Highly Efficient Carbamate Formation from Alcohols and Hindered Amino Acids or Esters Using *N*,*N*′-Disuccinimidyl Carbonate (DSC)

Hongmei Li,* Cheng-yi Chen, Jaume Balsells Padros

Department of Process Research, Merck Research Laboratories, P.O. Box 2000, Rahway, NJ 07065-0900, USA
Fax +1(732)5941499; E-mail: hongmei_li@merck.com

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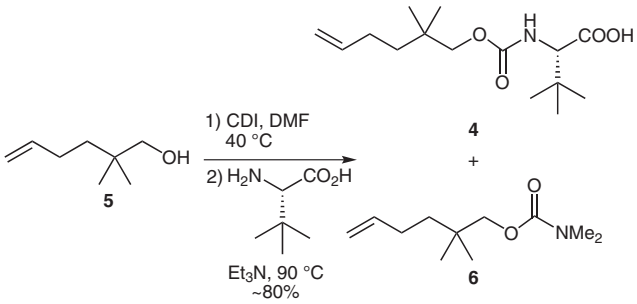
Abstract: A highly efficient and straightforward protocol to prepare carbamates from alcohols and hindered amino acids/esters mediated by *N*,*N*′-disuccinimidyl carbonate (DSC) in the presence of catalytic amount of pyridine is described. This method could be carried out under mild conditions in one pot, and a wide variety of carbamates were obtained in high yield with excellent purity.

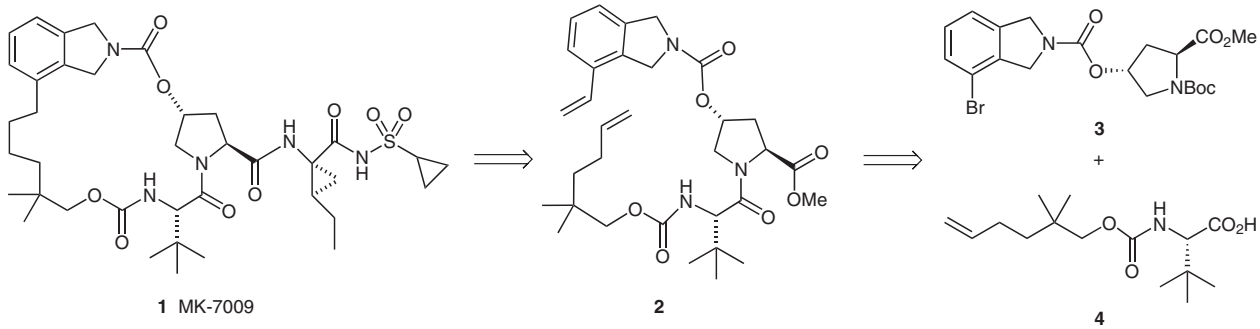
Key words: carbamate, *N*,*N*′-disuccinimidyl carbonate, DSC, hindered amino acids/esters, pyridine

Formation of carbamates is of great importance in the synthetic organic chemistry due to its wide applications in the fields of pharmaceutics, agriculture, and polymer industry.[1] For example, carbamate moieties constitute key elements in the structure of MK-7009, a novel HCV protease inhibitor, that is currently at the late-stage clinical development.[2] The chemical development of this compound to support preclinical/clinical studies called for a highly efficient protocol for the carbamate formation especially from the hindered amino acids with alcohols. Among many known methods developed for the carbamate formation, 1,1-carbonyldiimidazole (CDI)-promoted synthesis from alcohol and amine appeared to be most straightforward and practical.[3] Additionally, *N*,*N*′-disuccinimidyl carbonate (DSC)-mediated carbamates synthesis reported by Ghosh et al. at our research laboratories could serve as an alternative to the CDI protocol.[4] However, application of these methods to hindered amino acids or their derivative still remained elusive. We herein wish to report a general, highly efficient, and straightforward protocol to prepare carbamate from alcohols and hindered amino acids/esters mediated by *N*,*N*′-disuccinimidyl carbonate in the presence of catalytic amount of pyridine.

As shown in Scheme 1, carbamate **4** serves as a key building block for the synthesis of MK-7009. We recently encountered some problems in the preparation of highly pure carbamate **4** from alcohol **5** and the hindered amino acid, L-*tert*-leucine, using the commonly employed CDI protocol (Scheme 2). Activation of alcohol **5** by CDI went smoothly in DMF at 40 °C, however, the carbamate formation with L-*tert*-leucine required high temperatures (>90 °C) and long reaction times (12 h) due to low solubility and poor reactivity of L-*tert*-leucine in the reaction media. The reaction generated the desired carbamate **4** in only 80% yield and was plagued by the formation of ca. 17% of impurity **6** which then required additional chromatography or salt formation for the purification of the desired product.



Scheme 2 Carbamate formation with L-*tert*-leucine using CDI



Scheme 1 Retrosynthetic analysis of MK-7009

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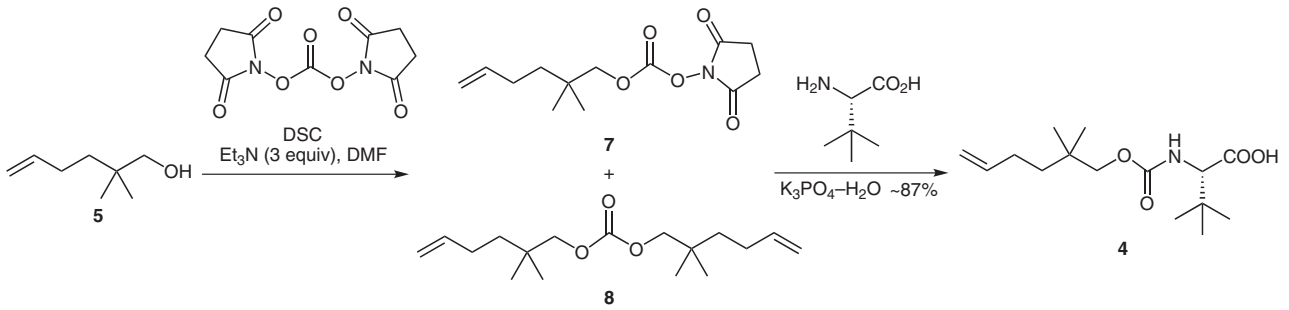
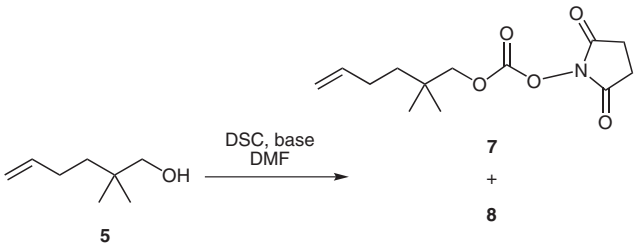


Scheme 3 Carbamate formation with L-*tert*-leucine using DSC

In 1992, Ghosh et al.[4] at Merck Research Laboratories reported an efficient and mild method for carbamate formation from various amines and alcohols by using commercially available DSC. This reagent has been recognized as a versatile reagent to activate amino and carboxyl groups to form asymmetric ureas and amide linkages.[5] Armed with this knowledge we decided to explore the DSC protocol for the formation of carbamate **4** from L-*tert*-leucine and alcohol **5** (Scheme 2). Activation of alcohol **5** with DSC in the presence of three equivalents of Et_3N in acetonitrile or DMF gave ca. 94% conversion into a mixture of 87% of intermediate **7** and 7% of carbonate **8**. We were delighted to find that subsequent reaction of intermediate **7** with hindered L-*tert*-leucine proceeded smoothly under mild conditions: aqueous media at ambient temperature. Furthermore, we noticed that no byproduct **6** was generated under these conditions.

Encouraged by this exciting lead we set to further optimize the activation of alcohol **5** by using DSC and a variety of bases in order to maximize efficiency for the coupling step (Scheme 3). Bases were screened for the activation as summarized in Table 1. Et_3N predominantly induced the formation of the mixed succinimide carbonate **7** (Table 1, entry 1) in 94% conversion after four hours at room temperature. When the reaction temperature was increased to 40 °C, the reaction went to 95% conversion after 15 hours in the presence of only a catalytic amount of Et_3N (Table 1, entry 2). Hünig's base worked equally well as Et_3N as a base (Table 1, entry 3). However, 5–9% of carbonate **8** was detected when using either Et_3N or Hünig's base. Stronger organic bases such as DBU and DABCO led to high conversion for the reaction but a poor impurity profile (Table 1, entry 4 and 5). Inorganic bases, such as potassium carbonate, were ineffective for the activation and led to poor conversion into the mixed succinimide carbonate **7** after 15 hours at 40 °C (Table 1, entry 6). We were delighted to find that 1–2 equivalents of pyridine effectively facilitated the activation such that the mixed succinimide carbonate **7** was obtained in quantitative yield in only 1–2 hours (Table 1, entry 7 and 8). In fact, catalytic amount of pyridine and DMAP (20 mol%) both effectively promoted the reaction to full conversion and clean reaction profiles after 15 hours at 40 °C. Based on these results, 20 mol% of pyridine was selected as the optimal base for the activation of alcohol **5**.

Table 1 Base Screening for DSC Activation of Alcohol **5**



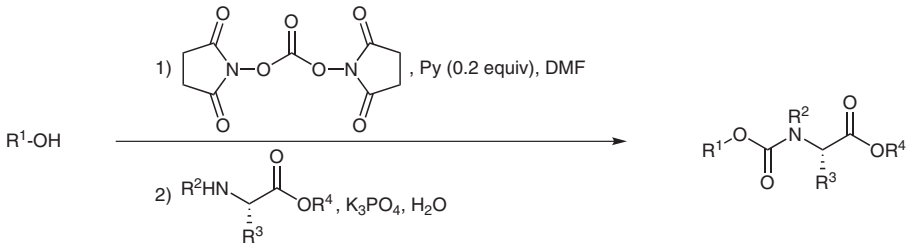
Entry	Base (equiv)	Temp (°C)	Time (h)	Conv. (%)	Yield of **7** (GCAP, %)
1	Et_3N (2.0)	r.t.	4	94	87
2	Et_3N (0.2)	40	15	95	86
3	Hünig's base (2.0)	r.t.	4	96	87
4	DBU (2.0)	40	1	ca. 90	ca. 50, messy
5	DABCO (2.0)	40	1	ca. 95	ca. 70
6	K_2CO_3 (2.0)	40	15	40	40
7	pyridine (2.0)	40	1	100	ca. 100
8	pyridine (1.0)	40	2	100	ca. 100
9	pyridine (0.2)	40	15	100	ca. 100
10	DMAP (0.2)	40	15	100	ca. 100

With the optimized conditions, alcohol **5** was activated with 1.2 equivalents of DSC in the presence of catalytic amount of pyridine (20 mol%) in DMF at 40 °C with >99% conversion into **7**. Subsequent addition of water, L-*tert*-leucine and 2–3 equivalents of K_3PO_4 at ambient temperature, smoothly afforded the desired carbamate **4** in nearly quantitative yield with excellent purity in 2–4 hours.[6] As a result, no further purification or salt formation was required to upgrade the purity. The carbamate **4** exists as amide rotamers as observed by the ^1H NMR, ^{13}C NMR, and NOE spectrum.[7]

As summarized in Table 2, this protocol was successfully applied to the carbamate formation from a variety of primary and secondary alcohols and hindered amino acid/ester.[7] Neopentyl alcohol **5** was coupled well with different hindered amino acids/esters giving corresponding carbamates in high yields (Table 2, entries 1–4). A less

hindered primary alcohol also worked well with primary and secondary amino acid/ester to provide carbamates in high yield (Table 2, entries 5 and 6). The reaction could be readily extended to secondary alcohols (entry 7–12) which formed carbamates bearing hindered primary and amino acid/ester moieties. Coupling of a secondary alcohol and aryl-substituted amino acid [(*S*)-(+)-2-phenylglycine] led to carbamate formation (up to 99%, Table 2, entry 10) with no eperimization detected by HPLC and NMR analysis. These examples prove that this protocol preserves the stereochemical integrity of the carbamates derived from a variety of highly hindered amino acids and chiral alcohols (Table 2, entry 8–12). Tertiary alcohols, for example, *tert*-butanol and thiol, however, gave poor conversion under the current conditions for the DSC activation step and hence warrant further investigation.

Table 2 Preparation of Carbamates from Hindered Amino Acids/Esters.



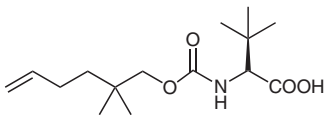
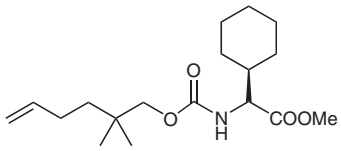
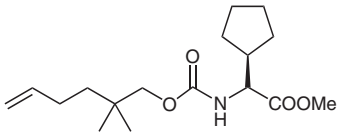
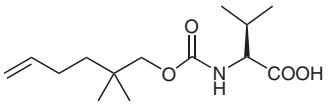
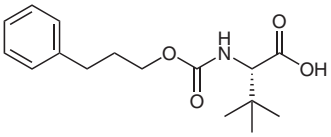
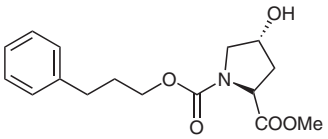
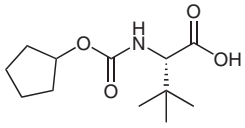
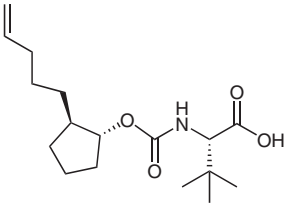
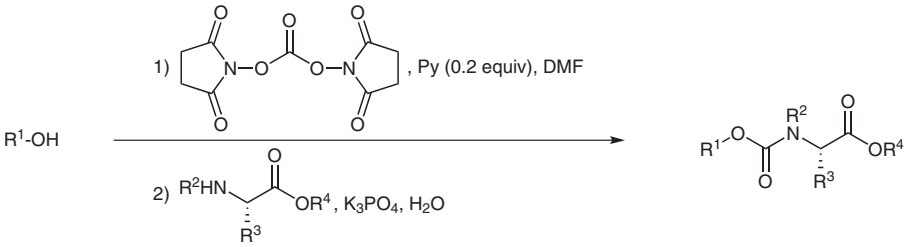
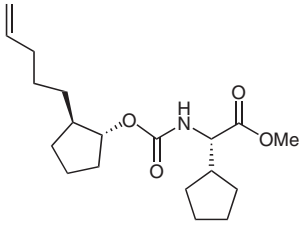
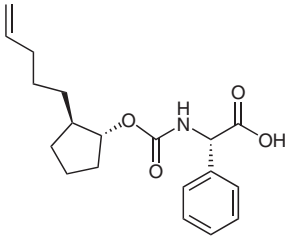
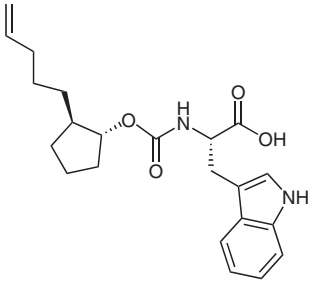
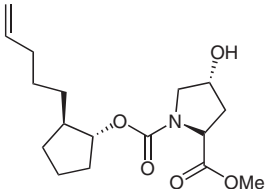
Entry	Product	Yield (%)
1		96
2		99
3		93
4		99
5		99
6		98
7		99
8		96

Table 2 Preparation of Carbamates from Hindered Amino Acids/Esters. (continued)



Entry	Product	Yield (%)
9		87
10		99
11		90
12		91

In conclusion, we have developed an efficient and chromatography-free protocol for the preparation of carbamates from primary or secondary alcohols with a variety of highly hindered amino acids/esters using commercial available *N*,*N*′-disuccinimidyl carbonate (DSC) and catalytic amount of pyridine in the presence of inorganic bases. This two-step method was easily carried out under mild conditions in one pot, and desired carbamates were obtained in an excellent yield and purity. We believe the current protocol could serve as a valuable addition to carbamate synthesis methodology, especially in the case of hindered amino acids or esters.

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(6) **General Procedure for Preparation of Carbamate 4**
To a solution of alcohol **5** (0.5 g, 3.9 mmol) in anhyd DMF (3 mL) was added DSC (1.2 g, 1.2 equiv) and pyridine (63 μL, 0.2 equiv). The mixture was heated and aged at 40 °C for 15 h until complete activation of **5** was observed as monitored by GC (>99% conversion). The mixture was cooled to ambient temperature for addition of H_2O (3 mL), keeping temperature below 30 °C. L-*tert*-Leucine (0.53 g, 1.0 equiv) and K_3PO_4 (1.66 g, 2 equiv), keeping the reaction temperature below 30 °C. The reaction mixture was then stirred at ambient temperature for 3–6 h until complete carbamate formation was observed as monitored by HPLC or TLC. To the reaction mixture was charged H_2O (10 mL) and EtOAc (10 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (5 mL). Both organic layers were combined, washed sequentially with 1 N HCl, H_2O and brine, and dried ($MgSO_4$). Concentration of the organic solution afforded the carbamate **4** as an oil, amide rotamers exists by NMR spectrum. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.93 (s, 6 H), 1.05 (s, 9 H), 1.35–1.38 (m, 2 H), 2.01–2.06 (m, 2 H), 3.80–3.82 (d, *J* = 10.0 Hz, 1 H), 3.87–3.89 (d, *J* = 10.0 Hz, 1 H), 3.98 (br, 0.3 H, minor rotamer), 4.21–4.23 (d, *J* = 10.0 Hz, 0.7 H, major rotamer), 4.93–4.95 (d, *J* = 10.0 Hz, 1 H), 5.01–5.04 (d, *J* = 15.0 Hz, 1 H), 5.27–5.29 (d, *J* = 10.0 Hz, 0.7 H, major rotamer), 5.78–5.86 (m, 1 H), 6.21–6.22 (br, 0.3 H, minor rotamer). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 24.1, 24.3 (minor rotamer), 26.5, 26.9 (minor rotamer), 28.30, 34.0, 34.6, 38.2, 62.0, 63.3 (minor rotamer), 73.2, 73.9 (minor rotamer), 114.1, 139.2, 139.9 (minor rotamer), 156.7, 176.4, 177.2 (minor rotamer).

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