Pergamon

Tetrahedron Letters 42 (2001) 5163–5165

TETRAHEDRON LETTERS

A mild and selective method for the cleavage of *tert*-butyl esters

Randy W. Jackson*

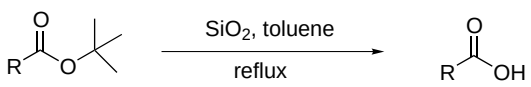
Department of Chemical Genomics, Celltech R&D, Inc., 1631 220th St. SE, Bothell, WA 98021, USA

Received 15 May 2001; revised 5 June 2001; accepted 6 June 2001

Abstract—A method for the cleavage of *t*-butyl esters using silica gel in refluxing toluene is reported. Good yields of the corresponding carboxylic acids are obtained, and the reaction is selective for *t*-butyl esters over *t*-butyl ethers and trimethylsilylethyl (TMSE) esters.

Acid labile protecting groups play an important role in organic synthesis. Among them, *tert*-butyl esters are commonly employed in the synthesis of peptides, alkaloids and other natural products and substrates of medicinal interest.[1] Removal of *t*-butyl esters often involves the use of strong protic acids such as trifluoroacetic and hydrochloric acid, or Lewis acids such as $ZnBr_2$ and silyl triflates.[1–3] The harshness of these conditions can often lead to unwanted side reactions and decomposition of sensitive substrates. In addition, chemoselectivity can be problematic if numerous acid-sensitive protecting groups reside in the same molecule. In an effort to identify a generally mild and selective method for the deprotection of *t*-butyl esters a systematic study of acidic cleavage methods was undertaken. Herein is reported a method using silica gel as an efficient reagent for the cleavage of *t*-butyl esters (Scheme 1).

The reaction of *t*-butyl esters with standard flash chromatography grade silica gel in refluxing toluene gave high yields of the corresponding carboxylic acid. A typical procedure is as follows.[4] A solution of the ester (0.5 mmol) and silica gel (2.5 g, 230–400 mesh) in toluene (10 mL) is refluxed with vigorous agitation until the starting material is consumed, typically 0.5–7 h. Upon cooling, the solution is diluted with 10% methanol in methylene chloride, Celite® is added, and the solution filtered through a pad of Celite®. The solids are washed with methanol/methylene chloride, and the filtrate concentrated to afford the product. For scale-up purposes it is convenient to use a Dean–Stark trap to azeotropically remove adventitious water in order to prevent clumping of the silica gel.



Scheme 1. General scheme for silica gel promoted cleavage of *t*-butyl esters.

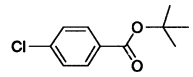
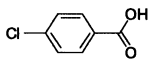
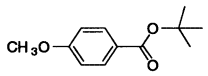
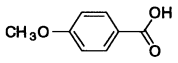
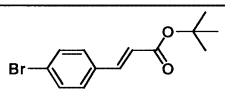
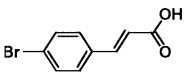
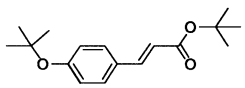
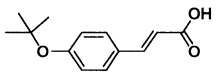
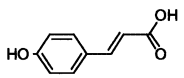
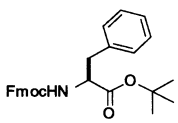
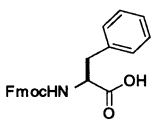
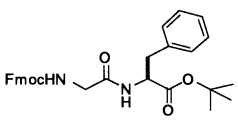
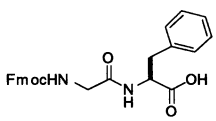
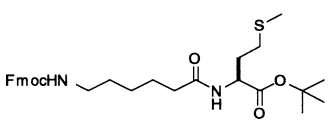
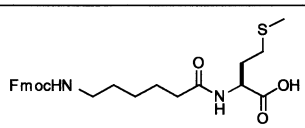
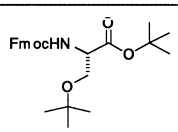
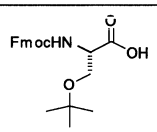
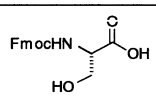
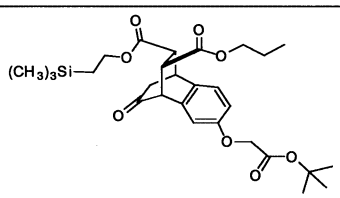
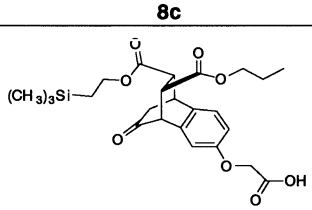
The results of the deprotection reactions are shown in Table 1. The derived carboxylic acids are obtained in acceptably high purities and normally require no further purification for subsequent chemical transformations.[4] A variety of substrates are amenable to the reaction conditions and good to high yields of the carboxylic acids are obtained. Benzene is also an acceptable solvent, however, the associated increase in reaction times due to a lower reflux temperature makes this a less desirable solvent. For example, refluxing a benzene solution of **2a** with SiO_2 for 21 h resulted in only 63% conversion to the acid. The enoates **3a** and **4a** are stable to the reaction conditions, and the E/Z ratios of 96/4 and 97/3, respectively, were unchanged in the products. Also, protected amino acids and peptidic substrates readily undergo the deprotection reaction to afford high yields of the corresponding carboxylic acids. Interestingly, the hydrophobic substrates tend to require longer reaction times than the more polar amino acid derivatives. This suggests that the rate of the reaction is dependent upon the relative affinity of the starting material for the silica gel, the more polar substrates having higher affinities than the hydrophobic ones.

The chemoselectivity of the silica gel deprotection was explored using the substrates shown in entries 4,8 and 9. Of interest was to determine whether the ester groups could be removed in the presence of other acid labile

* Fax: +1 425 489 8019; e-mail: randy.jackson@celltechgroup.com

0040-4039/01/$ - see front matter
PII: S0040-4039(01)00980-7

Table 1. Cleavage of *t*-butyl esters with SiO_2 in refluxing toluene[5]

Entry	Substrate	Time	Product	Yield
1	 **1a**	7h	 **1b**	74%
2	 **2a**	7h	 **2b**	68%
3	 **3a**	5h	 **3b**	87%
4	 **4a**	4.5h	 **4b**	53%[a]
			 **4c**	25%[a]
5	 **5a**	1.25h	 **5b**	94%
6	 **6a**	1h	 **6b**	91%
7	 **7a**	1h	 **7b**	85%
8	 **8a**	1.25h	 **8b**	76%[a]
			 **8c**	8%[a]
9	 **9a**	1h	 **9b**	78%[b]

[a] Based on ^1H NMR ratio of products

[b] Yield after flash chromatography using 90/9/1 dichloromethane/methanol/acetic acid

functionalities. As can be seen from entries 4 and 8 the selectivity for the cleavage of *t*-butyl esters over *t*-butyl ethers can be variable.[6] After a reaction time of 1.25 h in refluxing toluene, the fully protected serine derivative **8a** was completely consumed. The product was obtained in 84% total yield, and analysis of the ^{1}H NMR showed a 9/1 ratio of mono-deprotected/bis-deprotected material. There was no evidence of Fmoc-serine *t*-butyl ester in the reaction product. The 4-*t*-butoxycinnamate derivative **4a** undergoes reaction in a less selective manner, affording the mono- and bis-deprotected products **4b** and **4c** in a ratio of 2.1/1. In analogy to the serine derivative **8a**, no evidence of the phenol *t*-butyl ester was observed. Thus, the extent of selectivity encountered in the cleavage of *t*-butyl esters over *t*-butyl ethers appears to be substrate dependent, with the rate of ester cleavage potentially being a prime determinant.

The trimethylsilyethyl (TMSE) ester is another protecting group often utilized for carboxylic acids, and a common mode of deprotection is acid-catalyzed cleavage, conditions which will often result in the removal of *t*-butyl esters. Entry 9 shows that TMSE esters survive the SiO_2-promoted cleavage conditions, in this case affording the acid in 78% yield after chromatography. The high preference for cleavage of *t*-butyl esters over TMSE esters has also been observed in a structurally non-related substrate.[7] These results indicate that these two carboxylic acid protecting groups can generally be employed in an orthogonal protecting group strategy.[8]

In conclusion, it has been shown that the use of standard flash chromatography grade silica gel is a novel alternative for the cleavage of *t*-butyl esters and enhances the usefulness of this functional group. The mild cleavage conditions broadens the synthetic applications in which protected carboxylates can be utilized, and the moderate to high selectivity observed in the presence of other acid-labile protecting groups extends the utility of the *t*-butyl ester as an orthogonal protecting group.

Acknowledgements

The author wishes to express his gratitude to Dr. Nathan Ihle for helpful discussions.

References

1. (a) Green, T. W.; Wuts, P. G. *Protective Groups in Organic Synthesis*; John Wiley & Sons: New York, 1999; (b) Kocienski, P. J. *Protecting Groups*; Thieme Medical Publishers: New York, 1994; pp. 125–128.
2. Wu, Y.-q.; Limburg, D. C.; Wilkinson, D. E.; Vaal, M. J.; Hamilton, G. S. *Tetrahedron Lett.* **2000**, *41*, 2847–2849.
3. Jones, A. B.; Villalobos, A.; Linde, II, R. G.; Danishefsky, S. J. *J. Org. Chem.* **1990**, *55*, 2786–2797.
4. Preparation of **2b**: To a solution of **2a** (104.6 mg, 0.50 mmol) in toluene (10 mL) was added SiO_2 (2.5 g, EM Science Silica Gel 60, 230–400 mesh). The solution was refluxed under N_2 for 7 h, cooled to ambient temperature and diluted with 20 mL of 10% methanol/methylene chloride. Celite® was added, and the solution filtered through a pad of Celite® under vacuum. The solids were washed with methanol/methylene chloride, and the filtrate concentrated in vacuo. Residual toluene was readily removed by successive concentrations of ethyl acetate and hexane solutions of the product. The acid **2b** was obtained as a white solid (51.6 mg, 68%) with ^{1}H NMR and LC/MS properties identical to an authentic sample of *p*-anisic acid (Aldrich Chemical Co.).
5. Products were identified by comparison with authentic material or by 300 MHz ^{1}H NMR and MS. The starting materials were prepared as follows: **1a** and **2a** were prepared via reaction of the benzoyl chloride with KO^{t}Bu in THF; **3a** and **4a** were prepared via Wittig reactions of the substituted benzaldehyde with (*t*-butoxycarbonylmethylene)triphenylphosphorane in refluxing toluene; **5a** and **8a** were prepared by reacting Fmoc-Cl with Phe-O^{t}Bu and Ser(^{t}Bu)-O^{t}Bu, respectively, in methylene chloride in the presence of *N*-methylmorpholine (NMM); **6a** and **7a** were prepared via coupling reactions of the appropriate Fmoc-amino acid with the corresponding amino acid (*t*-butyl ester) in methylene chloride using HATU and NMM; the synthesis of **9a** will be described elsewhere.
6. Examples of selective removal of *t*-butyl esters in the presence of *t*-butyl ethers: (a) Makara, G. M.; Marshall, G. R. *Tetrahedron Lett.* **1997**, *38*, 5069–5072; (b) MacPherson, L. J.; Bayburt, E. K.; Capperelli, M. P.; Carroll, B. J.; Goldstein, R.; Justice, M. R.; Zhu, L.; Hu, S.-i.; Melton, R. A.; Fryer, L.; Goldberg, R. L.; Doughty, J. R.; Spirito, S.; Blancuzzi, V.; Wilson, D.; O'Byrne, E. M.; Ganu, V.; Parker, D. T. *J. Med. Chem.* **1997**, *40*, 2525–2532.
7. Jackson, R.W., unpublished results.
8. Examples of selective removal of *t*-butyl esters in the presence of TMSE esters: (a) Schmidt, U.; Zah, M.; Lieberknecht, A. *J. Chem. Soc., Chem. Commun.* **1991**, 1002–1004; (b) Cassidy, M. A.; Crockett, N.; Leeper, F. J.; Battersby, A. R. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2079–2090.