Reaction of Hindered Trialkylsilyl Esters and Trialkylsilyl Ethers with Triphenylphosphine Dibromide: Preparation of Carboxylic Acid Bromides and Alkyl Bromides under Mild Neutral Conditions[1]

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A new route for a simultaneous deprotection-activation of hindered trialkylsilyl esters is described. *tert*-Butyldimethylsilyl, triisopropylsilyl, and *tert*-butyldiphenylsilyl carboxylates reacted with triphenylphosphine dibromide at room temperature in dichloromethane to give acid bromides in high yields. Reaction between hindered trialkylsilyl ethers and triphenylphosphine dibromide afforded alkyl bromides in excellent yields. The formation rate of acid bromides and alkyl bromides was increased when the reactions were carried out in the presence of a catalytic amount of $ZnBr_2$.

Protection[2] as well as activation[3] of carboxylic acids are two important operations in organic synthesis. The conversion of carboxylic acids into the corresponding carboxylic acid halides[4] is often the method of choice for activating carboxylic acids. Most current methods that accomplish this conversion involve acidic conditions, and therefore if a carboxylic acid contains an acid-sensitive functionality, the desired carboxylic acid halide may be obtained in low yield or not at all. Within recent years, silylation as a protective method in the synthesis of organic compounds has been increasing in use.[2,5] Therefore, the direct conversion of a silyl ester to an acid halide has the obvious advantage that the otherwise necessary steps of deprotection and isolation of the acid are obviated.

An earlier paper from our laboratory showed the conversion of trimethylsilyl carboxylates into their corresponding acid bromides.[6] The *tert*-butyldimethylsilyl group[7] has been reported to be of more value than the trimethylsilyl group as a protective group for alcohols and carboxylic acids because its stability to several reagents such as Wittig, Jones, and Grignard reagents. This encouraged us to investigate the reaction of hindered trialkylsilyl esters with triphenylphosphine dibromide reagent as potential route for a simultaneous deprotection-activation of the carboxyl group.

$$\underset{\mathbf{1}:\ R^1=R^2=Me,\ R^3=t\text{-}Bu}{\underset{\mathbf{2}:\ R^1=R^2=R^3=i\text{-}Pr}{\underset{\mathbf{3}:\ R^1=R^2=Ph,\ R^3=t\text{-}Bu}{RCOOSiR^1R^2R^3}}} + \underset{\mathbf{4}}{Ph_3PBr_2} \xrightarrow[rt]{CH_2Cl_2} \underset{\mathbf{5}}{RCOBr} + \underset{\mathbf{6}}{BrSiR^1R^2R^3}$$

Our finding is that when equimolar amounts of **1** and **4** were mixed at room temperature in dichloromethane as solvent, a smooth reaction was observed, yielding **5** in high isolated yields. The preparation of carboxylic acid bromides has been performed on a variety of structurally different *tert*-butyldimethylsilyl carboxylates to determine the scope and limitations of this method. Some experimental results are summarized in Table I and illustrate the efficiency, the applicability and the scope of the present

Table I. Conversion of TBDMS Esters[a] 1 into Acid Bromides 5 or Their Derivatives

run	R	time[b]	yield,[c] %	bp, °C (mmHg)[d] [mp, °C] found	lit.
a	C_6H_5	25 h	89[f]	130-133 (16)	199.2 (760)[j]
		20 min	85[e,f]		
b	4-ClC_6H_4	3.5 h	91	130-131 (14)	142 (27)[k]
		1.0 h	92[e]		
c	4-$O_2NC_6H_4$	6 h	90[g]	[94-95]	[96][j]
		75 min	87[e,g]		
d	2,4,6-$(CH_3)_3$-C_6H_2	15 min	99[g]	[101-104]	[103-104][l]
e	2-$CH_3C_6H_4$	1.5 h	90[h]	[125]	[125][i]
f	$C_6H_5CH_2$	15 min	91	140-143 (16)	150-155 (50)[j]
g	$(C_6H_5)_2CH$	40 min	84[f]	[59-60]	[60][j]
h	$(CH_3)_3C$	25 min	76[h]	135-140 (20)	60.5 (1)[m]
		3 min	80[e,h]		
i	(*E*)-Ph-CH=CH	30 min	97[g]	150-155 (16)	110 (0.1)[k]
j	CH_2=C-(CH_3)	30 min	84[g]	115-117 (760)	117 (760)[n]
k	oleyl	30 min	90	115-120 (0.1)	218.5 (20)[n]
l	$(CH_3)_2$-C=CH	20 min	90	115-120 (760)	56-59 (10)[k]
m	PhCH(O-$SiMe_2$-*t*-Bu)-	15 min	70[g]	160 (0.2)	*o*
n	N≡CCH_2	30 min	75[i]	125-130 (0.1)	95 (0.02)[p]
o	$PhCONHCH_2$	15 min	90[g]	150-155 (0.1)	69-95[q]
p	CH_3OCH_2	10 min	92[g]	146-145 (760)	142 (758)[n]

[a] These compounds were prepared by our method. See: Aizpurua, J. M.; Palomo, C. *Tetrahedron Lett.* **1985**, *26*, 475. [b] Reaction times observed until disolution of reagent **4**. [c] Isolated yields. [d] Reported boiling points are those observed during distillation with a Kugelröhr apparatus and are uncorrected. [e] $ZnBr_2$ was added. [f] Isolated as methyl ester. [g] Isolated as ethyl ester. [h] Isolated as anilide. [i] Isolated as benzyl ester. [j] Rappoport, Z. *Handbook of Tables for Organic Compounds Identification*, 3rd ed.; CRC Press: Cleveland, 1967. [k] Bestmann, H. J.; Mott, L. *Justus Liebigs Ann. Chem.* **1966**, *693*, 132. [l] Burton, H.; Praill, P. F. G. *J. Chem. Soc.* **1975**, 729. [m] Applequist, D. E.; Kaplan, L. *J. Am. Chem. Soc.* **1965**, *87*, 2194. [n] Weast, R. C. *Handbook of Chemistry and Physics*, 57th ed.; CRC Press: Cleveland, 1976-1977. [o] See the Experimental Section. [p] Dahn, H.; Hauth, H. *Helv. Chim. Acta* **1959**, *42*, 1214. [q] Martin, D.; Weise, A.; Nadolski, K. *Chem. Ber.* **1965**, *98*, 3286.

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Table II. Deprotection-Activation of 1b and 1c by the Reagent 4

substrates	catalyst	time	yield,[a] %
2,4,6-$(CH_3)_3C_6H_2COOSiPh_2$-*t*-Bu	none	30 min	85
	$ZnBr_2$	5 min	87
$PhCH_2COOSi(i\text{-}Pr)_3$	none	35 min	90
	$ZnBr_2$	6 min	91
4-$O_2NC_6H_4COOSi(i\text{-}Pr)_3$	none	22 h	87
	$ZnBr_2$	2 h	85

[a] The corresponding carboxylic acids were isolated as ethyl esters.

method. Conversion of *tert*-butyldimethylsilyl carboxylates into bromides, or their derivatives, usually proceeds completely at room temperature within 0.5 and 5 h, depending of the nature of the substrate **1**. Silyl esters involving unactivated or deactivated aromatic rings (runs a–c) yielded the corresponding acid bromides in high yields after 2–6 h at room temperature, whereas silyl esters having electron-donating substituents (runs d and e) gave the expected acyl bromides in short reaction time. Likewise, primary, secondary, and tertiary carboxylic silyl esters (runs f–h) were cleanly converted into the corresponding bromides independently of the steric hindrance of the substrates. Moreover, the reaction conditions are mild enough to be applied to acid-sensitive compounds (runs i–m). For example, while the conversion of the *tert*-butyldimethylsilyl ester **1m**, which contains an acid-sensitive silyl moiety, to the corresponding ethyl ester proceeded in good yield, the reaction of the α-(hydroxyphenyl)acetic acid with **4** under the same conditions gives the corresponding ethyl ester in much lower yield together with benzaldehyde. The preparation of carboxylic acid bromides of derivatives having other functional groups such as cyano, amide, and alkoxy was also examined in order to determine the synthetic effectiveness of this method. For example, cyanoacetic acid, which is known to undergo spontaneous polymerization,[8] hippuric acid, which easily forms oxazolones, and methoxyacetic acid were cleanly esterified in high yields without affecting their functional groups.

Furthermore, we have found that when reaction between *tert*-butyldimethylsilyl esters **1** and reagent **4** was performed in the presence of a catalytic amount of zinc bromide, the conversion rate was remarkably increased, giving the acid bromide in a few minutes, as shown by the results listed in Table I (runs a–c and h). This feature has more significance when other more sterically hindered silyl groups were used as protecting groups instead of the *tert*-butyldimethylsilyl group (Table II). Thus, *tert*-butyldiphenylsilyl 2,4,6-trimethylbenzoate, triisopropylsilyl phenylacetate, and triisopropylsilyl 4-nitrobenzoate gave the corresponding bromides in reaction times and yields comparable to the *tert*-butyldimethylsilyl carboxylates when zinc bromide was used as catalyst.

In view of the results obtained, next we examined the reaction of reagent **4** with trialkylsilyl ethers. The conversion of alcohols into their corresponding bromides is frequently a useful and necessary synthetic operation. However, in most synthetic strategies involving polyfunctional compounds, it is necessary to protect first the hydroxyl group, carry out the desired transformation, then deprotect the hydroxyl function, and finally convert it into the desired bromide.

During recent research in the synthesis of β-lactams, our synthetic strategy required the preparation of several bromides from the corresponding silyl ethers.[9]

$$\underset{\mathbf{7}}{ROSiR^1R^2R^3} \xrightarrow[rt]{4,\ CH_2Cl_2} \underset{\mathbf{8}}{RBr} + \mathbf{6}$$

It has been reported that triphenylphosphine dibromide converts both hydroxyl[10] and ether[11] functions into bromides in good yields; also Schmutzler and co-workers[12] have reported that tributylfluorophosphonium bromide converts trimethylsilyl ethers into bromides. However, no application of these procedures to other silyl ethers has been given. Our new finding is that when a *tert*-butyldimethylsilyl ether was treated with reagent **4** in dichloromethane at room temperature, the pure bromide was isolated in good yield. Some examples are given in Table III to illustrate the efficiency of the method. As shown in the table, *tert*-butyldimethylsilyl ethers were cleaved more readily than those of more sterically hindered ones. Thus, the *tert*-butyldiphenylsilyl ether **7b** and the triisopropylsilyl ether **7d** upon treatment with reagent **4** yielded the expected bromides **8** after 7.5 h of stirring of the reaction mixture at room temperature; however, if the reaction was carried out under the influence of zinc bromide in a catalytic amount, the conversion rate was notably increased. The preparation of these bromides with no detectable elimination illustrates the mildness of the reaction conditions.

In conclusion we have found new applications of triphenylphosphine dibromide. The versatility of the present deprotection–activation method of hindered trialkylsilyl carboxylates and the mild preparation of bromides from hindered trialkylsilyl ethers is obvious as demonstrated here by this limited number of examples and may be readily extended to further synthetic applications.

Experimental Section

General Procedures. Melting points were determined on a Büchi SMP-20 melting point apparatus and are uncorrected. Proton NMR spectra were measured on a Varian EM-360 spectrometer and are reported in parts per million downfield from internal tetramethylsilane. The couplings (*J*) are in hertz (Hz). Mass spectra (MS) were taken at 70 eV on a Hewlett-Packard HP 5995C mass spectrometer. Elemental analyses were provided by Colegio Universitario de Alava. All the starting materials used in this work either were commercially available in generally 98% or higher purity and used without further purification or were prepared by literature procedures. The *N*-(2-hydroxyethyl)-β-lactams and their silyl ethers were prepared by our procedures.[9] Triphenylphosphine was supplied by BASF S.A.

Deprotection–Activation of Trialkylsilyl Carboxylates 1. General Procedure. A solution of **1** (5 mmol) in dichloromethane (15 mL) was added to a stirred suspension of reagent **4** (5 mmol) in dichloromethane (10 mL). The reaction mixture was stirred at room temperature until a clear solution was formed (Table I). Stirring was continued for 15 min again. On completion, the organic solvent was evaporated. The residue was then extracted with ether/hexane (1:1, 3 × 10 mL), and the extracts were concentrated, the resulting acid bromide being purified by reduced pressure distillation. For derivatives the reaction mixture was treated with an excess of the corresponding alcohol (1 mL) and pyridine (1 mL) and stirred for 60 min. The organic solvent was

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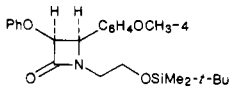
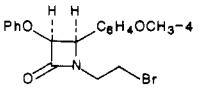
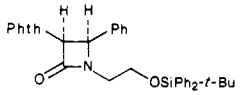
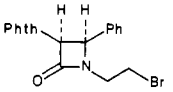
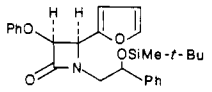
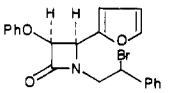
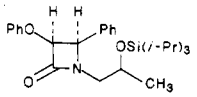
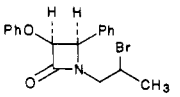
Table III. Bromides from Trialkylsilyl Ethers and Reagent 4

compd 7	product 8	time	catalyst	yield,[a] %	mp, °C/torr (bp, °C/torr)[b]
4-$CH_3OC_6H_4CH_2OSiMe_2$-*t*-Bu	4-$CH_3OC_6H_4CH_2Br$	15 min	none	90[b]	120/0.2 (218–220/760)[c]
$CH_3(CH_2)_{13}OSiMe_3$-*t*-Bu	$CH_3(CH_2)_{12}CH_2Br$	10 min	none	91[c]	180–185/20 (179/20)[d]
 7a	 8a	10 min	none	94	68–70
 7b	 8b	7.5 h 2.5 h	none $ZnBr_2$	80 85	197–198
 7c	 8c	15 min	none	75	130–134
 7d	 8d	7.5 h 30 min	none $ZnBr_2$	70 75	139–141

[a] Yield of isolated products. All new compounds gave satisfactory spectrscopic data and elemental analyses. All the synthetic β-lactams are racemic mixtures. Phth = phthalimido group. [b] Observed during distillation with Kugelrohr apparatus and are uncorrected. [c] *Handbook of Chemistry and Physics*, 57th ed.; CRC Press: Cleveland, 1976–1977. [d] Rappoport, Z. *Handbook of Tables for Organic Compounds Identification*, 3th ed.; CRC Press: Cleveland, 1967.

washed successively with water (20 mL) and 1 N HCl (20 mL) and worked-up as above.

[(*tert*-Butyldimethylsiloxy)phenyl]acetyl Ethyl Ester. To a suspension of **4** (3.3 mmol) in dichloromethane (7.5mL) was added a solution of α-[(*tert*-butyldimethylsiloxy phenyl]acetyl *tert*-butyldimethylsilyl ester (3 mmol) in dichloromethane (3mL) at room temperature, and the resulting mixture was stirred for 15min at the same temperature. After this time, a mixture of ethanol (1 mL) and pyridine (0.5 mL) was added, and the resulting solution was stirred at room temperature for 15 min. Workup as above gave a waxy residue that was washed with boiling hexane. The combined extracts were evaporated under reduced pressure and then distilled to give the title pure product (see Table I): ^1H NMR ($CDCl_3$) δ 7.43–7.10 (m, 5 H, arom), 5.08 (s, 1 H, CH), 3.96 (q, J = 7 Hz, 2 H, CH_2), 1.03 (t, J = 7 Hz, 3 H, CH_3), 0.86 (s, 9 H, CCH_3), −0.05 (s, 3 H, $SiCH_3$), −0.16 (s, 3 H, $SiCH_3$); MS for $C_{16}H_{26}O_3Si$, calcd m/e 294, found 294.

Preparation of Alkyl Bromides. General Procedure. To a suspension of **4** (2.2mmol) in dichloromethane (5mL) was added a solution of the corresponding silyl ether (2 mmol) in dichloromethane (3 mL) at room temperature, and the resulting mixture was stirred at the same temperature until the reagent was dissolved. Stirring was continued for 15 min again, and then dichloromethane (15mL) was added and the solution washed with water (2 × 10 mL). The organic layer was dried with sodium sulfate and the solvent evaporated under reduced pressure, giving a waxy residue that was purified by distillation or crystallization. Yields and reaction times are compiled in Table III. Proton NMR data taken in $CDCl_3$ and analytical data include the following. **8a**: δ 7.33–6.63 (m, 9 H, arom), 5.42 (d, J = 5 Hz, 1 H, CH), 5.02 (d, J = 5 Hz, 1 H, CH), 4.03–3.15 (m, 4 H, CH_2CH_2Br), 3.75 (s, 3 H, OCH_3). Anal. Calcd for $C_{18}H_{18}BrNO_3$: C, 57.45; H, 4.83; N, 3.72. Found: C, 56.97; H, 4.86; N, 3.71. **8b**: δ 7.61 (s_b, 4 H, arom), 7.11 (s_b, 5 H, arom), 5.49 (d, J = 5 Hz, 1 H, CH), 5.10 (d, J = 5 Hz, 1 H, CH), 4.21–3.11 (m, 4 H, CH_2CH_2Br). Anal. Calcd for $C_{19}H_{15}BrN_2O_3$: C, 57.15; H, 3.79; N, 7.02. Found: C, 57.36; H, 3.91; N, 7.23. **8c**: δ 7.33 (s_b, 5 H, arom), 7.33–6.66 (m, 5 H, arom), 6.36–6.20 (m, 3 H, furyl), 5.33 (d, J = 5 Hz, 1 H, CH), 5.16 (d, J = 5 Hz, 1 H, CH), 5.33–5.00 (m, 1 H, CHBr), 4.13 (d d, J = 6 Hz, J' = −14 Hz, 1 H, NC*H*CHBr). Anal. Calcd for $C_{21}H_{13}BrNO_3$: C, 61.17; H, 4.41; N, 3.40. Found: C, 61.42; H, 4.46; N, 3.52. **8d**: δ 7.36 (s_b, 5 H, arom), 7.36–6.66 (m, 5 H, arom), 5.53 (d, J = 5 Hz, 1 H, CH), 5.30 (d, J = 5 Hz, 1 H, CH), 4.55–4.03 (m, 1 H, CHBr), 3.95 (d, d, J = 4 Hz, J' = −16 Hz, NC*H*CHBr), 3.06 (d, d, J = 9 Hz, J' = −16 Hz, 1 H, NC*H*CHBr), 1.63 (d, J = 7 Hz, 3 H, CH_3). Anal. Calcd for $C_{18}H_{18}BrNO_2$: C, 60.00; H, 5.05; N, 3.89. Found: C, 60.51; H, 5.21; N, 4.10.

Registry No. **1a**, 75732-41-1; **1b**, 105040-96-8; **1c**, 96185-30-7; **1d**, 105040-97-9; **1e**, 78324-00-2; **1f**, 78323-99-6; **1g**, 105040-98-0; **1h**, 96185-31-8; **1i**, 78324-06-8; **1j**, 105040-99-1; **1k**, 105041-00-7; **1l**, 105041-01-8; **1m**, 78324-07-9; **1n**, 105041-02-9; **1o**, 105041-03-0; **1p**, 105041-04-1; **2c**, 105041-13-2; **2f**, 105041-12-1; **3d**, 105041-11-0; **4**, 1034-39-5; **5a**, 618-32-6; **5b**, 874-59-9; **5c**, 13277-61-7; **5d**, 67958-02-5; **5e**, 20045-96-9; **5f**, 22535-03-1; **5g**, 57369-76-3; **5h**, 27644-18-4; **5i**, 105041-05-2; **5j**, 6997-65-5; **5k**, 105041-06-3; **5l**, 10606-43-6; **5m**, 105041-07-4; **5n**, 105041-08-5; **5o**, 105041-09-6; **5p**, 105041-10-9; **7a**, 105041-14-3; **7b**, 105041-15-4; **7c**, 105041-16-5; **7d**, 105041-17-6; **8a**, 105041-18-7; **8b**, 105041-19-8; **8c**, 105041-20-1; **8d**, 105041-21-2; $ZnBr_2$, 7699-45-8; 4-$CH_3OC_6H_4CH_2OSiMe_2$-*t*-Bu, 101803-60-5; $CH_3(CH_2)_{13}OSiMe_2$-*t*-Bu, 77774-34-6; 4-$CH_3OC_6H_4CH_2Br$, 2746-25-0; $CH_3(CH_2)_{12}CH_2Br$, 112-71-0.