**9a** (2-methylphenyl)	**10a** (R^1=Me, R^2=H, R^3=H), >95
3	**9b** (3-methylphenyl)	**10b** (R^1=H, R^2=Me, R^3=H), >95
4	**9c** (4-methylphenyl)	**10c** (R^1=H, R^2=H, R^3=Me), >95
5	**9d** (biphenyl)	**10d** (R^1=H, R^2=H, R^3=Ph), >95
6	**9e** (1-naphthyl)	**10e**  , >95
7	**9f** (2-naphthyl)	**10f**  , >95
8	**9g** (1-pyrenyl)	**10g**  , >95%

[a] All reactions were run for 20 h at 20 °C. [b] Product purity was determined by RP-HPLC.

may afford more potent ligands for a given receptor. However, the pyrroloisoquinoline moieties of the peptide isosteres **8** and **10a**−**g** are constructed in a way that generally

(17) (a) Nielsen, T. E.; Meldal, M. *J. Org. Chem.* **2004**, *69*, 3765−3773. (b) Nielsen, T. E.; Meldal, M. *J. Comb. Chem.* **2005**, submitted.

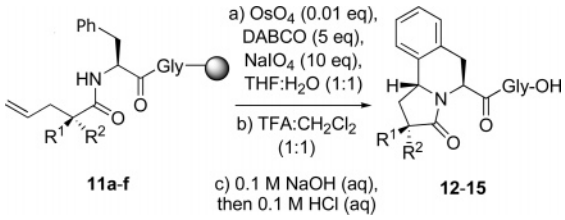
(18) For solid-phase *N*-acyliminium Pictet−Spengler reactions, see also: (a) Wang, H.; Ganesan, A. *Org. Lett.* **1999**, *1*, 1647−1649. (b) Bonnet, D.; Ganesan, A. *J. Comb. Chem.* **2002**, *4*, 546−548.

(19) Selected examples: (a) Baldwin, J. E.; Freeman, R. T.; Schofield, C. *Tetrahedron Lett.* **1989**, *30*, 4019−4020. (b) Genin, M. J.; Johnson, R. L. *J. Am. Chem. Soc.* **1992**, *114*, 8778−8783. (c) Baldwin, J. E.; Hulme, C.; Edwards, A. J.; Schofield, C. J. *Tetrahedron Lett.* **1993**, *34*, 1665−1668. (d) Baldwin, J. E.; Hulme, C.; Schofield, C. J.; Edwards, A. J. *J. Chem. Soc., Chem. Comun.* **1993**, 935−936. (e) Khalil, E. M.; Ojala, W. H.; Pradhan, A.; Nair, V. D.; Gleason, W. B.; Mishra, R. K.; Johnson, R. L. *J. Med. Chem.* **1999**, *42*, 628−637. (f) Khalil, E. M.; Pradhan, A.; Ojala, W. H.; Gleason, W. B.; Mishra, R. K.; Johnson, R. L. *J. Med. Chem.* **1999**, *42*, 2977−2987. (g) Qiu, W.; Gu, X.; Soloshonok, V. A.; Carducci, M. D.; Hruby, V. J. *Tetrahedron Lett.* **2001**, *42*, 145−148. (h) Ndungu, J. M.; Gu, X.; Gross, D. E.; Ying, J.; Hruby, V. J. *Tetrahedron Lett.* **2004**, *45*, 3245−3247.

(20) For a recent review on turn mimics, see: Maison, W. In *Highlights in Bioorganic Chemistry*; Schmuck, C., Wennemers, H., Eds.; Wiley-VCH: Weinheim, 2004; Chapter 1.2, 18−29.

terminates the peptide from the N-terminal. The methodology would therefore be more versatile if the heterocyclic core structures could also be built into the peptide sequence. For the introduction of a stereochemically well-defined amino handle on the pyrroloisoquinoline scaffold, enantiopure Fmoc- and Boc-protected allylglycine derivatives should serve well for solid-phase peptide synthesis. Accordingly, L-allylglycine derivatives **11a**−**c** and D-allylglycine derivatives **11d**−**f** were prepared and subjected to the OsO_4−$NaIO_4$−DABCO reaction conditions (Table 4). The unprotected derivatives **11a** and **11d** were poor substrates for the reaction (Table 4, entries 1 and 4), as only traces of the products **12** and **14** were detected by ES MS ($[M + H]^+ =$ 304.1, found 304.1). The crude chromatograms displayed several peaks, including diol intermediates as major impurities (ca. 50%, $[M + H]^+ = 354.1$, found 354.2). Rewardingly, the protected derivatives **11b**,**c** and **11e**,**f** were fully compatible with the reaction (Table 4, entries 2, 3, 5, 6) and provided the Pictet−Spengler products **12**−**15** in excellent purities (>95%).

Table 4. Oxidative Cleavage of Allylglycine Derivatives Followed by Intramolecular *N*-Acyliminium Pictet−Spengler Reactions[a]



entry	substrate	product, purity (%) [b]
1	**11a** ($R^1 = NH_2$, $R^2 = H$)	**12** ($R^1 = NH_2$, $R^2 = H$), trace
2	**11b** ($R^1 = NHFmoc$, $R^2 = H$)[c]	**12**, >95
3	**11c** ($R^1 = NHAc$, $R^2 = H$)	**13** ($R^1 = NHAc$, $R^2 = H$), >95
4	**11d** ($R^1 = H$, $R^2 = NH_2$)	**14** ($R^1 = H$, $R^2 = NH_2$), trace
5	**11e** ($R^1 = H$, $R^2 = NHFmoc$)[c]	**14**, >95
6	**11f** ($R^1 = H$, $R^2 = NHAc$)	**15** ($R^1 = H$, $R^2 = NHAc$), >95

[a] All reactions were run for 20 h at 20 °C. [b] Product purity was determined by RP-HPLC. [c] Fmoc protecting group was removed with 20% piperidine (DMF) prior to the basic hydrolysis.

In summary, we have successfully improved the classical OsO_4−$NaIO_4$-mediated oxidative cleavage of olefins for solid-phase synthesis. By addition of DABCO to the reaction mixture, the formation of hydroxymethyl ketone side products was completely suppressed and the aldehyde was quantitatively generated.[21] Aldehydes derived from protected allylglycine derivatives underwent quantitative amide backbone condensation to give 5-hydroxylactams, and subsequent nonaqueous acid treatment generated the corresponding pyrroloisoquinolines via quantitative and highly diastereoselective Pictet−Spengler cyclizations from the phenyl moiety of the neighboring phenylalanine residue of the peptide sequence.

Acknowledgment. The Danish National Research Foundation is gratefully acknowledged for financial support. T.E.N. thanks Prof. David Tanner for stimulating discussions.

Supporting Information Available: Analytical data for all compounds cleaved from the solid support. This material is available free of charge via the Internet at http://pubs.acs.org.

OL050870R

(21) **Representative Procedure for Oxidative Cleavage of Peptide Olefins.** A suspension of solid-supported alkene **4** (1.0 equiv, 3×10^{-3} mmol, 10.0 mg), $NaIO_4$ (10.0 equiv, 0.03 mmol, 6.4 mg), and DABCO (5.0 equiv, 0.015 mmol, 1.7 mg) in THF−water (1:1) was shaken for 10 min, after which time OsO_4 (0.01 equiv, 3×10^{-5} mmol, 0.38 μL of a 2.5 wt % solution in 2-methyl-2-propanol) was added. The initially reddish reaction mixture was shaken for 20 h at 20 °C. Subsequently, the resin was washed with water (×6), 10% TFA (aq) (×3), water (×6), DMF (×6), and CH_2Cl_2 (×6) in a plastic syringe fitted with a Teflon filter. The resin was lyophilized to remove all traces of solvent. For release of material **5** from the solid phase, beads were treated with 0.1 M NaOH (aq) for 2 h, neutralized with an equimolar amount of 0.1 M HCl (aq), and finally diluted with CH_3CN. The resulting solution was filtered through a Teflon filter and analyzed by RP-HPLC and ESMS.