Published in final edited form as:

Tetrahedron Lett. 2012 July 18; 53(29): 3758–3762. doi:10.1016/j.tetlet.2012.05.035.

A reliable Pd-mediated hydrogenolytic deprotection of BOM group of uridine ureido nitrogen

Bilal A. Aleiwi and Michio Kurosu*

Pharmaceutical Sciences, College of Pharmacy, University of Tennessee Health Science Center, 881 Madison, Memphis, TN 38163, USA

Abstract

The benzyloxymethyl (BOM) group has been utilized widely in syntheses of a variety of natural and non-natural products. The BOM group is also one of few choices to protect uridine ureido nitrogen. However, hydrogenolytic cleavage of the BOM group of uridine derivatives has been unrealizably performed via heterogeneous conditions using Pd catalysts. One of the undesirable by-products formed by Pd-mediated hydrogenation conditions is the over-reduced product of which the C5–C6 double bond of the uracil moiety was saturated. To date, we have generated a wide range of uridine-containing antibacterial agents, where the BOM group has been utilized in their syntheses. In screening of deprotection conditions of the BOM group of uridine ureido nitrogen under Pd-mediated hydrogenation conditions, we realized that the addition of water to the ⁱPrOH-based hydrogenation conditions can suppress the formation of over-reduced uridine derivatives and the addition of HCO₂H (0.5%) dramatically improve the reaction rate. An optimized hydrogenation condition described here can be applicable to the BOM-deprotections of a wide range of uridine derivatives.

Keywords

Ureido nitrogen; Uridine; Benzyloxymethyl (BOM) group; Hydrogenolytic cleavage; Pd-C; MraY inhibitors

1. Introduction

To date, a large number of uridine-containing natural products that show significant biological activities have been isolated from the culture of *Streptomyces* spp.¹

Uridine-containing antibiotics such as the muraymycins and capuramycin have gained great interest in the development of new antibacterial agents for multidrug (MDR)-bacterial infections.² In our ongoing program of discovery of new MraY (catalyzing the biosynthesis of lipid I from UDP-N-acyl-Murpentapeptide) inhibitors for MDR-resistant *Mycobacterium tuberculosis*,³ we have generated a 200-membered library molecules based on the core structures of muraymycins and capuramycin (Figure 1). In their syntheses we utilized the benzyloxymethyl (BOM) group as a convenient protecting group for the uridine ureido nitrogen of the uracil moiety.⁴

© 2012 Elsevier Ltd. All rights reserved.

*Corresponding author. Tel.: +1-901-448-1045; fax: +1-901-448-6940; mkurosu@uthsc.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

However, we encountered that success of deprotection of the BOM group of the uridine derivatives vary depending on the structure and physico-chemical properties of uridine derivatives. Chemical structures of representative key intermediates are shown in Figure 2. Various hydrogenation conditions for the deprotection of BOM protecting group have been reported in literatures using Pd catalysts in alcoholic solvents.⁵ Recently, Ducho and co-workers reported that in hydrogenolytic deprotection of the BOM group of the uridine derivative the over-reduction of the C5–C6 double of the uracil moiety could be minimized (~5%) by using Pd-black in MeOH in the presence of ⁿBuNH₂.⁶ However, in our studies addition of *primary* amines to suppress the over-reduction of the uracil double bond during deprotections of the BOM group resulted in generation of the desired product in capricious yields with significant amounts of the over-reduced product(s).⁷

In order to identify versatile hydrogenolytic deprotection conditions of the BOM group of uridine derivatives that do not produce the by-products (*vide supra*), we have screened hydrogenation conditions by varying Pd sources in a wide range of solvent systems. Herein, we report a simple but reliable hydrogenolytic condition that remove the BOM and Bn groups of uridine derivatives without affecting the C5–C6 double bond of the uracil moiety.

2. Results and discussion

We have screened hydrogenolytic BOM-deprotection conditions with Pd-C, Pd black, Pd(OH)₂, and PtO₂ that convert **1** to **2** without contamination of the over-reduced product **11**. A series of hydrogenation conditions examined are summarized in Table 1. Hydrogenation of **1** with 10% Pd-C in MeOH provided a mixture of **1** and **2** with predominantly **2** (entry 1). The same reaction with Pd-black, or Pd(OH)₂ in MeOH resulted in the formation of a large amount of the over-reduced product **11** (entries 2 and 3). PtO₂-Catalyzed hydrogenation reaction in MeOH gave **11** exclusively (entry 4). Significant solvent effect on the BOM deprotection with 10% Pd-C was observed. Reaction rate in EtOH or EtOAc or ⁱPrOH were much slower than that in MeOH (entries 5–7). However, the **2/11** selectivity ratio was significantly improved in the reaction in EtOAc or ⁱPrOH. It was found that the reaction in ⁱPrOH-H₂O (10/1) yielded the desired product **2** in 25% yield (>95% yield based on recovering **1**) after 6h without contamination of **11** (entry 8). The conversion of **2** from **1** was slightly improved under medium pressure conditions (50 psi) (entry 9). In order to accelerate the Pd-C mediated hydrogenolytic cleavage of the BOM group of **1** in ⁱPrOH-H₂O (10/1), the effect of additives was investigated. All attempts with water tolerate Lewis acids such as CeCl₃•7H₂O and La(OTf)₃ gave rise to the formation of the by-product **11** (data not shown in Table 1). The addition of HCO₂NH₄ to the reaction mixture did not noticeably improve the reaction rate, and resulted in the formation of **2** and **11** (80/20 ratio) in 90% yield after 12h (entry 10). It was found that the addition of (CF₃)₂CHOH was very effective in the selective BOM-deprotection of **1**; under these conditions **1** could be converted to **2** in 90% yield after 12h (entry 11). Addition of AcOH (0.5%) was also effective in the selective deprotection of the BOM-group of **1** (entry 12), but the reaction was not completed in 6h. The Pd-C catalyzed hydrogenation in ⁱPrOH-H₂O (10/1) was dramatically accelerated by addition of HCO₂H (0.5%); the reaction was completed within 6h to afford **2** in quantitative yield (entry 13). It was realized that under the conditions of entry 13, hydrogenolytic cleavage of the BOM group of **1** was completed even in 2h (entry 14). The reaction rate was increased under a medium pressure condition (50 psi) to yield **2** without contamination of the by-product **11** (entry 15).

In order to obtain more insight into the optimized deprotection conditions (H₂ (1atm), 10% Pd-C / ⁱPrOH-H₂O (10/1), HCO₂H (0.5%)) for the BOM-protecting group using **1**, we have applied these conditions to a wide variety of the BOM-protected uridine derivatives. Selected examples are summarized in Table 2. Simultaneous deprotections of the BOM and

Bn groups of **1b** and **1c** using the conditions utilized in entries 1~3 in Table 1 resulted in the formation of the desired products **6b** and **6c** in very poor yields (0~20%) with the formation of a large amount of the over-reduced products in which the uracil moiety was saturated with H₂. On the contrary, simultaneous hydrogenolytic cleavages of the BOM and Bn groups of **1b** and **1c** using the optimized conditions (H₂ (1atm), 10% Pd-C / ⁱPrOH-H₂O (10/1), HCO₂H (0.5%)) gave rise to the corresponding products **6b** and **6c** in quantitative yield (entries 1 and 2 in Table 2). Deprotections of the molecules, **2a** and **2b**, possessing the α-hydroxyamide functional group furnished the desired products **7a** and **7b**, respectively in quantitative yield within 3h. Significantly, the 1,3-diamino derivatives **3a** and **3b** could be converted to the corresponding BOM-deprotected diamine **8a** and **8b**, respectively, after a basic work-up to remove the HCO₂H salts. On the other hand, hydrogenolytic deprotection of the BOM and Cbz groups of **3a** with 10% Pd/C in MeOH resulted in an incomplete reaction mixture containing the BOM protected-**8a** in 90% yield even after prolonged reaction time. We have observed that conversion of the BOM-deprotections are very for the BOM-protected uridines possessing free-amine in molecules. Thus, BOM-deprotection was not observed for **3a** with 10% Pd/C in MeOH due to the fact that Cbz deprotection occurred prior to the BOM deprotection to form the free amine. However, a deactivation mechanism of the Pd catalyst by the complexation with the free amine is diminished in the Pd-mediated hydrogenation reactions by using a water containing solvent. Hydrogenolytic cleavage of the BOM group of the mannosides **4a** using the optimized condition gave rise to **9a** in 97% yield. In general, deprotections of the *O*-Cbz group require relatively long hydrogenation time even with the conditions of 10% Pd-C or Pd-back in MeOH in the presence of AcOH at 100 psi.⁸ The optimized conditions utilized in Table 2 could convert **4a** to **9b** in 95% yield within 12h without contamination of the over-reduced product. Similarly, the BOM group of the riboside **4c** and the BOM and *O*-Cbz group of **4d** could be efficiently deprotected to furnish **9c** and **9d** in high yield. The BOM- and *N*-Cbz-groups of the amino-ribosyl uridine **5a** were deprotected via the optimized hydrogenolytic cleavage conditions (10% Pd-C in ⁱPrOH-H₂O (10/1) in the presence of HCO₂H (0.5%)) to provide **10a** in 97% within 3h. In our screening of hydrogenation conditions with Pd species for the simultaneous deprotections of **5a**, the only conditions demonstrated in Table 2 provided the desired product **10a** in high yield without affecting the uracil double bond.

In summary, we have demonstrated hydrogenolytic cleavage reactions of the BOM group of a series of complex uridine derivatives with simple hydrogenation conditions (10% Pd-C in ⁱPrOH-H₂O (10/1) in the presence of HCO₂H (0.5%) at 1 atm H₂ pressure).⁹ Under these conditions, the BOM-protected uridines were cleanly converted to the corresponding deprotected uridines without formation of the by-products where the uracil C5–C6-double bond was saturated. Unlike the reported conditions to suppress the generation of the over-reduced uracil products by using amines,¹⁰ the components in the hydrogenation conditions reported here can readily be removed after the reaction by filtration followed by simple evaporation of all volatiles. Thus, an optimized hydrogenation condition reported here has a beneficial in systematic deprotections of the BOM group to generate a series of uridine derivatives. As we have demonstrated deprotections of the Bn, *N*-Cbz, and *O*-Cbz groups during the BOM-deprotection reactions, the hydrogenation conditions summarized in Table 2 should be applicable to debenzylations of a wide range of compounds possessing multiple benzyl groups in a single molecule.

Acknowledgments

The authors thank the National Institutes of Health (NIAID grant AI084411-02) and The University of Tennessee for generous financial supports. NMR data were obtained on instruments supported by the NIH Shared Instrumentation Grant.

References and notes

- (a) Yamaguchi H, Sato S, Yoshida S, Takeda K, Itoh M, Seto H, Otake N. *J. Antibiot.* 1986; 39:1047–1053. [PubMed: 3759655] (b) McDonald LA, Barbieri LR, carter GT, Lenoy E, Lotvin J, Peterson PJ, Siegel MM, Singh G, Williamson RT. *J. Am. Chem. Soc.* 2002; 124:10260–10261. [PubMed: 12197711] (c) Muramatsu Y, Ishii MM, Inukai M. *J. Antibiot.* 2003; 56:253–258. [PubMed: 12760681] (d) Igrashi M, Nakagawa M, Doi S, Hattori N, Naganwa H, Hamada M. *J. Antibiot.* 2003; 56:580–583. [PubMed: 12931868] (e) Kimura K, Bugg TDH. *Nat. Prod. Rep.* 2003; 20:252–273. [PubMed: 12735700] (f) Bryskier A, Dini AC. *Agents: Antibacter. Antifung.* 2005:377–398. (g) Timothy DH, Lloyd AJ, Roper DI. *Infect. Disorders: Drug Targets.* 2006; 6:85–106. (h) Murakami R, Fujita Y, Kizuka M, Kagawa T, Muramatsu Y, Miyakoshi S, Takatsu T, Inukai M. *J. Antibiot.* 2007; 60:690–695. [PubMed: 18057698] (i) Winn M, Goss RJM, Kimura K, Bugg TDH. *Nat. Prod. Rep.* 2010; 27:279–304. [PubMed: 20111805] (j) Guillemette C, Levesque E, Harvey M, Bellemare J, Menard V. *Drug Metabo. Rev.* 2010; 42:24–44. (k) Yamamoto T, Koyama H, Kurajoh M, Shoji T, Tsutsumi Z, Moriwaki Y. *Clinica Chimica Acta.* 2011; 412:1712–1724.
- (a) Fang X, Gibbs BS, Coward JK. *Bioorg. Med. Chem. Lett.* 1995; 5:2701–2706. (b) Boojamra CG, Lemoine RC, Blais J, Vernier NG, Stein KA, Magon A, Chamberland S, Hecker SJ, Lee VJ. *Bioorg. Med. Chem. Lett.* 2003; 13:3305–3309. [PubMed: 12951115] (c) Hotoda H, Furukawa M, Daigo M, Murayama K, Kaneko M, Muramatsu Y, Ishii MM, Miyakoshi S, Takatsu T, Inukai M, Kakuta M, Abe T, Harasaki T, Fukuoka T, Utsuic Y, Ohyac S. *Bioorg. Med. Chem. Lett.* 2003; 13:2829–2832. [PubMed: 14611838] (d) Yamashita A, Norton E, Petersen PJ, Rasmussen BA, Singh G, Yang Y, Mansour TS, Ho DM. *Bioorg. Med. Chem. Lett.* 2003; 13:3345–3350. [PubMed: 12951123] (e) Koga T, Fukuoka T, Harasaki T, Inoue H, Hotoda H, Kakuta M, Muramatsu Y, Yamamura N, Hoshi M, Hirota T. *J. Antimicro. Chemother.* 2004; 54:755–760. (f) Dini, Christophe. *Curr. Top. Med. Chem.* 2005; 5:1221–1236. [PubMed: 16305528] (g) Reddy VM, Einck L, Nacy CA. *Antimicro. Agents Chemother.* 2008; 52:719–721. (h) Ichikawa S. *Chem. Pharm. Bull.* 2008; 56:1059–1072. [PubMed: 18670104] (i) Dini C, Drochon N, Feteanu S, Guillot JC, Peixoto C, Aszodi J. *Bioorg. Med. Chem. Lett.* 2001; 11:529–531. [PubMed: 11229763]
- (a) Kurosu M, Li K, Crick DC. *Org. Lett.* 2009; 11:2393–2397. [PubMed: 19405507] (b) Kurosu M, Li K. *J. Org. Chem.* 2008; 73:9767–9771. [PubMed: 18783274] (c) Kurosu M, Biswas K, Crick DC. *Org. Lett.* 2007; 9:1141–1145. [PubMed: 17311394] (d) Kurosu M, Narayanasamy P, Crick DC. *Heterocycles.* 2007; 72:339–352. (e) Kurosu M, Mahapatra S, Narayanasamy P, Crick DC. *Tetrahedron Lett.* 2007; 48:799–803. (f) Wang Y, Kurosu M. *Tetrahedron.* 2012 in press.
- Synthesis of uridine-containing natural products using the BOM-protecting group, see; Ichikawa S, Shuto S, Minakawa N, Matsuda A. *J. Org. Chem.* 1997; 62:1368–1375. Fraser AS, Kawasaki AM, Jung ME, Muthiah M. *Tetrahedron Lett.* 2000; 41:1523–1526. Prakash TP, Kawasaki AM, Lesnik EA, Owens SR, Manoharan M. *Org. Lett.* 2003; 5:403–406. [PubMed: 12583729] Hirano S, Ichikawa S, Matsuda A. *Angew. Chem. Int. Ed.* 2005; 44:1854–1856. Hirano S, Ichikawa S, Matsuda A. *J. Org. Chem.* 2007; 72:9936–9946. [PubMed: 18027965] Kodama T, Matsuo C, Ori H, Miyoshi T, Obika S, Miyashita K, Imanishi T. *Tetrahedron.* 2009; 41:2116–2123. Tanino T, Ichikawa S, Shiro M, Matsuda A. *J. Org. Chem.* 2010; 75:1366–1377. [PubMed: 20143822] Jensen TB, Pasternak A, Madsen AS, Petersen M, Wengel J. *Chem. Bio. Chem.* 2011; 12:1904–1911.
- (a) Connor DS, Klein GW, Taylor GN, Boeckman RK, Medwid JB. *Org. Syn.* 1972; 52:C10–C19. (b) Hanessian S, Kloss J, Sugawara T. *J. Am. Chem. Soc.* 1986; 108:2758–2759. (c) Goff DA, Harris RN, Bottaro JC, Bedford CD. *J. Org. Chem.* 1986; 51:4711–4714. (d) Kunz, H.; Waldman, H. *Protecting Groups.* Chapter 3.1. In: Trost, BM.; Fleming, I., editors. *Comprehensive Organic Synthesis.* Vol. 6. Oxford, United Kingdom: Pergamon Press; 1991. p. 631–701. (e) Prakash TP, Manoharan M, Kawasaki AM, Fraser AS, Lesnik EA, Sioufi N, Leeds JM, Teplova M, Egli M. *Biochemistry.* 2002; 41:11642–11648. [PubMed: 12269806]
- Spork AP, Wiegmann D, Granitzka M, Stalke D, Ducho C. *J. Org. Chem.* 2011; 76:10083–10098. [PubMed: 22059552]
- We screened a wide range of *primary* and *secondary* amines, and pyridines to suppress the over-reductions of the uracil double bond during hydrogenolytic deprotections of the BOM group of the uridine derivatives. Addition of amines to Pd-mediated hydrogenation conditions did not provide the desired BOM-deprotected products in a satisfactory yield.

8. (a) Daubert BF, King CG. J. Am. Chem. Soc. 1939; 61:3328–3330.(b) Bajwa JS. Tetrahedron Lett. 1992; 33:2299–2302.(c) Shue Y-K, Carrera GM, Tufano MD, Nadzan AM. J. Org. Chem. 1991; 56:2107–2111.
9. General procedure for BOM deprotections: To a stirred solution of the BOM protected uridine derivative (1 eq.) in ¹PrOH:H₂O (10:1) and HCO₂H (0.5%) was added 10% Pd-C (10%) under N₂. H₂ gas was introduced to the reaction mixture using a double-folded balloon. Upon completion, the reaction mixture was filtered through a Celite pad and washed with EtOAc (or MeOH). All volatiles were evaporated *in vacuo*. When the HCO₂H-amine salt was generated, the crude mixture was dissolved in CHCl₃, and washed with aq. NaHCO₃. The combined organic extracts were dried over Na₂SO₄ and evaporated *in vacuo*. Purification by a silica gel chromatography afforded the desired compound (yields were given in Table 1 and 2).
10. Reported amine additives for controlled-hydrogenation conditions with Pd species have relatively high boiling point.

Figure 1.
Muraymycin A₁ and capuramycin.

Figure 2.
Representative structures of the key intermediates for the syntheses of MraY inhibitors.

Table 1

Screening of conditions for hydrogenolytic cleavage of the BOM group of **1**.

entry	catalyst	conditions	time (h)	ratio (2/11)	yield (%)
1	10% Pd/C	MeOH ^a	6	20/80	>95
2	Pd black	MeOH ^a	6	10/90	>95
3	Pd(OH) ₂	MeOH ^a	6	5/95	>95
4	PtO ₂	MeOH ^a	6	0/100	>95
5	10% Pd/C	EtOH ^a	6	30/70	50
6	10% Pd/C	EtOAc ^a	6	95/5	<10
7	10% Pd/C	iPrOH ^a	6	95/5	25
8	10% Pd/C	iPrOH-H ₂ O (10/1) ^a	6	100/0	25
9	10% Pd/C	iPrOH-H ₂ O (10/1) 50 psi	6	100/0	30–40
10	10% Pd/C	iPrOH-H ₂ O (10/1) ^a HCO ₂ NH ₄ (0.5%)	12	80/20	90
11	10% Pd/C	iPrOH-H ₂ O (10/1) ^a (CF ₃) ₂ CHOH (0.5%)	12	100/0	90
12	10% Pd/C	iPrOH-H ₂ O (10/1) ^a AcOH (0.5%)	6	100/0	90
13	10% Pd/C	iPrOH-H ₂ O (10/1) ^a HCO ₂ H (0.5%)	6	100/0	>99
14	10% Pd/C	iPrOH-H ₂ O (10/1) ^a HCO ₂ H (0.5%)	2	100/0	>99
15	10% Pd/C	iPrOH-H ₂ O (10/1) HCO ₂ H (0.5%) 50 psi	0.5	100/0	>99

^aThe reaction was conducted at 1 atm H₂ pressure.

Table 2

Hydrogenolytic cleavage of the BOM group of uridine derivatives.

entry	starting material	product	reaction time (h)	yield (%)	entry	starting material	product	reaction time (h)	yield (%)
1			12	>99	7			3	97
2			12	95	8			12	95
3			3	>99	9			3	97
4			3	>99

entry	starting material	product	reaction time (h)	yield (%)	entry	starting material	product	reaction time (h)	yield (%)
5			3	92	10			12	97
6			3	>99	11			3	97

^aThe product was basified to decomplex the HCO₂H salt.