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Three-Component Condensation Leading to β-Amino Acid Diamides: Convergent Assembly of β-Peptide Analogues

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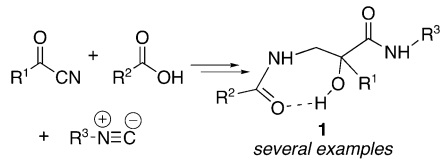
Modern drug discovery depends heavily on the use of multiple-component condensation (MCC) reactions for the rapid assembly of complex, druglike molecular frameworks.[1] However, the number of useful and robust MCC reactions remains limited. Straightforward reaction analysis suggests that significant advances in this area might be achieved by modifying known MCC reactions, for example, by broadening input types or increasing the component number (i.e., >three-component Mannich or >four-component Ugi reactions). Less obvious are logical strategies for the discovery of additional MCC reactions. In efforts aimed at the latter enterprise, we recently described a single-reactant replacement (SRR) approach based on mechanistic profiling of the Passerini reaction that led to a new synthesis of substituted oxazoles.[2,3]

Using that approach, we have developed a Passerini condensation of acyl cyanides with isonitriles and carboxylic acids leading in two steps to functionalized diamides and β-peptides of α-hydroxy-β-amino acids **1** (Scheme 1). Besides resisting proteases,[4] such β-peptides form stable helical and sheet structures when incorporated into larger peptides[5] and mimic turn elements in proteins. Compounds such as **1** embody the well-known norstatine peptide isostere found in potent aspartyl protease inhibitors.[6] Molecular modeling of **1** (PCModel, Serena Software) implicates the α-hydroxy group in two low-energy hydrogen bonded conformations, with the lower-energy conformer having the anti orientation of R^3.[7]

Scheme 1



Guided by the SRR approach, we decided to replace the aldehyde or ketone component normally used in a Passerini condensation with a carbonyl electrophile containing latent nucleophilic functionality (Nu, Figure 1). Such a nucleophile would be expected to divert either the initially formed iminoester **2** or α-acyloxycarboxamide **3** to a different molecular scaffold **4**. For example, an embedded amine nucleophile (Nu = NH_2) would result in the rearrangement of intermediates **2** or **3** to diamides such as **1** and its congeners.

Acyl cyanides are of interest because the nitrile group in the expected product **5** (Scheme 2)[8] might be selectively reduced in situ to an amine, whereupon spontaneous O-to-N acyl shift would afford substituted β-peptides such as **1**. Besides being shelf-stable, acyl cyanides are also readily available from carboxylic acids,[9] thus enhancing the utility of the method.

In fact, a neat mixture of acetyl cyanide, acetic acid, and cyclohexylisonitrile reacted (rt, 3 h) to form α-acetoxy-α-cyanoamide **5a**, which crystallized directly in 68% yield. Table 1 summarizes the scope of successful condensations.

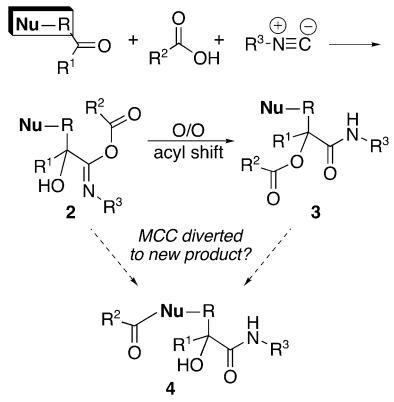
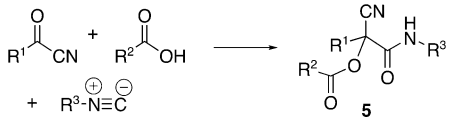


Figure 1. Effect of an embedded nucleophile in the Passerini reaction.

Scheme 2



Reactions were generally run neat, whereupon the desired products crystallized directly, or using CH_2Cl_2 as a solvent. Condensations were successful using a range of aliphatic or alicyclic acyl cyanides. However, aromatic and α,β-unsaturated acyl cyanides failed to react. Condensations also worked well with a broad range of carboxylic acids and isonitriles, including N-protected α-amino acids and isocyanoesters,[10] which were of interest in assembling peptidomimetic structures (e.g., **5m**, **5n**, **5u**−**x**).[11]

To synthesize **1**, the nitrile group in **5** was reduced to amine salt **8** (Scheme 3) by catalytic hydrogenation (10% Pd/C, H_2, CH_3OH, rt, 5 equiv of HCl) in the presence of acid, so as to suppress exchange of **8** with imine **6**. Under these conditions, disappearance of the nitrile was rapid (within 4 h). Filtration and basification of the hydrogenation reaction mixture triggered the expected rearrangement of **8** leading to the desired β-amino acid diamides **1**, which were isolated by reacidification and chromatographic purification. Adducts **5c**, **5d**, **5i**, and **5t**, derived from α-branched acyl cyanides (R^1 = cyclohexyl, *tert*-butyl), were inert to hydrogenation, presumably because of steric factors.

Initial reductions of **5** also produced significant quantities of a byproduct **9**, which likely arose by reversible addition of methanol to imine **6** followed by O-to-N acyl migration in **7**. However, by simply extending the hydrogenation times, the methoxy-substituted diamides **9** could usually be suppressed (<1%) while simultaneously improving the yields of **1**. Table 2 summarizes several representative examples of this reductive rearrangement.

The structures of **1a** and **1k** were unambiguously identified by comparison with authentic samples.[12] ^1H NMR spectra showed

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Table 1. Synthesis of α-Acyloxy-α-cyanocarboxamides **5**

R^1	R^2	R^3	product	% yield
CH_3	CH_3	C_6H_{11}	**5a**	68
n-C_7H_{15}	CH_3	C_6H_{11}	**5b**	74
C_6H_{11}	CH_3	C_6H_{11}	**5c**	58
t-Bu	CH_3	C_6H_{11}	**5d**	61
CH_3OCH_2	CH_3	C_6H_{11}	**5e**	49
CH_3	PhCH═CH	C_6H_{11}	**5f**	50
CH_3	*n*-C_7H_{15}	C_6H_{11}	**5g**	75
n-C_7H_{15}	*n*-C_7H_{15}	C_6H_{11}	**5h**	64
C_6H_{11}	$PhCH_2CH_2$	C_6H_{11}	**5i**	62
n-C_7H_{15}	Ph	C_6H_{11}	**5j**	50
CH_3	CH_3	*t*-Bu	**5k**	67
n-C_7H_{15}	CH_3	*t*-Bu	**5l**	41
CH_3	Cbz-(*S*)-Phe	*t*-Bu	**5m**	62
CH_3	Boc-(*S*)-Phe	*t*-Bu	**5n**	70
CH_3	CH_3	*n*-Bu	**5o**	63
CH_3OCH_2	Ph	*n*-Bu	**5p**	67
CH_3	CH_3	EtO_2CCH_2	**5q**	40
CH_3OCH_2	$PhCH_2CH_2$	EtO_2CCH_2	**5r**	32
CH_3	CH_3	$MeO(CH_2)_2$	**5s**	51
t-Bu	*n*-C_7H_{15}	$MeO(CH_2)_2$	**5t**	82
CH_3	Cbz-(*S*)-Phe	MeO-(*S*)-Ala	**5u**	37
CH_3	CH_3	MeO-(*S*)-Ala	**5v**	60
CH_3	CH_3	BnO-(*S*)-Val	**5w**	62
CH_3	Boc-(*S*)-Phe	MeO-(*S*)-Ala	**5x**	44

Scheme 3

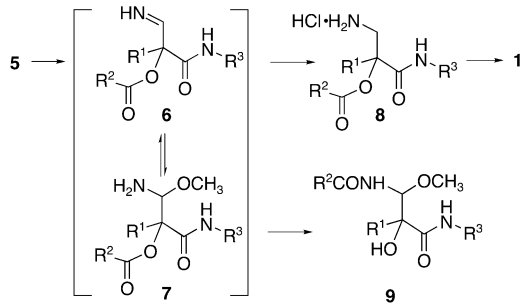

Table 2. Reductive Rearrangement of **5** to β-Amino Acid Diamides **1**

reactant	time (h)	product	% yield
5a	22	**1a**	57
5b	46	**1b**	44[a]
5h	46	**1h**	45
5k	23	**1k**	73
5n	16[b]	**1n**	30
5p	46	**1p**	76
5r	22	**1r**[d]	43[e]
5s	23	**1s**	56
5v	16	**1v**	66
5x	23[b,c]	**1x**	35

[a] Diamide **9b** formed in 8% yield. [b] Using THF as a solvent. [c] Using RaNi and Pd/C as cocatalysts. [d] Isolated as the corresponding methyl ester. [e] Diamide **9r** formed in 11% yield.

characteristic ABX resonances at 3.3−3.6 ppm for the CH_2NH substructure in the product diamides.

The Pd/C-catalyzed hydrogenation of **5n** and **5x** in CH_3OH did not form **1n** and **1x** but instead produced BOC-Phe-OMe in >50% yield. This unexpected[13] methanolysis of α-acylaminoesters, which appears to be general,[14] was circumvented by conducting hydrogenations in THF, although most reductions of **5** gave higher yields in CH_3OH/HCl. It was also possible to synthesize diamides **1** in a one-pot process directly from acyl cyanides with comparable overall yields.

In summary, mechanistic profiling of a known MCC reaction using the SRR approach results in a highly convergent synthesis of β-amino acid diamides and related β-peptide analogues. The methodology is particularly well-suited to preparing α/β peptides embodying the heterogeneous α/β/α backbone motif (e.g., **1x**), recent examples of which display antimicrobial properties.[5b,15] Taken together with the new route to oxazoles[2,3] developed by applying SRR to a different reactant in the same MCC, the present results indicate the multidimensionality of this approach in generating disparate product outcomes from the same template reaction. Besides being general and versatile, the SRR approach can also be applied iteratively. Thus, one may expect that sequential applications to MCC reactions will likely lead to new molecular frameworks and scaffolds bearing little resemblance to the cognate reactions on which they were initially based.

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Supporting Information Available: Representative experimental procedures for the synthesis of compounds **5** (Table 1) and **1** (Table 2) as well as supporting spectroscopic data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) Condensations with N-protected (*S*)-α-amino acids and (*S*)-α-isocyanoesters afforded 1:1 mixtures of the (*S*,*S*,*S*)- and (*S*,*R*,*S*)-diastereomers. No other diastereomers were detected, indicating that the α-isocyanoesters were configurationally stable.
(12) Prepared by the condensation of $BOCNHCH_2COCH_3$, acetic acid, and either cyclohexyl isonitrile or *tert*-butyl isonitrile following literature protocols: (a) Semple, J. E.; Owens, T. D.; Nguyen, K.; Levy, O. E. *Org. Lett.* **2000**, *2*, 2769−2775. (b) Banfi, L.; Guanti, G.; Riva, R. *Chem. Commun.* **2000**, 985−986.
(13) Methanolysis of peptidyl esters catalyzed by calcium acetate has been observed: Miranda, M. T. M.; Theobaldo, F. C.; Tominaga, M. *Int. J. Peptide Prot. Res.* **1991**, *37*, 451−456.
(14) Hydrogenation of **5r** formed the corresponding methyl ester of **1r**. Controls showed that transesterifications were catalyzed by Pd/C in the absence of H_2 and HCl. Similar observations were made using a supported Pt(0) catalyst. No methanolysis occurred when **5n** was stirred with PtO_2 in CH_3OH, but if the PtO_2 was first reduced to Pt(0), **5n** formed BOC-Phe-OMe in 90% yield after 12 h.
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