ORGANIC LETTERS

2000
Vol. 2, No. 14
2117−2120

The Selective Reaction of Primary Amines with Carbonyl Imidazole Containing Compounds: Selective Amide and Carbamate Synthesis

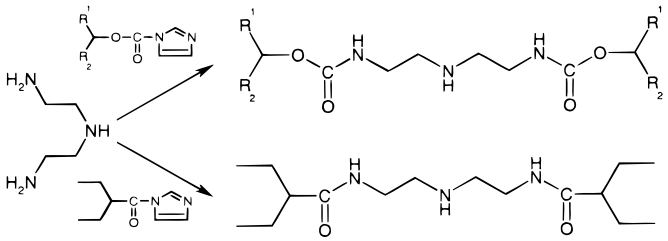
Steve P. Rannard*,† and Nicola J. Davis‡

Unilever Research Port Sunlight, Quarry Road East, Bebington, Wirral L63 3JW, England

steven.rannard@unilever.com

Received May 5, 2000

ABSTRACT



A new highly selective synthesis of amides and carbamates is described. In both cases the syntheses involve the formation of carbonyl imidazole intermediates which subsequently undergo previously unreported selective reactions with primary amines. Acid imidazolides with sufficient chain length will exclusively react with primary amines even in the presence of secondary and tertiary functionality. The imidazole carboxylic esters of secondary or tertiary alcohols also react selectively with primary amines, forming controlled carbamate structures.

Highly selective chemistry, capable of selecting between primary and secondary functional groups on the same molecule, has applications in a number of different synthetic strategies to form controlled structures without lengthy protection/deprotection steps. Recently we reported the use of imidazole carboxylic esters in the controlled and selective formation of dialkyl carbonates of polyols containing mixtures of primary, secondary and tertiary hydroxyls.[1] The selectivity was also used to controllably form cyclic carbonates.

The imidazole carboxylic esters were formed via the reaction of 1,1′-carbonyl diimidazole (CDI) with different alcohols. Our studies[2] have shown that if the parent alcohol of the imidazole carboxylic ester is either secondary or tertiary, further reaction to form carbonates is exclusively limited to primary alcohols with no detectable reaction at secondary or tertiary hydroxyl groups.

During our previous study[1] the reactivity of these imidazole carboxylic esters with amines was also described briefly; they were noted not to react with the secondary amine functional group present in an amino-triol during a cyclic carbonate synthesis.

CDI has also been used for many years to form amides and peptides[3] by reaction with aliphatic acids to form acid imidazolides, analogues of acid chlorides, and subsequent reaction with amines. The advantages of this method include the mild reaction conditions which minimize racemization of the amino acid,[4] the lack of formation of amine hydrochloride when using acid chlorides, and the removal of lengthy purification stages.

† Work carried out at Courtaulds Corporate Technology, Coatings and Sealants, Coventry, CV6 5RS, U.K.

‡ Current address: Dextra Laboratories Limited, The Innovation Centre, The University, Reading, RG6 6BX, England. Fax: 0118 986 1894.

(1) Rannard, S.; Davis, N. *Org. Lett.* **1999**, *1*(6), 933
(2) Rannard, S.; Davis, N. WO97/23443.
(3) Staab, H. A. *Angew. Chem., Int. Ed. Engl.* **1962**, *1*, 351
(4) Paul, R.; Anderson, G. W. *J. Am. Chem. Soc.* **1960**, *82*, 4596.

10.1021/ol006020n CCC: $19.00
Published on Web 06/17/2000

Our studies of selective carbonate formation led us to undertake a more detailed investigation of the possible selectivity of imidazole carboxylic esters and acid imidazolides with primary and secondary amines during the formation of carbamates and amides.

The amines chosen for the study are shown in Figure 1

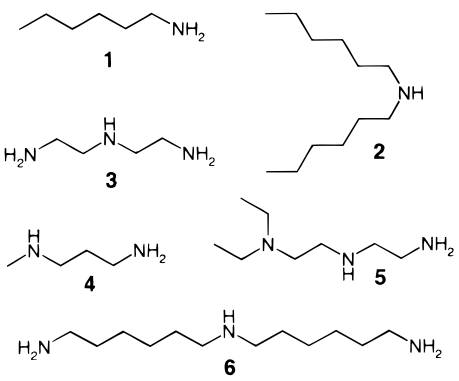


Figure 1. Amines used in selective urethane and amide synthesis.

and include 1-hexylamine **1**, dihexylamine **2**, and diethylene triamine **3**.

The imidazole carboxylic esters **7a**−**9a** which have been shown to react selectively with primary alcohols were chosen for investigation of carbamate synthesis. A series of aliphatic and aromatic acids with varying structures, **10**−**14**, were chosen to investigate the selective synthesis of amides. The alcohols, acids, and carbonyl imidazole intermediates are shown in Table 1.

Each of the imidazole carboxylic esters **7a**−**9a** was synthesized as described previously[1] and reacted with primary amine **1** and secondary amine **2**.[5] Reaction with **1** successfully formed carbamate in all cases and in high yield. Since **9a** is the synthetic equivalent of *tert*-butyl chloroformate, the reaction of **1** with **9a** forms the *t*-BOC protected amine via a facile one-pot reaction avoiding the use of di-*tert*-butyl dicarbonate (*t*-BOC anhydride).[6] Reaction of **2** with **7a**−**9a** only formed carbamate when **7a** was used. Unreacted imidazole carboxylic ester was recovered when using **8a** and **9a** with no detectable carbamate formation. The difference between the reactions of **8a** and **9a** with primary and secondary amines is identical to the reaction of these

Table 1. Starting Materials and Carbonyl Imidazole Intermediates

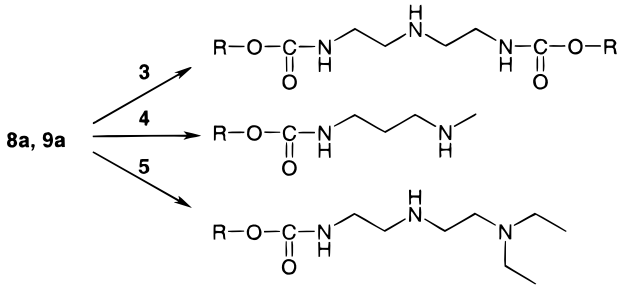
Starting material	Carbonyl imidazole intermediate
Alcohols[a]	
OH **7**	**7a**
OH **8**	**8a**
OH **9**	**9a**
Acids[b]	
CH_3CO_2H **10**	**10a**
$CH_3CH_2CO_2H$ **11**	**11a**
CO_2H **12**	**12a**
CO_2H **13**	**13a**
14 CO_2H	**14a**

[a] Synthesis details have been previously reported.[1] [b] Intermediates are not isolated but synthesized and reacted in situ.

intermediates with primary, secondary, and tertiary alcohols[1] during carbonate formation.

To study the possible selectivity of carbamate formation, **8a** and **9a** were reacted with the triamine **3**, using an equimolar ratio based on primary amine groups. Mass spectrometry of the products after a simple aqueous wash yielded molecular ions, confirming formation of only two carbamate groups per triamine (MH^+ [**8a** + **3**] = 444.69 and MH^+ [**9a** + **3**] = 304.62), Scheme 1. No higher mass

Scheme 1



(5) **Typical experimental procedure:** The procedure for reacting imidazole carboxylic esters with amines is exemplified by the reaction of **9a** with **3**. Dry toluene (150 mL), **9** (40 mmol), KOH (1 mmol), and CDI (40 mmol) were added to a 250 mL round-bottom flask fitted with a dry N_2 inlet and magnetic stirrer and heated to 60 °C with stirring for 3 h. **3** (20 mmol) was added dropwise. The solution was left to stir at 60 °C for a further 3 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 colorless gum. Yield = 95.4%. ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 1.45 ppm (s, $(CH_3)_3$), 2.75 (m, CH_2-$NHCH_2$), 3.20 (m, $O(C{=}O)NHCH_2$). ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 28.39 ($CH_3)_3$, 48.60 (CH_2NHCH_2), 78.89 (CR_4), 156.33 ($NH(C=O)O$). *m/z* (Es^+) 304.60 (MH^+, 100%). **9a** may also be synthesized and isolated in a separate reaction if required.

(6) Ponnusamy, E.; Fotador, U.; Spisni, A.; Fiat, D. *Synthesis* **1986**, *48*.

ions were detected. In both cases, formation of the carbamate at the primary amine functional group only was confirmed by ^{1}H and ^{13}C NMR due to the unchanged signals at δ = 2.75 ppm (C*H*$_2$NHC*H*$_2$) and δ = 48.60 (*C*H$_2$NH*C*H$_2$) and the corresponding carbonyl at δ = 156.50 ppm (NH(*C*=*O*)O).

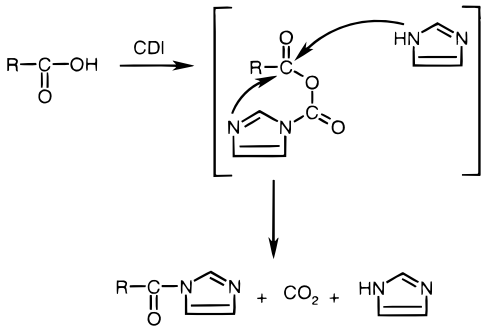
As stated earlier, the reaction of amines with **9a** yields a *t*-BOC-protected amine. **9a**, which therefore allows the controlled introduction of amine protection at primary amine groups in polyamines containing mixtures of differently substituted amines.

The versatility of the selective protection was studied further by reacting **9a** with **4** (three methylene groups between amines) and **5** (containing primary, secondary, and tertiary amines). In all cases the imidazole carboxylic ester was added in a 1:1 ratio based on the primary amine functionality. The introduction of the *t*-BOC group occurred at the primary amine in each case without carbamate formation at the secondary amine functional group (confirmed by ^{1}H and ^{13}C NMR). Mass spectrometry yielded the expected molecular ions for selective and single carbamate formation (MH$^+$ [**9a** + **4**] = 189.36 and MH$^+$ [**9a** + **5**] = 259.23). A summary of selective carbamate synthesis is shown in Scheme 1.

The success of the selective carbamate formation was expected on the basis of a previous observation that **9a** formed carbonate only when reacted with an amino diol. The reaction of acid imidazolides with amines was not investigated previously, and there are no reports of selective amide formation using this route.

The formation of an acid imidazolide is a trivial process and involves equimolar addition of CDI to a solution of acid in an anhydrous solvent at room temperature or higher. The addition of CDI is accompanied by instant effervescence as CO_2 is liberated.[3] The reaction is thought to proceed via an intermediate imidazole anhydride which decomposes after either an intra- or intermolecular nucleophilic attack by an imidazole group, Scheme 2.

Scheme 2



The synthesis of acid imidazolides proceeds smoothly for both aromatic and aliphatic acids, and a number of differing acid structures have been investigated in this study, **10**−**14**.

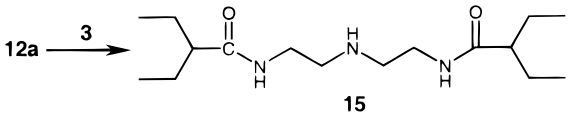
In a study identical to that for the selective carbamate formation, **10**−**14** were converted to the corresponding acid imidazolides **10a**−**14a** and reacted further with the primary amine **1** and secondary amine **2**. The isolation of acid imidazolides is not easy, as they are highly reactive and moisture sensitive; therefore they are formed in situ and reacted without purification. In all cases, the formation was monitored by CO_2 evolution and the dissappearance of the starting acid by TLC. It is also very important to purge the system with dry N_2 before addition of amine as the reaction of amines with CO_2 hampers the amide formation.

In all cases, the acid imidazolides **10a**−**14a** reacted with **1** to form amides in high yield.[7] However, when the same reaction was attempted with **2**, the formation of amide with **12a** was not possible. Amide synthesis however with **2** was successful with the other acid imidazolides, **10a**, **11a**, **13a**, and **14a**.

In an attempt to favor amide formation between **12a** and **2**, a series of different reaction conditions were applied including changing solvents (CH_2Cl_2, THF, and toluene) and increasing temperature (rt to reflux). Amide formation was not detected even when the reaction was conducted at reflux temperature in toluene for 8 h.

Amide formation between **12a** and **3** produced the selective amino diamide at room temperature via reaction at the primary amine functionality only, Scheme 3. The successful

Scheme 3



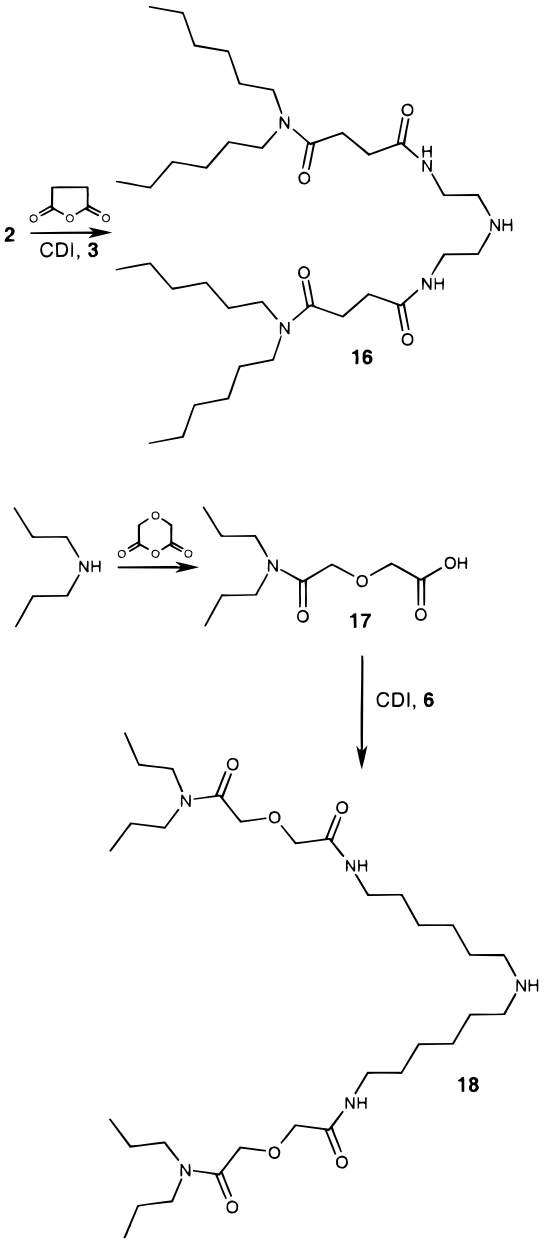
15

reaction was again analyzed using mass spectrometry, which confirmed the addition of only two acids (MH$^+$ **15** = 300.66) and ^{1}H and ^{13}C NMR which confirmed amide formation δ = 177.05 ppm (NH(*C*=*O*)) and unchanged signals at δ = 2.75 ppm (C*H*$_2$NHC*H*$_2$) and δ = 48.91 (*C*H$_2$NH*C*H$_2$).

The selective amide synthesis was unexpected and appeared to be due to the increased steric hindrance of acid **12** and subsequently acid imidazolide **12a**. To investigate the amide synthesis further, amine **2** was reacted with succinic

(7) **Typical experimental procedure:** The synthesis of aliphatic and aromatic amides is exemplified by the selective synthesis of **15**. **12** (67.5 mmol) was added to a 100 mL round-bottom flask containing HPLC grade toluene (50 mL) and fitted with a reflux condenser, a dry N_2 inlet, and a magnetic stirrer. The solution was heated to 60 °C and stirred. CDI (67.5 mmol) was added to the solution and stirred until the CO_2 evolution had ceased. The solution was heated for a further 30 min and purged with dry nitrogen. **3** (33.5 mmol) was added to the solution and allowed to stir at 60 °C for a further 2 h and then cooled to room temperature. The reaction mixture was concentrated in vacuo, and the remaining clear liquid was dissolved in CH_2Cl_2 and washed three times with water (3 × 10 mL). The washed CH_2Cl_2 solution was dried with anhydrous Na_2SO_4, filtered, and concentrated to give the product as a clear liquid. Yield 92.7%. ^{1}H NMR (300 MHz; $CDCl_3$) δ = 0.85 (t, C*H*$_3$CH$_2$), 1.3−1.7 (m, C*H*$_2$CH$_3$), 1.95 (m, CH), 2.75 (m, C*H*$_2$NHC*H*$_2$), 3.35 (m, C*H*$_2$NHC(=O)). ^{13}C NMR (75 MHz; $CDCl_3$) δ = 12.23 (*C*H$_3$CH$_2$), 25.86 (*C*H$_2$CH$_3$), 48.91 (*C*H$_2$NHC*H*$_2$), 51.09 (CH), 177.05 (NH(*C*=O)). *m*/*z* (ES$^+$) 300.66 (MH$^+$).

Scheme 4



anhydride to form an amido acid which we believe to be less sterically hindered than **12**. The reaction of the amido acid with CDI and subsequently with **3** also gave selective amide formation as shown by NMR and mass spectrometry (MH^+ **16** = 639.14), Scheme 4.

To ensure that the selectivity was not purely driven by steric hindrance, a final reaction was conducted which involved decreasing the size of the starting amine by substituting dihexylamine, **2**, with a much smaller amine, dipropylamine. Succinic anhydride was replaced with diglycolic anhydride in order to increase the distance between the amide group and the acid functionality while introducing a more flexible ether link, and diethylenetriamine, **3**, was replaced with bis-hexamethylene triamine, **6**, to remove any possible influence on reactivity due to the proximity of the amines in the triamine.

The formation of amido acid **17** was confirmed by mass spectrometry (MH^- **17** = 216.40). Reaction of the acid with CDI and subsequently with **6** yielded the selective diamide as expected (MH^+ **18** = 614.67). The selectivity appears to be derived from the presence of substituents γ to the imidazolide carbonyl group. Selectivity also appears to be limited to aliphatic acids although further work is required to confirm this assumption. Although steric factors cannot be ruled out, steric hindrance alone cannot explain the selectivity of acid **12** and the subsequent selectivity of the ring opened cyclic anhydrides, e.g., **17**.

In summary, we have identified new selective chemistry that allows the facile controlled formation of either carbamates or amides selectively at the primary amine functionality of polyamines containing mixtures of primary, secondary, and tertiary amines. The selectivity of carbamate formation appears to be determined by the structure of the parent alcohol of the imidazole carboxylic ester used. Selective amide formation is still somewhat confusing but may be limited to the reaction of aliphatic acids containing substituents γ to the acid imidazolide. Further work is required to confirm the nature of the selectivity in this case.

Acknowledgment. The authors thank the members of the Courtaulds Corporate Technology Analytical Group especially Tim Jenkins for mass spectrometry and Ian Herbert and Christine Wallace for their help with NMR spectroscopy.

OL006020N