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Use of 2-Ethoxy-1-(ethoxycarbonyl)-1,2-dihydroquinoline as a Convenient Reagent for the Selective Protection or Derivatization of 2-Hydroxycarboxylic Acids

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Abstract

EEDQ has been utilized as a convenient reagent for the selective protection of the hydroxy group of 2-hydroxycarboxylic acids. In the presence of an appropriate amine nucleophile, EEDQ has also been utilized as a reagent for the derivatization of both of the hydroxy and carboxylic acid group of 2-hydroxycarboxylic acids.

Keywords: 2-ethoxy-1-(ethoxycarbonyl)-1,2-dihydroquinoline (EEDQ), 2-hydroxycarboxylic acids and derivatives, carbonates

Optically active 2-hydroxycarboxylic acids are important as starting materials, building blocks or intermediates in the synthesis of biologically active natural products [1-3]. During the process of utilizing optically active 2-hydroxycarboxylic acids in enantioselective synthesis, protection of 2-hydroxy group is often required [4]. Various methods are available for the protection of hydroxy groups and for this purpose, in general, ethers, esters and carbonates have been utilized as protecting groups [5-7]. Most of these methods are applicable in protecting the hydroxy group of 2-hydroxycarboxylic acids or their derivatives [4]. However, to the best of our knowledge, 2-ethoxy-1-(ethoxycarbonyl)-1,2-dihydroquinoline (EEDQ, **1**) first disclosed by Belleau et. al. [8] has not been used as a reagent for the selective protection of the hydroxy group of 2-hydroxycarboxylic acids.

In this paper, we wish to report that EEDQ can be successfully utilized as a convenient reagent for the selective ethoxycarbonyl protection of 2-hydroxy group of 2-hydroxycarboxylic acids. The ethoxycarbonyl protection of hydroxy group is quite attractive in that the protecting group can be easily removed by simply treating with weak base (1% K_2CO_3 in methanol) [5]. EEDQ is well known to allow the coupling of carboxylic acids with amines or alcohols to afford peptides [9], amides [10,11] or esters [12]. However, when 2-hydroxycarboxylic acids were treated with 1.2 equivalent of EEDQ without nucleophiles in methylene chloride at room temperature, their ethyl carbonates **3** were easily obtained (Scheme 1).

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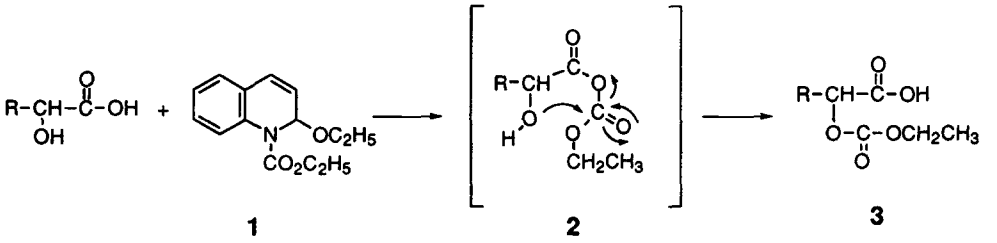


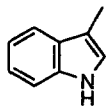
Scheme 1

The coupling reaction of carboxylic acids with amines or alcohols in the presence of EEDQ has been proposed to proceed by reaction of a mixed anhydride intermediate [9,12]. Similarly, the reaction of 2-hydroxycarboxylic acids with EEDQ might be hypothesized to afford mixed anhydrides **2** as shown in Scheme 1, Mixed anhydrides **2** are then proposed to afford ethyl carbonates **3** of 2-hydroxycarboxylic acids by the intramolecular ethoxycarbonyl transfer reaction. However, the reaction of 3-hydroxybutyric acid with EEDQ was found not to afford corresponding ethyl carbonate at all. This result supports that ethyl carbonates **3** are obtained through the intramolecular ethoxycarbonyl transfer reaction with the five membered ring transition state.

The reaction shown in Scheme 1 was successfully applied to various 2-hydroxycarboxylic acids and the results are summarized in Table 1. As shown in Table 1, various ethyl carbonates **3** were obtained in high yield by simply stirring 2-hydroxycarboxylic acid and EEDQ at room temperature. A general procedure for the reaction of 2-hydroxycarboxylic acid with EEDQ is as following: EEDQ (1.2 equiv.) was added to a solution of 2-hydroxycarboxylic acid (0.1 g) dissolved in dichloromethane (30 ml). The reaction mixture was stirred for 5 hr. at room temperature and then washed with 2N HCl solution. The organic solution was dried over anhydrous sodium sulfate and then evaporated under reduced pressure. The crude product was purified by short column silica gel chromatography. The spectral data (IR, NMR, Mass) of ethyl carbonates **3** were consistent with the assigned structures. Optical purity of ethyl carbonates **3** prepared from optically active 2-hydroxycarboxylic acids (for example, lactic acid and mandelic acid) was checked to be consistent with the starting materials by HPLC analysis on a chiral column [13,14] after converted into their anilide derivatives.

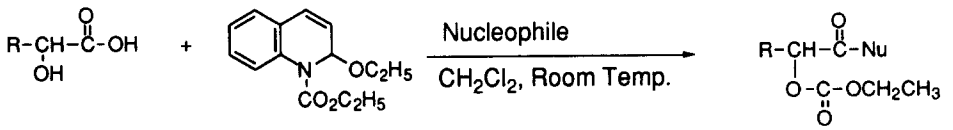
Table 1

The results of the reaction of various 2-hydroxycarboxylic acids with EEDQ to afford ethyl carbonates **3**.

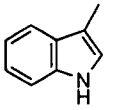
Entry	3 (R)	Yield (%)[a]	Entry	3 (R)	Yield (%)[a]
1	CH_3	92	5	$CH_3(CH_2)_5$	92
2	$(CH_3)_2CH$	87	6	C_6H_5	94
3	$(CH_3)_2CHCH_2$	91	7	$C_6H_5CH_2$	99
4	$CH_3(CH_2)_3$	91	8		99

a) Isolated yields.

Table 2
One pot synthesis of O-ethoxycarbonyl 2-hydroxycarboxylic acid derivatives 4 with EEDQ



1 4

Entry	Nucleophile	4 R	4 Nu	Yield (%) a)
1	$CH_3CH_2CH_2NH_2$	CH_3	$CH_3CH_2CH_2NH$	97
2	$(CH_3CH_2CH_2)_2NH$	CH_3	$(CH_3CH_2CH_2)_2N$	91
3	$C_6H_5NH_2$	CH_3	C_6H_5NH	84
4	$C_6H_5CH_2NH_2$	CH_3	$C_6H_5CH_2NH$	94
5	$CH_3CH_2CH_2NH_2$	C_6H_5	$CH_3CH_2CH_2NH$	94
6	$(CH_3CH_2CH_2)_2NH$	C_6H_5	$(CH_3CH_2CH_2)_2N$	97
7	$C_6H_5NH_2$	C_6H_5	C_6H_5NH	94
8	$C_6H_5CH_2NH_2$	C_6H_5	$C_6H_5CH_2NH$	98
9	$CH_3CH_2CH_2NH_2$	$(CH_3)_2CHCH_2$	$CH_3CH_2CH_2NH$	95
10	$(CH_3CH_2CH_2)_2NH$	$(CH_3)_2CHCH_2$	$(CH_3CH_2CH_2)_2N$	95
11	$C_6H_5NH_2$	$(CH_3)_2CHCH_2$	C_6H_5NH	88
12	$C_6H_5CH_2NH_2$	$(CH_3)_2CHCH_2$	$C_6H_5CH_2NH$	95
13	$CH_3CH_2CH_2NH_2$	$CH_3CH_2CH_2CH_2CH_2CH_2$	$CH_3CH_2CH_2NH$	99
14	$(CH_3CH_2CH_2)_2NH$	$CH_3CH_2CH_2CH_2CH_2CH_2$	$(CH_3CH_2CH_2)_2N$	95
15	$C_6H_5NH_2$	$CH_3CH_2CH_2CH_2CH_2CH_2$	C_6H_5NH	98
16	$C_6H_5CH_2NH_2$	$CH_3CH_2CH_2CH_2CH_2CH_2$	$C_6H_5CH_2NH$	95
17	$CH_3CH_2CH_2NH_2$	$C_6H_5CH_2$	$CH_3CH_2CH_2NH$	99
18	$(CH_3CH_2CH_2)_2NH$	$C_6H_5CH_2$	$(CH_3CH_2CH_2)_2N$	96
19	$C_6H_5NH_2$	$C_6H_5CH_2$	C_6H_5NH	97
20	$C_6H_5CH_2NH_2$	$C_6H_5CH_2$	$C_6H_5CH_2NH$	99
21	$CH_3CH_2CH_2NH_2$	 A	$CH_3CH_2CH_2NH$	99
22	$(CH_3CH_2CH_2)_2NH$	A	$(CH_3CH_2CH_2)_2N$	98
23	$C_6H_5NH_2$	A	C_6H_5NH	99
24	$C_6H_5CH_2NH_2$	A	$C_6H_5CH_2NH$	98

a) Isolated yields.

A similar reaction conducted with 2 equivalents of EEDQ in the presence of an amine nucleophile is expected to afford O-ethoxycarbonyl 2-hydroxycarboxylic amide **4** via tandem two step procedure such as the intramolecular ethoxycarbonyl transfer reaction with one equivalent of EEDQ and then the coupling reaction with another equivalent of EEDQ between

the free carboxylic acid group of O-ethoxycarbonyl 2-hydroxycarboxylic acid and an amine nucleophile. Indeed, the reaction of 2-hydroxycarboxylic acids with two equivalents of EEDQ in the presence of an amine nucleophile afforded O-ethoxycarbonyl 2-hydroxycarboxylic amide **4** in high yield especially when two equivalents of amine nucleophile were used and the results are summarized in Table 2. As shown in Table 2, various amine nucleophiles such as primary amine, secondary amine, aniline, benzylamine, were all effective for the derivatization reaction.

A general procedure for the preparation of O-ethoxycarbonyl 2-hydroxycarboxylic amides **4** is as following: To a solution of 2-hydroxycarboxylic acid (0.1 g) dissolved in dichloromethane (30 ml) was added EEDQ (2.0 equiv.). The reaction mixture was stirred for 5 min. at room temperature and an appropriate amine nucleophile (2.0 equiv.) was added. The whole reaction mixture was stirred for 5 hr. at room temperature and then washed with 2N HCl solution. The organic solution was dried over anhydrous sodium sulfate and then evaporated under reduced pressure. The crude product was purified by short column silica gel chromatography. All products **4** exhibited spectral data (IR, NMR, Mass) in accord with the assigned structures. The possible occurrence of racemization during the process of derivatization of optically active 2-hydroxycarboxylic acids such as lactic acid and mandelic acid was not detected by HPLC analysis on a chiral column [13,14].

In conclusion, in this study, we demonstrated that EEDQ can be used as a convenient reagent for the selective protection of 2-hydroxy group of 2-hydroxycarboxylic acids or for the derivatization of both of hydroxy and carboxylic acid functional groups of 2-hydroxycarboxylic acids by a simple one pot reaction.

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