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Mechanistic studies of DCC/HOBt-mediated reaction of 3-phenylpropionic acid with benzyl alcohol and studies on the reactivities of 'active ester' and the related derivatives with nucleophiles

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ABSTRACT

Despite of the extensive study for peptide synthesis, DCC-mediated esterification is left still unclear. Therefore, DCC- and DCC/HOBt-mediated reactions of 3-phenylpropionic acid (**1**) with benzyl alcohol were carried out under several mechanistic considerations. Further, in order to determine the reactivities of the so-called 'active esters' compounds changing the substituents bearing carbonyl and related derivatives group for the purpose of the development of new class of non-symmetry cross-linkers, we have studied the reaction of model compounds, *N*-(3-phenylpropionyloxy)benzotriazole (**6**), *N*-(3-phenylpropionyloxy)phthalimide (**7**), 3-phenylpropionyloxybenzothiazole (**8**), and *N*-(3-phenylpropionyl)benzotriazole (**9**) with various nucleophiles under similar conditions were carried out for the comparison. It was revealed to exhibit the order of **6**>>**8**>**9**>**7**.

1. Introduction

A variety of improvement of amide synthesis, particularly peptide synthesis using *N*,*N*′-dicyclohexylcarbodiimide (DCC) or similar derivatives have been continued to develop for long time.[1–8] Further, the activation of carboxylic acids using 1-hydroxybenzotriazole (HOBt) as an efficient coupling additive in the presence of base in peptide synthesis have been well documented.[2,4,5,9,10] For esterification under neutral conditions, DCC-mediated procedures seem to be also useful. However, the yield is not always high enough. For example, we experienced that the reaction of cholesterol with linolenic acid in the presence of DCC resulted in poor yield of the corresponding ester.[11] Therefore, to improve the yield; the use of coupling additive, such as HOBt in the DCC-mediated procedure is also conceivable similarly in the peptide syntheses. However, compared with amide (peptide) synthesis, there has been no report about the efficient coupling protocols to ester linkage between carboxylic acid and hydroxyl groups. Particularly, the mechanism in the presence of HOBt has been left uncertain. Thus, in order to apply the DCC/HOBt-mediated reaction to moderate and neutral esterification procedure in our continuing research to develop new antigens for the production of monoclonal antibodies,[11,12] we need to recheck the DCC-mediated reaction under various conditions. Further, the study has been extended on reactivities of the so-called 'active ester' and the related derivatives toward hydroxyl compounds, to develop versatile methods for esterification under mild conditions. Herein, we report the mechanistic studies of DCC/HOBt-mediated reaction of 3-phenylpropionic acid (**1**) with benzyl alcohol under several conditions, and the studies on the reactivities of 'active ester' and the related derivatives,[13,14] *N*-(3-phenylpropionyloxy)benzotriazole (**6**), *N*-(3-phenylpropionyloxy)phthalimide (**7**), 3-phenylpropionyloxybenzothiazole (**8**), and *N*-(3-phenylpropionyl)benzotriazole (**9**) toward various nucleophiles.

2. Results and discussion

2.1. Mechanistic studies of DCC/HOBt-mediated reaction of 1 with benzyl alcohol

In the condensation reaction using DCC, the initial formation of the *O*-acylisourea intermediate DCC-adduct **2** (Scheme 1) and subsequent formation of acid anhydride **5** were proposed by Khorana.[15] The existence of this intermediate **2** has been supported by the studies on intramolecular *O*-acylisourea formation.[16] To improve the yield and reaction time, Petersen and Balcom, have demonstrated the importance of the reaction media and concluded that less basic solvents, such as CH_2Cl_2 are more effective than THF by the kinetic investigation on the formation of acyl anhydride.[17]

In order to recheck the esterification mechanism in the presence of DCC under several conditions, we have carried out several

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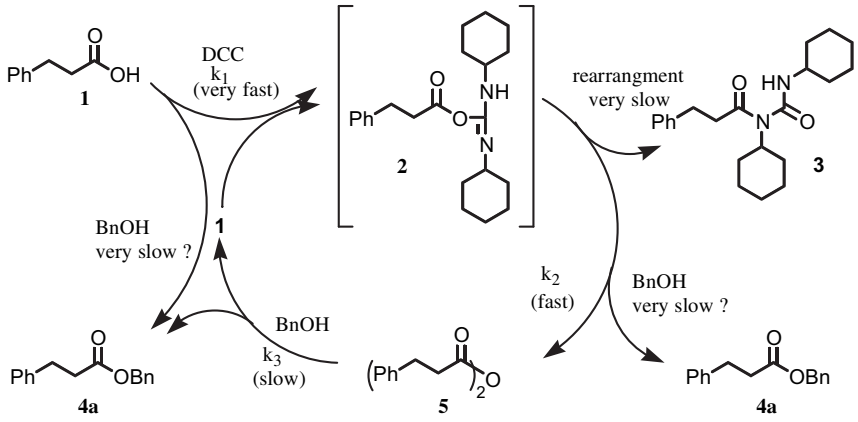
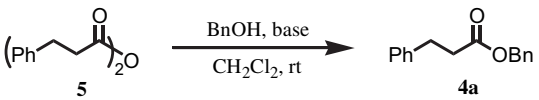


$k_1 >> k_2 > k_3$ (estimated by systematic evaluation in control experiments)

Scheme 1. Esterification of benzyl alcohol in the presence of DCC.

control-reactions in the reaction of **1** with benzyl alcohol. The reaction of **1** with 2.0 equiv benzyl alcohol in the presence of 2.0 equiv DCC found to afford benzyl 3-propionate (**4a**)[14] in a rather low yield of 53% together with the formation of acyl urea **3** in 34% yield, despite of prolonged reaction time. During the reaction, **2** was not observed and the gradual formation of 3-phenylpropionic anhydride (**5**), followed by the formation of **4a** was observed. In a short time (5 min), reaction of **1** with 0.5 equiv of DCC gave only **5** in 31% yield, indicating this reaction rate is not extremely high. The reaction of **1** with 2.0 equiv of DCC for 5 min found to afford only **5** in 62% yield and the complete absence of **2**. In this case, if the attacking rate to **2** by **1** is slow compared with that of the formation of **2**, the formation of **2** should be observed. This means that the attacking rate to **2** by **1** is faster than that of the formation of **2**. The reaction of **5** with benzyl alcohol in the absence of DCC found to be not very fast, and showed almost same reaction rate as in the presence of DCC. The same reaction in the presence of base, such as 4-dimethylaminopyridine (4-DMAP) observed to be very fast (cf. entry 3 in Table 1). The reaction of *N*, *N*′-dicyclohexyl urea with **5** found to undergo slow formation of **3**. When the same DCC-mediated reaction of **1** with benzyl alcohol in the presence of 2.0 equiv 4-DMAP revealed to be rapid formation of **4a** in 83% yield. This result is interpreted by base catalysis by 4-DMAP in acylation step of benzyl alcohol with **5**. The reaction of **1** with benzyl alcohol in the presence of 4-DMAP was also examined, however, expectedly none of **4a** was observed after 3 days. To evaluate the ability of DCC as a base, the reaction of **5** with benzyl alcohol in the presence of DCC was carried out; however, the rate acceleration was not observed. In this case **3** was also formed. These results are summarized in Table 1. All these observations clearly suggest that the real intermediate of the DCC-mediated esterification of **1** with benzyl alcohol in the absence of base is not **2** but **5**, and the rate determining step for **4a** formation is the attacking of alcohol to **5**. The reaction mechanistic was depicted in Scheme 1.

Table 1
Reaction of **5** with benzyl alcohol under several conditions

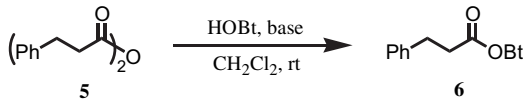


5 **4a**

Entry	Base (1.0 equiv)	Estimate rate
1	None	Very slow (>10 h)
2	DCC	Slow (10 h)
3	4-DMAP	Fast (5 min)

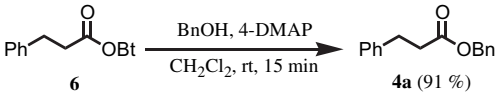
Next, we examined the effect of addition of HOBt in the DCC-mediated esterification of **1** with benzyl alcohol in the absence of base. However, only the rapid formation of **6** was observed and none of **4** was obtained after prolonged reaction time. The addition of 2.0 equiv amount of 4-DMAP as a base under the same conditions revealed the rapid formation of **4a** in excellent yield in a very short time. In this reaction the attacking step of alcohol to **6** seems to be crucial and the addition of the base influences greatly to increase nucleophilicity by base catalysis. The formation of the 'active ester' as intermediate **5** apparently by the isolation of **6** in the reaction of HOBt with **1** in the presence of DCC.[18,19] For the formation of **6** in this reaction, two routes are possible: one is via the DCC-adduct **2** and the other is via the anhydride **5**. Because of the formation of anhydride **5** in the reaction of **1** in the presence of DCC was fast. To obtain clue to distinguish the two routes, we checked the reactivity of HOBt with **5** under several conditions and the results are shown in Table 2. As shown in Table 2 the reaction was very fast in all cases, surprisingly even in the absence of base (entry 1). Therefore, the mechanism for the formation of the ester **4a** in this protocol (acid/alcohol/DCC/HOBt/4-DMAP) will be depicted as in Scheme 2. Namely, initially the 'active-ester' **6** is formed by the reaction of HOBt with **5** that was formed by the reaction of **2** with **1** and, then subsequently, **6** was attacked rapidly by benzyl alcohol to form **4a** under base catalysis of 4-DMAP.

Table 2
Reaction of **5** with 1-hydroxybenzotriazole under several conditions



5 **6**

Entry	Base (1.0 equiv)	Estimate rate
1	None	Fast (5 min)
2	DCC	Fast (5 min)
3	4-DMAP	Fast (5 min)



6 **4a** (91 %)

Scheme 2. Reaction of **6** with benzyl alcohol in the presence of 4-DMAP.