Tetrahedron Letters 49 (2008) 4817–4819

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Mild, efficient and rapid O-debenzylation of *ortho*-substituted phenols with trifluoroacetic acid

Steven Fletcher *, Patrick T. Gunning *

Department of Chemistry, University of Toronto, Mississauga, ON L5L 1C6, Canada

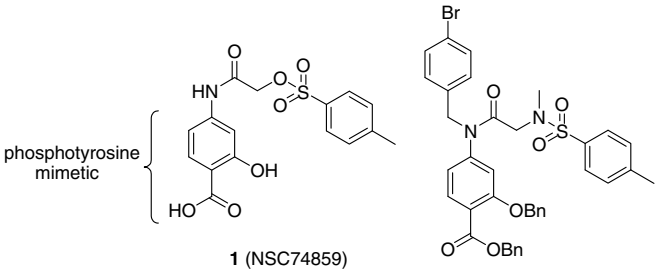
ARTICLE INFO

Article history:
Received 21 May 2008
Revised 2 June 2008
Accepted 4 June 2008
Available online 10 June 2008

ABSTRACT

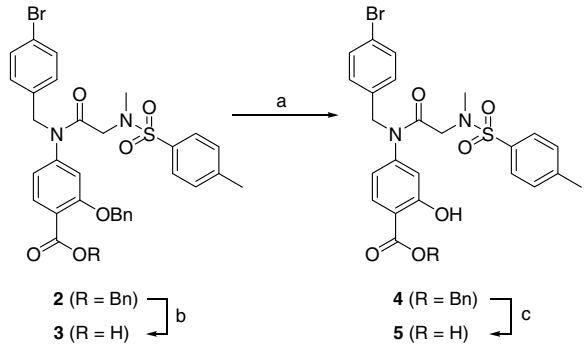
The mild and efficient deblocking of aryl benzyl ethers with TFA is reported. Cleavage was fastest with *ortho*-electron-withdrawing groups on the phenolic ring, which we have attributed to a proton chelation effect, furnishing the deprotected phenols in excellent yields. The corresponding *para*-methoxybenzyl, allyl and *iso*-propyl ethers were also cleanly removed under these conditions. In addition, the selective aryl benzyl ether debenzylation in the presence of benzyl ester, Cbz carbamate and Boc carbamate functionalities was also observed.

Phosphotyrosines feature in the design of inhibitors of several protein targets, including protein tyrosine phosphatase 1B (PTP1B).[1] However, these moieties suffer from hydrolytic lability to cellular phosphatases and poor cell penetration due to the associated dianionic charge.[1] To address these issues, salicylic acid derivatives (and closely-related analogues) have become popular mimetics of phosphotyrosine in small molecule inhibitors.[1–5] Turkson et al. have recently reported on NSC74859 (**1**), a potent, salicylic acid-based inhibitor of the oncogenic protein Stat3.[6] As part of our structure–activity relationship (SAR) studies on NSC74859 (**1**), we sought to debenzylate both the phenol ether and benzoate ester in **2** without reducing the aryl-bromide bond, a common undesired side reaction that occurs with hydrogen gas and Pd/C catalyst.[7]



1 (NSC74859) **2**

O-Benzyl-protected phenols are known to undergo debenzylation with trifluoroacetic acid (TFA)[8] by an initial protonation of the weakly basic phenol oxygen, although additives such as strong organic acids (e.g., trifluoromethanesulfonic acid[9]) or a large excess of nucleophilic scavenger (e.g., thioanisole, which accelerates the reaction by a 'push–pull' mechanism[10]) are typically required. Recent work by Ploypradith et al. describes the mild deprotection of aromatic ethers with sub-stoichiometric *para*-toluenesulfonic acid on solid support.[11] In a special case, *O*-benzyl-protected *ortho*-nitrophenol was cleaved rapidly (<5 min) with neat TFA,[12] which we considered was due to the ability of the substrate to chelate a proton since the structurally-similar *ortho*-hydroxybenzoates (salicylates) are well-known to chelate copper ions and iron ions. We reasoned that **2** (and indeed **3**) may similarly undergo accelerated debenzylation with TFA. In fact, as shown in Scheme 1, treatment of **2** (or **3**) with a 1:1 mixture of TFA/toluene led to rapid debenzylation (5 min for **2**; 1 h for **3**) in 91% yield for **2** (or 85% yield for **3**). In this Letter, we will explore the structural requirements of the phenol component that increase the lability of the *O*-benzyl phenol ether bond in the presence of TFA. In addition,



Scheme 1. Reagents and conditions: (a) TFA/toluene, 1:1, rt, 5 min, 91% (for **4**) or 1 h, 85% (for **5**); (b) LiOH·H_2O, THF/H_2O, 3:1, rt, 24 h, 83%; (c) NaOH, THF/H_2O, 3:1, 60 °C, 4 h, 61%.

* Tel.: +1 905 828 5354; fax: +1 905 828 5425 (P.T.G.).
E-mail addresses: steven.fletcher@utoronto.ca (S. Fletcher), patrick.gunning@utoronto.ca (P. T. Gunning).

0040-4039/$ - see front matter

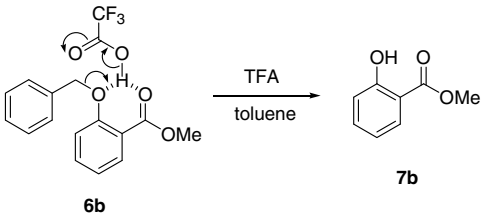
we will explore the selectivity of this mild debenzylation technique with respect to other aromatic ethers and examine the stability of other benzyl-based protecting groups to these reaction conditions.

A series of 12 *O*-benzyl-protected phenols was prepared by standard procedures in near quantitative yields. Each of these ethers was then deprotected with a 1:1 mixture of TFA/toluene; our observations are summarized in Table 1. In certain cases, O→C benzyl migration (Friedel–Crafts reaction) by-products (⩽10%) were occasionally inseparable from the product by silica gel flash column chromatography. Thus, several benzyl cation captors were investigated for their abilities to improve yields and purities of the debenzylation reactions. Three to ten equivalents of *p*-cresol, anisole and triethylsilane were employed, but these exerted little effects on reducing by-product formation. Conversely, we discovered that including the more nucleophilic scavenger thioanisole as an additive to the co-solvent toluene typically, after silica gel flash column chromatography, furnished products in ⩾95% purities (and higher yields), as judged by ^{1}H NMR. Nevertheless, we envisaged any Friedel–Crafts impurities would be more readily separable on slightly more complex aryl benzyl ethers, as we observed with the substrates shown in Scheme 1 and Tables 3 and 4 (>99% purities (^{1}H NMR) in each case). Whilst likely leading to even higher yields and purities, large excesses of thioanisole (50 equiv) are also known to accelerate TFA-mediated debenzylation.[10] However, in our hands just 3 equiv of thioanisole had little effect on the rate of debenzylation, allowing us to attribute the deprotection rates solely to the structure of the phenol. Electron-rich phenols are good scavengers of benzyl cations,[13] and since preliminary experiments with electron-rich phenols generated complex mixtures of Friedel–Crafts by-products under these debenzylation conditions, we chose to investigate only electron-poor phenols in this study.

O-Benzyl-protected phenols with π-*ortho*-electron-withdrawing groups (**6a**, **6b**, **6d**, **6f**) were swiftly (several in less than 3 h cf. 24 h for unsubstituted phenol **6l**) and cleanly debenzylated, with less than 5% of the undesired C-benzylated phenol by-products. In contrast, *meta*- and *para*-electron-withdrawing groups slowed down the debenzylation (e.g., entries **6g** and **6h**), relative to the control compound **6l**, which itself could only be obtained in moderate purity by this method. The σ-withdrawing (and π-donating) bromophenols **6i–k** were insufficiently deactivated to benzyl cation scavenging and were contaminated with several by-products. Importantly, *n*-butyl benzyl ether **8** was unaffected by TFA under the reaction conditions, indicating this procedure is selective for aryl benzyl ethers. In addition, the results in Table 1 suggest that this procedure is suitable only for phenols substituted with π-electron-withdrawing groups.

Since the debenzylation mechanism with TFA proceeds via an initial protonation of the phenol ether oxygen, the more available the ether oxygen lone pairs are, the faster the reaction will be. Hence, the slower reaction times for the phenols bearing *meta*- and *para*-electron-withdrawing groups make sense, although this is not true for the *ortho*-functionalized aryl benzyl ethers. As hypothesized for the bis-benzyl salicylate derivative **2** earlier, we considered these *ortho*-substituted phenols were capable of chelating the acidic hydrogen atom from TFA which therein facilitated the acid-mediated debenzylation via a six-membered cyclic intermediate, as proposed in Scheme 2. A similar chelation intermediate has been put forward by Baldwin and Haraldsson to account for the Lewis acid $MgBr_2$-mediated debenzylation of aromatic benzyl ethers *ortho* to an aldehyde group.[14]

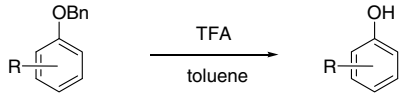
Accordingly, to test this hypothesis we expanded this series of *ortho*-substituted aryl benzyl ethers, and the results from their debenzylation reactions with TFA are summarized in Table 2. These substrates have been listed in order of increasing approximate



6b **7b**

Scheme 2. Proposed chelation mechanism to account for accelerated TFA-mediated debenzylation with *ortho*-substituted phenols.

Table 1
TFA-mediated debenzylation of *O*-benzyl-protected phenols[a]

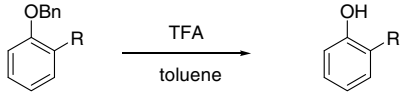


6 **7**

Substrate	R	Time (h)[b]	Yield[c] (%)
6a	*o*-CO_2Me, m[d]-NHAc	5 min	93
6b	*o*-CO_2Me	5 min	94
6c	*p*-CO_2Me	36[e]	63 (85[f])
6d	*o*-CO_2Bn	5 min	93
6e	*p*-CO_2Bn	36[e]	58 (79[f])
6f	*o*-NO_2	3	97
6g	*m*-NO_2	36[e]	75 (98[f])
6h	*p*-NO_2	36[e]	66 (98[f])
6i	*o*-Br	16	—[g]
6j	*m*-Br	30	—[g]
6k	*p*-Br	36	—[g]
6l	H	24	—[g]
n-BuOBn (**8**)	—	24	No reaction

[a] The reaction was carried out with **6** (0.5 mmol) in a 1:1 mixture of TFA/toluene (5 ml) at rt, with 3 equiv of thioanisole.
[b] Time taken for all starting material to be consumed.
[c] Isolated yield after silica gel flash column chromatography.
[d] *meta* to phenol oxygen AND *para* to ester.
[e] Reaction was slow and incomplete after 3 days.
[f] Yield based on recovered starting material.
[g] Complex mixture of products.

Table 2
TFA-mediated debenzylation of *O*-benzyl-protected, *ortho*-substituted phenols[a]



6 **7**

Substrate	R	pK_{aH}[b]	Time[c] (h)	Yield[d] (%)	Relative rate
6m	CO_2NH_2	−2	24	83	1
6n	CHO	−7	3.5	94[e]	6.9
6o	CO_2H	−8	1	91	24
6b	CO_2Me	−8.5	5 min	94	288
6d	CO_2Bn	−8.5	5 min	93	288
6p	CN	−10	>48	51 (95[f])	—
6f	NO_2	−12	3	97	8
6i	Br	—	16	—[g]	1.5
6l	H	—	24	—[g]	1

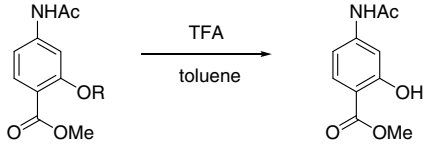
[a] The reaction was carried out with **6** (0.5 mmol) in a 1:1 mixture of TFA/toluene (5 ml) at rt, with 3 equiv of thioanisole.
[b] Approximate pK_{aH} of conjugate acid of R group.[15]
[c] Time taken for all starting material to be consumed.
[d] Isolated yield after silica gel flash column chromatography.
[e] Including thioanisole in the deprotection of **6n** led to further by-products, thus no scavenger was used and compound **7n** could be obtained in only 90% purity.
[f] Yield based on recovered starting material.
[g] Complex mixture of products.

acidity of the conjugate acid (decreasing pK_{aH}) of the *ortho*-electron-withdrawing substituent.[15] There appears to be an optimal pK_{aH} of around −8.5, that is exhibited by carboxylic esters, which lead to the fastest rate of debenzylation with TFA. In an approximate bell-shaped distribution of reaction rate versus *ortho*-substituent pK_{aH}—that was interrupted only by *ortho*-cyanophenol **6p**—protonatable groups with pK_{aH}'s <−8.5 or >−8.5 were less effective at accelerating the TFA-mediated debenzylation. These data concur with our chelation hypothesis: groups that are too basic bind more strongly to the TFA proton making it less available for sharing with, and ultimately releasing to, the phenol ether oxygen; groups that are weakly basic do not bind the TFA proton as well, leading to reduced chelation and hence less rate enhancement. The anomalous result for *ortho*-cyanophenol **6p** was anticipated since this compound was selected as a negative control. Phenol **6p** is geometrically incapable of chelating a proton, because the linear, *sp*-hybridized nitrile functionality directs its basic nitrogen atom ($pK_{aH} \approx -10$) away from the phenol oxygen. As predicted, there was no rate enhancement for the TFA-mediated debenzylation of **6p** relative to phenol **6l**. In fact, **6p** was only slowly debenzylated, at a rate that was comparable with the *m*-nitro and *p*-nitro derivatives **6g** and **6h**, respectively.

We next wanted to investigate the selectivity for the deprotection of the benzyl group over other phenol protecting groups. Accordingly, the benzyl group in salicylate derivative **9a** was varied with *para*-methoxybenzyl (PMB; **9b**), methyl (**9c**), allyl (**9d**) and *iso*-propyl (*i*-Pr; **9e**). These substrates were then debenzylated with a 1:1 mixture of TFA/toluene; our findings are reported in Table 3. Any impurities this time were minor and readily separable from the products, eliminating the need for the additive thioanisole. The relative rates at which these protecting groups were removed was *para*-methoxybenzyl > benzyl > allyl > *iso*-propyl ≫ methyl, which reflects the stability of the carbocations. These data suggest that in salicylates such as **9**, the benzyl phenol protecting group (R = Bn) can be removed with TFA in the presence of the corresponding allyl, *iso*-propyl and methyl ethers.

Finally, we explored the selectivity of this mild debenzylation technique over other benzyl-based protecting groups, as shown in Table 4. As the results demonstrate, it was possible to deblock the *O*-benzyl ether in the presence of a benzyl ester (**6d**) and in the presence of a benzyl carbamate (**11b**), thereby increasing the orthogonality of *O*-benzyl phenol ethers of salicylate derivatives. Interestingly, it was even possible to cleave the benzyl group in **11c** with TFA in the presence of an *N*-Boc-protected aniline.

Table 3
TFA-mediated deprotection of O-blocked phenol ether derivatives of methyl 4-acetamidosalicylate[a]

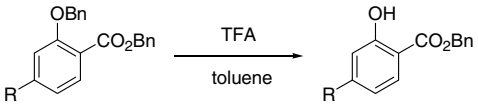


9 **10**

Substrate	R	Time[b] (h)	Yield[c] (%)
9a	Bn	5 min	91
9b	PMB	2 min	90
9c	Me	48	0[d]
9d	Allyl	20	91
9e	*i*-Pr	36	92

[a] The reaction was carried out with **9** (0.5 mmol) in a 1:1 mixture of TFA/toluene (5 ml) at rt.
[b] Time taken for all starting material to be consumed.
[c] Isolated yield after silica gel flash column chromatography.
[d] Only starting material remained after 48 h, at which point the reaction was aborted.

Table 4
Selectivity investigation into the TFA-mediated debenzylation of aryl benzyl ethers[a]



11 **12**

Substrate	R	Yield[b] (%)
6d[c]	H	93
11a	NHAc	92
11b	NHCbz	93
11c[d]	NHBoc	54

[a] The reaction was carried out with **11** (0.5 mmol) in a 1:1 mixture of TFA/toluene (5 ml) at rt for 5 min, then all solvents were evaporated.
[b] Isolated yield after silica gel flash column chromatography.
[c] For compound **6d**, 3 equiv of thioanisole were also used.
[d] After 5 min, the reaction mixture was diluted with CH_2Cl_2 and then immediately neutralized with 1 M NaOH. The organic layer was then separated and evaporated.

In summary, we have presented the mild, efficient and rapid deblocking of *ortho*-substituted aryl benzyl ethers with TFA. Debenzylation was fastest when the *ortho* group was a carboxylic ester, which we have attributed to a proton chelation effect. Other *ortho* groups that accelerated the TFA-mediated debenzylation included carboxylic acid, aldehyde and nitro. In addition, we have shown that in such *ortho*-functionalized phenols, benzyl could be removed in the presence of the corresponding *iso*-propyl, allyl and methyl ethers. Moreover, the benzyl ether could be selectively cleaved in the presence of benzyl ester, Cbz carbamate and Boc carbamate functionalities.

Acknowledgements

The authors gratefully acknowledge financial support for this work from the Canadian Foundation of Innovation and the University of Toronto (Connaught Foundation).

References and notes

1. Zhang, S.; Zhang, Z.-Y. *Drug Discov. Today* **2007**, *12*, 373–381.
2. (a) Pei, Z.; Li, X.; Liu, G.; Abad-Zapatero, C.; Lubben, T.; Zhang, T.; Ballaron, S. J.; Hutchins, C. W.; Trevillyana, J. M.; Jirouseka, M. R. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3129–3132; (b) Xin, Z.; Liu, G.; Abad-Zapatero, C.; Pei, Z.; Szczepankiewicz, B. G.; Li, X.; Zhang, T.; Hutchins, C. W.; Hajduk, P. J.; Ballaron, S. J.; Stashko, M. A.; Lubben, T. H.; Trevillyana, J. M.; Jirouseka, M. R. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3947–3950.
3. Tautz, L.; Bruckner, S.; Sareth, S.; Alonso, A.; Bogetz, J.; Bottini, N.; Pellecchia, M.; Mustelin, T. *J. Biol. Chem.* **2005**, *280*, 9400–9408.
4. Shrestha, S.; Bhattarai, B. R.; Chang, K. J.; Leea, K.-H.; Choa, H. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2760–2764.
5. Liljebris, C.; Larsen, S. D.; Ogg, D.; Palazuk, B. J.; Bleasdale, J. E. *J. Med. Chem.* **2002**, *45*, 1785–1798.
6. Siddiquee, K.; Zhang, S.; Guida, W. C.; Blaskovich, M. A.; Greedy, B.; Lawrence, H. R.; Yip, M. L. R.; Jove, R.; Laughlin, M. M.; Lawrence, N. J.; Sebti, S. M.; Turkson, J. *Proc. Natl. Acad. Sci. U.S.A.* **2007**, *104*, 7391–7396.
7. Pandey, P. N.; Purkayastha, M. L. *Synthesis* **1982**, 876–878.
8. (a) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; John Wiley & Sons: New York, 1999; (b) Kocienski, P. J. *Protecting Groups*, 3rd ed.; Georg Thieme: Stuttgart, Germany, 2003.
9. Kiso, Y.; Isawa, H.; Kitagawa, K.; Akita, T. *Chem. Pharm. Bull.* **1978**, *26*, 2562–2564.
10. Kiso, Y.; Ukawa, K.; Nakamura, S.; Ito, K.; Akita, T. *Chem. Pharm. Bull.* **1980**, *28*, 673–676.
11. Ploypradith, P.; Cheryklin, P.; Niyomtham, N.; Bertoni, D. R.; Ruchirawat, S. *Org. Lett.* **2007**, *9*, 2637–2640.
12. Marsh, J. P., Jr.; Goodman, L. *J. Org. Chem.* **1965**, *30*, 2491–2492.
13. (a) Eberle, A. N. *J. Chem. Soc., Perkin Trans. 1* **1986**, 361–367; (b) Bodanszky, M.; Tolle, J. C.; Deshmane, S. S.; Bodanszky, A. *Int. J. Pept. Protein Res.* **1978**, *12*, 57–68.
14. Haraldsson, G. G.; Baldwin, J. E. *Tetrahedron* **1997**, *53*, 215–224.
15. (a) *Ionization Constants of Organic Acids in Solution*; Serjeant, E. P., Dempsey, B., Eds. IUPAC Chemical Data Series No. 23; Pergamon Press: Oxford, UK, 1979; (b) see also: http://www2.lsdiv.harvard.edu/labs/evans/pdf/evans_pKa_table.pdf.