Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 47 (2006) 8109–8113

Mild and efficient deprotection of the amine protecting *p*-methoxyphenyl (PMP) group

Jorge M. M. Verkade,[a] Lieke J. C. van Hemert,[a] Peter J. L. M. Quaedflieg,[b] Paul L. Alsters,[b] Floris L. van Delft[a] and Floris P. J. T. Rutjes[a,*]

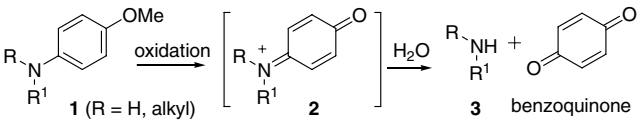
[a]*Institute for Molecules and Materials, Radboud University Nijmegen, Toernooiveld 1, NL-6525 ED Nijmegen, The Netherlands*
[b]*DSM Pharmaceutical Products—Advanced Synthesis, Catalysis and Development, PO Box 18, NL-6160 MD Geleen, The Netherlands*

Received 16 August 2006; revised 25 August 2006; accepted 8 September 2006
Available online 29 September 2006

Abstract—Mild and efficient procedures for deprotection of the amine nitrogen protecting *p*-methoxyphenyl (PMP) group are described. Periodic acid and trichloroisocyanuric acid (TCCA) were found to be particularly effective in realizing amine liberation using 1 and 0.5 equiv of the oxidant, respectively. Extension of the periodic acid-mediated conditions to simultaneous alcohol oxidation by combination with a catalytic amount of sodium dichromate led to smooth conversion of PMP-protected Mannich products into the corresponding β-amino acids in a one-pot procedure.

With the advent of new catalytic strategies to produce enantiopure products,[1] *p*-anisidine stands out as the starting material of choice for a variety of processes that involve imine intermediates. In particular, asymmetric Mannich reactions catalyzed by L- or D-proline proceed smoothly using *p*-anisidine-derived Schiff bases of aldehydes and ketones.[2] Other applications involve the (asymmetric) reduction of *p*-methoxyphenyl (PMP)-protected imines,[3] the involvement of *p*-anisidine in a three-component reaction to form *N*-PMP-protected amino acid amides,[4] and application in asymmetric Diels–Alder reactions.[5]

Furthermore, a Cu-catalyzed procedure for introduction of the PMP-group as a protecting group for amino functions has been described.[6] Obviously, all of these strategies at one point require liberation of the desired amine by oxidative deprotection of the *p*-methoxyphenyl function (Scheme 1). The inevitable deprotection of the PMP group was identified by us as a crucial and important drawback for scale-up and commercial application of any type of methodology involving *N*-PMP intermediates. Currently, most reports describe oxidative removal with ceric ammonium nitrate (CAN) at low pH,[7] but appear to neglect the serious disadvantages associated with this procedure. Usually, a large excess of CAN (4–5 equiv) is required, the reaction has a laborious work-up procedure involving column chromatography, CAN is expensive, and highly toxic. Some of these disadvantages also apply to phenyl iodoacetate ($PhI(OAc)_2$), which has also been reported as a deprotecting agent.[8] In recognition of these drawbacks, the Mioskowski group—in a search for better deprotection methods—recently reported an electrochemical procedure for the oxidative removal of the PMP substituent.[9] However, electrochemical reactions are poorly amenable to scale up, requiring special production equipment.



Scheme 1. Deprotection of PMP-protected amines.

Based on these arguments, we set out to develop a new methodology that can be applied broadly for deprotection of the PMP-group with cheap reagents and beneficial atom economy for potential large scale application in an industrial setting. We decided that the readily

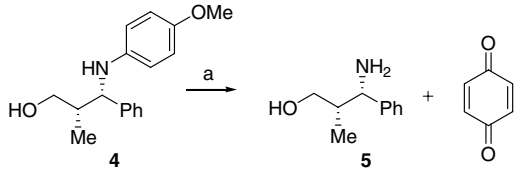
Keywords: *p*-Methoxyphenyl (PMP) deprotection; β-Amino acids; Asymmetric Mannich reactions; Organocatalysis; Oxidative deprotection.
* Corresponding author. Tel.: +31 24 365 3202; fax: +31 24 365 3393; e-mail: F.Rutjes@science.ru.nl

0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.09.044

accessible reduced Mannich product **4**[10] would be a useful starting point to search for oxidation reagents that might be effective in realizing PMP deprotection. Initially, an HPLC assay was adopted that allowed us to determine the conversion in time (after 8 and 20 h) of PMP-protected amine **4** into the corresponding free amine **5** upon treatment with varying amounts (1 or 4 equiv) of oxidant. As can be seen from Table 1, CAN and $PhI(OAc)_2$ in the presence of 1 equiv of sulfuric acid were indeed effective in deprotecting, albeit with moderate conversions. We were, however, pleasantly surprised to find that under these acidic conditions, readily available and cheap oxidants such as trichloroisocyanuric acid (TCCA) and periodic acid (H_5IO_6) were capable of deprotecting the PMP group effectively (entries 7–12). The data show that the addition of a strong protic acid is crucial in the deprotection reactions, since without the acid the oxidants do not give any conversion of the starting material at all (entries 7 and 10).

This is in agreement with a mechanism involving initial formation of the benzoquinone-derived iminium ion **2**, which under the reaction conditions hydrolyzes to the desired free amine **3** (Scheme 1). The apparently illogical decrease in yield upon going from 1 to 4 equiv of TCCA (entries 8 and 9) can be explained by overoxidation of the liberated amino alcohol in the latter case. Periodic acid shows a relatively low conversion after 8 h, but very good conversion after 24 h (entry 11), while additional equivalents of oxidant yielded no improvement (entry 12). Other halogen-containing oxidants have also been tested under these acidic conditions such as the hypervalent Dess–Martin reagent (entries 5 and 6), hypochlorous acid (entries 13 and 14), and a series of electrophilic halide reagents (entries 15–25). Without exception, in all cases conversion of **4** into **5** was observed, but with reduced effect compared to TCCA and periodic acid. Finally, several inorganic oxidants were applied, but appeared unsuccessful for this transformation (entries 26–30).

Table 1. Deprotection of PMP-protected amine **4** using various oxidants



4 **5**

Entry	Equivalent	Oxidant	Conversion[a] to **5** at $t = 8$ h (%)	Conversion[a] to **5** at $t = 20$ h (%)
1	1	CAN	35	34
2	4	CAN	71	42
3	1	$PhI(OAc)_2$	54	47
4	4	$PhI(OAc)_2$	59	64
5	1	DM	47	48
6	4	DM	58	67
7	1	TCCA	<5[b]	<5[b]
8	1	TCCA	79	82
9	4	TCCA	36	0
10	4	H_5IO_6	<5[b]	<5[b]
11	1	H_5IO_6	20	81
12	4	H_5IO_6	32	75
13	1	HOCl	40	41
14	4	HOCl	65	81
15	1	PBP	58	60
16	1	NCS	41	59
17	4	NCS	81	62
18	1	NBS	77	79
19	4	NBS	75	55
20	1	NIS	57	59
21	4	NIS	80	78
22	1	Br_2	50	—
23	4	Br_2	50	—
24	1	I_2	53	17
25	4	I_2	55	21
26	4	H_2O_2	<5	—
27	4	$KMnO_4$	15[c]	—
28	4	$NaBO_3{\cdot}4H_2O$	0	—
29	4	$Na_2CO_3{\cdot}1.5H_2O_2$	0	—
30	4	$K_2Cr_2O_7$	0	—

Conditions: (a) 1 or 4 equiv oxidant, 1 equiv H_2SO_4, 5 mol % benzoic acid (internal standard), MeCN/H_2O 1:1, rt.

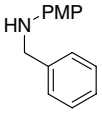
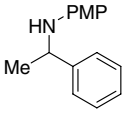
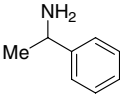
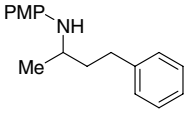
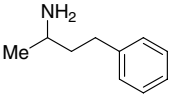
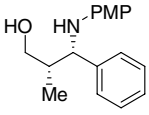
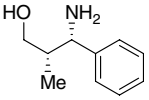
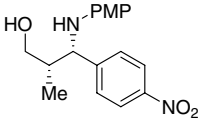
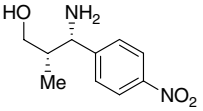
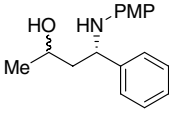
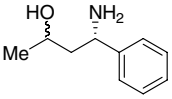
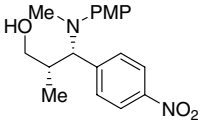
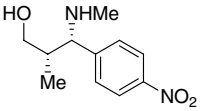
[a] Conversions were determined using HPLC (Inertsil ODS-3 column) on crude samples from the reaction mixture.

[b] Carried out without the addition of H_2SO_4.

[c] Several by-products were detected by HPLC. (DM = Dess–Martin periodinane, PBP = pyridinium bromide perbromide, NCS = *N*-chlorosuccinimide, NBS = *N*-bromosuccinimide, NIS = *N*-iodosuccinimide.)

To verify the results of our initial screening, we performed a series of preparative scale experiments on the initial substrate **4** as well as on the PMP-protected amines **6**–**11** with TCCA and periodic acid (Table 2). In the case of TCCA, 0.5 equiv appeared optimal since only two of the three chlorine substituents are involved in the oxidation,[11] whereas one equivalent of periodic acid was required. As can be judged from Table 2, the corresponding free amines **5**, **12**–**17** were formed with satisfactory results.[12,13] Subjection of PMP-protected benzylamine **6** to TCCA provided the free amine **12** in good yield, but proceeded poorly with periodic acid which led us to conclude that for these conditions a substituent at the benzylic α-position is desired (entries 1 and 2). Indeed, PMP-protected α-methylbenzylamine **7** gave excellent yields of the desired product **13** with both oxidants (entries 3 and 4). *N*-PMP-protected 4-phenylbutan-2-amine **8** underwent deprotection with similar efficiency to give 4-phenylbutan-2-amine (**14**, entries 5 and 6). Deprotection of the reduced Mannich adducts **4** and **9**, **10** also proceeded readily to furnish the corresponding amines in excellent yields (entries 7–12). Finally,

Table 2. Preparative scale *N*-PMP deprotections

Entry	*n*-PMP amine	Oxidant	*T* (°C)	*t* (h)	Product (yield %)[a]
					
1	**6**	TCCA	21	16	**12** (73)
2	**6**	H_5IO_6	21	16	**12** (<5)
					
3	**7**	TCCA	21	16	**13** (99)
4	**7**	H_5IO_6	21	16	**13** (89)
					
5	**8**	TCCA	21	16	**14** (73)
6	**8**	H_5IO_6	21	16	**14** (80)
					
7	**4**	TCCA	21	16	**5** (80)
8	**4**	H_5IO_6	21	16	**5** (99)
					
9	**9**	TCCA	21	16	**15** (99)
10	**9**	H_5IO_6	21	16	**15** (95)
					
11	**10**	TCCA	21	16	**16** (81)
12	**10**	H_5IO_6	21	16	**16** (95)
					
13	**11**	TCCA	90	0.1	**17** (77)
14	**11**	H_5IO_6	90	1.5	**17** (66)

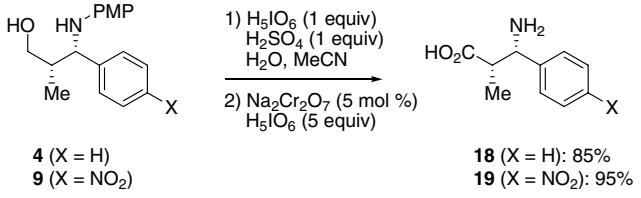
Conditions: 1 equiv H_2SO_4, 1 equiv H_5IO_6 or 0.5 equiv TCCA, MeCN/H_2O 1:1, 21 or 90 °C.

[a] Isolated yield of HCl salt after aqueous work-up (>95% pure according to HPLC).

tertiary amine **11** was subjected to the same conditions, but showed minimal conversion in both cases. However, upon heating to 90 °C the same oxidative cleavage took place resulting in the secondary amine **17** in a reasonable yield with both TCCA and periodic acid (entries 13 and 14). It may be expected that the yield could be further increased by optimization of the reaction conditions. It must be noted that our PMP removal procedure is accompanied by a straightforward and practical work-up, which sharply contrasts with the laborious CAN chromatography protocol. In all cases, after completion of the reaction, work-up involved washing the aqueous mixture with CH_2Cl_2 (to remove benzoquinone) before adjustment to pH 10.5 and extraction with ethyl acetate. Upon acidification of the organic layer with a solution of HCl in ethyl acetate and subsequent concentration, the deprotected amines were obtained in high purity (>95% according to HPLC) as the corresponding HCl salts.

The deprotection sequence was further extended in the synthesis of two β-amino acids[14] via a one-pot deprotection oxidation sequence (Scheme 2). First, the Mannich adducts **4** and **9** were treated with the periodic acid deprotection conditions and after completion, a catalytic amount of sodium dichromate and an additional 5 equiv of periodic acid were added to the aqueous solution, resulting in oxidation of the alcohol to the carboxylic acid function.[15] The crude mixture was purified using ion exchange chromatography to yield the corresponding β-amino acids **18** and **19** in good yields.[16] Given the vast number of 1,3-aminoalcohols that are accessible via asymmetric Mannich reaction, the latter pathway represents an easy and efficient entry into a large variety of β-amino acids.

In conclusion, the extensive use of the *p*-methoxyphenyl (PMP) group in asymmetric organocatalysis requires easy and scalable deprotection procedures in order to render these processes economically viable. We have developed novel, mild and efficient oxidative cleavage conditions involving a series of electrophilic halide reagents, which are effective if the deprotection is carried out at low pH. Periodic acid and trichloroisocyanuric acid (TCCA) were identified as being particularly effective for N-deprotection, requiring only 1 and 0.5 equiv, respectively, to give a high yield of the desired amine. The periodic acid-mediated conditions were used in combination with a catalytic amount of sodium dichromate—added to the same pot after completion of the deprotection—to convert asymmetric Mannich products, in a one-pot procedure, into the corresponding



4 (X = H)
9 (X = NO_2)

18 (X = H): 85%
19 (X = NO_2): 95%

Scheme 2. Formation of β-amino acids.

β-amino acids. Studies to elucidate the exact mechanism of the oxidation process and to determine the scope and limitations of these deprotection conditions are currently ongoing.

Acknowledgements

M. Willems is acknowledged for a practical contribution. This work forms part of the Ultimate Chiral Technology project supported in part with funds provided by SNN (Cooperation Northern Netherlands) and EFRO (European Fund for Regional Development).

References and notes

1. For general reviews, see, for example: (a) List, B. *Chem. Commun.* **2006**, 819–824; (b) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138–5175.
2. For reviews, see: (a) Marques, M. M. B. *Angew. Chem., Int. Ed.* **2006**, *45*, 348–352; (b) Córdova, A. *Acc. Chem. Res.* **2004**, *37*, 102–112.
3. For racemic methods, see, for example: (a) Menche, D.; Hassfeld, J.; Li, J.; Menche, G.; Ritter, A.; Rudolph, S. *Org. Lett.* **2006**, *8*, 741–744; For asymmetric reductive amination, see, for example: (b) Storer, R. I.; Carrera, D. E.; Ni, Y.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2006**, *128*, 84–86; (c) Hoffmann, S.; Majeed Seayad, A.; List, B. *Angew. Chem., Int. Ed.* **2005**, *44*, 7424–7427.
4. Cannella, R.; Clerici, A.; Panzeri, W.; Pastori, N.; Punta, C.; Porta, O. *J. Am. Chem. Soc.* **2006**, *128*, 5358–5359.
5. Sundén, H.; Ibrahem, I.; Eriksson, L.; Córdova, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 4877–4880.
6. Lu, Z.; Twieg, R. J. *Tetrahedron Lett.* **2005**, *46*, 2997–3001.
7. (a) Sakai, T.; Korenaga, T.; Washio, N.; Nishio, Y.; Minami, S.; Ema, T. *Bull. Chem. Soc. Jpn.* **2004**, *77*, 1001–1007; (b) Hata, S.; Iguchi, I.; Iwasawa, T.; Yamada, K.; Tomioka, K. *Org. Lett.* **2004**, *6*, 1721–1723; (c) Overman, L. E.; Owen, C. E.; Pavan, M. P. *Org. Lett.* **2003**, *5*, 1809–1812; (d) Chi, Y.; Zhou, Y.-G.; Zhang, X. *J. Org. Chem.* **2003**, *68*, 4120–4122; (e) Fustero, S.; Garcia Soler, J.; Bartolomé, A.; Sanchez-Rosello, M. *Org. Lett.* **2003**, *5*, 2707–2710; (f) Fustero, S.; Bartolomé, A.; Sanz-Cervera, J. F.; Sanchez-Rosello, M.; Soler, J. G.; Ramirez de Arellano, C.; Fuentes, A. S. *Org. Lett.* **2003**, *5*, 2523–2526; (g) Córdova, A. *Synlett* **2003**, 1651–1654.
8. (a) Janey, J. M.; Hsiao, Y.; Armstrong, J. D., III. *J. Org. Chem.* **2006**, *71*, 390–392; (b) Ibrahem, I.; Casas, J.; Córdova, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 6528–6531; (c) Córdova, A.; Notz, W.; Zhong, G.; Betancort, J. M.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2002**, *124*, 1842–1843; (d) Porter, J. R.; Traverse, J. F.; Hoveyda, A. H.; Snapper, M. L. *J. Am. Chem. Soc.* **2001**, *123*, 10409–10410.
9. De Lamo Marin, S.; Martens, T.; Mioskowski, C.; Royer, J. *J. Org. Chem.* **2005**, *70*, 10592–10595.
10. Córdova, A. *Chem. Eur. J.* **2004**, *10*, 1987–1997.
11. Quaedflieg, P. J. L. M.; Alsters, P. L.; Pojarliev, P.; Jary, W. G. WO Patent 2005040149, 2005; *Chem. Abstr.* **2005**, *142*, 430492.
12. All new compounds were appropriately characterized with FTIR, ^1H and ^{13}C NMR and high resolution mass data.
13. *Representative procedure for deprotection using TCCA*: To a solution of **7** (0.25 g, 1.1 mmol) in MeCN/H_2O (20 mL, 1:1) were added TCCA (0.26 g, 0.55 mmol) and 1 M aqueous H_2SO_4 (1.1 mL). The mixture was stirred for 16 h

at rt and then washed with CH_2Cl_2 (3×100 mL). The resulting aqueous phase was subsequently brought to pH 10.5 through addition of 5 M aqueous KOH and extracted with EtOAc (4×100 mL). The combined organic layers were brought to pH 1 via addition of EtOAc/HCl, dried ($MgSO_4$), and concentrated to afford the HCl salt of **13**. Spectral data of **13·HCl**: ^{1}H NMR (400 MHz, D_2O): δ 1.65 (d, $J = 6.9$ Hz, 3H), 4.55 (q, $J = 6.2$ Hz, 1H), 7.49 (m, 5H); ^{13}C NMR (100 MHz, D_2O): δ 19.5, 51.2, 126.7, 129.4, 129.4, 137.9; IR ν (cm^{-1}): 2972, 2879, 1609, 1513, 1084, 1032, 763, 696, 537, HRMS (ESI) calcd for $C_8H_{12}N$ (M+) 122.0970, found 122.0981. *Representative procedure for deprotection using periodic acid*: To a solution of **7** (0.25 g, 1.1 mmol) in MeCN/H_2O (20 mL, 1:1) were added H_5IO_6 (0.25 g, 1.1 mmol) and 1 M aqueous H_2SO_4 (1.1 mL). The mixture was stirred for 16 h at rt and washed with CH_2Cl_2 (3×100 mL). The resulting aqueous phase was subsequently brought to pH 10.5 through addition of 5 M aqueous KOH and extracted with EtOAc (4×100 mL). The combined organic layers were brought to pH 1 via addition of EtOAc/HCl, dried ($MgSO_4$) and concentrated to afford the HCl salt of **13**.

14. For a general entry into the synthesis of β-amino acids, see, for example: *Enantioselective Synthesis of β-Amino Acids*; 2nd ed.; Juaristi, E. E., Soloshonok, V. A., Eds.; Wiley & Sons: Hoboken, 2005; pp 195–213.
15. Schmieder-van de Vondervoort, L.; Bouttemy, S.; Padron, J. M.; le Bras, J.; Muzart, J.; Alsters, P. L. *Synlett* **2002**, 243–246.
16. Representative experimental procedure for β-amino acid formation: To a solution of the amine (1.9 mmol) in MeCN/H_2O (20 mL, 1:1) were added 1 M aqueous H_2SO_4 (1.9 mmol) and H_5IO_6 (0.42 g, 1.9 mmol. The reaction mixture was stirred at ambient temperature for 16 h. Subsequently, $Na_2Cr_2O_7{\cdot}2H_2O$ (27 mg, 0.092 mmol) was added, followed by H_5IO_6 (2.1 g, 0.92 mmol) and the mixture was stirred for an additional 16 h. After completion, the reaction mixture was washed with CH_2Cl_2 (3×50 mL) and purified by ion exchange chromatography (DOWEX $50W \times 8$) to give the corresponding β-amino acid as a white solid. Spectral data: Compound **18**: ^{1}H NMR (300 MHz, D_2O): δ 1.27 (d, $J = 6.8$ Hz, 3H), 3.01 (m, 1H), 4.47 (d, $J = 8.1$ Hz, 1H), 7.47 (m, 5H); ^{13}C NMR (75 MHz, D_2O): δ 13.5, 45.4, 57.1, 126.7, 128.6, 128.8, 134.8, 179.5; IR ν (cm^{-1}): 2972, 1559, 1454, 1401, 1368, 1208, 1107, 1065, 1032, 755, 700; HRMS (ESI) calcd for $C_{10}H_{12}NO_2Na_2$ 224.0663, found: 224.0666. Compound **19**: ^{1}H NMR (300 MHz, D_2O): δ 1.27 (d, $J = 6.9$ Hz, 3H), 2.98 (m, 1H), 4.59 (d, $J = 8.1$ Hz, 1H), 7.66 (d, $J = 8.4$ Hz, 2H), 8.33 (d, $J = 8.4$ Hz, 2H); ^{13}C NMR (75 MHz, D_2O): δ 179.4, 147.4, 142.2, 128.0, 123.7, 56.5, 45.7, 13.4; IR ν (cm^{-1}): 2969, 1737, 1365, 1229, 1216, 735, 668, 611; HRMS (ESI) calcd for $C_{10}H_{12}N_2O_4Na$ 247.0695, found: 247.0716.