Acid- and Base-Stable Esters: A New Protecting Group for Carboxylic Acids

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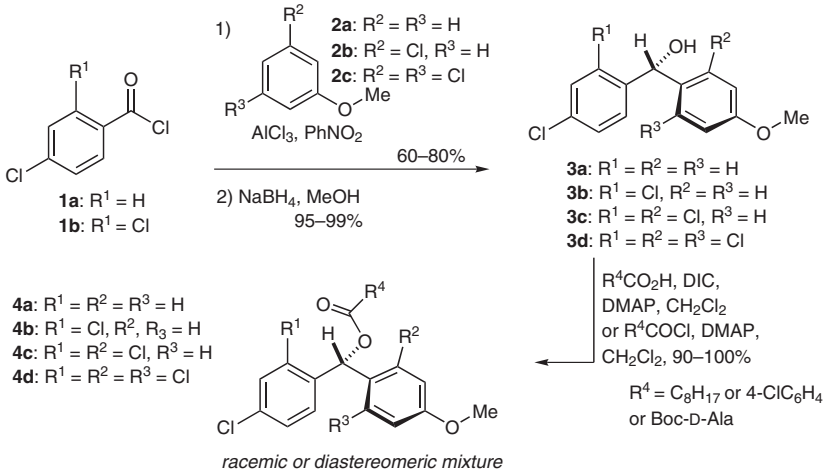
Abstract: An acid- and base-stable protecting group for carboxylic acids is described. The esters of (2,6-dichloro-4-methoxyphenyl)(2,4-dichlorophenyl)methanol are stable to Brønsted and Lewis acids, Brønsted bases, and a wide variety of nucleophiles; however, the esters can be conveniently deprotected by a solvolytic displacement reaction with 20% trifluoroacetic acid.

Key words: acid-stable ester, base-stable ester, carboxylic acid protecting group, chlorodiphenylmethyl esters

In connection with ongoing studies on the development of novel drug-like MraY inhibitors,[1] we have delivered a set of small optimized libraries based on uridine-β-hydroxyamino acid.[2] In order to efficiently generate such libraries in solution, we sought a protecting group for the carboxylic acid which can be cleaved simultaneously with the acetonide by a volatile and mild acid such as trifluoroacetic acid. In addition, a protecting group for the carboxylic acid should have stability to relatively strong Brønsted and Lewis acids, bases, and a wide variety of nucleophiles. Although a large number of acid-cleavable protecting groups [i.e., trityl, TBDPS, MOM, THP, 2-(trimethylsilyl)ethyl, *t*-Bu, PMB, ortho esters, and their related protecting groups] for carboxylic acids have been utilized in organic syntheses, these protecting groups did not fulfill the requirement of stability against conditions being utilized in the library productions; trityl, silyl, and PMB protecting groups are too labile to acids, while MOM, SEM, *t*-Bu, and ortho esters require harsh acidic conditions for regeneration of the carboxylic acids.[3] Thus, we have developed a new protecting group for carboxylic acids which is stable to acids, bases, and a wide variety of nucleophiles, but can be regenerated with trifluoroacetic acid.

A diphenylmethyl ester is an acid-labile functional group and has been utilized as a temporary protecting group for carboxylic acids. In our experiments, diphenylmethanol exhibited similar nucleophilicity to allylic alcohol and is not efficiently esterified with carboxylic acids via conventional carboxylic acid activation methods (i.e., DCC, BOP-Cl, and mixed anhydride). In order to stabilize diphenylmethyl esters by tuning electronic properties of diphenyl moieties, several chloro-substituted diphenylmethyl esters were synthesized and tested for their stability against representative acids, such as $TsOH·H_2O$ (20% in CH_2Cl_2–THF), HF (10% in MeCN), $BF_3·OEt_2$ (10% in CH_2Cl_2), and $La(OTf)_3$ (10% in aq THF). Interestingly, as summarized in Scheme 1, all (4-chlorophenyl)(4-methoxyphenyl)methanols **3a–d**, conveniently synthesized by Friedel–Crafts reaction of 4-chlorobenzoyl chlorides **1** with anisoles **2**, followed by sodium borohydride reduction, could be efficiently esterified using EDCI, DCC,



Scheme 1 Synthesis of the chloro-substituted diphenylmethyl esters **4a–d**

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DIC, or acid chloride methods.[4] Esters **4a**–**c** regenerated the corresponding acids upon treatment with 20% TsOH within one hour, and also were not stable with 10% HF, 15% TFA, 10% $BF_3{\cdot}OEt_2$, and 10% $La(OTf)_3$. Surprisingly, the tetrachloro-substituted diphenylmethyl esters **4d** showed an unusual acid stability; no regeneration of the acids from esters **4d** was observed with 20% TsOH for over 36 hours.

As summarized in Table 1, esters **4d** (R^4 = Me or C_8H_{17}) also exhibited excellent stability to a variety of Brønsted and Lewis acids such as 15% TFA, 30% HF, 2 N HCl, HBr/AcOH, $TiCl_4$, $ZnCl_2$, $AlCl_3$, $B(C_6F_5)_3$, BCl_3, BBr_3, $BF_3{\cdot}OEt_2$, TMSOTf, and $La(OTf)_3$ at room temperature. Moreover, esters **4d**: 1) showed stability under basic conditions: no saponifications were observed with NH_4OH (40% in aq THF–MeOH), LiOH (10% in aq THF–MeOH), NaOH (6 N in aq MeOH),[5] TlOEt (in aq THF), and DBU (10% in aq THF) at room temperature for over 24 hours; 2) showed excellent stability to nucleophiles: esters **4d** were not susceptible to the nucleophilic attacks of primary and secondary amines (in aq THF at 80 °C), NH_2NH_2 (in aq THF at r.t.), alkylthiols (in THF at 80 °C), NaN_3 (in DMF at 90 °C), H_2O_2/NaOH (in aq THF at r.t.), and MeMgBr (0 °C to r.t.); 3) were not enolizable with LDA, NaHMDS, KHMDS,[6] and *n*-Bu_2BOTf/DIPEA (at –78 °C to r.t.); 4) were stable under reducing conditions such as Zn/HCl, Ag(Hg), B_2H_6, $NaBH_4$ (in MeOH at 60 °C), Li(O-*t*-Bu)$_3$AlH, Raney Ni, H_2/$RhCl(PPh_3)_3$, and H_2/Pd–C (in EtOAc or 1,4-dioxane); 5) remained intact under palladium-mediated coupling reaction conditions (Suzuki–Miyaura and Heck reactions); 6) did not react with iodine and NBS; and 7) were photolytically stable: no change upon irradiation at 200–350 nm (in 1,4-dioxane for 72 h).

Thus, we succeeded in stabilizing the diphenylmethyl ester against a wide variety of acids, bases, and nucleophiles.

In order to understand the unusual stability of esters **4d** against bases and a wide variety of nucleophiles, we ana-

Table 1 Reactivities of Esters **4d** (R^4 = Me or C_8H_{17}) against a Variety of Reagents[q]

20% TsOH[a]	2 N HCl[b]	30% HF[b]	15% TFA[c]	HBr/AcOH	BCl_3[c]	BBr_3[c]	TMSOTf[c]	$AlCl_3$[c]	$B(C_6F_5)_3$[c]	$La(OTf)_3$[c]
L	L	L	L	L	L	L	L	L	L	L
$TiCl_4$[c]	$ZnCl_2$[c]	10% $BF_3{\cdot}OEt_2$[c]	LiOH/ THF[d]	6 N aq NaOH[e]	1 N aq NaOH, 50 °C		TlOEt[g]	NH_4OH[h]	NH_2NH_2[g]	DBU[g]
L	L	L	L	L	M[f]		L	L	L	L
H_2O_2/NaOH[g]	*n*-Bu_2NH[i]	*n*-$BuNH_2$[i]	*n*-BuSH[i]	NaN_3[j]	MeMgBr[k]	*n*-BuLi	NaHMDS[m]	KHMDS[m]	*n*-Bu_2BOTf[n]	Zn/HCl[o]
L	L	L	L	L	L	M[l]	L	L	L	L
Al(Hg)[o]	B_2H_6[k]	$NaBH_4$[p]	*i*-Pr_2AlH[c]	$LiAlH_4$[k]	Li(O-*t*-Bu)$_3$AlH[k]	H_2/Pd–C/EtOAc		H_2/Pd–C/1,4-dioxane		H_2/RhCl $(PPh_3)_3$
L	L	L	H	H	L	L		L		L
Raney Ni[o]	$PhB(OH)_2$ / $Pd(PPh_3)_4$/ TlOEt[g]	$PhCH{=}CH_2$/$Pd_2(dba)_3$/*t*-$Bu_3P{\cdot}HBF_4$/ DIPEA[k]			I_2[h]		NBS[k]		*hν* (200–350 nm)[o]	
L	L	L			L		L		L	

[a] In CH_2Cl_2–THF (1:1).
[b] In MeCN.
[c] In CH_2Cl_2.
[d] At 50 °C for over 1 h.
[e] At r.t. for over 36 h.
[f] 50% regeneration of **3d** (see Scheme 1).
[g] In aq THF.
[h] In aq THF–MeOH.
[i] In THF at 80 °C.
[j] In DMF at 90 °C.
[k] In THF at r.t. for over 1 h.
[l] ~70% of **4d** was recovered after 1 h at –78 °C.
[m] In THF at –78 to 0 °C for over 1 h.
[n] In CH_2Cl_2 in the presence of DIPEA.
[o] In 1,4-dioxane.
[p] In MeOH at 60 °C.
[q] H indicates that the protecting group is readily cleaved; M indicates that the protecting group is cleaved very slowly; L indicates that the protecting group is stable.

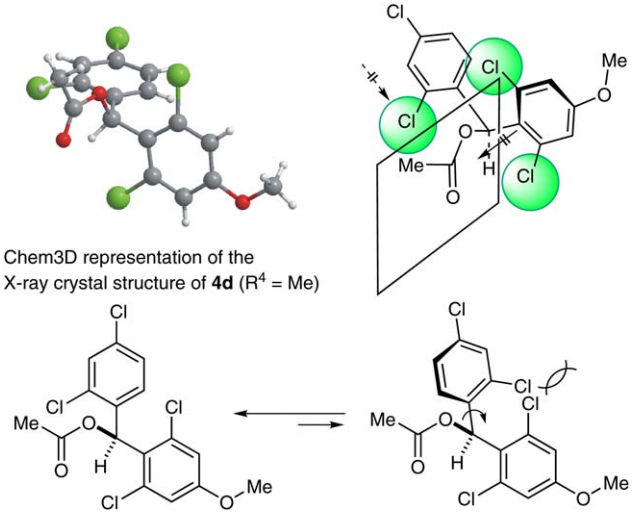


Figure 1

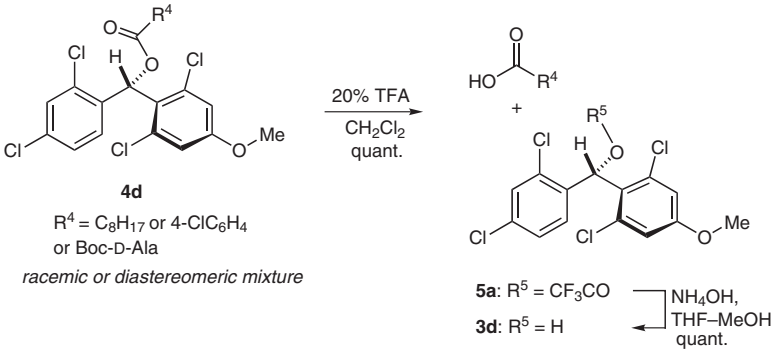
lyzed a lowest-energy conformer of **4d** (R^4 = Me) by single-crystal X-ray structure analysis (Figure 1). It was revealed that the dihedral angles formed by the two planar chloro-substituted benzene rings and by the –CO–O– linkage and the ether methine proton are 83.5° and 159.8°, respectively.[7] There must be a significant electronic repulsion between the *o*-chloro atoms in the two benzene rings. The *o*-chloro atom in the dichlorophenyl moiety is located toward the carbonyl ester plane. Thus, the chloro atoms at the *o*-positions in the two benzene rings hinder nucleophilic attack at the ester carbonyl from both the *re*- and *si*-faces. In addition, the 3,5-dichloro atoms in the anisole moiety attenuate an electron-donating character of the methoxy group. Therefore, esters **4d** would exhibit stability against bases, nucleophiles, and acids. To the best of our knowledge this is the first example of esters which are stable to both acids and bases. Esters **4d** could be conveniently cleaved using 20% trifluoroacetic acid in dichloromethane to afford the corresponding acids (R^4CO_2H) and the trifluoroacetate **5a** in quantitative yields. The trifluoroacetate **5a** also survived most acidic conditions tested in Table 1 and SiO_2, but could be easily cleaved with aqueous ammonia in tetrahydrofuran–methanol within three hours to regenerate **3d** in quantitative yield (Scheme 2). Alternatively, esters **4d** were 1) cleaved by a hydrogenation reaction (H_2/Pd–C in MeOH) to regenerate the carboxylic acids (Table 1), and 2) reduced with $LiAlH_4$ or DIBAL-H to afford the corresponding alcohols ($R^4 = C_8H_{17}$ and *p*-ClC_6H_4) in high yields.

In conclusion, we have developed an acid- and base-stable protecting group for carboxylic acids, which would be very useful for the generation of library molecules containing carboxylic acid functional groups in that: 1) the ester is stable to a wide variety of nucleophiles and reagents, and 2) the esters can be cleaved by solvolytic cleavage with 20% trifluoroacetic acid within one hour. The novel protecting group for carboxylic acids described here will be useful in multistep syntheses of target molecules including complex natural products, carbohydrates, and nucleotides. It is worth mentioning that alcohol **3d** could be efficiently synthesized in only two steps (Friedel–Crafts acylation, followed by $NaBH_4$ reduction) using inexpensive chemicals. Moreover, alcohol **3d** can be regenerated, as illustrated in Scheme 2. Thus, the new protecting group **3d** should be a valuable asset not only for small-scale organic reactions but also for industrial-scale syntheses.[8]

IR absorptions on NaCl plates were run on a Perkin Elmer FT-IR 1600 spectrometer. ^{1}H NMR spectral data were obtained using Varian 300 MHz and 400 MHz instruments. The residual solvent signal was utilized as an internal reference. ^{13}C NMR spectral data were obtained using a Varian 100 MHz spectrometer. Chemical shifts were reported in parts per million (ppm) downfield from TMS, using the middle resonance of $CDCl_3$ (77.0 ppm) as an internal standard. For all NMR spectra, δ values are given in ppm and *J* values in Hz. Mass spectra were obtained at Colorado State University's Central Instrument Facility. Reagents and solvents are commercial grade and were used as supplied. Reaction vessels were flame-dried or oven-dried and cooled under an inert atmosphere when necessary.

2,6-Dichloro-4-methoxyphenyl)(2,4-dichlorophenyl)methanol (3d)

Anhyd $AlCl_3$ (4.5 g, 33.9 mmol) was placed in a round-bottom flask and $PhNO_2$ (150 mL) was added. At –78 °C, 2,4-dichlorobenzoyl chloride (**1b**) (4.7 mL, 33.9 mmol) and 3,5-dichloroanisole (**2c**) (5.0 g, 28.2 mmol) were added. The reaction mixture was kept at –78 °C for 1 h, then warmed to r.t. over 24 h. The mixture was diluted with Et_2O (50 mL) at 0 °C and the reaction was quenched with 1 N NaOH (~30 mL); the mixture was vigorously stirred until a white precipitate had been formed. The precipitates were filtered and



Scheme 2 Solvolytic displacement reaction with trifluoroacetic acid

washed with CH_2Cl_2 (50, 30, and 20 mL). The combined organic solvents were dried (Na_2SO_4), filtered, and concentrated under reduced pressure (~10 mmHg). Purification by silica gel chromatography (hexanes–$CHCl_3$, 4:1) provided (2,6-dichloro-4-methoxyphenyl)(2,4-dichlorophenyl)methanone (8.3 g, 85%) as a white powder.

IR (film): 1619, 1584, 1553, 1400, 1309 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.68 (d, *J* = 8.2 Hz, 1 H), 7.54 (d, *J* = 2.1 Hz, 1 H), 7.37 (dd, *J* = 8.1, 2.1 Hz, 1 H), 6.95 (s, 2 H), 3.87 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.6, 163.8, 142.0, 138.3, 137.7, 136.4, 130.3, 129.9, 127.8, 122.9, 118.4, 117.9, 114.6, 56.1.

HRMS–FAB: *m/z* [M + Na]$^+$ calcd for $C_{14}H_8Cl_4O_2Na$: 370.91761; found: 370.91765.

(2,6-Dichloro-4-methoxyphenyl)(2,4-dichlorophenyl)methanone (1.0 g, 2.8 mmol) was dissolved in MeOH (15 mL) and cooled to 0 °C. $NaBH_4$ (318 mg, 8.4 mmol) was added to the mixture. The reaction was quenched with aq NH_4Cl (15 mL) and the mixture was extracted with EtOAc (100, 30, and 20 mL). The combined extracts were washed with brine (15 mL), dried (Na_2SO_4), and concentrated under reduced pressure. Purification by silica gel chromatography (hexanes–EtOAc, 5:1) provided **3d** (980 mg, 97%) as a white powder.

IR (film): 3482, 1438, 1410, 1325 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.69 (d, *J* = 8.4 Hz, 1 H), 7.38 (d, *J* = 3.0 Hz, 1 H), 7.31 (dd, *J* = 8.2, 3.0 Hz, 1 H), 6.91 (s, 2 H), 6.61 (d, *J* = 2.1 Hz, 1 H), 3.85 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.6, 137.8, 136.3, 133.9, 133.0, 130.5, 129.6, 129.6, 128.0, 126.6, 115.4, 115.4, 70.2, 55.9.

HRMS–FAB: *m/z* [M + Na]$^+$ calcd for $C_{14}H_{10}Cl_4O_2Na$: 372.93326; found: 372.93327.

(2,6-Dichloro-4-methoxyphenyl)(2,4-dichlorophenyl)methyl Nonanoate; Typical Procedure for the Esterification of 3d

To a stirred soln of alcohol **3d** (148 mg, 0.42 mmol) in CH_2Cl_2 (3.0 mL) was added *n*-nonanoic acid (84 mg, 0.53 mmol), DIC (98 μL, 0.60 mmol), and DMAP (146 mg, 1.2 mmol). After 3 h at r.t., the reaction was quenched with 0.5 N HCl (3 mL) and the mixture was extracted with EtOAc (30 mL). The combined extracts were washed with aq $NaHCO_3$ (15 mL) and brine (15 mL), dried (Na_2SO_4), and concentrated under reduced pressure. Purification by silica gel chromatography (hexanes–EtOAc, 20:1 to 10:1) provided the title nonanoate (194 mg, 0.39 mmol, 94%) as an oil.

IR (film): 1615, 1428, 1315 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.49 (s, 1 H), 7.36 (m, 2 H), 7.21 (m, 1 H), 7.06 (d, *J* = 1.8 Hz, 1 H), 6.80 (d, *J* = 2.1 Hz, 1 H), 3.72 (s, 3 H), 2.42 (t, *J* = 1.8 Hz, 2 H), 1.28 (m, 12 H), 0.89 (t, *J* = 6.7 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.3, 159.4, 136.2, 135.6, 134.6, 134.0, 133.5, 130.1, 129.4, 126.2, 122.5, 122.3, 111.1, 68.5, 56.2, 34.1, 31.7, 29.2, 29.1, 29.0, 24.8, 22.6, 14.1.

HRMS–FAB: *m/z* [M + Na]$^+$ calcd for $C_{23}H_{26}Cl_4O_3Na$: 513.05338; found: 513.05340.

(2,6-Dichloro-4-methoxyphenyl)(2,4-dichlorophenyl)methyl (2*R*)-2-(*tert*-Butoxycarbonylamino)propanoate

To a stirred soln of alcohol **3d** (25 mg, 0.071 mmol) in CH_2Cl_2 (1.0 mL) was added Boc–D-Ala–OH (20 mg, 0.11 mmol), DIC (26 μL, 0.17 mmol), and DMAP (27 mg, 0.22 mmol). After 3 h at r.t., the reaction was quenched with 0.5 N HCl (1 mL) and the mixture was extracted with EtOAc (15 mL). The combined extracts were washed with aq $NaHCO_3$ (10 mL) and brine (10 mL), dried (Na_2SO_4), and concentrated under reduced pressure. Purification by preparative TLC (hexanes–EtOAc, 5:1) provided a diastereomeric mixture of the title (2*R*)-propanoate (34 mg, 92%) as a solid.

IR (film): 1615, 1610 cm^{-1}

^1H NMR (400 MHz, $CDCl_3$): δ = 7.45 (m, 2 H), 7.36 (m, 2 H), 7.23 (m, 4 H), 7.06 (m, 2 H), 6.81 (m, 2 H), 5.03 (m, 1 H), 4.44 (m, 1 H), 3.73 (s, 3 H), 3.70 (s, 3 H), 1.43 (s, 18 H), 1.37 (d, *J* = 7.2 Hz, 3 H), 1.15 (d, *J* = 6.4 Hz, 3 H)

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.9, 159.4, 136.4, 136.2, 135.9, 134.4, 134.1, 134.0, 133.9, 133.6, 130.3, 129.5, 129.4, 126.3, 122.6, 122.5, 121.7, 111.1, 79.9, 69.8, 56.2, 56.1, 49.2, 28.3, 18.9, 18.5

HRMS–FAB: *m/z* [M + Na]$^+$ calcd for $C_{22}H_{23}Cl_4O_5NNa$: 544.02280; found: 544.02282

Typical Procedure for the Deprotection

The ester of **3d** was dissolved in 20% TFA in CH_2Cl_2 (0.3 M) and kept for 1 h at r.t. All volatiles were evaporated in vacuo to provide the carboxylic acid and **5a**. The carboxylic acid was separated from **5d** by a silica-gel plug (hexanes–EtOAc, 10:1 to $CHCl_3$–MeOH, 5:1) or a back-extraction procedure [solvent system: EtOAc–H_2O (for the extraction of **5d** under a basic conditions ($NaHCO_3$), $CHCl_3$–H_2O (for the extraction of the carboxylic acid under an acidic conditions (dil. HCl)].

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(4) The nucleophilicity of diphenylmethanol may be increased due to: 1) introduction of the methoxy group at the 4-position, and 2) stereoelectronic effects of the chloro substituents on the aromatic rings.
(5) 50% regeneration of **3d** was observed with 1 N aq NaOH at 50 °C for one hour.
(6) No deuterium exchange at the α-position of the esters upon quenching with CD_3OD and aldol reactions with benzaldehyde were observed.
(7) The –CO–O– linkage and the ether methine proton showed a deviation of 20.2° out of a preferential common plane.
(8) We have synthesized a variety of esters with N-protected D- or L-amino acids. Significant separation of signals for a diastereomeric mixture of esters at the α-position of the carbonyl group is observed in the ^1H NMR spectra; however, so far no separation of the diastereomers of **4d** has been observed on TLC. These characteristics may be applied to the determination of the stereochemistry of unknown α-chiral carboxylic acids by using optically pure **3d**. The synthesis of (+)-**3d** and (–)-**3d** will be reported elsewhere.