A Simple One-Step Conversion of Carboxylic Acids to Esters Using EEDQ†

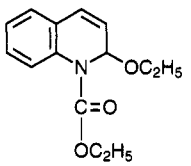
Boulos Zacharie,* Timothy P. Connolly, and Christopher L. Penney

Department of Medicinal Chemistry, BioChem Therapeutic Inc., 275 Armand-Frappier Blvd., Laval, Québec, Canada H7V 4A7

Received April 7, 1995

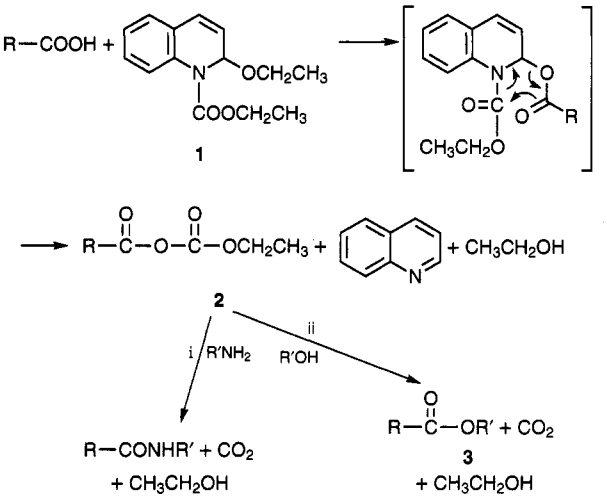
The esterification of carboxylic acids is a commonly encountered reaction in organic chemistry. A large number of ester protecting groups have been described in the literature.[1] Although a variety of conditions for ester formation have already been developed,[2] they are not always satisfactory in yield and/or simplicity of operation. Most require either the presence of strong acids, bases, or other catalysts or the application of heat. Simple processes that allow esterification under mild conditions are very desirable. These procedures are of considerable interest, especially in the manipulation of many peptides, macrolides, and natural products. Our goal, therefore, was to develop a general and simple one-step procedure for the preparation of esters, under neutral conditions, from their parent acids.

Several methods are reported for the activation of carboxylic acids and subsequent conversion to esters and other derivatives. The most common are carbodiimides,[3] *N*-acyl derivatives of imidazole,[4] acyl carbonates,[2f,5] 1,1′-(carbonyldioxy)dibenzotriazoles,[6] chlorotrimethylsilane,[2a,7] several organophosphorus reagents,[8] sulfonyl chlorides,[2e] sulfuryl chloride fluoride,[9] and 2-ethoxy-1-(ethoxycarbonyl)-1,2-dihydroquinoline (EEDQ,[10] **1**). The latter reagent is a well-known coupling agent for the formation of peptide bonds.[11] It allows the coupling of protected amino acids with amino acid esters in a single operation and with little or no racemization.



1

Scheme 1. Directed Esterification of Carboxylic Acids with Alcohols Using EEDQ



Another advantage of EEDQ is that hydroxylic amino acids do not require side-chain protection since under conditions encountered during peptide synthesis *carboxylic esters do not form*. The coupling reaction is expected to proceed by reaction of the mixed anhydride intermediate **2** with amines to give amide derivatives (Scheme 1, path i). We hypothesized that the reaction of an excess of alcohol with the active anhydride **2** would form the corresponding esters (Scheme 1, path ii). Indeed, treatment of a mixture of reactant carboxylic acid with EEDQ in the presence of excess alcohol at room temperature overnight or by heating at reflux for a few hours gave the corresponding ester in high yield. Two minor variations were developed. In those reactions where the alcohol has a low boiling point and/or is inexpensive, it may be used as the reaction solvent. In those reactions where the alcohol has a high boiling point and/or the cost prohibits its use as solvent, 5–6 equiv of alcohol is added to an inert solvent such as chloroform. Excess alcohol is necessary because, as shown in Scheme 1, activation of the carboxylic acid with EEDQ generates the mixed anhydride **2** with ethanol as byproduct. Ethanol could react with intermediate **2**, if a competing nucleophile is not present, to give the corresponding ethyl ester.[12] Indeed, this was observed by us during some difficult peptide coupling reactions. To avoid this reaction, an excess of alcohol is therefore employed as reactant.

Our results are summarized in Table 1. A variety of acids are converted efficiently to their alkyl and benzyl esters. The method is general and applicable to α,β-unsaturated (entry 10), aromatic (entry 14), and aliphatic acids. The reaction conditions are very mild, and as a result, different functionalities (entries 9, 11, 12, and 14) as well as acid sensitive (entries 7 and 8) and/or base sensitive (entry 23) groups are unaffected.

† Presented at the Fourteenth American Peptide Symposium (Columbus, OH, June 18–23).

(1) (a) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*; John Wiley & Sons: New York, 1991. (b) Buchler, C. A.; Pearson, D. E. *Survey of Organic Synthesis*; Wiley-Interscience: New York, 1970.

(2) For selected examples, see: (a) Brook, M. A.; Chan, T. H. *Synthesis* **1983**, 201. (b) Ramaiah, M. *J. Org. Chem.* **1985**, *50*, 4991. (c) Shono, T.; Ishige, O.; Uyama, H.; Kashimura, S. *J. Org. Chem.* **1986**, *51*, 546. (d) Jouin, P.; Castro, B.; Zeggaf, C.; Pantaloni, A.; Senet, J. P.; Lecolier, S.; Sennyey, G. *Tetrahedron Lett.* **1987**, *28*, 1661. (e) Jászay, Z. M.; Petneházy, I.; Töke, L. *Synthesis* **1989**, 745. (f) Takeda, K.; Akiyama, H.; Nakamura, H.; Takizawa, S.; Mizuno, Y.; Takayangi, H.; Harigaya, Y. *Synthesis* **1994**, 1063.

(3) Gorecka, A.; Leplawy, M.; Zabrocki, J.; Zwierzak, A. *Synthesis* **1978**, 475.

(4) Paul, R.; Anderson, G. W. *J. Am. Chem. Soc.* **1960**, *82*, 4596.

(5) (a) Voinescu, V.; Herman, M.; Ramontian, E. *Rev. Chim. (Bucharest)* **1968**, *19*, 678. (b) Kim, Y. C.; Lee, J. I. *Tetrahedron Lett.* **1983**, *24*, 3365.

(6) Ueda, M.; Oikawa, H.; Teshirogi, T. *Synthesis* **1983**, 908.

(7) Nakao, R.; Oka, K.; Fukomoto, T. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 1267.

(8) (a) Hendrickson, J. B.; Shwartzman, S. M. *Tetrahedron Lett.* **1975**, 277. (b) Mestres, R.; Palomo, C. *Synthesis* **1982**, 288. (c) Cabre, J.; Palomo, A. L. *Synthesis* **1984**, 413.

(9) Olah, G. A.; Narang, S. C.; Garcia-Luna, A. *Synthesis* **1981**, 790.

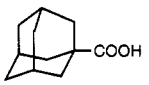
(10) (a) Belleau, B; Martel, R.; Lacasse, G.; Ménard, M.; Weinberg, N. L.; Perron, Y. G. *J. Am. Chem. Soc.* **1978**, *90*, 823. (b) Belleau, B.; Malek, G. *J. Am. Chem. Soc.* **1968**, *90*, 1651.

(11) Dugas, H.; Penney, C. *Bioorganic Chemistry; A Chemical Approach to Enzyme Action*; Springer-Verlag: New York, 1981.

(12) The amount of ethyl ester byproduct, relative to the desired ester, was calculated by ^{1}H NMR. Although the byproduct could form up to 10% of the total yield at room temperature, typically it constituted less than 2% of the reaction under refluxing conditions.

0022-3263/95/1960-7072$09.00/0

Table 1. Esterification of RCOOH with R'OH using EEDQ

entry	RCOOH	R'OH	reaction conditions[a]			yield (%)[b,c]
			equiv of R'OH	time	temp	
1	Z-Gly-OH	MeOH	solvent	O/N	rt	94
2	Z-Ala-OH	MeOH	solvent	O/N	rt	80
3	Z-Gly-OH	EtOH	solvent	O/N	rt	95
4	Z-Ala-OH	EtOH	solvent	O/N	rt	80
5	Z-Pro-OH	EtOH	solvent	5 h	reflux	88
6	stearic acid	EtOH	solvent	O/N	rt	84
7	Boc-Phe-OH	EtOH	6	O/N	rt	79
8	Di-Boc-diaminopropionic acid	EtOH	6	O/N	rt	70
9	4-chlorophenylacetic acid	EtOH	solvent	5 h	reflux	94
10	*trans*-cinnamic acid	EtOH	solvent	O/N	rt	80
11	6-bromohexanoic acid	EtOH	solvent	O/N	rt	75
12	3-(4-hydroxyphenyl)propionic acid	EtOH	solvent	5 h	reflux	84
13		EtOH	solvent	O/N	rt	91
14	*p*-anisic acid	EtOH	solvent	5 h	reflux	56
15	Z-Gly-OH	cyclohexanol	12	O/N	rt	76
16	Z-Gly-OH	$HO(CH_2)_2I$	6	O/N	rt	66
17	Z-Gly-OH	*i*-PrOH	solvent	5 h	reflux	92
18	Z-Ala-OH	*i*-PrOH	solvent	5 h	reflux	77
19	Z-Ala-OH	*t*-BuOH	solvent	5 h	reflux	70
20	Z-Gly-OH	*t*-BuOH	solvent	5 h	reflux	65
21	Z-Phe-OH	$PhCH_2OH$	6	O/N	rt	92
22	Z-Phe-OH	allyl alcohol	solvent	5 h	reflux	87
23	Fmoc-Ala-OH	EtOH	solvent	O/N	reflux	88

[a] 1.2 equiv of EEDQ. [b] Isolated yield. [c] All products had spectroscopic characteristics consistant with the assigned structures.

Sterically hindered acids (entry 13) as well as protected amino acids (entries 1–5, 7, 8, and 15–23) were also converted to their corresponding esters in high yield. The procedure is not limited to primary and secondary alcohols (entries 17 and 18) since *tert*-butyl alcohol reacted under similar conditions to give *tert*-butyl esters (entries 19 and 20) in reasonable yield. Additionally, esterification of tyrosine with a nonprotected phenolic hydroxyl (entry 12) was also successful. Finally, this method is applicable to esters which are difficult to prepare by traditional methods (entries 15, 16, and 22).

No evidence of racemization was observed in the preparation of the dipeptide ester Z-Val-Ala-OCH_3 from the parent acid. Comparison of the ^1H NMR and optical rotation with an authentic sample demonstrated the absence of diastereoisomers.

EEDQ is a stable, readily available reagent which offers a number of advantages over the use of other commonly used esterification reagents and procedures. One set of reaction conditions is suitable for a variety of esters, the manipulation of EEDQ does not require strictly anhydrous conditions or an inert atmosphere, and the purification of product is uniquely simple. The ester products are conveniently isolated by aqueous acid wash of the crude residue to remove quinoline. The synthesis is therefore amenable to scale-up. Further, EEDQ is easier to handle than carbodiimides such as *N,N*-dicyclohexylcarbodiimide (DCC), which can elicit contact dermatitis. Urea byproducts generated from carbodiimide reactions are more difficult to remove than quinoline. Another disadvantage of DCC arises when used with DMAP: the procedure is inappropriate for compounds with base-labile functionalities.[13] More recently a new esterification methodology was reported which employs BOP reagent.[14] This procedure is limited to primary and secondary alcohols and the workup is tedious. Furthermore, no data was provided regarding racemization during esterification.

In conclusion, we have discovered a new use for a well-known peptide coupling agent, EEDQ. Depending upon reagent concentrations and reaction conditions, EEDQ may be used to affect efficient esterification of carboxylic acids.

Experimental Section

Melting points were measured on a Fisher-Johns melting point apparatus and are uncorrected. ^1H NMR spectra were obtained on a Bruker DRX-400 or on a Varian VXR 300 spectrometer. Mass spectra were recorded on a Kratos MS-50 TA instrument. EEDQ was obtained from Aldrich (Milwaukee, WI), and all amino acids wre obtained from Bachem Bioscience (King of Prussia, PA).

General Procedure for the Preparation of Ester. EEDQ (1.2 mmol) was added to a solution of the acid (1 mmol) dissolved in alcohol (20 mL) or in chloroform (20 mL) containing excess alcohol (6 mmol). The reaction was stirred for 12 h at room temperature or at reflux for 5 h, and the solvent was evaporated under reduced pressure. The residue was dissolved in ethyl acetate (20 mL), washed with 5% hydrochloric acid, and dried with anhydrous sodium sulfate. Ethyl acetate was evaporated under reduced pressure to afford the crude product which was purified by short column flash silica gel chromatography. In the case of acid-labile compounds, the acid wash was omitted and the crude product chromatographed directly after removal of the reaction solvent.

Acknowledgment. We appreciate the thoughtful reading of this manuscript by Drs. S. Abbott and J. Gillard. We also thank Ms. L. Marcil and Ms. N. Pilote for secretarial and technical assistance.

Registry numbers (supplied by author): *N*-(Benzyloxycarbonyl)glycine methyl ester, 1212-53-9; *N*-(benzyloxcarbonyl)alanine methyl ester, 28819-05-8; *N*-(benzyloxycarbonyl)glycine ethyl ester, 1145-81-9; D-Alanine, *N*-[(phenylmethoxy)carbonyl]-, ethyl ester, 157774-53-3; 1,2-pyrrolidinedicarboxylic acid, 2-ethyl 1-(phenylmethyl) ester, (*S*), 51207-69-3; ethyl stearate, 111-61-5; *N*-(*tert*-

(13) Campbell, D. A. unpublished data, see ref 13.
(14) Kim, M. H.; Patel, D. V. *Tertrahedron Lett.* **1994**, 5603.

butoxycarbonyl)phenylalanine ethyl ester, 53588-99-1; alanine, *N*-[(1,1-dimethylethoxy)carbonyl]-3-[[(1,1-dimethylethoxy)carbonyl]amino]-, ethyl ester, 109461-78-1; ethyl (4-chlorophenyl)acetate, 14062-24-9; ethyl cinnamate, 103-36-6; ethyl 6-bromohexanoate, 25542-62-5; ethyl 3-(4-hydroxyphenyl)propionate, 23795-02-0; ethyl 1-adamantanecarboxylate, 2094-73-7; ethyl 4-methoxybenzoate, 94-30-4; glycine, *N*-carboxy-*N*-benzyl cyclohexyl ester, 108977-05-5; glycine, *N*-[(phenylmethoxy)carbonyl]-, 2-iodoethyl ester, 156539-07-0; isopropyl (benzyloxycarbonyl)glycinate, 36124-95-5; *N*-(benzyloxcarbonyl)alanine isopropyl ester, 121616-33-9; *N*-(benzyloxycarbonyl)alanine *tert*-butyl ester, 50300-96-4; *N*-(benzyloxycarbonyl) glycine *tert*-butyl ester, 16881-32-6; L-phenylalanine, *N*-[(phenylmethoxy)carbonyl]-, phenylmethyl ester, 60379-01-3; L-phenylalanine, *N*-[(phenylmethoxy)carbonyl]-, 2-propenyl ester, 64286-85-7; L-alanine, *N*-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-, ethyl ester, 117402-82-1.

JO9506645

Additions and Corrections

Vol. 59, 1994

William Adcock,* Jason Cotton, and Neil A. Trout. Electrostatic *vs* Hyperconjugative Effects as Stereoinductive Factors in the Adamantane Ring System.

Page 1872, Table 3, entry for S = H in CH_2Cl_2 should be 31 (%*E*) 69 (%*Z*). Table 4, footnote 2, ϱ_{FS} should be −1.021.

Page 1873, Table 5, footnote 2, ϱ_{FS} should be −1.635. Table 6, footnote 2, ϱ_{FS} should be 2.502.

JO9540209

Vol. 60, 1995

A. S. C. Chan,* T. T. Huang, J. H. Wagenknecht, and R. E. Miller. A Novel Synthesis of 2-Aryllactic Acids via Electrocarboxylation of Methyl Aryl Ketones .

Page 742. In refs 9−15 we failed to include the work by Silvestri and co-workers on the use of a sacrificial aluminum anode for the electrocarboxylation of various aryl methyl ketones including the 6-methoxynaphthyl and *p*-isobutylphenyl precursors to naproxen and ibuprofen. The representative articles are as follows: (1) Silvestri, G.; Gambino, S.; Filardo, G. *Tetrahedron Lett.* **1986**, *27*, 3429. (2) Silvestri, G.; Gambino, S.; Filardo, G. U.S. Pat. 4,708,780, 1987.

JO954016X

Nina E. Heard* and JoLyn Turner. Synthesis of a Novel *N*-Hydroxypyrrole via Lithium Perchlorate Accelerated Diels−Alder Methodology.

Page 4302, paragraph 4, line 2 should read *N*-siloxypyrrole **12**[1].

Page 4302, paragraph 2, line 3 should read reaction.[5]...and line 4 should read diethyl ether).[6]. 4. Footnote 7 should be added to the experimental synthesis of compound **13** as follows: ...**-ene-2-carbonitrile (13). Method A.**[7] Siloxypyrrole....

Page 4303, Table 1. Column head for column 8 should read yield **13**[d]. Entry 9 in column 8 should read 0%[g].

JO954017P