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Direct peptide coupling of novel amino acid derivatives produced by rearrangement of catalytically generated ammonium ylides

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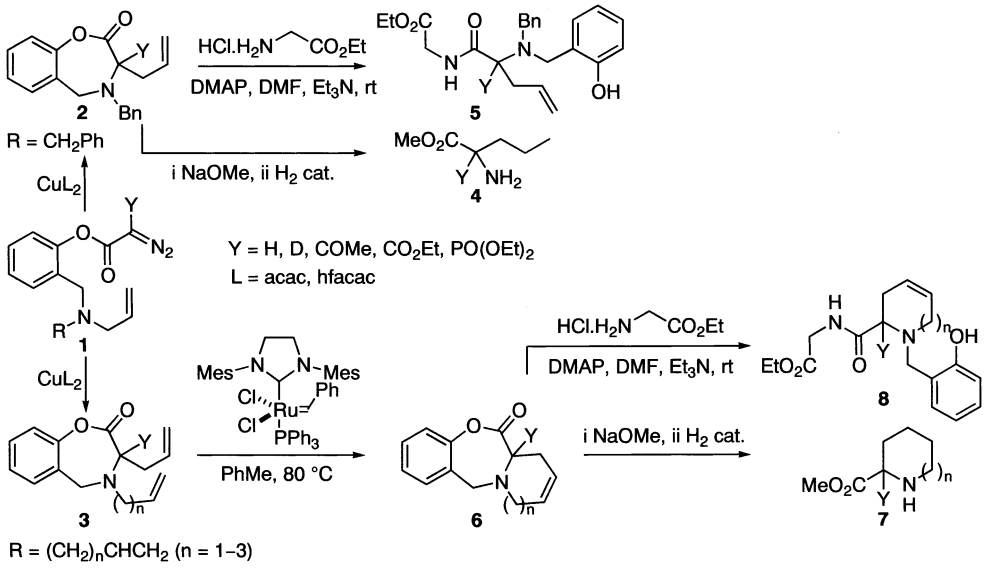
Abstract—Protected amino acids can be prepared from substrates in which a diazo ester is aryl-tethered to an allylic amine, by catalytic intramolecular ammonium ylide generation and [2,3] rearrangement. When the aryl tether is sufficiently electron-deficient, direct coupling of the rearrangement product with a hindered amino acid ester to give a dipeptide is possible, and ammonium ylide generation, rearrangement and peptide coupling can be accomplished in a one-pot fashion.

The demand for novel non-natural amino acids has increased dramatically in recent years. Much of this demand has been driven by the replacement of natural amino acids with non-natural surrogates in order to generate peptidomimetics with therapeutic potential and enhanced metabolic stability.[1] The incorporation of α,α-disubstituted amino acids into peptides to promote the formation of specific secondary structural elements such as β-turns and helices, and deliver predetermined tertiary structure has also become an important area of research.[2] In addition, unusual α,α-disubstituted amino acids are encountered in a wide variety of bioactive targets (e.g. oxazolomycin and myriocin)[3] and some have been shown to function as enzyme inhibitors[4] and CNS-active glutamate analogues.[5]



Scheme 1.

Keywords: amino acid; ammonium ylide; rearrangement; peptide coupling.
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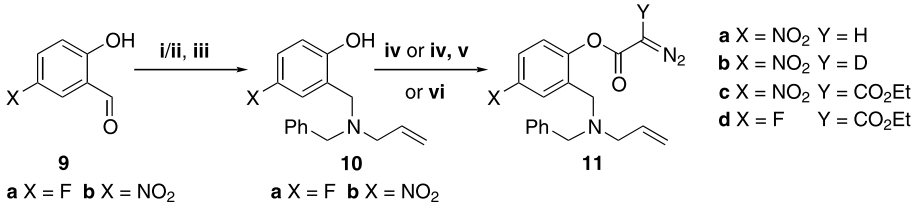
In a recent publication, we reported that it was possible to prepare unusual protected non-natural amino acids from the diazo esters **1** (Scheme 1).[6] In the reaction, copper-catalysed carbenoid formation is followed by ammonium ylide formation and immediate rearrangement gives the azalactones **2** or **3**. In the case of the azalactones **2**, lactone cleavage followed by standard catalytic hydrogenolysis affords the amino acid esters **4**. Alternatively, the azalactones **2** are sufficiently reactive to undergo direct coupling with glycine ethyl ester to give the *N*,*N*-diprotected dipeptides **5**, but extended reaction times are required. However, the azalactones are not sufficiently reactive to undergo direct coupling with esters of other amino acids.[6]

In our original studies, we also demonstrated that the azalactones **3** bearing an unsaturated *N*-substituent undergo ring-closing metathesis to give the protected cyclic amino acid derivatives **6**.[6] Sequential lactone cleavage and hydrogenation affords the cyclic amino esters **7**, and direct coupling of the protected cyclic amino acid derivatives **6** with glycine delivers the dipeptides **8**.

The ability to couple the fully protected amino acid derivatives **2** and **6** directly to other amino acids and polypeptides without further activation or deprotection is one of the most attractive features of our methodology. However, the synthetic utility of this route is limited by the fact that these azalactones are not sufficiently reactive to couple directly with α-substituted amino acids. In order to expand the scope of our methodology, we have redesigned our substrates so that the protected amino acid derivatives resulting from ylide rearrangement display a greater propensity to undergo peptide coupling. We now present the results of our studies with these second-generation substrates.

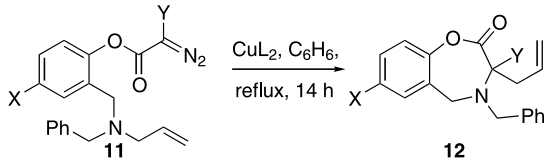
It is well known that activated *N*-protected amino acid aryl esters such as *p*-nitrophenyl and pentafluorophenyl esters are very efficiently coupled to other amino acids.[7] Thus, we expected that incorporation of one or more electron-withdrawing substituents into the aryl unit would deliver rearrangement products that displayed enhanced reactivity with regard to direct coupling with protected α-amino acids. However, we were aware that we might encounter stability problems prior to and during ylide generation if we were to make the aryl system too electron-deficient. We therefore explored two sets of substrates in which the position *para* to the phenolic ester group is substituted with a fluoro group or the more electron-demanding nitro group. The precursors were prepared from the aldehydes **9** by simple reaction sequences (Scheme 2).[8] Reductive amination of the aldehydes with benzylamine and then reaction with allyl bromide gave the allylic amines **10a** and **10b**. The 4-nitro-substituted phenol **10b** was converted into the diazo ester **11a** by deprotonation with sodium hydride and acylation with succinimidyl diazoacetate; the corresponding deuterated diazo ester **11b** was then obtained by deuterium exchange. The ethyl esters **11c** and **11d** were obtained by acylation of the phenols **10a** and **10b** with ethyl diazomalonyl chloride.

The copper-catalysed cyclisation reactions of the substrates **11** generally proceeded as expected (Eq. (1), Table 1). Treatment of the substrates **11** with an appropriate copper(II) catalyst delivered reasonable yields of



Scheme 2. *Reagents and conditions:* **i** $PhCH_2NH_2$, 4 Å sieves, $NaBH_4$, EtOH, rt (X = F 81%); **ii** $PhCH_2NH_2$, $NaBH(OAc)_3$, $ClCH_2CH_2Cl$, rt (X = NO_2 83%); **iii** $BrCH_2CHCH_2$, K_2CO_3, CH_2Cl_2 or MeCN (**10a** X = F 87%, **10b** X = NO_2 69%); **iv** NaH, succinimidyl diazoacetate, THF, rt (**11a** 75%); **v** K_2CO_3, THF, D_2O, rt (**11b** 74%, >95% D-incorporation); **vi** $ClCOC(N_2)CO_2Et$, 2,6-lutidine, CH_2Cl_2, rt (**11c** 65%, **11d** 73%).

Table 1.



(1)

Entry	Ligand (L)	Substrate	X	Y	Product	Yield (%)
1	acac	**11a**	NO_2	H	**12a**	29
2	hfacac	**11c**	NO_2	CO_2Et	**12c**	63
3	hfacac	**11d**	F	CO_2Et	**12d**	75

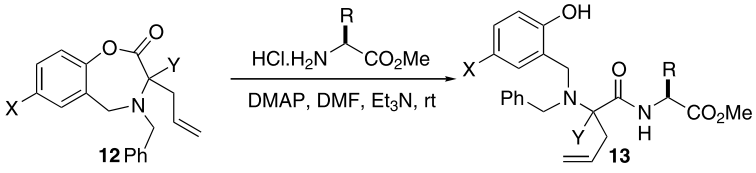
the azalactones **12** arising from ammonium ylide formation and rearrangement. Unfortunately, the azalactone **12a** proved to be so reactive to nucleophilic attack that substantial hydrolysis of this compound occurred during purification by column chromatography on Florasil® or silica gel and the isolated yield was significantly reduced.

Having successfully converted our cyclisation precursors **11** into the azalactones **12**, we then explored the direct coupling of these intermediates to a variety of amino acids (Eq. (2), Table 2). In previous studies, we had discovered that it took five days for complete coupling of azalactones such as **12** (X = H, Y = H) with glycine ethyl ester. The fluoro-substituted azalactone **12d** was found to be much more reactive than the compound without this substituent (X = H), and coupling to glycine methyl ester was complete in just over four hours (entry 1, Table 2). It was also possible to couple the azalactone **12d** to alanine methyl ester (entry 2, Table 2), although this reaction did take 24 hours. A remarkable increase in reactivity was observed when the nitro-substituted azalactone **12c** was employed as the reacting partner. Coupling of this compound with glycine methyl ester was complete in just 20 minutes (entry 3, Table 2) and the corresponding reaction with alanine methyl ester was also rapid (entry 4, Table 2). Remarkably, coupling of the azalactone **12c** to the relatively hindered partner valine methyl ester was complete within two hours (entry 5, Table 2), and the corresponding reaction of the less hindered azalactone **12a** was complete in just over one hour. In all cases, excellent yields were obtained during the peptide coupling reactions of the nitro-substituted azalactones.

The rapid and high-yielding direct coupling of hindered amino acids to the protected amino acid derivatives obtained by ylide generation and rearrangement, suggested that it might be possible to perform both operations in a one-pot fashion. In order to explore the feasibility of this reaction, we performed copper-mediated cyclisation of the substrates **11a–c** followed by immediate addition of (*S*)-valine methyl ester (Eq. (3), Table 3). One-pot cyclisation and coupling reactions with this relatively hindered amino acid ester did indeed proceed in excellent yield, and the coupling reactions were complete in one hour when they were performed at reflux.

In summary, we have demonstrated that our nitro-substituted precursors **11** (X = NO_2) undergo efficient carbenoid formation, cyclisation and ylide rearrangement to give the azalactones **12** (X = NO_2), and that these compounds display greatly enhanced reactivity with regard to direct coupling with esters of α-amino acids. In addition, we have shown that it is possible to

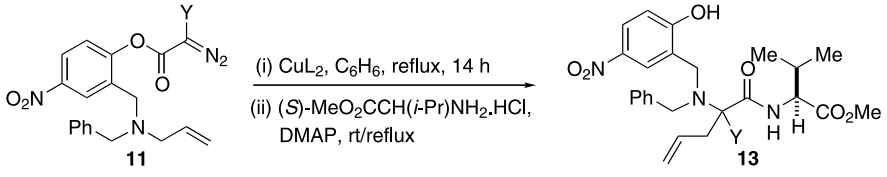
Table 2.



(2)

Entry	Substrate	X	Y	R	Reaction time	Product	Yield (%)
1	**12d**	F	CO_2Et	H	4 h 15 min	**13a**	73
2	**12d**	F	CO_2Et	Me	24 h	**13b**	84
3	**12c**	NO_2	CO_2Et	H	20 min	**13c**	87
4	**12c**	NO_2	CO_2Et	Me	45 min	**13d**	92
5	**12c**	NO_2	CO_2Et	*i*-Pr	2 h	**13e**	89
6	**12a**	NO_2	H	*i*-Pr	1 h 5 min	**13f**	88

Table 3.



(3)

Substrate	Ligand (L)	Y	Temp. (ii)	Time (ii) (h)	Product	Yield (%)
11a	acac	H	rt	10–20	**13f**	50
11a	acac	H	Reflux	1	**13f**	49
11b	acac	D	rt	10–20	**13g**	52
11c	hfacac	CO_2Et	rt	10–20	**13e**	81
11c	hfacac	CO_2Et	Reflux	1	**13e**	74

perform these operations in a one-pot fashion without isolation of the intermediate azalactones **12**.

Now that we have addressed reactivity issues, the final task is to perform ylide formation and rearrangement in an enantioselective fashion. Studies toward this goal are currently in progress and results of this work will be reported in due course.

Acknowledgements

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8. The substituted salicaldehydes **9a** and **9b** are readily available: 2-hydroxy-5-fluorobenzaldehyde (**9a**) was prepared from 2-bromo-4-fluorophenol by lithium–halogen exchange and reaction with dimethylformamide, and 2-hydroxy-5-nitrobenzaldehyde (**9b**) is commercially available.