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SHORT COMMUNICATION

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Reactive Esters in Amide Ligation with β-Hydroxyamines

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Amide formation between mildly activated esters and 1,2-amino alcohols occurs without the need for coupling reagents. The reaction pathway involves facile intermolecular transesterification and intramolecular O→N transacylation. The method is environmentally friendly and offers no risk of racemization via highly activated acylating intermediates.

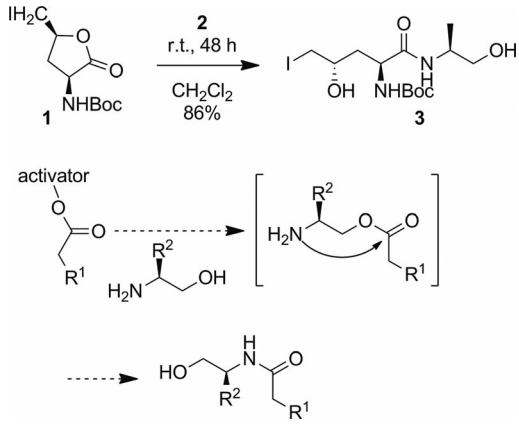
Introduction

The preparation of amides is among the most heavily investigated organic reactions. Methods and reagents for amide formation developed for solid-phase peptide synthesis are widely applied outside that field. However, these methods are often unsuitable for solution-based preparative processes because they use excessive amounts of expensive coupling reagents and create significant waste streams. Nonetheless, advances in amide formation continue to be reported,[1] and these methods address such issues as catalysis, sustainability, and versatility.

Results and Discussion

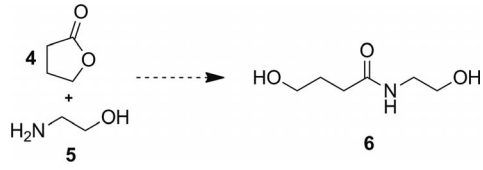
During studies on the synthesis of non-ribosomal polypeptide natural products,[2] we observed a facile reaction between lactone **1** (obtained by iodolactonization of allylglycine)[3] and alaninol (**2**) to form β-hydroxyamide **3** (Scheme 1). We surmised that this process might occur via reaction of the activated ester of the lactone by initial transesterification, followed by rearrangement of the ester to the more stable hydroxy amide. Good evidence for the proposed transesterification/transacylation pathway was obtained by substituting *t*BuMe$_2$SiO–alaninol in this reaction; only starting material was recovered.

Support for the proposed pathway is also found in the work of Movassaghi,[4] who studied reactions of β-amino alcohols with a range of esters employing a N-heterocyclic carbene (NHC) catalyst. We chose one reaction from Movassaghi's study, γ-butyrolactone and ethanolamine giving



Scheme 1. Facile lactone amidation via transesterification.

known compound **6** (Scheme 2), to further examine amide ligations via transesterification. Results are summarized in Table 1. Reactions were performed at a 1-M initial ester concentration. Entry 1 (Table 1) gives the result for Movassaghi's NHC-catalyzed reaction; however, he did not examine the uncatalyzed background reaction, which we studied in Entry 2 (Table 1). It shows that the NHC provides only a ca. twofold rate acceleration in the reaction of **4**, with a major decrease in convenience because it requires an inert atmosphere.



Scheme 2. Butyrolactone reaction with ethanolamine.

Variations in reaction parameters (solvent, additives, time, temperature) were examined to increase ligation efficiency. To permit economy with more precious amino alcohols, equimolar amounts of **5** and **4** were used. The reaction of **4** is slower than **1**, owing to the electron-withdrawing α-amino group of **1**. Patience or mild heating still

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Table 1. Reaction optimization for the preparation of **6**.

Entry	Time [h]	*T* [°C]	Solvent	Catalyst	Yield [%]
1	6	25	THF	NHC	88
2	6	25	THF	none	51
3	60	25	CH_2Cl_2	none	83
4	6	reflux	CH_2Cl_2	none	79
5	6	25	toluene	none	74
6	12	25	toluene	none	79
7	18	25	toluene	none	84
8	1	120[a]	toluene	none	85
9	6	25	hexane[b]	none	84
10	6	25	cyclohexane[b]	none	84
11	6	25	toluene	TBD	88
12	1	25	toluene	TBD	78
13	1	25	hexane[b]	TBD	86
14	1	25	cyclohexane[b]	TBD	92

[a] Microwave heating. [b] Heterogeneous.

Table 2. Reaction scope for lactone hydroxyamidation.

Entry	Lactone	Aminol	Method A	Method B
1	**4**	**2**	38	81
2	**4**	**9**	25	70
3	**4**	**10**	27	74
4	**4**	**11**	65	79
5	**7**	**5**	90	58
6	**7**	**2**	87	48
7	**7**	**9**	83	60
8	**7**	**10**	83	58
9	**7**	**11**	92	55
10	**8**	**5**	84	73
11	**8**	**2**	64	40
12	**8**	**9**	59	36
13	**8**	**10**	60	31
14	**8**	**11**	38	55

allows **6** to be obtained in high yield. The fastest reaction occurs with microwave heating. Somewhat surprising was that the reaction improves in nonpolar solvents, with the best solvents being hydrocarbon-based. For hexanes and cyclohexane, the lactone was insoluble, so the reaction essentially occurred neat.

A variety of transesterification catalysts were investigated, including Et_3N, Ti^{IV} salts, and carboxylic acids, but all had no effect. However, triazabicyclodecene (TBD),[5] a recently identified catalyst, proved effective even at 5 mol-% (earlier work used 10 mol-%). Fast reactions required the combination of an amino alcohol with the TBD catalyst and a nonpolar solvent.

Other available γ-lactones and amino alcohols (Figure 1) were examined under the conditions from Entry 8 (Table 1, method A) and Entry 14 (Table 1, method B). Yields from each combination under the same conditions are given in Table 2. To permit structure–reactivity relationships to be discerned, reactions were not individually optimized. γ-Butyrolactone is particularly efficient in TBD-catalyzed reactions, but Boc-homoserine lactone (**7**) and (*R*)-pantolactone (**8**) are better ligated under microwave heating. Lactones **7** and **8** are expected to be more reactive than γ-butyrolactone owing to their polar α-substituents, as ascertained by method A. Their steric hindrance may inhibit reaction with TBD.

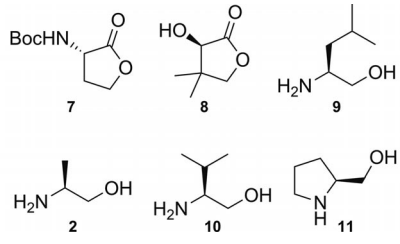
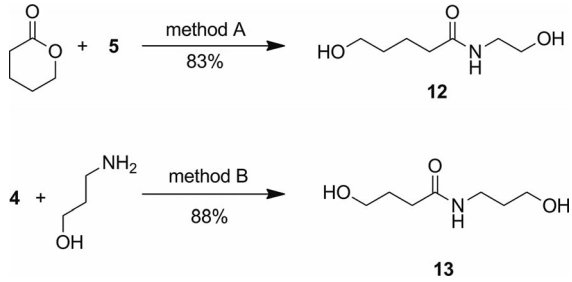


Figure 1. Lactones and 1,2-amino alcohols studied in this amide ligation.

δ-Caprolactone was nicely reactive under method A despite its reduced ring strain compared to butyrolactone (Scheme 3), but results nearly as good were obtained with method B. Method B also works well with 3-amino-1-propanol, so these reactions are not limited to β-amino alcohols.



Scheme 3. Chain length variation in each reactant.

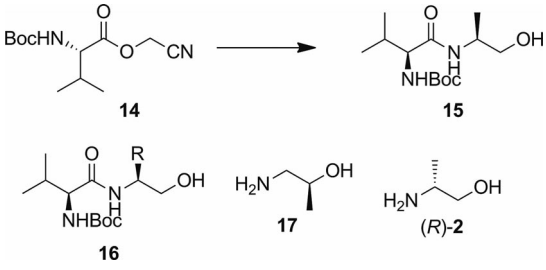
While these results were interesting and useful, lactones are only a small subset of carboxylic acid derivatives, so another mildly activated ester was sought that could be prepared from any acid. We were particularly interested in applying this ligation to α-amino acids. A number of examples of transesterification reactions of cyanomethyl esters of amino acid derivatives with nucleotide hydroxy groups are known,[6] prompting our evaluation of their reactions with amino alcohols. Because conventional formation of peptide bonds at hindered valine residues can be challenging, valine was used to test the idea.

Formation of the cyanomethyl ester of Boc-valine proceeded in quantitative yield with bromoacetonitrile (2 equiv.) and Cs_2CO_3 in acetonitrile (1 h, r.t.). Conditions for ligation of alaninol (1.5 equiv.) to **14** were then examined (Table 3, Scheme 4). All of these reactions were performed at a concentration of 1 M. Adequate reactivity was observed in THF, but reactions were faster with the addition of 20% acetic acid and heating at reflux. Other aprotic solvents were examined, and for the most part the solvent effect was small, but cyclohexane again proved superior. The best results (Table 3, entries 16, 17) were seen with extended reaction at ambient temperature or a quick reaction with microwave heating. TBD was not a very effective catalyst for this reaction.

Table 3. Reaction optimization for the preparation of **15**.

Entry	Time [h]	*T* [°C]	Solvent	Additive	Yield [%]
1	60	25	THF	none	71
2	1.5	100[a]	THF	none	61
3	24	reflux	THF	AcOH	68
4	60	25	MeCN	AcOH	53
5	60	25	THF	AcOH	78
6	1.5	100[a]	THF	AcOH	75
7	24	reflux	CH_2Cl_2	AcOH	66
8	60	25	toluene	AcOH	58
9	60	25	DCE	AcOH	58
10	1.5	100[a]	DCE	AcOH	55
11	60	25	EtOAc	AcOH	68
12	1.5	100[a]	EtOAc	AcOH	71
13	1.5	100[a]	toluene	AcOH	57
14	60	25	hexane	AcOH	74
15	1.5	100[a]	hexane	AcOH	74
16	60	25	cyclohexane	AcOH	90
17	1.5	100[a]	cyclohexane	AcOH	82
18	1.5	25	cyclohexane	TBD	68

[a] Microwave heating.

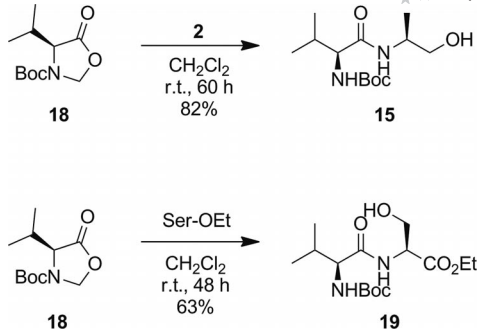


Scheme 4. Ligation via cyanomethyl esters.

One potential drawback of ligations via cyanomethyl esters is the coproduction of formaldehyde and the cyanide ion (or glycolonitrile). Reactions were therefore completed by addition of 2 equiv. of sodium ferrate, a mild oxidant that destroys both,[7] and raising the pH of the solution to 9. The absence of cyanide was established with cyanide test strips.

Ligations of diverse amino alcohols with **14** to give amides **16** were then examined under the conditions of entry 6 (Table 3). An additional reactant examined was **17**, which gave the amide in 79% yield and demonstrated that secondary alcohols can participate in the postulated transesterification step. The *R* isomer of alaninol provided authentic samples of the diastereomer of **15** (71% yield) that would be produced if the coupling of **2** with **14** caused racemization. By comparing the ^{13}C NMR spectra of these products, it was possible to establish >99.5% retention of configuration in this ligation. The other amino alcohols studied here gave good results in reactions with **14**: **5**, 87%; **9**, 83%; **10**, 81%; **11**, 92%.

This success stimulated investigation of α-amino acid esters that combine lactone and acetal functionality: oxazolidinones. They can be derived in one step from Boc amino acids under acidic or basic conditions[8] and offer the same inductive activation from the α-amino group as **1**. Here, Boc-valine oxazolidinone **18** reacted with alaninol to give **15** in high yield under the mildest of conditions (Scheme 5).



Scheme 5. Ligations with oxazolidinones.

Because serine and cysteine are simply more complex amino alcohols and amino thiols, the idea of forming peptide bonds through processes similar to these has a substantial history. There are straightforward intellectual progenitors, such as native chemical ligations, "isopeptides" or "switch peptides",[9] as well as more convoluted approaches using auxiliary groupings.[10] Here, we took the simple approach of treating **18** with ethyl serinate, which gave dipeptide **19** without racemization and in adequate yield for an initial investigation (Scheme 5).

Conclusions

To explain our observation of facile hydroxyamide ligation of mildly activated esters, we hypothesize that the 1,2-amino alcohol is especially reactive toward transesterification, which could be due to an internal hydrogen bond between the amine and the OH group (Figure 2). This could also explain the preference for nonpolar solvents, as they do not compete with the internal nitrogen as H-bond acceptors.

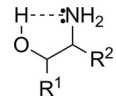


Figure 2. Internal hydrogen bonding may enhance amino alcohol transesterification.

Experimental Section

D-(–)-Pantolactone (2.00 g, 15.4 mmol), ethanolamine (939 mg, 15.4 mmol), and anhydrous toluene (15.4 mL) were added to a round-bottomed flask with a stir bar. The reaction mixture was heated at 120 °C for 1 h in a CEM Discover monomode microwave reactor. Temperature was monitored with the IR temperature feature of the reactor. After concentration, the residue was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH, 90:10) to provide the product as a light yellow oil (2.666 g, 91% yield). The ^1H NMR spectrum matched literature data.[11]

Supporting Information (see footnote on the first page of this article): Copies of the ^1H and ^{13}C NMR spectra for key new compounds.

Acknowledgments

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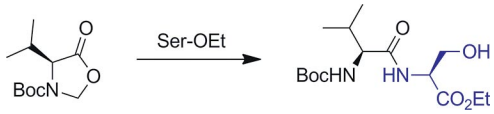
Amide Ligation



Exploiting a surprisingly easy initial transesterification process, amides are formed from hydroxyamines and lactones or cyanomethyl esters. Reactions occur rapidly without risk of racemization.

Keywords: Amides / Acylation / Green chemistry / Transesterification / Peptides

