JOC*Note*

Selective *tert*-Butyl Ester Deprotection in the Presence of Acid Labile Protecting Groups with Use of $ZnBr_2$

Ramesh Kaul, Yann Brouillette, Zohreh Sajjadi, Karl A. Hansford, and William D. Lubell*

Département de chimie, Université de Montréal, C.P. 6128, Succursale Centre Ville, Montréal, Québec, Canada H3C 3JC

lubell@chimie.umontreal.ca

Received May 25, 2004

Abstract: Chemoselective hydrolysis of *tert*-butyl esters in the presence of other acid-labile groups has been explored by employing α-amino esters and $ZnBr_2$ in DCM. Although *N*-Boc and *N*-trityl groups were found to be labile, PhF protected amines were compatible with these Lewis acid deprotection conditions such that a variety of *N*-(PhF)amino acids were prepared in good yields from their corresponding *tert*-butyl esters.

The acid labile protecting groups, such as the *tert*-butyl ester and *tert*-butyloxycarbonyl (Boc) amine protecting groups, are commonly used in amino acid, peptide and natural product synthesis.[1,2] When such protecting groups are used ensemble, their selective deprotection often becomes a desirable step for an effective synthesis sequence. Typically, strong protic acids,[1] such as HCl, H_2SO_4, and TFA, are not selective under aqueous conditions and effect cleavage of all acid labile protection. On the other hand, in organic solvents, such acids have demonstrated practical selectivity. For example, the *N*-Boc group can be specifically removed in the presence of a *tert*-butyl ester by using 1 M HCl in ethyl acetate,[3] as well as by using concentrated H_2SO_4 in *tert*-butyl acetate.[4] These protocols have proven effective for the selective deprotection of the amine of a variety of *N*-(Boc)-amino *tert*-butyl esters. Recently, the opposite selectivity was reported and it was claimed that *tert*-butyl esters could be selectively cleaved in the presence of an *N*-Boc group by using Lewis acids such as $CeCl_3 \cdot 7H_2O-NaI$ in acetonitrile,[5] and $ZnBr_2$ in DCM.[6] Previously, reports have also claimed that $ZnBr_2$ in DCM could mediate selective *N*-Boc deprotection from secondary amines in the presence of *N*-Boc protected primary amines.[7]

Exploring one of these protocols for the synthesis of (3*S*,6*R*,10*S*)-3-*N*-(Boc)amino quinolizidin-2-one-10-carboxylic acid,[8] we treated the corresponding *tert*-butyl ester[9] **1a** with 500 mol % of $ZnBr_2$ in DCM at room temperature for 12 h. After aqueous workup as described,[6] TLC analysis of the crude product showed a baseline material corresponding to the free amino acid indicating that both the *N*-(Boc)amino and *tert*-butyl ester groups were cleaved. The quinolizidinone amino acid **2a** was then recovered as its *N*-Boc derivative by treating the aqueous solution with Boc anhydride and sodium bicarbonate.

In our hands, this failure provoked a more detailed investigation of the use of $ZnBr_2$ in DCM for the selective removal of *tert*-butyl esters in the presence of acid labile protecting groups. In particular, we examined the $ZnBr_2$ conditions on substrates bearing Boc, trityl, and 9-(9-phenylfluorenyl) (PhF) amino protecting groups as well as allyl esters and *tert*-butyl ethers. A series of *N*-protected amino *tert*-butyl esters were treated under the same standard conditions, namely, the substrates were dissolved in DCM and exposed to 500 mol % of $ZnBr_2$ with stirring at room temperature for 24 h (12 h in the case of *N*-(Boc)glycine *tert*-butyl ester **1b** for comparison with the earlier report).[6]

N-(Boc)glycine *tert*-butyl ester **1b** had been reported to be selectively converted to its respective acid without loss of Boc protection with use of $ZnBr_2$ in DCM for 12 h.[6] Revisiting this claim, *N*-(Boc)glycine *tert*-butyl ester **1b** was treated with $ZnBr_2$ under the identical conditions. After 12 h, both the N- and C-terminal protecting groups were lost and baseline material was detected by TLC. Treatment of the aqueous phase from the reaction workup with 1.5 equiv of 9-fluorenylmethyl succinimidyl carbonate (Fmoc-OSu) for 12 h provided *N*-(Fmoc)glycine in 80% overall yield from **1b**. Similarly, *N*-(Boc)-, *N*-(trityl)-, and *N*-(PhF)alanine *tert*-butyl esters (**1c**−**e**) were treated with $ZnBr_2$ in DCM and both the Boc and trityl groups were cleaved along with the *tert*-butyl ester as demonstrated by TLC (4:1:1 ^{n}BuOH:AcOH:H_2O). Free alanine was similarly recovered as its Fmoc derivative by treatment of the aqueous phase as described above for **2b**. On the other hand, *N*-(PhF)alanine *tert*-butyl ester **1e** was selectively hydrolyzed to its corresponding *N*-(PhF)amino acid **2e** in 75% yield.

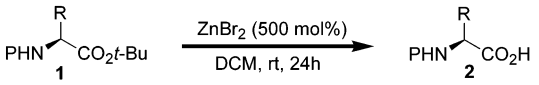
On investigation of the scope of the deprotection of *tert*-butyl esters in the presence of PhF amino protection, the use of no less than 500 mol % of $ZnBr_2$ and longer reaction times (24 h) provided good conversion and yield (Table 1). In DCM, $ZnBr_2$ forms a suspension. Although $ZnBr_2$ is readily soluble in THF, no reaction was observed in THF. Coordination of $ZnBr_2$ by the Lewis basic THF may likely compete with ester complexation and thereby prevent hydrolysis.

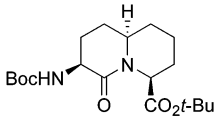
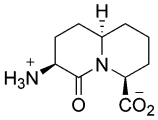
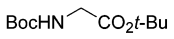
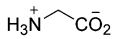
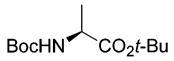
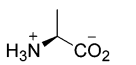
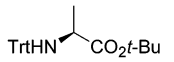
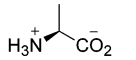
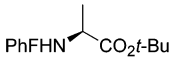
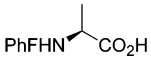
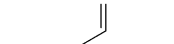
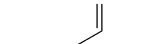
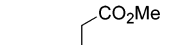
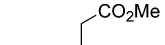
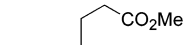
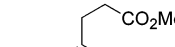
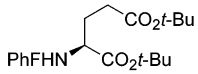
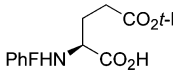
A series of functional groups were shown to be compatible with these hydrolysis conditions including olefins (**2f**) and methyl (**2g** and **2h**) and allyl esters (**2n** and **2o**) as

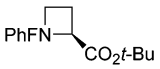
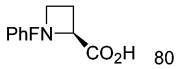
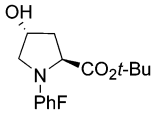
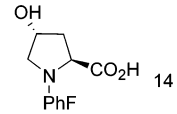
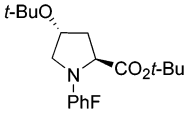
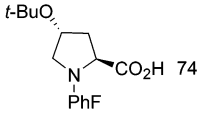
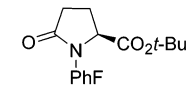
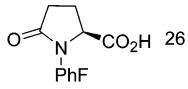
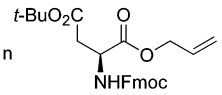
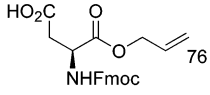
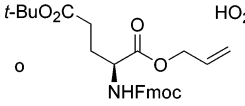
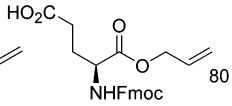
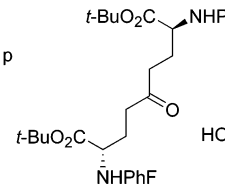
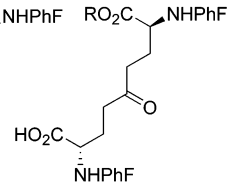
(1) Green, T. W.; Wuts, P. G. M. *Protecting Groups in Organic Synthesis*; John Wiley & Sons: New York, 1999; pp 65−67 and 404−408.
(2) Bodanszky, M.; Bodanszky, A. *The Practice of Peptide Synthesis*, 2nd Ed.; Springer-Verlag: Berlin, Germany, 1994.
(3) Gibson, F. S.; Bergmeier, S. C.; Rapoport, H. *J. Org. Chem*. **1994**, *59*, 3216.
(4) Lin, L. S.; Lanza, T.; Laszlo, Stephen E. de.; Truoung, Q.; Kamenecka, T.; Hagmann, W. K. *Tetrahedron Lett*. **2000**, *41*, 7013.
(5) Marcantoni, E.; Massaccesi, M.; Torregiani, E. *J. Org. Chem*. **2001**, *66*, 4430.
(6) Wu, Y-Q.; Limburg, D. C.; Wilkinson, D. E.; Vaal, M. J.; Hamilton, G. S. *Tetrahedron Lett*. **2000**, *41*, 2847.
(7) Nigam, S. C.; Mann, A.; Taddei, M.; Wermuth, C. G. *Synth. Commun*. **1989**, *19*, 3139.
(8) Halab, L.; Becker, J. A. J.; Darula, Z.; Tourwé, D.; Kieffer, B. L.; Simonin, F.; Lubell, W. D. *J. Med. Chem*. **2002**, *45*, 5353.
(9) Gosselin, F.; Lubell, W. D. *J. Org. Chem*. **2000**, *65*, 2163.

10.1021/jo0491206 CCC: $27.50
Published on Web 08/12/2004

TABLE 1. *N*-Protected Amino Acids 2 from *N*-Protected Amino *tert*-Butyl Esters 1



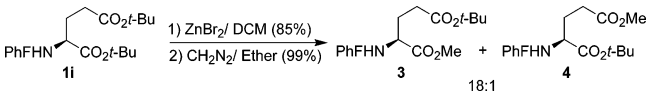
Entry	*tert*-Butyl Ester 1	Acid 2	Yield (%)
a			75[a]
b			80[b]
c			73[b]
d			80[b]
e			75
f			78
g			75
h			75
i			85[c]

Entry	*tert*-Butyl Ester 1	Acid 2	Yield (%)
j			80
k			14
l			74
m			26
n			76
o			80
p			2p, R = H 36[c] 2p', R = *t*-Bu 38[c]

[a] Isolated yield after reprotection with Boc. [b] Isolated yield after reprotection with Fmoc. [c] 1000 mol % of $ZnBr_2$.

well as *tert*-butyl ethers (**2l**). On the other hand, more Lewis basic functionality such as alcohols (**2k**) and amides (**2m**) inhibited the reaction. For example, exposure of (2*S*,4*R*)-4-hydroxy-*N*-(PhF)proline *tert*-butyl ester **1k** to 500 mol % of $ZnBr_2$ in DCM for 24 h gave only 14% of the corresponding acid **2k** along with 45% of recovered starting material. Increasing the amount of $ZnBr_2$ to 1500 mol % only doubled the yield (27%) of acid **2k**. Similarly, the amide, (2*S*)-*N*-(PhF)pyroglutamate *tert*-butyl ester **1m**, reacted with 500 mol % of $ZnBr_2$ to give acid **2m** in only 26% yield; however, employment of 1000 mol % of $ZnBr_2$ improved the yield to 61%. In addition, in the presence of 1000 mol % of $ZnBr_2$, diamino azelate ketone **1p** gave diacid **2p** in only 36% yield along with monoacid **2p′** in 38% yield, presumably because of catalyst inhibition by the ketone moiety.

Remarkable selectivity was observed with *N*-(PhF)-glutamate α,γ-di-*tert*-butyl ester **1i**. After treatment with 1000 mol % of $ZnBr_2$ in DCM for 24 h followed by aqueous workup, ^{1}H NMR spectral analysis showed cleavage of one *tert*-butyl ester group. The resulting crude monoester monoacid (**2i**) was converted to its corresponding methyl *tert*-butyl diester (**3**) by using diazomethane in diethyl ether. Comparison of the proton spectra of authentic



α-*tert*-butyl-γ-methyl-*N*-(PhF)glutamate (**4**)[10] with the

(10) Koskinen, A. M. P.; Rapoport, H. *J. Org. Chem.* **1989**, *54*, 1859.

resulting diester demonstrated the predominant product to be α-methyl-γ-*tert*-butyl-*N*-(PhF)glutamate (**3**). Relative to the singlet of γ-methyl ester **4**, the corresponding singlet for α-methyl ester **3** appeared at 0.4 ppm downfield due to the influence of the neighboring aromatic PhF group. Similarly, the α-*tert*-butyl ester singlet appeared at 0.2 ppm downfield of its γ-*tert*-butyl singlet counterpart. Integration of the methyl ester singlets at 3.2 and 3.6 ppm demonstrated that the ratio of α- to γ-methyl esters **3**:**4** was 18:1. γ-*tert*-Butyl *N*-(PhF)glutamate **2i** was thus produced regioselectively in 85% yield. Selectivity for the α- versus the γ-*tert*-butyl ester of *N*-(PhF)-glutamate likely arises from initial coordination of $ZnBr_2$ by the PhF-bearing nitrogen prior to Lewis acid activation of the *tert*-butyl ester. Similar coordination of the α-amine and α-carboxylate groups by copper carbonate has been used for the selective protection of the ω-amine of Orn and Lys.[11] Moreover, complexation of the α-amine and α-carboxylate groups by copper carbonate has been used to selectively hydrolyze the α-methyl ester of aspartate α,β-dimethyl ester.[12] To the best of our knowledge, this application of $ZnBr_2$ represents the first example of selective hydrolysis of an α-*tert*-butyl ester of an α-amino α,ω-di-*tert*-butyl dicarboxylate. In addition, the selective hydrolysis of *tert*-butyl ester **1l** in the presence of α-*tert*-butyl ether was observed and may also be due to precoordination of $ZnBr_2$ to the PhF nitrogen prior to ester cleavage.

Evidence that the $ZnBr_2$ ester cleavage proceeded without α-epimerization was provided from examples **2a**, **2k**, and **2p**, which were delivered as pure diastereomers. Moreover, specific rotations of α-amino acids after *tert*-butyl ester removal compared well with those of materials obtained from independent synthesis indicating that racemization had not occurred after the $ZnBr_2$ treatment.

A probable mechanism for $ZnBr_2$-mediated *tert*-butyl ester hydrolysis has been proposed involving coordination of zinc to both oxygens of the ester followed by decomplexation with water.[6] In the case of PhF amino esters, the alkylamine likely coordinates to the zinc prior to the coordination of α-carbonyl oxygen and cleavage of the *tert*-butyl ester with evolution of isobutene.

In conclusion, attempts failed to selectively remove *tert*-butyl esters in the presence of *N*-(Boc)amines and in contrast to an earlier report,[6] instead of the *N*-(Boc)amino acid, *N*-deprotected amino acid was produced. On the other hand, selective deprotection of *tert*-butyl esters in the presence of *N*-(PhF)amines with $ZnBr_2$ in DCM provided an effective means for obtaining *N*-(PhF)amino acids possessing a wide range of functional group diversity. Lewis basic groups, such as alcohols, amides, and ketones, may retard the reaction. Notable regiocontrol was demonstrated by the selective hydrolysis of the α-*tert*-butyl ester of α,γ-di-*tert*-butyl *N*-(PhF)glutamate with these conditions. This chemoselective Lewis acid hydrolysis of acid functional groups should be of general utility for the synthesis of multifunctional systems.

Experimental Section

General Procedure for the Selective Removal of *tert*-Butyl Esters. A stirred solution of *N*-protected amino acid *tert*-butyl ester (1 mmol) in 5 mL of dichloromethane was treated with 500 mol % of $ZnBr_2$ at room temperature, stirred for 24 h, treated with water (20 mL), and stirred again for 2 h. The organic phase was separated. The aqueous layer was extracted twice with dichloromethane (20 mL). The organic portions were dried, filtered, and evaporated to yield the corresponding acid. The resulting acids were chromatographed with 1:1 ethyl acetate/hexane containing 1% acetic acid as eluant.

(*2S*)-*N*-(PhF)azetidine-2-carboxylic acid (2j): yield 80% from **1j**; mp 107.5−108.5 °C; $[\alpha]^{20}_D$ 130.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR δ 7.68−7.08 (m, 13H), 3.63 (m, 1H), 3.5 (dd, 1H, *J* = 16.9, 8.31 Hz), 3.31 (dd, 1H, *J* = 9.07, 7.75 Hz), 2.04 (m, 2H); ^{13}C NMR δ 172.5, 75.9, 59.5, 46.8, 20.3; HRMS calcd for $C_{23}H_{19}NO_2$ [M^+] 341.1415, found 341.1406.

Acknowledgment. This work was supported by grants from Fonds Québécois de la Recherche sur la Nature et les Technologies (FQRNT), Valorisation-Recherche Québec (VRQ), and the Natural Sciences and Engineering Research Council of Canada (NSERC). We thank Mr. Dalbir Sekhon for mass spectral analysis. Mr. Guillaume Jeannotte and Mr. Simon Surprenant are respectively thanked for supplying *N*-(trityl)- and *N*-(PhF)alanine *tert*-butyl esters.

Supporting Information Available: General experimental details and characterization data for **1a**, **1g**, **1h**, **1m**, **1p**, **2e**, **2g**, **2h**, and **2p**, as well as ^{1}H and ^{13}C NMR spectra of **1d**−**f**, **1i**−**o**, **2a**, **2f**, and **2i**−**p**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0491206

(11) Crivici, A.; Lajoie, G. *Synth. Commun*. **1993**, *23*, 49.
(12) Dener, J. M.; Zhang, L.-H.; Rapoport, H. *J. Org. Chem*. **1993**, *58*, 1159.
(13) Christie, B. D.; Rapoport, H. *J. Org. Chem*. **1985**, *50*, 1239.
(14) Lubell, W. D.; Rapoport, H. *J. Org. Chem*. **1987**, *109*, 236.
(15) Lubell, W. D.; Jamison, T. F.; Rapoport, H. *J. Org. Chem*. **1990**, *55*, 3511.
(16) Humphrey, J. M.; Bridges, R. J.; Hart, J. A.; Chamberlin, A. R. *J. Org. Chem*. **1994**, *59*, 2467.
(17) Atfani, M.; Lubell, W. D. *J. Org. Chem*. **1995**, *60*, 3184.
(18) Lombart, H. G.; Lubell, W. D. *J. Org. Chem*. **1996**, *61*, 9437.
(19) Barlos, K.; Papaioannu, D.; Theodoropoulos, D. *J. Org. Chem*. **1982**, *47*, 1324.
(20) Gosselin, F.; Lubell, W. D. *J. Org. Chem*. **1998**, *63*, 7463.
(21) Golakoti, T.; Yoshida, W. Y.; Chaganty, S.; Moore, R. E. *Tetrahedron* **2000**, *56*, 9093.
(22) Trzeciak, A.; Bannwarth, W. *Tetrahedron Lett*. **1992**, *33*, 4557.
(23) Lodder, M.; Wang, B.; Hecht, S. M. *Tetrahedron* **2000**, *56*, 9421.
(24) Gmeiner, P.; Feldman, P. L.; Chu-Moyer, M. Y.; Rapoport, H. *J. Org. Chem*. **1990**, *55*, 3068.