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# Argentic oxide mediated N-dearylation of β-lactams

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ABSTRACT

A method is described for the N-dearylation of *N*-(4-methoxy- or 4-ethoxyphenyl)-2-azetidinones with argentic oxide. The yields are good-to-excellent and the reaction is simple, efficient, and fast.



Argentic oxide (AgO) is used as an oxidizing agent in chemical reactions.[1] Soluble nitrate, perchlorate, sulfate, and fluoride salts of silver yield AgO quantitatively, when oxidized with alkaline solutions of sodium or potassium persulfate.[2] Argentic oxide is also commercially available.[3]

Oxidative cleavage of hydroquinone ethers with argentic oxide has been reported previously.[4] Weinreb[5] and co-workers have described the oxidative O-deprotection of *p*-methoxyphenyl ethers using AgO.

β-Lactams are very important pharmacophores in compounds for treatment of diseases caused by bacterial infections.[6] In addition, β-lactams have been recently shown to possess other relevant biological activities.[7] Also, the 2-azetidinone ring has been employed successfully in a large variety of synthetic methods toward various nitrogen-containing target compounds.[8]

N-Unsubstituted 2-azetidinones offer major synthetic opportunities in the synthesis of β-lactam antibiotics such as the carbapenems, penams, monobactams, nocardicins, and the glutamine synthetase inhibitor, tabtoxin.[9] The application of N-unsubstituted 2-azetidinones in the semi-synthesis of the anticancer agents Taxol and Taxotere has also been reported.[10] Several protecting groups are often used for N1-protection of β-lactams and can be cleaved by various methods to give N-unsubstituted β-lactams.[11] Currently, most reports describe oxidative removal of an alkoxyphenyl group with ceric ammonium nitrate (CAN),[12] but appear to neglect the serious disadvantages associated with this procedure. Usually, a large excess of CAN (3 equiv) is required and its use is not productive in large scale reactions because of the high equivalent weight of CAN (548). In recognition of these drawbacks, Corley reported an electrochemical procedure for the oxidative N-dearylation of 2-azetidinones.[13] However, electrochemical reactions are poorly amenable to scale-up, requiring specialised equipment. According to the standard reduction potential table,[14] Ag(II) [Ag(II) + e = Ag(I), 1.98 V] has a larger potential than that of Ce(IV) [Ce(IV) + e = Ce(III), 1.72 V]. In this Letter we describe the use of AgO for the oxidative N-dearylation of β-lactams for the first time.

First, we examined the oxidation of 2-azetidinone **1a** using AgO. When 2-azetidinone **1a** was mixed with AgO in aqueous 1,4-dioxane at room temperature, no reaction was observed after 10 h. When a mineral acid was added, the reaction took place immediately to give N-unsubstituted 2-azetidinone **2a**. Hence, various mineral acids were tested to find the optimum. According to Table 1, nitric acid was the most efficient and, at least 3 equiv each of $HNO_3$ and AgO were needed. The lower yield when using phosphoric acid (entry 4) is due to precipitation of $Ag_3PO_4$ during the reaction.[4a]

Next, optimization of the reaction conditions was investigated by consideration of the effects of solvent, temperature, molar ratio of reagents, and time (Table 2). The best result was obtained in 1,4-dioxane with 3 equiv of AgO at room temperature over 5 min.

Using the optimized reaction conditions, 4-methoxyphenyl and 4-ethoxyphenyl β-lactams **1a–l** were converted into the corresponding NH-β-lactams **2a–l** in good-to-excellent yields (Scheme 1).

We also compared this new procedure with oxidative N-dearylation using CAN (Table 3).[15] According to Table 3, the isolated

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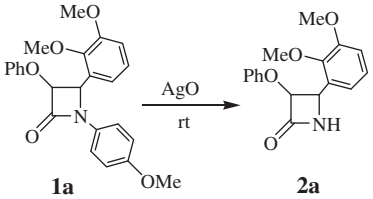
yields of N-unsubstituted 2-azetidinones **2a–k** (entries 1–11) were comparable with those obtained using CAN. 3-Chloro-2-azetidinone **1l** (entry 12) was converted into the corresponding N-unsubstituted 2-azetidinone in lower yield with AgO than with CAN. The N-dearylations of β-lactams **1a–l** were faster using AgO than CAN. The structures of N-unsubstituted β-lactams **2a–l** were confirmed from spectroscopic data and elemental analyses.[12h–j,16] The stereochemistry of the starting β-lactams was retained in the products.

In conclusion, the use of AgO allowed us to develop a simple and efficient synthetic method for obtaining N-unsubstituted β-lactams via oxidative N-dearylation of N-alkoxyphenyl-β-lactams. The reaction is rapid and high yields of products were obtained.

**Table 1**
N-dearylation of β-lactam **1a** with AgO[a]




**1a** **2a**

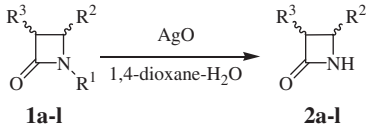
| Entry | Acid (mmol) | Yield (%) |
|---|---|---|
| 1 | $H_2SO_4$ (3 mmol) | 63 |
| 2 | $HNO_3$ (3 mmol) | 88 |
| 3 | $HClO_4$ (3 mmol) | 69 |
| 4 | $H_3PO_4$ (3 mmol) | 54 |
| 5 | $HNO_3$ (2 mmol) | 59 |
| 6 | $HNO_3$ (4 mmol) | 83 |

[a] All reactions were performed with 3 equiv of AgO at rt for 10 min.

**Table 2**
Optimization of the N-dearylation of β-lactam **1a** with AgO[a]

| Entry | Solvent | Temp (°C) | AgO (mmol) | Time (min) | Yield (%) |
|---|---|---|---|---|---|
| 1 | 1,4-Dioxane | rt | 3 | 10 | 88 |
| 2 | $CH_3CN$ | rt | 3 | 10 | 62 |
| 3 | THF | rt | 3 | 10 | 75 |
| 4 | DMF | rt | 3 | 10 | 51 |
| 5 | 1,4-Dioxane | 0 °C | 3 | 10 | 82 |
| 6 | 1,4-Dioxane | rt | 2 | 10 | 66 |
| 7 | 1,4-Dioxane | rt | 4 | 10 | 86 |
| 8 | 1,4-Dioxane | rt | 3 | 20 | 80 |
| 9 | 1,4-Dioxane | rt | 3 | 5 | 91 |
| 10 | 1,4-Dioxane | rt | 3 | 3 | 90 |

[a] Equimolar $HNO_3$ and AgO were used for all reactions.




**1a-l** **2a-l**

**Scheme 1.**

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## References and notes

1. (a) Lingane, J. J.; Davis, D. G. *Anal. Chim. Acta* **1956**, *15*, 201–206; (b) Tanaka, M. *Bull. Chem. Soc. Jpn.* **1953**, *26*, 299–302; (c) Syper, L. *Tetrahedron Lett.* **1967**, *8*, 4193–4198; (d) Bondinell, W. E.; Snyder, C. D.; Rapoport, H. *J. Am. Chem. Soc.* **1969**, *91*, 6889–6891; (e) Bondinell, W. E.; Snyder, C. D.; Rapoport, H. *J. Org. Chem.* **1971**, *36*, 3951–3960.
2. Hammer, R. N.; Kleinherg, J.; Holtzclaw, F., Jr.; Johnson, K. W. R. *Inorg. Synth.* **1953**, *4*, 12–14.
3. CAS No. 11113-88-5. For example, Acros product No. 20785 or Aldrich product No. 223638.
4. (a) Snyder, C. D.; Rapoport, H. *J. Am. Chem. Soc.* **1972**, *94*, 227–231; (b) Tomatsu, A.; Takemura, S.; Hashimoto, K.; Nakata, M. *Synlett* **1999**, 1474–1476; (c) Jacobs, J.; Deblander, J.; Kesteleyn, B.; Abbaspour Tehrani, K.; De Kimpe, N. *Tetrahedron* **2008**, *64*, 5345–5353; (d) Halina Wojtowicz, H.; Młochowski, J.; Syper, L. *Synth. Commun.* **2006**, *36*, 1991–2000.
5. Sisko, J.; Henry, J. R.; Weinreb, S. M. *J. Org. Chem.* **1993**, *58*, 4945–4951.
6. (a) Alcaide, B.; Almendros, P.; Luna, A.; Torres, M. R. *Org. Biomol. Chem.* **2008**, *6*, 1635–1640; (b) Long, T. E.; Turos, E. *Curr. Med. Chem.: Anti-Infect. Agents* **2002**, *1*, 251–268; (c) Southgate, R. *Contemp. Org. Synth.* **1994**, *1*, 417–432; (d) Morin, R. B.; Gorman, M. *Chemistry and Biology of β-Lactam Antibiotics*; Academic Press: New York, 1982; (e) De Kimpe, N. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Padwa, A., Eds.; Pergamon: Oxford, 1996; Vol. 1B, p 507.
7. (a) O'Driscoll, M.; Greenhalgh, K.; Young, A.; Turos, E.; Dickey, S.; Lim, D. V. *Bioorg. Med. Chem.* **2008**, *16*, 7832–7837; (b) Bai, X.; Xu, X.; Fu, R.; Chen, J.; Chen, S. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 101–104; (c) Turos, E.; Reddy, G. S. K.; Greenhalgh, K.; Ramaraju, P.; Abeylath, S. C.; Jang, S.; Dickey, S.; Lim, D. V. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 3468–3472; (d) Tozsera, J.; Sperka, T.; Pitlik, J.; Bagossia, P. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3086–3090; (e) Banik, B. K.; Becker, F. F.; Banik, I. *Bioorg. Med. Chem.* **2005**, *13*, 3611–3622; (f) Nivsarkar, M.; Thavaselvam, D.; Prasanna, S.; Sharma, M.; Kaushik, M. P. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1371–1373; (g) Sutton, J. C.; Bolton, S. A.; Harti, K. S.; Huang, M. H.; Jacobs, G.; Meng, W.; Zhao, G.; Bisacchi, G. S. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2233–2239; (h) Marchand-Brynaert, J.; Dive, G.; Galleni, M.; Gerard, S. *Bioorg. Med. Chem.* **2004**, *12*, 129–138; (i) Adlington, R. M.; Baldwin, J. E.; Chen, B.; Cooper, S. L.; McCoull, W.; Pritchard, G. J.; Howe, T. J.; Becker, G. W.; Hermann, R. B.; McNulty, A. M.; Neubauer, B. L. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1689–1694.
8. (a) D'hooghe, M.; Mollet, K.; Dekeukeleire, S.; De Kimpe, N. *Org. Biomol. Chem.* **2010**, *8*, 607–615; (b) Alcaide, B.; Almendros, P.; Redondo, M. C. *Eur. J. Org. Chem.* **2007**, 3707–3710; (c) Mishra, R. K.; Coates, C. M.; Revell, K. D.; Turos, E. *Org. Lett.* **2007**, *9*, 575–578; (d) Alcaide, B.; Almendros, P.; Carrascosa, R.; Rodríguez-Acebes, R. *Eur. J. Org. Chem.* **2008**, 1575–1581; (e) Ge, H.; Spletstoser,

**Table 3**
Comparision of the N-dearylation of β-lactams **1a–l** with AgO and CAN

| Entry | $R^1$ | $R^2$ | $R^3$ | Stereochemistry | Product | Yield (%) | |
|---|---|---|---|---|---|---|---|
| | | | | | | AgO | CAN[a] |
| 1 | 4-$MeOC_6H_4$ | 2,3-$(MeO)_2C_6H_3$ | PhO | *cis* | **2a** | 91 | 89 |
| 2 | 4-$MeOC_6H_4$ | 3,4-$(MeO)_2C_6H_3$ | 3-$NO_2$PhthN | *cis* | **2b** | 86 | 78 |
| 3 | 4-$EtOC_6H_4$ | 4-$MeOC_6H_4$ | PhO | *cis* | **2c** | 83 | 85 |
| 4 | 4-$EtOC_6H_4$ | CH=CHPh | PhthN | *cis* | **2d** | 88 | 84 |
| 5 | 4-$EtOC_6H_4$ | 4-$O_2NC_6H_4$ | PhO | *cis* | **2e** | 85 | 81 |
| 6 | 4-$MeOC_6H_4$ | 3,4-$(MeO)_2C_6H_3$ | PhO | *cis* | **2f** | 87 | 90 |
| 7 | 4-$EtOC_6H_4$ | 4-$MeC_6H_4$ | PhthN | *trans* | **2g** | 85 | 78 |
| 8 | 4-$EtOC_6H_4$ | 4-$ClC_6H_4$ | 2,4-$Cl_2C_6H_3O$ | *cis* | **2h** | 82 | 82 |
| 9 | 4-$EtOC_6H_4$ | 4-$O_2NC_6H_4$ | 2-NaphthO | *cis* | **2i** | 87 | 80 |
| 10 | 4-$EtOC_6H_4$ | 4-$O_2NC_6H_4$ | MeO | *cis* | **2j** | 83 | 79 |
| 11 | 4-$MeOC_6H_4$ | 4-$MeOC_6H_4$ |  | *trans* | **2k** | 84 | 88 |
| 12 | 4-$MeOC_6H_4$ | 4-$MeOC_6H_4$ | Cl | *cis* | **2l** | 70 | 83 |

[a] 3 equiv of CAN in $CH_3CN/H_2O$ (3:1), 45 min, rt.

J. T.; Yang, Y.; Kayser, M.; Georg, G. I. *J. Org. Chem.* **2007**, *72*, 756–759; For a review, see: (f) Alcaide, B.; Almendros, P.; Aragoncillo, C. *Chem. Rev.* **2007**, *107*, 4437–4492; (g) Alcaide, B.; Almendros, P. *Curr. Med. Chem.* **2004**, *11*, 1921–1949; (h) Deshmukh, A. R. A. S.; Bhawal, B. M.; Krishnaswamy, D.; Govande, V. V.; Shinkre, B. A.; Jayanthi, A. *Curr. Med. Chem.* **2004**, *11*, 1889–1920; (i) Alcaide, B.; Almendros, P. *Synlett* **2002**, 381–393; (j) Alcaide, B.; Almendros, P. *Chem. Soc. Rev.* **2001**, *30*, 226–240; (k) Ojima, I.; Delaloge, F. *Chem. Soc. Rev.* **1997**, *26*, 377–386; (l) Ojima, I. *Acc. Chem. Res.* **1995**, *28*, 383–389; (m) Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Oiarbide, M. *Synlett* **2001**, 1813–1826.

9. (a)*Topics in Antibiotic Chemistry*; Sammes, P. G., Ed.; Ellis Horwood Ltd: London, 1980; Vol. 3, (b) O'Sullivan, J.; Abraham, E. P. In *Antibiotics*; Springer: Berlin, 1981; Vol. 4,; (c)*Recent Progress in the Chemical Synthesis of Antibiotics*; Lukacs, G, Ohno, M., Eds.; Springer: Berlin, 1990; (d)*Organic Chemistry of β-Lactams*; Georg, G. I., Ed.; VCH: New York, 1993; (e) Cossio, F. P.; Lecea, B.; Palomo, C. *J. Chem. Soc., Chem. Commun.* **1987**, 1743–1744.
10. Suffness, M. *Taxol Science and Applications*; CRC Press: Boca Raton, Florida, USA, 1995.
11. (a) Jarrahpour, A.; Zarei, M. *Molecules* **2007**, *12*, 2364–2379; (b) Turos, E.; Heldreth, B. B.; Long, S.; Jang, T. E.; Reddy, G. S. K.; Dickey, S.; Lim, D. V. *Bioorg. Med. Chem.* **2006**, *14*, 3775–3784; (c) Podlech, J.; Linder, M. R. *J. Org. Chem.* **1997**, *62*, 5873–5883; (d) Tavani, C.; Bianchi, L.; Dell'Erba, C.; Maccagno, M.; Mugnoli, A.; Novi, M.; Petrillo, G.; Sancassan, F. *Tetrahedron* **2003**, *59*, 10195–10201; (e) Aszodi, J.; Bonnet, A.; Teutsch, G. *Tetrahedron* **1990**, *46*, 1579–1586; (f) Georg, G. I.; He, P.; Kant, J.; Mudd, J. *Tetrahedron Lett.* **1990**, *31*, 451–454;; (g) Palomo, C.; Aizpurua, J. M.; Galarza, R.; Benito, A.; Khamrai, U. K.; Eikesetha, U.; Linden, A. *Tetrahedron* **2000**, *56*, 5563–5570; (h) Hamlet, A. B.; Durst, T. *Can. J. Chem.* **1983**, *61*, 411–415; (i) Bhauaral, K.; Cainelli, G.; Panunzio, M. *Synlett* **1990**, 229–230; (j) Jarrahpour, A.; Zarei, M. *Tetrahedron Lett.* **2010**, *51*, 5791–5794.
12. (a) Green, T. W.; Wuts, P. G. M. *Green's Protective Group in Organic Synthesis*, 4th ed.; John Wiley & Sons: New Jersey, 2007. 903; (b) Del Buttero, P.; Moltenia, G.; Pilati, T. *Tetrahedron* **2005**, *61*, 2413–2419; (c) Gimbert, Y.; Greene, A. E.; Lucatelli, C.; Viton, F. *J. Org. Chem.* **2002**, *67*, 9468–9470; (d) Fukuyama, T.; Frank, R. K.; Jewell, C. F. *J. Am. Chem. Soc.* **1980**, *102*, 2122–2123; (e) Balasubramanian, S.; Gordon, K. H. *Org. Lett.* **2001**, *3*, 53–56; (f) Sutton, J. C.; Bolton, S. A.; Hartl, K. S.; Huang, M.-H.; Jacobs, G.; Meng, W.; Ogletree, M. L.; Pi, Z.; Schumacher, W. A.; Seiler, S. M.; Slusarchyk, W. A.; Treuner, U.; Zahler, R.; Zhao, G.; Bisacchi, G. S. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3229–3233; (g) Kronenthal, D. K.; Han, C. Y.; Taylor, M. K. *J. Org. Chem.* **1982**, *47*, 2765–2768; (h) Jarrahpour, A.; Zarei, M. *Synlett* **2008**, 381–385; (i) Jarrahpour, A.; Zarei, M. *Synth. Commun.* **2008**, *38*, 1837–1845; (j) Jarrahpour, A.; Zarei, M. *Phosphorus Sulfur Silicon* **2009**, *184*, 1738–1749.
13. Corley, E. G.; Karady, S.; Abramson, N. L. *Tetrahedron Lett.* **1988**, *29*, 1497–1500.
14. Lide, D. R. *CRC Handbook of Chemistry and Physics*, 87th ed.; CRC Press: Boca Raton, Florida, 2006–2007. pp 20–29, section 8.
15. *General procedure*: To a solution of β-lactams **1a–l** (1.0 mmol) in 15 mL of 1,4-dioxane was added AgO (0.37 g, 3 mmol) at room temperature. Vigorous stirring of the mixture gave a uniform dispersion of the oxidant. Nitric acid (3 N, 1 mL) was added to initiate oxidation, and the reaction mixture was stirred for an additional 5 min. The solution was diluted with $H_2O$ (10 mL) and the mixture was extracted with EtOAc ($3 \times 10$ mL) and washed with 10% aqueous $NaHCO_3$ (20 mL). The aqueous layer was extracted again with EtOAc (10 mL) and all the organic layers were combined and washed successively with 10% $NaHSO_3$ ($2 \times 10$ mL), brine (20 mL) and then dried over $Na_2SO_4$. After filtration and evaporation of the solvent under reduced pressure, the crude product was purified by recrystallization from a minimum amount of $Et_2O$. 4-(4-Methoxyphenyl)-3-vinylazetidin-2-one (**2k**): White solid. mp 48–50 °C IR (KBr) $cm^{-1}$: 1768 (CO, β-lactam), 3419 (NH); $^1H$ NMR (250 MHz, DMSO-$d_6$) $\delta$ 3.63 (OMe, s, 3H), 3.85 (H-3, dd, 1H, $J$ = 2.4, 7.9), 4.90 (H-4, dd, 1H, $J$ = 2.2, 2.4), 5.30–5.38 (vinylic H, m, 2H), 5.91–6.00 (vinylic H, m, 1H), 6.64–7.11 (ArH, m, 4H), 8.76 (NH, br s, 1H); $^{13}C$ NMR (62.9 MHz, DMSO-$d_6$) $\delta$ 56.2 (OMe), 64.6 (C-3), 66.8 (C-4), 112.9, 115.5, 127.8, 137.2, 139.6, 157.5 (C=C, aromatic carbons), 161.1 (CO, β-lactam); GC–MS $m/z$ = 203 [$M^+$]; Anal. Calcd for $C_{12}H_{13}NO_2$: C, 70.92; H, 6.45; N, 6.89. Found: C, 70.84; H, 6.57; N, 6.81; 3-Chloro-4-(4-methoxyphenyl)azetidin-2-one (**2l**): White solid. Mp 89–91 °C IR (KBr) $cm^{-1}$: 1759 (CO, β-lactam), 3424 (NH); $^1H$ NMR (250 MHz, DMSO-$d_6$) $\delta$ 3.66 (OMe, s, 3H), 4.51 (H-4, dd, 1H, $J$ = 2.5, 5.1), 5.01 (H-3, d, 1H, $J$ = 5.1), 6.78–7.23 (ArH, m, 4H), 8.91 (NH, br s, 1H); $^{13}C$ NMR (62.9 MHz, DMSO-$d_6$) $\delta$ 55.8 (OMe), 62.7 (C-4), 68.3 (C-3), 114.2, 127.9, 137.0, 154.6 (aromatic carbons), 162.9 (CO, β-lactam); GC–MS $m/z$ = 213 [$M^+$, $^{37}Cl$], 211 [$M^+$, $^{35}Cl$]; Anal. Calcd for $C_{10}H_{10}ClNO_2$: C, 56.75; H, 4.76; N, 6.62. Found: C, 56.62; H, 4.85; N, 6.67.
16. Data for known compounds have been reported previously. See: (a) Jarrahpour, A.; Motamedifar, M.; Zarei, M.; Mimouni, M. *Phosphorus Sulfur Silicon* **2010**, *185*, 287–297; (b) Jarrahpour, A.; Zarei, M. *Tetrahedron* **2009**, *65*, 2927–2934; (c) Jarrahpour, A.; Zarei, M. *Tetrahedron Lett.* **2007**, *48*, 8712–8714; (d) Jarrahpour, A.; Zarei, M. *Molecules* **2006**, *11*, 49–58; (e) Jarrahpour, A.; Zarei, M. *Tetrahedron Lett.* **2009**, *50*, 1568–1570; (f) Jarrahpour, A.; Zarei, M. *Tetrahedron* **2010**, *66*, 5017–5023.