Chemoselective Protection of Carboxylic Acid as Methyl Ester: A Practical Alternative to Diazomethane Protocol†

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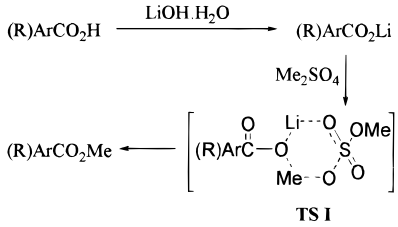
Functional group protection is an indispensable artifice employed to prevent or to modify the reaction of a specific functional group during a synthetic sequence. Development of newer methods for protection/deprotection of functional groups constitutes a topic of constant interest.[1] In this context carboxylic acid protection is an important transformation and is frequently achieved via methyl ester formation[2] because of ease of deprotection.[1,3]

Methods for conversion of carboxylic acids into esters can be envisioned in terms of two general schemes: (i) nucleophilic attack (by an alcohol) on the carboxyl carbon involving the tetrahedral intermediate[4] and (ii) alkylation of the carboxyl oxygen. In the first, the poor leaving group property of OH^- necessitates the use of an acid catalyst and thus problems are usually encountered with acid-sensitive compounds. The reversibility of such an esterification reaction demands the removal of water and use of a large excess of alcohol to achieve reasonable yields. Esterification also is difficult for sterically hindered acids because of increased steric interaction in the tetrahedral intermediate. Although activation (for nucleophilic attack) through conversion to an acid halide, anhydride, mixed anhydride, or thiol ester may circumvent the above problems, these methods require additional steps and potentially costly reagents.

Esterification by alkylation of the carboxyl oxygen is not reversible. Since the tetrahedral intermediate is not involved, esterification of a sterically hindered acid should not experience much trouble. However, as carboxylic acid groups are, in general, poor nucleophiles, the second approach requires the use of highly active electrophiles (e.g., diazoalkanes) or the activation of the carboxylic acid via its anion formation. Methyl esters may be prepared by treatment of carboxylic acids with diazomethane,[5] but the safety considerations (because of the toxicity and explosive nature of diazomethane) make it unsuitable for large scale reactions.

Scheme 1



Therefore we focused on the strategy of carboxylic acid activation. Recent developments in the area include the use of $P(OMe)_5$,[6] Me_3OBF_4-$^iPr_2NEt$,[1a] Me_3SOH,[7] Li_2CO_3-MeI,[8] CsF-2-fluoropyridinium salt-MeOH,[9] *O*-methylcaprolactim at 80 °C for 16 h,[10] K_2CO_3-$Ph_2S^+MeBF_4^-$-CuBr (cat.),[11] K_2CO_3-(18-C-6)-Cl_3CO_2Me,[12] Cs_2CO_3-(18-C-6)-MeI,[1a,13] CsF-MeI,[14] aqueous K_2CO_3-Bu_4NBr-MeI,[15] and Me_4NOH at 260 °C.[16] These methods have the limitations of the use of costly reagents and/or harsh reaction conditions.

Although the reaction of carboxylate anion and Me_2SO_4 should be an attractive method for methyl ester formation, the strategy has rather been neglected. The limited number of published procedures[2a,17] involve use of aqueous alkali (leading to side reactions such as hydrolyses of Me_2SO_4 and the ester formed), stringent reaction conditions, and costly reagents (e.g., dicyclohexylethylamine or DBN) as proton acceptors.

We report herein an efficient chemoselective protection of carboxylic acids under mild conditions that replaces toxic diazomethane or costly reagents by $LiOH·H_2O$-Me_2SO_4. This protocol exploits the simultaneous electrophilic activation of the carboxyl function and nucleophilic activation of Me_2SO_4 by virtue of coordination with Li^+ (Scheme 1).[18] In a typical experimental procedure, the carboxylic acid was treated with a stoichiometric amount of $LiOH·H_2O$ in dry THF. After the acid−base reaction (10−30 min), the resultant Li-carboxylate was reacted

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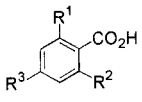
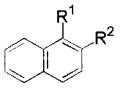
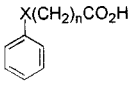
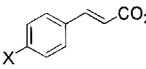
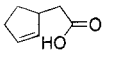
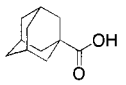
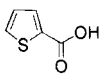
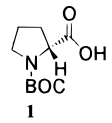
Table 1. Chemoselectivity of Carboxylic Acid Protection as Methyl Esters

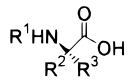
	Entry	Carboxylic acid	Time (h)	Yield (%)[a,b]
	1	$R^1 = R^2 = R^3 = H$	3	96 (74)
	2	$R^1 = R^2 = H$, $R^3 = Cl$	2	85
	3	$R^1 = R^3 = H$, $R^2 = Cl$	2	80
	4	$R^1 = R^2 = H$, $R^3 = NO_2$	0.5	83 (65)
	5	$R^1 = R^2 = H$, $R^3 = OH$	3	72
	6	$R^1 = R^2 = H$, $R^3 = OMe$	2	70
	7	$R^1 = R^2 = H$, $R^3 = NH_2$	2	76
	8	$R^1 = R^2 = R^3 = Me$	3	96 (80)
	9	$R^1 = CO_2H$, $R^2 = H$	1	85
	10	$R^1 = H$, $R^2 = CO_2H$	2	95
	11	$R^1 = OH$, $R^2 = CO_2H$	1	100
	12	$R^1 = CO_2H$, $R^2 = OH$	1	77 (65)
	13	$X = CH_2$, $n = 0$	2	88 (66)
	14	$X = CH_2$, $n = 1$	3	80
	15	$X = O$, $n = 1$	2	85
	16	$X = S$, $n = 1$	3	100 (77)
	17	$X = H$	0.5	86 (78)
	18	$X = OMe$	3	66
	19		2	75
	20		3	83
	21		0.5	100 (65)
	22	**1**	2	100
	23	**2**	1	84 (64)
	24	**3**	2	100
	25	**4**	1	77
	26	**5**	2	100

[a] Isolated yields. [b] Figures in parentheses are corresponding yields using 0.5 equiv of DMS.

with Me_2SO_4 (0.5−1 equiv) under reflux (0.5−3 h). The THF was distilled off, and the residue was diluted with saturated aqueous $NaHCO_3$ and extracted with Et_2O. In most of the cases, the reaction afforded a clean product requiring no further purification. Wherever necessary, purification was carried out via crystallization (for solid esters) in Et_2O−hexane or chromatography on neutral alumina (5% EtOAc−hexane as eluent). Excellent chemoselectivity has been observed (Table 1) for substrates bearing the phenolic hydroxyls[19] (entries 5, 11, 12, and 26) or the amine (entry 7) functionalities.[20] Similarly, the amide function (entries 22−26) does not experience any competitive *N*-[21] or *O*-[22] methylation.[23] BOC-protected amino acids **1**−**5** (Figure 1) (entries 22−26) are efficiently



1



2: $R^1 = BOC$, $R^2 = R^3 = H$
3: $R^1 = BOC$, $R^2 = R^3 = Me$
4: $R^1 = BOC$, $R^2 = CH_2Ph$, $R^3 = H$
5: $R^1 = BOC$, $R^2 = CH_2C_6H_4OH(p)$, $R^3 = H$

Figure 1.

Table 2. Effect of Base on the Protection of Benzoic Acid as Methyl Ester

entry	base	yield (%)[a,b]
1	$LiOH·H_2O$	96
2	LiOH	77
3	NaOH	30
4	KOH	64
5	CsOH	73
6	Li_2CO_3	25
7	Li_2CO_3 + 1 equiv H_2O	50
8	Li_2CO_3 + 2 equiv H_2O	88
9	Na_2CO_3	48
10	K_2CO_3	72
11	Cs_2CO_3	51
12	NaOH + 1 equiv LiBr	50

[a] Isolated yields. [b] Reactions were carried out in THF under reflux for 3 h.

protected as the methyl ester without affecting the BOC functionality or the optical purity of the molecules (wherever applicable).[24] Conventionally *N*-protected amino acids are esterified via a mixed anhydride[1a] or a urethane *N*-protected carboxyanhydride[25] process. Also, the reaction may be carried out at room temperature. For example, treatment of the amino acids **1** and **5** afforded the corresponding methyl esters in 75% and 80% yields, respectively. Limited examples (entries 1, 4, 8, 12, 13, 16, 17, 21, and 23) demonstrate that both of the methyl groups of Me_2SO_4 may be made available for esterification, thus representing examples of atom economy.[26]

The mild basicity of $LiOH·H_2O$ coupled with the covalent nature of the O−Li bond make chemoselective ester formation for substrates bearing a phenolic OH group feasible despite the poor nucleophilic property of a carboxylate anion. The important role of the Li^+ counterion was due to its coordinating capability to bring the incoming Me group close to the carboxylate anion in the proposed transition state (TS I) and is confirmed by the observed poor yields when using other alkali metal hydroxides and carbonates in place of $LiOH·H_2O$ (Table 2). This is further demonstrated by the increase in product yield with NaOH in the presence of LiBr (compare entries 3 and 12). The water molecule associated with the base appears to exhibit an effect,[27] since the use of Li_2CO_3 under similar conditions does not lead to

(19) Basak, A.; Nayak, M. K.; Chakraborti, A. K. *Tetrahedron Lett.* **1998**, *39*, 4883.

(20) The ^1H NMR spectrum of the crude product corresponding to entry 7 showed the formation of *N*-methylated (10%) and *N*-,*O*-dimethylated (5%) products. The ^1H NMR and GC−MS spectra of the crude products corresponding to entries 5, 11, 12, and 26 did not show any methylation of the phenolic hydroxyl group.

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(22) Julia, M.; Mestdach, H. *Tetrahedron* **1983**, *39*, 433.

(23) The methyl ester of the corresponding unprotected amino acids could not be made with this protocol as the amino acids are insoluble in THF.

(24) The methyl esters of optically pure acids **1**, **4**, and **5** were obtained in >98% ee as determined by the ^1H NMR spectra in the presence of $Eu(hfc)_2$.

(25) Chevallet, P.; Fehrentz, J.-A.; Kiec-Kononowicz, K.; Devin, C.; Castel, J.; Loffet, A.; Martinez, J. *Lett. Pept. Sci.* **1996**, *2*, 297.

(26) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 259.

(27) Shinkai, S.; Fukunaga, T.; Manabe, O.; Kunitake, T. *J. Org. Chem.* **1979**, *44*, 4990.

Scheme 2

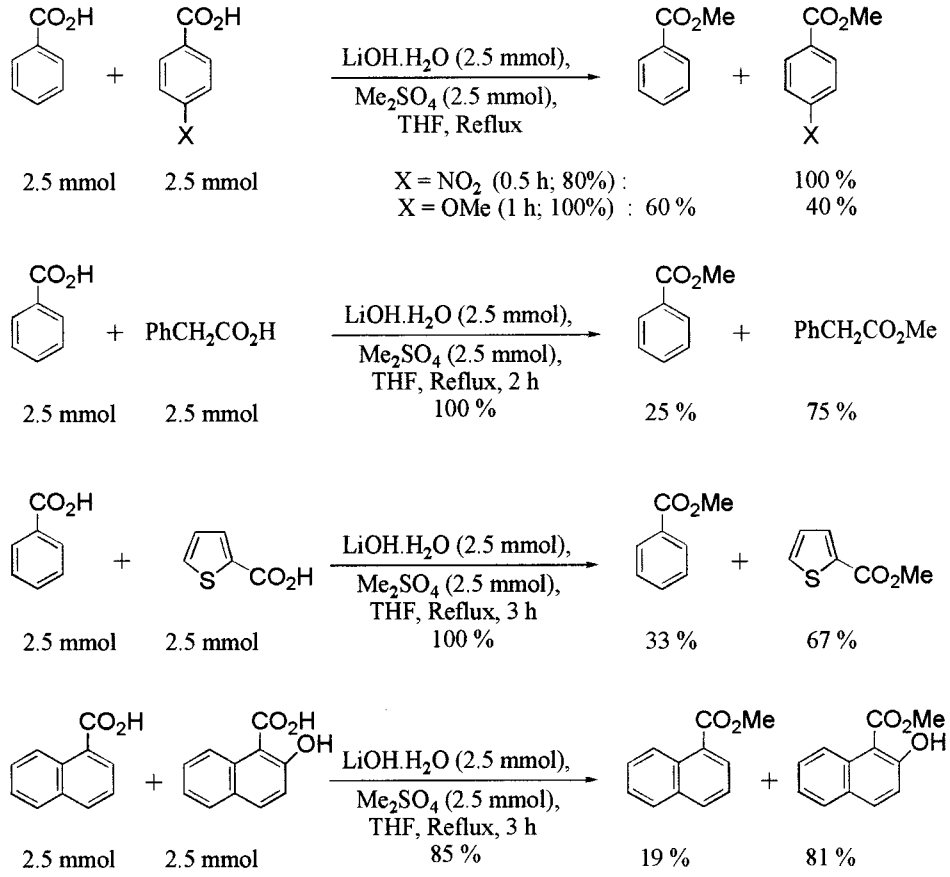

Table 3. Effect of Solvent on the Protection of Benzoic Acid as Methyl Ester

entry	solvent	yield (%)[a,b]
1	DMF	62
2	acetone	55
3	MeCN	71
4	DME	66
5	dioxane	56
6	THP	50
7	THF	96

[a] Isolated yields. [b] All reactions were carried out using $LiOH·H_2O$ under reflux for 3 h except for entry 1 wherein the reaction was performed at 80 °C.

significant ester formation. This "specific solvation" effect was confirmed by the fact that reactions carried out by addition of 2 equiv of water to the Li-carboxylates, generated from Li_2CO_3 and the carboxylic acid, afforded excellent yields (entry 8, Table 2). Use of other solvents such as DMF, acetone, MeCN, DME, THP and dioxane in place of THF was proved to be ineffective for the esterification (Table 3).

The selectivity of the method was further tested by using mixtures of carboxylic acids having different pK_a values[28a] (Scheme 2), and as expected, the stronger carboxylic acid was preferentially esterified. Thus, when an equimolar mixture of benzoic acid (pK_a 4.19) and 4-nitrobenzoic acid (pK_a 3.41) was subjected to esterification, the methyl ester formation of only the latter was observed, whereas a 3:2 selectivity was observed for the mixture of benzoic acid and 4-methoxybenzoic acid (pK_a 4.47). A 1:3 selectivity during the competition between benzoic acid and phenylacetic acid (pK_a 4.28) indicated that when the carboxylic acids have comparable acid strength the more nucleophilic carboxylate anion is preferentially alkylated. In analogous competitions between benzoic acid vs 2-thiophenecarboxylic acid (pK_a 3.53) and 1-naphthoic acid (pK_a 3.70) vs 2-hydroxy-1-naphthoic acid (pK_a 3.2),[28b] esterification occurred with selectivities of 1:2 and 1:4, respectively.

In conclusion, the present procedure provides an efficient method for the methyl ester protection of carboxylic acids. The notable advantages of this method are (a) the mild reaction conditions, (b) the use of cheaper and nontoxic reagent, (c) the general applicability, (d) the selectivity (tolerance of several sensitive functionalities during esterification), and (e) the high yields.

Experimental Section

General. The carboxylic acids are available commercially. THF was distilled prior to each use adopting the Na−benzophenone protocol under argon. Commercially available Me_2SO_4 was made acid-free following standard procedure.[5]

The NMR and IR spectra of the following esters were in complete agreement with those of the authentic samples: methyl benzoate, methyl 4-chlorobenzoate, methyl 2-chlorobenzoate, methyl 4-nitrobenzoate, methyl 4-hydroxybenzoate, methyl 4-methoxybenzoate, methyl 4-aminobenzoate, methyl 2-naphthoate, methyl phenylacetate, methyl phenoxyacetate, methyl *trans*-cinnamate, *N*-(*tert*-butoxycarbonyl)glycine methyl ester, *N*-(*tert*-butoxycarbonyl)-L-phenylalanine methyl ester, *N*(*tert*-butoxycarbonyl)-L-tyrosine methyl ester (Aldrich), methyl thiophene-2-carboxylate (Lancaster), and methyl 2,4,6-trimethylbenzoate.[29] Methyl 1-naphthoate, methyl 1-hydroxy-2-naphthoate, methyl 2-hydroxy-1-naphthoate, methyl dihydrocinnamate, methyl thiophenoxyacetate, methyl *trans*-4-methoxycinnamate, meth-

(28) (a) Weast, R. C. *Handbook of Chemistry and Physics*; CRC: Cleveland, 1987−88; 68th ed.; (b) Gladilovich, D. B.; Grigor'ev, N. N.; Stolyarov, K. P. *Chem. Abstr.* **1977**, *88*, 66457c.

yl 2-cyclopentene-1-acetate, methyl 1-adamantanecarboxylate, *N*-(*tert*-butoxycarbonyl)-L-proline methyl ester, and *N*-(*tert*-butoxycarbonyl)-α-methylalanine methyl ester were obtained from the corresponding carboxylic acids following standard procedure.[5] Physical data of these methyl esters are given below.

Physical Data. Methyl 1-naphthoate: IR (neat) 1716 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.92 (s, 3 H), 7.39−7.54 (m, 3 H), 7.8 (d, J = 7.78 Hz, 1 H), 7.93 (d, J = 8.22 Hz, 1 H), 8.10 (d, J = 7.28 Hz, 1 H), 8.82 (d, J = 8.43 Hz, 1 H); EIMS (*m*/*z*) 186 (M^+), 155 (100). **Methyl 1-hydroxy-2-naphthoate:** IR (KBr) 1660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.90 (s, 3 H), 7.18 (d, J = 8.96 Hz, 1 H), 7.40−7.53 (m, 2 H), 7.66 (d, J = 8.67 Hz, 2 H), 8.32 (d, J = 8.26 Hz, 1 H), 11.90 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 161.63, 137.90, 130.08, 128.14, 126.45, 125.47, 124.92, 124.58, 119.29, 52.98; EIMS (*m*/*z*) 202 (M^+), 170 (100). **Methyl 2-hydroxy-1-naphthoate:** IR (KBr) 1649 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.04 (s, 3 H), 7.09 (d, J = 9.02 Hz, 1 H), 7.31 (t, J = 7.9 Hz, 1 H), 7.47 (t, J = 8.81 Hz, 1 H), 7.68 (d, J = 7.97 Hz, 1 H), 7.83 (d, J = 9.02 Hz, 1 H), 8.66 (d, J = 8.81 Hz, 1 H), 12.19 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 172.85, 164.38, 136.91, 129.10, 128.47, 125.29, 123.66, 119.29, 52.43; EIMS (*m*/*z*) 202 (M^+), 170 (100). **Methyl dihydrocinnamate:** IR (neat) 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.55 (t, J = 7.56 Hz, 2 H), 2.87 (t, J = 7.56 Hz, 2 H), 3.58 (s, 3 H), 7.10−7.23 (m, 5 H). **Methyl thiophenoxyacetate:** IR (neat) 1729 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.63 (s, 2 H), 3.68 (s, 3 H), 7.24−7.43 (m, 5 H). **Methyl *trans*-4-methoxycinnamate:** IR (neat) 1716 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.72 (s, 3 H), 3.76 (s, 3 H), 6.23 (d, J = 15.94 Hz, 1 H), 6.83 (d, J = 6.8 Hz, 2 H), 7.40 (d, J = 6.8 Hz, 2 H), 7.57 (d, J = 15.94 Hz, 1 H). **Methyl 2-cyclopentene-1-acetate:** IR (neat) 1694 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.34−1.44 (m, 2 H), 2.00−2.08 (m, 2H), 2.18−2.35 (m, 5 H), 3.60 (s, 3 H), 5.59 (m, 1 H), 5.69 (m, 1 H). **Methyl 1-adamantanecarboxylate:** IR (neat) 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.64 (brs, 6 H), 1.81−1.85 (m, 6 H), 1.94 (brs, 3 H), 3.57 (s, 3 H). ***N*-(*tert*-Butoxycarbonyl)-L-proline methyl ester:** IR (neat) 1743, 1689 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.34 (s, 9 H), 1.82−1.92 (m, 3 H), 2.10−2.15 (m, 1 H), 3.38−3.49 (m, 2 H), 3.65 (s, 3 H), 4.17−4.21 (m, 1 H). ***N*-(*tert*-Butoxycarbonyl)-α-methylalanine methyl ester:** IR (neat) 1740, 1715 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.36 (s, 3 H), 1.42 (s, 6 H), 3.66 (s, 3 H).

General Procedure for Esterification. Representative Procedure. 2-Hydroxy-1-naphthoic acid (470.5 mg, 2.5 mmol) in dry THF (2.5 mL) was treated with $LiOH \cdot H_2O$ (104.9 mg, 2.5 mmol) at room temperature for 30 min followed by Me_2SO_4 (0.12 mL, 1.25 mmol), and the mixture was heated under reflux for 3 h. Solvent was distilled off, and the mixture was diluted with saturated aqueous $NaHCO_3$ and extracted with Et_2O to afford the ester (white solid, 404.3 mg, 80%), which was in full agreement with spectral data (IR, ^1H and ^{13}C NMR, and CIMS) of an authentic sample. The yield could be improved to 96% by using 2.5 mmol of Me_2SO_4. This procedure was followed for esterification of all of the substrates included in Table 1. All products are known compounds and are easily identified by their spectral data.

Selective Esterification in Intermolecular Competition. 1-Naphthoic acid (430.45 mg, 2.5 mmol) and 2-hydroxy-1-naphthoic acid (470.5 mg, 2.5 mmol) in dry THF (5 mL) were treated with $LiOH \cdot H_2O$ (104.9 mg, 2.5 mmol) at room temperature for 30 min followed by Me_2SO_4 (0.24 mL, 2.5 mmol), and the mixture was heated under reflux for 3 h. Solvent was distilled off, and the mixture was diluted with saturated aqueous $NaHCO_3$ and extracted with Et_2O to afford the ester (425 mg, 85% with respect to 2-hydroxy-1-naphthoic acid). The ^1H NMR spectrum revealed two OMe singlets at δ 3.92 and 4.11 in a ratio of 19:81, corresponding to methyl 1-naphthoate and methyl 2-hydroxy-1-naphthoate. Other competitive experiments (Scheme 2) were performed in a similar way, and in each case the selectivity was determined through relative proton integration of the ester OMe signals in the ^1H NMR.

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