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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-aminoalcohols occurs without the need for coupling reagents. The reaction pathway involves facile intermolecular trans-esterification and intramolecular O→N trans-acylation. The method is environmentally responsible and offers no risk of racemization via highly activated acylating intermediates.

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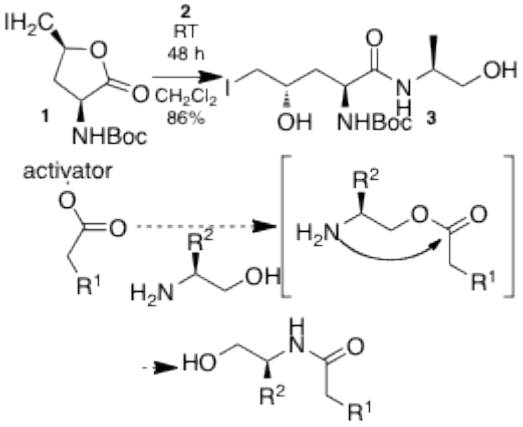
Introduction

Amide preparations must be 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. Yet, they are often not well-suited to preparative processes in solution because they use large excesses of expensive coupling reagents and create significant waste streams. Advances in amide formation continue to be reported,[1] however, which address such issues as catalysis, sustainability, and versatility.

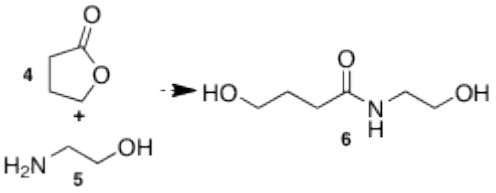
Results and Discussion

During studies on syntheses 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 lactone's activated ester in an initial trans-esterification, followed by rearrangement of the ester to the more stable hydroxy amide. Good evidence for the proposed trans-esterification/trans-acylation pathway was obtained by substituting *tert*-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-aminoalcohols 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 the known compound **6** (Scheme 2), to further examine amide ligations via trans-esterification. Results are summarized in Table 1. Reactions were performed at a 1M initial ester concentration. Entry 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. It shows that the NHC provides only a ~2-fold rate acceleration in reaction of **4**, with a major decrease in convenience because it requires an inert atmosphere.



Scheme 1. Facile lactone amidation via transesterification.



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 aminoalcohols, amounts of **5** equimolar with **4** were used. The reaction of **4** is slower than **1**, easily understood owing to the electron-withdrawing α-amino group of **1**. Patience or mild heating still allows **6** to be obtained in high yield, though. The fastest reaction occurs with microwave heating. Somewhat surprising was that reaction improves in non-polar solvents, with the best being hydrocarbons. For hexanes and cyclohexane, the lactone was insoluble, so reaction essentially occurred neat.

A variety of transesterification catalysts were investigated, including Et$_3$N, Ti(IV) salts, and carboxylic acids, to no effect.

However, triazabicyclodecene (TBD),[5] a recently identified catalyst, proved effective even at 5 mol-% (earlier work used 10 mol-%). Fast reactions require the combination of aminoalcohol with TBD catalyst and non-polar solvent.

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

Entry	Time (h)	Temp(°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	*c*-hexane[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	*c*-hexane[b]	TBD	92

[a] microwave heating. [b] heterogeneous.

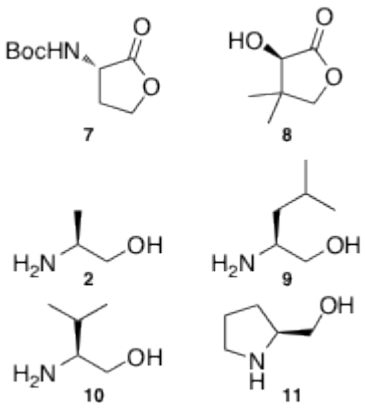


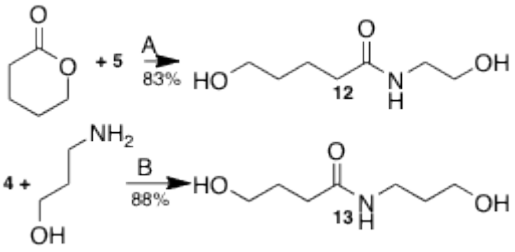
Figure 1. Lactones and 1,2-aminoalcohols studied in amide ligations.

Other available γ-lactones and aminoalcohols (Figure 1) were examined under conditions from Entry 8 (Method A) and Entry 14 (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 borne out with Method A. Their steric hindrance may inhibit reaction with TBD.

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

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-aminoalcohols.



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-aminoacids. A number of examples of trans-esterification reactions of cyanomethyl esters of aminoacid derivatives with nucleotide hydroxyl groups are known,[6] prompting our evaluation of their

reactions with aminoalcohols. Since conventional formation of peptide bonds at hindered valine residues can be challenging, valine was used to test the idea.

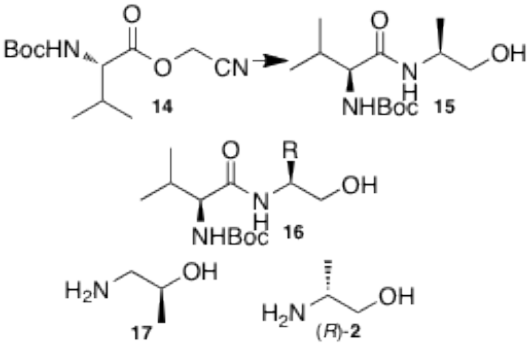
Formation of the cyanomethyl ester of Boc-valine proceeds in quantitative yield with bromoacetonitrile (2 eq) and Cs_2CO_3 in acetonitrile (1 h, r.t.). Conditions for ligation of alaninol (1.5 eq) to **14** were then examined (Table 3, Scheme 4). All of these reactions were performed at 1M. Adequate reactivity was observed in THF, but reactions were faster with 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 (entries 16, 17) were seen with extended reaction at ambient temperature or a quick reaction with microwave heating. TBD was not an effective catalyst for this reaction.

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

Entry	Time (h)	Temp(°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	*c*-hexane	AcOH	90
17	1.5	100[a]	*c*-hexane	AcOH	82
18	1.5	25	*c*-hexane	TBD	68

[a] microwave heating.

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

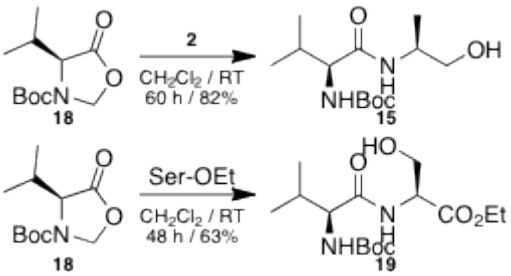


Scheme 4. Ligation via cyanomethyl esters.

Ligations of diverse aminoalcohols with **14** to give amides **16** were then examined under the conditions of entry 6. The reactants were expanded to include **17**, which gives the amide in 79% yield and demonstrates that secondary alcohols can participate in the postulated trans-esterification 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. 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**: **2**: 78%; **5**: 87%; **9**: 83%; **10**: 81%; **11**: 90%.

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

Since serine and cysteine are simply more complex aminoalcohols and aminothiols, 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. Ligations with oxazolidinones.

Conclusions

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

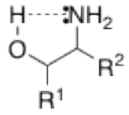


Figure 2. Internal hydrogen bonding may enhance aminoalcohol transesterification.

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-bottom 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 with flash chromatography on silica gel eluting with CH_2Cl_2/MeOH (90/10) to provide the product as light yellow oil (2.666 g, 91 % yield). The ^{1}H NMR spectrum matched literature data.[11]

Supporting Information (see footnote on the first page of this article): Scanned NMR spectra for 17 key new compounds.

Acknowledgments

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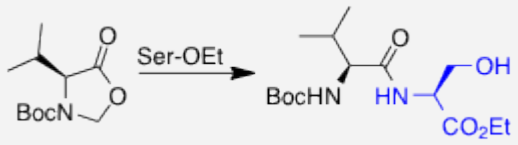

Exploiting a surprisingly easy initial trans-esterification process, amides are formed from hydroxyamines and lactones or cyanomethyl esters. Reactions occur rapidly without risk of racemization.

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Supporting Information

^{1}H and ^{13}C NMR spectra of the following compounds:
New products (13) in Table 2.
Compound **12**
Compound **13**
Compound **14**
Compound **15**
Compound **19**