

Solvent-modulated chemoselective deprotections of trialkylsilyl esters and chemoselective esterifications

Adam Shih-Yuan Lee* and Feng-Yih Su

Department of Chemistry, Tamkang University, Tamsui 251, Taiwan

Received 24 May 2005; revised 8 July 2005; accepted 11 July 2005

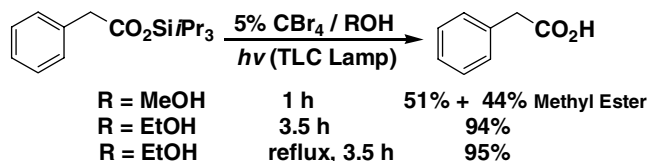
Abstract—A series of trialkylsilyl esters were deprotected or transesterified into their corresponding carboxylic acids or methyl esters under a catalytic amount of CBr_4 in alcohol reaction system. This method enables to desilylate secondary sp^3 -carbon, sp^2 -carbon, sp -carbon and aryl tethered trialkylsilyl esters to carboxylic acids, whereas primary sp^3 -carbon tethered trialkylsilyl esters were further converted into their methyl esters under CBr_4/MeOH reaction conditions. The highly chemoselective deprotections can be modulated and achieved by the introduced protecting trialkylsilyl groups and the used alcohols such as MeOH and EtOH under this photochemically-induced reaction conditions.

© 2005 Elsevier Ltd. All rights reserved.

Selective deprotections of trialkylsilyl ether and ester to their corresponding alcohol and carboxylic acid is an important tool and useful method in organic synthesis.^{1–4} Although selective desilylating methods for trialkylsilyl ethers⁵ have been extensively developed and reported only a few selective deprotections for trialkylsilyl esters to carboxylic acids have been reported in the literature.^{6–13}

Our previous studies showed that a highly chemoselective deprotection method for trialkylsilyl ethers^{14,15} and β -(trimethylsilyl)ethoxymethyl ethers¹⁶ and methoxyethoxymethyl esters¹⁷ can be hydrolyzed by using a catalytic amount of CBr_4 in methanol or isopropanol under thermal or ultrasonic reaction conditions. The desilylation reaction for trialkylsilyl ester is easier and faster than trialkylsilyl ether under acidic hydrolysis. Thus, we believed and expected that the desilylation system developed by us can be applied to the deprotection of trialkylsilyl-protected carboxylic acids. We first, investigated this desilylating reaction condition for trialkylsilyl ester under a milder photochemical reaction condition instead of a thermal reaction condition (Scheme 1).

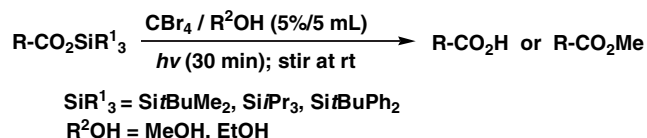
A reaction mixture of triisopropylsilyl phenylacetate and CBr_4 (0.05 equiv) in MeOH was irradiated at room



Scheme 1.

temperature for 1 h by using a TLC lamp as light source and a mixture of phenylacetic acid and methyl phenylacetate was obtained as products. The deprotection of triisopropylsilyl phenylacetate to phenylacetic acid was obtained with 94% yield when the more steric hindered EtOH was used instead of MeOH. The deprotection of triisopropylsilyl phenylacetate to phenylacetic acid also was achieved under CBr_4/EtOH refluxing reaction condition. The deprotection yield of trialkylsilyl ester under 3.5 h of photochemical reaction condition is consistent with the reaction condition in which the irradiation time was decreased to 0.5 h and then stirred at room temperature for 3 h without irradiation. Thus, this mild photochemically-induced desilylating method was introduced as the typical reaction condition for investigation of trialkylsilyl ester deprotection. Therefore, we investigated the desilylating reactions for trialkylsilyl esters with several trialkylsilyl groups such as *tert*-butyldimethylsilyl, triisopropylsilyl and *tert*-butyldiphenylsilyl groups under the photochemically-induced CBr_4/MeOH reaction conditions. Herewith, we wish to report a mild, highly efficient and chemoselective deprotection and

* Corresponding author. Tel.: +886 2 2621 5656x2543; fax: +886 2 2622 3830; e-mail: adamlee@mail.tku.edu.tw



Scheme 2.

transesterification method for trialkylsilyl esters under CBr_4 in alcoholic reaction conditions¹⁸ (Scheme 2).

A series of trialkylsilyl esters were investigated under CBr_4/MeOH (5 mol%/5 mL) photoirradiation reaction conditions and the results are shown in Table 1. The results showed that only primary sp^3 -carbon tethered trialkylsilyl esters (entries 1–3 and 5) were further transformed to their corresponding methyl esters under this typical reaction conditions whereas other configuration

(secondary sp^3 -carbon, sp^2 -carbon, sp -carbon and aryl) tethered trialkylsilyl esters were desilylated to their corresponding carboxylic acids. It should be noted that it did not undergo further esterification^{19,20} when secondary sp^3 -carbon tethered trialkylsilyl ester was introduced under the reaction conditions. The experimental results showed that desilylation rate was determined by the tethered configuration of trialkylsilyl ester and the steric hindrance of protected trialkylsilyl group. The desilylation rate becomes much slower when the more steric hindered trialkylsilyl group such as *tert*-butyldiphenylsilyl group was introduced. It is difficult for *tert*-butyldiphenylsilyl benzoate to undergo desilylation reaction even after a relatively prolonged reaction time (Table 1, entry 6). We also observed that desilylation rate of sp^2 -carbon tethered trialkylsilyl esters was much faster than secondary sp^3 -carbon, sp -carbon and aryl tethered trialkylsilyl esters under the reaction conditions.

Table 1. Desilylations of trialkylsilyl esters

Entry	Substrate	Product	Σ	Time (h)	Yield ^a (%)
1			Si- <i>t</i> -BuMe ₂	3	92
			Si- <i>i</i> -Pr ₃	8	89
			Si- <i>t</i> -BuPh ₂	9	81
2			Si- <i>t</i> -BuMe ₂	3	96
			Si- <i>i</i> -Pr ₃	12	93
			Si- <i>t</i> -BuPh ₂	24	90
3			Si- <i>t</i> -BuMe ₂	3.5	88
			Si- <i>i</i> -Pr ₃	7	83
			Si- <i>t</i> -BuPh ₂	10.5	80
4			Si- <i>t</i> -BuMe ₂	2.5	93
			Si- <i>i</i> -Pr ₃	15	75 (19) ^b
			Si- <i>t</i> -BuPh ₂	16	22 (60) ^b
5			Si- <i>t</i> -BuMe ₂	2	96
			Si- <i>i</i> -Pr ₃	5	86
			Si- <i>t</i> -BuPh ₂	11	84
6			Si- <i>t</i> -BuMe ₂	9	89
			Si- <i>i</i> -Pr ₃	26	81
			Si- <i>t</i> -BuPh ₂	48	NR (98) ^b
7			Si- <i>t</i> -BuMe ₂	5	93
			Si- <i>i</i> -Pr ₃	30	90
			Si- <i>t</i> -BuPh ₂	48	54 (40) ^b
8			Si- <i>t</i> -BuMe ₂	1	98
			Si- <i>i</i> -Pr ₃	2.5	92 (4) ^b
			Si- <i>t</i> -BuPh ₂	5	91 (7) ^b
9			Si- <i>t</i> -BuMe ₂	5	92
			Si- <i>i</i> -Pr ₃	30	89
			Si- <i>t</i> -BuPh ₂	48	61 (33) ^b

^a The yields were determined after chromatographic purification.

^b The recovery yield of the starting material after chromatographic purification.

Table 2. Deprotections of primary sp^3 -C tethered trialkylsilyl esters^a

Entry	Substrate	Product	Σ	Time (h)	Yield ^b (%)
1			Si- <i>t</i> -BuMe ₂	1	97
			Si- <i>i</i> -Pr ₃	4	73 (25) ^c
			Si- <i>t</i> -BuPh ₂	12	5 (91) ^c
2			Si- <i>t</i> -BuMe ₂	2	96
			Si- <i>i</i> -Pr ₃	3.5	95
			Si- <i>t</i> -BuPh ₂	10	NR (97) ^c

^a The EtOH was used instead of MeOH for these deprotection reactions.

^b The yields were determined after chromatographic purification.

^c The recovery yield of the starting material after chromatographic purification.

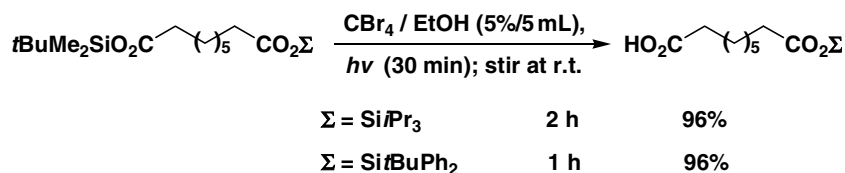
Our experimental studies showed that primary sp^3 -carbon tethered trialkylsilyl esters were hydrolyzed and further converted to their corresponding methyl esters under CBr_4 /MeOH reaction conditions. The transformations of carboxylic acids with alcohols into their corresponding alkyl esters by using a catalytic amount of CBr_4 under thermal reaction conditions were previously reported by this laboratory.^{21,22} The further esterification process of primary sp^3 -carbon tethered trialkylsilyl esters can be inhibited when EtOH was used instead of MeOH. Thus, we further investigated several primary sp^3 -carbon tethered trialkylsilyl esters under CBr_4 /EtOH reaction conditions. All primary sp^3 -carbon tethered trialkylsilyl esters were deprotected to carboxylic acids and the results are shown in Table 2. The desilylations of primary sp^3 -carbon tethered *tert*-butyldimethylsilyl esters to carboxylic acids were achieved with high yields under the reaction conditions. The desilylation rate becomes much slower when the more steric hindered *tert*-butyldiphenylsilyl group was introduced. *tert*-Butyldiphenylsilyl phenylacetate was resistant under CBr_4 /EtOH reaction condition (Table 2, entry 2).

The experimental results showed that the desilylating rate becomes much slower when more bulky trialkylsilyl group is introduced (desilylation rate t -BuMe₂Si > *i*-Pr₃Si > *t*-BuPh₂Si) or more steric hindered alcohol is used (Table 1). The desilylation of primary sp^3 -carbon

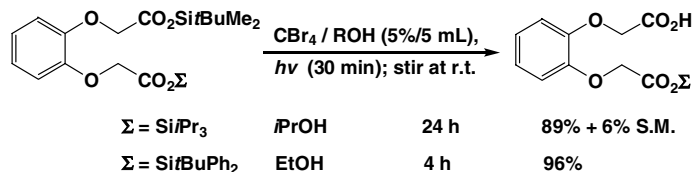
tethered *tert*-butyldiphenylsilyl esters was less reactive even when inert EtOH was used as solvent (Table 2). This leads us to further investigate this highly chemoselective desilylating process among trialkylsilyl groups for primary sp^3 -carbon tethered silyl esters. 1-*tert*-Butyldimethylsilylcarboxyl-7-trialkylsilylcarboxylheptane was investigated under CBr_4 /EtOH reaction condition. *tert*-Butyldimethylsilyl (TBDMS) group of primary sp^3 -carbon tethered silyl ester was deprotected selectively whereas triisopropylsilyl (TIPS) and *tert*-butyldiphenylsilyl (TBDPS) groups were resistant under the reaction conditions (Schemes 3 and 4).

Triisopropylsilyl benzoate undergoes desilylation reaction much more slowly under CBr_4 /MeOH reaction condition and *tert*-butyldiphenylsilyl benzoate is resistant under the reaction condition (Table 1, entry 6). The *tert*-butyldimethylsilyl (TBDMS), Triisopropylsilyl (TIPS) and *tert*-butyldiphenylsilyl (TBDPS) groups protected silyl esters were investigated under the reaction conditions and only TBDMS group was deprotected selectively whereas TIPS and TBDPS groups were resistant under the reaction conditions (Scheme 5).

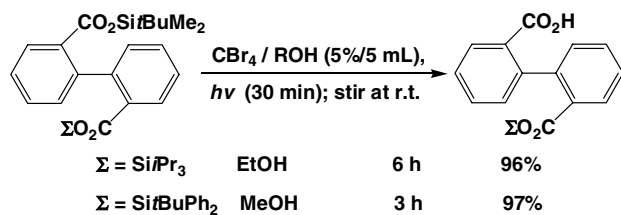
Our studies showed that primary sp^3 -carbon tethered trialkylsilyl esters were desilylated and further converted to their corresponding methyl esters under CBr_4 /MeOH reaction conditions. The results led us to investigate further this highly chemoselective transesterification



Scheme 3.



Scheme 4.



Scheme 5.

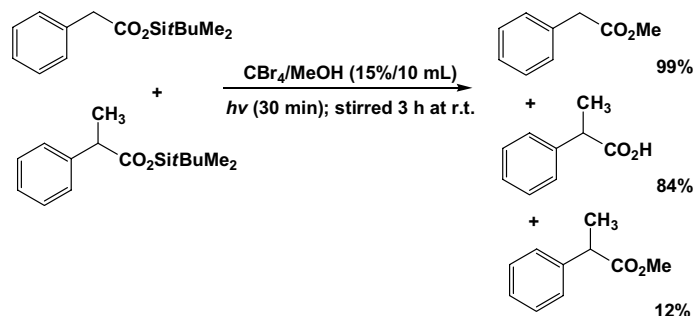
process which distinguishes between primary sp^3 -carbon tethered and secondary sp^3 -carbon tethered *tert*-butyldimethylsilyl esters (Table 1, entries 5 and 7). A mixture of *tert*-butyldimethylsilyl 2-phenylethanoate and *tert*-butyldimethylsilyl 2-phenylpropanoate in CBr_4/MeOH (15 mol%/10 mL) was investigated under the reaction conditions (Scheme 6). The primary sp^3 -carbon tethered TBDMS ester was converted into its methyl ester in 99% yield, whereas the secondary sp^3 -carbon tethered TBDMS ester was deprotected into carboxylic acid (84%) and 12% of the corresponding methyl ester was obtained under the reaction conditions.

We also investigated the selectivity between *tert*-butyldimethylsilyl cyclohexylpropanoate (primary sp^3 -carbon tethered) and *tert*-butyldimethylsilyl cyclohexylmethano-

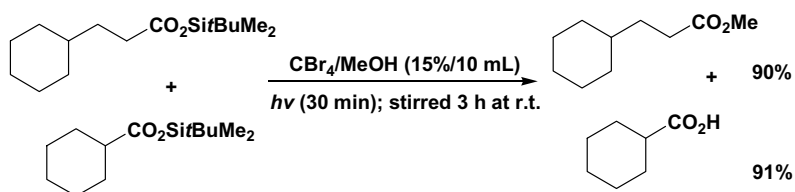
ate (secondary sp^3 -carbon tethered) in CBr_4/MeOH (10%/10 mL) reaction condition (Scheme 7). The primary sp^3 -carbon tethered TBDMS ester underwent transesterification into its methyl ester in 90% yield, whereas the secondary sp^3 -carbon tethered TBDMS ester was desilylated to its carboxylic acid with 91% yield under the reaction condition.

The experimental results showed that the further transesterification reaction of *tert*-butyldimethylsilyl benzoate is much slower than *tert*-butyldimethylsilyl phenylacetate under CBr_4/MeOH reaction condition (Table 1, entries 5 and 6). Thus, a mixture of *tert*-butyldimethylsilyl benzoate and *tert*-butyldimethylsilyl phenylacetate was investigated under the reaction condition and TBDMS phenylacetate was converted into its methyl ester in 99% yield, whereas TBDMS benzoate was desilylated to its acid with 90% yield and 8% of TBDMS benzoate was recovered (Scheme 8).

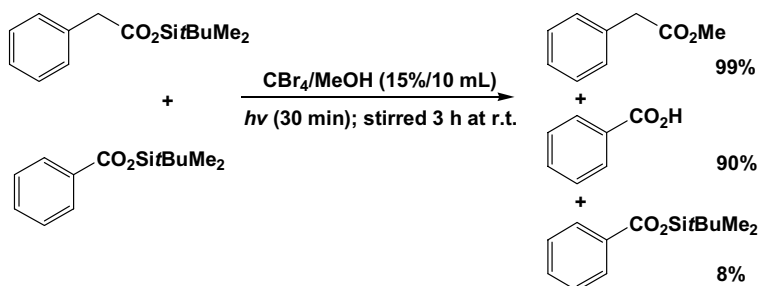
Primary and secondary tethered *tert*-butyldiphenylsilyl esters undergo desilylation or transesterification reactions under CBr_4/MeOH reaction condition much slower than primary and secondary tethered *tert*-butyldimethylsilyl esters (Tables 1 and 2). These results led us to investigate the chemoselective transesterification



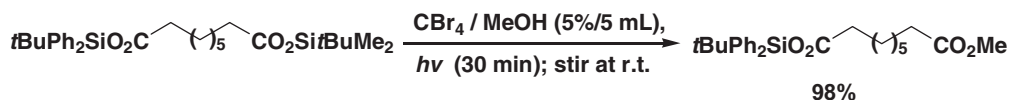
Scheme 6.



Scheme 7.



Scheme 8.



Scheme 9.

reactions between primary sp^3 -carbon tethered TBDPS ester and primary sp^3 -carbon tethered TBDMS ester under the reaction condition (Scheme 9). 1-*tert*-Butyldimethylsilylcarboxyl-7-trialkylsilylcarboxylheptane was investigated and primary sp^3 -carbon tethered TBDMS ester was selective transesterificated to its methyl ester whereas TBDPS ester was resistant under the reaction condition.

In conclusion, this reaction condition provides a simple and highly chemoselective desilylation method for trialkylsilyl esters. This method enables us to desilylate secondary sp^3 -carbon, sp^2 -carbon, sp -carbon and aryl tethered trialkylsilyl esters to their corresponding carboxylic acids, whereas primary sp^3 -carbon tethered trialkylsilyl esters were further converted into their methyl esters under CBr_4/MeOH reaction conditions. The primary sp^3 -carbon tethered trialkylsilyl esters can be deprotected to their corresponding carboxylic acids under CBr_4/EtOH reaction condition. The chemoselective deprotections and transesterifications among different trialkylsilyl esters are manipulated by the bulkiness of silyl groups and the used solvent.

Acknowledgements

We thank the National Science Council in Taiwan (NSC 92-2113-M-032-005) and Tamkang University for financial support.

References and notes

- Kocienski, P. J. *Protecting Group*; Georg Thieme: New York, 1994.
- Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*; John Wiley and Sons: New York, 1991.
- Ogliaruso, M. A.; Wolfe, J. F. In *Synthesis of Carboxylic Acids, Esters and Their Derivatives*; Patai, S., Rappoport, Z., Eds.; John Wiley and Sons: New York, 1991.
- Nelson, T. D.; Crouch, R. D. *Synthesis* **1996**, 1031.
- Crouch, R. D. *Tetrahedron* **2004**, *60*, 5833, and references cited therein.
- Nicolaou, K. C.; Ninkovic, F.; Sarabia, F.; Vourloumis, D.; He, Y.; Vallberg, H.; Finlay, M. R. V.; Yang, Z. *J. Am. Chem. Soc.* **1997**, *119*, 7974.
- Abel, S.; Faber, D.; Huter, O.; Giese, B. *Synthesis* **1999**, 188.
- Angle, S. R.; Henry, R. M. *J. Org. Chem.* **1998**, *63*, 7490.
- Smith, A. B., III; Lin, Q.; Doughty, V. A.; Zhuang, L.; McBriar, M. D.; Kerns, J. K.; Brook, C. S.; Murase, N.; Nakayama, K. *Angew. Chem., Int. Ed.* **2001**, *40*, 196.
- Furstner, A.; Weintritt, H. *J. Am. Chem. Soc.* **1998**, *120*, 2817.
- Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 2817.
- Evans, D. A.; Trotter, B. W.; Cote, B.; Coleman, P. J.; Dias, L. C.; Tyler, A. N. *Angew. Chem., Int. Ed.* **1997**, *36*, 2744.
- De Groot, A. H.; Dommissie, R. A.; Lemiere, G. L. *Tetrahedron* **2000**, *56*, 1541.
- Lee, A. S.-Y.; Yeh, H.-C.; Shie, J.-J. *Tetrahedron Lett.* **1998**, *39*, 5249.
- Lee, A. S.-Y.; Yeh, H.-C.; Tsai, M.-H. *Tetrahedron Lett.* **1995**, *36*, 6891.
- Chen, M.-Y.; Lee, A. S.-Y. *J. Org. Chem.* **2002**, *67*, 1384.
- Lee, A. S.-Y.; Hu, Y.-J.; Chu, S.-F. *Tetrahedron* **2001**, *57*, 2121.
- A solution of trialkylsilyl ester (1.0 mmol), CBr_4 (0.05 mmol) and anhydrous CH_3OH (5 mL) or EtOH in a Pyrex culture tube is irradiated directly by a TLC lamp at room temperature (UVItec Limited, 8 W, 254 nm) for 30 min and then stirred without irradiation at room temperature. After the reaction was complete (analysis by TLC), the organic solvent was removed directly under reduced pressure. Further purification is achieved on a flash chromatograph with ethyl acetate/hexane mixture as the eluate.
- Vourloumis, D.; Kim, K. D.; Petersen, J. L.; Magriotis, P. A. *J. Org. Chem.* **1996**, *61*, 4848.
- Shishido, K.; Irie, O.; Shibuya, M. *Tetrahedron Lett.* **1992**, *33*, 4589.
- Lee, A. S.-Y.; Yang, H.-C.; Su, F.-Y. *Tetrahedron Lett.* **2001**, *42*, 5301.
- Chen, M.-Y.; Lee, A. S.-Y. *J. Chin. Chem. Soc.* **2003**, *50*, 103.