Solid-Phase Synthesis of Heterocycles Containing an 1-Acyl-3-oxopiperazine Skeleton

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A major challenge in combinatorial chemistry today is the development of new methods and synthetic strategies for efficient formation of carbon−carbon and carbon−heteroatom bonds with the prospect of synthesizing new compounds of potential biological and therapeutic value. In the last 4 years, a number of powerful C−C, C−N, and C−S bond-forming strategies have been reported on the solid phase and validated in the synthesis of compound libraries.[1] As a part of our program directed toward the development of new solid-phase reactions, we have been searching for general and efficient methods to synthesize heterocyclic scaffolds that would be suitable for combinatorial library syntheses. One of the strategies we have found particularly effective in the design of new libraries is to employ a tandem *N*-acyliminium ion cyclization−nucleophilic addition[2] as ring-forming processes utilizing a traceless linker concept.[3,4] In this paper, we report a tandem *N*-acyliminium ion cyclization−nucleophilic addition reaction sequence that provides direct access to new bi-, tri-, and tetracyclic derivatives of 1-acyl-3-oxopiperazines **1**−**4**. From a structural point of view, these classes of compounds constitute interesting examples of conformationally rigid peptidomimetic cyclic molecules. In particular, bicyclic 3-oxopiperazinone **2b** represents an interesting probe for a constrained type-I β-turn motif with an inherent potential for combinatorial exploration of functional diversity.[5]

The synthetic approach we have developed toward the target structures **1**−**4** is shown in Scheme 1. The initial studies have centered on optimal conditions for attachment of bromoacetaldehyde diethyl acetal to the TentaGel OH resin. Azeotropic removal of ethanol from the mixture with 1,2-dichloroethane in the presence of quinoline toluenesulfonate resulted in complete transacetalization within 4 h. The loading level was determined to be 0.31 mmol/g by quantification of bromine by elemental analysis. This acetal-type linker, which serves as a latent source of aldehyde, was further tested to explore the scope of bromine displacement with a number of amines. Transformations of bromoacetal resin **5** into the corresponding amino acetals **6** were achieved by treatment of bromo acetal resin **5** with a 2 M solution of primary amines in DMSO for 15 h at 60 °C. The completeness of this transformation was assessed by ion-selective electrode technique,[6] and the loading level of resin **6** was determined to be 0.30 ± 0.02 mmol/g. Acylation of secondary amines **6** with a number of amino acids followed by Fmoc deprotection[7] was the next step in our synthetic strategy. A procedure utilizing tetramethylfluoroformamidinium hexafluorophosphate[8] (TFFH) in the presence of EtN(*i*-Pr)$_2$ was found to be the most reliable, providing the reaction is given a longer time (48 h). Resin-bound structures **7** were thus obtained as common intermediates for subsequent acylation with a number of acyl components containing different nucleophilic centers.

Coupling of 2-fluoro-5-nitrobenzoic acid under standard TFFH/EtN(*i*-Pr)$_2$ conditions followed by subsequent displacement of fluorine with a primary amine provided compounds **12a**,**b**. Under similar conditions, acylation of **7** with Fmoc-Ala-OH, Fmoc-Cys(StBu)-OH, and Fmoc-Trp-OH followed by Fmoc deprotection[7] and N-acylation of the primary amino group (acetic anhydride/pyridine, PhNCO, BzCl/EtN(*i*-Pr)$_2$, MeOCOCl/EtN(*i*-Pr)$_2$) provided structures **13**−**15a**,**b**. An additional step was required to deprotect cysteine-SH in **14a**,**b**. Complete deprotection of Cys(S-*t*-Bu) was achieved when a mixture of water (0.5 mL) and PBu$_3$ (20 equiv, 1 mL) in *N*-methylpyrrolidinone (5 mL) was added to a resin suspension in *N*-methylpyrrolidinone and the suspension shaken for 2 h at room temperature. Finally, upon treatment with formic acid at room temperature, resin-bound compounds **12**−**14a**,**b** smoothly cyclized to give products **1**−**3** (Table 1). Although the isolated yields are only modest to good, the purities of crude products are in most cases quite high.[10] Attempted Pictet−Spengler cyclization of derivatives **15a**,**b** containing an indole π par-

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(4) The linker strategy discussed in this paper is not a true traceless concept as described in ref **3a**,**h** but rather a combination of protecting-group-type linker with the release by cyclization.

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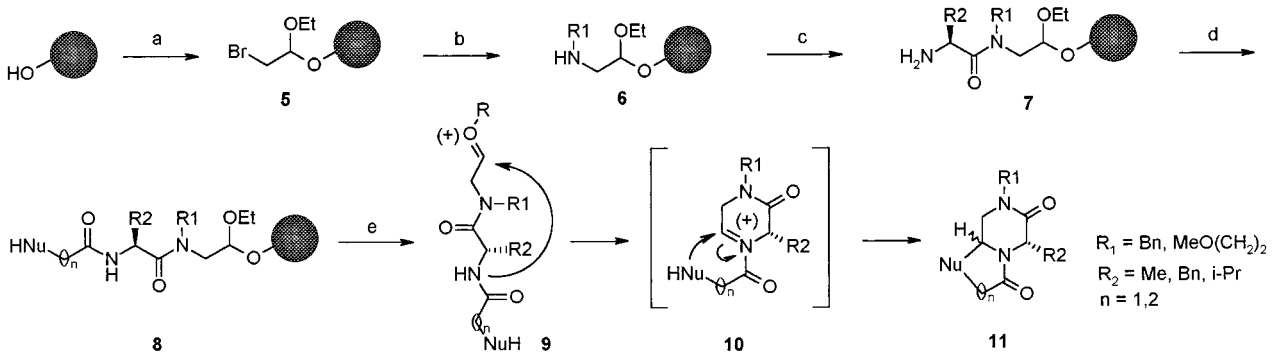
Scheme 1[a]

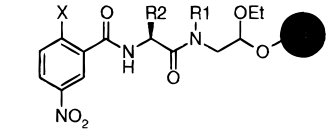


[a] Key: (a) 2-bromo-1,1-diethoxyethane, quinoline toluenesulfonate, 1,2-dichloroethane, reflux; (b) 2 M R_1NH_2 in DMSO; (c) Fmoc-AA2-OH, TFFH, DIEA in 1,2-dichloroethane, then 20% piperidine in DMF; (d) $HNu(CH_2)_nCOOH$, TFFH, DIEA in 1,2-dichloroethane; (e) HCOOH, rt to 60 °C.

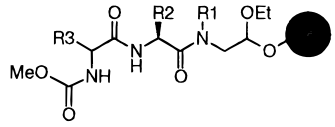
Table 1. *N*-Acyliminium Ion Cyclizations of Resin-Bound 12−15a,b, Giving 1−4a,b

compd	R1	R2	R3	subst[a] (mmol/g)	HPLC purity[b] (%)	mass recovery[c] (%)	isolated[d] yield (%)
1a	Bn	(S)-Me	iPr	0.26	93	79	39
1b	MeO-$(CH_2)_2$	(S)-Bn	iPr	0.33	95	96	87
2a	Bn	(S)-Me	(R)-iPr	0.30	94	69	51
2b	Bn	(S)-iPr	(S)-Me	0.31	95	69	44
3a	Bn	(S)-Me	Ph	0.31	76	78	18
3b	Bn	(S)-Me	PhNH	0.29	63	87	28
4a	Bn	(S)-Me	Me	0.29	99	88	63
4b	Bn	(S)-Me	OMe	0.30	91	88	63

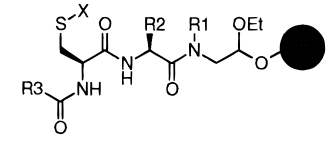
[a] Based on loading of first amino acid as judged by Fmoc-reading. [b] Calculated from integrated peak areas recorded by the HPLC analysis (220 nm) of the crude products cleaved from the solid support. [c] Yields of crude material for solid-supported synthesis based on the initial loading of amino acetal resin **6** as shown in Scheme 1. [d] Yields for purified compounds based on the initial loading of amino acetal resin **6**.



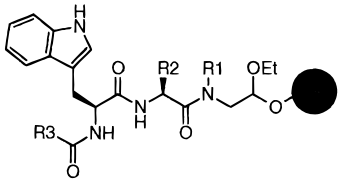
12a: R_1 = Bn; R_2 = Me
12b: R_1 = $MeO(CH_2)_2$; R_2 = Bn
X = F, i-PrHN



13a: R_1 = Bn; R_2 = Me; R_3 = i-Pr
13b: R_1 = Bn; R_2 = i-Pr; R_3 = Me



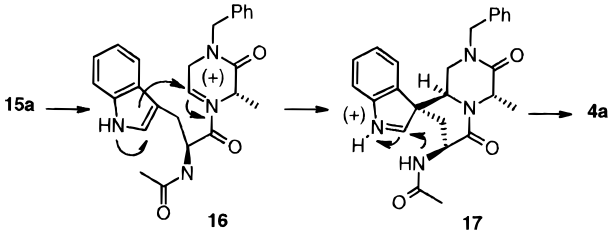
14a: R_1 = Bn; R_2 = Me; R_3 = Ph
14b: R_1 = Bn; R_2 = Me; R_3 = PhNH
X = t-BuS, H



15a: R_1 = Bn; R_2 = Me; R_3 = Me
15b: R_1 = Bn; R_2 = Me; R_3 = OMe

ticipant did not lead to the expected product of *N*-acyliminium ion alkylation at the 2-position of the indole ring. Instead, treatment of **15a**,**b** with formic acid at 60 °C gave the tetracyclic products **4a**,**b**, both in high purity and good yields. These products showed diagnostic spectroscopic signals for a quaternary carbon and a methine group, the latter shifted remarkably downfield in both ^1H and ^{13}C NMR spectra, while 2- and 3-position indole protons and carbons were absent. Detailed assignments of each proton and carbon were accomplished by analysis of 2D NMR data including H(C), H COSY, NOESY, and COLOC. One possible mechanistic explanation for the formation of **4a**,**b** would be an acid-catalyzed formation of *N*-acyliminium intermediate **16** with subsequent indole-C_3 attack followed by trapping of the iminium ion **17** by the amide nitrogen (Scheme 2).[11] In general, only a single diastereomer was observed by HPLC, TLC, ^1H, and ^{13}C NMR analysis for the products **1**−**4**. The major diastereomer of **1**−**4a**,**b** is believed to have a trans relationship of the hydrogen at the bicyclic junction and the α-hydrogen of the first amino acid. Assignment of relative stereochemistry is based on 1D-difference NOE experiments and is further supported by analogy with stereoselectivity observed for similar intramolecular *N*-acyliminium ion cyclizations.[2b,12] To address the question of double stereodifferentiation, D-Val was used as a second amino acid in **2a**. Results of preliminary experiments suggest that the stereochemistry at this part of the molecule has no influence on the overall diastereoselectivity.

Scheme 2



In conclusion, we have developed a new method for the solid-phase synthesis of multifunctional heterocyclic scaffolds using a tandem *N*-acyliminium ion cyclization−nucleophilic addition reaction.

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Supporting Information Available: Experimental details for the synthesis and NMR spectra of all compounds (19 pages).

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(10) The structural assignment of compounds **1**−**4a**,**b** was made on the basis of ^1H NMR, ^{13}C NMR, and ESMS.

(11) Another possibility for obtaining the product **4** is the initial C_2 attack followed by a $C_2 \rightarrow C_3$ rearrangement with subsequent trapping of iminium ion in **17** by the amide nitrogen. Ungemach, F.; Cook, J. M. *Heterocycles* **1978**, *9*, 1089−1119.

(12) ^1H NMR (300 MHz) indicated **2a**,**b** to exist as a ca. 2:1 mixture of conformers in $CDCl_3$ and DMSO-d_6. NOE studies for **2a**,**b** were inconclusive in determining the stereochemistry at the N−CH−N center.