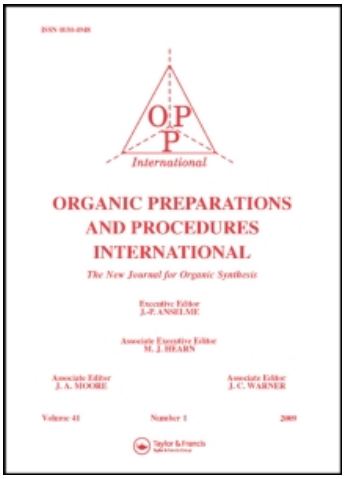

Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

ACTIVATION OF CARBOXYLIC ACIDS BY PYROCARBONATES. SCOPE AND LIMITATIONS. A REVIEW

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To cite this Article Pozdnev, V. F.(1998) 'ACTIVATION OF CARBOXYLIC ACIDS BY PYROCARBONATES. SCOPE AND LIMITATIONS. A REVIEW', Organic Preparations and Procedures International, 30: 6, 631 — 655
To link to this Article: DOI: 10.1080/00304949809355325
URL: http://dx.doi.org/10.1080/00304949809355325

ORGANIC PREPARATIONS AND PROCEDURES INT., 30 (6), 631-655 (1998)

ACTIVATION OF CARBOXYLIC ACIDS BY PYROCARBONATES. SCOPE AND LIMITATIONS. A REVIEW

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INTRODUCTION

Dialkyl pyrocarbonates were discovered by Boehm and Mehta when treatment of the alkaloid emetin with ethyloxycarbonyl chloride followed by addition of sodium hydroxide, led to the continuous production of a liquid; it decomposed upon heating but was not the desired *N*-ethoxycarbonylemetine. Fractionation of the liquid under reduced pressure yielded a pure substance, identified as carbonic acid monoethyl ester anhydride and designated as diethyl pyrocarbonate.[1] In the same study di-*n*-propyl pyrocarbonate was first synthesized. In the sixties, the utilization of diethyl pyrocarbonate as a wine conservant (wine sterilization, and preservatives in soft drinks) gave fresh impetus to the study of these compounds.[2] Another step in the progress of pyrocarbonate chemistry was the closely related use of di-*tert*-butyl pyrocarbonate (Boc_2O) in the preparation of *N*-*tert*-butoxycarbonylamino acids which are important derivatives in peptide synthesis.[3-6] In the 80's, it was discovered that the reactivity of di-*tert*-alkyl pyrocarbonates is highly increased in the presence of DMAP leading to the acylation of such weak nucleophiles as amides, lactams, and carbamates. This aspect of the chemistry of Boc_2O was recently reviewed.[7] In the same decade, reactions of dialkyl pyrocarbonates with carboxylic acids were investigated. In this review, work on carboxylic acids' activation by dialkyl pyrocarbonates is discussed and is based mainly on the author's own research.

I. NOMENCLATURE

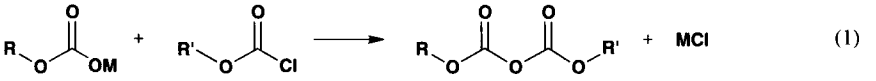
Having discovered a new class of carbonic acid derivatives, Boehm and Mehta[1] named them pyrocarbonic esters (in analogy to inorganic "pyro" acids - pyrophosphates, pyrosulphates etc.). Later, Howe and Morris[8] introduced the term "dicarbonates" for this class of compounds. Since that time, both terms have been in use. However, the name di-*tert*-butyl dicarbonate is used more frequently than di-*tert*-butyl pyrocarbonate, while the name diethyl dicarbonate occurs less frequently than does diethyl pyrocarbonate. The general term "dicarbonate" is not quite adequate because it is also the designation accepted for diol dicarbonates.[9]

II. METHODS OF PREPARATION

The methods for the synthesis of dialkyl pyrocarbonate are based on the use of sodium or potassium alkyl carbonates,[10,11] prepared from alkoxides with excess carbon dioxide, and/or alkyloxycarbonyl chlorides, which are obtained by phosgenation of alcohols.[12-14]

1. From Alkali Alkylcarbonates and Alkyl Chloroformates

The method for the synthesis dialkyl pyrocarbonate from alcohol free sodium or potassium alkyl carbonates and from alkyl chloroformates) is analogous to the synthesis of carboxylic acid anhydrides from their respective acyl chlorides and from alkali salts. First employed by Kovalenko to

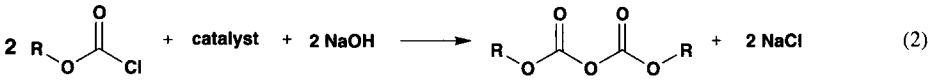


(1)

obtain dimethyl (63% yield)[15] and diisopropyl (50%)[16] pyrocarbonates, it is applicable to the synthesis of both symmetrical[15,16] and mixed dialkyl pyrocarbonates.[17,18] It was recently used to obtain dibenzyl[19,20], diallyl[21], and allyl propenyl[22] pyrocarbonates.

2. From Alkyl Chloroformates and Alkali Hydroxides in the Presence of a Catalyst

This reaction was first used to generate dialkyl pyrocarbonates, Boehm and Metha also prepared di-*n*-propyl pyrocarbonate by the same reaction. Later still, Schamschurin and Krivoschchekova in a study of a series of amines, found that promedol (1,2,5-trimethyl-4-phenyl-4-piperidol propionate hydrochloride) could likewise be used as a catalyst in pyrocarbonate synthesis.[23,24]

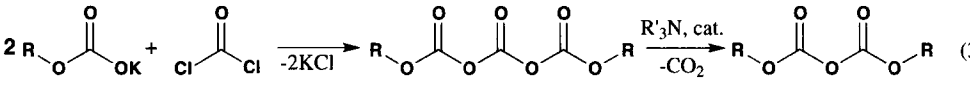


(2)

The method is only applicable to the synthesis of symmetrical dialkyl pyrocarbonates and hence, is of rather limited use. In all cases[1,23,24] however, the yield of diethyl pyrocarbonate was fairly high (65-90%).

3. From Alkali Alkylcarbonates and Phosgene

The reaction of "dry" (alcohol-free) sodium or potassium alkyl carbonates with phosgene, in an appropriate ratio, affords an alkylcarbonic acid dianhydride (tricarbonate) as an intermediates. Tricarbonates with primary and secondary alkyl groups are not stable and easily decompose to pyrocarbonates (dicarbonates) and CO_2.



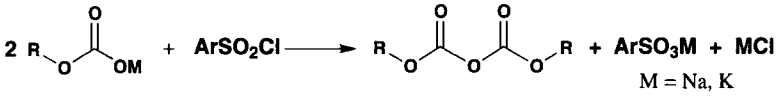
(3)

Howe and Morris were the first to obtain the dimethyl-, diethyl- and diisopropyl pyrocarbonates in good yields in such a way.[8] However, Boc_2O was obtained in very low yield (5%). Several years later, Dean and Tarbell isolated di-*tert*-butyl tricarbonate and found that it could be converted to

Boc_2O in high yield by keeping it in solution in tetrachloromethane in the presence of strongly basic trialkylamines (1,4-diazabicyclo-2,2,2-octane).[25,26] Boc_2O was purified by distillation *in vacuo* and characterized as a stable crystalline compound[26] which decomposed upon heating at 100°. Later, di-1-adamantyl pyrocarbonate was obtained by the same method.[27]

4. From Alkali Alkylcarbonates and Arylsulfonyl Chlorides

Heating of an arylsulfonyl chloride with an excess of a sodium alkyl carbonate also affords the dialkyl pyrocarbonate. Thus, heating tosyl chloride and "dry" sodium ethyl carbonate in acetone gives diethyl pyrocarbonate in 53% yield.[28]

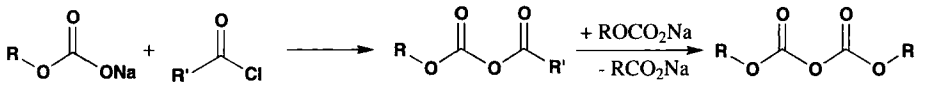


(4)

The yields of dimethyl and diethyl pyrocarbonates were further improved by using bensene-sulfonyl chloride[29] or 1-naphthylsulfonyl chloride.[30] When pyrocarbonates are synthesized from primary alcohols, it is essential that the alkyl carbonic salt be free of the starting alcohol because it reacts with the arylsulfonyl chloride to give hydrochloric acid. The necessity for careful alcohol removal from alkyl carbonic salts is a complication in the process. In the preparation of dialkyl pyro-carbonates from secondary and tertiary alcohols and benzenesulfonyl chloride,[31,32] it is possible to use sodium alkyl carbonates as a mixture with the corresponding alcohol.

5. From Sodium Alkylcarbonates and Acyl Chlorides

Trichloroacetyl chloride and some aromatic acid chlorides may also be used as condensing reagents in the synthesis of di-*tert*-alkyl pyrocarbonates from sodium *tert*-alkyl carbonates. In such cases, sodium *tert*-alkyl carbonates could be used as a mixture with starting alcohols.[33-35] Mixed anhy-drides are formed as intermediates and some, formed from aroyl chlorides and sodium *tert*-butyl carbonate, can be obtained as crystalline compounds.[36]



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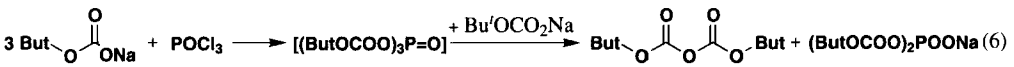
When pyrocarbonates (*tert*-butyl,[35] 1,1-dimethyl-2-phenylethyl,[37] 1,1-dimethylpropyl[38]) were synthesized from trichloroacetyl chloride and sodium *tert*-alkyl carbonates, the mixed anhydrides were not identified. The. yields of di-*tert*-alkyl pyrocarbonates obtained by this method were 45-70%.

6. From Sodium tert-Butylcarbonate and Phosphorus Oxychloride

Di-*tert*-butyl pyrocarbonate may also be synthesized from four equivalents of sodium *tert*-butyl carbonate and phosphorus oxychloride (60-65% yield).



(6)

tris-(*tert*-Butyloxycarbonyl)phosphate is presumably the first product formed and it reacts with sodium *tert*-butyl carbonate to afford Boc_2O and di-*tert*-butyloxycarbonylphosphate sodium salt,

which was isolated from waste water as a crystalline substance. This compound readily reacted with the sodium salt of amino acids to give N-Boc-amino acids.[39]

III. REACTIONS OF DIALKYL PYROCARBONATES WITH NUCLEOPHILES

1. Reaction with Amines

The reaction of dialkyl pyrocarbonates as anhydrides of carbonic acids with primary and secondary amines is most typical. In the original report on dialkyl pyrocarbonate synthesis,[1] it was demonstrated that both dimethyl and di-*n*-propyl pyrocarbonates readily reacted with ammonia, hydrazine, and aromatic amines forming appropriate *N*-alkyloxycarbonyl derivatives. Di-*tert*-alkyl pyrocarbonates, which are commonly used for the introduction of easily removable protective groups by protolysis, react readily not only with hydrazine[37,40] but also with hydrazides of carboxylic acids.[37,38,41] Mixed alkyl *tert*-butyl pyrocarbonates react with amines to give a mixture of two carbamates.[18] The first communication on the synthesis of di-*tert*-alkyloxycarbonylamino acids from di-*tert*-alkyl pyrocarbonates appeared in a little known journal[3] but it was fully confirmed in subsequent studies.[5,6] In particular, it was found that Boc_2O, in addition to primary and secondary amines, readily acylates the imidazole ring of histidine,[5,42] the sulfhydryl group of cysteine,[43] the hydroxyl group of tyrosine and other amino acids containing phenolic hydroxyl groups,[44] guanidine in arginine[45] - as well as amino groups in amino carbohydrates.[46] Di-1,1-dimethylethyl[47] or 1,1-dimethyl-2-phenylethyl[48] pyrocarbonates are also capable *N*-acylating alkaline salts of amino acids in aqueous organic solvent mixtures to give the corresponding amino acids derivatives.

The technique for obtaining Boc-amino acids with Boc_2O has become a routine procedure, with innumerable application examples in the last 10 years.

2. Reactions with Oxygen Nucleophiles: Phenols and Alcohols

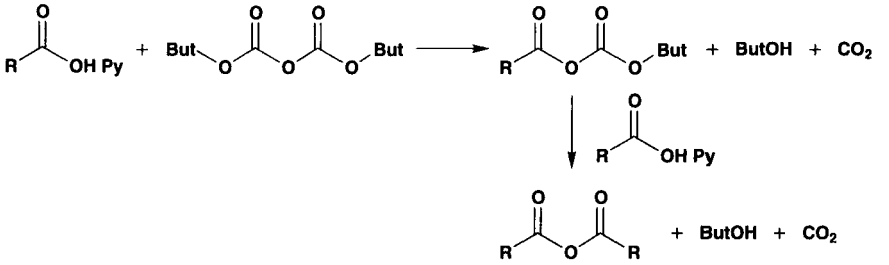
On heating, diethyl pyrocarbonate reacts with phenol to generate of ethyl phenyl carbonate.[1] In the presence of alkali at pH 10-11, Boc_2O readily acylates aromatic hydroxy groups.[44] Under phase-transfer conditions, Boc_2O may be used for the introduction of the t-Boc group into hydroxy and thiol functionalities.[49] Although pyrocarbonates derived from primary and secondary alcohols decompose rapidly in the presence of pyridine or 4-dimethylaminopyridine (DMAP), Boc_2O is fairly stable under these conditions, but its acylating power is greatly enhanced. It was shown that, in dry ethyl acetate, Boc_2O forms a rather stable and highly reactive complex with DMAP.[50] In particular, in the presence of DMAP, Boc_2O reacts with alcohols to give alkyl *tert*-butyl carbonates.[51,52] With DMAP as a catalyst, Boc_2O is capable of acylating many N-, O- and C-nucleophiles,[7] and converting primary amines to isocyanates.[53]

3. Reactions with Carboxylate Ion. Esterification

Mixed anhydrides of carboxylic and half-ester carbonic acids, commonly obtained from carboxylic acids and alkyloxycarbonyl chlorides in the presence of trialkylamine (or from 1-alkyloxy-

carbonyl-2-alkyloxy-1,2-dihydropyridine), are highly activated carboxylic acid derivatives which are widely used in organic chemistry, particularly in peptide synthesis.[54,55]

Dialkyl pyrocarbonates are also able to react with carboxylic acids giving mixed anhydrides. Formation of mixed anhydrides from dialkyl pyrocarbonates and carboxylic acid salts was first reported by Thoma and Rinke.[17] The same study reported a useful method to obtain ethyl esters by heating carboxylic acids in excess diethyl pyrocarbonate. Several years later, this method was employed by other investigators who heated carboxylic acids in diethyl or dimethyl pyrocarbonate to obtain ethyl[56] or methyl[57] esters, respectively, in high yields. The mixed anhydrides, which are formed as intermediates, react with pyrocarbonate-generated alcohols to give esters. Later it was found that esters could be obtained from di-*prim*- or *sec*-alkyl pyrocarbonates without heating and with minimal excess pyrocarbonate, if the reaction was carried out in the presence of pyridine[51] or DMAP.[58,59] In aprotic solvents in the presence of pyridine, Boc_2O also reacts with carboxylic acids to form mixed anhydrides.[60] However, mixed anhydrides cannot be obtained from Boc_2O as the sole products. While accumulating in the reaction mixture, they interact with the starting acids to form symmetrical anhydrides. At an equimolar ratio, a mixture of anhydrides is formed. If two equivalents of carboxylic acids are treated with one equivalent of Boc_2O, the symmetrical anhydrides are isolated as the main reaction products in high yields;[51,60,61] Boc_2O is converted to CO_2 and *tert*-butyl alcohol. Under the



(7)

reaction conditions used, *tert*-butyl alcohol does not hinder the anhydrides formation. Other dialkyl pyrocarbonates with primary and secondary alkyl groups can also be used to obtain symmetrical anhydrides of carboxylic acids.[51,62] However, with these reagents the addition of either *N*-methylmorpholine or triethylamine instead of pyridine is required because the alcohols generated from the dialkyl pyrocarbonates react with the anhydrides to form the corresponding esters when pyridine is used.[51] However, the Boc_2O-pyridine system has a wider application and hence is preferable. At the same time, in the presence of *N*-methylmorpholine or triethylamine, Boc_2O reacts with carboxylic acids much more slowly leading to lower yields of the symmetrical anhydrides.

The advantages of the Boc_2O-pyridine system as a condensing reagent extend beyond the synthesis of symmetric anhydrides. Addition of certain nucleophilic reagents such as phenols, as well as primary, secondary, and *tert*-butyl alcohols (in the presence of DMAP) to a mixture of Boc_2O with a carboxylic acid in the presence of pyridine in aprotic solvent leads to the acylation of the nucleophile by the carboxylic acid. The success of this process is predicted on the fact that Boc_2O reacts more slowly with the nucleophilic reagent than with the carboxylic acid.

TABLE 1. Preparation of Symmetrical Carboxylic Acid Anhydrides

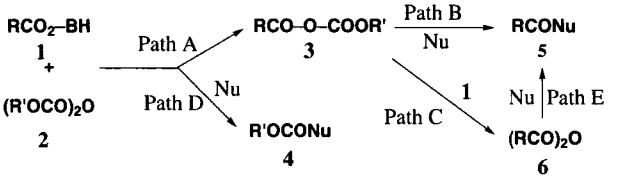
$$2\ RCOO^-BH^+ + (R'OCO)_2O \rightarrow (RCO)_2O + 2\ R'OH + 2\ CO_2$$

R	R'	B(base)	solvent	Yield (%)	mp. (°C)	$[\alpha]_D$	Lit. data mp. (°C)	$[\alpha]_D$	Ref.
PhCH=CH	Et	NMM	benzene	93	136-137		136-137		1
PhCH=CH	*i*-Pr	NMM	benzene	86	136-137				
PhCH=CH	*t*-Bu	Py	EA	93	136-137				
FuCH=CH	Et	NMM	EA	84	76-77		75-76		2
FuCH=CH	*i*-Pr	Et_3N	EA	88	76-77				
FuCH=CH	*t*-Bu	Py	EA	92	76-77				
Boc-Asp*	*t*-Bu	Py	EA	75	133-134	-39.0[a]	133-134	-38.9[a]	3
Z-Phe	*t*-Bu	Py	benzene	60	139-140	+29.5[b]	128-129	+27.3[b]	4
Z-Val	*t*-Bu	Py	benzene	71	99-101	+19.5[b]	99-101	+17.3[b]	4

* an internal anhydride, a) in AcOH; b) in $CHCl_3$. 1. A. V. Schrecker, *J. Am. Chem. Soc.*, **76,** 5803 (1954). 2. I. Masao, *J. Pharm. Soc. Jpn*, **75**, 60 (1955); 3. E. Schreder and E. Klieger, *Ann.*, **673**, 208 (1964). 4. F. M. F. Chen, K. Kuroda and N. L. Benoiton, *Synthesis*, 928 (**1978**),

The mechanism of this reaction has not yet been fully clarified. Acylation of nucleophiles can be effected either by the mixed anhydrides, formed at the first stage of the carboxylic acid-Boc_2O interaction, and/or by the symmetrical anhydrides, the choice of the pathway depending on the reactivity of nucleophilic agent used. However, this does not diminish the practical significance of the method. From a preparative viewpoint, the procedure for preparing carboxylic acid derivatives with the use of dialkyl pyrocarbonates as condensing reagents appears to be rather simple and the yields of the final products sufficiently high.

Possible pathways of the initial reagent's conversion to final reaction products may be represented as follows:



(8)

The reaction process begins with the interaction of carboxylate ion (1) with dialkyl pyrocarbonate (2) (pathway A) to give mixed anhydride (3), alcohol (R'OH) and CO_2. At the same time, dialkyl pyrocarbonate (2) may also react with nucleophile (pathway D) with the formation of R'OCO-Nu (4), alcohol and CO_2. Mixed anhydride (3) may also react along two pathways. While reacting with Nu (pathway B) it converts to RCO-Nu (5) and, possibly to (4). In reacting with carboxylate ion (pathway C), mixed anhydride (3) converts to a symmetrical anhydride (6) which then reacts with Nu^- (pathway E) to form RCO-Nu (5) and carboxylic acid (1). The exact mechanism of this cascade of competitive and successive reactions is complex and is not yet fully elucidated.

4. Esterification Using Di-tert-butyl Pyrocarbonate

The procedure of esterification of carboxylic acids with the Boc_2O-pyridine system is simple and reaction conditions are rather mild. The reaction mixture is made up of the carboxylic acid (one equivalent), 0.2-1 equivalent of pyridine, 1-1.3 equivalent of Boc_2O, and 1-1.5 equivalent of the alcohol or phenol in an aprotic solvent, such as dioxane, tetrahydrofuran, benzene, or ethyl acetate. The reaction is carried out with constant stirring at 15-20°, and the progress of the reaction is

TABLE 2. Preparation of Aryl Ester of *N*-Protected Amino Acids Using the Boc_2O-Pyridine System as Condensing Reagent

Compound	Yield (%)	mp. (°C)	$[\alpha]_D$ c 1	Lit. data mp. (°C)	Lit. data $[\alpha]_D$	Ref.
Z-AlaOPh	86	93-95	-49.2[a]	94-96	-48.2	1
Z-GlyOPh	86	66-67	–	67-68		1
Z-PheOPh	96	107-108	-18.0[a]	105-107	-18.9	1
Boc-Cys(Bzl)OPh	85	86-87	-30.1[a]	81	-30.1	2
$(Boc\text{-}CysOPh)_2$	81	157-158	-103[a]			
Boc-MetOPh	92	72-73	-45.1[a]	72	-43	2
Boc-ProOPh	54	60-61	-64[a]	63	-66	2
Boc-TrpOPh	74	150-151	-13.3[a]	153	-11.6	2
Boc-PheONaph	82	117-118	-14.7[b]			
Z-AlaOQn	80	99-100	-68[b]	102-103	-67.9	3
Z-PheOQn	93	142-143	-69.7[b]	139-140	-70	3
Boc-Tyr(Boc)OQn	71	102-103	-31.3[b]			
Boc-D-TrpOQn	92	186-187	+65.8[a]			
Z-PheONp-4	81	123-124	-24.9[b]			4
Z-ProONp-4	70	90-91	-67.7[b]	94-96	-68.2	5
Z-ValONp-4	82	62-63	-24.5[b]	62-64	-25	6
Boc-AlaONp-4	60	82-83	-52.3[b]	83	-52.5	7
Boc-Cys(Bzl)ONp-4	65	94-95	-40.3[b]	95-96	-37.5	8
Boc-GlyONp-4	64	63-64	–	66-68		7
Boc-LeuONp-4	65	92-93	-48.2[b]	94-95	-48	8
Boc-Tyr(Bu^t)ONp-4	81	138-139	-2.8[b]			

a) c 1, CH_3OH. b) c 1, DMF, 1% AcOH. 1. I. J. Galpin, P. M. Hardy, G. W. Kenner, J. R. McDermott, R. Ramage, J. H. Seely and R. G. Tyson, *Tetrahedron*, **35**, 2577 (1979); 2. B. Castro, G. Evin, C. Selve and R. Seyer, *Synthesis*, 413 (**1977**); 3. H. D. Jakubke and A. Voit, *Chem. Ber.*, **99**, 2419 (1966); 4. M. Bodanszky and V. du Vigneaud, *J. Am. Chem. Soc.*, **81**, 6072 (1959); 5. M. Bodanszky and V. du Vigneaud, *J. Am. Chem. Soc.*, **81**, 5688 (1959); 6. M. Itoh, *Chem. Pharm. Bull. Jpn*, **18**,784 (1970); 7. E. Sandrin and R. A. Boissonas, *Helv. Chim. Acta*, **46**, 1637 (1963); 8. H. C. Beyermann, C. Boers-Boonekamp, M. Brink and H. Zimmermanova, *Rec. Trav. Chim. Pays-Bas*, **87**, 257 (1968).

monitored by the amount of CO_2 formed. In addition to aryl esters, acylation of phenols often leads to the formation of aryl *tert*-butyl carbonates, whose proportion increases with the increasing acidity of the phenol. However, with phenyl, naphthyl, 8-quinolyl, and 4-methylcoumaryl-7 esters of *N*-protected amino acids, the carbonate by-products are insignificant or virtually absent, while the yields of esters are often over 90%. (Table 2).

TABLE 3. Preparation of 2-Nitrophenyl Esters of *N*-Protected Amino Acids, R-COONp-2, Using the Boc_2O-Pyridine System as Condensing Reagent

R	Yield (%)	mp. (°C)	$[\alpha]_D$ c 1, DMF	Lit. data[a,b] mp. (°C)	$[\alpha]_D$
Boc-γ-Abu-	87	93-95			
Boc-Ala-	85	86-89	-75	86-87	-79
Boc-Cys(Bzl)-	85	100-101	-74	103-105	-74
Boc-Glu(Bzl)-	70	123-124	-52	124-125	-54
Boc-Gln-	80	147-148	-55	151-152	-55
Boc-Gly-	86	96-97	-	96-98	-
Boc-His(Boc)-	80	104-106	-34		
Boc-Ile-	72	oil	-	oil	
Boc-Leu-	74	55-56	-69	56-57	-68
Boc-Lys(Z)-	83	103-105	-40		
Boc-Lys(Tfa)-	85	138-140	-39		
Boc-Lys(Form)-	76	116-117	-52		
Boc-Met-	84	104-105	-71	104-105	-73
Boc-Phe-	76	145-146	-64	146	-65
Boc-Pro-	78	63-67	-85	63-70	-84
Boc-Trp-	73	153-157	-57	155-156	-62
Boc-Tyr(Boc)-	80	131-132	-43		
Boc-Phe(4-NO_2)-	75	150-151	-80		
Boc-Val-	70	oil	-	53-56	-44
Z-Ala-	91	93-94	-51	94	-51
Z-Gly-	83	70-72	-	75	-
Z-Phe-	88	108-109	-63	109-110	-63

1a M. Bodanzsky, K. W. Funk and M. L. Fink, *J. Org. Chem.*, 38, 3565 (1973); b. M. Bodanzsky, M. Kondo, C. Y. Lin and G. F. Sigler, *J. Org. Chem.*, 39, 444 (1974).

With 4-nitrophenyl esters, much more *tert*-butyl 4-nitrophenyl carbonate is formed, and its presence hinders the isolation of 4-nitrophenyl esters, especially those esters which have a low melting point and are poorly crystallized. Better results have been obtained with 2-nitrophenyl esters[63]. The efficiency of the reaction in this latter case may be partly due to the reduced nucleophilicity of 2-nitrophenol and also to the low melting point of *tert*-butyl-2-nitrophenyl carbonate,

allowing this latter substance to be removed during crystallization of the final products with hexane. The use of this method led to these products in higher yields compared to reactions using dicyclohexylcarbodiimide.[51,63] (Table 3).

TABLE 4. Preparation of Primary Alkyl Esters of *N*-Protected Amino Acids Using the Boc_2O-Pyridine System as Condensing Reagent

Compound	Yield (%)	mp. (°C)	$[\alpha]_D$ c 1	Lit. data mp. (°C)	Lit. data $[\alpha]_D$	Ref.
Boc-Tyr(Bzl)OBzl	95	81-82	-15.4[a]			
Boc-Trp-OBzl	76	139-140	-8.7[b]	136-137	-9[b]	1
Z-AlaOBzl(4-NO)	90	99-100	-18.3[b]	98-99	-16.8[b]	2
Boc-Ala-OCet	87	67-68	-42.6[b]	68-70	-33.0[a]	3
Boc-Gly-OCet	70	61-62	-	62-64	-	3
Boc-Phe-OCet	89	86-87	-9.0[b]	56-58	-7.4[b]	3
Boc-Ala-OFm	96	76-78	-25[b]			
Boc-Gly-OFm	93	72-75	-			
Boc-Val-OFm	71	67-68	-33.1[b]			
Boc-Leu-OFm	93	70-72	-34.9[b]			
Boc-Ile-OFm	64	61-62	-24.9[b]			
Boc-Pro-OFm	89	88.5-90	-44.0[b]			
Boc-PheOFm	89	125-126	-6.5[c]	125-126	-6[c]	4
Boc-Ser(Bzl)-OFm	86	oil	-10.0[b]			
Boc-TrpOFm	84	96-97	-5.2[c]			
Boc-Glu(OBzl)-OFm	76	98-99	-25.[6]			
Boc-Cys(Bu^t)-OFm	94	76.5-77.5	-20.7[b]			
Boc-Tyr(Bzl)-OFm	81	110-111	-15.0[b]			
Boc-Thr(Bzl)-OFm	88	oil	-10.5[b]			
Boc-Lys(Z)-OFm	91	67-71	-24.1[b]			
Z-AlaOFlm	74	93-95	-32.1[b]	90-91	-38.1[b]	5
Boc-Phe(NO_2)-OFm	86	167-168	-7.0[c]			
Boc-Phe(NO_2)-OPrg	75	66-67	-37.8[a]			
Boc-Ala-OTfe	90	49-50	-36.6[d]			
Boc-D-Ala-OTfe	89	49-50	+34.9[d]			

a) in DMF; b) in MeOH; c) in $CHCl_3$; d) in EtOH. 1. U. Weber, *Z. Naturforsch.*, **31b**, 1157 (1976); 2. P. A. Stadler, *Helv. Chim. Acta.*, **61**, 1675 (1978); 3. V. V. Kalashnikov and V. V. Samukov, *Khim. Prirod. Soedin.*, 412 (**1988**); 4. M. A. Bednarek & M. Bodanszky, *Int. J. Pept. and Prot. Res.*, **21**, 196 (1983); 5. H. Kessler and R. Siegmeter, *Tetrahedron Lett.*, **26**, 281 (1983);

Primary alcohols are readily acylated by carboxylic acids with the Boc_2O-pyridine system.[51,64] In particular, this system has been successfully utilized to obtain benzyl and substituted

benzyl esters of *N*-protected amino acids. Hence it is of interest in peptide synthesis. Benzyl, 4-nitrobenzyl, and 9-fluorenylmethyl[65] esters have been easily obtained by this method. Esterification by 2,2,2-trifluoroethanol, 2-cyanoethanol, and propargyl alcohols has been no less efficient (Table 4).

Acylation of polymeric benzyl alcohol and polyethyleneglycol with Boc-amino acids for solid phase peptide synthesis has also been successful.[64] Allylic esters may also be obtained (V.F. Pozdnev, unpublished data).

Using the Boc_2O-pyridine system, it is possible to obtain esters of *N*-protected amino acids with secondary alcohols in good yields.[51,66,67] Addition of catalytic amounts of DMAP speeds the reaction and, in some cases, leads to enhanced yields. As a result the addition of DMAP, the *tert*-butyl ester of the acid accompanies the target product. However, it can be easily removed during purification. Using Boc_2O, pyridine, and catalytic amounts of DMAP, the cholesteryl esters of *N*-protected amino acids[66] and *trans*-2-acetoxycinnamic acid have been obtained in good yields.[67]

The synthesis of depsipeptides by this method has also been efficient.[51,66] A series of menthyl esters of Boc-amino acids have also been synthesized by the above method. (Table 5).

TABLE 5. Preparation of Secondary Alkyl Esters of *N*-Protected Amino Acids Using Boc_2O as Condensing Reagent

Compound	Yield (%)	mp. (°C)	$[\alpha]_D$ c 1	Lit. data mp. (°C)	Lit. data $[\alpha]_D$	Ref.
c-Ala-OMn	80	103-104	-108.7[a]			
Boc-D-AlaOMn	83	76-77	-22.5[a]			
Boc-ValOMn	90	60-62	-74.3[a]			
Boc-D-ValOMn	87	oil	-13.3[a]			
Boc-PheOMn	93	60-64	-47.3[a]			
Boc-D-PheOMn	91	oil	-19.0[a]			
Z-PheOMn	89	64-68	-38.6[a]			
Z-D,L-PheOMn	98	oil	-			
Boc-AlaOChs	83	107-109	-36.0[b]	109-110	-36.7	1
Boc-γ-AbuOChs	90	120-122	-26.3[b]	122.5		2
Z-PheOChs	84	115-116	-12.0[b]			
(AcO)-Cumar-OChs	94	116-117	-	-		3
Fmoc-ValOBzh	79	142-143	-21.6[b]			
Fmoc-Val-LacOBu^t	80	86-87	-55.6[a]			
Z- Phe(4-NO_2) -LacOBu^t	90	oil	-29.4[a]			

a) n EtOH, b) in $CHCl_3$. 1. L. Lapatsanis, C. Profilis and P. Catsoulacos, *J. Chem. Eng. Data*, **25**, 287 (1980); 2. V. E. Shashona, J. N. Jacob, R. Ridge, A. Campbell and R. J. Baldessarini, *J. Med. Chem.*, **25**, 659 (1984). 3. V. F. Pozdnev, K. Planutis, and A. I. Tochilkin, *Bioorg. Khim.*, **17**, 1347 (1991).

Unambiguous proof for the absence of epimerization of optically active amino acids on activation with the Boc_2O- pyridine system has been obtained by reverse-phase HPLC of *N*-protected amino acid menthyl esters. It has been found that diastereomers of Boc-alanine, Boc-valine, Boc- and Z-phenylalanine menthyl esters can be readily separated by reverse phase HPLC and that L-amino acid derivatives are free of D-isomer derivatives.[66]

If no other nucleophilic reagents are added to the reaction mixture (consisting of carboxylic acid, Boc_2O, pyridine, and DMAP), the reaction products (symmetric anhydride and *tert*-butanol) interact to produce a carboxylic acid *tert*-butyl ester. To accelerate the process, it is expedient to add some *tert*-butanol to the reaction mixture.

However, when *tert*-butyl esters of *N*-alkyloxycarbonyl amino acids are prepared with excess Boc_2O, the reaction mixture gets colored and the amount of by-products increases. In order to minimize side-reactions, the acid must be introduced in a slight excess.

The preparation of *tert*-butyl esters can be carried out at room temperature in the presence of pyridine and catalytic amounts of DMAP in a mixture of 1,4-dioxane (or ethyl acetate) and *tert*-butanol as solvent.[51,68] With the use of Boc_2O, certain acids have been converted to *tert*-butyl esters with high yields. (Table 6). Despite certain limitations, the Boc_2O-pyridine system is generally applicable for the synthesis of a variety of esters under mild reaction conditions.

TABLE 6. Preperation of *tert*-Butyl Esters of *N*-Protected Amino Acids, R-COOBu^t, Using Boc_2O as Condensing Reagent

Compound	Yield (%)	mp. (°C)	$[\alpha]_D$ c 1	Lit. data mp. (°C)	Lit. data $[\alpha]_D$	Ref.
Pht-Gly	90	94-95	-	94-95	-	1
Boc-Glu(Bzl)	87	oil	-19.4[a]	oil		2
Boc-Phe	93	38-40	+29.3[b]			
Boc-Phe(4-NO_2)	93	57-57.5	-7.3[a]			
Boc-DL-Phe(2-NO_2)	68	111-112	-			
Z-Ala	80	oil	-11.5[c]	oil	10.8[c]	3
Z-Phe	78	72-74	+36.0[b]	79-80	+37.6[b]	4
Z-Pro	94	47-49	-53.0[d]	44-45	-52.3[d]	4
Z-Val	90	oil	-12.0[a]	oil	-4.7[a]	2
Z-Trp	33	67-70	-10.5[a]			
Z-Tyr(Boc)	71	oil	-30.7[a]			

a) MeOH; b) in CH_2Cl_2; c) in AcOEt; d) in EtOH; 1. E. Taschner, J. F. Biernat, B. Rzeszotarska and C. Wasielewski, *Ann.*, **646**, 123 (1961); 2. M. K. Dhaon, R. K. Olsen, and K. Ramasamy, *J. Org. Chem.*, **47**, 1962 (1982); 3. S. Wang, B. F. Gisin et al., *J. Org. Chem.*, **42**, 1286 (1977); 4. G. M. Anderson and F. M. Gallacham, *J. Am. Chem. Soc.*, **82**, 3359 (1960).

5. Synthesis of Arylamides

Since aromatic amines are also poor nucleophiles, the Boc_2O-pyridine system can be applied to the synthesis of arylamides.[69-72] Such a study seems to be of practical interest because some arylamides of amino acids and peptides are widely used in enzymology and in clinical diagnoses as substrates of proteolytic enzymes.

The possibility of applying dialkyl pyrocarbonates in arylamide synthesis has been examined. Apart from the di-*tert*-butyl pyrocarbonate-pyridine system some other reagents such as diethyl-, diisopropyl- and di-*sec*-butyl pyrocarbonates can be used.[70] Since pyrocarbonates with primary and secondary alkyl groups degraded more readily in the presence of pyridine, the reactions in these cases have been carried out with *N*-methylmorpholine or triethylamine as base. With Boc_2O in the presence of triethylamine, the arylamides can also be formed but much more slowly. The influence of pyrocarbonate alkyl group on the yield of arylamide is insignificant, but nevertheless it is perceptible. In preparing Boc-AlaNHAzp using various dialkyl pyrocarbonates, the best result is obtained with Boc_2O; however, with other pyrocarbonates the phenylazoanilide yields can also be rather high. Of all dialkyl pyrocarbonates tested in the Boc-ProNHNp synthesis, Boc_2O has been found to be the best (Table 7). From a preparative respect, the procedure for the synthesis of *N*-protected amino acid arylamides (4-nitroanilides, 4-phenylazoanilides, as well as 4-methylcoumaryl-7-amides[70] and quinolyl-6-amides[71]) with dialkyl pyrocarbonates as condensing reagents is rather simple, and the yields of the desired products are sufficiently high. In a typical procedure, all reagents are mixed at once in an appropriate solvent, and the reaction mixture is stirred at room temperature (17-22°) for 6-16 h.

TABLE 7. Preperation of Arylamides of *N*-Protected Amino Acids Using Dialkyl Pyrocarbonates as Condensing Reagents

Compound	Yield (%)	mp. (°C)	$[\alpha]_D$ c 1	Lit. data mp. (°C)	Lit. data $[\alpha]_D$	Ref.
Boc-AlaNHNp	71	168-169	-58.0*	160	-58.6*	1
Boc-ArgNHNp HCl	64	178-180	-11.6*	187	-12.8*	1
Z-ArgNHNp HCl	64	180-181	-12.0*	176-179	-12.0*	2
Boc-GlyNHNp	61	194-195	-	192		1
Boc-PheNHNp	69	168-169	+74.0**			
Boc-ProNHNp	59	198-199	-54.5**			
Boc-ProNHNp[a]	55	194-195	-54.0**			
Boc-ProNHNp[b]	68	194-195	54.0**			
Z-ProNHNp	66	159-160	-66.5**	158-160	-56	3
Z-AlaNHNh	80	185-187	-26.5**	189-190		4
Z-ValNHNh	96	205-206	+2.0**	213.5		4
Z-PheNHNh	94	173-175	+45.5**	173-174		4
Z-Arg$(Z)_2$NHNh	90	202-203	+4.5**	192-194		4

TABLE 7. *Continued...*

Compound	Yield (%)	mp. (°C)	$[\alpha]_D$ c 1	Lit. data mp. (°C)	$[\alpha]_D$	Ref.
Boc-AlaNHAz	79	173-174	-19.5**			
Boc-AlaNHAz[b]	67	172-174	-19.0**			
Boc-AlaNHAz[c]	67	172-174				
Boc-ArgNHAz HCl	65	197-198	-14.8***			
Z-ArgNHAz HCl	67	154-155	-13.5*			
Boc-ProNHAz	82	205-206	-72.4**			
Boc-β-AlaNHQn	85	140-141				
Boc-Arg(Boc)$_2$NHQn	66	103-105	+4.0**			
Boc-Asp(OBu^t)NHQn	68	80-82	-23.7**			
Boc-GlyNHQn	73	145-147				
Boc-Glu(OBu^t)NHQn	80	112-113	-16.9**			
Boc-Cys(Bzl)NHQn	71	148-149	+24.2**			
Boc-LeuNHQn	81	78-80	-20.3**			
Boc-Lys(Z)NHQn	73	107-108	-13.6**			
Boc-Lys(For)NHQn	86	177-178	-16.2**			
Boc-Lys(Boc)NHQn	70	oil				
Boc-Lys(Tfa)NHQn	80	172-173	-15.0**			
Boc-ProNHQn	70	153-155	-73.7**			
Boc-Tyr(Boc)NHQn	83	143-145	+5.0**			
Z-AlaNHQn	85	169-171	32.8**	171-172		5
Z-Arg(Z)$_2$NHQn	71	195-196	+4.6**			
Z-Arg(Boc)$_2$NHQn	56	175-177	+8.7**			
Z-PheNHQn	88	167-168	-46..0**	163-165		6

* in MeOH; ** in DMF; *** in EtOH. a) using diethyl pyrocarbonate as condensing reagent; b) using di-isopropyl pyrocarbonate as condensing reagent; c) using di-*sec*-butyl pyrocarbonate as condensing reagent. 1. D. T. S. Rijkers, H. C. Hemker, G. H. L.Nefkens, and G. I. Tesser,. *22 Europ. Peptide Symposium, sep. 1992, Abstracts*, P2 (**1992**). 2. H.Oyamada, T. Saito, S. Inaba, and M. Ueki, *Bull. Chem. Soc. Jpn*, **64**, 1422-(1991). 3. T. Yoshimoto, M. Fischl, R. C. Orlowski, and R. J. Walter, *J. Biol. Chem.*, **253**, 3708-(1978). 4. H. Nesvadba, *Monatsh. Chem.*, **93**, 386 (1962). 5. R. J. Brynes, P. Andrade and D. Gordon,. *Anal. Biochem.*, **126**, 447 (1982). 6. R. J.Brynes, P. Bevilacqua, and A. Green, *Anal. Biochem.*, **116**, 408 (1981)

The choice of solvents to be used in this reaction is wide. In particular, benzene, ethyl acetate, tetrahydrofuran, dichloromethane, 1,4-dioxane, and dimethylformamide can be used. Dimethylformamide is the most suitable solvent in the synthesis of *N*-alpha-substituted arginine arylamides.

It is very likely that in some cases the solvent influences both the reaction rate and the ratio of the final products. However, in the synthesis of Boc-AlaNHAz, with di-sec-butyl pyrocarbonate

and *N*-methylmorpholine, the yields in dioxane and benzene were nearly the same[69,70] (Table 7).

Since aromatic amines and pyrocarbonates still react with each other during the reaction, these reagents are introduced in a slight (approximately 30%) excess over carboxyl components. The *N*-arylcarbamate formed in this reaction as a by-product is removed by crystallization of the arylamide or by column chromatography on silica gel. Arylamides of *N*-protected arginine have also been obtained in rather high yields by this method. Good results have been achieved with completely substituted arginines such as with N^{α}-Boc-arginine or N^{α}-Z-arginine, whose guanidine groups were protonated by strong acids. Use of Boc_2O solves to some extent the problem of Arg-NHMc synthesis. Using the Boc_2O-pyridine system by means of N^{α}-Z-arginine or N^{α}-Boc-arginine carboxyl activation, it is possible to obtain in high yields Mc-amides which can be easily crystallized to a purity sufficient for their further use (Table 8).

TABLE 8. Preparation of 4-Methylcoumaryl-7-amides of *N*-Protected Amino Acids Using the Boc_2O-Pyridine System

Compound	Yield (%)	mp. (°C)	$[\alpha]_D$ c 1, DMF	Lit. data mp. (°C)	$[\alpha]_D$	Ref.
Boc-AlaNHMc	66	191-192	-51.1	219-220	33.5	1
Boc-ArgNHMc HCl	85	189-191	-18.8			
Boc-ArgNHMc $QnSO_3H$	66	164-165	-14.9*			
Aoc-ArgNHMc HCl	46	194-195	-18.3			
Pboc-ArgNHMc HCl	36	194-195	14.9			
Boc-Asp(OBu^t)NHMc	50	159-160	-22.7			
Boc-Cys(Bzl)NHMc	71	168-170	+30.5			
Boc-Lys(Z)NHMc	43	138-139	-9.1			
Boc-Lys(Tfa)NHMc	77	174-175	-11.8			
Boc-ProNHMc	70	193-194	-63.3			
GlpNHMc	79	250-251	-72.0	256-260	-32.5	2
Z-AlaNHMc	70	227-228	-32.6			
Z-ArgNHMc HBr	64	183-185	-3.9			
Z-ArgNHMc HCl	71	209-210	-16.6	210-211	-17.0	3
Z-ArgNHMc $QnSO_3H$	78	132-133	-19.0*			
Z-Cys(Bzl)NHMc	71	168-170	+30.5	172-174		4
Z-PheNHMc	73	204-206	+57.7	198-203	+56	1
Z-Gly-ProNHMc	84	135-140	-120.7	115-120	-102	5
Boc-Ala-ProNHMc	79	139-140	-131.1			

* in CH_3OH. 1. S. Khammungkhune and G. Sigler, *Synthesis*, 614 (**1980**); 2. K. Fujiwara and D. Tsuru, *J. Biol. Chem.*, **83**, 1145 (1978). 3. Y. Kanaoka, T. Takahashi, H. Nakayama, K. Takaga, T. Kimura and S. Sakakibara, *Chem. Pharm. Bull.*, **25**, 3126 (1977). 4. Y. Kanaoka, T. Takahashi, H. Nakayama, T. Ueno and T. Sekine, *Chem. Pharm. Bull.*, **30**, 1485 (1982). 5. T. Yoshimoto, K. Ogita, R. Walter, D. Koida, and D. Tsuru, *Biochim. Biophys. Acta.*, **569**, 184 (1979).

The nature of the N^{α}-alkyloxycarbonyl protecting group of arginine has little or no effect on arylamide formation. However, it does come in to play during isolation of the target product. In the synthesis of ROCO-Arg-NHMc with varying N^{α}-blocking groups (Boc-, Aoc, Pboc-, Z-), the best result is obtained with Z-Arg-NHMc because it is easily crystallized (Table 8). Apart from Mc-amides, *p*-nitroanilide and 4-phenylazoanilides have likewise been synthesized in reasonable yields from Z-Arg-OH and Boc-Arg-OH with the Boc_2O-pyridine system.[69,70] Z-Arg$(Z)_2$-NHQn is also formed rather well and was easily isolated as a crystalline compound.[69,71] (Table 7).

For the majority of amino acids, including fully protected arginine and lysine, the yields of arylamides are resonably high (70-80%). Only the 4-nitroanilide[69,72] and 4-methylcoumar-7-yl amide[70] of N^{α}-Boc-N^{ε}-Z-lysine have been obtained in low yields, whereas N^{α}-Boc,N^{ε}-Z-Lys-NHQn[71] is readily formed. (Tables 7 & 8).

6. Synthesis of Amides

Amides of carboxylic acids are a large class of natural and synthetic biologically active compounds. Many drugs and peptide hormones are amides. Although a large body of data is available in this field of synthetic organic chemistry,[73,74] developing new methods (in particular, with the use of mixed carboxylic-carbonic anhydrides) for amide synthesis is still topical.[75,76] In any case, the key problem of amide synthesis rests with the efficient activation of the carboxy group.

The use of Boc_2O in the synthesis of carboxylic acid amides is possible in several ways. The first approach involves the synthesis of symmetrical anhydrides or activated esters and their subsequent transformation into amides using ammonia. However, this method is of little value from a preparative viewpoint, because of it presupposes a two-stage process (anhydride or ester synthesis with subsequent ammonolysis). Furthermore, upon treatment of a symmetrical anhydride with ammonia, one equivalent of acid is lost, while nitrophenol or a similar by-product is formed from an activated ester. To remove these, additional purification is required, which complicates the procedure.

Another approach employing intermediates of the anhydride type, obtainable by the reaction of carboxylate-ion with dialkyl pyrocarbonate, is preferable. According to this method, the reaction of pyrocarbonate with carboxylic acid is to be carried out in the presence of an ammonia derivative, with which the pyrocarbonate reacts more slowly than with the carboxylate ion.[75] With this point in mind, it seems worthwhile to use ammonium salts of carboxylic acids for amide synthesis. It should be mentioned that ammonium salts can be transformed into pyridine salts in the presence of pyridine; the released ammonia reacts with Boc_2O to yield *tert*-butyl carbamate (Boc-NH_2). If carboxylate-ion (carboxylic acid salt with ammonia or pyridine) reacts with Boc_2O faster than does ammonia, the mixed anhydride formed will be converted into carboxamide. Thus, a mixture of carboxamide and carbamate can be obtained with the ratio dependent on reaction conditions and nature of carboxylic acid. Indeed, when one equivalent of Boc_2O and 0.1-1 equivalent of pyridine were added to a suspension or solution of Boc-amino acid ammonium salt in acetonitrile, the yields of amides were not high (30-50%). Significant amounts of Boc_2O were required for carbamate formation.[77]

TABLE 9. Preparation of *N*-Protected Amino Acid and Dipeptide Carboxamides, RCO-NH_2, Using Boc_2O-Pyridine System

RCO	Solvent	Yield (%)	mp. (°C)	$[\alpha]_D$ c 1	Lit. data mp. (°C)	Lit. data $[\alpha]_D$	Ref.
Boc-Ala	DO	83	126-127	-1,4	124-125	-2,7	1
Z-Ala	DO	78	136-137	-4,5[b]	130-131	-4,5[e]	2
Boc-Asp(OBzl)	DO	95	158-160	+7,8	157-160	-2,6	1
Glp	DMF	92	152-160	-19.0	-	-	
Z-Glp	MeCN	84	156-157	+1.4	-	-	
$(Z\text{-Cys})_2$	DMF	87	193-194	-172[c]	199-201	-	3
Boc-Glu(OBzl)	DO	90	122-123	+4.1	120-122	+4.0	1
Z-Gly	DMF	80	134-135	-	138-139	-	2
Boc-Leu	DO	82	145-146	-11.1	144-146	-11.4	1
Fmoc-Leu	DO	70	138-139	-17.6	-	-	
Boc-Met	DMF	88	120-121	-7.3	-	-	
Boc-Phe	DO	80	142-144	+16.7	142-149	+16.7	1
Boc-D-Phe	MeCN	77	141-143	-14.5	-	-	
Z-Phe	MeCN	92	163-164	-8.5	161-162	-2.6	1
Fmoc-Phe	DO	73	162-163	-18.2	-	-	
Boc-Pro	DO	82	102-104	-49.4	104-106	-43.4	1
Boc-Trp	MeCN	93	137-138	+6.7	133-136	+7.7	1
Boc-Tyr(Boc)	MeCN	78	160-161	+9,8	-	-	
Boc-Tyr(Bzl)	DO	76	170-172	+13.6	170-171	+16.0	1
Z-Val	DO	78	205-208	+22.9[c]	204-206	+25.5[f]	2
Z-Ala-Pro	DO	91	160-161	-40.2	-	-	
Z-Ile-Pro	DO	83	114-115	-93.8	-	-	
Z-Gly-Gly	DO	50	180-182	-	179-181	-	4
Z-Gly-Pro	DMF	90	145-146	-43.0	150-151	-	5
Z-Pro-Phe	DO	75	170-172	-54.6	-	-	
Z-Trp-Pro	DMF	92	97-98	-16.3	-	-	
Z-Met-Pro	DO	76	136-137	-65.5	-	-	

a) c 1, EtOH at 18°. b) in MeOH,c) in DMF. 1. S. Nozaki and I. Muramatsu, *Bull. Chem. Soc. Jpn*, **61**, 2647 (1988). 2. G. Galaverna, R. Corradini, A. Dossena and R. Marchelli, *Int. J. Peptide and Protein Res.*, **43**, 53 (1993). 3. Y. Hirotsu, T. Shiba and T. Kaneko, *Bull. Chem. Soc. Jpn*, **43**, 1564 (1970). 4. J. S. Fruton and M. Bergmann, *J. Biol. Chem.*, **145**, 871 (1942). 5. E. L. Smith and M. Bergmann, *J. Biol. Chem.*, **153**, 627 (1944).

Amidation proceeds more efficiently when the reaction of a carboxylic acid with the Boc_2O-pyridine system is carried out in the presence of ammonium bicarbonate.[75] *N*-Protected amino acids

react with ammonium bicarbonate rather slowly in aprotic solvents (acetonitrile, dioxane, etc.). However, on addition of Boc_2O and pyridine to such mixtures, CO_2 is vigorously released and the carboxamide is formed as a main product with *tert*-butyl carbamate as an impurity.[77,78] In some cases, the starting acid reacts quatitatively. Variations in the order of addition of reagents have no significant effect on the yields of amides. From a preparative viewpoint, the procedure is rather simple and the yields of carboxamides of *N*-protected amino acids are high.

Generally, a mixture consisting of *N*-protected amino acid, pyridine, ammonium bicarbonate, and Boc_2O in an aprotic solvent is stirred at room temperature. Acetonitrile, dioxane, or DMF can be used as solvents. Ammonium bicarbonate and the pyrocarbonate are used in a slight excess (up to 30%) over the carboxyl component because both these compounds are able to react to form Boc-NH_2. Pyridine accelerates the reaction, and for this reason 0.5-1 equivalent of pyridine is employed. The reaction proceeds vigorously and is complete in 4-6 h. The results obtained are presented in Table 9.

As seen from the data, the procedures are rather efficient, affording amides of simple *N*-protected amino acids and aminodicarboxylic acids with ester groups. Boc-Tyr(Boc)-NH_2 and amides of Z-pyroglutamic and Fmoc-amino acids, all being potentially sensitive to the action of ammonia, are also formed without complications. As can be expected, amidation of amino acids with unprotected side-chain functionality (Boc-Ser-OH, Boc-His-OH, Z-Arg-OH, and Boc-Thr-OH) affords a mixture of products. Protected dipeptides with C-terminal proline can be readily converted into amides upon activation with the Boc_2O-pyridine system in the presence of ammonium bicarbonate (Table 9).

7. Synthesis of Alkylamides

With the Boc_2O-pyridine system, carboxamides of *N*-protected amino acids are obtainable by a one-pot reaction under mild conditions and with high yields. However, until now this approach seemed to be inapplicable to the synthesis of alkylamides since Boc_2O readily reacts with alkylamines. Accordingly, we have applied an alkylammonium hydrogen carbonate approach to the synthesis of carboxylic acid alkylamides.[79]

Strange as it may seem, hydrochlorides of some aliphatic amines, when mixed with potassium hydrogen carbonate in dry acetonitryle, react with Boc_2O slowly, even in the presence of pyridine. However, upon addition of a carboxylic acid to such a mixture, Boc_2O reacts readily with the acid (with vigorous liberation of CO_2). Under these experimental conditions (with low concentrations of free amine) Boc_2O is able to react both with the amine to form Boc-amine, and with the carboxylate-ion to generate the mixed anhydride. The latter reacts, in a competitive manner, with amine to give alkylamide. It is the ratio of reaction rates which determines the ratio of the final products: Boc-amine and carboxalkylamide. Apparently, the balance of the reaction products formed is largely determined by the free amine concentration in the reaction mixture, which in its turn, is dependent on the solubility and stability of the alkylammonium hydrogen carbonates. As a result of these conversions, a mixture of alkylamide, Boc-amine and the initial carboxylic acid is formed. With approximately equivalent amounts of carboxylic acid and Boc_2O, both in a slight excess (10-15%) over the amine, the Boc-amine formation yield is about 20-30%. If the amine is in excess with respect to the acid, the

formation of Boc-amine occurs to the same extent. The amount of Boc-amine formed does not depend on the order of reagent addition. The results obtained are presented in Table 10.

By this method, alkylamides can be synthesized from primary amines and carboxylic acids in satisfactory to high yields. *N*-Blocked dipeptides are also convertible into alkylamides. In some simple cases, the method may be applied to the synthesis of protected dipeptides (last exsempl in Table 10).

TABLE 10. Preparation of *N*-alkylamides using the Boc_2O-pyridine system

Compound	Yield (%)	mp. (°C)	$[\alpha]_D$ c 1	Lit. data mp. (°C)	$[\alpha]_D$	Ref.
(Boc-β-Ala-$NHCH_2CH_2S)_2$	55	134-136	-	132-134	-	1
Boc-Leu-$NHCH_3$	65	122-123	-14.8[a]	118-120	-15.3[a]	2
Boc-Leu-NHHex-c	77	177-178	-11.8[b]	174-176	-12.4[b]	3
Boc-Phe-$NHCH_2Ph$	67	133-134	+3.5[c]	132-133	+3.9[c]	4
Boc-Phe-NHHex-c	86	144-145	+4.6[c]	143-144	+5.0[c]	5
Boc-Phe-NHBu^t	75	133-134	+8.0[c]	131-133	+6.0[c]	5
Boc-Phe-$NHCH_3$	73	146-147	+15,4[d]			
Boc-D-Phe-$NHCH_3$	77	143-144	-7,3[d]			
Boc-Tyr(OMe)$NHCH_3$	80	143-144	+24.7[d]			
Z-Ala-NHC_2H_5	75	132-133	+11.7[b]	127-128	+11.2[b]	6
Z-Gly-NHBu^t	60	65-66	-	68-71	-	7
Z-Leu-$NHCH_3$	71	128-130	-30.8[a]	130-131	-29.5[a]	8
Z-Pro-$NHCH_2CH_2Ph$	70	87-88	-59.0[a]	84-86	-59[a]	9
Z-Val-$NHCH_3$	76	182-183	-10.2[c]	180-181	-14.5[c]	10
Z-Ala-Pro->NHC_2H_5	67	104-105	-98.6[a]	110-113	-96.0[a]	6
Z-Gly-Pro->NHC_2H_5	65	128-129	-83.4[a]	126-127	-75.0[a]	6
Fac-NH-Hex-c	82	168-169	-			
Fac-$N(CH_2)_5$	44	64-66				
Z-Ala-$PheOCH_3$	68	103-104	-14.8[e]	95-96	-12.0[e]	11

a) in CH_3OH; b) in DMF; c) in $CHCl_3$; d) in C_2H_5OH; e) in CH_3COOH. 1. V. M. Kopelevich, A. V. Lisenkova, V. F. Pozdnev, L. N. Bulanova and V. I. Gunar, *Bioorgan. Khim.*, **5**, 254 (1979). 2. C. Somlai, G. Szokan and L. Balaspiri, *Synthesis*, 285 (**1992**). 3. B. Filippi, L. Biondi, F. Filira and R. Rocchi, *Farm. Ed. Sci.*, **38,** 713 (1983). 4 D. Hagiwara, H. Miyake, H. Morimoto, M. Murai, T. Fujii and M. Matsuo, *J. Med. Chem.*, **35**, 3184 (1992,). 5. D. Obrecht, U. Bohdal, C. Broger, D. Bur, C. Lehmann, R. Ruffieux, P. Schonholzer, C. Spiegler, and K. Muller, Helv. Chim. *Acta*, **78,** 563 (1995). 6. C. H. Hassal, W. H. Johnson and N. A. Roberts, *Bioorg. Chem.*, **8,** 299 (1979). 7. S. Bjorkman, S. Castensson and H. Sievertsson, *J. Med. Chem.*, **22**, 931 (1979). 8. G. Pietrzynski and B. Rzeszotarska, *Bull. Polish. Acad. Sci. Chem.*, **39**, 1 (1991). 9. E. Kasafirec, I. Sutiakova, M. Bartik and A. Sturk, *Coll. Czech. Chem. Comm*, **53**. 2877 (1988). 10. G. Pietrzynski, Z. Kubica, and B. Rzeszotarska, *Bull. Polish Acad. Sci. Chem.*, **37,** 363 (1989). 11. Y. Isova and T. Ichikawa, *Bull. Chem. Soc. Jpn,* **52**, 796-(1979).

IV. CONCLUSION

Dialkyl pyrocarbonates are convenient reagents with wide possibilities for use in preparative organic chemistry. Reaction of dialkyl pyrocarbonates with carboxylic acids is simple and useful esterification method with in mild conditions: practically neutral media and ambient temperature. Amongst dialkyl pyrocarbonates, di-*tert*-butyl pyrocarbonate is a reagent with specific and unique properties. It is suitable for introduction of the *tert*-butyloxycarbonyl protecting group in different classes compounds, and as a condensing reagent in presence of pyridine to generate alkyl (primary, secondary, and *tert*-butyl), and aryl esters as well as carboxamides, aryl- and alkylamides in a simple one-pot procedure.

Abbreviations used are: AcOH - Acetic Acid; Aoc - 1,1-dimethylpropyloxycarbonyl; Az - 4-phenylazoanylides; Bzh - Benzhydryl; Boc_2O - di-*tert*-butyl pyrocarbonate; *i*-Boc - isobutyloxycarbonyl; *s*-Boc - *sec*-butyloxycarbonyl; Bu^t - *tert*-butyl; Boc - *tert*- butyloxycarbonyl; Bzl - Benzyl; Cet - 2-Cyanethyl; Chs - Cholesteryl; DMAP - 4-dimethylaminopyridine; EA - Ethyl Acetate; Et - ethyl; Fu - 2-Furyl; Fac - trans-(2-furyl)-acrylo-3-yl; Hex-c - cyclohexyl; Lac - L-Lactic acid; Me - methyl; Mc - 4-methylcoumar-7-yl; Mn - L-Menthyl; Np - nitrophenyl; Nph - 2-naphtyl; Pboc- 1,1-dimethyl-2-phenylethyloxycarbonyl; Ph - Phenyl, Prg - Propargyl; Py - pyridine; RP HPLC - reverse phase high performance liquid chromatography; Tfa - Trifluoracetyl; Tfe - 2,2,2-Trifluoroethyl; Qn - quinol-6-yl; Z - benzyloxycarbonyl. DMF- dimethylformamide; MeOH - methanol; EtOH - ethanol; NMM - *N*-Methylmorpholine; THF - tetrahydrofuran; The abbreviations for amino acids and protecting groups are those of the UPAC-IUB Commission on Biochemical Nomenclature. When not indicated, the symbols for the chiral amino acids represent the L-isomer.

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(Received January 7, 1998; in final form May 8, 1998)