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Controlled Synthesis of Asymmetric Dialkyl and Cyclic Carbonates Using the Highly Selective Reactions of Imidazole Carboxylic Esters

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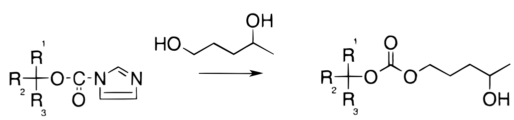
ABSTRACT



A new highly selective synthesis of dialkyl carbonates is described. The procedures rely on the previously unknown selectivity of imidazole carboxylic esters synthesized by the reaction of 1,1′-carbonyldiimidazole with alcohols. The imidazole carboxylic esters of secondary or tertiary alcohols form carbonates through the exclusive reaction with primary alcohols in polyols containing mixtures of primary, secondary, and tertiary hydroxyl groups without the need for protection. Controlled cyclic carbonate formation is also described.

The use of protection/deprotection chemistry during the formation of controlled or asymmetric structures often leads to unacceptable synthetic costs or lengthy procedures that may cause decreases in overall yield. Many extremely elegant synthetic methodologies using protection chemistry have been reported, especially in the field of carbohydrate chemistry.[1] Natural systems utilize highly selective reaction mechanisms often involving enzymatic catalysis[2] to produce precise molecular structures. The use of enzymatic reactions in the laboratory has been highly successful, but these synthetic pathways may involve long reaction times and relatively low yield. Highly selective chemical reactions that target specific functional groups in multifunctional molecules are extermely useful as they do not require protection chemistry.[3] During our study of compounds containing the carbonyl imidazole reactive group, we have discovered new selective bond-forming reactions that lead to controlled structures without the need for protection/deprotection strategies or enzymatic synthetic routes.

The use of carbonyl chlorides such as phosgene, chloroformates, acid chlorides, and carbamoyl chlorides to form amides, esters, ureas, carbamates, and carbonates is very well known, as are their toxicity and hydrolytic instability and the difficulties with isolation.[4] An alternative to phosgene is 1,1′-carbonyldiimidazole (CDI).[5] CDI has been used widely in peptide coupling, small molecule synthesis and also to prepare polymers.[6] Advantages of this reagent include its ease of handling (as it is a solid) and its relatively low toxicity. Also CDI may be used to synthesize imidazole carboxylic esters which may be considered as analogues of chloroformates.

We have investigated the formation and reactivity of imidazole carboxylic esters via the reaction of CDI with different alcohols and have discovered a surprising structure−reactivity dependence. A number of alcohol structures have

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(3) (a) Happaerts, T.; Ghosez, L. *Org. Synth.* **1998**, *75*, 177. (b) Toste, F. D.; Still, W. J. *Synlett* **1995**, 159. (c) Bose, D. S.; Lakshminarayana, V. *Synthesis* **1999**, 66.

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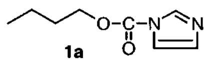
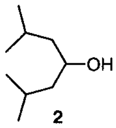
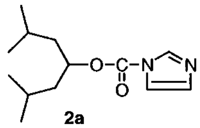
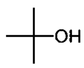
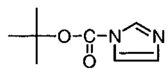
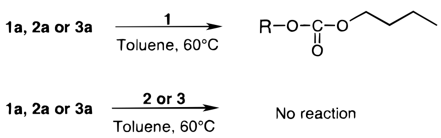
Table 1. Synthesis of Imidazole Carboxylic Esters

Starting Alcohol	Imidazole Carboxylic Ester Product	Isolated Yield (%)
 **1**	 **1a**	94[a]
 **2**	 **2a**	98[b]
 **3**	 **3a**	92[b]

[a] A 1.5 molar excess of CDI was used to prevent the formation of the biscarbonate. [b] An excess of alcohol was used to ensure complete reaction of CDI.

been studied, and the findings are illustrated by the selection of primary, secondary, and tertiary alcohols, **1**−**3**, and their imidazole carboxylic esters, **1a**−**3a**, shown in Table 1, and the reaction of the imidazole carboxylic esters with the alcohols **1**−**3**, shown in Scheme 1, and a number of polyols,[8] **4**−**10**, shown in Table 2.

Scheme 1

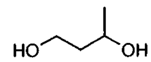
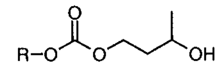
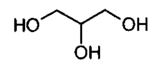
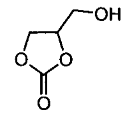
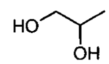
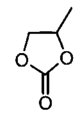
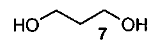
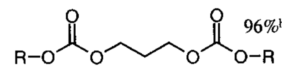
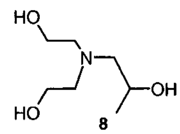
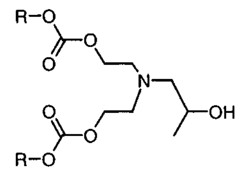
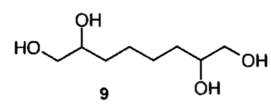
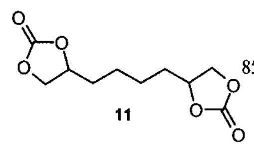
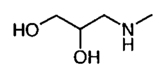
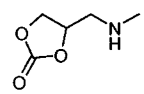


First, the reaction procedure required for the formation of **1a** varies from those that may be used to synthesize **2a** and **3a**. **1a** requires an excess of CDI to limit the unwanted formation of dibutyl carbonate, but the complete formation of **2a** and **3a**[7] is possible even in the presence of a large excess of the alcohol.

These differences suggested possible selectivity which was studied by the further reaction of each of the imidazole carboxylic esters **1a**−**3a** with each of the alcohols **1**−**3**.[8] The reaction of **1a**−**3a** with the primary alcohol **1** was successful in all cases, but all attempts to react **1a**−**3a** with either **2** or **3** produced no detectable dialkyl carbonate formation. When analyzing the crude reaction mixture, the starting alcohol and unreacted imidazole carboxylic esters could be identified easily. Therefore the imidazole carboxylic esters appear to react selectively with primary alcohols.

Further evidence for selectivity can be seen if the formation of the asymmetric dialkyl carbonate of **1** and either **2** or **3** is considered. Due to the selectivity of the reaction, it is only

Table 2. Reaction of Imidazole Carboxylic Esters with Various Polyols

Starting Polyol	Product and Isolated Yield (%)	
 **4**		97%[a]
 **5**		Mixture of products [b,c]
 **6**		85%[b]
 **7**		96%[b]
 **8**		98%[b]
 **9**	 **11**	85%[b]
 **10**	 **12**	82%[b]

[a] Reaction is completely selective when using **2a** and **3a** only, but **1a** leads to 20% reaction observed at the secondary hydroxyl. [b] Reactions only conducted using **2a** and **3a**. [c] Main component of mixture.

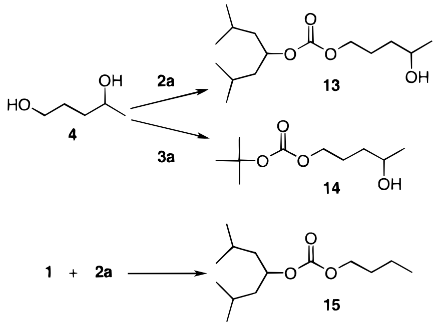
(7) **Typical Experimental:** The general procedure for the synthesis of imidazole carboxylic esters of secondary and tertiary alcohols can be exemplified by the procedure for the production of **3a** from **3**. Dry toluene (250 mL) was added to a 500 mL round-bottom flask fitted with a dry N_2 inlet and magnetic stirrer. 1,1'-carbonyldiimidazole, CDI (178 mmol), was added followed by *t*-butanol (357 mmol) and KOH (1 mmol). The mixture was heated at 60 °C with stirring for 4 h. The clear solution that formed was left to cool. The solution was concentrated in vacuo, dissolved in CH_2Cl_2 (100 mL), and washed three times with water (3 × 50 mL). The solution was dried with anhydrous Na_2SO_4 and concentrated in vacuo to give a clear liquid that solidifed on standing. Selected data for **3a**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 1.62 ppm (s, CH3), 7.02 (s, Im-H), 7.38 (s, Im-H), 8.08 (s, Im-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 27.56 (CH_3), 85.20 (R_3C-O), 116.88 (C-N), 129.97 (C-N), 136.79 (C-N), 146.85 (C═O); *m/z* (Es$^+$) 169.05 (MH$^+$, 100%). When using primary alcohols, a 1.1 molar excess of CDI is added to the flask and the alcohol is added dropwise over a period of at least 30 min.

(8) **Typical Experimental Procedure:** The procedure for reacting imidazole carboxylic esters with alcohols and polyols is exemplified by the synthesis of **13**. Dry toluene (150 mL) was added to a 250 mL round-bottom flask fitted with a dry N_2 inlet and magnetic stirrer. **2a** (40 mmol) was added to the solvent followed by KOH (1 mmol). The reaction was heated to 60 °C with stirring, and **4** (36.4 mmol) was added dropwise. The solution was left to stir at 60 °C for 4 h. The clear mixture was left to cool. The reaction was concentrated in vacuo, dissolved in CH_2Cl_2 (100 mL), and washed three times with water (3 × 50 mL). The solution was dried with anhydrous Na_2SO_4 and concentrated in vacuo to give a clear liquid. Selected data for **13**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 0.92 ppm (m, CH_3), 1.19 ppm (d, CH-C*H*$_3$), 3.83 (m, HOC*H*-CH_3) 4.15 (t, O(C═O)OCH_2), 4.88 (m, O(C═O)OCH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 67.64 (HO*C*H-CH_3), 67.95 (O(C═O)O*C*H_2), 75.97 (O(C═O)O*C*HR_2), 155.55 (C═O); *m/z* (Es$^+$) 275.60 (MH$^+$, 100%). In most cases it is preferable to synthesise the imidazole carboxylic ester in situ (as in ref 7) and add the alcoholic reagent directly to the flask without workup. In this case, **2a** would be synthesized and **4** would be directly added to the reaction mixture after 4 h at 60 °C.

possible to synthesize these materials from the reaction of **2a** or **3a** with **1** and not through the reaction of **1a** with **2** or **3** which suggests steric constraints as a possible rationale for the selectivity as the environment of the carbonyl of the imidazole carboxylic esters change quite considerably.

The selectivity was studied further using 1,4-pentanediol, **4**, which contains both primary and secondary alcohol sites. When reacting **1a** with **4**, carbonate formation was predominantly at the primary alcohol site but an approximately 20% reaction could be detected at the secondary hydroxyl. However, when reacting **2a** and **3a** with **4**, there was no carbonate formation at the secondary hydroxyl and reaction at the primary site only has been seen even if **2a** and **3a** are present in large excesses and the mixture is refluxed for several hours, Scheme 2.

Scheme 2



Evidence of selectivity is found in the API-MS examination of the products.[8] More conclusively, ^{1}H and ^{13}C NMR spectra confirm that no reaction occurs at the secondary hydroxyl as carbon and proton signals for the R_2CH-OH group of **4** remain unchanged after reaction. For example, the spectra of **4** are compared with those of **13** and **15** in Table 3. ^{13}C assignments were confirmed by DEPT spectra.

Table 3. ^{1}H and ^{13}C NMR Evidence for Selective Carbonate Formation with Imidazole Carboxylic Esters

Compound	^{1}H NMR Data δ (ppm), species	^{13}C NMR Data δ (ppm), species
4	1.19, CH_3(CH)OH 3.59, CH_2OH 3.78, CH_3(CH)OH	62.65, CH_2OH 67.86, CH_3(CH)OH
13	1.19, CH_3(CH)OH 3.83, CH_3(CH)OH 4.15, CH_2O(C=O)O 4.88, R_2CHO(C=O)O	67.64, CH_3(CH)OH 67.95, CH_2O(C=O)O 75.97, R_2CHO(C=O)O
15	4.12, CH_2O(C=O)O 4.88, R_2CHO(C=O)O	67.73, CH_2O(C=O)O 75.73, R_2CHO(C=O)O

Selective carbonate formation using **3a** provides an easy and single-step selective *t*-Boc protection of the primary hydroxyl which would normally be achieved using reagents such as *t*-Boc anhydride followed by careful separation of the three possible products.

Carbonate formation in triols[8] was studied via the reaction of **2a** and **3a** with **8** and **5**. In the case of **8** the reaction of the imidazole carboxylic esters gave 100% yield of carbonates via reaction at the primary hydroxyl groups without reaction at the secondary hydroxyl, but the reaction of **2a** and **3a** with **5** did not proceed as expected. To simplify the reaction, two diols, 1,2- and 1,3-propanediol (**6** and **7**), were chosen as models for **5** and were reacted with **2a** and **3a**. In both cases, the reaction with **7** proceeded as expected with the formation of the bis-carbonate; however, when **2a** or **3a** was reacted with **6**, propylene carbonate was formed and the corresponding alcohols **2** or **3** were recovered. We believe that the cyclic carbonate formation proceeds via the selective reaction of **2a** or **3a** at the primary hydroxyl followed by an intramolecular substitution involving the neighboring secondary hydroxyl. The cyclization appears to be structure dependent and reliant on 1,2-substitution as the synthesis of the hydroxy carbonates of **4** and **8** and biscarbonates of **7** show no cyclic carbonate formation.

The imidazole carboxylic ester **3a** was also reacted with tetrol **9** and amino diol **10**. The bis-cyclic carbonate **11** was synthesized as expected with evidence of cyclization derived from the comparison of the ^{1}H and ^{13}C NMR spectra of **9** and **11**. The ^{1}H NMR (CD_3OD) spectrum of the starting tetrol **9** shows two complex peaks: one at $\delta = 1.60$ ppm corresponding to the $(CH_2)_4$ unit and a further peak at $\delta = 3.64$ ppm which has been assigned as the CH(OH)CH_2(OH) diol groups. The CH(OH) and CH_2(OH) are also easily detected in the ^{13}C DEPT (CD_3OD) spectrum at $\delta = 73.68$ and 67.88 ppm, respectively. The ^{1}H NMR ($CDCl_3$) spectrum of **11** however showed a marked simplification of the previously complex signal of the diol groups. Three peaks are now present at $\delta = 3.98$ (t, 1H, CH(H)), 4.44 (t, 1H, CH(H)), and 4.61 ppm (m, 1H, CH(R)), indicating the inequivalence of the CH_2 protons in the cyclic carbonate ring. The ^{13}C signals for both carbons were also shifted significantly. Small signals are present in the spectrum for incomplete reaction which aids the interpretation of the ^{13}C spectra with respect to the change of NMR solvent. The ^{13}C ($CDCl_3$) signals for the diol unit of unreacted tetrol **9** are very similar to those of the spectrum run in CD_3OD and are at $\delta = 74.17$ and 67.31 ppm. The cyclic carbonate shows signals at $\delta = 77.07$ and 69.57 ppm. The carbonate carbonyl is also present at $\delta = 155.34$ ppm, confirming carbonate formation.

If the reaction had proceeded with carbonate formation only at the primary alcohol, we would have expected to still see a complex ^{1}H NMR spectrum and only marked changes for the CH_2(OH) ^{13}C signal.

The synthesis of the amino cyclic carbonate **12** also proceeded without complication and shows an unexpected additional selectivity as there was no detectable reaction with the secondary amine functionality.

In summary, we have identified a series of new structure-specific selective reactions using well-known reagents. The imidazole carboxylic esters formed by the reaction of 1,1′-carbonyldiimidazole and either secondary or tertiary alcohols will react selectively with primary hydroxyls in polyols containing mixtures of primary, secondary, and tertiary hydroxyls without the need for protection chemistry. This can be used to introduce *t*-Boc protection at primary hydroxyl sites controllably. If the polyol consists of 1,2-diol substitution, it is possible to form cyclic carbonates without unwanted side reactions or reaction with secondary amine functional groups.

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