reaction times and their composition was determined.

The samples of benzene and benzyl methyl ether were directly analyzed by GC using a 13-ft column of 6% OV-17 on 80/100-mesh Chromosorb W-AW and a 6-ft column of 10% Carbowax 20M on 80/100-mesh Chromosorb W-HP, respectively. The samples obtained from 1-hexyne were analyzed similarly with a 20-ft 20% β,β'-oxybis(propionitrile) on 80/100-mesh Chromosorb W-AW-DMCS. The mass balance was determined by calibration with GC standards: toluene for reduction mixtures of benzene; cyclopentanone for reduction mixtures of benzyl methyl ether 7; and cyclohexane for reduction mixtures of hexyne. It was found to be only 70%. However, no byproducts were detected and the disappearance of substrates and formation of products were proportional to the amount of charge transferred throughout each electrolysis. This indicates that both substrate and product are lost from the catholyte either by evaporation with the nitrogen stream or by migration to the anolyte. No attempt was made to improve the mass balance since the above reactions were examples to prove a principle. The material balances for the reduction of the substrates with higher molecular weight were quantitative. To verify the nature of the products, they were isolated and compared with authentic samples (GC, NMR, IR).

The samples and reaction mixtures of all steroid substrates were worked up by pouring into water and then repeated extractions with ether. The organic fraction was washed with water and dried, and the solvent was removed. The residue was weighed and analyzed to determine composition and yield. The mass balance for these substrates was >90% and the composition of the mixtures was determined by NMR.

A detailed description of the analysis of the resaction mixtures of 1-4 has been reported.[5] The reaction mixtures from 5 were analyzed similarly. In this case the disappearance of the carbonyl function was also qualitatively followed by IR.

The final product of the reduction of 10 was 12; which was identified by comparing its NMR spectrum with the one reported in the literature.[8] Analysis of the reaction mixtures at different reaction times seemed to indicate that the ethynyl function reacts faster than the aromatic ring. After transfer of charge equivalent to 2 F mol^{-1}, 47% of the ethynyls and 16% of the aromatic rings were reduced but 37% of the reactant were still present in the mixture. However, since we were not able to develop selective reduction of the ethynyl or the methoxy benzene functions of 10 only, we did not attempt resolution of the mixtures.

Electrochemical Measurements. Polarography and cyclic voltammetry were performed by using a Princeton Applied Research PAR-173 potentiostat, PAR-175 universal programmer, and a Houston Omnigraphic 2000 x-y recorder. CV's at fast potential scan rates were recorded on a Tektronix 5111 storage oscilloscope. Polarography was performed on a polarographic capillary from which the drops were knocked off every 0.2 s. A hanging mercury drop electrode was prepared[13] and used for cyclic voltammetry. The counterelectrode was a Pt wire and the reference was a SCE.

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Registry No. 1, 100-66-3; 2, 1730-48-9; 3, 1035-77-4; 4, 17550-03-7; 5, 1624-62-0; 6, 1091-93-6; 7, 538-86-3; 8, 108-88-3; 9, 4313-57-9; 10, 72-33-3; 11, 6885-48-9; 12, 4350-64-5; benzene, 71-43-2; 1,4-dihydrobenzene, 628-41-1; 1-hexyne, 693-02-7; 1-hexene, 592-41-6; hexane, 110-54-3.

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A Simple and Mild Esterification Method for Carboxylic Acids Using Mixed Carboxylic-Carbonic Anhydrides

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A simple and mild esterification method using mixed carboxylic-carbonic anhydrides has been developed. Simple aliphatic carboxylic esters are prepared in high yields by the reaction of acids with equimolar amounts of chloroformates (2,2,2-trichloroethyl chloroformate is an exception) and triethylamine in the presence of a catalytic amount of 4-(dimethylamino)pyridine. Although aromatic acids give a mixture of the ester, the acid anhydride, and the carbonate under normal conditions utilized in this study, it is found that increasing the amount of 4-(dimethylamino)pyridine drastically decreases the formation of the acid anhydride and the carbonate, affording a satisfactory yield of the ester. This method reaches a limit with sterically hindered acids and the formation of the acid anhydride and the carbonate is favored.

The mixed carboxylic-carbonic anhydrides, reasonably stable and readily available compounds, have been of considerable interest for a long time. Their synthetic usefulness has been demonstrated in peptide synthesis[1] and in the reduction of carboxylic acids into the corresponding alcohols.[2]

The preparation of carboxylic esters by the decomposition of mixed carboxylic-carbonic anhydrides has been extensively studied by Tarbell[3] but the outcome of the mixed anhydride reaction was disappointing as a means for the preparation of esters in several instances.[4] In general, the decomposition of mixed carboxylic-carbonic anhydrides proceeds by two different pathways, yielding two types of products: the ester and the symmetrical acid anhydride and the carbonate (eq 1), although the course

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of the reaction depends on the structure of substituents such as R and R′ to some extent. For instance, it has been reported that several aryl chloroformates can be used to esterify carboxylic acids via the intermediacy of the mixed anhydrides (eq 2).[5] Furthermore, it is known that tertiary amines like triethylamine do not alter the course of the decomposition of the mixed anhydrides, although the addition of tertiary amines lowers the temperature of decomposition.[3] Contrary to the stability of the mixed carboxylic–carbonic anhydrides toward tertiary amines, facile decomposition of the mixed anhydrides of α-keto acids in the presence of a catalytic amount of triethylamine into the corresponding α-keto esters has been recently reported (eq 3).[6]

$$\mathrm{RCOOH + ClCOOR' \xrightarrow{Et_3N} RCOOCOOR' \begin{cases} \rightarrow \mathrm{RCOOR' + CO_2} \\ \rightarrow \mathrm{(RCO)_2O + (R'O)_2CO + CO_2} \end{cases}} \quad (1)$$

$$\mathrm{RCOOH + ClCOOAr \xrightarrow{pyridine} [RCOOCOOAr] \rightarrow RCOOAr + CO_2} \quad (2)$$

$$\mathrm{RCOCOOH + ClCOOR' \xrightarrow{Et_3N} [RCOCOOCOOR'] \rightarrow RCOCOOR' + CO_2} \quad (3)$$

$$\mathrm{RCOOH + ClCOOR' + Et_3N \xrightarrow[DMAP]{cat.} RCOOR' + CO_2} \quad (4)$$

Recently, we have communicated a new direct esterification method by the reaction of the mixed carboxylic–carbonic anhydrides, generated from equimolar amounts of carboxylic acids, alkyl chloroformates, and triethylamine, with a catalytic amount of 4-(dimethylamino)-pyridine (eq 4).[7] This paper describes a full detail of the scope, limitations, and mechanistic insight of this new esterification method.

Results and Discussion

In the course of examining the synthetic utility of 2-pyridyl esters,[8] we have found that the addition of a catalytic amount of 4-(dimethylamino)pyridine (DMAP)[9,10] is exceedingly effective in the conversion of the mixed anhydrides, generated from equimolar amounts of acids, 2-pyridyl chloroformate,[11] and triethylamine, into the corresponding 2-pyridyl esters in high yields.[8a] The reaction proceeded rapidly and smoothly in methylene chloride at room temperature. This finding led us to examine the possibility of converting the mixed anhydrides into the corresponding esters with alkyl chloroformates[12] in the presence of DMAP.

First, the reaction was examined with pure isolated carboxylic–carbonic anhydrides. When caprylic–ethyl carbonate anhydride was treated with 0.1 equiv of DMAP in methylene chloride at room temperature for 15 min, ethyl caprylate was obtained in 91% yield after distillation. The presence of caprylic anhydride in the reaction mixture was not detected by NMR and IR. For simplicity and convenience, the reaction was generally performed by the addition of a catalytic amount of DMAP to the solution of an equimolar mixture of an acid, alkyl chloroformate, and triethylamine in methylene chloride at 0 °C without isolation of the mixed anhydrides.

The preparation of carboxylic esters has been performed on a variety of structurally different acids and alkyl chloroformates 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 method. Simple primary aliphatic carboxylic acids such as caprylic acid and phenylacetic acid, upon treatment with equimolar amounts of various alkyl chloroformates and triethylamine in the presence of 0.1–0.3 equiv of DMAP, yielded the corresponding esters in essentially quantitative yields without contamination by the acid anhydrides and the carbonates. Likewise, secondary aliphatic acids such as isobutyric acid and cyclohexanecarboxylic acid were rapidly and cleanly converted into the corresponding esters.

The esterification of aromatic carboxylic acids was found to be critically dependent on the nature of chloroformates. Reaction of benzoic acid with *p*-nitrophenyl chloroformate gave *p*-nitrophenyl benzoate in 88% yield. This result is in a good agreement with previously reported results.[5,8a] However, the use of alkyl chloroformates led to the formation of the acid anhydride and the carbonate as by-products. Thus, reaction of benzoic acid with equimolar amounts of ethyl chloroformate and triethylamine in the presence of 0.1 equiv of DMAP yielded a 56:33 mixture of ethyl benzoate and benzoic anhydride. Fortunately, we have found that increasing the amount of DMAP drastically decreases the formation of the acid anhydride and the carbonate. Thus, applications of 0.2 and 0.5 equiv of DMAP to an equimolar mixture of benzoic acid, ethyl chloroformate, and triethylamine yielded 82% and 91% of ethyl benzoate along with 10% and <1% of benzoic anhydride, respectively. Similar results were realized with *p*-chlorobenzoic acid.

Furthermore, this method reaches a limit with sterically hindered acids such as pivalic acid and mesitoic acid. Pivalic acid, upon treatment with equimolar amounts of benzyl chloroformate and triethylamine in the presence of 0.1 equiv of DMAP, yielded approximately a 1:1:1 mixture of benzyl pivalate, pivalic anhydride, and dibenzyl carbonate. Application of 0.5 equiv of DMAP did not alter the course of the reaction and the product ratio remained unchanged. In the case of the highly hindered mesitoic acid, exclusive formation of mesitoic anhydride was observed without the formation of a trace amount of the ester.[13]

The esterification of carboxylic acids having other functional groups such as cyano, amide, THP ether, and hydroxy group was also examined in order to determine the synthetic effectiveness of this method. For example, cyanoacetic acid, hippuric acid, and 6-[(tetrahydropyranyl)oxy]hexanoic acid were cleanly esterified in high yields without affecting their functional groups. However, in the esterification of hydroxy acids with ethyl chloroformate, a mixture of the ethyl ester and the lactone was obtained in a variable ratio, depending upon the nature of hydroxy acids.

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Table I. Esterification of Carboxylic Acids

$$RCOOH + ClCOOR' + Et_3N \xrightarrow[CH_2Cl_2,\ 0\ °C]{\text{cat. DMAP}} RCOOR'$$

R	R′	molar equiv of DMAP	time, h	yield, %[a] RCOOR′	bp, °C (mmHg)[d] [mp, °C]	lit.
$CH_3(CH_2)_6$	CH_3	0.1	0.25	98	36–38 (0.9)	193 (760)[e]
	CH_2CH_3	0.1	0.5	95	66–70 (3.0)	208.5 (790)[e]
	$CH_2C_6H_5$	0.1	0.5	97	125–130 (1.5)	148 (3)[f]
	$CH(CH_3)_2$	0.3	0.25	96	52–55 (1.0)	93.8 (10)[e]
	$CH[CH(CH_3)_2]_2$	0.3	1	96	96–100 (3.5)[g]	
	p-$NO_2C_6H_4$	0.1	0.25	97	140–142 (1.0)	174–175 (6)[h]
$C_6H_5CH_2$	CH_3	0.1	1	94	60–63 (1.1)	218 (760)[e]
	$CH_2C_6H_5$	0.1	1	94	137–140 (1.5)	155–157 (4)[i]
$(CH_3)_2CH$	CH_2CH_3	0.1	0.25	92	110 (760)	111 (760)[e]
	$CH_2C_6H_5$	0.1	0.25	89	76–80 (2.5)[j]	
	$CH[CH(CH_3)_2]_2$	0.3	1	93	50–55 (3.0)[k]	
	p-$NO_2C_6H_4$	0.1	0.5	94	[36–37]	[36.5–37)[h]
c-C_6H_{11}	CH_2CH_3	0.1	1	92	38–41 (1.0)	196 (760)[e]
	$CH_2C_6H_5$	0.2	1	92	132–136 (3.0)	134–136 (3)[l]
	$CH(CH_3)_2$	0.3	0.25	96	60–64 (5.0)	72–73 (8)[m]
$(C_6H_5)_2CH$	CH_3	0.1	0.5	98	[59–60]	[60][e]
	CH_2CH_3	0.1	0.25	93	[57–59]	[59][e]
	$CH_2C_6H_5$	0.1	0.25	95	193–198 (1.0)	203–205 (1)[n]
	$CH(CH_3)_2$	0.1	0.25	95	[40–41]	[43–43.5][o]
C_6H_5	CH_2CH_3	0.1	3	56 (33)	52–55 (1.1)	213 (760)[e]
	CH_2CH_3	0.2	3	82 (10)		
	CH_2CH_3	0.5	0.5	91 (<1)		
	p-$NO_2C_6H_4$	0.1	0.5	88	[142–144]	[146][p]
p-ClC_6H_4	CH_2CH_3	0.1	2	76 (12)	71–75 (5.0)	218 (760)[e]
	CH_2CH_3	0.2	1	85 (7)		
	CH_2CH_3	0.5	0.5	89 (<1)		
	p-$NO_2C_6H_4$	0.1	0.5	85	[137–138]	[138][c]
$(CH_3)_3C$	$CH_2C_6H_5$	0.1	1	47 (52)[b]	67–70 (2.0)	60.5 (1)[r]
	$CH_2C_6H_5$	0.5	1	48 (52)[b]		
2,4,6-$(CH_3)_3C_6H_2$	CH_2CH_3	0.2	3	0 (98)	[101–103][s]	[103–104][t]
	CH_2CH_3	1	0.5	0 (95)		
	$CH_2C_6H_5$	0.1	4	0 (81)		
$CNCH_2$	$CH_2C_6H_5$	0.1	0.25	96	135–140 (1.0)	95 (0.02)[u]
$CH_3CH(Br)$	$CH_2C_6H_5$	0.1	0.25	88	97–101 (1.0)	139–141 (7)[v]
$CH_3CH_2CH(Br)$	CH_2CH_3	0.1	0.25	90	51–54 (8.0)	43.4 (5.5)[e]
t-$C_6H_5CH{=}CH$	CH_2CH_3	0.2	0.5	90	90–94 (1.0)	144 (15)[e]
$C_6H_5CO(CH_2)_2$	CH_2CH_3	0.1	0.25	94	130–134 (1.5)	127–128 (1)[w]
$C_6H_5CONHCH_2$	CH_2CH_3	0.1	0.5	72	[61–63]	[63–65][x]
THP-$O(CH_2)_5$	CH_2CH_3	0.1	0.25	95	107–110 (290)[y]	
$HO(CH_2)_5$	CH_2CH_3	0.1	0.25	27 (73)[c]		
$HO(CH_2)_{10}$	CH_2CH_3	0.1	0.25	67 (21)[c]		

[a] Isolated yields. The numbers in parentheses indicate isolated yields of the acid anhydrides. [b] The yield was determined by NMR analysis and dibenzyl carbonate was isolated in 45% yield. [c] The yields were determined by GLC analysis. [d] Reported boiling points are those observed during distillation with Kugelrohr apparatus and are uncorrected. [e] "Handbook of Chemistry and Physics", 60th ed.; CRC Press: Boca Raton, F. [f] Zeinalov, B. K.; Magerramova, A. K. *Chem. Abstr.* **1963**, *59*, 8647h. [g] NMR ($CDCl_3$) δ 0.96 (d, 6 H, J = 7), 0.98 (d, 6 H, J = 7), 0.75–2.08 (m, 17 H), 2.36 (t, 2 H, J = 7), 4.60 (dd, 1 H, J = 7); IR (film) 1735 cm^{-1}. [h] Kreisky, S. *Acta Chem. Scan.* **1957**, *11*, 913. [i] Fujii, T.; Tashiro, M.; Ohara, K.; Kumai, M. *Chem. Pharm. Bull.* **1960**, *8*, 266. [j] NMR ($CDCl_3$) δ 1.18 (d, 6 H, J = 7), 2.58 (m, 1 H), 5.12 (s, 2 H), 7.30 (s, 5 H); IR (film) 1735 cm^{-1}. Inamata, K.; Kinoshita, H.; Fukuda, H.; Tanabe, K.; Kotake, H. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 1866. [k] NMR ($CDCl_3$) δ 0.90 (d, 6 H, J = 7), 0.92 (d, 6 H, J = 7), 1.18 (d, 6 H, J = 7e, 1.82 (m, 2 H), 2.51 (m,1 H), 4.57 (dd, 1 H, J = 7); IR (film) 1735 cm^{-1}. [l] Ismailov, A. G.; Salimova, B. A. *Chem. Abstr.* **1969**, *71*, 12628q. [m] Eidus, Y. T.; Ordyan, M. B.; Shokina, L. I.; Kanevskaya, M. A. *Chem. Abstr.* **1966**, *65*, 3761g. [n] Mukaiyama, T.; Nambu, H.; Okamoto, M. *J. Org. Chem.* **1962**, *27*, 3651. [o] Mean, E. M.; Escobar, M. T. H. *Chem. Abstr.* **1955**, *49*, 6889d. [p] Zahn, H.; Schade, F. *Chem. Ber.* **1963**, *96*, 1747. [q] Matsukawa, T.; Ban, S.; Imada, T. *Chem. Abstr.* **1952**, *46*, 454e. [r] Applequist, D. E.; Kaplan, L. *J. Am. Chem. Soc.* **1965**, *87*, 2194. [s] Melting point of mesitoic anhydride. [t] Burton, H.; Praill, P. F. G. *J. Chem. Soc.* **1955**, 729. [u] Dahn, H.; Hauth, H. *Helv. Chim. Acta* **1959**, *42*, 1214. [v] Stork, G.; Clarke, F. H. *J. Am. Chem. Soc.* **1961**, *83*, 3114. [w] Reppe, W. *Chem. Abstr.* **1956**, *50*, 16788h. [x] Martin, D.; Weise, A.; Nadolski, K. *Chem. Ber.* **1965**, *98*, 3286. [y] Overman, L. E.; Jessup, P. J. *J. Am. Chem. Soc.* **1978**, *100*, 5179.

It is of interest to note that the behavior of 2,2,2-trichloroethyl chloroformate is somewhat different from that of alkyl chloroformates utilized in this study. Addition of 0.1 equiv of DMAP to an equimolar mixture of caprylic acid, 2,2,2-trichloroethyl chloroformate, and triethylamine (method A) resulted in the formation of 2,2,2-trichloroethyl caprylate, caprylic anhydride, and bis(2,2,2-trichloroethyl) carbonate in approximately equal proportions, whereas the reaction in the absence of DMAP gave similar results, suggesting that the mixed anhydride may decompose rapidly before it is attacked by DMAP. Facile decomposition of mixed anhydrides, derived from 2,2,2-trichloroethyl chloroformate, into the corresponding esters in satisfactory yields was reported in the chemistry of cephalosporin antibiotics.[14] Thus, reaction of several carboxylic acids with 2,2,2-trichloroethyl chloroformate was studied in detail and the results are summarized in Table II. Since bis(2,2,2-trichloroethyl) carbonate exhibited a sharp singlet at 4.82 ppm in the NMR spectrum,[15] while 2,2,2-trichloroethyl esters of caprylic, diphenylacetic, and benzoic acid exhibited sharp singlets at 4.72, 4.74, and 5.02 ppm, respectively, the product ratios were determined by NMR

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Table II. Reaction of RCOOH with $ClCOOCH_2CCl_3$ and Et_3N in the Presence of DMAP in CH_2Cl_2

R	method[a]	molar equiv of DMAP	reactn condn		product ratio[b]	
			temp, °C,	time, h	ester	carbonate
$CH_3(CH_2)_6$		0	0–25	1	50	50
	A	0.1	0	0.3	50	50
	A	0.1	−78	0.5	90 (76)[c]	10
	B	0.1	0	0.2	85	15
	B	0.5	0	0.1	87	13
	B	0.1	−78	0.5	75	25
	B	1.0	−78	0.2	90	10
C_6H_5		0	0–25	16	42	58
	A	0.1	−78	0.7	5	95
	A	0.5	−78	0.3	20	80
	B	0.5	−78	0.3	30	70
	B	1.0	−78	0.2	35	65
	B	0.1	25	0.1	55	45
	B	0.5	25	0.1	65	35
$(C_6H_5)_2CH$		0	25	0.2	80	20
	A	0.1	−78	0.2	99 (95)[c]	<1
	B	0.1	0	0.2	99 (90)[c]	<1

[a] A: Addition of DMAP into a equimolar mixture of an acid, 2,2,2-trichloroethyl chloroformate, and triethylamine. B: Addition of 2,2,2-trichloroethyl chloroformate into a reaction mixture of an acid, triethylamine, and DMAP. [b] The product ratios were determined by NMR analysis. [c] The numbers in parentheses indicate the isolated yields of the corresponding 2,2,2-trichloroethyl esters.

Table III. Preparation of Esters of N-Protected L-α-Amino Acids[a]

α-amino acid ester product	% yield of ester	obsd		lit.	
		mp, °C	$[\alpha]_D$ (c, solvent, t °C)	mp, °C	$[\alpha]_D$ (c, solvent, t °C)[b]
Z-Ala-OCH_3	96	oil	−33.0 (2, MeOH, 16)	45–46	−33.9 (2, MeOH, amt)[d]
Boc-Val-OCH_3	95	oil	−23.2 (2, MeOH, 15)	oil	−22.7 (2, MeOH, amt)[d]
Z-Val-OCH_2CH_3	94	oil	−18.5 (1, MeOH, 15)	oil	−19.6 (1, MeOH, 20)[e]
Z-Phe-OCH_2CH_3	98	oil	−10.7 (1.4, EtOH, 15)	oil	−10.1 (1.4, EtOH, 20)[f]
Boc-Phe-OBzl	93	63–65	−11.8 (2, MeOH, 15)	64–65	−12.8 (2, MeOH, amt)[d]
Boc-Val-OBzl	91	oil	−29.7 (1, MeOH, 15)	oil	−33.3 (2, MeOH, amt)[d]
Z-Leu-$OC_6H_4NO_2$-*p*	98	93–94	−32.6 (2, DMF, 20)	95	−33.5 (2, DMF, 20)[g]
Z-Pro-$OC_6H_4NO_2$-*p*	91	94–95	−67.2 (2, DMF, 20)	94–96	−68.0 (2, DMF, 20)[g]
Boc-Asp(OBzl)-OCH_3	88	67–68	−7.1 (1, acetone, 15)		−7.6 (1, acetone, amt)[d]
Z-Glu(OBzl)-OCH_2CH_3	96	oil	−17.7 (1, MeOH, 18)[c]		−21.4 (1, MeOH, amt)[c,d]

[a] All reactions were carried out with an equimolar mixture of amino acids, alkyl chloroformates, and triethylamine using 0.1 equiv of DMAP in methylene chloride at 0 °C for 30 min. [b] amt = ambient temperature. [c] Specific rotation of Z-Glu-OCH_2CH_3 prepared from ester product. [d] Dhaon, M. K.; Olsen, R. K.; Ramasamy, K. *J. Org. Chem.* **1982**, *47*, 1962. [e] Yamada, T.; Isono, N.; Inui, A.; Miyazawa, T.; Kuwata, S.; Watanabe, H. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 1897. [f] Ito, A.; Takahashi, R.; Baba, Y. *Chem. Pharm. Bull.* **1975**, *23*, 3081. [g] Bodanszky, M.; Vigneaud, V. D. *J. Am. Chem. Soc.* **1959**, *81*, 5688.

analysis. First, when the reaction was carried out at −78 °C in order to prevent the possibility of the thermal decomposition of the mixed anhydride, ester formation was favored, yielding a 90:10 mixture of the ester and the carbonate. Next, we tried to modify the sequence of adding DMAP. Addition of 2,2,2-trichloroethyl chloroformate to a solution of caprylic acid and triethylamine containing 0.1 equiv of DMAP (method B) resulted in a 80:20 mixture of the ester and the carbonate. Although ester formation was greatly favored under the present conditions, the amount of DMAP employed and reaction temperatures did not significantly alter the course of the reaction and product ratios. In the case of benzoic acid, the results obtained here are more complicated than the results with caprylic acid. In general, carbonate formation was more favored when the reaction was carried out in the presence of DMAP at −78 °C than in the absence of DMAP at room temperature. The presence of a catalytic amount of DMAP drastically promoted the decomposition of the mixed anhydride but increasing the amount of DMAP did not significantly alter course of the reaction, though the product ratios were dependent on reaction temperature, the amount of DMAP employed, and the sequence of adding DMAP to some extent. However, diphenylacetic acid was cleanly esterified in the presence of 0.1 equiv of DMAP at −78 and 0 °C, whereas the reaction in the absence of DMAP at room temperature afforded a 80:20 mixture of the ester and the carbonate, indicating that the success of ester formation is dependent on the nature of carboxylic acids to some extent.[14]

Since the carboxylic group of α-amino acids is generally protected as an alkyl ester during peptide synthesis, a great need still exists for a useful and facile method to prepare esters of N-protected α-amino acids without loss of optical activity, although there are several methods currently available.[16] Thus, the present method has been applied for esterification of N-protected α-amino acids.

Esterification was carried out by addition of 0.1 equiv of DMAP to an equimolar mixture of *N*-Boc amino acids or *N*-Z amino acids, alkyl chloroformate, and triethylamine in methylene chloride at 0 °C. The reaction proceeded smoothly and was complete within 30 min. Furthermore, the reaction proceeded without observable racemization in most amino acids as seen by comparison with reported specific rotations in Table III, though aspartic and glutamic acid may be racemized to some extent.

Although the reaction mechanism has not been fully elucidated, the possible mechanisms are shown in Scheme I. The esterification proceeds apparently via the intermediacy of the mixed carboxylic–carbonic anhydride. The mixed anhydride may be converted into an acylpyridinium

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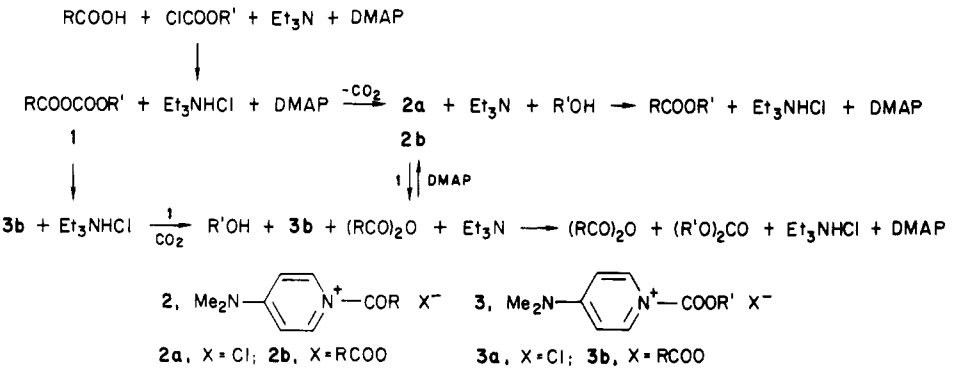
Scheme I



species (**2a**) by nucleophilic attack of DMAP on the carboxyl carbonyl center of the mixed anhydride as a major pathway along with an (alkoxycarbonyl)pyridinium species (**3a**) by nucleophilic attack of DMAP on the carbonate center as a minor pathway in most carboxylic acids. The carbon dioxide evolution would provide a driving force for the major pathway. Nucleophilic attack by the alcohol on the acyl group of **2a** gives the ester and DMAP, which is reused in the formation of **2a**. Also, the acid anhydride, which can be formed via nucleophilic attack by carboxylate anion of **3b** on the carboxyl carbonyl center of the mixed anhydride, can be converted into **2b** by DMAP to raise the yield of the ester, while the reaction of **3a** with the alcohol affords the carbonate. The formation of the acid anhydride from the mixed anhydride and carboxylate anion was demonstrated by the isolation of caprylic anhydride in 90% yield by the reaction of caprylic–ethyl carbonate anhydride with equimolar amounts of caprylic acid and triethylamine in methylene chloride at 0 °C for 45 min.[17]

In the cases of aromatic acids, it is assumed that increasing the amount of DMAP increases the reaction rate of conversion of the acid anhydride into **2b** and would, therefore, prevent the formation of the carbonate by consuming the alcohol due to fast reaction of **2b** with the alcohol.

However, in the case of pivalic acid, a mixture of approximately equal amounts of the ester, the acid anhydride, and the carbonate was obtained even with 0.5 equiv of DMAP, indicating that nucleophilic attack by DMAP on the two reactive carbonyl centers of the mixed anhydride occurs with roughly a 1:1 ratio and pivalic anhydride is inert toward DMAP. In the case of mesitoic acid, the reaction proceeds exclusively via the intermediacy of **3b** due to the steric hindrance on the carboxyl carbonyl center of the mixed anhydride. Contrary to facile formation of an acylpyridinium species with most acid anhydrides and DMAP in nonpolar solvents such as carbon tetrachloride and methylene chloride, it is noteworthy that reaction of hindered acid anhydrides such as pivalic anhydride and mesitoic anhydride with benzyl alcohol in the presence of 1 equiv of DMAP in methylene chloride at room temperature for 6 h did not occur and the starting materials were recovered unchanged.

The generality of this method is demonstrated by the considerable variation possible in both carboxylic acids and alkyl chloroformates. With the exception of sterically hindered acids and 2,2,2-trichloroethyl chloroformate, most acids can be esterified with chloroformates as the alcohol component. Furthermore, the use of stoichiometric amounts of two main reactants, the extremely mild conditions utilized, the ready availability of chloroformates, easy manipulation, and simple workup should make this procedure the method of choice in the esterification of complex and sensitive molecules.

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Experimental Section

NMR spectra were recorded with a Varian T-60A spectrometer, and chemical shifts are expressed as δ units relative to tetramethylsilane. Infrared spectra were recorded on a Perkin-Elmer 267 and frequencies are given in reciprocal centimeters. GLC analysis was performed on a Varian 2800 gas chromatograph with an FID detector. Optical rotations were recorded on an Autopol III automatic polarimeter. Melting points were determined on an Electrothermal melting point apparatus and are uncorrected. Reported boiling points are those observed during distillation with a Kugelrohr apparatus and are uncorrected.

Since the reactions performed are all similar in many respects, typical reactions will be described as specific examples.

Preparation of Ethyl Caprylate. To a solution of caprylic acid (435 mg, 3.0 mmol) and triethylamine (330 mg, 3.3 mmol) in methylene chloride (10 ml) at 0 °C was added ethyl chloroformate (326 mg, 3.0 mmol). After 5 min of stirring at 0 °C, DMAP (36 mg, 0.3 mmol) was added into the reaction mixture at 0 °C. The resulting solution was stirred at 0 °C for 0.5 h, diluted with methylene chloride (20 mL), and washed with saturated $NaHCO_3$ (20 mL), 0.1 M HCl (10 mL), and saturated NaCl (20 mL). The aqueous layers were extracted with methylene chloride (20 mL) and the combined extracts were dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. The residue was distilled in vacuo to afford ethyl caprylate (495 mg) in 95% yield: NMR ($CDCl_3$) δ 0.72–2.00 (m, 16 H), 2.35 (t, H, J = 7), 4.32 (q, 2 H, J = 7); IR (film) 1735 cm^{-1}.

Preparation of 2,2,2-Trichloroethyl Caprylate. Method A. To a solution of caprylic acid (287 mg, 2.0 mmol) and triethylamine (220 mg, 2.2 mmol) in methylene chloride (6 mL) at −78 °C was added 2,2,2-trichloroethyl chloroformate (425 mg, 2.0 mmol). After 10 min of stirring at −78 °C, DMAP (25 mg, 0.2 mmol) was added into the reaction mixture. The resulting solution was stirred at −78 °C for 0.5 h, diluted with methylene chloride (30 mL), and washed with saturated $NaHCO_3$ (20 mL), 0.1 M HCl (10 mL), and saturated NaCl (30 mL). The aqueous layers were extracted with methylene chloride (30 mL). The combined extracts were dried over anhydrous $MgSO_4$ and evaporated to dryness. The NMR spectrum showed two singlets of 2,2,2-trichloroethyl caprylate (δ 4.72, s, CH_2CCl_3) and bis(2,2,2-trichloroethyl) carbonate (δ 4.82, s, CH_2CCl_3) in a ratio of 82:18. Distillation of the residue in vacuo gave 2,2,2-trichloroethyl caprylate (417 mg) in 76% yield: bp 78–82 °C (1.65 mmHg); NMR ($CDCl_3$) δ 0.75–2.05 (m, 13 H), 2.48 (t, 2 H, J = 7), 4.72 (s, 2 H); IR (film) 1760 cm^{-1}.

Method B. To a solution of caprylic acid (290 mg, 2.0 mmol), triethylamine (210 mg, 2.1 mmol), and DMAP (24 mg, 0.2 mmol) in methylene chloride (6 mL) at 0 °C was added 2,2,2-trichloroethyl chloroformate (423 mg, 2.0 mmol). The resulting solution was stirred at 0 °C for 15 min, diluted with methylene chloride (30 mL), and washed with saturated $NaHCO_3$ (20 mL), 0.1 M HCl (10 mL), and saturated NaCl (20 mL). The methylene chloride solution was dried over anhydrous $MgSO_4$ and evaporated to dryness. The NMR spectrum of the crude product showed two singlets at 4.72 and 4.82 ppm in a peak ratio of 74:26.

Preparation of Z-Ala-OCH_3. To a solution of *N*-(benzyloxycarbonyl)alanine (447 mg, 2.0 mmol) and triethylamine (213 mg, 2.1 mmol) in methylene chloride (6 mL) at 0 °C was added methyl chloroformate (190 mg, 2.0 mmol). After 10 min of stirring at 0 °C, DMAP (23 mg, 0.2 mmol) was added and the resulting solution was stirred at 0 °C for 15 min. The reaction mixture was diluted with methylene chloride (40 mL) and washed with saturated $NaHCO_3$ (20 mL), 0.1 M HCl (10 mL), and saturated NaCl (30 mL). The aqueous layers were extracted with methylene chloride (20 mL). The combined extracts were dried over anhydrous $MgSO_4$ and evaporated to dryness. The residue was subjected to silica gel column chromatography with methylene chloride as an eluant to yield pure Z-Ala-OCH_3 (455 mg, 96%): NMR ($CDCl_3$) δ 1.40 (d, 3 H, J = 7), 3.73 (s, 3 H), 4.40 (q, 1 H, J = 7), 5.12 (s, 2 H), 5.52–5.95 (m, 1 H), 7.31 (b s, 5 H); IR (film) 1730, 1710 cm^{-1}.

Reaction of Caprylic–Ethyl Carbonate Anhydride with Caprylic Acid in the Presence of Triethylamine. To a solution of caprylic acid (288 mg, 2.0 mmol) and triethylamine (205 mg, 2.0 mmol) in methylene chloride (6 mL) at 0 °C was added ethyl chloroformate (220 mg, 2.0 mmol) and the resulting solution was stirred for 10 min at room temperature. The reaction mixture was diluted with methylene chloride (20 mL), washed with cold water (20 mL), and cold saturated NaCl (20 mL), dried over anhydrous $MgSO_4$, and evaporated to afford caprylic–ethyl carbonate anhydride (415 mg, 96%). To a solution of caprylic–ethyl carbonate anhydride (415 mg, 1.9 mmol) in methylene chloride (2 mL) at 0 °C was added a solution of caprylic acid (275 mg, 1.9 mmol) and triethylamine (202 mg, 2.0 mmol) in methylene chloride (3 mL). The resulting solution was stirred at 0 °C for 45 min, diluted with methylene chloride (30 mL), washed with saturated NaCl (20 mL), dried over anhydrous $MgSO_4$, and evaporated to dryness. The residue was distilled to afford caprylic anhydride (462 mg) in 90% yield. The product was identical with an authentic sample in spectral data and physical data.

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The First Selective Linear Codimerization of Terminal Acetylenes and 1,3-Dienes Catalyzed by Dihydridotetrakis(trialkylphosphine)ruthenium Complexes

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1,3-Butadiene and its derivatives reacted with aliphatic terminal acetylenes in the presence of a catalytic amount of $RuH_2(P\text{-}n\text{-}Bu_3)_4$ or $RuH_2(PEt_3)_4$ in benzene at 60–100 °C to give linear codimers in high yields with high chemo-, regio-, and stereoselectivity. For example, the reaction of 1,3-butadiene with 1-hexyne afforded (*E*)-3-decen-5-yne quantitatively. Methyl (*E*)-2,4-hexadienoate reacted with 1-hexyne to give methyl (*E*)-5-methyl-2-undecen-6-ynoate in 86% yield. When this reaction was used, a skeleton of a terpenoid was constructed. The reaction of 1-octyne with 1,3-butadiene in the presence of $RuH_2(PPh_3)_4$ afforded the oxidative cocoupling compound (*E*)-1,3-dodecadien-5-yne instead of the corresponding codimer. The deuterium distributions in the products of the reaction of 3,3-dimethyl-1-butyne-1-*d* with methyl (*E,E*)-2,4-hexadienoate and methyl (*E*)-2,4-pentadienoate were examined.

Introduction

Recently, organic synthesis catalyzed by ruthenium complexes have been greatly expanded. A number of exchange reactions of functional groups,[1] cyclization,[1a,2] reduction,[3] and oxidation[4] reactions catalyzed by ruthenium complexes have been reported. However, when attention is focussed on catalytic carbon–carbon bond formation reactions, the number of characteristic reactions of ruthenium is limited, e.g., carbonylation of olefins or acetylenes,[5] telomerization of olefins with alkyl halides,[6] polymerization and oligomerization of olefins[7] or acetylenes,[8] homologation of methyl acetates,[9] hydrogenation of carbon monoxide to ethylene glycol,[10] and [2 + 2] cross addition of norbornenes with acetylenes.[11] In the course of our study on characteristic carbon–carbon bond formation catalyzed by ruthenium complexes, the first selective linear codimerization of terminal acetylenes with 1,3-dienes catalyzed by dihydridotetrakis(trialkylphosphine)ruthe-

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