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Efficient approach for the diversity-oriented synthesis of macro-heterocycles on solid-support

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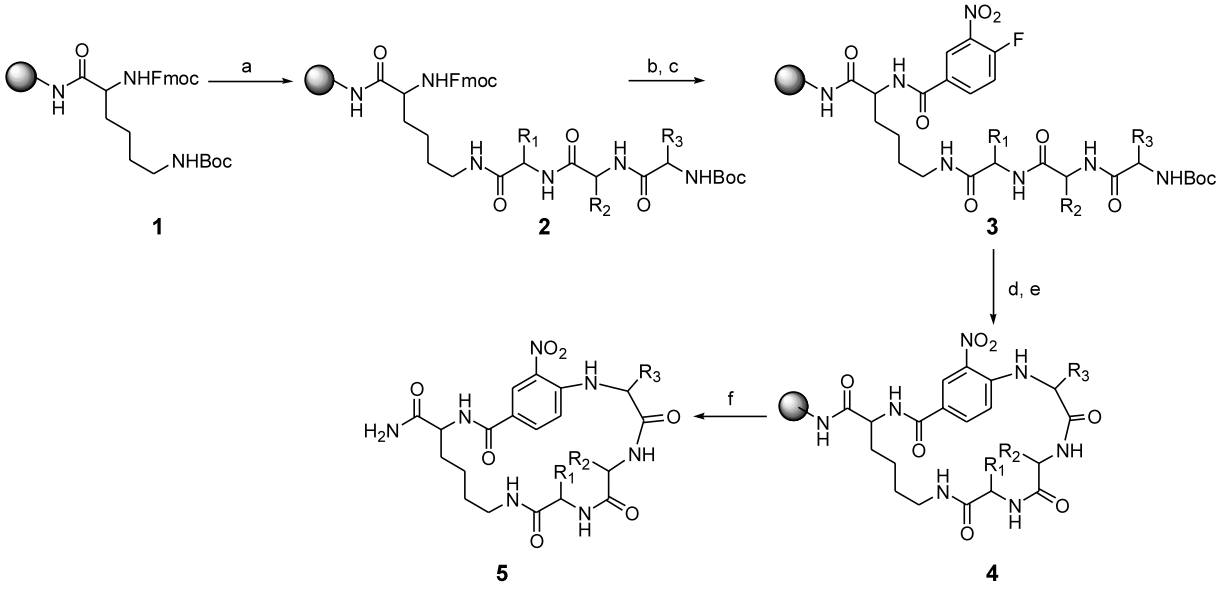
Abstract—The generation of macro-heterocycles starting from resin bound orthogonally protected lysine and using nucleophilic aromatic substitution is described. The method of cyclization required the coupling of *o*-fluoro-*p*-nitro benzoic acid followed by intramolecular displacement of the fluoro group. The described method allows a versatile synthetic route to the synthesis of libraries of macro-heterocycles in an attempt to establish lead drug candidates. The desired cyclic products were obtained in good yields and purities.

Macrocycles are being studied for their potential utility as drug candidates. They have been shown to have a broad range of activities including antitumor activities and antibiotic activities such as the structurally complex vancomycin family.[1] In addition, some groups are using macrocycles to simulate β-turns[2] and mimic the extended conformation of short peptide sequences[3] as well as taking advantage of their aggregation phenomena to form hollow columns and tubes.[4] Reported approaches on the solid-phase synthesis of macrocyclic compounds include intramolecular nucleophilic substitution, intramolecular amide formation, disulfide formation and intramolecular Suzuki reactions.[2b,5] In this paper, we describe an efficient method for the synthesis of 21-membered macrocycles on the solid-support based on an intramolecular nucleophilic aromatic sub-



Scheme 1. *Reagents and conditions*: (a) Boc SPPS; (b) 20% piperidine in DMF; (c) 4-fluoro-3-nitrobenzoic acid, DIC; (d) 55% TFA in DCM; (e) 5% DIEA in DCM; (f) HF/anisole, 90 min.

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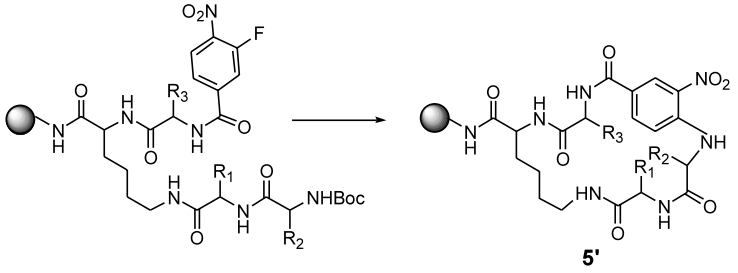
stitution. Previous reports on the solid-phase S_NAr macrocyclization using 2-fluoro-5-nitrobenzoic acid described the formation of 13- to 16-membered ring systems as β-turn peptidomimetics.[6] The solid-phase S_NAr has also been applied as a versatile synthetic route for the cyclization of tripeptides on solid-support.[7]

Starting from resin-bound orthogonally protected Fmoc-Lys-(Boc) **1**, macrocyclic compounds **5** were syn-



Scheme 2.

Table 1. Observed $[M+H]^+$ and purities for some macrocyclic compounds **5**, **5′** and **6**

Entry	R_1	R_2	R_3	Calculated MW	Observed $[M+H]^+$	Purity (%)
5a	$-CH_2C_6H_5$	$-CH_3$	$-CH_3$	581.6	582.3	90
5b	$-CH_2C_6H_5$	$-CH_3$	$-CH_3$*	581.6	582.3	90
5c	$-CH_2C_6H_5$	$-CH_3$	$-CH_2C_6H_5OH$	673.7	674.7	75
5d	$-CH_2C_6H_5$	$-CH_3$	$-CH_2C_6H_5OH$*	673.7	674.7	75
5′a	$-CH_2C_6H_5$	$-CH_3$	$-CH_2CH(CH_3)_2$*	623.3	624.1	80
5′b	$-CH_2C_6H_5$	$-CH_3$	$-CH_3$	581.6	581.9	65
5′c	$-CH_2C_6H_5$	$-CH_2CH(CH_3)_2$	$-CH_3$	623.3	624.2	70
5′d	$-CH_2C_6H_5$	$-CH_2CH(CH_3)_2$*	$-CH_3$	623.3	624.2	68
6a	$-CH_2C_6H_5$	$-CH_3$	–	510.5	511.2	30

The products were run on a Keystone 053–715 C_{18} column, 5–95% B (A: 0.05% TFA in H_2O; B: 0.05% TFA in ACN) over 7 min. Purity was estimated based upon analytical traces at $\lambda = 214$ nm.
* D-Amino acids were used.

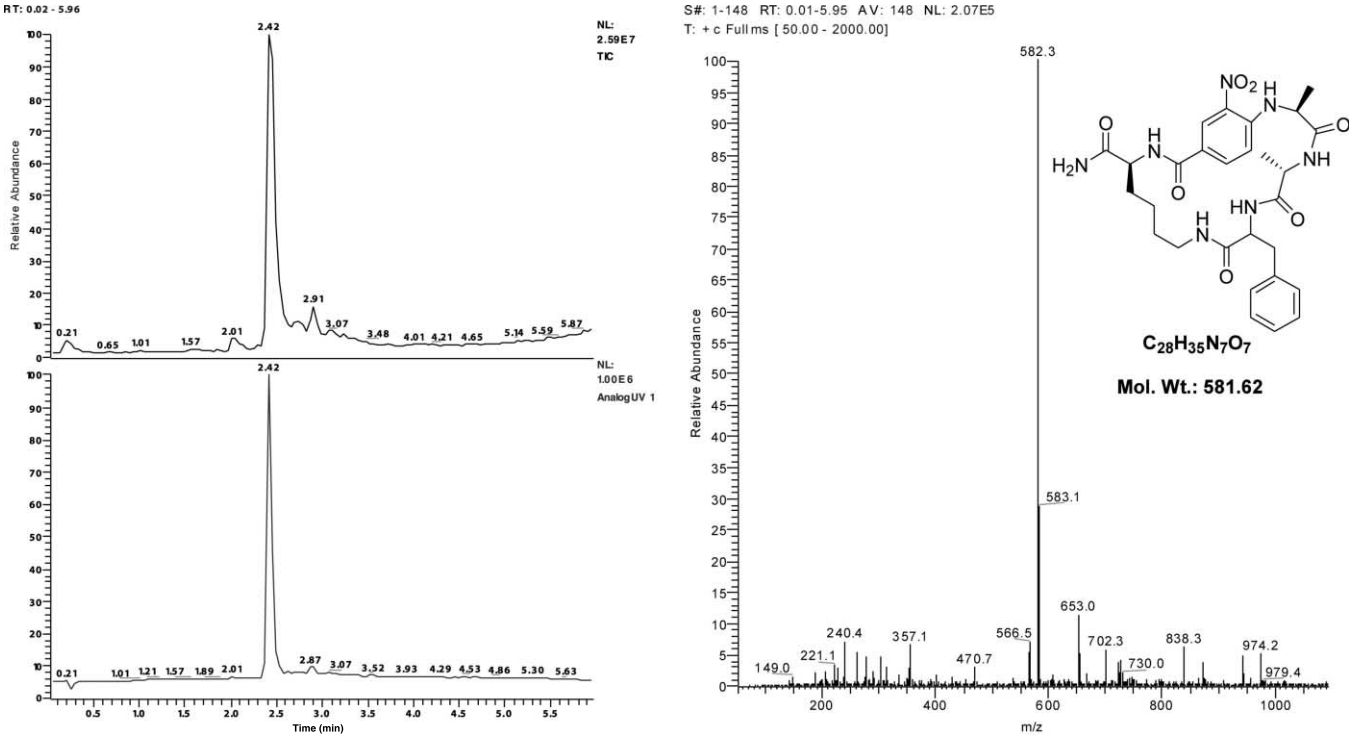
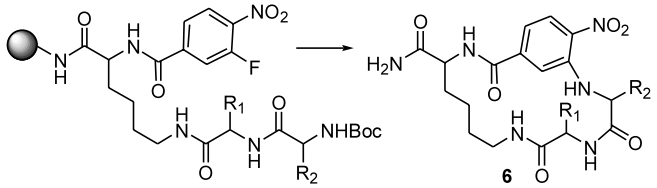


Figure 1. LC–MS of compound **5a** where $R_1 = (S)\text{-}CH_2C_6H_5$, $R_2 = (S)\text{-}CH_3$ and $R_3 = (S)\text{-}CH_3$.



Scheme 3.

thesized following stepwise *tert*-butyloxycarbonyl (Boc) deprotection and standard repetitive Boc-amino-acid couplings yielding the linear peptide **2**. Following removal of the Fmoc group, the resulting free amine was acylated with 4-fluoro-3-nitrobenzoic acid to form compound **3**. The Boc group was cleaved and upon treatment with base an intramolecular cyclization occurred via nucleophilic substitution of the fluoro group (Scheme 1). The desired products **5** were obtained following cleavage of the solid-support and were analyzed by LC–MS.

In an attempt to form a 21 member ring **5′**, we investigated the approach outlined in Scheme 2, where one amino acid was incorporated on the N^{α} amino group of lysine. Different L and D amino acids were tested in the R_1, R_2, and R_3 positions. No significant differences in purity or yields were observed when using the two approaches. As shown in Table 1, good yields and good purities (ranging from 65 to 90%) were obtained. Figure 1 illustrates a representative LC–MS spectra of the macro-heterocycle **5** obtained from phenylalanine at the R_1 position, alanine at the R_2 position and alanine at the R_3 position.

Several attempts were made to prepare smaller 18 member rings **6** by using two α-amino acids (Scheme 3). Low purities (<30%) were obtained for the desired macroheterocycle, with the major products being the uncyclized peptide and head-to-tail dimers formed from the fluoro group being substituted by amines from adjacent resin-bound linear peptides. The use of resins having a lower substitution may reduce the dimerization and improve the yields of the desired product.

We have presented a straightforward approach for the parallel diversity-oriented synthesis[8] of macrocyclic compounds by intramolecular nucleophilic aromatic substitution. The approach can be used to generate large collections of macro-heterocycles developed from linear peptides. This work is currently being used to prepare libraries of macro-heterocycles that will be tested in different assays for biological activity.

Acknowledgements

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