Solid-phase synthesis of fused 1,4-diazepanone peptidomimetics via tandem *N*-iminium ion cyclization–nucleophilic addition

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ABSTRACT

We herein describe the solid-phase synthesis of protected *N*-oxoalkyl-derivatized peptides designed for subsequent acid-mediated, tandem *N*-acyliminium ion cyclization–nucleophilic addition reaction. The target compounds contained fused 1,4-diazepanones incorporated into a peptide backbone and served as conformational constraints. The scope and limitation of the ring formation were studied, and the structural requirements and reaction conditions for cyclization are outlined.

Our ongoing research efforts have focused on the design and solid-phase synthesis of compounds characterized by structural features largely missing in current compound decks used for high-throughput screening (HTS); we have placed particular emphasis on compounds with 3D architectures (presence of sp³ carbons) and on the stereoselective formation of new stereogenic centers.[1] We have previously described the synthesis of nitrogenous fused and bridged heterocycles that were exploited in HTS and also incorporated into a peptide chain as peptide constraints. The synthesis of these compounds was performed in the solid phase using tandem *N*-acyliminium ion cyclization–nucleophilic addition.[2–8]

Tandem *N*-acyliminium ion cyclization–nucleophilic addition is a powerful strategy for synthesizing diverse fused ring systems,[9–11] including conformational constraints in peptides.[12–15] In our recent work, we described the synthesis of five- and six-membered fused and bridged heterocycles.[2–7] The cyclic iminium ion was formed from an aldehyde attached via a two-carbon spacer to an amide nitrogen of a peptide. In a peptide chain, the cyclic iminium can be formed from two directions (Scheme 1): either toward the peptide amino terminus (referred to as westbound, iminium **II**) or toward the peptide carboxyl terminus (eastbound, iminium **III**).[5]

The synthesis of medium-sized fused bicycles via iminium ion chemistry is typically achieved via the formation of five- or six-membered cyclic *N*-acyliminium ion intermediates, followed by nucleophilic attack to close the second larger ring (from five- to eight-membered rings).[9,16,17] However, studies on the seven-membered *N*-acyliminium ion intermediates are scarce.[18–20] Seven-membered cyclic iminium ions can be formed in a peptide chain from two different types of precursors: polymer-supported *N*-(2-oxo-ethyl)-derivatives containing β-amino acids (Fig. 1, Series A) or polymer-supported *N*-(3-oxo-propyl)-derivatives containing α-amino acids (Fig. 1, Series B). Two directions of cyclic iminium formation are possible (eastbound and westbound) and we have recently reported formation of medium sized fused rings in the eastbound direction.[8] In this contribution we focused on the structural features directing the cyclic iminium ion formation only in the westbound direction.

Synthesis of model compounds: All of the polymer-supported acyclic precursors, **1–4**, were synthesized using standard solid-phase chemistry protocols and commercially available building blocks, as described in our previous Letters.[2–7] To incorporate the nitrogenous heterobicycles as conformational constraints into peptides, we used amino acids as the most convenient building blocks. The aldehyde was incorporated in its protected form as a dialkyl acetal on two- and three-carbon spacers attached to an amide nitrogen (Series A and Series B, respectively). The synthesis was performed on Wang[21] and Rink amide[22] resins using standard protocols for the solid-phase synthesis of peptides. To incorporate
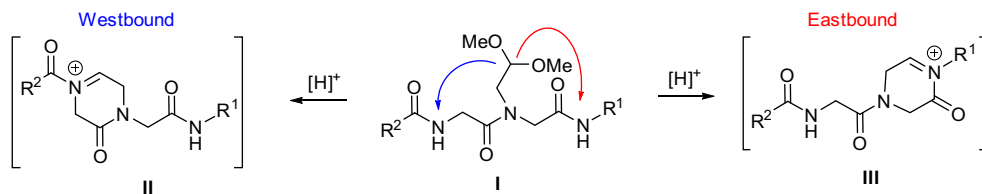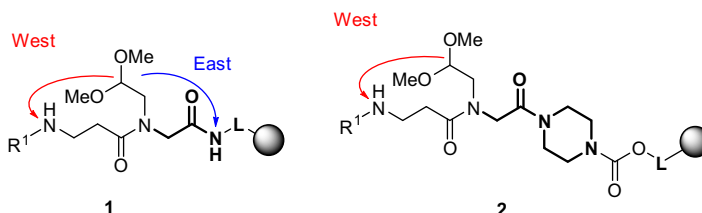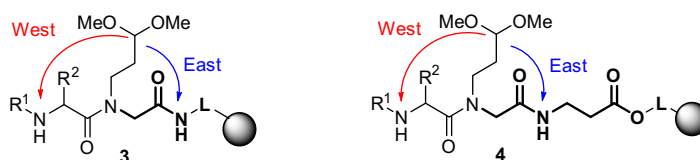
Scheme 1. Eastbound and westbound directions of iminium formation.

SERIES A: Polymer-supported protected *N*-(3-oxo-ethyl)-derivatives

**SERIES B:** Polymer-supported protected *N*-(3-oxo-propyl)-derivatives

Figure 1. Polymer-supported model compounds.

the protected aldehyde, the resin-bound amines were acylated with bromoacetic acid and subsequently reacted with aminoacetaldehyde (Series A, Fig. 1) and aminopropionaldehyde dialkyl acetal (Series B, Fig. 1). Acid-mediated exposure de-masked the acetal protecting group with concurrent cleavage of the resin-bound precursors from the acid–labile linkers. The second ring closure by nucleophilic addition was studied using two ring sizes (i.e., five- and six-membered rings) and both *N*-acyl and *N*-arylsulfonyl-derivatized internal nitrogen nucleophiles (Fig. 1).

The regioselectivity was studied on model compounds **1**, **3**, and **4**, allowing two directions of cyclization (eastbound and westbound). In addition, we also investigated cyclic iminium formation on model compound **2**, which forced the iminium formation in only the westbound direction as a result of the incorporation of piperazine, which blocked the eastbound direction of cyclization (Fig. 1).

Polymer-supported N-(2-oxo-ethyl)-derivatives (Series A). Synthesis of fused 1,4-diazepan-5-ones: The linear precursor **1** can form *N*-iminium ions in two directions: toward the carboxyl peptide terminus (eastbound) to form six-membered **5** or toward the peptide amino terminus (westbound) to afford seven-membered **6**. In the presence of an internal nucleophile at the R[1] position, the second ring can also be closed, forming fused heterocycle **7**

(Fig. 2 and Scheme 2). To evaluate the regioselectivity of the cyclic iminium formation as a function of the R[1] substituent, we prepared resins (**1**) with four different R[1] substituents (carbamate **1a**, sulfonamide **1b**, urea **1c**, secondary amine **1d**, and amide **1e**). 4-Nitrobenzenesulfonamides (Nos-amides) are particularly interesting because they represent a good internal nucleophile for cyclic iminium formation and because the Nos group can be cleaved under mild conditions to allow further derivatization. Derivatives **1a**–**1d** do not contain an internal nucleophile at the R[1] position; thus, the initially formed iminium ions were deprotonated in neutral buffer (reverse phase HPLC purification in aqueous ammonium acetate/acetonitrile) and the enamides **5** and **6** were formed (Table 1, entries 1–4). The results indicate that the urea derivative **1c** provided the best regioselectivity for the westbound seven-membered iminium formation (entry 3), whereas the *N*-alkyl derivative **1d** reacted completely in the opposite eastbound direction for the iminium-ion cyclization (entry 4). The latter result is likely attributable to the protonation of the amino group by TFA. Next, we prepared a model compound, **1e**, containing an internal nucleophile (R[1] = Nos-β-Ala). However, the major product was the eastbound cyclized 3,4-dihydropyrazin-2-one (**6**, entry 5, 36% yield), with the fused-ring product **7** formed in only 12% yield as a racemic mixture.[4]
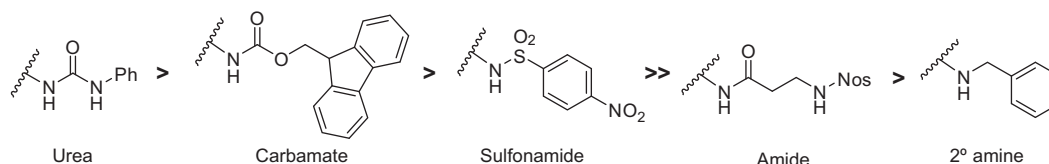
Figure 2. Relative tendency toward the westbound direction of cyclization.
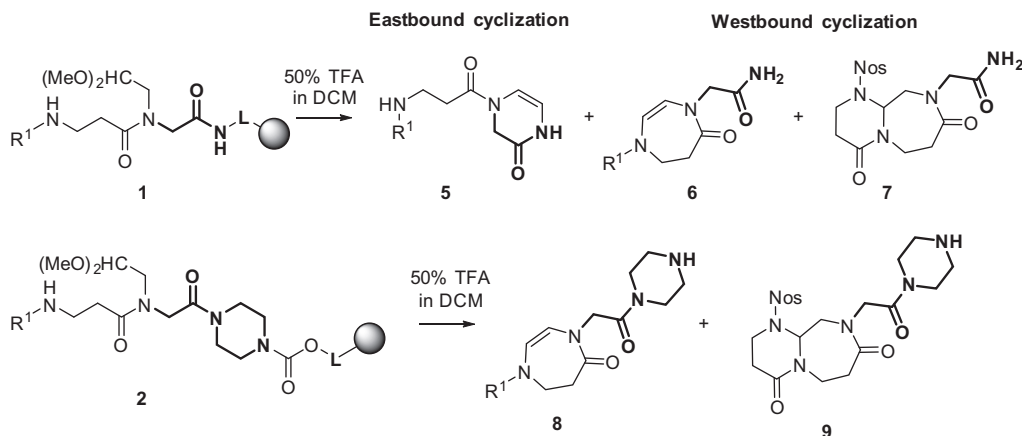
Scheme 2. Cyclization of polymer-supported *N*-(2-oxo-ethyl)-derivatives.

Table 1
Cyclization of polymer-supported *N*-(2-oxo-ethyl)-derivatives

Entry	Resin	R^1	**5** (%)	**6** (%)	**7** (%)	Purity (%)	Product	Yield^a (%)	Product	Yield^a (%)
1	**1a**[b]	Fmoc	7	93	NA	68	**5a**	NI	**6a**	58
2	**1b**[b]	Nos	22	88	NA	54	**5b**	13	**6b**	48
3	**1c**[c]	PhNHCO	ND	100	NA	71			**6c**	54
4	**1d**[b]	Bn	100	—	NA	43	**5d**	33		
5	**1e**[b]	Nos-β-Ala	73	ND	24	74	**5e**	36	7	12
Entry	Resin	R^1		**8** (%)	**9** (%)	Purity (%)	Product	Yield^a (%)	Product	Yield^a (%)
6	**2b**[b]	Nos		100	NA	48	**8b**	23		
7	**2c**[c]	PhNHCO		100	NA	52	**8c**	38		
8	**2e**[b]	Nos-β-Ala		23	77	65	**8e**	8	**9**	NI

Note: Relative ratios of compounds **5**–**9** were calculated from LC traces and ^{1}H NMR spectra; ND, not detected; NA, not applicable; NI, not isolated.
[a] Yield after HPLC purification.
[b] Cleavage time overnight.
[c] Cleavage time 1 h.

Therefore, we designed a model compound, **2**, that prevented the *N*-acyliminium ion formation in the eastbound direction by incorporation of piperazine. The resin-bound precursor **2** was prepared with a different substituent at the R^1 position. As expected, enamide **8** was formed as a major product (Table 1, entries 6 and 7) from the model compounds missing the internal nucleophile. The resin **2e** containing an internal nucleophile (R^1 = Nos-β-Ala) yielded a mixture of enamide **8e** and fused-ring compound **9** in a 23/77 ratio (entry 8). Further attempts to alter the size of the fused ring from six- to five-membered (R^1 = Nos-Ala and R^1 = Nos-Ala-Ser) in precursors **2e** and **2f** provided a complex mixture in which the desired fused ring was present as a minor component.

The ^{1}H NMR spectrum of the seven-membered fused compound, **7**, indicated the presence of the 9a-H protons as a doublet at 5.65 ppm, which is a diagnostic resonance for a fused ring system. Accordingly, the ^{13}C NMR spectrum showed the corresponding fusion carbon C$_{9a}$ at 69.1 ppm. Therefore, tandem *N*-iminium ion cyclization–nucleophilic addition resulted in the formation of a new stereogenic center.

Polymer-supported N-(3-oxo-propyl)-derivatives (Series B): synthesis of fused 1,4-diazepan-2-ones: An alternative scenario for the synthesis of fused 1,4-diazepan-2-ones was based on polymer-supported *N*-(3-oxo-propyl)-derivatives **3** and **4** (Scheme 3). Acid treatment of resins **3a** and **3b** afforded enamides **10** as the only products. These results suggest a preference for the formation of the endo *N*-acyliminium ion intermediate via the eastbound direction rather than the exo *N*-acyliminium ion intermediate. However,

when an efficient internal nucleophile was introduced into the lineal precursor such as compound **3c**, which was prepared by sulfonylation with 2-Nos-Cl and subsequent reduction of the nitro group, the only product detected was the diastereoisomeric mixture of fused bicycles (*R*)-**12** and (*S*)-**12**, which were isolated in good yield (entry 3, Table 2). The 2-aminobenzenesulfonamide **3c** was purposely selected because it represents a constrained internal nucleophile that has provided excellent six-membered fused ring formation in our previous work.[3]

Encouraged by the formation of the seven-membered fused ring, we prepared the model compounds **4a**–**d**, which contain a β-amino acid-derived internal nucleophile attached to the N-terminal amino acid (Scheme 3). The amino group was derivatized as a sulfonamide on the basis of our previous Letters that indicated that the Nos group provided the best results in the syntheses of 6+6 fused rings.[3–5] Additionally, incorporation of β-Ala as the carboxy terminal amino acid allowed for the incorporation of the protected aldehyde in the 'middle' of a peptide. Gratifyingly, the fused bicycles **15a**–**d** were cleanly formed as a mixture of diastereoisomers (entries 4–7, Table 2). Because the eastbound direction of iminium formation was not observed in most of the examples, the model compounds with piperazine were not studied.

The ^{1}H NMR spectra of the seven-membered fused compounds (**15**) showed the presence of the 9a-H protons as a doublet of doublets at 4.96–5.89 ppm, which is a diagnostic resonance for a fused ring system. The ^{13}C NMR spectra showed the signal of the corresponding fusion carbon C$_{9a}$ at 65.8–88.0 ppm.
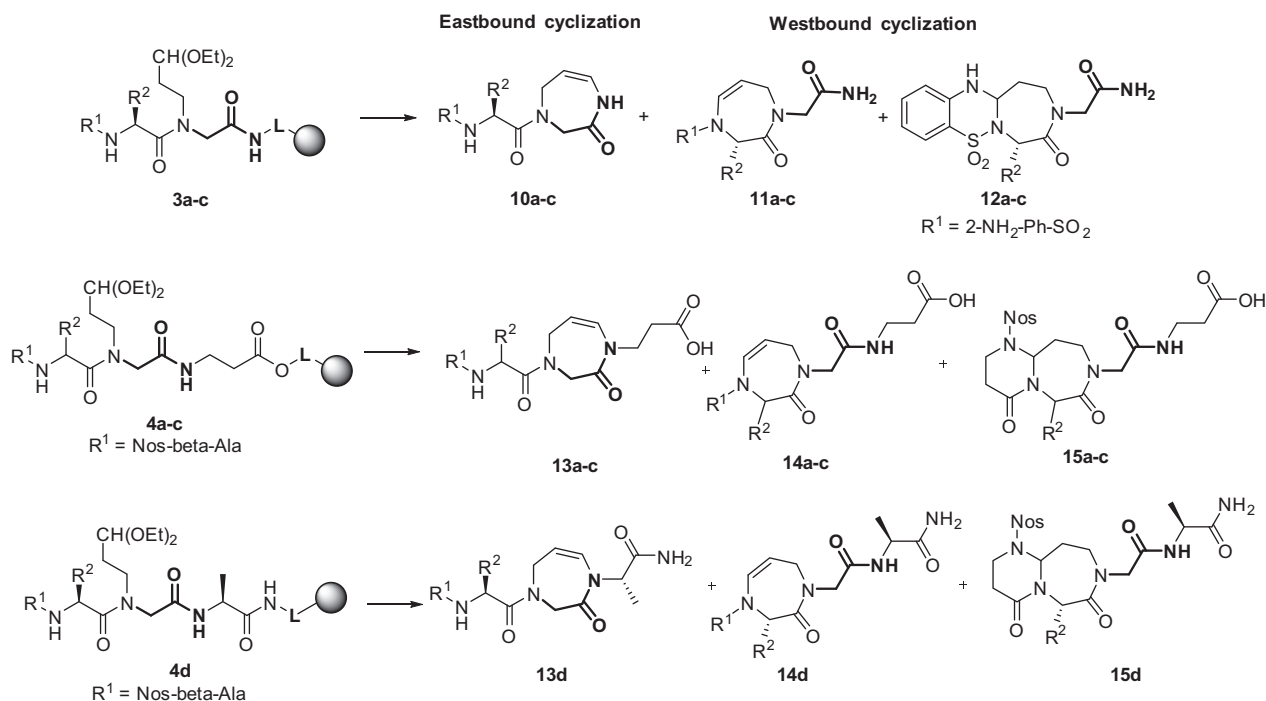
Scheme 3. Cyclization of polymer-supported *N*-(3-oxo-propyl)-derivatives.

Table 2
Cyclization of polymer-supported *N*-(3-oxo-propyl)-derivatives

Entry	Resin	R^2	R^1	**10** (%)	**11** (%)	**12** (%)	Purity (%)	Product	Yield[a] (%)
1	**3a**	(*S*)-CH₃	Nos-β-Ala	30	ND	NA	30[b]	**10a**	25
2	**3b**	(*S*)-CH₃	Nos-Ala	99	ND	NA	32	**10b**	20
3	**3c**	(*S*)-CH₃	2-NH₂-C₂H₄-SO₂	ND	ND	100	72	(*S*)-**12c**	28[d]
								(*R*)-**12c**	17[d]
Entry	Resin	R^2	R^1	**13** (%)	14 (%)	**15** (%)	Purity (%)	Product	Yield[a] (%)
4	**4a**	(*S*)-CH₃	Nos-β-Ala	22	ND	78	78	(*R*,*S*)-**15a**	37(25/12)[c]
5	**4b**	(*R*)-CH₃	Nos-β-Ala	ND	ND	100	65	(*R*,*S*)-**15b**	12(6/6)[c]
6	**4c**	H	Nos-β-Ala	ND	ND	100	65	(*R*,*S*)-**15c**	40[c]
7	**4d**	(*R*)-CH₃	Nos-β-Ala	ND	ND	100	47	(*R*)-**15d**	22[d]
								(*S*)-**15d**	12

Note: Relative ratios of compounds **10–15** were calculated from LC traces and ¹H NMR spectra; ND, not detected; NA, not applicable; NI, not isolated.

[a] Yield after HPLC purification.
[b] Major component was acyclic aldehyde.
[c] Isolated as a mixture of diastereoisomers.
[d] Pure diastereoisomer.

Conclusion

Polymer-supported *N*-(2-oxo-ethyl)-derivatized and *N*-(3-oxo-propyl)-derivatized peptides were evaluated as precursors for seven-membered fused ring peptidomimetics. *N*-(2-Oxo-ethyl)-derivatives were determined to be useful intermediates for the incorporation of a single 1,4-diazepin-5-one but not for the formation of a fused ring system. *N*-(3-Oxo-propyl)-derivatives; however, provided the target fused seven-membered ring system via westbound cyclization of the iminium ion.

Acknowledgements

Supplementary data

Supplementary data (the reaction conditions for the individual steps of the syntheses have been reported in our previous communications[2–7]) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.08.015.

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